REPORT

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health technology assessment

CHILDHOOD IMMUNISATION

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
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EXECUTIVE SUMMARY

The World Health Organisation Expanded Programme on Immunisation (EP) recommends that all countries immunize against poliomyelitis, diptheria, pertussis, tetanus and measles. Those countries with high incidence of tuberculosis (TB) infection are also to immunize against TB. It has been generally accepted that no immunization schedule is ideal and the EPI recommends that each country determine its own schedule that best suits its need. Besides the EPI vaccines, there are other vaccines available such as the Haemophilus influenza type B vaccine.

In Malaysia for instance the immunization coverage for the year 1996 was 100% for BCG, 94.3% for DPT (third dose), 93.9% for Oral Polio vaccine (third dose), 86.1% for measles and 89% for hepatitis B (third dose) (Ministry of Health Malaysia, 1998).

The objective of this study is to determine the effectiveness, safety and cost implication in the current immunization schedule if necessary. Each vaccine is assessed separately and based on the evidence the following is recommended:

- BCG – to be continued according to the current immunisation schedule
- DPT – accelerated immunisation schedule at 6 week, 3 month and 5 month with a booster at 12-24 months and another at 4-6 year.
- POLIO – the current schedule of OPV should be continued, while IPV can be given to immuno-compromised patient.
- MMR – the first dose should be given at 12 months, accept for Sabah where it's proposed that it be given at 9 month. The second dose should be given at 6-7 year.
- HEPATITIS B – to continue the current universal immunisation schedule at 0, 1, &6 month.
- HEMOPHILUS INFLUENZA B (HIB) – HIB conjugate vaccine be given at 3, 4, 5 months with an additional dose at 12-15 months.
- JAPANNESE ENCEPHALITIS (JE) – for high risk areas only. JE vaccine to be administered with DPT booster at 18 months, followed by a second dose at 19 months and a booster at 30 months.
- HEPATITIS A – universal vaccination is not recommended and should be given only in specific group e.g travellers.
- PNEUMOCOCCAL VACCINE – data on true burden of pneumococcal infection in children locally is needed before a policy can be formulated.

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CHILDHOOD IMMUNISATION

1. INTRODUCTION

Immunisation is an attempt to replace the anticipated natural primary contact between the human body and a hostile organism, with a safer artificial contact, so that any subsequent natural contact takes place in a state of heightened immunity. While advances in public health and medicine have reduced the morbidity and mortality rates accompanying certain infectious diseases, immunisation represents the single-most mass approach to prevention (Zimmerman, 1987).

The World Health Organization (WHO) Expanded Programme on Immunisation (EPI) recommends that all countries immunise against poliomyelitis, diphtheria, pertussis, tetanus and measles, while countries with a high incidence of tuberculosis (TB) infection should immunise against TB. Hepatitis B vaccine was expected to be integrated into national immunisation programmes in all countries by 1997 (WHO/EPI/GEN/ 95.03).

Table 1 below shows the immunisation schedule recommended by the EPI. :

Table 1: I*mmunisation schedule for infants recommended by the WHO EPI*

Age	**Vaccines**	**Hepatitis B vaccine ****	
		Scheme A	**Scheme B**
Birth	BCG, OPV 0	HB 1	
6 weeks	DPT 1, OPV 1	HB 2	HB 1
10 weeks	DPT 2, OPV 2		HB 2
14 weeks	DPT 3, PV 3	HB 3	HB 3
9 months	Measles, Yellow fever *		

* In countries where Yellow fever poses a risk.
** Scheme A is recommended in countries where perinatal transmission of Hepatitis B virus is frequent (eg. Southeast Asia). Scheme B may be used in countries where perinatal transmission is less frequent (eg. Sub-Saharan Africa).

It has generally been accepted that no immunisation schedule is ideal, and thus the EPI recommends that each country determine its own schedule that best suits its need. A strategic guiding principle of any immunisation program is that protection must be achieved before infants are at high risk from a disease. In most developing countries, diseases included within the EPI strike early in life, and thus it is important to protect children through immunisation as early as possible. Apart from this, any immunisation schedule represents some degree of compromise. However, in addition, while acknowledging that seroconversion is age-dependent, the emphasis needs to be on obtaining protection in the infant at as young an age as possible (WHO/EPI/GEN/ 86/7).

Besides the EPI vaccines, several other vaccines are readily available, and being used in different countries, but are as yet not recommended for use worldwide by the EPI. Some of these vaccines, such as Japanese encephalitis vaccine, are against diseases that are prevalent only in limited geographical areas; others such as Hemophilus influenza type b

(Hib) vaccine are used in industralised countries, but their high costs precludes their wide use in developing countries; yet others, such as pneumococcal vaccines, are effective in adults, but, however, preparations for use in infants under 2 years of age have yet to be developed (WHO/EPI/GEN/ 95.03).

Table 2 below illustrates the current immunisation schedule of the Ministry of Health, (MOH) Malaysia:

Table 2: Immunisation Schedule, MOH, Malaysia

Immunisation	Age (months)								Age (years)		
	0	1	2	3	4	5	9	18	6	12	15
BCG	■								No scar	▒	
HepB	■	■				■					
DPT				■	■	■		▒	DT		T
OPV				■	■	■		▒	▒		
Measles							■				
Rubella										■	

Note: ■ **Primary immunization** ▒ **Booster**

The immunisation programme in Malaysia commenced about 40 years ago with the DPT vaccine. This was followed by the BCG vaccine in 1961 and the OPV vaccine in 1972. Measles immunisation was added to the programme in 1984, with immunization against Rubella being introduced in 1988, and against Hepatitis B in 1989 (Pathmanathan, 1990). The immunisation coverage for Malaysia for 1996 was 100% for BCG, 94.3% for DPT (third dose), 93.9% for OPV (third dose), 86.1% for measles, and 89.0% for Hepatitis B (third dose) (Ministry of Health Malaysia, 1998).

2. OBJECTIVES

To determine the effectiveness, safety and cost implications of vaccines in the current immunisation schedule, as well as of other vaccines so as to revise the current immunization schedule if necessary.

3. METHODOLOGY

Each vaccine has been assessed separately so that the methodology is elaborated under individual vaccines. Evidence obtained from the relevant literatures were than graded according to the modified CAHTA Scale (Appendix)

4. RATIONALE FOR PROPOSED CHANGES

4.1 DPT/OPV

Earlier schedule for DPT/OPV from 3 months in the previous schedule to 2 months. The reason for this, there is still a clinical problem of pertussis in infants under 3 months of age.

4.2 Measles

Introduction of two- dose measles vaccination

Evidence for single dose measles provides inadequate protection, as sero-conversion at 9 months vaccination is only 85%. As a result of the single dose measles policy, there has been a measles outbreak recently in certain states in Malaysia and in other countries.

4.3 Rubella

Introduction of universal two dose rubella vaccination

Selective immunisation only to girls, which was practiced in the previous schedule, does not eliminate rubella. As a consequence unimmunised women continue to be exposed to rubella by children and Congenital Rubella Syndrome still exists despite rubella immunisation since 1988. There is also strong evidence, which shows that waning of antibody levels with single dose. A universal 2-dose rubella vaccination, which has been practiced in many other countries, will eliminate circulation of wild virus in the community.

4.4 Hib

Introduced in the present schedule as a conjugated vaccine with DPT and polio.

Incidence of invasive Hib in Malaysia is 139:100 000 per year; Hib causes 50% of bacterial meningitis and 20% pneumonia in children under 5. The Hib vaccine available is highly efficacious (90-98%) and safe. Evidence has showed that the vaccine is cost

effective. In all countries where Hib vaccine has been introduced there has been a rapid decline of invasive Hib disease.

Table 3: Recommended Immunisation Schedule for Infants and Children

Vaccine	Age (months)									Age (years)		
	0	1	2	3	4	5	9	12	18	6	12	15
BCG	■									No scar	▒	
HepB	■	■				■						
DPT			■	■		■			▒	DT		Td
OPV			■	■		■			▒	▒		
Hib			■	■		■						
Measles*							■					
MMR								■		■		

Note ■ **Primary immunization** ▒ **Booster**

***** For Sabah only

4.5 Infants and Children Presenting for Immunisation NOT at the Recommended Age

The recommended schedule for infants and children who do not present for immunization at the recommended age is as shown in Table 4. Children who have missed a vaccination visit should continue the vaccination as schedule.

Table 4: Recommended Immunisation Schedule of Infants and Children

Time of Immunisation	Age of Infants & Children at First Visit		
	< 2 months	2 months – 1 years	> 1 year
1st visit	BCG $HepB_1$	BCG, $HepB_1$ OPV_1 DPT_1 Hib_1 (Measles – if more than 9 months)	BCG, $HepB_1$ OPV_1 DPT_1 Hib_1 MMR
2nd visit (1 month later)	DPT_1 Hib_1 OPV_1 $HepB_2$	DPT_2, Hib_2 OPV_2 $HepB_2$	DPT_2 Hib_2 OPV_2 $HepB_2$
3rd visit (1 month later)	DPT_2 Hib_2 OPV_2	DPT_3 Hib_3 OPV_3	-

4th visit (1 month later)	DPT_3 Hib_3 OPV_3 $HepB_3$	$HepB_3$	DPT_3 Hib_3, OPV_3 $HepB_3$
4 months later	Measles	-	-
2 – 8 months later	DPT & OPV (booster)	DPT & OPV (booster)	DPT & OPV (booster)

Note: Subsequent booster doses: follow "Recommended Immunisation Schedule for Infants & Children"

4.6 Special Groups of Children

Special groups of children include those with immunodeficiency disorders:

i. inherited immunodeficiency state(s)
ii. leukaemia, lymphoma, Hodgkin's disease, etc.
iii. immunosuppressive therapy and radiation therapy
iv. corticosteriod therapy (prednisolone > 2mg/kg/day for more than 7 days or 20 mg/day if weight > 10kg)
v. post-marrow transplant

In these immunodeficiency patients, **live** but not killed vaccines are contra-indications

Table 5: Recommended Immunisation Schedule in Immunodeficient Children

Immunisation	**Immunosuppresive therapy**	**HIV**	**Contacts**
BCG	No	No	Yes
HepB	Yes	Yes	Yes
DPT	Yes	Yes	Yes
OPV	No	IPV (Killed vaccine)	IPV
Hib	Yes (3 + Booster)	Yes (3 + Booster)	Yes (3 + Booster)
Measles	No	Special*	Yes
MMR	No	Special*	Yes

*Note: * Special group refer to Asymptomatic (N) or Symptomatic (A).*

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BCG VACCINE

1. INTRODUCTION

Tuberculosis is caused by the bacillus *Mycobacteruim tuberculosis* which is responsible for some 8 million new cases of tuberculosis and 3 million deaths per year, mostly in developing countries, with about 400,000 new cases in industralised countries (WHO 1993). In Malaysia, the incidence of tuberculosis (all forms) was 63.6 per 100,000 population with 13,539 new cases in 1997. As can be seen, there was a decline until 1995, after which there has been a steady increase in incidence.

Table 1: Incidence (per100000 population) of tuberculosis (all forms), 1993-1997 (*KKM 1997)*

	1993	1994	1995	1996	1997
Incidence per 100 000 population (tuberculosis all forms)	62.2	59.8	58	61	63.6

The most important source of human infection of this disease is an infected person who spreads the highly infectious bacilli via respiratory droplets. Primary infection can occur at any age, but children are most often affected in those areas of high incidence and high population density. Even after resolution, the disease can be reactivated and again be spread. Agents that depress a person's immune system such as corticosteroid therapy or HIV infection, facilitate the reactivation of TB. Primary infection may be asymptomatic and often resolves spontaneously. However, it could also progress by local spread in the lungs to cause pleurisy or bronchopneumonia. If infection spreads through the blood stream, it can affect many organs, including the meninges, the bones, or the internal organ. The disease can be accompanied by tuberculous lymphadenopathy or this manifestation can occur alone, in the absence of other features (*WHO 1993).*

2. TECHNICAL FEATURES

Bacille Calmette-Gurein (BCG) vaccination has been accepted as one of the most important measures for the prevention of tuberculosis, since it is the most effective known adjuvant in animals and humans. It is also cheap, stable and safe. It is compulsory in 64 countries and is officially recommended in an additional 118 countries and territories *(WHO 1993).* WHO also currently recommends BCG vaccination for

asymptomatic HIV-infected children who are at high risk for infection with M. tuberculosis (i.e. in countries with a high prevalence of TB). WHO does not recommend BCG vaccination, on the other hand, for children who have symptomatic HIV infection or for persons known or suspected to be infected with HIV, since they are at minimal risk of infection with M. tuberculosis (MMWR 1996*).*

BCG vaccine is a suspension of live attenuated *Mycobacteruim bovis*. There are many BCG vaccines available worldwide, but these are all derived from the strain propagated by the Pastuer Institute and first tested in humans in 1921. BCG should be protected from light, stored at 2-8 °C, and never frozen. The vaccine is given by intradermal injection. (NHMRC, 1997). The limited data available from human studies suggests that the BCG strain being used for vaccination is not a significant determinant of the overall efficacy of the prevention of TB (*Brewer TF, 1995).* Artificial infection with BCG spreads from the inoculation site via the lymphatic system to local lymph nodes and produces an immunity equivalent to that produced by natural virulent bacilli. As in the case of natural tuberculosis infection, the resistance is cell mediated and is largely attributed to activated macrophages. BCG–induced immunity develops at about 6 weeks after vaccination (WHO 1993).

3. METHODOLOGY

The initial search was by using MEDLINE. The **k**eywords used for were *BCG efficacy (0-18 years)*, and the year limits used were 1966 – 2000. A total of 137 titles were obtained, and 56 of these were thought to be relevant, and the abstracts reviewed. Of these 32 were found to be relevant, but full articles could only be obtained for 6, with the remaining based on abstracts. Apart from this, immunisation handbooks from the United Kingdom and Australia were reviewed. Other sources of literature were reports on Tuberculosis from the WHO and from the Ministry of Health Malaysia.

4. RESULTS & DISCUSSION

4.1 Vaccine Efficacy

The Expanded Programme on Immunization (EPI) was launched by WHO in 1974, and at that time, less than 5% of the world's children had been immunised against six infectious diseases including tuberculosis. However, according to 1995 statistics, BCG has the highest vaccination coverage, 87% higher than any of the other 5 vaccines in the EPI for children. BCG must have saved a lot of infants, as the vaccine has been proved to be most effective against the blood-borne tuberculosis found in children **(**Hashimoto, 1997).

The results of 10 randomized controlled trials and case-control studies indicate the protective efficacy against tuberculosis as uncertain and unpredictable, varying from 80% to 0% (Hashimoto, 1999). This wide variation has been attributed to differences in vaccine strain, prevalence of (protective) local environmental mycobacteria, and host factors such as age at vaccination and nutritional status (NHMRC, 1997). Other reasons for a low efficacy of BCG immunisation include inadequate BCG vaccination techniques and incomplete administration of inoculation dose (Ivan'kova, 1990). BCG vaccination

of the newborn and infants reduces the risk of tuberculosis by over 50% on the average. Protection has been observed over many populations, study designs and forms of tuberculosis. The highest rates of protection against cases that are confirmed by laboratory tests, reflecting reduced error in disease classification and consequently more estimates of BCG efficacy stands at 83% (Coditz, 1995). The vaccine has shown an efficacy of 70-80% in protecting against tuberculosis when given to British school children, the protection lasting for at least 15 years (DHSS, 1996**).** Analysis by linear regression indicates that the decrease of TB incidence in children since 1959 has been 3-5 times more rapid (annual average decrease was 25.5%) than in adults. Multiple regression analysis indicates that BCG is the strongest explanatory variable among other antituberculosis measures in Hungary for decreasing TB incidence in children (Lugosi, 1998).

In Africa, the efficacy of BCG has been estimated to be 71%. BCG vaccination at birth must remain a public health priority especially in those countries with a high incidence of the disease (Lanckriet, 1995). The prevention of tuberculosis was prospectively studied in Togo, and Tuberculosis was identified in 53.4% of unvaccinated subjects versus 5.3% of vaccinated subjects. These findings clearly demonstrate the incomplete, but substantial protective effect of BCG vaccine in subjects exposed to tuberculous patients and provides further support for use of the BCG vaccine (Tidjani, 1992). In a retrospective analysis of the history of BGC vaccination in 367 children with active tuberculosis in Japan, BCG vaccination was shown to have a protective efficacy of 78%. Efficacy was estimated at 92% for children of ages 5 years and less (Takamatsu, 1995*).* A case-control study conducted in Cairo showed that the overall crude efficacy of BCG vaccination was 53%, but this dropped to 49% after controlling for the confounding effect of the "crowding index" (Kotb, 1993*).* The reported incidence of tuberculosis in people aged 15 years or younger in areas without a policy of neonatal BCG was shown to be significantly higher compared than those that practiced neonatal BCG vaccination in 1986 (Kelly, 1997). In Thailand, the protective efficacy of neonatal BCG vaccination was 83%, but was 96% when only 36 matched sets of laboratory-confirmed cases were analyzed (Sirinavin, 1991*).* Retrospective evaluation of BCG vaccination campaign of newborns in Barcelona revealed an efficacy of 32% (Gomez,1993*).* In Israel, the protective efficacy of BCG immunisation was 38% (24% for pulmonary and 64% for extra pulmonary) (Zibler, 1984).

A large-scale community-based study carried out in south India, showed complete lack of protective efficacy, seen at the end of 7½ years. BCG offered no overall protection in adults and a low level of overall protection (27%; 95% C.I. -8 to 50%) in children. The findings at 15 years showed that this population had high infection rates and high nonspecific sensitivity. It was concluded that BCG did not offer any protection against adult forms of bacillary pulmonary tuberculosis (Anonymous 1999). In Malawi, too, no statistically significant protection by BCG against tuberculosis was found (Ponnighaus, 1992.)

A meta-analysis of selected papers on BCG field trials found the protective effect against meningeal and miliary TB to be higher than against pulmonary TB (86% and 75% in

randomized controlled trials and case-control studies respectively) (Hashimoto, 1997). Meta analyses of BCG protective efficacy have confirmed that the vaccine efficacy for preventing serious forms of TB in children is high (i.e>80%) (MMWR,1996). Protection against tuberculous death, meningitis and disseminated disease is higher than for total TB cases, although this result may reflect reduced error in disease classification rather than greater BCG efficacy (Coditz, 1994*).* In a case-control study, the protective efficacy of BCG vaccine in preventing tuberculous meningitis (TBM) in children was found to be 77% (Thilothammal, 1996). In an active surveillance of TBM cases confirmed by positive cerebrospinal fluid culture, the protective efficacy of BCG vaccination was estimated to be 87.5% (Schwoebel, 1994*).* BCG vaccination does not prevent tuberculosis infection but reduces the risk of death from tuberculosis, meningitis and disseminated disease. However, it should be noted that most trials have observed high levels of protection against meningeal, if not pulmonary disease and these findings encourage the continued use of the vaccine in high-risk infants (NHMRC, 1997). In India, the efficacy of BCG in the prevention of TB meningitis was 84% (Sharma, 1989). In Myanmar, BCG vaccination conferred 80% protection against tuberculous meningitis (Myint, 1987*).*

A study to evaluate tuberculin sensitivity and side effects following 0.05 ml and 0.1 ml of BCG at birth and 0.1 ml of BCG at 4-6 weeks of age found no significant difference in mean tuberculin reaction, tuberculin positivity and mean scar size, in groups receiving 0.1 ml at birth or 4-6 weeks of age. However, the group receiving 0.05 ml at birth had a significantly lower mean tuberculin reaction, tuberculin positivity and mean scar size. No local or regional side effects were observed. Hence, it has been suggested that the present practice of giving 0.1 ml of BCG at birth should be continued (Aggarwal, 1995). The efficacy of BCG vaccination using different doses resulted in 0.1 ml dose showing better scars and purified protein derivative (PPD) response as compared to 0.05 ml (Valenzuela, 1998).

Pre-term infants of lower gestational age (<33 weeks) are less likely to develop BGC scar and a reactive PPD tuberculin test (Sedaghatian, 1998). BCG vaccination had similar effects even when there was associated malnutrition (Bhaskaran, 1992).

A review of 10 randomised trials to investigate the protective efficacy of BCG revealed that in seven trials, the efficacy decreased over time while in three it increased. The average efficacy more than 10 years after vaccination was 14%, and the variation was not statistically significant. Therefore BCG protection can wane with time after vaccination, and there is no evidence that BCG provides protection for more than 10 years after vaccination (Sterne, 1998). However, another study found that the duration of BCG efficacy against tuberculosis was confirmed to continue for 15 years after vaccination (Hashimoto, 1997). A WHO issued in 1995 mentions that there is no definitive evidence that repeated BCG vaccination confers additional protection against tuberculosis. Therefore WHO does not recommend repeated BCG vaccination in the absence of scientific evidence to support this practice. Multiple BCG revaccinations are thus not indicated in anyone (Hashimoto, 1997). The immunological status of BCG vaccinated and unvaccinated healthy children were evaluated to assess the efficacy of BCG.

Leucocyte migration inhibition values against PPD were compared. BCG seems to afford some protection in children and has to be administered at birth. Revaccination at the age of eight years may boost the waning immunity and may be considered in this age group **(**Vijayalakshmi, 1993).

4.2 Vaccine Safety

Although BCG vaccination often results in local adverse effects, serious or long-term complications are rare. BCG vaccinations are usually administered by the intradermal method, and reactions that can be expected after vaccination include moderate axillary or cervical lymphadenopathy and indurations and subsequent pustule formation at the injection site; these reactions can persist for as long as 3 months after vaccination. BCG vaccination often results in permanent scarring at the injection site. More severe local reactions include ulceration at the vaccination site, regional suppurative lymphadenitis with draining sinuses, and caseous lesions or purulent drainage at the puncture site; these manifestations might occur within the 5 months after vaccination and could persist for several weeks. Higher rates of local reactions may result from using subcutaneous injection in comparison with reactions from intradermal injection. In the United States, a recent study of the effects of BCG in adults who volunteered to receive the vaccine indicated that local reactions after BCG vaccination (e.g., muscular soreness, eraema, and purulent drainage) often occurred at the site of subcutaneous injection (MMWR, 1996).

The major host characteristics that may affect adverse reaction to BCG in immunisation programme are age, where there is a higher incidence of adenitis as compared to older infants and children, and the increased risk of disseminated reactions (and possible local reactions) in recipients with serious immune deficiency involving the T cell mediated system. In practical terms the major risk of concern is abnormal T cell function secondary to HIV infection, which is rarely present until several months after birth in perinatally infected infants **(**WHO, 1993).

The most serious complication of BCG vaccination is disseminated BCG infection. BCG osteitis affecting the epiphyses of the long bones, particularly the epiphyses of the leg, can occur from 4 months to 2 years after vaccination. The risk for developing osteitis after BCG vaccination varies by country, ranging from 0. 01 cases per million vaccinees in Japan to 32.5 and 43.4 cases per million vaccinees in Sweden and Finland, respectively. Regional increases in the incidence of BCG osteitis have been noted following changes in either the vaccine strain or the method of production. Case reports of other severe adverse reactions in adults have included erythema multiforme, pulmonary TB, and meningitis. Fatal disseminated BCG disease has occurred at a rate of 0.06-1.56 cases per million doses of vaccine administered; these deaths occurred primarily among immunocompromised persons. (MMWR, 1996 **)**

The safety of BCG vaccination in HIV-infected adults has not been determined by controlled or large studies. Disseminated BCG disease after vaccination has occurred in at least one child and one adult who were infected with HIV. Persons who are infected

with HIV are possibly at greater risk of lymphadenitis and other complications from BCG vaccine than are persons who are not infected with HIV (MMWR, 1996).

5. CONCLUSIONS

In summary, millions of persons worldwide have been vaccinated with BCG vaccine, and serious or long-term complications after vaccination were infrequent. Possible factors affecting the rate of adverse reactions include the BCG dose, vaccine strain, and method of vaccine administration. Case reports have indicated that BCG-related lymphadenitis, local ulceration, and disseminated BCG disease - which can occur several years after BCG vaccination - may be more frequent among persons who have symptomatic HIV infection than among persons who are not infected with HIV or who have asymptomatic HIV infection

6. RECOMMENDATIONS

There is sufficient evidence to continue with BCG immunization.

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8. EVIDENCE TABLE

BCG VACCINATION

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Safety				
1.	Julie Milsten Module 5: *Tuberculosis, Global Program For Vaccines And Immunization. Expanded Program On Immunization,* WHO, 93.15, p 7.	Recommendation by expert committee based on scientific literature	It depends on dose-response relationship, host characteristics (age, immune status)	Good
2.	Institut Perubatan Respiratori, HKL: *B.C.G. Vaccination:* 10	Report	Safest, uncommon complications	Poor
3.	Canada Communicable Disease Report: An Advisory Committee Statement. *The Risk And Prevention of TB In Travelers* Nov 1997; 23 (ACS-5) 1: 2.	Recommendation by expert committee based on scientific literature	Common for local complications and rare for serious side effect. Results in a positive TST vary widely and may be affected by vaccine strain, age at vaccination or other factors.	Good
Protective Efficacy of BCG				
1.	Report of the US Preventive Task Force. *Screening for TB infection-Including Bacille Calmette-Guerin Immunization.* 2nd Edition Infectious Diseases: 5.	Meta analysis, 14 trials and 12 case controls	BCG offers 50% protection against overall TB, 64-71% against TB meningitis and TB death.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	MMWR *Tuberculin Skin Test Survey In A Paediatric Population With High BCG Vaccination Coverage-* Bostwana, 1996- 46(36): 846-851, 1997 CDC: 3.	Multistage cluster survey	Urban and rural set up was chosen. BCG vaccination recommended in infants in countries with high TB rates. Mean TST sizwith high TB rates. Mean TST sizdose of BCG, interval since vaccination given, age, nutritional status at time of vaccination	Good
3.	Springett VH. *A re-examination of the variation in the efficacy of BCG vaccination against TB in clinical trials.* Tuber Lung Dis 1994 Jun: 75(3) : 227-33	Randomised control trials	Assessment of several trials.	Fair
4.	Schwoebel V *TB meningitis in France in 1990: Characteristic and impact of BCG vaccination.* Tuber Lung Dis 1994 Feb: 75(1): 44-8	Descriptive cross-sectional study	Current BCG program vaccination has measurable impact on the incidence of TB Meningitis in children under 5.	Fair
5.	Alet MN et al. *Retrospective evaluation of the effectiveness of the BCG vaccine campaign in new-borns of Barcelona* Med Clin (Barc) 1992 Nov 14;99 (16): 612-6	Matched pair analysis 250 cases retrospective case-control study	Weak efficacy of BCG vaccination campaign may be attributed not only to the unforeseen effects of the vaccine but also to the deficient operative aspects of the campaign itself	Good
6.	Technology Assessment Group, Harvard School of Public Health: *The efficacy of Bacillus Calmette Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analysis of the published literature* Paediatrics 1995 Jul: 96 (1 Pt 1):29-35	Meta analysis 1264 articles and abstracts were reviewed	BCG vaccination of new-borns and infants significantly reduces the risk of TB- by over 50% on average. Protection has been observed across many populations, study designs and forms of TB. Rates of protection against cases that are confirmed by laboratory tests, reflecting reduced error in disease classification and consequently more accurate estimates of BCG efficacy, are highest at 83%.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
7.	Lanckriet C et al *Efficacy of BCG vaccination of the new-born: evaluation by a follow-up study of contacts in Bangui* Int J Epidemiol 1995 Oct;24(5): 1042-9	Cohort study 1000 cases	BCG vaccinations at birth must remain a public health priority especially in countries with high incidence of the disease	Fair
8.	Aggarawal A et al *Timing and dose of BCG vaccination in infants as assessed by post vaccination tuberculin sensitivity* Indian Paediatr 1995 Jun; 32(6): 635-9	Randomised clinical trials 238 new-borns	The group receiving 0.05 ml at birth had a significantly lower mean tuberculin reaction. Hence the present practice of giving 0.1ml BCG at birth should be continued.	Good
9.	Thilothammal et al *Does BCG vaccine prevent tuberculosis meningitis?* Arch Dis Child 1996 Feb; 74(2): 144-7	Case-control studies	The efficacy of BCG vaccine in preventing tuberculosis meningitis in children was found to be 77%	Good
10.	Igari H et al. *Koch's phenomenon after BCG vaccination and the two-step tuberculin test in elementary school.* Kekkaku 1998 Jun; 73(6): 395-40	Cohort study 180 BCG vaccinated children	More than 69% of tuberculin negative who were vaccinated previously maintained immunity with BCG. Many school children may be given BCG vaccination unnecessarily. Taking into consideration the incidence of TB in children, discontinuation of BCG re-vaccination policy at elementary school entrance should be considered.	Poor Sample too small to generalize.
11.	Tala-Heikkila et al. *Bacillus Calmette-Guerin revaccination questionable with low tuberculosis incidence* AM J Respir Crit Care Med 1998 Apr;157 4 Pt 1): 1324-7	Case control Comparison between those revaccinated with those who were not	Cessation of BCG revaccination had no effect on the continuing overall decline of tuberculosis in Finland. The efficacy of BCG revaccination seems to be low or non existent in countries with low TB incidence.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
12.	Sterna JA, *Does Bacille Calmette-Guerin scar size have implication for protection against tuberculosis or leprosy?* Tuber Lung Dis 1996 Apr; 77(2): 117-23	85 314 cases for TB, 82 265 cases for leprosy cohort study-3 years	No evidence that increased BCG scar size is a correlate of vaccine induced protective immunity against either TB or Leprosy	Fair Measurement of scar size too subjective
13.	American Family Physician: CDC Issues *Recommendations On The Role Of BCG Vaccine In The Prevention And Control Of Tuberculosis* Special Medical Report: 3.	Medical consensus	The presence or size of a post vaccination tuberculin skin test reaction does not predict whether BCG will provide any protection against TB disease.	Poor
14.	Sirivanin s, et al. *Protective effect of neonatal Bacillus Calmette-Guerin vaccination against tuberculosis.* Paed.Infect.Dis.1991, 10:959-965	Matched case-control study	Neonatal BCG vaccination was protective against TB in children aged 14 years and younger. The estimated protective effect was 81% (95% CI 47-93%). The protective effect of BCG vaccine was estimated to be 95% during the first 5 years after BCG vaccination	Good
15.	Shannon A, et al. *Isoniazid resistant TB in a school outbreak: the protective effect of BCG* Ur.espir. 1991, 4, 778-782	Screening of 1160 pupils	The relative risk of non-vaccinated to vaccinated acquiring TB was 5.43 (95% CI 1.95-15.1). None of the exposed children who had been immunised with BCG in primary school developed TB. BCG vaccination offers protection against TB even among teenagers who were vaccinated as neonates.	Good to fair evidence

DIPHTHERIA, PERTUSSIS AND TETANUS (DPT)

1. INTRODUCTION

Diphtheria, Tetanus, and Pertussis monovalent and combination (DPT) vaccines are jointly discussed. The focus of this section, however, will be on the DPT vaccine. Each disease is dealt with separately, followed by an overview of the vaccines and a discussion on selected issues relating to using DPT and individual vaccines.

1.1 Diphtheria

1.1.1 Disease characteristics

Diphtheria is an acute infectious disease affecting the upper respiratory tract and occasionally the skin, vagina, and conjunctiva. The clinical manifestations result from the action of an exotoxin produced by *Corynebacterium diphtheria*. It usually causes a membranous nasopharyngitis and/or layngotracheitis that may cause respiratory obstruction. Diphtheria toxin exerts its effect on distant tissues and organs, especially the heart (myocarditis), and the cranial and peripheral nerves (weakness progressing to paralysis) [The Red Book 1997; The Green Book 1996; Australian Immunisation Handbook 1997].

Man is the only known reservoir of *Corynebacterium diphtheria*. Sources of infection include discharges from the nose, throat, eye and skin lesions of the infected person. The incubation period is 2-5 days. Illness is most common among the lower socio-economic groups living in crowded conditions. Patients with the disease may be infectious for up to 4 weeks, but carriers may shed organisms for a longer period [The Red Book, 1997; The Green Book, 1996; Australian Immunisation Handbook, 1997].

Most children, especially those from developing countries, acquire immunity through sub clinical or cutaneous infection. Despite this, outbreaks of Diphtheria do occur among children in these countries as well, thus emphasising the importance of universal immunisation. The case fatality rates of Diphtheria range from 3-23% [The Red Book, 1997; The Green Book, 1996: Australian Immunisation Handbook, 1997].

1.1.2 Incidence

Diphtheria is a notifiable disease in Malaysia. Table 1 shows the number of reported cases of diphtheria. As can be seen, the incidence rate shows a diminishing trend from 0.11 per 100000 populations in 1988 to 0.02 in 1998 (IDS, MOH 1999]. Prior to 1997, the largest number of diphtheria cases was reported from Sabah, but in 1998, cases were only reported from Peninsular Malaysia. During the period from 1989-1998, there were 12 deaths out of the 72 cases reported giving a case fatality rate of 16.7% [IDS, MOH 1999].

Table 1: Number of reported cases of Diphtheria in Malaysia 1988-1998 (IDS, MOH)

Year	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
Cases	20	36	9	12	4	4	0	1	0	2	5
(death)	(5)	(6)	(1)	(2)	(1)	(0)	(0)	(0)		(1)	(1)

1.1.3 Vaccine characteristics

The diphtheria antitoxin was introduced in the 1890s [Australian Immunisation Handbook, 1997]. Immunisation protects by stimulating the production of antitoxin that provides

immunity against the effects of the Diphtheria toxin. The immunogen is prepared by treating a cell-free purified preparation of toxin with formaldehyde, thereby converting it into diphtheria toxoid. The toxoid is usually adsorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide to increase its immunogenicity [The Green Book, 1996]. Antigens from *Bordetella pertussis* also act as an effective adjuvant.

Diphtheria vaccines should be stored at 2-8°C. If the vaccine has been frozen it should not be used [Australian Immunisation Handbook, 1997]. The dose is 0.5 ml given intramuscularly. Monocomponent diphtheria vaccines are less immunogenic, have no advantage in terms of seroconversion rates and are no longer available. The pertussis component of DTP vaccines does not affect the immune response of the diphtheria component [The Green Book, 1996].

1.2 Pertussis

1.2.1 Disease pattern

Pertussis is a highly infectious bacterial disease caused by *Bordetella pertussis* that is spread by droplet infection. Pertussis is highly communicable with attack rates of greater than 90% among unvaccinated household contacts [MMWR 1991:40 (No RR-10)]. The incubation period is 7-10 days. The initial catarrhal stage has an insidious onset and this is the most infectious period. It can progress to severe paroxysms of cough (paroxysmal stage) often with a characteristic respiratory whoop. The convalescent stage is usually long. Complications include post-tussive vomiting leading to weight loss, seizures due to cerebral hypoxia, bronchopneumonia, encephalopathy and death [The Red Book, 1997; The Green Book, 1996: Australian Immunisation Handbook, 1997].

While pertussis can occur at any age, about 20-40 % of reported cases occur in infants less than 6 months old, and approximately 60% occur in children younger than 5 years [The Red Book, 1997; Galazka, 1993]. Pertussis is most severe when occurring in the first year of life, the group at highest risk being preterm babies. Maternal antibodies do not give adequate protection against pertussis, and hence infants under 3 months can be infected before they are old enough to be vaccinated. Complications and deaths occur most commonly in infants under 6 months of age, mortality being 0.5 %, while the overall mortality from pertussis is 0.3% [Australian Immunisation Handbook, 1997].

In industrialised countries, epidemics occur every 3-4 years, mostly among children of school-going age. Adolescents and adults have now been recognised as a significant reservoir of infection [MMWR 1991:40 (No RR-10)].

1.2.2 Incidence

Although pertussis is a notifiable disease, due to under-reporting, the incidence of pertussis in Malaysia is difficult to determine. Table 2 below shows the number of reported cases of pertussis from 1988-1998. The reported incidence, in general, shows a diminishing rate from 0.15 per 100 000 populations in 1988 to 0.03 in 1998. However, most paediatricians in Ministry of Health hospitals clinically diagnose about 5-10 cases of pertussis per year, on the average, usually under the age of 6 months [Personal communication, May 2000]. No data is available on pertussis deaths.

Table 2: Reported Cases of Pertussis in Malaysia 1988-1998 [IDS, MOH 1999]

Year	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
Cases	27	25	24	20	21	18	12	8	7	3	6

1.2.3 Vaccine characteristics

Pertussis vaccines have been available since 1925 [Edwards, 1990]. Two types of pertussis vaccine are available in combination with diphtheria and tetanus toxoids - whole cell (DTP) and a cellular vaccine (DTaP).

Whole cell pertussis vaccines (DTP) are the most widely used vaccine against pertussis. It consists of a suspension of whole inactivated *Bordetella pertussis* bacteria combined with diphtheria and tetanus toxoids that are adsorbed on to Aluminium salt. The preparation contains multiple antigens [Galazka, 1993] including pertussis toxin, adenylate cyclase, lipopolysaccharide endotoxin, filamentous hemagglutinin and three agglutinogens. Untoward reactions to whole cell pertussis vaccines have led to poor public acceptance and low effectiveness in some countries [The Red Book, 1997; Australian Immunisation Handbook, 1997; Galazka, 1993]. The high rate of reactions to whole cell pertussis vaccines, coupled with public concerns, has resulted in the use of whole cell pertussis vaccines becoming controversial in some countries. This led to the development of acellular pertussis vaccines as an alternative.

Acellular pertussis vaccines (DTaP) became available in Japan in the early 1980s and have been used routinely since in children above 2 years [Australian Immunisation Handbook 1997, Galazka, 1993]. They have been licensed for use in some industrialised countries since the 1990s. DTaP contain one or more immunogens (antigens) derived from *Bordetella pertussis* and contain minimal or no endotoxin. The antigens include detoxified pertussis toxoid, filamentous hemagglutinin, agglutinogens and pertactin. All DTaP contain inactivated pertussis toxoid in different concentrations, but differ in the variety and strength of the other antigens [The Red Book, 1997; Australian Immunisation Handbook, 1997; Galazka, 1993].

Pertussis vaccines should be stored at 2-8°C and should not be frozen [The Green Book, 1996; Australian Immunisation Handbook, 1997]. The dose is 0.5 mL given intramuscularly. In primary immunization, Pertussis vaccines are given as a monocomponent vaccine, in combination with diphtheria and tetanus [Australian Immunisation Handbook, 1997].

1.3 Tetanus

1.3.1 Disease characteristics

Tetanus is an acute disease caused by a highly potent neurotoxin (tetanospasmin) produced by *Clostridium tetani*. This exotoxin acts at the myoneural junction of skeletal muscle, and on neuronal membranes in the spinal cord blocking inhibitory pulses to motor neurons. The disease is characterised by muscular rigidity with superimposed agonising contractions. The bacillus grows anaerobically at the site of wounds. Tetanus spores are present in soil and may be introduced into the body during injury through puncture wounds, burns or trivial wounds. Tetanus is not spread from person to person. The incubation period may vary between 2 days to 2 months, averaging about 10 days, although most cases occur within 14 days. Shorter incubation periods are said to have been associated with more heavily contaminated wounds, more severe disease, and a worse prognosis. Death results from

respiratory failure, hypotension or cardiac arrhythmias [The Red Book, 1997; The Green Book, 1996; Australian Immunisation Handbook, 1997; Galazka, 1993].

Neonatal tetanus arising from an infection of the baby's umbilical stump is an important cause of death in many developing countries where mothers are not appropriately immunised against tetanus during the antenatal period. In developed countries, tetanus mainly affects elderly persons because the younger age groups have been immunised [The Red Book, 1997; The Green Book, 1996]. The case fatality rates, even with good intensive care, range from 10-20% with higher rates at the extremes of ages [Australian Immunisation Handbook, 1997; Plotkin 1999].

1.3.2 Incidence

Both neonatal and adult tetanus are notifiable diseases in Malaysia. Table 3 below shows the number of reported cases of neonatal tetanus from 1988 until 1998. The reported incidence shows a general diminishing rate from 0.08 per 100 000 populations in 1988 to 0.06 in 1998, although there has been much inter-year variation. More than 90% of all cases are reported from Sabah. There were 32 deaths out of the 180 reported cases giving a case fatality rate of 17.8% [IDS, MOH 1999].

Table 3: Reported Cases of Neonatal Tetanus in Malaysia 1988-1998 [IDS, MOH 1999]

Year	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
Cases	15	21	11	13	28	20	9	27	23	15	13
(death)	(12)	(4)	(3)	(0)	(8)	(0)	(5)	(4)	(3)	(1)	(4)

There is insufficient data to answer questions about natural immunity to tetanus. There is also no clear data showing a rise in natural immunity with age. Hence, it has been postulated that there is no immunity induced by tetanus infection [Galazka, 1993].

1.3.3 Vaccine characteristics

Immunisation stimulates the production of antitoxin, which protects against the toxin produced by the organism. The immunogen is obtained by treating a cell free preparation of toxin with formaldehyde and thereby, converting it into the innocuous tetanus toxoid. It is usually adsorbed on to an adjuvant (either aluminium phosphate or aluminium hydroxide), to increase its immunogenicity. *Bordetella pertussis* vaccine also acts as an effective adjuvant.

Tetanus toxoid is stable and able to withstand room temperature for months [WHO, 1995]. However, tetanus vaccines as part of DPT should be stored at 2-8°C and should not be frozen or exposed to light [The Green Book, 1996; Australian Immunisation Handbook, 1997]. The dose is 0.5 ml given intramuscularly. For primary immunisation, tetanus vaccines should not be given as a monocomponent vaccine, but in combination with diphtheria (DT) and/or pertussis (DPT) [Australian Immunisation Handbook, 1997].

1.4 DPT Vaccine

DPT vaccine is a combination vaccine containing formaldehyde-inactivated diphtheria toxoid, formaldehyde-inactivated tetanus toxin and inactivated whole cell pertussis bacterium that are adsorbed on to aluminium salts [Bart, 1990]. It is stored at 2-8°C and the dosage is

0.5 ml is administered by intramuscular injection [The Green Book, 1996; Australian Immunisation Handbook, 1997; Bart, 1990].

DPT vaccine formulations include the following:

- Adsorbed diphtheria/ tetanus/whole cell pertussis vaccine (DTP)
- Adsorbed diphtheria/tetanus/acellular pertussis vaccine (DTaP)
- Adsorbed diphtheria/ tetanus vaccine (DT)
- Adsorbed tetanus/ low dose diphtheria vaccine for adults (Td)
- Adsorbed diphtheria vaccine (D)
- Adsorbed low dose diphtheria vaccine for adults (d)
- Adsorbed tetanus, T (only to be used if diphtheria toxoid is contraindicated)

[The Green Book, 1996; Australian Immunisation Handbook, 1997].

2. METHODOLOGY

An electronic search of MEDLINE database using various keywords, age limit of 0-18 years, and year limits was carried out. In addition, three country immunisation handbooks from USA, UK and Australia were utilized. Other important references were obtained from various sources.

The results of the search are as follows:

a. Total electronic search result = 217
b. Abstracts reviewed = 55
c. Useful/Relevant articles (i.e. pertaining to DPT vaccines & relevant to this HTA) = 24
d. Useful journal articles found using MMWR or books and reports sources = 9
e. Total papers reviewed and used = 15
f. Papers not available, abstracts used = 5
g. Books and reports reviewed (sections used) = 8
h. Total journal articles, books and reports reviewed = 28

The details of the above search are as follows:

a. "DPT vaccine" and "Efficacy" 1990 –2000 - 60 titles, 26 abst, 2 relevant
b. "DPT vaccine" and "Effectiveness" 1990 -2000 - 14 titles, 3 absts, 1 relevant
c. "DPT vaccine" and "Safety" 1990 -2000 - 84 titles, 20 absts, 4 relevant
d. "DPT vaccine" and "Cost" 1990 -2000 - 30 titles, 3 absts, 1 relevant
e. "Malaysia" and "Diphtheria" 1966-2000 - 11 titles, 2 absts, 1 relevant
f. "Malaysia" and "Tetanus" 1966-2000 - 10 titles, 1 relevant
g. "Malaysia" and "Pertussis" 1966-2000- 2 titles, none relevant
h. "Malaysia" and "immunisation" 1966-2000 - 6 titles, none relevant

3. RESULTS & DISCUSSION

3.1 Vaccine Efficacy

3.1.1 Diphtheria vaccine

There is no defined level of diphtheria antitoxin (as determined by neutralisation tests in animals or in cell cultures) that provides complete protection against diphtheria. However, it is generally accepted that a circulating diphtheria antitoxin level of 0.01 IU/ml provides clinical immunity, while for full protection, a level of 0.1 IU/ml may be needed [Galazka, 1993].

Primary immunisation with 3 doses of DTP vaccine stimulates the production of diphtheria antibody level in considerable excess of the minimum protective level (0.01 IU/ml). However, while the duration of natural immunity is life long, the duration of immunity after a primary immunisation series is variable. Studies on this issue have showed differing results, with duration of immunity ranging from 3-10 years [Galazka, 1993; MMWR, 1991]. These could be because of different vaccines, different vaccination schedules and different levels of community exposure to *Corynebacterium diphtheria* (presence of natural boosting). In contrast, a booster dose at 2 years or at school entry (4-6 years) stimulated abundant production of diphtheria antitoxin with mean levels above 0.1 IU/ml [Galazka, 1993].

There is an age-related host response to immunity with diphtheria toxoid; the most important factor being the modifying effect of passively acquired maternal antibodies in young infants. Passive diphtheria antibodies seem to show a transient suppression of the antibody response to the second injection of DPT vaccine, but no response is seen to the third injection of DPT vaccine [Galazka, 1993].

There is no data from randomised controlled trials on the clinical efficacy of diphtheria toxoid, but outbreak investigations have shown efficacies of over 87% [WHO, 1995]. A complete vaccination series substantially reduces the risk of developing diphtheria, while even vaccinated persons who develop the disease have milder illnesses. Vaccination does not, however, eliminate carriage of *Corynebacterium diphtheria* in the pharynx, nose or on the skin [MMWR, 1991; Chen, 1976].

3.1.2 Pertussis vaccine

As with diphtheria, the antitoxin (antibody) level correlation for pertussis has also not been established. Most studies measure pertussis antitoxin (FHA antibodies) and levels above 0.01 IU/ml can be considered a response to the vaccine and afford a minimum protective level [Galazka, 1993].

Although there is placental passage of some maternal pertussis antibodies, infants do not seem to be protected against clinical disease during the first months of life. The susceptibility of small infants to life-threatening pertussis has been well documented [The Red Book, 1997; Galazka, 1993]. Hence, pertussis immunisation should be administered prior to possible exposure, yet at an age when the infant is capable of responding. Studies have shown that the ability of infants to produce pertussis antibodies after vaccination with the whole cell vaccine is inversely related to the cord blood serum pertussis antibody titre, and thus, a good antibody response is observed in those infants with low cord blood titres and vice versa [Galazka, 1993]. In contrast, with the acellular pertussis vaccine, pre-immunisation levels of antibodies do not influence the immune response.

The optimal response to DPT vaccination has been said to be best achieved by beginning vaccination late, at the age of 5 months or later. However, the risk of pertussis in early

infancy emphasises the importance of early pertussis immunisation, and the suggested age for the first DPT is at 6 weeks of life [Bart 1990; Galazka, 1993].

The duration of immunity following pertussis vaccination is still unclear. Data from pertussis outbreaks suggest that booster doses are vital [Galazka, 1993].

3.1.3 Tetanus vaccine

Like the other vaccines, the amount of circulating antitoxin needed to ensure complete immunity against tetanus is not known. Again, a tetanus antitoxin level of 0.01 IU/ml serums as determined by neutralisation assay is considered the minimum protective level [Chen, 1976; Cherry, 1997]. Case reports of tetanus in persons with antitoxin levels greater than 0.01 IU/ml show that the severity of the disease was inversely proportional to the antitoxin level [Galazka, 1993].

The effectiveness of a two-dose tetanus toxoid (administered to women of childbearing age) in reducing neonatal tetanus, has been convincingly demonstrated by randomised controlled trials, hospital based studies and field trials. A review of these studies showed tetanus toxoid efficacy ranging from 80-100% [Chen, 1976; Galazka, 1993]. However, there have been reports of the failure of tetanus toxoid to prevent neonatal tetanus. A review of 14 studies reporting vaccine failure suggests that this problem will increase with improved immunisation coverage. The reason for vaccine failure is uncertain, but some of the causative factors may include poor maternal response, low potency vaccine, excessive toxin exposure, inadequate placental transfer and inaccurate immunisation history (not true vaccine failure). The review also quotes 12 studies reporting vaccine failures in adults, although these numbers are small [Galazka, 1993].

Tetanus toxoid has an efficacy of more than 95% (Chen, 1976). Effective protection against tetanus is provided by active immunisation. Complete primary immunisation (three doses) confers protection for at least 5 years. Immunity will last at least 10 years after the fourth dose and 20 years after the fifth dose [Chen, 1976; Galazka, 1993]. Active immunisation (ATT) is also recommended in the treatment of wounds [The Red Book, 1997].

3.1.4 Accelerated DPT immunisation schedule

The high risk of pertussis in early infancy has emphasised the importance of early pertussis immunisation. Hence, accelerated immunisation schedules have been introduced with the first dose of DPT at 6-8 weeks of age. A review of immunisation schedules of the various regions show that 64% of African, 19% of American, 11% of European, 23% of Western Pacific and 64% of South East Asian countries have an accelerated immunisation schedule (6, 10, 14 weeks of 2,3,4 months) [WHO, 1995].

A descriptive study with internal cases and controls that compared antibody levels at the age of 4 years in four different situations, found no significant differences in antibody levels among those who had completed primary immunisation before 6 months (accelerated immunisation schedule) and those who had it later. However, there were significantly higher antibody levels in those children who had received a DT booster dose at 18 months as compared with those who did not. All children had protective concentrations of diphtheria and tetanus antitoxin [Ramsay, 1991].

A case control study on antibody response to accelerated immunisation (2, 3, 4 months) with diphtheria, tetanus, and pertussis vaccine showed lower levels of protective antibodies with

the accelerated schedule, when compared with the normal schedule, at 6-8 weeks post-primary immunisation. However, these differences were much smaller when antibody levels at 12 months post-vaccination were compared (differences not significant for diphtheria & pertussis). All children had protective concentrations of tetanus antitoxin, while 6.5% of children in the accelerated schedule, and 9.7% in the longer schedule, had diphtheria antitoxin levels below the protective concentrations at 12 months post-vaccination. Most children had pertussis antitoxin (FHA antibodies) levels above 0.01 IU/ml at 12 months post-vaccination [Ramsay, 1993].

3.1.5 Whole-Cell versus acellular pertussis vaccines for DPT immunisation

A large randomised controlled trial, comprising 82,892 children, compared two-component, three-component, and five-component acellular pertussis vaccines with whole-cell pertussis vaccine in Sweden. The effectiveness of the DPT whole-cell vaccine, the five-component and three-component vaccines were similar in patients with culture-confirmed pertussis having paroxysmal cough for at least 21 days. There was a lower efficacy of the three-component vaccine against mild disease i.e. culture-confirmed pertussis without symptoms. The two-component acellular pertussis vaccines showed poor efficacy [Olin, 1997].

A multicenter double-blind study compared acellular pertussis DPT vaccine (DTaP) with whole-cell pertussis DPT vaccine (DTP) as a booster dose in children 4-to 6 years old. Antibody responses to pertussis antigens (filamentous hem agglutinin, and agglutinogens) and to diphtheria and tetanus toxoids were all brisk. The DTaP vaccine recipients had a more marked response in antibodies to filamentous hem agglutinin and a less marked response in agglutinins than whole-cell vaccine recipients [Morgan, 1990].

Another randomised control trial compared 13 acellular pertussis vaccines (DTaP) with conventional whole-cell (DPT) given in 1942 health infants at 2, 4, and 6 months of age. Each vaccine produced significant increases in antibodies directed against the included antigens, but post-immunisation antibody titres differed significantly among the DTaP vaccines. For each evaluated antigen, the majority of DTaP vaccines produced antibody responses that equaled or exceeded those produced by DPT. No DTaP was most or least immunogenic with respect to all included antigens. The study used one, two, three, four and five-component acellular pertussis vaccines, although an evaluation of the long-term efficacy of these has yet to analysed [Edwards, 1995].

Yet another randomised controlled trial involving 9 829 children, compared a two-component acellular, a five-component acellular with a whole-cell pertussis vaccine. In a control group a vaccine containing diphtheria and tetanus toxoids alone was administered. The vaccines were given at 2, 4, and 6 months of age. After three doses, the efficacy of the vaccines with respect to pertussis was significantly higher for the five-component DTaP vaccine (85.2%) compared to the two-component DTaP vaccine (58.9%) and the whole-cell vaccine (48.3%) [Gustafsson, 1996].

A double-blind randomised controlled trial involving 14,751 children compared two three-component acellular pertussis vaccines with whole cell DTP vaccine. Diphtheria and tetanus toxoids without pertussis (DT vaccine) were used as a control. For both the acellular DTP vaccines, the efficacy was 84% (95 CI, 76-90%) whereas the efficacy of the whole cell DTP vaccine was only 36% (95 CI 14-52%). The efficacy of the whole cell DTP vaccine was unexpectedly low. The antibody responses were greater to the acellular vaccines than to the

whole-cell vaccine [Greco, 1996]. Multi-component acellular pertussis vaccines are more protective than one or two component vaccines [Cherry, 1997].

3.1.6 Programme effectiveness and schedule

In Malaysia, over the past 20 years, diphtheria has been eliminated, while there has been a significant reduction in the cases of tetanus and pertussis [MOH, 1999]. This would probably due to the effectiveness of the DPT vaccine.

In the case of diphtheria, immunisation programmes result in a dramatic decline in both clinical disease and carrier rates. However, the high level of acquired immunity against diphtheria declines in late childhood and adolescence depending on the schedule of immunisation with diphtheria toxoids, and the incidence of diphtheria [Chen. 1976].

In the case of pertussis, vaccines appear to protect the individual against severe disease, but do not confer complete protection against infection. Hence, immunisation programmes have less of an effect on reducing transmission of the organism.

The devastating pertussis epidemic in industrialized countries in the 1950's have shown the drastic consequences of omitting pertussis vaccine from the primary childhood immunisation schedule. It is clear that rates of pertussis increase as immunisation levels decrease [WHO, 1995; Bart, 1990; Frenkel 1990]. A recent outbreak of pertussis in the United States reported 218 cases in Chicago over a period of one year. It was noted that in 52% of cases, the reason for being infected was a failure of the current immunisation schedule to protect young infants. Vaccine failure accounted for 28% and delayed vaccination for 20% [Kenyon 1996]. While such outbreaks have not been reported in Malaysia, pertussis persists among infants, especially among those under the age of 6 months. This may be related to the schedule of immunisation.

Tetanus can never be eradicated, but the effectiveness of tetanus toxoid as part of the immunisation programmes in reducing the neonatal tetanus has been convincingly demonstrated [WHO, 1995]. The key issues currently are the persistence of tetanus in neonates and pertussis among infants, and the side effects related to whole cell pertussis DPT vaccines and combination vaccines. The issue of neonatal tetanus relates to tetanus immunisation coverage in pregnancy, and aseptic delivery and post-delivery care. The World Health Organisation (WHO) views even a single case of neonatal tetanus as a failure of the health care delivery system [Bart, 1990].

It has been said that the first dose of DPT at 3 months of age is too late to protect infants against pertussis [Australian Immunisation Handbook, 1997; Bart 1990]. It has been shown that the first dose of the DPT can be lowered to 6 weeks of age without compromising imunogenicity, for both the whole cell and acellular pertussis DPT vaccines [WHO, 1995; Bart, 1990; Ramsay, 1993; Edwards, 1995; Gustafsson, 1996]. Booster doses of DPT at 12-24 months and at 4-6 years are recommended to maintain immunity against pertussis and diphtheria where the national incidence has been successfully reduced [WHO, 1995; Bart, 1990; Frenkel, 1990; MMWR, 1991)].

3.2 Safety and Side Effects

There has been much public concern related to the side effects (reactions) to whole cell pertussis DPT vaccines, primarily focused on the whole cell pertussis component of the vaccine.

Local reactions (generally erythema and induration with or without tenderness) are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia occur frequently. These reactions are substantially more common following the administration of DTP than of DT, but they are self-limiting and can be safely managed with symptomatic treatment [MMWR, 1996; The Red Book, 1997; The Green Book, 1996; Australian Immunisation Handbook, 1997].

Moderate-to-severe systemic events include high fever (i.e. temperature of 40.5° C or more), persistent, inconsolable crying lasting 3 hours or more, collapse (hypotonic-hyporesponsive episode, 3.5-291 per 100,000 doses), or short-lived convulsions (usually febrile, 0.3-90 per 100,000 doses). These events occur infrequently, and appear to be without sequelae [MMWR, 1996; The Red Book, 1997; The Green Book, 1996; Australian Immunisation Handbook, 1997; WHO, 1995].

Other more severe neurological events, such as prolonged convulsions or encephalopathy, although rare, have been reported in temporal association with DTP administration. Whether pertussis vaccine causes or is only coincidentally related to such illnesses, or reveals an inevitable event, has been difficult to determine conclusively. In addition, neurological complications and death after pertussis disease are considerably more common (encephalopathy 90-4000, convulsions 600-8000 and death 100-4000 per 100 000 cases of pertussis). If an association between DTP and chronic encephalopathy exists, the risk is primarily in the first 3 days after DTP vaccination. [MMWR, 1996; The Red Book, 1997; The Green Book, 1996; Australian Immunisation Handbook, 1997; WHO, 1995].

There have been anecdotal reports of infantile spasms, Sudden Infant Death syndrome and Reye's syndrome following DTP vaccination. Review of the data from many studies indicates that the vaccine cannot be causally related to any of these illnesses [MMWR, 1996; The Green Book, 1996].

The administration of further vaccination with DTP is contraindicated if either an immediate anaphylactic reaction or encephalopathy within 7 days following vaccination (not due to another identifiable cause) occurs in temporal relationship to the first dose. In addition, precautions for subsequent doses should be considered if there is high fever, collapse or shock-like state within 48 hours, persistent, inconsolable crying for 3 hours or more within 48 hours and convulsions with or without fever occurring within 3 days [MMWR, 1996; The Red Book, 1997; The Green Book, 1996; Australian Immunisation Handbook, 1997].

Severe reactions to vaccines containing diphtheria or tetanus antigens (DT vaccines) are extremely rare. Over use of tetanus toxoid can result in polyneuropathy with an estimated incidence of 0.4 per million doses of tetanus toxoid [Galazka, 1993; The Green Book, 1996; Australian Immunisation Handbook, 1997]. Despite some case reports, no increased risk of Guillain-Barre syndrome has been observed with the use of tetanus toxoid in whole-cell or acellular pertussis vaccines [The Red Book, 1997].

3.2.1 Safety and side effects of whole-cell versus acellular pertussis DPT vaccines

In a large randomised controlled trial comparing two-component, three-component, and five-component acellular pertussis vaccines with whole-cell pertussis vaccine, severe pertussis related side effects (e.g. hypotonic hyporesponsiveness), high fever and seizures occurred significantly more frequently in the whole-cell group than in the acellular groups. However, severe pertussis-related side effects were more frequent in the acellular groups than previously reported [Olin 1997].

A multimember double-blind study comparing acellular pertussis DPT vaccine (DTaP) with whole-cell pertussis DPT vaccine (DTP) as a booster dose in 4-6 year old children, found that the reaction rates with both vaccines were low. DTaP vaccine recipients had significantly less pain and warmth at the injection site than did DTP vaccine recipients [Morgan 1990].

A randomised controlled trial, involving 9829 children, comparing a two-component acellular, a five-component acellular with a whole-cell pertussis vaccine, using DT vaccine as a control, found the whole-cell vaccine to be associated with significantly higher rates of protracted crying, cyanosis, fever, and local reactions than the other two vaccines. The rates of other adverse events were similar for all vaccines including the control [Gustafsson, 1996].

A double-blind randomised controlled trial involving 14,751 children compared two 3-component acellular pertussis vaccines with whole cell DTP vaccine (DT vaccine was used as a control). Local and systemic adverse events were significantly more frequent after the administration of the whole-cell vaccine. For the acellular vaccines, the frequency of adverse events was similar to that in the control [Greco, 1996].

Another randomised, multicentered, double-blind controlled trial involving 2200 vaccinated infants, 2189 of whom contributed reaction data after 6375 vaccinations, found that for every acellular vaccine, every monitored reaction except vomiting occurred at a significantly lower frequency and severity than with whole cell DTP vaccine. Although there were differences among the acellular vaccines, none was consistently the most or least reactogenic, and all were associated with substantially fewer and less severe adverse reactions than a standard commercial whole-cell vaccine [Decker, 1995].

3.3 Cost Effectiveness

There were no published estimates of the overall cost benefit ratio of DPT vaccination over the last 10 years. A cost-effectiveness model developed to help set priorities for vaccine development found that one of the five most cost-effective improvements that would bring benefit by additional Quality-Adjusted Life Years was a combination DPT and hepatitis B vaccine [Shepard, 1995].

Acellular pertussis formulations have been found to be more expensive than whole cell pertussis. In Malaysia, a vial (10 doses) of whole cell pertussis DTP costs RM 7.80 working out to RM 0.78 per dose while a vial (single dose) of acellular pertussis DTP costs RM 28.00.

4. CONCLUSIONS

There is sufficient evidence of the efficacy of DPT vaccines. Acellular pertussis vaccines have substantially lower local and common systemic side effects than whole cell pertussis

vaccines. However, there is considerable variation in their efficacy. In addition, the long-term efficacy of acellular pertussis vaccines has yet to analysed. The evidence also shows that accelerated immunisation schedules are efficacious.

5. RECOMMENDATIONS

DPT immunisation should be continued but using an accelerated primary immunisation schedule (6 weeks, 3 months, 5 months). This would also optimise health care visits by both the mother (postnatal) and the infant (second dose hepatitis B vaccine). Booster doses of DPT at 12-24 months and at 4-6 years are recommended to maintain immunity against pertussis and diphtheria.

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7. EVIDENCE TABLE
DPT

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Efficacy				
1.	Ramsay MEB, Corbel MJ, Redhead K, et al. *Persistence of antibody after accelerated immunisation with diphtheria, tetanus, pertussis vaccine*. BMJ 1991; 302:1489-1491	Descriptive study at age 4 years with internal cases and controls (4 groups compared)	No significant differences in antibody levels for those who had completed primary immunisation before 6 months or after Significantly higher antibody levels for children who had received an 18 months DT booster dose.	Poor
2.	Ramsay MEB, Rao M, Begg NT, et al. *Antibody response to accelerated immunisation with diphtheria, tetanus, pertussis vaccine.* Lancet 1993; 342:203-205	Case control 57 cases and two control groups (50 & 32 children) Follow up until 12 mts post vaccination.	Lower levels of protective levels of antibodies with accelerated schedule when compared with normal schedule at 6-8 weeks post primary immunisation. However the difference was much smaller when antibody levels were compared at 12 months post vaccination (not significant for diphtheria & pertussis).	Poor
3.	Olin P, Rasmussen F, Gustafsson L, et al. *Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine.* Ad Hoc Group for the Study of Pertussis Vaccines. Lancet 1997; 350:1569-77	Randomised CT, blinded. 82,892 children (83% of all births) in 4 groups. Follow up until 18 mts post vaccination. Extensive national surveillance and monitoring for complications and failure of vaccination.	The efficacy of the DPT whole-cell vaccine and the five-component and three-component vaccines was similar against culture-confirmed pertussis with at least 21 days of paroxysmal cough. There was a lower efficacy of the three-component vaccine against mild disease.	Good.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
4.	Morgan CM, Blumberg DA, Cherry JD, et al. *Comparison of acellular and whole-cell pertussis-component DTP vaccines. A multicenter double-blind study in 4- to 6-year-old children*. Am J Dis Child 1990 Jan; 144(1): 41-5	Multicenter double-blind study. 83, 4- to 6-year-old children, in two study arms. Follow up until 12 mts post vaccination	The DTaP vaccine recipients had a more marked response in antibodies to filamentous hemagglutinin and a less marked response in agglutinins than whole-cell vaccine recipients. DTaP vaccine is immunogenic and less reactogenic than a DTP vaccine.	Good to Fair
5.	Edwards KM, Meade BD, Decker MD, et al. *Comparison of 13 acellular pertussis vaccines: overview and serologic response.* Pediatrics 1995; 96 (3 Pt 2): 548-57	Randomised CT, multicentered, double blind. 2342 infants enrolled and 1942 who met criteria. Follow up until 1 month after the third immunization	Each vaccine produced significant increases in antibodies Post immunization antibody titres differed significantly among the DTaP vaccines. Majority of DTaP vaccines produced antibody responses that equaled or exceeded those produced by whole-cell vaccine recipients. No DTaP was most or least immunogenic with respect to all included antigens .	Good
6.	Gustafsson L, Hallander HO, Olin P, et al. *A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine.* N Engl J Med 1996; 334(6): 349-55	Randomised CT, placebo controlled. 9829 children Follow up for a mean age of 2.5 years	After three doses, the efficacy of the vaccines with respect to pertussis was 58.9% for the two-component vaccine (95 CI 50.9-65.9%), 85.2% for the five-component vaccine (95 CI 80.6-88.8%), and 48.3% for the whole-cell vaccine (95 CI 37.0-57.6%)	Good
7.	Greco D, Salmaso S, Mastrantonio P, et al. *A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis*.	Double blind RCT involving 14,751 children. Follow up for mean of 17 months. Surveillance & monitoring for	Efficacy for both acellular DTP vaccines was 84% (95 CI, 76-90%) Efficacy of whole cell DTP vaccine only 36% (95 CI 14-52%). Efficacy of whole cell DTP vaccine unexpectedly low. Antibody responses greater to acellular vaccines than to whole-cell vaccine.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	N Engl J Med 1996 Feb 8; 334(6): 341-8	complications & failure of vaccination.		
8.	Galazka AM. *The immunological basis for immunisation series: Module 3 - Tetanus.* WHO/EPI/Gen/93.13. 1993	Extensive review of available literature on Tetanus immunisation	Tetanus disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for Tetanus control discussed	Good.
9.	Galazka AM. *The immunological basis for immunisation series: Module 4 - Pertussis.* WHO/EPI/Gen/93.14. 1993	Extensive review of available literature on Pertussis immunisation	Pertussis disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for Pertussis control discussed	Good.
10.	Galazka AM. *The immunological basis for immunisation series: Module 2 - Diphtheria.* WHO/EPI/Gen/93.12. 1993	Extensive review of available literature on Diphtheria immunisation	Diphtheria disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for Diphtheria control discussed	Good.
11.	The Australian immunisation handbook. 5th Edition. National Health & Medical Research Council, Australia 1997.	Recommendations by expert committee based on scientific literature	Diphtheria, Pertussis, Tetanus disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for Diphtheria, Pertussis, Tetanus control discussed	Good
12.	Immunisation Against Infectious Disease ("The Green Book"): Department of Health, United Kingdom. HMSO 1996.	Recommendations by expert committee based on scientific literature	Diphtheria, Peruses, Tetanus disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for Diphtheria, Pertussis, Tetanus control discussed	Good
13.	Red Book: Report of the committee	Recommendations by	Diphtheria, Peruses, Tetanus disease pattern,	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	on infectious diseases. Peter G, ed. 24th ed. Elk Grove Village, Il. American Academy of Pediatrics; 1997.	expert committee based on scientific literature	immunological basis of vaccine, efficacy of vaccine and success of various strategies for Diphtheria, Pertussis, Tetanus control discussed	
14.	Cherry JD. *Comparative efficacy of acellular pertussis vaccines: an analysis of recent trials.* Pediatr Infect Dis J 1997; (4 Suppl): S90-6.	Review of available literature on acellular pertussis vaccines	Multi-component acellular pertussis vaccines are more protective than one or two component vaccines	Only abstract available
15.	Chen ST. Puthucheary SD. *Some epidemiological aspects of diphtheria in Malaysia.* Tropical & Geographical Medicine. 1976; 28(3): 211-5.	Review of available data on pertussis vaccination	Asymptomatic carriers are an important epidemiological factor in diphtheria carrier rates for school children are high immunization does not prevent the carrier state .	Only abstract available
Programme Effectiveness (and population acceptability)				
1.	Immunisation policy *Global programme for vaccines and immunisation.* WHO/EPI/Gen/95.3, 1995	Recommendations by expert committee based on scientific literature	Provides epidemiological data on the reduction of diphtheria, tetanus, or pertussis cases in many countries. Supports the recommendation for accelerated immunisation schedule and booster doses	Good
2.	Frenkel LD. *Routine immunisation for American children in the 1990s* Ped Cli N Am 1990; 37(3): 531-547.	Review of scientific literature.	Provides epidemiological data on the reduction of diphtheria, tetanus, or pertussis cases in the USA since the introduction of the vaccines. Supports the recommendation for 2 booster doses	Poor
3.	Bart KJ, Lin KFYC. *Vaccine-preventable disease and immunisation in the developing*	Review of scientific literature.	Provides epidemiological data on the reduction of diphtheria, tetanus, or pertussis cases in the many countries. Supports the recommendation for accelerated	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	world. Pediatr Clin N Am 1990; 37(3): 734-756.		immunisation schedule and booster doses	
4.	Centers for Disease Control. *Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures: recommendations of the Immunization Practices* Advisory Committee (ACIP). MMWR 1991:40 (No. RR-10).	Evidence based review on available data on many issues related to DPT vaccine.	Review of evidence on DPT vaccination in relation to timing of doses, number of doses, programme effectiveness Current evidence support Outlines measures that assist in developing a successful programme.	Good
5.	Kenyon TA, et al. *Large outbreak of pertussis among young children in Chicago, 1993: investigation of potential contributing factors & estimation of vaccine effectiveness.* Pediatr Infect Dis J 1996; 15(8): 655-661	Descriptive report of an outbreak of pertussis in Chicago, USA	In 52% of cases, the reason for being infected was a failure of the current immunisation schedule to protect young infants. Vaccine failure accounted for 28% and delayed vaccination for 20%.	Only abstract available
6.	Chen ST. Puthucheary SD. *Some epidemiological aspects of diphtheria in Malaysia.* Tropical & Geographical Medicine. 1976; 28(3): 211-5.	Review of available data on pertussis vaccination	For the control of diphtheria, one should aim for 100% compliance.	Poor Only abstract available

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Safety and Side Effects				
1.	Olin P, Rasmussen F, Gustafsson L, et al. *Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine.* Ad Hoc Group for the Study of Pertussis Vaccines. Lancet 1997; 350:1569-77	Randomised CT, blinded. 82,892 children (83% of all births) in 4 groups. Follow up until 18 mts post vaccination. Extensive national surveillance and monitoring for complications and failure of vaccination.	Hypotonic hyporesponsiveness occurred significantly more frequently in the whole-cell group ($p < 0.05$) and was more frequent in the acellular groups than previously reported. High fever and seizures occurred more frequently after whole-cell vaccine than after any of the acellular vaccines ($p< 0.001$).	Good.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Centers for Disease Control. *Update: Vaccine Side Effects, Adverse Reactions, Contraindications, and Precautions Recommendations of the Advisory Committee on Immunization Practices (ACIP)* MMWR 1996; 45(RR-12): 1-35.	Evidence based review on available data on vaccine safety.	Review of evidence on DPT vaccine safety Potential adverse effects & contraindications listed	Good.
3.	Morgan CM, Blumberg DA, Cherry JD, et al. *Comparison of acellular and whole-cell pertussis-component DTP vaccines. A multicenter double-blind study in 4- to 6-year-old children.*	Multicenter double-blind study. 83, 4- to 6-year-old children, in two study arms. Follow up until 12 mts	The reaction rates with both vaccines were low. DTaP vaccine recipients had significantly less pain and warmth at the injection site than did DTP vaccine recipients	God to Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Am J Dis Child 1990 Jan; 144(1):41-5	post vaccination		
4.	Decker M, Edwards K, Steinhoff M, et al. *Comparison of 13 Acellular Pertussis Vaccines: Adverse Reactions.* Pediatrics. 1995; 96(3): 557-566.	Randomised CT, multicentered, double blind. 2200 vaccinated infants, 2189 contributed reaction data after 6375 vaccinations. Follow up until 1 month after the third immunization	For every acellular vaccine, every monitored reaction except vomiting occurred at a significantly lower frequency & severity than with whole cell vaccine. Although there were differences among the acellular vaccines, none was consistently the most or least reactogenic; all were associated with substantially fewer and less severe adverse reactions than a standard commercial whole-cell vaccine	Good
5.	Gustafsson L, Hallander HO, Olin P, et al. *A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine.* N Engl J Med 1996; 334(6): 349-55	Randomised CT, placebo controlled. 9829 children Follow up for a mean age of 2.5 years	The whole-cell vaccine was associated with significantly higher rates of protracted crying, cyanosis, fever, and local reactions than the other 3 vaccines. The rates of other adverse events were similar for the acellular vaccines and the control DT vaccine.	Good
6.	Greco D, Salmaso S, Mastrantonio P, et al. *A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis.* N Engl J Med 1996 Feb 8; 334(6): 341-8	Double blind RCT involving 14,751 children. Follow up for mean of 17 mths. Surveillance & monitoring for complications & failure of vaccination.	Local & systemic adverse events significantly more frequent after administration of whole-cell vaccine. For acellular vaccines, frequency of adverse events similar to control group.	Good
7.	Red Book: Report of the committee	Recommendations by	Potential adverse effects & contraindications listed	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	on infectious diseases. Peter G, ed. 24th ed. Elk Grove Village, Il. American Academy of Pediatrics; 1997.	expert committee based on scientific literature		
8.	Immunisation Against Infectious Disease ("The Green Book"): Department of Health, United Kingdom. HMSO 1996.	Recommendations by expert committee based on scientific literature	Potential adverse effects & contraindications listed	Good
9.	The Australian immunisation handbook. 5th Edition. National Health & Medical Research Council, Australia 1997.	Recommendations by expert committee based on scientific literature	Potential adverse effects & contraindications listed	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Cost-Effectiveness				
1.	Shepard DS, et al. *Setting priorities for the Children's Vaccine Initiative: a cost-effectiveness approach.* Vaccine 1995; 13(8): 707-714.	Cost-effectiveness model developed	One of the five most cost-effective improvement that would bring benefit by additional Quality-Adjusted Life Years was a combination DPT and hepatitis B vaccine	Only abstract available

POLIO

1. BACKGROUND

Poliomyelitis is an acute viral infection that ranges in severity from a nonspecific illness to paralysis with permanent disability. Although the disease has been known for a long time, the association of the clinical entity of paralytic poliomyelitis with a transmissible agent was first recognized in 1908 by Landsteiner and Popper using monkeys in their experiments (Kimpen, 1990).

WHO estimated that some 140 000 new cases of paralytic poliomyelitis occurred in 1992 worldwide (WHO, 1996). The cumulative number of children and adults with paralysis due to poliomyelitis is estimated at 10 to 20 million persons.

In 1988, the World Health Assembly set the goal of eradicating poliomyelitis by the end of the year 2000. Since then, poliovirus has disappeared rapidly from most areas in the world. The number of poliomyelitis cases has fallen by over 95% around the world, from an estimated 350 000 in 1988 to an estimated maximum of 20 000 in 1999, with the elimination of wild poliovirus from three of the five continents where it was endemic at the outset of the initiative (WHO, 1988).

Advances in virological methods, molecular biology, and immunology have dramatically enhanced our knowledge of polioviruses and types of poliovirus vaccines.

2. INTRODUCTION

2.1 Epidemiology

2.1.1 Global incidence

Epidemics of poliomyelitis occurred universally in the prevaccine era. However, after the introduction of a vaccine in 1955 the annual incidence in developed countries dropped dramatically. To-date, the disease has been eradicated in many countries. There have been no reports of cases of wild-type poliovirus disease in the Western hemisphere since 1991. The last reported case occurred in 1979 in USA during an epidemic in a religious sect that had refused immunization. Since then, nearly all cases in USA have been vaccine associated paralytic poliomyelitis (VAPP) attributed to oral polio vaccine (OPV), with approximately 8 to 9 cases being reported annually.

The last case of paralysis due to endemic wild poliovirus in the WHO Western Pacific Region was identified in March 1997 (Aylward, 2000). In the WHO European Region, wild poliovirus was last identified in November 1998 in South East Turkey. By the end of 1999, poliomyelitis had disappeared from much of Eastern Mediterranean area and no virologically confirmed case has been reported from north and South Africa except Egypt, for more than two years.

However, the disease continues to occur in some of the underdeveloped areas in the world. Outbreaks of poliomyelitis have occurred in some of the countries where the immunization was interrupted by war. However, the geographical extent of the remaining poliovirus circulation continues to shrink with the WHO eradication initiative. At the end of 1999, wild poliovirus was circulating in a maximum of 30 countries, primarily in sub-Saharan Africa and South Asia (Aylward, 2000).

2.1.2 Local incidence

Since the introduction of polio immunization in 1972, the number of paralytic poliomyelitis has reduced from more than 700 cases in the 1970's to no cases reported since 1986. However, in 1992 there were two cases of imported wild virus induced poliomyelitis (Ismail, 1993; MOH, 1992). Since then, no cases have been reported. Malaysia is currently active and carrying out Acute Flacid Paralysis (AFP) surveillance programme to confirm the eradication of poliomyelitis.

2.2 Aetiology

Polioviruses are classified into three distinct serotypes (type1, type2, and type3) based on their reaction with reference panels of neutralizing antisera (Bodian, 1949). These viruses belong to the genus enterovirus in the family picornaviridae.

Polioviruses are stable at acid pH and can survive for weeks at room temperature, and for many months at 0-8°C. As with other enteroviruses, polioviruses are resistant to ether, 70% alcohol and other laboratory disinfectants. Treatment with 0.3% formaldehyde, 0.1N HCl, or free residual chlorine at level of 0.3 to 0.45 parts per million rapidly inactivates polioviruses, as does exposure to a temperature of 50°C or higher, or to ultraviolet light (Minor, 1990).

Poliovirus 1 is responsible for most of the clinical cases in communities with low vaccine coverage, and in non-immunized subgroups of otherwise well immunized populations (Kimpen, 1990).

2.3 Response to Natural Infection

Humans are the sole reservoir for poliovirus. Wild polioviruses are spread directly or indirectly from person to person. Virus dissemination is facilitated by poor sanitation. Children under two years of age create a microenvironment of sub-optimal hygiene within the family and within daycare settings, readily facilitating faecal-oral and oral-oral (mouth-finger-mouth) transmission. Faeces can serve as a source of contamination of water, milk or food, and houseflies can passively transfer poliovirus from faeces to food (Gear, 1952). Perinatal transmission from mother to newborn infants can also occur. Infection is more common in infants and young children, and occurs at an earlier stage in living conditions of poor hygiene.

Wild poliovirus enters through the mouth, attaches to the receptors on the epithelium of the throat and intestine, and replicates inside these cells. Newly synthesized poliovirus is shed from the infected cells. The virus persists in the throat for about a week after onset

of illness and is excreted in faeces for weeks or months. From these sites, the virus spreads to cervical and mesenteric lymph nodes. Poliovirus enters the blood stream via the lymphatic. Virus from the blood stream can invade the central nervous system unless sufficiently high levels of neutralizing antibodies are available to block it. Within the central nervous system, the virus spreads along nerve fibers and in the process of its intracellular multiplication it destroys motor neurons, resulting in flaccid paralysis. Sensory neurons are however, not affected.

Communicability is greatest shortly before and after onset of clinical illness, when the virus is present in the throat, and excreted in high concentration in the faeces. The patient is potentially contagious as long as faecal excretion persists. In recipients of oral polio vaccine (OPV), the virus persists in the throat for 1 to 2 weeks, and it is excreted in the stool for several weeks. Immunodeficient patients may excrete the virus for prolonged periods. Direct neural spread of poliomyelitis may also occur in certain situations, such as during tonsillectomy with subsequent bulbar paralysis or following injection of an irritating substance into a limb leading to subsequent paralysis of that limb (Wyatt, 1990). The incubation period of abortive poliomyelitis is 3 to 6 days. For the onset of paralysis in paralytic poliomyelitis, the incubation period is usually 7 to 21 days, but occasionally it can be as short as 4 days.

2.4 Natural Immunity

Following natural exposure, IgM and IgG appear in the serum about 7 to 10 days after infection. Sufficiently high levels can block poliovirus entry into the central nervous system. Inititially, the IgM response is 2- to 8-fold greater than the IgG response. IgM levels peak at about 2 weeks after exposure and disappear from the serum within about 60 days. IgG levels increase steadily and persisting serum antibody belongs to this class. IgA antibody appears in the serum 2 to 6 weeks after exposure and remains at low levels, although in some individuals there is no rise in serum IgA. Serum antibodies are type specific. There may be a low degree of heterotypic antibody induced by infection, especially between type 1 and type 2 polioviruses (Ashkenazi, 1962). It is believed that serum-neutralizing antibodies (primarily IgG) persist for life. A survey carried out in an isolated Eskimo village showed that IgG antibodies produced from sub clinical infection with wild virus persisted for at least 40 years without subsequent exposure (Paul, 1951).

Passive immunity is transferred from the mother to the fetus via the placenta. The concentration of type 1 and type 2 IgG neutralizing antibody in the newborn is approximately equal to that of the mother. Type 3 titers are somewhat lower than of the mother, suggesting differential transplacental transfer of this serotype (Ananthakrishnan, 1988). The rate of decay of maternal antibody is constant, its half-life being estimated to be about 30 days (range 21 to 50 days), and these data have been confirmed in recent studies in developing countries.

Poliovirus infection also induces development of secretory IgA antibody (Ogra, 1968). Secretory antibody is produced by plasma cells originating in gut-associated lymphoid tissue, mainly Peyer's patches. These cells localize in mucosal sites, including the intestine, the pharynx, and the mammary glands. The persistence of secretory IgA

antibody may be related to the virulence of the infecting virus and to the number of virus particles presented to the intestinal and nasal mucosa. Appreciable levels of secretory antibody have been detected in the nasopharyngeal secretions of individuals 10 to 15 years after natural infection with wild type 1 poliovirus.

2.5 Clinical Disease

Approximately 90- 95% of poliovirus infection is asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic meningitis, sometimes with parasthesia, occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis with areflexia of involved limb occurs in 0.1% to 2% of infections, and residual paralytic disease involving the motor neurons (paralytic poliomyelitis) occurs in approximately 1 in 250 infections. Cranial nerve involvement and paralysis of respiratory muscles may occur. Findings in the cerebrospinal fluid (CSF) are characteristic of viral meningitis with mild pleocytosis and lymphocytic predominance.

Adults who contracted paralytic poliomyelitis in childhood may develop the post-polio syndrome 30 to 40 years later, which is characterized by muscle pain, exacerbation of weakness, and/or new paralysis or weakness. This secondary illness resembling motor neuron disease after an apparent silent period is sometimes known as late post-poliomyelitis muscular atrophy. A number of risk factors may affect the potential for infection with poliovirus or the severity of clinical poliomyelitis and these include immune deficiency, injections, malnutrition, physical activity, pregnancy and tonsillectomy.

Four type of poliovirus vaccines are currently available: inactivated polio vaccine (IPV) of Salk, oral polio vaccine (OPV) of Sabin, enhanced-potency inactivated vaccine of Van Wezel (eIPV) and combination with other vaccines such as DTP-IPV. The vaccines are trivalent, containing a mixture of the three strains of the poliovirus.

3. TECHNICAL FEATURES OF VACCINES

3.1 Oral Polio Vaccine (OPV)

Sabin's live attenuated poliovirus strains are used almost universally to prepare OPV because they provide good antibody levels and are less neurotropic. Since 1973, WHO has been directly responsible for the custody and distribution of Sabin strains of OPV, and has exercised strict supervision over production laboratories in cooperation with national control authorities (Cockburn, 1988). Because of its low cost, ease of administration, superiority in conferring intestinal immunity, and the potential to infect household and community contacts secondarily, trivalent OPV is recommended by WHO as the vaccine of choice for developing countries (WHO, 1991).

3.1.1 Antibody levels and duration of immunity of OPV

OPV induces both a systemic and a local immune response that prevents both central nervous system invasion and intestinal infection by polioviruses. OPV also induces mucosal immunity directed against viral antigenic determinants that are not available after immunization with IPV or eIPV.

A review based on data accumulated in developing countries over 25 years showed that, after three doses of trivalent OPV, there were wide variations in the percentages of children seroconverting with rates of 73% (range: 36%-99%) for type 1, 90% (range: 71%-100%) for type 2, and 70% (range: 40%-99%) for type 3 (Patriarca, 1991). The precise cause of lower seroconversion rates to type 1 and type 3 in some countries is not clear, although available data suggest that type 2 vaccine virus and enteric pathogens often interfere with the response to types 1 and 3. However, this interference may be partially overcome by modifying the absolute and relative dosage of the three Sabin vaccine virus types. The intervals between doses may also be important, in view of prolonged excretion of vaccine virus and the potential for interference with response to subsequent doses. Continuing intestinal infection (manifested by fecal excretion of one strain of OPV) could potentially interfere with the immune response to a subsequent dose (Patriarca, 1988).

A major reason for the success of OPV is its community effects, in that enteric multiplication of vaccine virus leads to its dissemination beyond the individuals being immunized. However, outbreaks can occur despite the high coverage by OPV. For example, a type I outbreak with 118 cases occurred in Oman in 1988-1989, despite coverage of 86% with 3 doses of OPV among children 1 to 4 years of age. It was postulated that the intestinal protection might have been overwhelmed by large quantities of wild virus during the outbreak (Sutter, 1991).

The probability of life-long protection of OPV is about 90% (Kimpen, 1990). Serological surveys carried out after 15 years or more of national coverage with OPV have indicated that at least 95% antibody prevalence against all three types of poliovirus in persons 2 years or older in Italy (Santoro, 1984), Singapore (Goh, 1987) and USA (Mayer, 1984).

The route of administration is by oral drops. Various countries apply slightly different immunization schedules from the guidelines provided by WHO or by the Committee on Infectious Diseases of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP). EPI, WHO recommends four doses of OPV to be given by 14 weeks of age, with a dose at birth in countries where poliomyelitis is still a problem, since poliomyelitis involves mainly infants less than 2 years of age. The beneficial effect of a dose of OPV at birth has been demonstrated most clearly in studies done in China, where a higher percentage of infants given a dose at birth had antibodies against all three types of poliovirus at younger ages (De-xiang, 1986).

The ACIP recommends the first dose of OPV to be administered at 2 months of age (minimum age of 6 weeks) and a second dose when the infant is 4 months old. It is

emphasized that a two-month interval is desired between the first two doses to avoid interference with replication. The minimum interval in most circumstances is 6 weeks. However, where accelerated poliomyelitis vaccination is warranted, this interval may be 4 weeks. A third dose is recommended when the child is 6 to 18 months of age to complete the primary series. A supplementary dose should be given before entering school, i.e. at 4 to 6 years of age. For children not immunized in the first year of life, 2 doses of OPV should be given approximately 6 to 8 weeks apart, followed by a third dose 2 to twelve months later.

The cold chain should be maintained to preserve the efficacy of the vaccine. The vaccine should be stored in the refrigerator at 4-10^{o}C, although the vaccine may be stable in a warmer temperature since it is stabilized with magnesium chloride.

3.2 Inactivated Polio Vaccine

Inactivated poliovirus vaccine (IPV) contains the three types of poliovirus grown in either monkey kidney or human diploid cells or Vero cells and inactivated with formaldehyde. The viruses used in IPV vaccines are the original Salk strains. Trace amounts of streptomycin, neomycin and polymyxin B may be present in the IPV formulation. Enahanced potency IPV is manufactured according to the method of van Wezel by means of micro carrier culture techniques in large fermentors, making mass production of vaccines with a high antigenic content possible. The same strains as IPV are used.

3.2.1 Antibody levels and duration of immunity of IPV

Immunization with IPV is followed by a rise in serum neutralizing antibody in the three-immunoglobulin isotypes (IgG, IgM and IgA). The presence of serum IgG persists after immunization although regular booster doses seem to be necessary to keep the immune system “updated”. The IgA response is less pronounced but is also persistent. Specific IgM is only present in the serum for about 3 months. The serum antibody response prevents invasion of the central nervous system during active infection, but it does not prevent infection of the lower alimentary tract and fecal shedding of the virus. IPV inhibits pharyngeal acquisition of poliovirus and, to a lesser degree, intestinal acquisition

Administration of IPV results in seroconversion in approximately 95% or more of vaccinees after two doses and in high titres of serum in 99% to 100% after three doses. Immunity, as with OPV vaccination is prolonged, perhaps lifelong.

Enhanced potency IPV has the advantage over IPV vaccine in that it stimulates a greater secretory antibody response, while it also generates an excellent systemic response. Studies in Europe, Africa and the United States showed an excellent antibody response, with seroconversion rate nearly 100% of the children after the second dose (Bernier, 1986). Mucosal immunity is induced by eIPV but to a lesser degree than that with OPV.

The route of administration is intradermal, on the anterolateral aspect of the thigh or arm. For children immunized with IPV only, the primary immuniztion series consist of three doses. The first two doses should be given at 1-2-month (4-8 weeks) intervals beginning

at 2 months of age (minimum age 6 weeks) and a third dose is recommended 6-12 months after the second dose. A supplemental dose of IPV should be given before the child enters school, i.e. at 4-6 years of age. Similar recommendation in the immunization schedule was given for eIPV. The stability is the same as OPV, and the cold chain be maintained since the vaccine should be stored at 4-10°C. Most studies report the antibody levels and duration of immunity for DTP-IPV as being similar to IPV.

3.3 Combined Polio Vaccines

Vaccine combining IPV with DTP is available (Tetracoq). In addition, IPV or OPV can be given concurrently with many other vaccines including DTP, hepatitis B, Hib, measles or MMR and chickenpox. The route of administration for Tetracog (DTP-IPV) is intramuscular as DTP vaccine contains adjuvant. The schedule and stability are also similar to IPV.

4. METHODOLOGY

An electronic search using MEDLINE database using various keywords, age limit of 0-18 years and year limits. In addition, WHO reports, Ministry of Health reports and. other important references were obtained from various sources. Year limits were from 1990 until May 2000. The keywords used were as follows:

- Poliovirus vaccine
- Poliovirus vaccine and efficacy
- Poliovirus vaccine and programme effectiveness/population acceptability
- Poliovirus vaccine and adverse reactions/safety/side effects
- Poliovirus vaccine and cost

  In order to obtain enough evidence for each section, a general search under the keyword "poliovirus vaccine" alone had to be made. This is because certain relevant papers may not appear under the specific keyword used, but would appear under the general search of "poliovirus vaccine" and relevant to the sub-topic. For example, some of the papers relevant to poliovirus vaccine and efficacy may not appear under the keyword search because the keyword used in these papers is immunogenicity or immune response. 859 titles were obtained, of which 543 abstracts were reviewed. The results are summarized below:

Aspect	*Total search*	*No of relevant titles*	*No of relevant abstracts*	*Other relevant abstracts (from general search)*	*Total no of relevant abstracts reviewed*	*Total paper reviewed*
Poliovirus & efficacy	44	23	23	32	55	10
Polio virus & programme effectiveness/population acceptability	30	15	15	20	35	12
Poliovirus & adverse reactions/safety	205	45	34	0	34	12
Poliovirus & cost effectiveness	25	13	12	0	12	6

5. RESULTS

5.1 Vaccine Efficacy

5.1.1 Oral Polio vaccine

In a large multi-centered randomized controlled trial carried out in Brazil and Gambia, involving 1409 infants, OPV was found to be efficacious. Overall seroconversion rates were 85% for poliovirus type 1, 94% for type 2 and 68% for type 3. Factors found to be associated with vaccine failure in this study include high levels of maternal antibodies, vaccination during rainy season, and diarrhoea at the time of vaccination, household exposure to other OPV recipients and breast-feeding (WHO, 1995). In other studies, diarrhoea was found to be a major factor associated with OPV failure (Posey, 1997; Myauz, 1996). These data support the current recommendation that children with diarrhoea receiving OPV should be reimmunized once their disease resolved.

In other smaller randomized controlled trials, the seroconversion rates were even higher. In one study involving 121 infants, the seroconversion rates to polio type 1, one, two and three months after the third dose were 89.5%, 94.7% and 100% respectively. This study also showed that the antibody response to type 3 viruses was delayed and more difficult compared to type 1 or 2. The main factor associated with the lack of seroconversion was concurrent infection with non-polio enteroviruses (NPE), found in 50% of the non-responders to polio type 1 and type 3, whereas no NPE was isolated in responders (Triki, 1997).

The seroconversion rates for all types of poliovirus were also higher if an extra dose is given at birth. Therefore, the authors recommend that an additional dose of OPV be given in countries where poliomyelitis is still a problem (Bhaskaram, 1997; Osei-Kwasi, 1995; Weckx, 1992). OPV is also equally effective if given to preterm babies at 34 to 35 weeks gestation (Thayyil-Sudhan, 1998).

5.1.2 Inactivated Polio Vaccine (IPV)

In recent randomized controlled trials, IPV was found to be as efficacious as OPV. The authors suggest that IPV is acceptable as a substitute for OPV for primary immunization. Seroconversion rates to polio 1, 2 and 3 in children given 2 doses of IPV 8 weeks apart were 90%, 70% and 97% respectively, compared to those given three doses 4 weeks apart, which were 90%, 80% and 98% respectively. Therefore, a 2-dose regime may be a less expensive alternative in developing county. In an earlier non-randomized controlled trial 2-dose IPV was found to induce lower immune response in comparison to OPV or sequential IPV followed by OPV (Nirmal, 1998; Borcic, 1998; Halsey, 1997).

However, in a large multi-centered randomized controlled trial IPV alone given at six, 10 and 14 weeks of age, was found to be inadequate to protect against poliovirus. In contrast, a combined schedule, where OPV was given at birth followed by both IPV and OPV at six, 10 and 14 weeks provided the highest levels of serum antibody response (MMR, 1997). This was supported by a few other studies (Modlin, 1997; Sutter, 1997; Faden, 1991).

The efficacy of eIPV on the other hand was found to be higher than OPV in seroconversion in a non-randomized controlled trial (Simsathien, 1994). However, it was less effective than OPV in preventing and limiting intestinal infection even though it induced higher serum antibody levels (Onrorato, 1991). Premature infants were found to be less likely to have protective levels of antibodies to type 3 poliovirus than term infants, even given the enhanced potency IPV (eIPV) (D'Angio, 1995).

5.1.3 Polio vaccine combined with other vaccines

There are many recent randomized controlled trials providing good evidence that seroresponses to IPV were excellent when combined with other vaccines. The immune response is unaffected if given concurrently with other vaccines, and, in the case of DTP-IPV, given in the same syringe (Langue, 1999; Gyhrs, 1998; Aristegui, 1998; Halperin, 1997; White, 1997; Dagan, 1997; Begue, 1997; Kurika, 1996; Rothstein, 1993). However, in one small-randomized controlled trial, the immune response to pertussis was found affected on combining DTP and IPV (Halperin, 1996).

5.2 Programme Effectiveness and Population Acceptability

5.2.1 Oral Polio vaccine (OPV)

Various studies have demonstrated the effectiveness of OPV in EPI and WHO initiatives for polio eradication in many developing countries such as China, Cuba and Brazil. No indigenous wild virus was detected despite a strengthened surveillance system (PanX, 1999; MMR, 1996;Despande, 1996; Kotb, 1993; Ward, 1993). However, it was found that a good immunity to all serotypes was not achieved in Germany after an era of OPV immunization (Francks, 1999).

The unavailability of OPV due to conflict or war has resulted in outbreaks of polio in certain areas of the world e.g. Uzbeskistan. Therefore, continuing efforts against poliovirus transmission by OPV vaccination is important (Sutter, 1997). A supplemental immunization strategy of national immunization days and mopping-up vaccination has successfully controlled an outbreak due to the importation of wild virus from a

neighbouring country in Namibia. Despite good coverage, outbreaks can still occur with large loads of virus (Biellik, 1997). There could also be lack of immunization coverage. Some of the reasons for non-acceptance of polio vaccination include lack of information, illness of the child, absence of the child on "PPI" day, lack of faith in immunization and fear of adverse reaction. Various methods were found to be useful in increasing the immunization coverage, e.g. computer generated contact by phone or mail (Dini, 2000), easy to read pamphlets (Davis, 1998), and opportunistic immunization (Morgan, 1998).

5.2.2 Inactivated Polio vaccine

A randomized controlled trial showed that parental knowledge was important for acceptability of IPV in comparision with OPV (Thomas, 1997). Various studies have shown that the additional injections did not impede compliance with polio immunization, and also demonstrated the feasibility of IPV being given alone, sequentially with OPV or in combination with other vaccines (Kolasa, 2000; MMR, 1998; MMR, 1998). Other studies have also provided good evidence of acceptability, feasibility and immunogenicity of a sequential regime of IPV and OPV (Kolas, 2000; WHO, 1998; WHO, 1997; Ion-Nedelcu, 1997; Tulchinsky, 1994).

5.3 Vaccine Safety and Adverse Effects

5.3.1 Oral Polio vaccine (OPV)

There have been many reports of Vaccine Associated Paralytic Poliomyelitis (VAPP) due to OPV. An epidemiological study estimated the risk of VAPP to be 1.3 cases per million vaccinees (Ridgway, 2000; Olin, 1998). In another multicentered cohort study, the risk of VAPP was estimated to be one case per 1.5 to 2.2 million doses of OPV administered. These cases were due to retro-mutations of the virus known to be associated with loss of Sabin attenuated phenotype (Andrus, 1995). In a non-randomized cohort study in Romania, VAPP was found to be associated with multiple intramuscular injections after exposure to OPV. VAPP might have been prevented by withholding intramuscular injections within 30 days of exposure to OPV (Strebel, 1995). Other neurological sequelae found to be associated with OPV are Guillain Barre Syndrome, transverse myelitis and facial paralysis (Freidrich, 1997).

Despite recent reports of the discovery of Simian virus 40 (SV40), there has been no evidence of the increased incidence of tumours like ependymoma or other brain cancers in the vaccinees (Stricker, 1998).

5.3.2 Inactivated Polio vaccine (IPV)

IPV does not cause VAPP. It is currently recommended to prevent VAPP in a sequential regime (Zimmermann, 1999). However, there are other reported adverse events known to be due to IPV like local reaction at the site (43%), neurological disorders (12%), hyperthermia (10%) and allergic reactions (10%). Rare, but serious, side effects include persistent crying, febrile seizures, apyretic seizures, uneasiness and shock (Jonville Bera, 1999).

5.3.3 Polio vaccine combined with other vaccines

In many randomized controlled trials, DTP-IPV was found to be safe without serious side effects except for those mentioned for IPV above (Gyhrs, 1999; Langue, 1999; Meriste, 1999; Mills, 1998; Carlsson, 1998; Dagan, 1997).

5.4 Cost Effectiveness

Global polio eradication with a 10 year effort may cost as much as USD 1000 million. More than 80% of the cost is for the purchase of 1 000 million doses of OPV at the UNICEF price of USD 0.08 per dose (Hull, 1994).

In a cost-benefit analysis done on global eradication of poliomyelitis, it was estimated that the benefits of polio vaccination would exceed the cost in the year 2007, with a saving of USD 136 00 million by 2040. There will be an estimated global saving of USD 1.5 million per year once polio has been eradicated (Bart, 1996).

In an outbreak in China, there was a loss of 2 713 107.32 yuan and reduced creating value of USD 18 583 942.35. The cost-benefit ratio was estimated to be 1:6.85 and a net benefit of 2 317 268 yuan could be gained if the expanded programme of immunization (EPI) was implemented to prevent the outbreak (Zhang, 1992).

There was a lack of data on the cost-effectiveness of a sequential or all-IPV schedule.

When the humanitarian, economic and consequent benefits of polio eradication initiatives were measured against the cost, strong arguments were made for eradication as a valuable disease control strategy in a few review articles (Aylward, 2000; Wood, 2000; Ruff, 1999). Without immunization, there would be 5 million deaths per year. The cost of saving those children was low, between USD 12-15 per child (Ragan, 1996).

6. CONCLUSIONS

It can be concluded that the three-poliomyelitis vaccine schedules, i.e. OPV-only, IPV only and sequential IPV-OPV is highly effective in protecting against poliomyelitis from wild type viruses and is well accepted in the population studied. OPV has the advantage of gut immunity. On the other hand, IPV has fewer side effects like VAPP. Sequential schedule would be ideal but the high cost of IPV would be an important issue for many developing countries.

7. RECOMMENDATIONS

There is sufficient evidence to recommend that OPV should be given according to the current immunization schedule. Sequential schedule of 2 IPV followed by OPV should be considered in the future if VAPP is a problem because poliomyelitis due to wild-type viruses has been eradicated in our country.

IPV is recommended for special cases like immuno-compromised patients and their household contacts, since OPV is contraindicated.

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9. EVIDENCE TABLE
POLIO

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Efficacy - Oral Polio Vaccine				
1.	Lu CY. Et al. *Immunogenicity of oral poliovirus vaccine in Taiwan.* Journal of Farmosan Medical Association. 98(12): 859-62, 1999	Cohort study (98 children)	After three doses of OPV, the antibody levels in all subjects were above protective concentrations. The fourth dose, given at 18 months of age further boosted the antibody titers.	Fair
2.	Thayyil-Sudhan S et al. *Is zero dose oral polio vaccine effective in preterm baby.* Annals of Tropical Paediatrics. 18(4): 321-4, 1998 Dec	RCT, 62 preterm babies	Oral polio vaccine is effective if given to preterm babies at 34-35 weeks post conception similar to term newborns	Good
3.	Posey et al. *The effects of diarrhoea on oral polio vaccine failure in Brazil.* Journal of Infectious diseases. 175 Suppl 1:S258-63, 1997 Feb.	RCT (728 infants)	Diarrhoea at OPV receipt was associated with vaccine failure to poliovirus type 1 and 3 only after 2nd dose of OPV. Children with diarrhoea who receive OPV should be reimmunized once their disease has resolved.	Good
4.	Myauz JA. *Effect of diarrhoea on the humoral response to oral polio vaccination.* Pediatric Infectious Disease Journal.	Case control cohort study)	Concurrent acute diarrhoea adversely affects the seroconversion rates of type 2 and 3 polioviruses.	Good to fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	15(3): 204-9, 1996			
5.	Triki H et al. *Influence of host related factors on the antibody response to trivalent oral polio vaccine in Tunisian infants.* Vaccine. 15(100:1123-9, 1997	RCT (121 infants)	The seroconversion rates to polio type 1, 2 and 3 one month after the 3rd dose were 94.7, 100 and 89.5% respectively. Delayed and more difficult responses to polio 3 compared to polio 2 and polio 1. Main reason for lack of seroconversion was concurrent infection with non-polio enteroviruses (NPE) found in 50% of non-responders to polio 1 and polio 3 whereas no NPE were isolated in vaccine responders.	Good
6.	Bhaskaram P. et al. *Systemic and mucosal immune response to polio vaccination with additional dose in newborn period.* Journal of Tropical Pediatrics. 43(4): 232-4, 1997	Non-RCT (51 infants)	The administration of additional dose in the newborn period significantly improved seroposivity and seroconversion rates compared to the conventional 3 or 5 dose schedules. Additional dose of oral polio vaccine should be given in countries where poliomyelitis continues to be a problem.	Good to fair
7.	Maldonado YA. et al. *Host and viral factors affecting the decreased immunogenicity of Sabin type 3 vaccines after administration of trivalent oral polio vaccine to rural Mayan children.* Journal of Infectious Diseases. 175(3): 545-553, 1997	Cohort studies (181 infants)	Decreased OPV immunogenicity was primarily attributable to interference of Sabin type 3 by Sabin type 2. Suggest to increase the dose of Sabin type 3 to improve the immunogenicity among infants in developing countries	Fair
8.	Aristegui Fernandez J. et al. *The immunogenicity of vaccines*	Non-RCT (677 children vs. 731 controls)	Immune response to DPT and polio vaccines was identical in both groups, and vaccine efficacy against	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	against diphtheria, tetanus, pertussis and polio administered orally at the age of 2, 4 and 6 months and their co-administration with hepatitis vaccine at 0, 2 and 6 months. Anales Espanoles de Pediatria. 44(1): 25-8, 1996		poliomyelitis was 96% for type 1, and 100% for type 2. The efficacy for type 3 poliomyelitis was 98% and 97% for group 1 and group 2 respectively. Simultaneous administration of Hepatitis B vaccine with DPT and oral polio vaccines did not interfere with the immune response to other antigens.	
9.	World Health Organization. *Factors affecting the immunogenicity of oral polio vaccine; a prospective evaluation in Brazil and Gambia. WHO Collaborative study Group on Oral Poliovirus vaccine.* Journal of Infectious Diseases. 171(5); 1097-106, 1995 May	Multicentre RCT (1409 infants)	Overall seroconversion rates at the end of the trial were 85% for poliovirus type 1, 94% for type 2 and 68% for type 3. Factors associated with vaccine failure include high levels of maternal antibody, vaccination during rainy season, diarrhoea at the time of vaccination, household exposure to other OPV recipients and breast-feeding ($p<0.05$ for each factor in logistic regression analysis).	Excellent
10.	Osei-Kwasi M. et al. *Randomized, controlled trial of trivalent oral polio vaccine (Sabin) starting at birth in Ghana.* Bulletin of World Health Organization. 73(1): 41-6, 1995	Randomized controlled trial (231 infants vs. 221 control infants)	Seroconversion rates were higher in infants given extra dose at birth. The seroconversion rates against polio virus types 1, 2 and 3 were higher in infants given trivalent oral polio vaccine (TOPV) at birth, 6 weeks, 10 weeks and 14 weeks after birth compared to controls given at 10, 14 and 18 weeks of age.	Good
11.	Da Villa G. et al. *Effective antibody response in newborn babies living in Maldives to simultaneous vaccination against*	RCT (243 infants)	The antibody response to all vaccines was effective when DPT, OPV and hepatitis vaccine were given concurrently.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	hepatitis B, poliomyelitis, diphtheria and tetanus. Vaccine. 13(9): 795-8, 1995			
12.	Farisano G. et al. *Poliovirus neutralizing antibody persistence after vaccination with the Sabin vaccine: a follow-up study.* Annals of Clinical & Laboratory Science. 25(2): 200-6, 1995	Cohort study (1976-1993)	The seroposivity rates were found to be equal or close to 100% in the follow up study of the cohort. OPV-induced humoral immunity probably lifelong similar to natural infection.	Fair
13.	Deivanayagam N. et al. *Clinical efficacy of trivalent oral poliomyelitis vaccine: a case control study*. Bulletin World Health Organization. 71(3-4): 307-9, 1993	Case control study patients with acute paralytic poliomyelitis, 78 cases, 315 controls	Vaccine efficacy for TOPV3 was 81% for 6-35-month age group and 86% for the 6-23-month age group. Vaccine efficacy after controlling for age was 83%. An unimmunized child was at 5 times greater risk of developing acute paralytic poliomyelitis than a fully immunized child.	Poor
14.	Khare S. et al. *Oral polio vaccination in infants: beneficial effect of additional dose at birth.* Indian Journal of Pediatrics. 60(2): 275-81, 1993	Non-RCT (87 vs. 55 infants)	The seroconversion rate is higher in infants given an additional dose of OPV at birth than those given 3 conventional doses starting at 6 weeks.	Fair
15.	Weckx LY et al. Bulletin of World Health organization. 70(1): 85-91, 1992	RCT (85 infants)	Seroconversion rates were higher in infants given an extra dose of TOPV at birth especially to type 3 polio virus	Good to fair
16.	Patriarca PA et al. *Factors affecting the immunogenicity of oral polio vaccine in developing*	Review article	Seroconversion rates of trivalent oral polio vaccine (TOPV) approaches 100% in industrialized countries but only 73% and 70% of children in developing countries have detectable antibody to poliovirus type 1	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	countries: review. Reviews of Infectious diseases. 13(5): 926-39, 1991		and 3 respectively after 3 doses of TOPV. Type 2 vaccine virus and enteric pathogens interfere with response to type 1 an d 3 vaccine viruses	
17.	Bhatawdekar AM. et al. *Efficacy of three doses of oral polio immunization beginning within the first four days of life.* Indian Pediatrics. 27(9); 911-4, 1990	Non-RCT (47 infants vs. 21 controls)	This study provides evidence that oral polio immunization beginning in the newborn period was as effective as when commenced at 3 months of age. However, the later onset of immunization schedule leaves more children susceptible to poliomyelitis during the first three months of life.	Good to fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Inactivated Polio Vaccine vs. Oral Polio Vaccine				
1.	Juhela S. et al. *Comparison of enterovirus-specific cellular immunity in two populations of young children vaccinated with inactivated or live poliovirus vaccines.* Clinical & Experimental Immunology. 117(1): 100-5, 1999	Non-RCT between Estonian children and Finnish children	Enterovirus-specific cellular immunity at 9-month of age was higher among the Estonian children given live attenuated polio vaccine compared to Finnish children given inactivated polio vaccine. Thus, lower incidence of IDDM in Estonian compared to Finnish since effective protection against diabetogenioc enterovirus strains in Estonian children.	Fair
2.	Tranger J. et al *Vaccination of infants with*	Non-RCT between Swedish and US children	Swedish infants were vaccinated with DPT, IPV and Hib vaccine at 3, 5 and 12 months of age vs. US infants at 2, 4,	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	a four-dose and a three-dose vaccination schedule. Vaccine. 18(9-100: 884-91, 1999	(118 vs. 103 controls)	6 and 15 months. Immunogenicity of vaccines in infancy can be improved by increasing the number of doses, by prolonging the intervals between doses and by increasing the amount of antigen in the vaccine.	
3.	Herremans TM et al. *Induction of mucosal immunity by inactivated poliovirus vaccine is dependent on previous mucosal contact with live virus.* Journal of Immunology. 162(8): 5011-8, 1999	Non-RCT with historical controls	IPV vaccination alone is insufficient to induce mucosal IgA response against poliovirus. In mucosally (OPV-) primed individuals, booster vaccination with IPV leads to strong mucosal IgA response.	Fair
4.	Piirainen L. et al. *Randomized, controlled trial with trypsin-modified IPV: assessment of intestinal immunity with live challenge virus.* Vaccine. 17(9-10); 1084-90, 1999	RCT	Trypsin-modified IPV was not more potent than the regular enhanced potency IPV (eIPV) in inducing resistance to intestinal poliovirus infection.	Good
5.	Nirmal S. et al. *Immune response of infants to fractional doses of intradermally administered inactivated vaccine*. Vaccine. 1699-100:918-31, 1998	RCT (78 infants)	Seroconversion rates to polio 1, 2 and 3 were 90, 70 and 97%, respectively in children given IPV intradermally 8 weeks apart compared to 90, 80 and 98% in those given 3 doses 4 weeks apart. These rates were comparable to those given 5 doses of OPV or 2 doses of IM. IPV. This may be a less expensive alternative for use in developing countries.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
6.	Borcic B. et al. *A comparative study of reactogenicity and immunogenicity of an oral and an inactivated polio vaccine.* Acta Medica Cratica. 52(3): 155-8, 1998.	RCT (100 children each group)	Seroconversion rates with OPV 95.2% - 99%, with IPV 96.5%- 100%. Antibody levels for polio type 1 and 3 were higher in IPV but for polio type 2, the level is higher in children given OPV. IPV is acceptable as a substitute for OPV for primary vaccination.	Good
7.	Kaul D. et al. *Mucosal responses to parenteral and mucosal vaccines.* Developments in Biological standardization. 95; 141-6, 1998	Review article	Parenteral vaccine such as eIPV has been effective in preventing systemic disease during subsequent exposure to natural infection. Also quite effective in inducing varying degrees of functional mucosal antibody responses detected by ELISA.	Poor
8.	*WHO: Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman and Thailand.* WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Journal of Infectious Diseases. 175 Suppl 1:S215-27, 1997	Multicenter RCT (1685 infants)	IPV alone given at 6, 10 and 14 weeks of age provided inadequate protection against poliovirus. Combined schedule- OPV was given at birth followed by both IPV and OPV at 6, 10 and 14 weeks provided highest levels of serum antibody response.	Good
9.	Modlin JF. et al. *Humoral and mucosal immunity in*	RCT (510 infants)	Sequential IPV-OPV immunization produces best immunity among infants and recommended for routine	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	infants induced by three sequential inactivated poliovirus vaccine-live attenuated oral poliovirus vaccine immunization schedules. Baltimore Area polio Vaccine Study Group. Journal of Infectious Diseases. 175 Suppl 1:S228-34, 1997		use in USA. Optimal schedule - 2 IPV doses and 2 OPV doses. The antibody response for two IPV doses only was lower than expected.	
10.	Halsey et al. *Inactivated Poliovirus vaccine alone or sequential inactivated and oral poliovirus vaccine in 2-, 4- and 6-month-old infants with combination Haemophilus type b/hepatitis B vaccine.* Pediatric Infectious Disease Journal. 16(7): 675-9, 1997	RCT (295 children)	IPV is highly immunogenic in a two-dose schedule. Administration of a third dose of IPV or a dose of OPV at 6 months of age is highly effective. Simultaneous administration of a combination H. Influenza type b/ hepatitis vaccine did not interfere with the response to IPV	Good
11.	Sutter RW. et al. *Sequential use of inactivated poliovirus vaccine followed by oral polio vaccine in Oman.* Journal of Infectious Diseases. 175 Suppl 1: S235-40, 1997	RCT (547 infants)	Seroprevalence for polio type 3 was higher in infants given sequential OPV at birth and three doses of OPV and IPV, than those given IPV alone. The seroposivity was lowest among those given OPV alone.	Good
12.	Ion-Nedelcu N. et al. *Sequential and combined use of inactivated and oral poliovirus vaccine.*	Cohort study	Sequential use of IPV at 2 and 3 months followed by both IPV and OPV at 4 and 9 months resulted in 100% neutralizing antibodies among the vaccinees after the third dose.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Journal of Infectious Diseases. 175 Suppl 1:S241-6, 1997			
13.	Halperin SA. et al. *Effects of inactivated poliovirus vaccine on the antibody response to Bordetella pertussis antigens when combined with DPT vaccine.* Clinical Infectious Diseases. 22(1): 59-62, 1996	Small sample RCT (44 received single injection, 40 separate injections)	Diminished antibody response to the pertussis vaccine when inactivated poliovirus vaccine was combined with the DPT vaccine.	Good
14.	Ogra PL. *Comparative evaluation of immunization with live attenuated and inactivated poliovirus vaccines.* Annals of the New York Academy of Sciences. 754:97-107, 1995	Review paper	OPV and eIPV when used alone are safe and highly effective in eradication of poliomyelitis. Sequential schedule of eIPV followed by OPV should result in decline of vaccine associated paralytic disease (VAP) in OPV recipients but little impact on the development of VAP in susceptible individuals.	Poor
15.	Linder N. et al. *Early immunization with inactivated poliovirus vaccine in premature infants.* Journal of Pediatrics. 127(1); 128-30, 1995	Small sample RCT (41 infants vs. 39 controls)	The immune response of premature infants given additional dosage of IPV and 5 to 10 days of age were higher than those receiving the conventional dosing.	Good
16.	D'Angio CT et al. *Immunologic response of extremely premature infants to tetanus, Hemophilus influenzae and polio immunizations.* Pediatrics. 96(1 pt 1): 18-22, 1995	Non-RCT (16 extremely low birth weight premature infants, 66 term babies as controls)	Preterm infants compared to term infants, protective levels of antibody ≥ 1:8 were obtained in polio type 1 (85% vs. 80%) and type 3 (100% vs. 100%) given the enhanced potency inactivated polio vaccine at 2 months and oral polio vaccine at 4 months Preterm infants were less likely than term infants to have protective levels of antibody to	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
			polio virus type 3 (315 vs. 90%).	
17.	Simasathien S. et al. *Comparison of enhanced potency inactivated polio vaccine (eIPV) versus standard oral poliovirus vaccine (OPV) in Thai infants.* Scandinavian Journal of Infectious diseases. 26(6): 731-8, 1994	Non-RCT	Enhanced potency inactivated vaccine was shown to induce significantly higher seroconversion rates than OPV to all 3 polioviruses after the 2nd and 3rd immunization. After 3 doses of each vaccine, all infants receiving eIPV proved seropositive whereas of those receiving OPV, 9% remained seronegative for type I, and 11% seronegative for type 3. Should consider eIPV, alone or in combination with OPV in Thailand and similar countries.	Fair
18.	Ramsay et al. *Antibody response and viral excretion after live polio vaccine or a combined schedule of live and inactivated polio vaccines.* Pediatric Infectious Disease Journal. 13(120: 1117-21, 1994	RCT (96 children vs. 97 controls)	A combined schedule of inactivated and live polio vaccines (single dose of inactivated polio vaccine followed by 2 doses of oral polio vaccine) produces equivalent individual protection against poliomyelitis and is unlikely to substantially alter circulation of polio virus in the community	Good
19.	Faden H. *Poliovirus vaccination: a trilogy.* Journal of Infectious Diseases. 168(1): 25-8, 1993	Review	2 doses of enhanced potency IPV followed by 2 doses of OPV provide systemic and local immunity against poliovirus 1,2 & 3.	Poor
20.	Kok PW et al. *Serological and virological assessment of oral and inactivated poliovirus vaccines in a rural*	Non-RCT (100 children – OPV, 50 children – 2 doses IPV, 50 children – 3 doses OPV)	Antibody response was greatest with 3 doses of IPV followed by 3 doses of OPV and 2 doses of IPV induced the least antibody response particularly for polio virus type 2	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	population in Kenya. Bulletin of the World Health Organization. 70(1) 93-103,1992			
21.	Faden H. *Results of a clinical study of polio vaccine: the Buffalo experience*. Pediatric Infectious Disease Journal. 10(12); 973-5, 1991	RCT (123 infants)	The highest titer of antibody response is obtained with infants immunized with the (IPV-IPV-OPV schedule, followed by IPV-OPV-OPV and then IPV-IPV and IPV. It appears that a vaccine schedule with the combination of IPV and OPV would be ideal.	Good
22.	Onorato IM. et al. *Mucosal Immunity induced by enhance-potency inactivated and oral polio vaccines.* Journal of Infectious Diseases 163(1): 1-6, 1991	RCT	E-IPV was less effective than OPV in preventing and limiting intestinal infection, even though it induced higher post-vaccination serum antibody levels.	Good
23.	Meier P. *Polio trial: an early efficient clinical trial.* Statistics in Medicine 9(1-2) 13-16, 1990	RCT	Salk vaccine is efficacious.	Good
Polio Vaccines in Combination with other Vaccines				
1.	Langue J. et al. *Safety and immunogenicity of Hib-tetanus toxoid conjugate, presented in a dual-chamber syringe with DTP-IPV combination vaccine.* European Journal of Pediatrics. 158(9): 717-22, 1999	RCT (487 infants)	DTP-IPV and PRP-T may be safely and effectively administered in infants using the dual-chamber syringe, as separate injections or in a single manually reconstituted injection.	Good
2.	Langue J. et al. *Safety and immunogenicity of Hib-tetanus toxoid conjugate, presented in a dual-chamber syringe with DTP-IPV combination vaccine.*	RCT (487 infants)	DTP-IPV and PRP-T may be safely and effectively administered in infants using the dual-chamber syringe, as separate injections or in a single manually reconstituted injection.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	European Journal of Pediatrics. 158(9): 717-22, 1999			
3.	Gyhrs A. et al. *Immunogenicity and safety of a tetravalent diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine.* Scandinavian Journal of Infectious Diseases 31(6): 579-85, 1999	RCT (186 vs. 84 controls)	DTaP-IPV vaccine is safe and immunogenic.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
4.	Meriste S. et al. Safety and immunogenicity of combined DTPa-IPV vaccine for primary and booster vaccination. Scandinavian Journal of Infectious Diseases. 31(6): 587-91, 1999	Non-controlled clinical series (237 children)	The combined DTPa-IPV used for primary and booster immunisation induced good immunity but was associated with large local reactions in 21.3% of children after the booster dose.	Poor
5.	Usonis V. et al. *Does Concomitant injection of a combined DTaP-Hepatitis B-IPV vaccine influences the reactogenicity and immunogenicity of commercial Hib conjugate vaccine* European Journal of Pediatrics. 158(5): 398-402, 1999	Non-controlled clinical series (549 subjects)	There was no interference in immune response when the Hib conjugate vaccine was concomitantly administered with DTaP-IPV vaccine as separate injections.	Poor
6.	Lagos R. et al. *Clinical acceptability and immunogenicity of a*	RCT	Immunogenicity is the same among 5 different groups of infants: 1) DTaP + OPV 2) DtaP-eIPV, separate injections 3) DTaP-eIPV single injection. 4) DTaP-eIPV combined	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	pentavalent parenteral combination vaccine containing diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type b conjugate antigens in 2-, 4- and 6-month-old Chilean infants. Pedaitric Infectious Disease Journal. 17(4): 294-304, 1998 Apr		+ separate injection of PRP-T 5) DTaP-eIPV combined & reconstituted PRP-T as single injection. Combined DTaP, eIPV and PRP-T in a single injection is well tolerated and elicits an acceptable immune response to each component	
7.	Carlsson RM et al. *Safety and immunogenicity of a combined dipththeria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatric Infectious Disease Journal. 17(11): 1026-33, 1998	RCT (234 infants)	The combined vaccine DTaP-IPV/Act-Hib vaccine was equally safe and immunogenic when administered according to both time schedules studied.	Good
8.	Mills E. et al. *Safety and immunogenicity of a five-component pertussis-diphtheria-tetanus-IPV-Hib conjugate vaccine administered to infants at 2, 4 and 6 months of age.* Vaccine. 16(6); 576-85, 1998	RCT	CDPT-IPV//PRP-T was immunogenic and safe.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
9.	Aristegui J. et al. *Assessment of the immunogenicity and reactogenicity of a quadrivalent diphtheria, tetanus, acellular pertussis and hepatitis B (DTPa-HBV) vaccine administered in a single injection with H. Influenza type b conjugate vaccine, to infants at 2,4 and 6 months of age.* Vaccine. 16(20): 1976-81, 1998	Double blind RCT (269 infants)	The administration of a mixture of DTPa-HBV and HiB vaccines concomitantly with oral polio vaccines is safe, well tolerated and immunogenic for all vaccine components	Good
10.	Halperin SA. et al. *Safety and immunogenicity of two inactivated polio vaccines in combination with an acellular pertussis vaccine and diphtheria and tetanus toxoids in 17- to 19-month old infants.* Journal of Pedaitrics. 130(4): 525-31, 1997	Multicenter, RCT (425 children at 17-19 months of age)	Inactivated poliovirus vaccine in combination with acellular pertussis vaccine and diphtheria and tetanus toxoids is immunogenic and safe.	Excellent

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
11.	White CJ. *Measles, mumps, rubella, and varicella combination vaccine: safety and immunogenicity alone and in combination with other vaccines given to children.* Clinical Infectious Diseases. 24(5): 925-31,1997	RCT (812 children)	Oral polio vaccine does not interfere with the immune response of MMR and varicella vaccines. It can be given concurrently. Level of varicella antibody significantly lower in vaccinees receiving MMRV than those receiving varicella vaccine in a separate syringe.	Good
12.	Dagan R. et al *Safety and immunogenicity of a combined pentavalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus and Haemophilus influenza type-b-tetanus conjugate vaccine in infants, compared with a whole cell pertussis pentavalent vaccine.* Pediatric Infectious Disease journal. 16(2): 1113-21, 1997	RCT (101 vs. 100 controls)	The two type of combined vaccine were similar in immunogenicity	Good
13.	Begue P. et al. *Immunogenicity and reactogenicity of a booster dose of diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccines given concurrently with Haemophilus type b conjugate vaccine or as pentavalent vaccine.* Pediatric Infectious Disease Journal.	RCT (145 children 15 to 24 months of age)	DTPa-IPV vaccine given separately or mixed with Hib vaccine was at least immunogenic and less reactogenic than the DTPw-Hib vaccine. A mixed DTPa-IPV-Hib vaccine recommended for routine use as a booster dose in primed children.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	16(8); 787-94, 1997 Aug.			
14.	Edwards KM. *Combination vaccines consisting of acellular pertussis vaccines.* Pediatric Infectious Disease Journal. 16(4suppl): S97-102, 1997	Review article	Combining DTaP, IPV and hepatitis B showed similar immunogenicity comparable to those given separately. However, some studies showed diminished Hib responses in combination vaccines that include Hib antigens, the clinical relevance of which was yet to be determined.	Poor
15.	Kurikka S. et al. *Comparison of five different vaccination schedules with Hib-tetanus toxoid conjugate vaccine*. Journal of Pediatrics. 128(40:524-30, 1996	RCT (196 children)	The seroresponses to IPV and other components of the combined vaccine were immunogenic starting at 1- 4 months of age.	Good
16.	Rothstein EP. et al. *Simultaneous administration of diphtheria and tetanus toxoids and acellular pertussis vaccine with MMR and oral polio vaccine.* American Journal of Diseases of Children. 147(8): 854-7, 1993 Aug	RCT double blind (97 infants)	Simultaneous administration of the DPT, MMR and OPV at 15 months of age did not interfere with immune reactions to all the components of the vaccines. But acellular pertussis vaccine (DtaP) has less local or systemic adverse reactions compared to whole cell pertussis (DTwP) vaccine.	Good
17.	Dashefsky B. et al. *Safety, tolerability and immunogenicity of concurrent administration of Haemophilus influenza type b conjugate vaccine, meningococcal protein conjugates with either MMR vaccine or DPT and oral polio vaccines in 14- to 23-month-old infants.*	RCT	Oral polio vaccine is efficacious and immunogenic when given in combination with H. Influenza type b conjugate vaccine	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Pediatric 85(4 pt 2): 682-9, 1990			
Program Effectiveness and Population Acceptability - Oral Polio Vaccine				
1.	Dini EF. et al. *The impact of computer-generated messages on childhood immunization coverage.* American Journal of Preventive Medicine. 18(2): 132-9, 2000	RCT (1227 children)	Computer generated contacts by phone, mail, or both combined used each time vaccines become due, efficacious in increasing immunization coverage of children under 2 years of age.	Good
2.	Baker JP. *Immunization and the American way; 4 childhood vaccines.* American Journal of Public Health. 90(20:199-207,2000	Review	Description of American experience in successfully translating laboratory knowledge into strategies suitable for mass application and implementation of ed mass immunization programs particularly in polio, diphtheria, pertussis and measles	Poor
3.	*Progress towards global poliomyelitis eradication: 1997-1998–* Morbidity & mortality weekly report. 48(20): 416-21, 1999	Review	Discussion of the progress made in implementing the recommended polio eradication strategies: achieving and maintaining high routine coverage with OPV, conducting national immunization days to reduce poliovirus circulation, establishing sensitive surveillance systems, carrying out mopping-up vaccination activities to eliminate remaining reservoirs of poliovirus transmission.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
4.	Mas Lago P. *Eradication of poliomyelitis in Cuba: a historical perspective.* Bulletin of world Health Organization. 77(8): 681-7, 1999	Review article	The strategy for eradication in Cuba was based on mass immunization campaigns for the annual delivery of two-doses of trivalent OPV. The interruption of wild virus transmission had been achieved since 1970 and no wild virus had been detected ever since. Countries that have successfully interrupted poliovirus circulation should maintain high immunization coverage as long as there are other countries in the world where poliovirus still exists.	Poor
5.	Saha I. et al. *Pulse polio immunization, 1995-96, an evaluation in West Bengal*. Journal of Indian Medical Association. 97(1): 8-10, 1999	Cohort study	Some of the major reasons for non-acceptance of pulse polio immunization were lack of information, illness of the child, absence of the child on the "PPI" day, lack of faith in immunization and fear of adverse reaction.	Fair
6.	D'Souza RM. *Australian's contribution to global polio eradication initiatives.* Australian & New Zealand Journal of Public Health. 23(3): 289-294, 1999	Cohort study	Description of meeting requirements of the Global Commission for Certification of Poliomyelitis Eradication for poliomyelitis elimination in Australia through documentation of surveillance of polio, a comprehensive national immunization program, network of laboratories for viral diagnosis, active surveillance of acute flaccid paralysis (AFP). Comprehensive immunization program and surveillance must continue for three years after global certification.	Fair
7.	Francks S. et al. *Epidemiological analysis of immunity to poliovirus after termination of an era of vaccination with OPV in Germany – an analysis of the German association against viral diseases.* International Journal of Medical Microbiology, Virology, Parasitology and Infectious diseases. 289(4): 475-481, 1999	Cohort study (3474 subjects)	A non-age-specific evaluation of seroprevalence to polio type 1 remained 81%, for polio type 2 86% while poliovirus type 3 decreased from 78% in 1990-1992 to 68% in 1997. In children age 5 to 14, the seroprevalence to type 3 decreased from 75% in 1990 to 47% in 1997.It concluded that a good immunity to all 3 sero types was not achieved by primary vaccination with OPV. Since 1998, after a period of using OPV for 37 years, use of IPV have been recommended in Germany	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
8.	Fine PE. Et al. *Transmissibility and persistence of oral polio vaccine viruses: implication for the global poliomyelitis eradication initiative*. American Journal of Epidemiology. 150(10): 1001-21, 1999	Review article	Discusses implications of OPV transmissibility for the strategy of stopping OPV after global eradication of wild polioviruses. Concern has been raised about the potential for persistence of transmission of OPV viruses, as they are known to revert to wild-type neurovirulence. So, this potential should be considered during planning for cessation of OPV vaccination.	Poor
9.	Pan X. *Investigation on the effect and strategy of polio eradication in Hainan province.* Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology. 20(2): 78-80, 1999	Cohort study	Effective program in Hainan province, China in controlling and eliminating polio by polio vaccine besides health education, strengthening of immunization programs and AFP surveillance.	Fair
10.	Andrianarivelo MR. et al. *Wild poliovirus circulation among healthy children immunized with oral polio vaccine in Antananarivo, Madagascar*. Tropical Medicine & International Health. 4(1); 50-7, 1999	Clinical series	Immunization with 3 doses of OPV did not prevent the intestinal carriage of wild poliovirus and there is a risk of transmission to susceptible children in the area.	Poor
11.	Davis TC.et al. *A polio immunization pamphlet with increased appeal and simplified language does not improve comprehension to an acceptable level.* Patient education & counseling.	RCT (610 parents)	Simplifying written immunization material and making it more suitable will increase appeal, but such modification may not raise comprehension to an acceptable level without the use of instructional graphics. Parents of all reading levels preferred easy to read pamphlets rather than just informative statements.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	33(1): 25-37, 1998			
12.	Morgan et al. Initiatives to improve childhood immunization uptake: a randomized controlled trial. British Medical Journal. 316 (7144) 1569-1570, 1998	RCT	Reminder phone calls to the child's health visitor or reminder letter to the parents did not improve immunization uptake. In another study, initiatives by primary healthcare teams such as opportunistic immunization of children attending the surgery and domiciliary immunization improved uptake but suggested that more trials needed to evaluate its effectiveness.	Good
13.	Reichler MR. et al. Outbreak of paralytic poliomyelitis in a highly immunized population in Jordan. Journal of Infectious Diseases. 175 Suppl 1: S62-70, 1997	Non- RCT	Demonstrated the importance of achieving high seroimmunity to infection in all geographic areas to prevent the reintroduction and spread of imported strains of wild poliovirus. Among poliomyelitis cases, 50% had received at least 3 doses of OPV - first few patients were immigrants and subsequent spread occurred in area with lower in seroimmunity.	Good to fair
14.	Hull HF. Et al. *Progress toward global polio eradication.* Journal of Infectious Diseases. 175 Suppl 1:S4-9, 1997	Review	Discussion of strategies recommended by the WHO for polio eradication: maintaining high routine immunization coverage, conducting nationwide mass immunization campaigns, building effective, laboratory based surveillance for AFP; and conducting local immunization campaigns directed at final reservoirs of virus transmission.	Poor
15.	*Progress toward poliomyelitis eradication.* MMWR. Update: 46(21): 468-73, 1997	Clinical descriptive study	Summarizes data on progress in South Asia region towards polio eradication as of April 1, 1997. The success in application of WHO strategies in preventing, detecting and interrupting the transmission of poliovirus resulted in 96% decrease in the number of polio cases during the 1989-1996 period.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
16.	Aylward RB. et al. *Strengthening routine immunization services in the western pacific through the eradication of poliomyelitis.* Journal of Infectious Diseases. 175 Suppl 1: S268-71, 1997	Cohort study	Evaluated and demonstrated the impact of polio eradication activities on routine immunization services in the Western Pacific region.	Fair
17.	Aylward RB. et al. *The eradication of poliomyelitis in Egypt: critical factors affecting progress to date.* Journal of Infectious Diseases. 175 Suppl 1:S56-61, 1997	Cohort study	Demonstrated that combination of high routine immunization coverage (.85%) with OPV combined with two properly conducted rounds of national immunization days resulted in marked reduction in reported cases of poliomyelitis (75%).	Fair
18.	Sutter RW. et al. *A large outbreak of poliomyelitis following temporary cessation of vaccination in Samarkand, Uzbekistan, 1993-1994.* Journal of Infectious Diseases. 175 Suppl 1:S82-5, 1997	Clinical series	Demonstrated the importance of continuing efforts against polio- virus transmission by OPV vaccination. Unavailability of OPV resulted in the outbreak in Samarkand, Uzbekistan.	Poor
19.	Biellik RJ. et al. *Polio outbreaks in Namibia, 1993-1995:lessons learned.* Journal of Infectious Diseases. 175 Suppl 1: S30-6, 1997	Clinical series	Demonstrated the effectiveness of supplemental vaccination strategy of national immunization days and mopping-up vaccination in controlling the outbreak due to importation of wild virus from an endemic neighbor country.	Poor
20.	Salisbury DM. et al. *Polio eradication: surveillance*	Review	Acute flaccid paralysis surveillance done for 3 years and the rates were lower than reported elsewhere, and were accepted for	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	implications for United Kingdom. Journal of Infectious Diseases. 175 Suppl 1; S 156-9, 1997		certification purposes. However, surveillance of polioviruses either in clinical samples or environment should be developed to distinguish wild or vaccine strain of polioviruses to assure that transmission of wild virus is unlikely.	
21.	Deshpande JM. et al. *Absence of wild poliovirus circulation among healthy children in a rural area with high oral poliovirus vaccination coverage*. Indian Journal of Medical Research. 103:289-93, 1996	Cohort study	Wild poliovirus was not detectable within five months after the last case of acute poliomyelitis. Displacement of wild virus from the environment and circulation of vaccine virus was achieved by high vaccination coverage in this area (95.8% for 7 to 12 months, 94% for 7 to 12 months old infants)	Fair
22.	*Progress towards poliomyelitis eradication –People's Republic of China, 1990-1996.* Morbidity & Mortality weekly Report. 459490:1076-9, 1996	Cohort study	Demonstrates the effectiveness of polio eradication program in China by implementing the four WHO recommended strategies. No indigenous wild poliovirus were detected despite a strengthened surveillance system	Fair
23.	Mas Lago et al. *Lessons from Cuba: mass campaign administration of trivalent oral polio vaccine and seroprevalence of poliovirus neutralizing antibodies*. Bulletin of World Health organization. 72(2): 221-5, 1994	Non-randomized controlled prospective trial	Mass immunization campaign strategies were sufficient to eradicate the transmission of wild polio- virus in Cuba even though 16.5% of the children remained unprotected for type 3 viruses even after 8 doses of OPV.	Good to fair
24.	Kotb MM. et al. *Epidemiological evaluation of oral polio vaccine efficacy in Cairo.* Journal of the Egyptian Public Health Association. 68(5-6): 617-25, 1993	Case control study	Only 86% of protection obtained after 3 doses of OPV and 92% after 4 doses of OPV. Higher rate of vaccine efficacy should be achieved to meet the challenge of eradication of poliomyelitis	Poor
25.	Ward NA et al. *The WHO-EPI initiative for global eradication of poliomyelitis.*	Review	Discusses the effectiveness of mass immunization of OPV in developing countries like Cuba and Brazil. The target of a world free of polio by the year 2000 can be achieved.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Biological. 21(4): 327-33, 1993			

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Inactivated Polio Vaccine (IPV)				
1.	Kolasa MS. et al. *Impact of the sequential poliovirus immunization schedule: a demonstration project.* American Journal of Preventive Medicine. 18920:140-5, 2000	Non-RCT with historical controls	Evaluated compliance with the sequential polio immunization schedule using IPV for the first 2 doses. Compliance with recommended doses of IPV was very high in this low-income & ethnically diverse population. Need for additional injections did not impede the delivery of childhood immunization.	Fair
2.	Anonymous. *Impact of sequential IPV/OPV schedule on vaccination coverage levels – United States, 1997.* Morbidity & Mortality Weekly Report. 47(47): 1017-9, 1998	Cohort study	Changing to initial 2 doses of IPV was not associated with decreased vaccination coverage levels.	Fair
3.	Dunn RA. et al. *Videotape increases parental knowledge about poliovirus vaccines and choices of polio vaccination schedules.* Pediatrics. 102(2) 26.1998	RCT (287 parents)	Complicated discussion of risk/ benefit ratio of two vaccines and their schedules of administration could be communicated effectively via a videotape presentation. It was more effective than vaccine information statement alone.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
4.	Thomas ML. et al. *Parental knowledge and choice regarding live and inactivated poliovirus vaccines.* Archives of Pediatrics &Adolescent Medicine. 151(8): 809-12, 1997	RCT (Parents of 240 children)	Most parents (62.5%) did not know the 2 polio vaccines and majority (75%) would consult someone (primarily their physician) before making the final choice of vaccine. If choice made without consultation, majority (61.3%) would choose to have their children receive 3 injections of IPV vs. 3 OPV schedule because of reduced risk of vaccine-associated paralytic poliomyelitis. OPV preferred by 37.9% because given orally. If the number of injections were the same for both vaccines, 76.3% of parents would choose the IPV schedule.	Good
5.	Anonymous. *Poliomyelitis prevention in the United States: introduction of a sequential vaccination schedule of IPV followed by OPV.* Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 46(RR-3): 1-25, 1997	Consensus statement.	New ACIP poliovirus vaccination policy with elimination of wild-virus associated poliomyelitis in USA and reduced acceptability of vaccine associated poliomyelitis: a sequential vaccination schedule of two doses of IPV followed by two doses of OPV is recommended for routine childhood vaccination. OPV alone is recommended for children who begin their primary vaccination schedule after 6 months of age. IPV alone is recommended for children who are immunosuppressed.	Poor
6.	Anonymous. *Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman and Thailand. WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines.* Journal of Infectious Diseases. 175 Suppl 1:S215-27, 1997	Multicenter RCT (1685 infants)	IPV alone given at 6, 10 and 14 weeks provided inadequate protection against poliovirus. Combined schedule where OPV was given at birth followed by both IPV and OPV at 6, 10 and 14 weeks provided highest levels of serum antibody response.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
7.	Ion-Nedelcu N. *Sequential and combined use of inactivated and oral poliovirus vaccines: Dolj District, Romania, 1992-1994.* Journal of Infectious Diseases. 175 Suppl 1: S241-6, 1997	Cohort study (16,566 infants)	Vaccination coverage by twelve months of age with a sequential schedule of 2 does of IPV at 2 and 3 months followed by both IPV and OPV at 4 and 9 months was >95%. 100% of children tested had neutralizing antibodies to all 3 types of poliovirus, and there were no cases of vaccine related paralysis. Sequential use of IPV followed by OPV is feasible, safe & has high immunogenicity.	Fair
8.	Reichler MR. et al. *Outbreak of paralytic poliomyelitis in a highly immunized population in Jordan.* Journal of Infectious Diseases. 175 Suppl 1: S62-70, 1997	Non- RCT	Important to achieve high seroimmunity to infection in all geographic areas to prevent the reintroduction and spread of imported strains of wild poliovirus. Among poliomyelitis cases, 50% had received at least 3 doses of OPV, the first few patients were immigrants and subsequent spread occurred in an area lower in seroimmunity compared to other areas.	Fair
9.	Anonymous. *Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized controlled trail in the Gambia, Oman and Thailand.* WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Bulletin of the World Health Organization. 74(3): 253-68, 1996	Multicenter RCT (1685 infants)	IPV given at 6, 10, and 14 weeks provided inadequate serological protection against poliovirus, especially type 1. Combined scheduled provided highest levels of serum antibody response, with mucosal immunity equivalent to OPV alone.	Good
10.	Tulchinsky T. et al. Successful control of poliomyelitis by a combined OPV/IPV polio	Descriptive study	Control of poliomyelitis by a combined program of OPV and IPV compared to previous program of 4 doses of OPV. Incidence of poliomyelitis still high with 4 doses of	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	vaccine program in the West Bank and Gaza. Israel Journal of Medical Sciences. 30(5-60; 489-94, 1994		OPV due to interference in uptake from other entero viruses in environment.	
Vaccine Safety & Side Effects - Oral Polio Vaccine				
1.	Ridgway D. *The logic of causation and the risk of paralytic poliomyelitis for an American child.* Epidemiol. Infect. 12491): 113-20, 2000	Epidemiological analysis	Estimation of risk of paralytic polio using epidemiological data and explicit assumptions. Estimated risks of paralytic polio for infants immunized with oral polio vaccine (1.3 cases per million), inactivated polio vaccine (0.54 cases per million), or a sequential schedule 0.54-0.92 cases per million)	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Shoenfeld et al. *Vaccination and autoimmunity – 'vaccinosis': a dangerous liaison?* Journal of Autoimmunity. 14910:1-10, 2000	Review	Association of autoimmune illnesses ranging from autoantibody production to rheumatoid arthritis with vaccinations including polio vaccine discussed. Concluded that the available data is conflicting. Some autoimmune phenomena such as Gullain-Barre syndrome are related to immunization.	Poor
3.	Chitske et al. *Paralytic poliomyelitis associated with live oral*	Clinical series	Case of paralytic poliomyelitis due to poliovirus type 2 after oral poliomyelitis vaccination.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	poliomyelitis vaccine in children with HIV infection in Zimbabwe: case report. BMJ 31(7187): 841-3, 1999			
4.	***Fenichel GM.*** ***Assessment:* Neurological risk of immunization: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.** ***Neurology 52(8): 1546-52, 1999***	Expert review	Summarizes the reported neurological adverse effects of oral polio vaccine.	Poor
5.	Ismail EA. et al. *An epidemiological, clinical, and therapeutic study of childhood Guillain Barre syndrome in Kuwait: is it related to the oral polio vaccine?* Journal of Child Neurology. 13(10): 488-92, 1998	Cohort study	No correlation between oral polio vaccine administration and Guillain-Barre syndrome in Kuwait.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
6.	Diamanti E. et al. *Surveillance of suspected poliomyelitis in Albania, 1985-1995: suggestion of increased risk of vaccine associated poliomyelitis.* Vaccine. 1699-10): 940-8, 1998	Cohort study	Surveillance study on a cohort of children in Albania - 11 out of 93 cases of acute flaccid paralysis were poliomyelitis. 6 of the 11 cases were vaccine associated with type 2 and 3 poliovirus of vaccine origin with retro mutations known to be associated with loss of Sabin attenuated phenotype.	Fair
7.	Strickler HD et al. *Contamination of poliovirus vaccines with Simian virus 40 (1955-1963) and subsequent cancer rates.* JAMA. 279(40:292-5, 1998	Retrospective cohort study	After 30 years of follow up, exposure to SV40-contaminated poliovirus vaccine not associated with increased rates of ependymomas and other brain cancers, osteosarcomas or mesotheliomas in USA despite recent reports of SV 40 virus DNA detection in these tumours	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
8.	***Freidrich F.*** **Rare adverse events associated with oral poliovirus vaccine in Brazil.** ***Brazilian Journal of Medical and Biological Research. 30(6): 695-703, 1997***	Review	Molecular characterization of polioviruses isolated in previous eight years from paralysis cases classified as Gullain Barre syndrome, transverse myelitis and facial paralysis discussed, and confirmed the vaccine origin of the strains & demonstrated mutations known to increase neurovirulence. In most cases last dose of OPV given months or years before onset of disease.	Poor
9.	***Olin P. et al.*** **Potential exposure to SV40 in polio vaccines used in Sweden during 1957: no impact on** ***cancer incidence rates 1960 to 1993.*** ***Development in Biological Standardization. 94:227-33, 1998***	Cohort study	This study demonstrated that the use of potentially SV40 contaminated inactivated polio vaccines in Sweden was not associated with increased cancer incidence. However, the exposed cohorts have not yet reached the age for increased risk of brain cancer or mesothelioma.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
10.	***Weibel et al.*** **Reporting vaccine associated paralytic poliomyelitis: concordance between the CDC and the National Vaccine Injury Compensation Program.** ***American Journal of Public Health. 86(50, 734-737, 1996***	Non-randomized controlled study	Demonstrated that the compensation program captured additional cases of VAPP.	Fair
11.	***Andrus JK. et al.*** **Risk of vaccine-associated paralytic poliomyelitis in Latin America. 1989-91.** ***Bulletin of the World Health Organization. 73(1): 33-40, 1995***	Multicenter, cohort study	Large surveillance study on cohorts of mass immunization campaigns in Latin America showed that the risk for VAPP was estimated to be one case per 1.5 to 2.2 million doses of OPV administered, 1.4 million doses in England &Wales, 2.5 million doses in USA. Strategies of polio eradication rely on mass campaigns do not alter the risk of VAPP.	Fair
12.	***Strebel et al.*** **Intramuscular injections within 30 days of immunization with oral poliovirus vaccine – a risk factor for vaccine-associated paralytic poliomyelitis.**	Non-randomized controlled study	VAPP may rarely occur in a child who receives multiple intramuscular injections shortly after exposure to OPV, either as a vaccine recipient or through contact with a recent recipient. This may explain the high rate of VAPP in Romania where intramuscular injections of antibiotics in infants with febrile illness is common. 86% of the VAPP might have been prevented by elimination of intramuscular injection within 30 days of exposure to OPV.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	The New England Journal of Medicine. 332(8): 500-506, 1995			

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
13.	***Izurieta HS et al.*** **Vaccine- associated paralytic poliomyelitis in the United States: no evidence of elevated risk after simultaneous intramuscular injection of vaccine.** ***Pediatric Infectious Disease Journal. 14(100:840-6, 1995***	Clinical series	Review of injection histories of VAPP cases reported to CDC from 1980 to 1993 found no evidence of elevated risk after simultaneous intramuscular injection of vaccine. This is in contrast to the 10 fold higher risk of VAPP in Romania that was associated to multiple i.m. injections of antibiotics within 30 days of onset of paralysis. Out of the 119 cases of poliomyelitis reported, 73% were VAPP and immunologically normal, 45% were oral polio recipient cases, another 45% were OPV contact cases and about 10% were community acquired.	Poor
14.	***Freidrich F.*** **Neurologic complications associated with oral poliovirus vaccine and genomic variability of the vaccine strains after multiplication in humans.** ***Acta Virologica. 42(3): 187-94, 1994***	Review	Discusses the side effects of OPV. Molecular biology studies have proven that the vaccine origin of isolates and demonstrated genomic modifications known to increase neurovirulence. Other complications such as meningitis, encephalitis, convulsions, transverse myelitis and Guillain Barre syndrome have also been rarely associated with the use of OPV.	Poor
15.	***Georgescu MM et al.*** **High diversity of poliovirus strains isolated from the central nervous system from patients with virus-associated paralytic poliomyelitis.** ***Journal of Virology. 68(120:8089-101, 1994***	Clinical series	Wide variety of poliovirus vaccine genomic structures appeared to be implicated in the etiology of VAPP. It can be either non-recombinant or recombinant (vaccine/vaccine or vaccine/non-vaccine). All of the CNS-isolated strains lost the attenuated phenotype of Sabin strains.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
16.	***Stratton KR et al.*** **Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine.** ***JAMA 271 (20): 1602-5, 1994***	Expert committee Report after 18 review of all the studies available	Evidence favored the acceptance of a causal relationship between oral polio vaccine and Guillain Barre syndrome. Evidence established between oral polio vaccine & poliomyelitis & death from polio vaccine strain virus infection.	Fair
17.	***Strebel PM. et al.*** **Paralytic poliomyelitis in Romania, 1984-1992. Evidence for a high risk of vaccine associated disease and reintroduction of wild virus infection.** ***American Journal of Epidemiology. 140(12): 1111-24, 1994***	Cohort study	Provides evidence for vaccine associated paralytic poliomyelitis in recipient and contact for OPV - of 132 cases of poliomyelitis, 93 were vaccine associated.	Fair
18.	***Georgescu MM. et al*** **High diversity of poliovirus strains isolated from the central nervous system from patients with vaccine associated paralytic poliomyelitis.** ***Journal of Virology. 68912): 8089-101, 1994***	Clinical series	Stool isolate in VAPP might not be always representative of the etiologic agent of the neurological disease. Only 5 out of 8 isolates from the CNS & stool were similar. Of 9 CNS vaccine-derived strains, 4 non-recombinant and 5 recombinant.	**Poor**

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Inactivated Polio Vaccine				
1.	American Academy of Pediatrics. *Prevention of poliomyelitis: recommendations for use of only inactivated poliovirus vaccine for routine immunization. Committee of Infectious Diseases.* Pediatrics. 104(6): 1404-6, 1999	Consensus statement	The incidence of VAPP has decreased in the USA after the recommendation of use of IPV. To eliminate VAPP in the context of decreasing risk of wild-type poliovirus importation, the AAP recommends an all-IPV schedule for routine childhood immunization beginning 2000 and OPV should no longer be purchased for routine use.	Poor
2.	Zimmerman RK.et al. *Poliovirus vaccine options.* American Family Physician. 59(1): 113-8, 125-6, 1999	Review	134 out of 142 cases of paralytic poliomyelitis in USA from 1980 to 1996 were vaccine associated paralytic poliomyelitis (VAPP). The risk for VAPP is 1 case per 750,000 doses for first dose of OPV and 1 case per 2.4 million cases of overall OPV. The American Academy of Family Physician recommended that the first 2 doses of poliovirus vaccine should be IPV followed by 2 doses of OPV or an all IPV schedule.	Poor
3.	Jonville-Bera AP et al. *Adverse effects of the vaccines Tetracoq, IPAD/DTCP and DTCP. A French study of regional drug monitoring centers.* Archives de Pediatrie. 6(5): 510-5, 1999	Cohort study (606 children)	Common adverse events for Tetracoq were local reactions at site of injection (43%), neurological disorders (12%), hyperthermia (10%) and allergic reaction (10%). Rare but serious side effects include persistent crying, febrile seizures, apyretic seizures, uneasiness and shock.	Fair
4.	Ehrengut. *Role of provocation poliomyelitis in vaccine-associated poliomyelitis.* Acta Paediatrica Japonica. 39(6):	Cohort study	In 1963-1977, there were 10 cases of vaccine-associated poliomyelitis in Germany based on clinical diagnosis (only based on the temporal relation of the vaccination and onset) among the 9.96 million OPV vaccinees.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	658-62, 1997		Between 1980- 1985, there were 6 cases of provocation poliomyelitis among the 2.9 million IPV vaccinees.	
5.	Ion-Nedelcu N. et al. Sequential and combined use of inactivated and oral poliovirus vaccine. Journal of Infectious Diseases. 175 Suppl 1:S241-6, 1997	Cohort study	Sequential use of IPV at 2 and 3 months followed by both IPV and OPV at 4 and 9 months was safe and feasible.	Fair
Polio Vaccines in Combination with Other Vaccines				
1.	Gyhrs A. et al. *Immunogenicity and safety of a tetravalent diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine.* Scandinavian Journal of Infectious Diseases 31(6): 579-85, 1999	RCT (186 vs. 84 controls)	DTaP-IPV vaccine is safe and no serious adverse events were seen except for local reactions, febrile and crying episodes that were similar to the DTP-IPVvaccine.	Good
2.	Langue J. et al. *Safety and immunogenicity of Hib-tetanus toxoid conjugate, presented in a dual-chamber syringe with DTP-IPV combination vaccine.*	RCT (487 infants)	DTP-IPV and PRP-T may be safely and effectively administered in infants using the dual-chamber syringe, as separate injections or in a single manually reconstituted injection. Pain and unusual crying significantly more in infants who received 2 injections than in the dual chamber syringe	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	European Journal of Pediatrics. 158(9): 717-22, 1999			
3.	Meriste S. et al. *Safety and immunogenicity of combined DTPa-IPV vaccine for primary and booster vaccination*. Scandinavian Journal of Infectious Diseases. 31(6): 587-91, 1999	Non-controlled clinical series (237 children)	The combined DTPa-IPV used for primary and booster immunisation was associated with large local reactions in 21.3% of children after the booster dose.	Poor
4.	Jonville-Bera AP et al. *Adverse effects of the vaccines Tetracoq, IPAD/DTCP and DTCP. A French study of regional drug monitoring centers.* Archives de Pediatrie. 6(5): 510-5, 1999	Cohort studies	The commonest reported adverse effects were local reaction at site of injection (43%), neurological disorders (12%), hyperthermia (10%) and allergic reactions (10%). Serious adverse effects include persistent crying, febrile seizures, apyretic seizures, uneasiness and rarely shock.	Fair
5.	Mills E. et al. *Safety and immunogenicity of a five-component pertussis-diphtheria-tetanus-IPV-Hib conjugate vaccine administered to infants at 2, 4 and 6 months of age.* Vaccine. 16(6); 576-85, 1998	Randomised control trial	CPDT-IPV//PRP-T was safe, but adverse reactions were twice as common in the whole cell pertussis group.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
6.	Carlsson RM et al. *Safety and immunogenicity of a combined dipththeria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenza type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatric Infectious Disease Journal. 17(11): 1026-33, 1998	RCT (234 infants)	The combined vaccine DTaP-IPV/Act-Hib vaccine was equally safe and when administered according to both time schedules studied. There were no serious adverse reactions and the rates of febrile events and local reactions were low in both groups	Good
7.	White CJ. *Measles, mumps, rubella, and varicella combination vaccine: safety and immunogenicity alone and in combination with other vaccines given to children.* Clinical Infectious Diseases. 24(5): 925-31,1997	RCT (812 children)	Oral polio vaccine was safe when given with MMR and varicella vaccines	Good
8.	Dagan R. et al *Safety and immunogenicity of a combined pentavalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus and Haemophilus influenza type-b-tetanus conjugate vaccine in infants, compared with a whole cell pertussis pentavalent vaccine.* Pediatric Infectious Disease Journal. 16(2): 1113-21, 1997	RCT (101 vs. 100 controls)	DTaP-IPV group had less local and systemic adverse events than the DTwP-IPV group.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
9.	Halperin SA. et al. ***Safety and immunogenicity of two inactivated polio vaccines in combination with an acellular pertussis vaccine and diphtheria and tetanus toxoids in 17- to 19-month old infants.*** Journal of Pediatrics. 130(4): 525-31, 1997	Multicenter, RCT (425 children at 17-19 months of age)	Inactivated poliovirus vaccine in combination with acellular pertussis vaccine and diphtheria and tetanus toxoids is safe. Although minor adverse events were common, no difference between the IPV-DTaP group and the OPV-DTaP group.	Good
10.	Dashefsky B. et al. *Safety, tolerability and immunogenicity of concurrent administration of Haemophilus influenza type b conjugate vaccine, meningococcal protein conjugates with either MMR vaccine or DPT and oral polio vaccines in 14- to 23-month-old infants.* Pediatric 85(4 pt 2): 682-9, 1990	RCT	Oral polio vaccine is safe and immunogenic when given in combination with H. Influenza type b conjugate vaccine	Good
Cost Effectiveness - Oral Polio Vaccine				
1.	Aylward RB et al. *Disease eradication as public health strategy: a case study of poliomyelitis eradication.* Bulletin of World Health Organization. 78(3): 285-297, 2000	Review	Polio eradication initiative discussed including the costs and benefits, technical feasibility and operational feasibility. When the humanitarian, economic and consequent benefits of this initiative is measured against the costs, a strong argument is made for eradication as a valuable disease control strategy.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Wood DJ et al. Stopping poliovirus vaccination after eradication; issues and challenges. Bulletin of the world Health Organization. 78(3): 347-357, 2000	Review	A risk-benefit analysis is needed before vaccination can be continued. Some questions that need research include reemergence of poliomyelitis in unvaccinated population and prolonged excretion of vaccine-derived poliovirus in individuals with immune deficiency.	Poor
3.	Ruff TA. *Immunization strategies for viral diseases in developing countries.* Review of Medical Virology. 9920:121-38, 1999	Review	Expanded Programme on Immunization associated with increase in infant immunization coverage from 5% to 80%, and the prevention of at least 3 million deaths annually, at very low cost. Target of polio eradication by year 2000 appears feasible.	Poor
4.	*Progress toward poliomyelitis eradication – Africa, 1996.* Morbidity and Mortality Weekly Report. 46(15): 321-5, 1997	Expert report	Progress achieved in 1996 toward polio eradication in Africa with the implementation of supplemental vaccine activities. The estimated cost was $0.50 per child vaccinated during national immunization days.	Poor
5.	Bart KJ et al. *Global eradication of poliomyelitis: benefit-cost analysis.* Bulletin of the world Health Organization. 74(1): 35-45, 1996	Cost benefit analysis (1986-2040)	Cost-benefit analysis of poliomyelitis eradication initiative based on the model that assumed differential costs for OPV and vaccine delivery in industrialized and developing countries, ignoring all benefits aside from reduction in direct costs for treatment and rehabilitation. Break-even point (at which benefits exceeds cost) was 2007, with a saving of US$ 136000 million by 2040. It estimated global saving of US$1.5 million/yr. once polio has been eradicated. Thus, poliomyelitis Eradication Initiative is economically justified.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
6.	Ragan E. et al. *Global immunization: Is a child's life worth $15?* Canadian Medical Association Journal. 155(10): 1492-4, 1996	Expert opinion in Journal article	Deaths amongst children would 5 million/yr. instead of 1.8 million without immunization. The cost of saving these children is low, between USD 12 -15 per child. It would cost USD1.4 billion annually to immunize fully all the developing world's newborn children.	Poor
7.	***Cochi et al.*** **To conquer poliomyelitis forever.** ***The Lancet. 345(8965): 1589-1590, 1995***	Expert opinion	Need for broad-based financial and political support in eradication of polio. The WHO estimated an additional $100 million is needed annually during 1996-2000 beside the donations obtained thus far. In the first 10 years following eradication, global saving would be in excess of $10 billion.	Poor
8.	***Zhang Y.*** **The economic loss of poliomyelitis outbreak in Pi County and economic beneficial analysis on EPI.** ***Chung Hua Liu Hsing Ping Hsueh Tsa Chih. 13(3); 162-4, 1992***	Cost benefit analysis	Analyzes the economic loss of 2,713,107.32 yuan and lessened creating value of 18,583,942.35 yuan for China in the 1989 outbreak of poliomyelitis in Jiangsu province China. Cost-benefit ratio estimated to be 1: 6.85 & net benefit of 2,317,268.16 yuan could be gained if the expanded program of immunization was implemented well to prevent the outbreak.	Good
Cost Effectiveness - Inactivated Polio Vaccine				
1.	Sutter RW. et al. *Poliovirus vaccines. Progress toward global poliomyelitis eradication and changing routine immunization recommendation in the United States.* Pediatric Clinic of North America. 47(2); 287-308, 2000	Review	Lack of data on the cost –effectiveness of a sequential polio vaccination or an all-IPV schedule though they are safe and immunogenic.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Miller et al. *Cost effectiveness of incorporating inactivated poliovirus vaccine into the routine childhood immunization schedule.* JAMA. 276912): 967-971, 1996	Detailed cost effective analysis	Changing to an IPV-only or a sequential schedule would cost $28.1 million and $14.7 million, respectively in USA. The costs per case of VAPP prevented estimated as $3.0 million and $3.1 million for each respectively. Introduction of IPV into the routine immunization schedule would not be cost beneficial at current vaccine prices and with the current compensation awards paid to VAPP cases. Use of sequential schedule may be justified as VAPP continues to occur in the absence of wild poliovirus transmission in USA.	Good
3.	Patriarca et al. *Progress in polio eradication.* The Lancet. 342(8885): 1461-1464, 1993	Review	Although the cost of OPV ($0.09) is less than IPV ($0.35) cost of delivering OPV during mass campaigns to eradicate polio has been estimated at $0.68 - $3.60. It can be easily incorporated into existing immunization schedule by substituting DTP with DTP-IPV. One disadvantage in developing country is the lack of technical resources in producing DTP-IPV while local manufacturers produce 70% of DTP. Therefore, a change in schedule could have important economical impact.	Poor

HEPATITIS B VACCINE

1. INTRODUCTION

Hepatitis B (HB) is a major chronic viral illness worldwide with long-term complications of cirrhosis and hepatocellular carcinoma resulting in high morbidity and mortality. As treatment is far from satisfactory the best strategy is prevention. These include public education to create awareness of the disease, avoidance of at-risk behaviour and possible sources of transmission, strict adherence to universal precautions and good infection control procedures, including adequate sterilisation and safe handling of all clinical specimens, passive immunisation with HB immunoglobulin (HBIG) and active immunisation with HB vaccine (inactivated HbsAg particles adsorbed on aluminium hydroxide adjuvant).

The HB vaccine is an inactivated vaccine. There are two types i.e. plasma-derived and recombinant vaccines. HB immunisation provides adequate protection in the majority of recipients and prevents both vertical and horizontal transmission, thus reducing the pool of chronic carriers responsible for spreading HB infection. In the long-term, it is hoped this will lead to elimination of HB from mankind. This is recognised by the World Health Organisation, which recommended that all countries adopt such an immunisation strategy by 1997. Immunisation of laboratory and hospital staff was implemented in 1988. National mass HB immunisation programme was started in Malaysia in January 1989. The Ministry of Health of Malaysia has been supplying free HB vaccine to all newborns from January 1989 at the implementation of nationwide EPI mass HB immunisation programme. From 1989 to 1993, the recombinant HB vaccine, Engerix B (Smith, Kline and Beecham) was used. In 1994, a low-cost plasma-derived HB vaccine, HB vaccine-KGCC (Korean Green Cross Corporation, Seoul, Korea) was introduced and was in use until 1997. From early 1997, a recombinant yeast derived HB vaccine, Euvax B (Lucky Pharmaceutical Division, Dae Jeon, Korea) has been given to all newborns. However, other vaccines are available to private clinics and hospitals.

1.1 Disease Pattern

1.1.1 Hepatitis B infection

Viral hepatitis B is caused by the HB virus, a double-stranded DNA virus of the hepadnavirus family (Mowat, 1995). The virus has an inner nucleocapsid core (HbcAg) which produces Hepatitis B encoded antigen (HbeAg) that is found in the blood during massive viraemia. These patients are most infectious. The outer lipoprotein coat has the S gene that encodes HbsAg and has three start codons for pre-S1, pre-S2 and S proteins. A number of genetic variants of HB virus (mutants) evoke unusual and ineffective immune responses. These patients develop HbsAg replication in spite of adequate concentrations of anti-Hbs after HB immunisation. Mutants developing in HbsAg positive mothers with anti-Hbe have caused fulminant hepatitis in their infants. The incubation period is 60-110 (mean 90) days but may range from 30-180 days.

Transmission can occur vertically from an HbsAg positive mother to her newborn, or horizontally from an HbsAg-positive family member/ close contact (e.g. drug abusers, sexual contact, chronic renal failure patients, organ transplant, immigrants from high carrier rate areas, and via fomites/ abrasions like with toothbrushes and sharp objects like razors), and

blood/ blood products (e.g. haemophiliacs, thalassaemics). However, approximately a third of the cases result from unknown sources.

The single most important epidemiological feature affecting endemicity is the age at which infection is acquired. In areas of high endemicity, infection is mostly acquired perinatally from mother to child (vertically) or horizontally in early childhood (Australian Immunisation Handbook, 1997; Beasley, 1983; Stevens, 1975). Chronic infection occurs more frequently in these cases, with 65-93% at risk of chronicity (compared to only 6-10% risk of chronic HB in infections acquired in adult life). Worldwide, this mode of transmission is responsible for 40% of HB infections annually. Although long-term carriage of HB in children is usually asymptomatic (Stevens, 1975), chronic infection can progress to chronic hepatitis, cirrhosis, fulminant liver failure and hepatocellular carcinoma. (Chang, 1989).

1.1.2 Acute HB infection

Acute infection is usually mild and produces asymptomatic acquisition of HbsAg or an anicteric hepatitis that rarely causes mild fever, abdominal pain, vomiting, anorexia, arthralgia, and rash. A rise in transaminases can occur with 20% being still abnormal after a year. Fulminant hepatitis with a mortality of 60-70% occurs in less than 1% of cases, mainly in infants born to HbsAg positive mothers who are HbeAg negative but anti-Hbe positive due to mutant viruses.

1.1.3 Chronic HB infection

Chronic carriers have serum HbsAg for longer than 6 months. A persistent carrier state occurs in 70-90% of acute infections in infancy and declines to 6-10% in infections after the 6^{th} year of life. Many chronic carriers are asymptomatic and a potential source of infection. This phase is followed by the immune clearance phase characterised by relapses and remissions and evidence of chronic hepatitis. This reflects the body's attempts at clearing the virus. Asymptomatic carriers tested positive with normal liver enzymes are considered "healthy" carriers, and about 20% of these carriers progress to cirrhosis years later. Patients with active viral replication (HbsAg and HB viral DNA positive) are at greatest risk.

1.2 Incidence

1.2.1 Incidence worldwide

HB is the most prevalent chronic viral infection, with an estimated 300-400 million HB virus carriers worldwide and 50 million new cases annually (Merican, 1998). There are 1.5 million deaths per year, approximately 30% of which are related to complications of underlying liver disease. More than 1 in 100 infants born around the world are expected to die from HB annually. The prevalence of HB in children parallels that in adults. Carrier rates vary geographically: United States, Northern Europe, Australia 0.1-0.2%; Mediterranean, Eastern Europe, USSR, Central and South America, China, Africa 1-5%; Central Africa, South East Asia up to 10 %. Nearly 80% of all HB carriers are in Asia and chronic HB accounts for up to 80% of deaths due either to cirrhosis or liver cancer.

1.2.2 Incidence in Malaysia

In Malaysia, the incidence of HB has declined from 9.38 per 100 000 population in 1988 to 2.97 per 100 000 population in 1996. However, there are still about 1 million hepatitis

B carriers in this country or 5% of the total population (Merican, 1998). The HB carrier rate in Malaysia has been reported to be 3.1% in the normal population (Tan, 1986) and 6.9% in adult healthy blood donors (Ton, 1983), with a higher prevalence rate in certain at-risk populations like intravenous drug users (Mangalam, 1986), promiscuous heterosexuals (Rajakumar, 1984), and health care personnel (Ton, 1984).

To ensure safe blood transfusion, the National Centre for Transfusion Services in Malaysia started blood donor screening for HbsAg in 1987 using the immunoelectroosmophoresis (IEOP) method. Preliminary screening of blood donors revealed an overall prevalence of 1.4% (Lopez, 1985). There appeared to be a higher prevalence in Chinese (2.2%) compared to Malays (1.6%) and Indians (0.4%). A very high prevalence was noted in East Malaysians (11.4%). This is about 17 times higher than the rates observed in blood donors in the United Kingdom and United States, where the carrier rate was less than 0.1% then. In 1979, the more sensitive radio immunoassay (RIA) method for screening Hbs Ag was introduced. In 1984, an overall prevalence of 3.14% was found (Chinese 5.02%, Malays 2.9%, Indians 0.8%). The relatively low positive rate among Indians has been a consistent finding in other seroepidemiological studies. Hence, studies in Malaysia show a high prevalence rate of HB infection, with carrier rates ranging from 3-11% depending on ethnic group. In a study in Singaporean Chinese children, the HbsAg prevalence was higher in males than females (Quak, 1982).

In 1985, a survey of pregnant women in Kuala Lumpur showed that 10.1% of Indonesian mothers, 5.6% Chinese, 2.2% Malays and 0.8% Indians were HbsAg positive. Forty-one point one percent of all mothers who were HbsAg positive were also HbeAg positive (Ton, 1982).

1.3 HB Vaccine

1.3.1 Vaccine Characteristics (including schedule and route)

The HB vaccine consists of non-infectious, inactivated subunit HbsAg particles. In the plasma-derived vaccine, the HbsAg is from HbsAg-positive pooled donor plasma (Hepatitis B Vaccine-KGCC). In the recombinant vaccines the HbsAg is derived from genetically-engineered Saccharomyces cerevisae yeast cells (EuvaxB, Engerix-B, HB Vax II) or H. Polymorph yeast (Hepavax Gene). A portion of the hepatitis B virus gene, coding for HbsAg is cloned into yeast and the vaccine is produced from cultures of this recombinant yeast strain. This is followed by adsorption onto aluminium hydroxide and addition to thiomersal 0.005% preservative. The vaccines are white, opalescent liquids and are stored at 2-8^{o}C but NOT frozen. The cold chain should always be maintained. Currently, licensed products contain different concentrations of antigen per ml.

Table 1: Types and Formulations of HB Vaccines Available in Malaysia

Name and Manufacturer	Type of Vaccine	Recommended Age	† Dose (Volume)
Hepatitis B Vaccine-KGCC	Plasma-derived	< 10 years	10 mcg (0.5ml)
(Korean Green Cross Corporation, Korea)		>10 years, adults	20 mcg (1.0ml)
EUVAX-B	Recombinant	< 10 years	10 mcg (0.5ml)
(LG Chemical Ltd. Niche Pharma		>10 years	20 mcg (1.0 ml)
Corporation Sdn. Bhd.)		Dialysis patients	40 mcg (2.0 ml)
Engerix B	Recombinant	0-12 years*	10 mcg (0.5ml)
(Smith-Kline Beecham)		Adults	20 mcg (1.0 ml)
		Intradermal dose	2 mcg (0.1 ml)

HB Vax II (Pasteur Merieux MSD)	Recombinant	0-10 years 11-19 years Adults (>20y) Dialysis formulation	2.5mcg (0.25ml 5 mcg (0.5ml) 10mcg (1.0 ml) 40mcg (1.0 ml)
Hepavax Gene (Korean Green Cross Corporation, Korea)	Recombinant	< 10 years > 10 years Adults	10 mcg (0.5 ml) 20 mcg (1.0 ml)

Note: * *up to 16 years if full compliance to schedule guaranteed*
† *more commonly used dosages and volumes.*

1.4 Primary Immunisation

The **standard schedule** is the 3-dose schedule. For newborn and infants (age cut-off times differ for different vaccines), the first dose of 0.5ml is given at birth intramuscularly in the anterolateral of the thigh. For older adolescents and adults, 1 ml is given intramuscularly in the deltoid muscle. The second dose is given 1-2 months after the first dose and the third dose at 5-6 months after the first dose. It is never given in the buttock. (i.e. doses at 0, 1 and 5-6 months).

In Malaysia, the current HB immunization policy is as follows:

i. Infants of HbsAg negative mothers should receive three doses of recombinant HB vaccine at birth, at 1 month and at 5 months of age.
ii. Infants of HbsAg or HbeAg positive mothers receive the three doses of HB vaccine at birth, at 1 month and at 5 months of age, and in addition are advised to be given dose of HBIG at birth.
iii. However, since currently, there is no compulsory/routine screening of pregnant women for HbsAg status, all newborns receive three doses of recombinant HB vaccine at birth, at 1 month and at 5 months of age.
iv. Immunisation of high-risk older children, adolescence and adults who are HbsAg negative is encouraged. The vaccine is given free of charge up to the age of 12 years.

2. METHODOLOGY

An electronic search of MEDLINE database using various keywords, and year limits was carried out. In addition, three country immunisation handbooks (USA, UK, Australia) WHO reports, Ministry of Health reports and. other important references were obtained from various sources. Additional data was obtained from surveillance by the Disease Control Division, Ministry of Health of Malaysia, while literature on vaccines from pharmaceutical companies was also used. The keywords used and the year limits were as follows:

Key words used for search and years searched

a. Hepatitis B vaccine and children 1990-1999
b. Malaysia and hepatitis B vaccine 1967-1999

The results are summarized below:

- Total electronic (Medline) search = 895
- Relevant titles (pertaining to hepatitis B vaccine & in English & in humans) = 429

- Abstracts reviewed = 250
- Full papers reviewed = 114
- Papers not available (abstracts used) = 136
- Books and reports reviewed (sections used) = 4

3. RESULTS

3.1 Vaccine Efficacy

The HB vaccine is highly immunogenic in infants and children who complete a 3-dose vaccination sequence (Liao, 1999; Lin, 1999; Kato, 1999; Assad, 1999; Al-Faleh, 1999; Wu, 1999; Okoth, 1998; Del Canto, 1997; Whittle, 1995; Xu, 1995). The use of this 3-dose regimen has been shown to be highly efficacious. The vaccine is effective in preventing HB infection in individuals who produce specific anti-Hbs. Approximately 95-100% achieve seroprotective levels of anti-Hbs (>10mIU/ml) after 3 doses (Poovarawan, 1997; Giammanco, 1998; Pichichero, 1997(Steven, 1992). These rates are unaffected by concurrent administration of HBIG to infants born to HBeAG/HbsAg positive mothers. The frequency of seroconversion increases progressively from approximately 35% after the first dose, to over 90% after the third injection. There is evidence of immunity in most vaccinated subjects after two doses of the 3-dose regimen. However, the third dose is necessary to increase the percentage of response and may provide longer protection.

The usage of smaller doses of vaccine (2.5 or 5 micrograms) showed a lower antibody level compared to the 10 micrograms per dose regime. Although a standard dose of 10 microgram per dose is said to be a better choice than the lower dose, the Singapore study over a period of 4 years showed that the lower dose regimen was equally effective and that no booster is necessary for at least 4 years after immunisation (Goh, 1992). In studies, although vaccine dose was an important predictor of antibody persistence, particularly before 5 years of age, the dosage did not have a strong association with risk of infection (Goh, 1992; Van Herck, 1999; Wu, 1999; Steven, 1992). Table 2 below indicates a classification of response according to Anti-Hbs levels:

Table 2: Levels of Anti-Hbs and Classification of Response

Anti- Hbs level (mIU/ml)	Classification of Response
< 10	Non-responder
10 – 100	Poor responder
> 100	Good responder

Recombinant vaccines appear to induce somewhat lower geometric mean levels of anti-Hbs, but similar rates of seroconversion and protection as compared to the plasma-derived vaccines (Fang, 1994; Sinniah, 1994; Aristegui, 1995). Higher (double) doses may be required in patients who are known to be poor responders (Rosman, 1997) including chronic renal failure patients (Vazquez, 1997), haemodialysis patients, HIV positive and other immunosuppressed patients (those on immunosuppressive therapy, post transplant, patients with primary immunodeficiency).

3.1.1 Booster doses

The need for booster doses of HB vaccine is still unclear because of a lack of pertinent data on infection in persons at different levels after immunization, and on the duration of antibody persistence (Bulkow, 1998; Tilzey, 1995). The relationship between the duration of

protection and the level of anti-Hbs is still uncertain (Goh, 1992). Low or undetectable levels of anti-Hbs may not necessarily indicate loss of protection (Van Herck, 1998). Anti-Hbs levels greater than 100mIU/ml persist in some individuals for much longer than 5 years and there is evidence that protective immunity is still present when anti-Hbs levels have fallen below 100 mIU/ml (Bulkow, 1998). Studies show that there is a direct correlation between the peak initial response to HB vaccine and the persistence of antibody beyond 10 years (Van Herck, 1999; Wu, 1999; Steven, 1992).

A single booster dose of 1ml of vaccine, 5 years after completion of a primary course, is sufficient to retain immunity in those who continue to be at risk of infection. The use of booster doses is generally not recommended for those under 10 years of age who were immunised as neonates or young children. Poor responders should receive a booster dose, while non-responders should receive a repeat course of vaccine (Shahana, 1995). .

Although some individuals lose circulating levels of anti-Hbs many years after immunisation, an anamnestic response to a booster dose of vaccine usually occurs (Moyen, 1990). Exaggerated or rapid rise of anti-Hbs in response to wild-type HB virus or a booster of HB vaccine was seen in individuals with no or low anti-Hbs titre (Van Herck, 1999; Wistrom, 1999; Goh, 1992;). Anamnestic responses also occur more frequently at around 4 years of age (Lai, 1993). Anti-Hbs levels gradually wane over time and the duration of maintaining protective levels correlates strongly with the peak level achieved, and hence the long term risk of HB infection. The risk of late infection increased markedly when antibody levels decreased below 10 mIU/ml (Hadler, 1986).

Thus, available evidence indicates that because of the persistence of immunological memory, a booster dose may not be indicated in vaccinees that have responded to the full regimen of immunisation.

3.1.2 Vaccine efficacy in carriers

Maternal transmission of HB in endemic areas is responsible for a large proportion (40-50%) of the total carrier pool. An early age of infection substantially increases the overall burden of chronic carriage in endemic regions (Poovorawan, 1997; Conjeevaram, 1995). The overall vaccine protection against HbsAg carriage is 96-99% at 1 year of age (Poovorawan, 1997) to 80-83% at 5 years of age (Lee, 1995; Xu 1995) in infants born to mothers with HbeAg. Maternal anti-Hbc antibody disappeared in 99% children before 2 years of age. 4 % of these children became hepatitis B carriers (HbsAg positive) before 1 year of age and 12% have persistence or reappearance of anti-Hbc in HbsAg negative children (Lee, 1995). Many studies demonstrate that vaccination with HB vaccines, with the first dose given at birth clearly prevents perinatal transmission of HBV infection in infants of HBV carrier mothers (Ding, 1993; Stevens, 1992). In some studies, protection was found to be higher if HBIG was given with the first dose of HB vaccine at birth (Sangfelt, 1995; Xu, 1985; Wong, 1984; Beasley, 1983). In other studies, no difference in protective efficacy was found whether HBIG was given at birth (Poovorawan, 1997; Poovorawan, 1992; Lo, 1985). In the UK and Australia, early antenatal screening or screening at delivery is recommended for mothers with established risk factors (i.e. where group carriage rate is > 2%). These babies who are born to HbeAg/HbsAg positive mothers or mothers with acute hepatitis during pregnancy are given intramuscular injection of HBIG 100 IU (0.5 ml) within 12 hours of birth (not later than 48 hours), as well as active immunisation. HBIG. Although the best results in preventing perinatal infection is achieved by combining passive and active immunisation at birth, the cost of specific HBIG is prohibitive in many parts of the world. In highly endemic areas

where perinatal transmission plays a key role in maintaining chronic HB carriage, the only realistic hope for HB control is universal immunisation of all newborns with HB vaccine without HBIG. This compromise may give the best prospect of protection to the greatest number of children (Mowat, 1995). For infants born to HB carrier mothers, an accelerated schedule (0,1,and 2 months) has been used where a more rapid immunisation is required. However, a booster may be necessary at 12 months (Wu, 1999; Steven, 1992).

3.1.3 Vaccine efficacy in premature babies

Some preterm babies do not respond as well as normal term babies to HB vaccine. In premature babies, the chance of being a high responder to HB vaccine (high anti-Hbs level) positively correlates with an increase in gestational age (Kesler, 1998; Daksba, 1997; Chirico, 1993; Chawareewong, 1991) and birth weight (Lau, 1992; Lay, 1985). These studies recommend that for preterm babies born to HbsAg negative mothers, not at immediate risk of exposure to HB, the 1st dose of vaccine can be deferred until the infant weighs 2000g or more (Genesca, 1985; Huang, 1997). The 1st dose can be given at birth with additional doses at 1,6, (12) months (preferably with measurement of anti-Hbs levels 2-4 months after the last dose) or to delay immunising babies with birth weights less than 2000g until 2 months of age using the 3 dose schedule (i.e. at 2,3 and 8 months of age) and preferably measuring anti-Hbs levels after the 3rd dose.

However, babies born to HbsAg positive mothers are at immediate risk of contracting HB infection and immunisation with HBIG should be given at birth (American Academy of Pediatrics, 1994; Sanvapat, 1994). HBIG will protect these preterm babies who have slow development of antibody production to the first dose of HB vaccine at birth. (Del Canto, 1993) Other studies show that birth weight did not affect the immunogenicity of the vaccine after completion of three doses at the end of 1 year (Sanvapat, 1994; Del Canto, 1993).

3.1.4 Vaccine efficacy in HIV positive cases

HB vaccine may be given safely to HIV positive persons who are not infected or immune to HB. However, response rates are poor (Rustein, 1994; Zuccotti, 1994; Arrazola, 1995), and high (double) dosage has to be given on 3 occasions. Anti-Hbs levels should be measured on completion of last dose.

3.1.5 Accelerated immunisation schedule

This schedule has been used where more rapid immunisation is required e.g. instances of exposure to very high risk HB positive blood, to prevent perinatal transmission (Marsano, 1996; Goldfarb, 1994). In this schedule, the 2nd dose is given a month after the 1st dose, the 3rd dose 2 months after the 1st dose with a booster dose at 12 months (i.e. doses at 0,1,2 and 12 months). Different dosing regimens have also been used (Rosman, 1997; Marsano, 1996; Goldfarb, 1994; Bassily, 1995).

3.1.6 Combination vaccines

The HB vaccine is available in combination with other vaccines that have been developed to reduce the number of painful injections while maximising protection with a single injection and improving compliance and uptake of immunisation. Combination vaccines include a tetravalent vaccine consisting of diphtheria, tetanus and whole cell pertussis vaccine combined with HB vaccine, and a bivalent vaccine consisting of Haemophilus influenzae type b combined with HB vaccine. Studies show that these combination vaccines are safe and as immunogenic as the individual vaccines (Fendrick, 1999; Giammanco, 1998; Chiu, 1998; West, 1997; Aristegui, 1995). However, these combinations are more expensive.

3.2 Route of Administration

HB vaccine should normally be given intramuscularly into the anterolateral thigh in babies and the deltoid muscle in adults and older children. The vaccine should not be injected into the buttock because this results in lower seroconversion rates and reduced vaccine efficacy, possibly due to injection into fatty tissue. However, in hemophiliacs, subcutaneous or intradermal route may be used. The likelihood of an effective antibody response is however reduced following use of the intradermal route (Li Volti, 1998; Pegues, 1995).

3.3 Programme Effectiveness

Implementation of mass immunisation programmes has been successful in reducing rates of HB carriage in various countries (Lin, 1999; Goh, 1997; Wainwright, 1997; Del Canto, 1997; Lansang, 1996; Kim, 1995; Whittle 1995; Coursaget, 1994).

3.3.1 Population acceptability

Many studies have shown that the HB vaccine is acceptable to the population. Some of the factors that improve compliance are early visits of infants to the doctor postnatally (Ross, 1998); awareness to adherence model of pediatricians/ doctors attitudes (Freed, 1996; Freed, 1994; Pathman, 1996), telephone or computerised remainders (Alemi, 1996). On the other hand some of the reasons for poor compliance are fear of contracting the HB virus from the vaccine, immunisation scheduling difficulties or lack of time to get immunised (Lee, 1995); poor level of education of patient (Sellors, 1997); attitudes and behaviour 'pain, time, money' 'inconvenience', 'lazy', 'lack of interest' (Cimas-Hernando, 1994); financial barriers (Sharfstein, 1997); poor education of patients by doctors (Zola, 1997) and poor level of awareness and understanding about the vaccine (Briggs, 1994)

3.4 Vaccine Safety and Side Effects

HB vaccine is generally well tolerated and safe. The most common adverse reactions are:

a) Transient, minor soreness and redness at the injection site (5-15%), low-grade fever (2-3%), nausea, dizziness, malaise, rash, an influenza-like syndrome, arthritis, arthralgia and myalgia. These reactions occur less frequently in infants and children than adults. These resolve within 24-48 hours of vaccine administration. The frequency of these reactions decreased with subsequent doses of vaccine.
b) Anaphylaxis is very rare (usually in adults).
c) Serious suspected neurological diseases e.g. Gillian Barre syndrome, demyelinating diseases have rarely been reported, but there is inadequate evidence to either accept or reject the possibility of a causal relationship with HB (Pirmohamed, 1997; Shaw, 1988). A possible association was found between Guillian-Barre Syndrome and receipt of plasma-derived vaccine in adults, but not with recombinant vaccines in children (Shaw, 1988).
d) A few reports of generalised febrile reactions attributed to yeast allergy (Grotto, 1998), lichenoid reaction (Saywell, 1997), inflammatory joint disease (Ferazzi, 1997) and periarteritis nodosum.

3.5 Cost Effectiveness

Many studies have been done confirming cost savings when routine HB immunisation is incorporated into their existing childhood Expanded Programme of Immunisation. These studies use modeling to measure cost effectiveness as the net cost per Quality-Adjusted Life Year (QALY) and other economic analytical methods (Alimonos, 1998; Shepard, 1995).

The cost benefit of the mass HB Immunisation Programme in Malaysia is difficult to compute. Apart from unquantifiable indices such as lives saved, suffering and morbidity of chronic liver disease and liver failure, man-hours of work, the actual financial cost to the government, health sectors and the community varies with the facilities that are available to detect and treat the disease and its complications.

4. CONCLUSION

There is sufficient evidence of effectiveness and high immunogenicity, and safety of the HB vaccine. In addition, there is sufficient evidence of cost savings with routine HB immunization.

5. RECOMMENDATIONS

It is recommended that the current HB immunization schedule of all newborns receiving three doses of recombinant HB vaccine at birth, at 1 month and at 5 months of age be continued.

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plasma-derived vaccine without booster doses in children. Hepatology 1999 Mar; 29(3): 924-7.

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7. EVIDENCE TABLE
HBV

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Efficacy				
1.	Liao SS, et al. *Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow -up study among Chinese children.* Vaccine 1999 Jun; 17(20-21): 2661-6.	Randomized, double blind, placebo-controlled trial. 649 children. Follow -up -15 years.	Vaccine efficacy of 96% was shown. Only 1.9% of vaccinated children developed HbsAg positivity compared to 16.7% in the control group.	Good
2.	Del Canho F, et al. *Ten-year neonatal hepatitis B vaccination program, The Netherlands, 1982-1992: protective efficacy and long-term immunogenicity.* Vaccine 1997 Oct; 15(5): 1624-30.	Meta-analysis of 3 randomized, controlled trials. 705 infants born to HbsAg-positive mothers. Follow-up- 5 years.	1.1% of all infants of Hbe-Ag mothers became HbsAg carriers within 1 year of life. Protective efficacy rate (PER) of active-passive immunization at 12 months was 92%, mainly due to by maternal HBV-DNA levels i.e. PER was 100% if maternal HBV-DNA < 150pg/ml and 68% if HBV-DNA>150pg/ml.	Good
3.	Xu Zy, et al. *Long-term efficacy of active post-exposure immunization of infants for prevention of hepatitis B virus infection. United States-People's Republic of China Study Group on Hepatitis.* J Infect Dis 1995 Jan; 171(1): 54-60.	Placebo-controlled trial. 166 infants. 5-year follow-up.	At the end of 5 years, 80% immunized infants continued to have protective levels of anti-Hbs.	Fair
4.	Lin X, et al. *Long-term efficacy study of hepatitis B vaccination in newborns-results of 11 years' follow-up*. Chung Hua Liu Hsing Ping Hsueh	Randomised, controlled trial. 3578 children. Follow -up 11 years.	Very low HbsAg positivity of 0.46-0.98% from the 1st - 11th year. Long-term efficacy was 85.42% in vaccinated group. Efficacy of HB vaccine long lasting and a booster dose not necessary up to age 11 years.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Tsa Chih 1999 Jun; 20(3): 174-7.			
5.	Kato H, et al. *Long term efficacy of immunization against hepatitis B virus in infants at high risk analyzed by polymerase chain reaction* Vaccine 1999 Nov; 18(7-8); 581-7.	Cohort study. 251 infants. Follow -up 4-6 years.	251 high-risk infants were given HBIG at birth and a course of HB vaccine. 36% at 1 year follow-up and 14% at 4-6 years follow-up had HBV-DNA detected by PCR. Conclusion: Most of HB infections occur early, during the 1st year. Immunisation against HB effectively protects infants at high-risk against viral transmission, at least up to 4-6 years.	Fair
6.	Al-Faleh FZ, et al. *Sero-epidemiology of hepatitis B virus infection in Saudi children 8 years after a mass hepatitis B vaccination programme.* J Infect 1999 May; 38(3): 167-70.	Cohort study. 4791 children. Follow-up 8 years.	HbsAg carrier rate fell from 6.7% (pre-vaccination era) to 0.3% (8 years post-vaccination programme initiated.) Overall, seroconversion after HB vaccine is 77%. Tremendous impact of the mass HB vaccination programme on the seroepidemiology of HB infection in Saudi Arabia.	Fair
7.	Wu JS, et al. *Hepatitis B vaccination in high-risk infants: 10-year follow-up.* J Infect Dis 1999 Jun; 179(6): 1319-25.	Cohort study. 805 children. Follow-up 10 years.	At 10 years, cumulative persistence of anti- Hbs was 85% and cumulative incidence of HB virus infection was 15%. 12-month anti-Hbs titre was the strongest predictor of efficacy: the higher the initial titre, the lower the risk of anti-Hbs loss. Maternal HbeAg-positivity correlates with lower level of anti-Hbs persistence. Because the level of anti-Hbs persistence remained high and few became carriers, booster revaccination within 10 years seems unnecessary.	Fair
8.	Okoth FA, et al. *Human plasma-derived hepatitis B vaccine: Kenyan experience.* East Afr Med J 1998 Nov; 75(11): 647-8.	Cohort study. 107 vaccinees. Followed up for 1 month after the 3rd dose of HB vaccine.	97% developed anti-Hbs. HB vaccine produced good immune response in vaccinees.	Fair
9.	Da Villa, et al. *Persistence of anti-Hbs in*	Cohort study. Follow-up 5-10 years.	97% subjects given recombinant vaccines and 80.4 % subjects given plasma-derived vaccine have protective	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	children vaccinated against viral hepatitis B in the first year of life. Vaccine 1996 Nov; 14(16): 1503-5.		anti-Hbs levels. 95.9% subjects given booster dose developed anti-Hbs levels showing the presence of a solid immunological memory.	
10.	Yuen MF, et al. *12 -year follow-up of a prospective randomized trial of hepatitis B recombinant DNA yeast vaccine versus plasma-derived vaccine without booster doses in children.* Hepatology 1999 Mar; 29(3): 924-7.	Randomized cohort study. 318 children Follow-up 12 years.	Long-term protective immunity was better with 3 doses than with 2 doses of vaccine i.e. 81.4 % vs. 60.4% with protective anti-Hbs levels. Booster doses were not necessary because of effective anamnestic response.	Fair
Plasma-Derived Vs Recombinant Vaccines				
1.	Fang JW, et al. *Female children respond to recombinant hepatitis B vaccine with a higher titre than male.* J Trop Pediatr. 1994 Apr; 40(2): 104-7.	Randomised CT. 180 children randomised. 6 defaulted & 3 anti- Hbc positive and excluded. Followed-up for 6 months.	All children included in study attained anti-Hbs titre> 10MIU/ml (highly immunogenic). Female children responded with higher peak titres. No, major side effects (safe).	Good.
2.	Sinniah M, et al. *Immunogenicity of a Plasma-derived Hepatitis B Vaccine in Children and Adults.* Med J Malaysia. 1994 Dec; 49(4): 336-40.	Cohort study. 73 children vaccinated. Followed-up for 300 days.	Plasma - derived HB vaccine after the 3rd dose has good (100%) seroconversion.	Fair
Different Dosing Regimens				
1.	Rosman AS, et al. *Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial.*	Randomized, double blind trial. 110 patients. Follow-up for 12 months after the 1st dose of	2 groups: Standard dose vaccine i.e. 20ug at 0, 1 and 6 months OR 40ug at 0, 1, 2 and 6 months. Anti-Hbs measured 12 months after 1st dose. 75% of high-dose regimen seroconverted. Mean titre anti-Hbs greater in high dose	Good.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Am J Med. 1997 Sep; 103(3): 217-22.	vaccine.	group. A high & accelerated dose regimen improves the serological response & is recommended in haemodialysis patient.	

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Marsano LS, et al. *Comparison of a Rapid Hepatitis B Immunization Schedule to the Standard Schedule for Adults.* Am J Gastroenterol 1996; 91(1): 111-5.	Prospective, randomized, single-blinded, controlled trial. 230 HbsAg negative Volunteers. Follow-up -7 months.	The rapid schedule vaccination gives a rate that is quicker but identical to the rate of seroconversion of the standard schedule.	Good
3.	Goldfarb J, et al. *Comparative study of the immunogenicity and safety of two dosing schedules of Engerix-B hepatitis B vaccine in neonates*. Pediatr Infect Dis J. 1994 Jan; 13(1): 18-22.	Randomized, multicentre study. 2 groups of newborns: Routine vaccination at 0,1& 6 months vs. accelerated schedule of 0,1& 2 months in. 222 infants tested data.	Accelerated schedule developed seroprotectivity more quickly. 92.6% vs. 66.1% had seroprotectivity at 3 months. However, Geometric Mean Titres at 7 months were lower in accelerated schedule; 420.0 vs. 3141.8 mIU/ml. The effectiveness in preventing perinatal infections and necessity for booster remains to be studied.	Good.
4.	Bassily S, et al. *Comparative study of the immunogenicity and safety of two dosing schedules of Hepatitis B Vaccine in neonates.* J Trop Med Hyg1995; 53(4): 419-22.	RCT 590 infants randomized to 3 groups: Grp A- 2.5ug given at 0, 2 & 6 months; Grp B- 2.5ug given at 2, 4 & 9 months; Grp C (Control)- only BCG, DPT, polio & measles given. Follow-up for 18 months.	85% and 96% of grp A & B respectively developed good immune responses. Recombinant Hepatitis B vaccine is safe & immunogenic in either regimen. However, delay of booster dose until 9 months after birth produced a higher response.	Good.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Combination Vaccines				
1.	Chiu HH, et al. *Diphtheria, tetanus and whole cell pertussis vaccine combined with hepatitis B vaccines: a comparison of two doses (10 microg and 5 microg).* Pediatr Infect Dis J. 1998 Mar; 17(3): 206-11.	Double blind, randomized, 2-armed, single centre study. 120 infants. Follow-up samples of anti-Hbs taken at birth and pre and post vaccination. Vaccine given at birth then at 1.5, 3.5 & 6 months. (Randomized to have 10 or 5 microg**).**	Both groups had similar reactogenicity profiles. Group 1 (given 10 microg) had higher protective titres of anti-Hbs than Group 2 (given 5 microg); 696 vs. 488 mIU/ml. Both tetravalent vaccines are safe and immunogenic. DTPwHB vaccine may play an important role to promote integration of HB vaccine into the EPI in hepatitis B-endemic areas	Good.
2.	West DJ, et al. *Safety and Immunogenicity of a bivalent Haemophilus influenzae type b/ hepatitis B vaccine in healthy infants. Hib Vaccine Study Group.* Pediatr Infect Dis J. 1997 Jun; 16(6): 593-9.	Open, multicentre, randomized trial 882 infants randomized to receive Hib/HepB or concurrent Hib vaccine & HepB vaccine at 2. 4 12 and 15 months Follow-up at each vaccination and 2 months after 2nd and 1 month after 3rd vaccine dose.	COMVAX was well tolerated and immunologically comparable to concomitant injections.	Good.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Different Routes of Administration (Intramuscular Vs Intradermal)				
1.	Li Volti S, et al. *Hyporesponsiveness to intradermal administration of hepatitis B vaccine in insulin dependent diabetes mellitus.* Arch Dis Child 1998; 78: 54-7)	Cohort (with control) study. 18 IDDM compared with 24 healthy children. Follow-up 7 months.	Anti-Hbs measured at 4-5 weeks after last dose of vaccine. Statistically lower immune response in IDDM in intradermal group. Similar response in both IDDM and controls in intramuscular group. Poor response due to impaired macrophage activity resulting in failure of antigen presentation. Hepatitis B vaccine should be given intramuscularly in IDDM.	Fair.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Pegues DA, et al. *Immune response to Intramuscular Revaccination after Primary Intradermal Vaccination against Hepatitis B.* Clin Infect Dis. 1995 Feb; 20(2): 335-41.	Cohort study. 136 patients who did not respond to 3 doses of intradermal HBV. Followed-up 14 and 210 days.	61% of initial no responders, 96% of lost responders and 31% of new vaccinees developed seroconversion. Persons who do not seroconvert after intradermal vaccination should receive 3 doses of hepatitis vaccine intramuscularly.	Fair
Babies of Hb Positive Mothers				
1.	Poovorawan Y, et al. *Long term hepatitis B vaccine in infants born to hepatitis e antigen positive mothers.* Arch Dis Child 1997; 77;F47-F51.	Cohort study. 243 infants. Hepatitis B vaccine given at 0,1 and 6 months or 0, 1,2 and 12 months with or without Ig at birth. Follow-up 8 years.	At 12 months, overall vaccine protection was 96.2%. No chronic carrier beyond age of 3 years. Vaccine provides immediate protection against HbsAg carriage and long-term protection against fetally acquired HbsAg. At 60 months, hepatitis B serological markers without disease, indicating re-exposure to HBV, reappeared in 5/167 children (boostered and non-boostered)	Fair
2.	Lee PI, et al. Long-term efficacy of recombinant hepatitis B vaccine and risk of natural infection in infants born to	Cohort study 171 infants. Follow-up for 5 years.	4% chronic carriers before 1 year of age and persisted until end of study. Seropositivity for anti- Hbs dropped from 99% at 1 year to 83% at 5 years. Maternal anti-Hbc disappeared in	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	mothers with hepatitis B e antigen. J Pediatr 1995 May; 126(5): 716-21.		99% children before 2 years of age. Natural infections occurred in 12%. Long-term protection with hepatitis B vaccine is satisfactory and a booster at 5 years is unnecessary.	
3.	Sangfelt P, et al. *Prevention of Hepatitis B by immunization of newborn infant- a long-term follow-up studies in Stockholm, Sweden.* Scand J Infect Dis. 1995 Dec; 27: 3-7.	Cohort study. 212 babies. Follow-up 2-9 years.	Children born to HbeAg positive mothers should receive HBIG with vaccine, whereas Children with mothers HbeAg negative, vaccine only sufficient.	Fair
4.	Poovorawan Y, et al. Long-term efficacy of hepatitis B vaccine in infants born to hepatitis Be antigen-positive mothers. Pediatr Infect Dis J, 1992; 11(10): 816-21.	Cohort study. 263 infants. HB vaccine given at birth, 1,2 & 12monthsEnrolled consecutively to receive/ not to receive HBIG; or HB vaccine given at birth, 1 & 6 months & randomised to receive HBIG or not. Follow up 2-4 years.	No statistical difference in long-term protective efficacy bet the 2 schedules or bet use of vaccine alone or vaccine plus HBIG.	Fair.
Preterm/ Low Birth Weight Babies				
1.	Kesler K, et al. *Immune responses of prematurely born infants to hepatitis B vaccination: results through three years of age*. Pediatr Infect Dis J. 1998 Feb; 17(2): 116-9.	Cohort study. 69 prem babies. 108 full term babies. Comparing response of prem to full term babies to hepatitis B vaccine. Followed -up 3 years.	Both early and late samples of anti-Hbs from prem babies were lower than in full term babies. Late sample had lower titre than earlier sample. Prem and term babies have similar decline in anti-Hbs titre during first 3 years, but prem generally have lower titre. The immunogenicity of the vaccine beyond 3 years & need for revaccination requires further study.	Fair
2.	Daksba MP, et al.	Cohort study. 2 groups:	Infants immunised early (within 3 days) had a response	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Immunogenicity of hepatitis B vaccine in healthy very low birth weight infants. J Pediatr 1997; 130(4): 641-3.	22 infants < 1000g & 28 infants 1001-1501g Hepatitis B vaccine given at 0, 1 and 6 months. Follow-up anti-Hbs taken before 1st dose and 6 weeks after 2nd dose and 8 weeks after 3rd dose.	rate of 68%. If immunisation was initiated at 1 month of age, a 96% response rate was noted, irrespective of birth weight and weight at time of immunisation.	

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
3.	Belloni C, et al. *Immunogenicity of hepatitis B vaccine in term and preterm infants.* Acta Pediatr 1998 Mar; 87(3): 336-8.		Prem and Low birth weight infants (<2500g) respond to HBV vaccine in the same measure as normal term infants.	Good to fair.
HIV POSITIVE BABIES/MOTHERS				
1.	Rutstein RM, et al. *Response to hepatitis B immunization by infants exposed to HIV.* AIDS 1994 Sep, 8(9) 1281-4.	Cohort study. Comparing anti- Hbs responses of 24 HIV-infected infants and 17 uninfected infants. Total 41 infants Follow-up 12 months.	92% HIV-uninfected infants had an antibody response to the HB vaccine. 6/17 (35%) HIV-infected infants had an antibody response. CD4 in HIV-infected infants lower. No significant difference bet CD4 in HIV-infected responders and non-responders.	Fair
2.	Zuccotti GV, et al. *Hepatitis B vaccination in infants of mothers infected with human immunodeficiency virus.*	Cohort study 18 infants of HIV-infected mothers. Hepatitis B vaccine given at 0, 1 and 6	All 13 infants whose HIV antibody disappeared had seroconversion. Only 1/5 HIV-infected child seroconverted. The other 4/5 HIV- infected children who did not mount an antibody	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	J Pediatr 1994 Jul; 125(1); 70-2.	monthsNonresponders receive a 4th dose at 9-10 months. Follow-up up to 18 months	response progressed rapidly to full-blown AIDS. HIV-infected infants respond poorly to hepatitis B vaccine.	
3.	Arrazola MP, et al. *Hepatitis B vaccination in infants of mothers infected with human immunodeficiency virus.* J Med Virol. 1995 Mar; 45(3) 339-41.	Cohort study. 118 HIV-positive neonates. All given Hepatitis B vaccine at 0,1 and 6 months. Followed up for 11 months.	95/118 neonates lost their HIV antibodies. 94.2% of these neonates who lost their HIV antibodies responded to the vaccine. 23 neonates who remained HIV-positive, only 7 produced anti HBs.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Booster Trials				
1.	Bulkow LR, et al. *Increases in levels of antibody to hepatitis surface antigen in an immunized population.* Clin Infect Dis. 1998 Apr; 26(4) 933-7.	Cohort study. 1595 vacinees. Followed for 10 years.	8.2% of 1595 vacinees had boosts in anti-Hbs (i.e. a 4-fold rise in anti-Hbs not accompanied by presence of anti-Hbc or interim vaccination) Persons with boosts did not differ from persons without boosts. Continued exposure to HBV among vacinees and the continued protection against disease that the vaccine provides.	Fair
2.	Poovorawan Y, et al. *Long-term antibody persistence after booster vaccination with combined tetravalent diphtheria, tetanus, whole cell Bordetella pertussis and hepatitis B vaccine in healthy infants.* Ann Trop Paediatr. 1997 Dec; 17(4):	Open randomized trial. 119 infants Booster dose given at 18 months and anti-Hbs taken at 1 month and 1 year later.	At 1-month post booster, 97.8% infants had seroprotective levels of anti-Hbs. 1 year later, 93.9% remained seroprotected. DTPw-HB vaccine showed good long-term anti-Hbs persistence.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	301-8.			
3.	Tilzey AJ. *Hepatitis vaccine boosting: the debate continues. Commentary*. Lancet 1995 Apr; 22; 345(8956): 1000-1.	Review/ commentary		Poor
4.	Shahana AC, et al. *Responses to hepatitis B vaccine boosters in Human Immunodeficiency Virus- Infected Children.* Pediatr Infect Dis J1995 Jan; 14(1): 65-7.	Cohort study. 14 children. Booster given 5 months after 3rd dose. Repeat anti-Hbs taken 3 months after booster dose.	Only 2/14 children (14%)developed protective antibody levels. Responders were younger and had higher CD4 counts.	Fair
5.	Goh KT, et al. *Comparison of the immune response of 4 different dosages of a yeast-recombinant hepatitis B vaccine in Singapore children. A 4-year follow-up study.* Bulletin of the World Health Organisation 992; 70(2): 233-9.	Cohort study. 146 children were included in the study. 4-year follow-up.	Persistence of immunological memory at 4 y (88-100% have anti-Hbs and 70-87% have titre anti-Hbs> 10imu/l). A booster dose may not be indicated in vaccinees that have responded to the full schedule of immunisation.	Fair.
6.	Van Herck, Van Damme P, Thoelen S, Meheus A. *Long term persistence of anti-Hbs after vaccination with a recombinant*	Non-controlled clinical series. Study done on 188 adults - mean age 23.3 years. Followed up for 7	Comparing 3 doses (at 0, 1 & 2 months) and a single booster at 12 months, with 3 doses followed by a booster at 4 years later, both gave a protective immune response at 7 yr.	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	DNA yeast derived hepatitis B vaccine: 8 years results. J Public Health: S0264410X (98) 00126-1.	years.		
7.	Wistrom J, et al. *Booster vaccination with recombinant hepatitis B 4 years after priming with one single dose.* Vaccine 17(1999): 2162-5.	Small RCT in 104 adults (medical students). Followed up for 4 years.	Comparing anti-Hbs levels after a booster at 12 months after a 3-dose regimen at 0, 1 & 6 months; and a single booster dose after the initial dose 4years earlier. A single booster dose after 4 y from an initial dose confers a rapid & strong anti-Hbs response.	Good
8.	Wu JS, et al. *Hepatitis B vaccination in high-risk infants: 10 years follow-up.* J Infec Dis 1999 Jun; 179: 1319-25.	Cohort study. 805 neonates born to mothers with positive HbsAg were included into the study and follow-up for 10 years.	The level of antibody remained high in 85% and only 15% became carriers; booster revaccination within 10 years seems unnecessary.	Fair
9.	Steven CE, et al. *Prospects for control of hepatitis B virus infection: implications of childhood vaccination and long-term protection.* Pediatrics 1992; 90(1): 170-3.	Cohort study. 104 infants of HbsAg & HbeAg positive mothers. Followed up for 10 years.	Immune responses and efficacy of HB vaccine in infants studied were excellent with anti_Hbs persistence in 90%. A 3-dose regimen without booster was used. 3-5% subjects became chronic HB carriers. In addition, there was a dose-related response where higher 10-20 micrograms per dose vaccine induce higher & longer antibody response. Protection persisted at least for 5 to 10 years.	Fair
10.	Yuen MF, et al. *Twelve-year follow-up of a prospective randomized trial of hepatitis B recombinant DNA yeast*	Randomized controlled trial. 318 children. Followed-up for 12 years.	Booster doses were not necessary, probably because of effective anamnestic response. At 12 years follow-up, 60-79% subjects had anti-Hbs >10imu/l.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	vaccine versus plasma-derived vaccine without booster doses in children. Hepatol 1999 Mar; 29(3): 924-7.			
Programme Effectiveness				
1.	Goh KT. *Prevention and control of hepatitis B virus infection in Singapore.* Ann Acad Med Singapore.1997 Sep; 26(5): 671-81.	Multiple study types. (Cohort & surveillance) Over 2500 vaccinations over 11 years.	Perinatal transmission reduced by 80% to 100%. Long-term protection of chronic carrier state. Incidence of acute hepatitis B declined from 10.4/10000 in 1985 to 4.8/10000 in 1996. Primary liver cancer reduced from 27.8/100000/year during 1978-1982 to 19.0/100000/year during 1988-1992.	Fair
2.	Wainwright RB, et al. *Protection by Hepatitis B Vaccine in a Yupik Eskimo Population- Results of a 10-year study.* J Infect Dis 1997 March; 175:674-7.	Large sample, partially randomised, demonstration project. 1630 susceptible persons vaccinated followed-up 10 years.	At 6 months, 94% had anti-Hbs at levels >10 mIU/ml. After 10 years, 76% still had anti-Hbs > 10 mIU/ml. Only 13 participants (10 vaccine responders, 3 non-responders) had HbcAb and none had HbsAg or clinical hepatitis.	Good to fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
3.	Lansang MAD. *Epidemiology and control of hepatitis B infection: a perspective from the Philippines* Asia. Gut 1996; 38 (suppl 2): S43-7.	Large sample randomised. 1537 babies, followed-up for 6-12 months.	Coverage rate for fully immunised 1-yr olds ranged from 80.9-84% and anti-Hbs seroconversion rates ranged from 72-88%.	Good to fair
4.	Kim SC, et al. *Universal hepatitis B Immunization.*	Descriptive cross-sectional survey. 133 term nurseries, 144 NICU's,	85% pediatricians provide universal hepatitis B vaccination. More than half of NICU's provide HBV routinely to their preterm infants just before discharge.	Good to fair.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Pediatrics. 1995 May; 95(5): 764-6.	131 pediatricians sampled.		
5.	Coursaget P, et al. *Twelve-year follow-up study of hepatitis B immunization of Sengalese infants.* J Hepatol 1994; 21:250-4.	Non randomised, controlled prospective trial. 203 children. Followed-up for 9-12 years.	Anti-Hbs detected in 81% children who received a booster at school age and 68% of those who did not. HbsAg detected in 19% from control group compared to 2% of immunised infants, corresponding to a protective efficacy of 88%. Long-term protection very high & a booster at school age not significantly increase this protection.	Good to fair.
Population Acceptability				
1.	Ross A, et al. *Initiating the first DTP vaccination age-appropriately: a model for understanding vaccination coverage.* Pediatrics. 1998 Jun, 101(6) : 970-4.	Cohort study. 426 children.	Early in-office visits make DTP1AA vaccination more likely. Introduction of the hepatitis B vaccine to the recommended series may place more emphasis on early visits and ultimately higher vaccination rates.	Fair
2.	Freed GL, et al. *Pediatrician and Family Physician Agreement with and Adoption of Universal Hepatitis B Immunization.* J Fam Pract. 1996 Jun; 42(6): 587-92.	Cohort study. Self-administered questionnaires were mailed to 3014 pediatricians and family physicians in 9 states.	Pediatricians were more likely to know about HBV recommendation (95% vs. 84%), agreed with it (83% vs. 57%) and adopted it into practice (90% vs. 64%).	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
3.	Freed GL, et al. *Universal Hepatitis B Immunization of Infants: Reactions of Pediatricians and Family Physicians over time.* Pediatrics. 1994; 93:747-51.	Cohort survey over 8 months.	In the first survey, more pediatricians than family physicians were aware of the new recommendation (82% vs. 48%) but only 37% pediatricians and 23% family physicians agreed to it. 8 months later, 66% pediatricians and 32% family physicians agreed to it but only 53% pediatricians and 23% family physicians adopted it into	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
			practice. Reasons: physician & practice characteristics, cost, perceived need for vaccine and aversion to multiple injections.	
Adverse Reactions				
1.	Ronchi F, et al. *Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine.* Arch Dis Child 1998 Mar; 78(3): 273-4.	3 case reports	Presence of anti-platelet antibodies. Treated with corticosteroids. Completely reversible and hence benign nature of a very rare complication.	Poor
2.	Pirmohamed M, et al. *Hepatitis B and neurotoxicity.* Postgrad Med J.1997 Jul; 73(861):462-3.	1 case report	Uncommon reaction Risk-benefit ratio still favours vaccination	Poor
3.	Baglivo E, et al. *Multiple Evanescent White Dot Syndrome after Hepatitis B Vaccine*. Am J Ophthalmol. 1996 Sep; 122(3): 431-2.	1 case report	Occurred 24h after a booster IM Hepatitis B vaccine. Recovery in 3 months.	Poor
4.	Ranieri VM, et al. *Liver inflammation and acute respiratory distress syndrome in a patient receiving hepatitis B vaccine: a possible relationship?* Intensive Care Med. 1997; 23:119-121.	1 case report	After 2nd dose of recombinant hepatitis B vaccine. Patient died. Very rare.	Poor
5.	Macdrio F, et al. *Nephrotic syndrome after recombinant hepatitis B vaccine*. Clin Nephrol, 1995 May; 43(5) 349.	1 case report	Complete remission with corticosteroids.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Cost Effectiveness of the Hb Immunisation Programme				
1.	Alimonos K, et al. *Prediction of response to hepatitis B vaccine in health care workers: whose titers of antibody to hepatitis B surface antigen should be determined after a three-dose series, and what are the implications in terms of cost effectiveness?* Clin Infect Dis. 1998 Mar; 26(3): 566-71.	Economic analysis.	It is possible to predict who will have a high probability of developing a protective response to hepatitis B vaccine, for these people determining post immunization anti-Hbs titres is unnecessary and not cost effective.	Good
2.	Shepard DS, et al. *Setting priorities for the Children's Vaccine Initiation: a cost-effectiveness approach*. Vaccine. 1995; 13(8): 707-14.	Model to measure cost effectiveness as the net cost per Quality-Adjusted Life Year (QALY)	Hepatitis B vaccine combined with diphtheria-tetanus-pertussis vaccine would generate a QALY inexpensively.	Good

MEASLES MUMPS RUBELLA (MMR)

1. INTRODUCTION

Measles, Mumps and Rubella monovalent and combination (MMR) vaccines will be jointly discussed. The focus of this section, however, will be on the MMR vaccine. Each disease will first be outlined, followed by an overview of the vaccines and a discussion on selected issues relating to using MMR and individual vaccines.

Vaccine characteristics

The MMR vaccine is a freeze-dried preparation containing live attenuated measles, mumps and rubella viruses. It should be stored at 2-8°C and reconstituted with a diluent before administration. 0.5 ml is given by intramuscular or deep subcutaneous injection (Dept. of Health, United Kingdom. 1996). The MMR vaccines available in Malaysia use the following viral strains (Academy of Medicine Malaysia, 1998):

Measles - attenuated *Enders-Edmonston, Schwartz, Edmonston Zegrab*
Mumps - *Jeryl Lynn B, Rubini*
Rubella - *Wistar RA 27/3.*

1.1 MEASLES

1.1.1 Disease pattern

Measles is a highly infectious viral (RNA) disease and a major health issue. It can affect almost the entire population in the absence of an immunisation programme. Measles is transmitted primarily by respiratory droplets from person to person. The incubation period is 10-12 days. Primary viraemia occurs 2-4 days following exposure, with an intense secondary viraemia occurring 3-4 days later. The prodrome begins with fever, malaise, conjunctivitis, coryza, and tracheobronchitis. An erythematous maculo-papular rash usually appears on 2nd-4th day after the onset of the prodomal symptoms and spreads from the head to the extremities. It lasts for 3-4 days and leaves a desquamation. Spots appear on the buccal mucosa (Koplik's spots) from 2 days before to 2 days after the onset of the rash. Persons are considered communicable from 4 days prior to and 4 days after the onset of the rash (Markowitz, 1990).

Measles can be complicated by otitis media in 7-9%, pneumonia in 1-6%, post-infectious encephalitis in 1-2 per 1,000, and subacute sclerosing panencephalitis in 1 per 25,000 infected persons (Cutts, 1993). Death occurs in 1-2 per 1,000 cases, predominantly due to respiratory or neurological complications (Markowitz, 1990; American Academy of Pediatrics). Case fatality rates of up to 3-15% have been documented in community studies from developing countries (Markowitz, 1990; Cutts, 1993). Mortality is highest in children under 2 years of age, in the malnourished, and those who live in crowded conditions (Markowitz, 1990).

1.1.2 Incidence

Although measles is a notifiable disease, the incidence of measles in Malaysia is difficult to determine due to under-reporting. The reported incidence rate shows a diminishing rate from 32.84 per 100,000 population in 1987 to 2.61 in 1997. The largest number of reports of cases in the later years have come from Sabah – in 1997 of a total of 565 cases, 206 were in Peninsular Malaysia, 269 in Sabah and 90 in Sarawak. With respect to reported measles related deaths, there were between 0 to 6 deaths per year from 1990 to 1996, almost exclusively occurring in Sabah (one reported death in Sarawak in 1995), but no reported deaths for 1997. Of particular importance are deaths under the age of 1 year as this relates to the timing of measles vaccination. For example, the four reported deaths in 1996 all occurred in Sabah and in children under the age of 1 year (Ministry of Health, Malaysia, 1998).

A local study, commissioned by this committee, utilised the Malaysian Paediatric Surveillance Unit mechanism to obtain data that are more accurate from all paediatricians in the country on measles related deaths for the year 1998. There were five deaths because of secondary infection related to measles infection (bronchopneumonia or septicaemia), in children under the age of 18 years reported, all from Sabah (Amar, 1999). Local published data on the morbidity due to measles in the child under the age of one year is limited. A study from Sabah in 1990 documented 143 measles-related admissions in children below 12 years of age, with a median age of one year, and with 13.3% in the 6 to 9 months age group. The majority (85.3%) were not immunised against measles. Most cases (86.0%) were complicated by malnutrition and pneumonia. The case fatality rate was 1.4%(Khoo, 1990). Unpublished data from Sabah for 1996-1997 show a large number of children admitted for measles related complications. Of the total admissions, 45% in 1996 and 39% in 1997 were under the age of 12 months. The majority of these were non-Malaysian children (Soo, 1999).

A study to determine the age specific prevalence of measles infection by serology was conducted between 1980-1983. Although limited to a data at a single institution, it showed that by 9 months of age, 26% of children had developed antibodies to measles (some of these could still be related to passively acquired maternal measles antibodies) (Chen, 1985). A more recent serological survey conducted in 1990 in Kelantan showed that 53.3% of infants below the age of one year did not have measles antibodies, although the sample for this data was small (Saraswathy, 1994).

1.1.3 Vaccine characteristics

The measles vaccine was developed in the 1950s when the Edmonston strain was isolated. From 1960-1970s, this strain had been further attenuated to four different strains that are currently used in the measles vaccine - AIK-C, Schwarz, Moraten, Edmonston-Zagreb (Cutts, 1993). Measles vaccine is a live attenuated vaccine, cultured in chick embryo cells. It is stable for up to 2 years if stored at 2-8° C. It is reconstituted with sterile distilled water and is administered subcutaneously at a dose of 0.5 ml.

Vaccine efficacy is 95% for persons vaccinated at 12 months and 98% for those vaccinated at 15 months of age (Markowitz, 1990; Watson, 1998). In 1982, the measles vaccine was introduced into the national immunisation programme in Malaysia. One local evaluation of vaccine efficacy showed seroconversion rates ranging form 93.7-98.9% for children aged from 9-24 months (Chen, 1985). Conversion rates were better for those aged 11-24 months (96.4-98.9%) than those ages 9-10 months (93.7-95.3%). Seroconversion rates from six African countries and Latin America show rates of 84-94% at 9 months as compared to 92-

100% at 12 months (Cutts, 1993). Additional work from the USA in the 1970s showed rates of failure to seroconvert of up to 15-21% in children immunised against measles at 9-12 months as opposed to 6% at 13-18 months (Isaacs, 1990).

Attempts to improve the seroconversion, and bring down the age of vaccination to 6 months, by using the high titer Edmonston-Zagreb (EZ) vaccine have met with limited success. Although effective, the EZ vaccine is more costly, not as immunogenic as found in initial trial, and some data suggests that the vaccine may not be entirely safe (Cutta, 1993).

Opinions as to the duration of measles vaccine induced immunity vary. The majority of vaccinated individuals appear to develop life long immunity but waning vaccine-induced immunity does exist (secondary vaccine failure). Data from China and Canada suggests secondary vaccine failure rates of 2% and 5% respectively (Cutts, 1993). However, a meta analysis on secondary vaccine failure quotes a rate of < 0.2% (Anders, 1996). When measles does occur in immunised persons reports suggest that the disease is milder than in unimmunised persons (Cutts, 1993). Hence, immunity after measles immunisation is a continuum from full protection to partial or temporary protection. There a minimum rate of primary vaccine failure of 2-5% (no protection) that is higher if the vaccine is given before 12 months of age (Cutts, 1993; Markowitz, 1990).

1.2 MUMPS

1.2.1 Disease pattern

Mumps is a paramyxovirus infection, occurring primarily in children, with a peak incidence at 5-9 years of age. The incubation period is 14-21 days. It is estimated that one third of infections are asymptomatic. The disease is characterised by bilateral, or occasionally unilateral, parotid swelling. Mumps is transmissible from several days before the parotid swelling to several days after it appears.

The complications of mumps include pancreatitis, oophoritis, orchitis (unilateral orchitis is reported in up to 20% of clinical cases of mumps in post-pubertal males, but sterility is rare), hepatitis, myocarditis and thyroiditis. Benign meningeal signs appear in up to 15% of cases but permanent sequelae are rare. In the pre-vaccination era, it was the commonest cause of viral meningitis under the age of 15 years (Department. of Health, UK1996; National Health & Medical Research Council, Australia, 1997). About 2.5 per 1000 mumps cases develop meningoencephalitis is with a 1.4% fatality. A serious rare complication is unilateral nerve deafness (Bakshi, 1990).

1.2.2 Incidence

While there is no available data on the incidence of mumps or its complications in Malaysia, data from the United Kingdom shows that in the pre-vaccination era, mumps accounted for over 1,000 admissions a year for viral meningitis. In the USA it is estimated that if no vaccine was used there would be nearly 2,000 cases of mumps meningitis and over 2,800 cases of encephalitis a year causing 95 cases of deafness and 40 deaths (Isaacs, 1990).

There is a single local case report of severe encephalomyelitis due to mumps (Tan, 1992). A serological study in Penang on 13 children with a discharge diagnosis of viral encephalitis found one case of mumps encephalomyelitis (Cardosa, 1995).

1.2.3 Vaccine characteristics

Mumps vaccine is a live attenuated vaccine prepared in chick embryo cell cultures developed in the 1960s. A number of different strains have been developed and the most widely used strain currently is Jeryl Lynn B (Bakshi, 1990). It is a freeze-dried preparation stored at 2-8°C, and reconstituted with diluent fluid to be given in a dose of 0.5 ml by intramuscular or deep subcutaneous injection (Department of Health, UK, 1996).

Seroconversion after a single dose of mumps vaccine is reported as ranging from 90-100%(Watson, 1998; Isaacs, 1990; Bakshi, 1990; Robertson, 1988). The duration of vaccine-induced immunity is unknown (antibodies are shown to persist for 9.5 years after MMR administration [Bakshi, 1990]) but epidemiological and serological data over the past 30 years indicate the persistence of antibodies and thus continuing protection against infection (Watson, 1998). Although there are fears that a single dose immunisation as part of the MMR may shift the occurrence of mumps infection to an older age group, epidemiological data has shown a dramatic overall reduction in cases and complications (Isaacs, 1990; Bakshi, 1990). It is anticipated that a two dose MMR policy will effectively deal with most cases of primary vaccine failure that have a risk of mumps in later life.

1.3 RUBELLA

1.3.1 Disease pattern

Rubella is an RNA virus belonging to the Togaviridae group of viruses. It is transmitted through droplet spread and congenital infection can occur in the foetus because of viraemia during pregnancy. The teratogenic effects are produced because of inflammatory response to the virus, and depressed mitosis resulting in hypoplasia in the developing foetus. Rubella presents clinically as a viral exanthema of no particular distinction. Its clinical diagnosis is often inaccurate and rubella is easily confused with other viral illnesses. It can often occur sub clinically.

Complications include arthritis (especially in the adult woman), and rarely, encephalitis or thrombocytopaenia. Infection usually confers life-long immunity but asymptomatic re-infection may occur. Rubella infection in pregnancy however is a serious illness. Rubella associated defects occur in 100% of pregnancies in the first 11 weeks, in 50% from 11-12 weeks and in 35% from 13-16 weeks. The common permanent manifestations of congenital rubella include sensorineural deafness, mental retardation, cataracts, congenital heart defect, retinopathy, spastic diplegia, growth retardation, hepatosplenomegaly, thrombocytopaenia and meningoencephalitis (Bakshi, 1990).

1.3.2 Incidence

As rubella is a nondescript illness, its true incidence in a community is difficult to determine. There is no nationwide Malaysian data on the annual incidence of children born with congenital rubella. In the United Kingdom, for example, there were 70 cases of congenital rubella syndrome (CRS) reported annually, prior to the introduction of rubella immunisation (However, it should be noted that the ratio of therapeutic abortions in cases of CRS was approximately 10:1) (Department of Health, United Kingdom).

Two Malaysian seroprevalence studies in the 1970s showed that 60-64% of women had detectable antibody titers to rubella (Dora, 1985). Another local report quotes 2-6 cases of CRS out of 6,000 newborns annually at University Hospital KL (Academy of Medicine Malaysia, 1985). A nationwide study done locally in the 1980s, found 574 children under the age of 4 years with clinical features suggestive of CRS. Of these, 196 had serological evidence for CRS, with the majority having significant congenital defects. The majority (55.1%) was under the age of 6 months (Dora, 1985). Using the data from those under 6 months and estimating the national annual number of births at 400,000, the minimum birth prevalence of CRS would be 0.27 per 1,000 births. In a more recent study, looking at the prevalence of ocular abnormalities in children from a Malaysian school for the deaf, 33 out of 165 children (20%) examined had ocular abnormalities relating to rubella retinopathy (i.e. CRS) (Elango, 1994).

1.3.3 Vaccine characteristics

Live attenuated rubella vaccine was developed in the 1960s. A number of different strains have been developed and the most widely used strain currently is Wistar RA 27/3 which is grown in human diploid cells (National Health & Medical Research Council, Australia, 1997). Rubella vaccine is a freeze-dried preparation that is stored at 2-8°C and after reconstituting with diluent fluid, it is administered in a dose of 0.5 ml subcutaneously.

Serum antibodies to rubella is induced in at least 95% of recipients following a single dose at 12 months of age or older (American Academy of Pediatrics, 1997). Vaccine induced antibody has been shown to persist for at least 16 years and protection against clinical rubella appears to be long term. However, primary vaccine failures do occur and antibody levels can wane (National Health & Medical Research Council, Australia 1997).

2. METHODOLOGY

An electronic search of MEDLINE database using various keywords, and year limits was carried out. In addition, three country immunisation handbooks (USA, UK, Australia) WHO reports, Ministry of Health reports and other important references were obtained from various sources. Additional data was obtained from a "once only" surveillance via the Malaysian Paediatric Surveillance Unit (MPSU) on measles-related deaths in Malaysia for Jan-Nov 1998. The keywords used and the year limits were as follows:

Key words used for search was "MMR" and years searched was between 1990 –1998.
Note: The abbreviation MMR is not specific for measles, mumps & rubella immunisation (e.g. maternal mortality, etc) but did include all the relevant articles on this vaccine.

- Malaysia and Measles 1966-1998
- Malaysia and Rubella 1966-1998
- Malaysia and Mumps 1966-1998
- Malaysia and Immunisation 1966-1998
- Malaysia and MMR 1967-1999

The results are summarized below:

- Total electronic (Medline) search = 373
- Relevant titles (pertaining to MMR vaccines & in English & in humans) = 78

- Abstracts reviewed = 48
- Full papers reviewed = 25
- Papers not available (abstracts used) = 15
- Books and reports reviewed (sections used) = 4

3. RESULTS

3.1 Vaccine Efficacy

The MMR vaccine is highly immunogenic with seroconversion rates of 96-100% for measles, 90-100% for mumps and 99-100% for rubella (Isaacs, 1990; Robertson, 1988; Elango, 1994). A randomised trial in the UK showed high seroconversion rates with the MMR vaccine and that measles seroconversion rates were comparable to the single antigen measles vaccine Edees, 1991). Failure to seroconvert to measles depends on the age of child at vaccination - up to 20% at 9-12 months, 3% at 12 months, 2% at 15 months (Isaacs, 1990; Robertson, 1988). Protection conferred by a single dose given after 12 months of age is long lasting in the majority of persons. However, between 5-10% of vaccinated individuals may either have primary vaccine failure or lose protection. 99% of individuals who receive two doses (separated by at least 4 weeks) after 12 months of age have long lasting immunity to measles (American Academy of Pediatrics, 1997).

Note:

Some aspects of vaccine efficacy, including efficacy for mumps and rubella, are covered in the discussion on individual vaccines above.

A randomized trial compared the safety and immunogenicity of two combined vaccines - Triviraten Berna Vaccine, Swiss Serum and Vaccine Institute (containing Edmonston Zagreb 19 strain of measles virus, the Rubini mumps virus strain and the Wistar RA 27/3 rubella strain) with MMR-Vax, Merck, Sharp & Dohme, West Point (containing the Enders attenuated Edmonston measles strain, the Jeryl Lynn mumps strain and the Wistar RA 27/3 rubella strain). Immunization with Triviraten Berna was associated with a significantly lower incidence of swelling and redness at the injection site in addition to a reduced rate of fever compared with MMR-Vax. Seroconversion rates for the measles and rubella vaccine components were comparable in all tests used (Schwarzer, 1998).

There is conflicting evidence on the efficacy of MMR vaccination under 12 months of age (Forleo-Neto, 1997; Singh, 1994). This may reflect the prevalence of measles, mumps and rubella in the community, i.e. higher prevalence resulting in more maternal antibodies, rather than the actual seroconversion of the vaccine. There has been a suggestion that as immunisation rates improve, maternal antibodies may wane sooner in mothers who received immunisation rather than natural disease. Hence, allowing for a lowering of the minimum age for measles and other immunization (Cutts, 1993).

3.2 Programme Effectiveness And Schedule

MMR has been used effectively in national immunisation programmes in industrialised countries, particularly the United States and Scandinavian countries, for more than 20 years Anders, 1996; Dept. of Health, United Kingdom, 1996; Singh, 1994). The key issues in these countries have been the timing of the first dose, and the introduction and timing of a second dose. These issues relate primarily to measles outbreaks and CRS.

The World Health Organisation (WHO) has recommended, since the 1980s, that measles be given at 9 months of age because of the high mortality in children under 1 year of age (Cutts, 1993;WHO, 1996). Although this may have been a problem for Malaysia in the past, there is no current evidence to support a significant number of measles related deaths in children under one year of age (Amar, 1998). However, some childhood deaths and measles with complications under the age of one year continue to occur, predominantly in Sabah and among the children of illegal immigrants (Khoo, 1994; Soo, 1999). The overall reduction of measles deaths in children less than one year of age in Malaysia is probably a result of high levels of population herd immunity achieved by the reasonably high rates of measles immunisation coverage (86.1% coverage in 1996) (Ministry of Health Malaysia, 1998; WHO, 1996).

Despite a high rate of rubella immunisation in school going children, there is evidence to suggest that CRS continues to be a health problem locally (Dora, 1985; Elango, 1994). While rubella immunization given to pre-pubertal, school-going girls subsequently increases the proportion of women with antibody to rubella, it does not interrupt the circulation of rubella in the community. This would be achieved by giving rubella immunisation to both boys and girls.

Countries that have combined measles and rubella immunisation and given a single dose of MMR at 12 months of age adopted this strategy have however noted measles outbreaks in adolescent school children (Peltola, 1994; Quadros, 1996; Heisler, 1994; American Academy of Pediatrics, 1998). Measles outbreaks have occurred among highly vaccinated populations of school age children because of primary vaccine failure. Another category of outbreaks includes pre school children living in poor urban areas (Quadros, 1996). This has led to recommendation for a second dose of MMR either at 4-6 or 11-12 years of age (Dept. of Health, United Kingdom, 1996; National Health & Medical Research Council, Australia 1997; American Academy of Pediatrics, 1998). It is currently recommended that the ideal age for a second dose of MMR be at school entry i.e. 6-7 years of age (American Academy of Pediatrics, 1998). This will allow for the largest coverage with optimal acceptability. The two-dose MMR programme also supports the WHO strategy for the eradication of measles. If a two-dose MMR programme is not acceptable for financial reasons then supplemental mass measles immunisation campaigns are required for school going children (Quadros, 1996; American Academy of Pediatrics, 1998).

While a single dose MMR policy interrupts the circulation of rubella in the community, it may increase the risk of CRS, especially in countries where the coverage of immunisation is not high. In such countries, prior to a single dose MMR immunisation programme, the transmission of rubella virus at a younger age is large, hence limiting the number of susceptible adult females at risk for CRS. However if MMR vaccination is introduced at a young age and immunisation coverage is not close to 100%, transmission of the wild virus in childhood is interrupted, but leaving larger numbers of susceptible adults females and a higher eventual rate of CRS (Anderson, 1990). As a result, most countries that have adopted MMR immunisation at 12-15 months of age have either retained the single antigen rubella vaccination for schoolgirls and susceptible women after pregnancy or introduced a two dose MMR vaccine programme, resulting in a dramatic drop in CRS (Watson, 1998; Bakshi, 1990; American Academy of Pediatrics, 1998; B'ottiger, 1997). Sweden was the first country to move from targeting schoolgirls, susceptible women after pregnancy and women at special risk for rubella, to a two dose MMR vaccination programme (at 18 months and 12 years)

since 1982. They have shown a dramatic drop in susceptible pregnant women from 12% in 1975 to below 2% in 1994 and no case of CRS since 1985 (B'ottiger, 1997).

3.3 Safety and Side Effects

Adverse reactions following vaccination with MMR are minimal (Isaacs, 1990; Davis, 1991). Mild common reactions include local pain, local induration, malaise, fever or a rash that usually occur a week after immunisation and last for 2-3 days (Watson, 1998; Dept. of Health, United Kingdom, 1996). Potentially serious complications include idiopathic thrombocytopaenic purpura (ITP), arthropathy, febrile convulsions, urticaria and parotid swelling. A countrywide 12-year surveillance of 1.5 million vaccinations in Finland reported ITP in 3.3 per 100,000 febrile fits 7 per 100,000 and urticaria 0.6 per 100,000 (Peltola, 1994). There were no reports of death or permanent sequelae. A cohort study comprising more than 18,000 children under the age of 3 years who received a first dose of MMR vaccine showed no episode of encephalopathy (Griffin, 1991). However, the mumps component of the MMR vaccine is known to be associated with meningitis at the estimated rate of 1 in 50,000 to 1 in 1 million doses but this is far less common than with the natural illness (10-15%) (Isaacs, 1990). Surveillance in Finland has shown that one third of all childhood encephalitis was reduced with the extensive use of MMR vaccine in a two dose strategy (Peltola, 1994).

A review of all evidence concerning the causal relationship between MMR vaccination and various adverse events by expert committees at the Institute of Medicine, Washington DC, determined that current evidence only establishes a causal relation between MMR vaccination and anaphylaxis, thrombocytopenia, febrile seizures, and acute arthritis (Watson, 1998). While there have been recent alarms linking MMR to autism and other chronic diseases, the number of reports is very small, and there is no basis of evidence for a causal link (Watson, 1998, Nicoll, 1998). There are a small number of unproven reports of a possible association between MMR vaccination and sensorineural deafness. The incidence of these events is lower than the incidence of congenital and acquired sensorineural hearing loss, indicating that this possible association is simply by chance (Stewart, 1993).

Considering side effects with regards to choice of the MMR vaccine, a randomised trial comparing immunization with Triviraten Berna resulted in a significantly lower incidence of swelling and redness at the injection site in addition to a reduced rate of fever compared with MMR-Vax (Schwarzer, 1998). A large national surveillance in Japan comparing 4 different MMR vaccines showed little difference in the rate of side effects except for the vaccine using the Urabe Am 9 mumps virus (Biken MMR vaccine), where a higher rate of aseptic meningitis was noted (Kimura, 1996).

Side effects tend to occur among vaccine recipients who are non-immune and, therefore, are very rare after revaccination i.e. with a second dose of MMR vaccine (Watson, 1998). A large study comparing the adverse effects of a second dose of MMR immunisation at 4-5 years as opposed to 10-12 years of age, found that true adverse events were uncommon in both groups, but arthropathy was more common when given to older children (Davis, 1997). The RA27/3 strain of rubella in the MMR vaccine, although more immunogenic, is associated with more arthropathy than the Cendehill strain (Isaacs, 1990).

General contraindications to MMR vaccine are those that apply to all live vaccines (American Academy of Pediatrics, 1997; Watson, 1998; Dept. of Health, United Kingdom, 1996; National Health & Medical Research Council, Australia, 1997). Concerns about

administration of MMR to children with egg allergy or sensitivity have largely been laid to rest, with only two (0.16%) reports of adverse reactions in sixteen studies of MMR administration to 1265 children with egg hypersensitivity (Department of Health, United Kingdom, 1996; Beck, 1991; Fasano, 1992). The data indicates that over 99% of children with allergy to eggs can safely receive MMR vaccine (Department of Health, United Kingdom, 1996).

3.4 Cost Effectiveness

The benefits of rubella immunisation, either in a 2 dose MMR regimen or single dose MMR with rubella immunisation in adolescents (expanded rubella initiative), has enormous economic benefits due to reduction in CRS. It has been estimated that US $7.70 is saved for each dollar spent (Bakshi, 1990). The average lifetime cost of CRS is estimated at between US $200,000 to $ 4 million (Frenkel, 1994). The cost benefit ratio of a two-dose rubella immunisation programme has been estimated as 1:23 (Riviere, 1992).

Mumps immunisation as part of a single dose MMR regimen has also been found to be cost effective (Bakshi, 1990). The cost benefit ratio being estimated at 1:7.4 (Riviere, 1992).

The World Bank, in a review of cost effective measures, evaluated measles immunisation as being one of the most cost effective health interventions currently available (Quadros, 1996). The 1997 International Meeting on "Global Measles Control and Elimination" concluded that "*different approaches have been taken to assess the economic costs, benefits, and cost-effectiveness of measles control, elimination, and eradication. These analyses indicate that programs to control measles are highly cost-effective. Additional programmatic investments to interrupt measles transmission are also cost-effective and may be cost-saving in some countries*". Attempts to increase the coverage of a single dose of measles (beyond 95%) or interrupt measles transmission by a two-dose strategy (as part of MMR) are both found to be cost effective (MMWR, 1998).

Estimates of the overall cost benefit ratio of MMR vaccination, conducted in the last 10 years in the USA, were 1:14.4 (White, 1985) and 1:14 (Hatziandreu, 1994). An economic evaluation of the benefits of a 2 dose MMR vaccination programme in Canada estimated a cost benefit ratio of 1:6.34 for the Ministry of Health and 1:3.25 for society (i.e. a saving of US $6.34 for every dollar spent for the Ministry of Health and US $3.25 for society) (Riviere, 1997). However, the cost of the MMR vaccine is double the cost of single antigen measles vaccine (WHO, 1996).

4. CONCLUSION

There is sufficient evidence of the effectiveness of a two dose MMR immunization schedule at 12 months and at school entry (6-7 years of age). In view of the large number of measles cases in the state of Sabah, there is sufficient evidence for the effectiveness of earlier immunisation at 9 months of age. MMR vaccines have also been found to be safe and cost-effective.

5. RECOMMENDATIONS

It is recommended that two doses of MMR vaccine be given to all children at the age of 12 months of age and at school entry (6-7 years of age) as part of the routine national immunisation policy. This should replace the existing policy to give measles immunisation

at 9 months and rubella immunisation at 12 years of age. In the state of Sabah, MMR should be given at 9 months of age. Rubella immunisation at 12 years of age should continue until the children who have received the second dose of MMR vaccine reach 12 years of age.

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7. EVIDENCE TABLE
MMR

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Efficacy				
1.	Frenkel LD. *Routine immunisation for American children in the 1990s*. Ped Cli N Am 1990; 37(3): 531-547.	Review of scientific literature.	Epidemiological data on the reduction of measles, mumps & congenital rubella cases in the USA since the introduction of the vaccines. Supports the recommendation for a 2 dose MMR policy	Good
2.	Isaac D, Menser M. *Measles, mumps, rubella and varicella. In Modern Vaccines - Current Practice and New Approach*. A Lancet Review 1990; pg. 50-58, Hodder & Stoughton, London.	Review of scientific literature.	Vaccine highly immunogenic. Seroconversion rates 96-100% for measles, 90-100% for mumps & 99-100% for rubella. Failure to seroconvert to measles depends on age of child at vaccination: up to 20% at 9-12 months, 97% at 12 months, 98% at 15 months.	Good
3.	Robertson CM, Bennett VJ, Jefferson N, Mayon-White RT. *Serological evaluation of a measles, mumps and rubella vaccine.* Arch Ds Child 1988; 63:612-616.	Controlled trial (not randomised in view of parents sensitivity towards a new vaccine). Reasonable sample size.	Seroconversion rates with MMR vaccine good (93% for measles, 100% for mumps, 99% for rubella). Measles seroconversion rates comparable to single measles vaccine. Side effects also documented	Good to Fair
4.	Edees S; Pullan CR; Hull D. *A randomised single blind trial of a combined mumps measles rubella vaccine to evaluate serological response and reactions in the UK population.* Public Health 1991, 105(2): 91-7 (abst)	Single blind study RCT comparing MMR vaccine (207 recipients) with measles vaccine (213 recipients)	Serological response to measles vaccine was similar in both groups (92-6% seroconversion with MMR, 96-8% with measles). Seroconversion against mumps & rubella with the MMR vaccine was 88% and 96% respectively. Side effects similar. Confirms the safety and efficacy of the MMR vaccine.	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
5.	Forleo-Neto E, Carvalho ES, Fuentes IC, et al. *Seroconversion of a trivalent measles, mumps, & rubella vaccine in children aged 9 & 15 months.* Vaccine 1997; 15(17-18): 1898-901 (abst)	Clinical trial comparing 9 mth old infants (109) given MMR vaccine with 15 mth old children (98) receiving monocomponent measles vaccine.	Seroconversion rates were high in both groups No serious events attributable to vaccination were observed Evidence for the efficacy of a two-dose schedule, i.e. at 9 and 15 months, is presented	Good to Fair
6.	Singh R; John TJ; Cherian T; Raghupathy P. *Immune response to measles, mumps & rubella vaccine at 9, 12 & 15 months of age.* Indian J Med Res 1994, 100:155-9 (abst)	Assessment of 123 children given MMR vaccine at 9, 12 & 15 months of age.	Responses to measles antigen better (> 95%) at 12 or 15 months than at 9 months (80%). Recommend optimum age for MMR vaccination is 12-15 months	Poor
Programme Effectiveness and Population Acceptability				
1.	Peltola H, et al. *The elimination of indigenous measles, mumps & rubella from Finland by a 12-year, two-dose program*. N Engl J Med 1994; 331:1397-402.	Multiple study types - (surveillance & RCT) - 1.5 mill. Vaccinations over 12 yrs	Highly effective - minimal clinical cases (< 30 per disease per yr by serologic testing) & good AB levels Strongly supports 2 dose MMR policy	Good
2.	Heisler MB, Richmond JB. *Lessons from Finland's successful immunisation program.* N Engl J Med 1994; 331:1446-47.	Editorial	Commentary on Finland programme in relation to other programmes, outlines strategies leading to successful programme	Poor
3.	Quadros CA, et al. *Measles elimination in the Americas*. JAMA 1996; 275:224-9.	PAHO Review of progress in N&S America	Outlines workable strategies for 1 or 2 dose immunisation. 2 doses when have resources & trying to reach vaccination failures, 1 dose when "poor" & health service not comprehensive. Aim of 2-dose programme is to interrupt	Good to fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
			circulation of the respective viruses. Critical to reduce adolescent epidemics.	
4.	Cutts FT. *The immunological basis for immunisation series: Module 7 - Measles.* 1993 WHO/EPI/Gen/93.17.	Extensive review of available literature on measles immunisation	Discuses in depth (based on data) measles disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for measles control	Fair
5.	National Health & Medical Research Council, Australia. *The Australian immunisation handbook.* 5th Edition 1997.	Recommendations by expert committee based on scientific literature	2 doses MMR recommended at 12 months & 10-16yrs. prevents late childhood & adolescent epidemics. 1st dose to be given at 9 months in risk groups (e.g. Aboriginal children)	Good
6.	Department of Health, United Kingdom *Immunisation Against Infectious Disease* ("The Green Book"): HMSO 1996.	Recommendations by expert committee based on scientific literature	2 doses MMR recommended after 12 months & before school entry. 2 doses required to prevent "late" epidemics. Two-dose programme is to interrupt circulation of the rubella virus among children & to effectively prevent cong. rubella syndrome.	Good
7.	American Academy of Pediatrics: Red Book: *Report of the committee on infectious diseases*. Peter G, ed. 24th ed. Elk Grove Village, Il. 1997.	Recommendations by expert committee based on scientific literature	2 doses MMR recommended at 12 months & 4-6yrs. 2 doses programme to prevent late childhood & adolescent epidemics as well as to effectively prevent cong. rubella syndrome.	Good
8.	Markowitz LE, Orenstein WA. *Measles vaccines*. Ped Clin N Am 1990; 37(3): 603-625	Extensive review of available literature on measles immunisation	Discuses in depth (based on data) measles disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for measles control	Good to Fair
9.	Bakshi SS, Cooper LZ. *Rubella and mumps vaccines*. Ped Clin N Am 1990; 37(3): 651-667	Extensive review of available literature on rubella and mumps vaccines	Discuses in depth (based on data) measles disease pattern, immunological basis of vaccine, efficacy of vaccine and success of various strategies for rubella and mumps control	Good to Fair
10.	Amar HSS, et al *One Off Surveillance for Measles*	Study commissioned by HTA group. Data for	Only 5 measles related deaths in children under the age of 18 years, all from Sabah. Deaths due to secondary	Fair.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Related Deaths in 1998. Malaysian Paediatric Surveillance Unit Report. January 1999	measles deaths based on national surveillance of paediatricians.	infection related to measles (bronchopneumonia or septicaemia)	
11.	American Academy of Pediatrics. *Age for routine administration of the second dose of MMR vaccine. Committee on infectious diseases,* Pediatrics 1998; 101(1): 129-133	Recommendations by expert committee based on scientific literature (evidence based)	Provides evidence for recommending a second dose of MMR at school entry i.e. 4-6 years of age. Allows for the largest coverage with optimal acceptability. Addresses primary vaccine failure, some secondary vaccine failure and reduces measles outbreaks in adolescents, supports WHO strategy for eradication of measles.	Good
12.	Watson JC et al. *Measles, Mumps, and Rubella - Vaccine Use and Strategies for Elimination of Measles, Rubella, & Congenital Rubella Syndrome & Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Morb Mortal Wkly Rep 1998 May 22; 47(RR-8): 1-57.	Evidence based review on available data on many issues related to MMR including vaccine safety.	Review of evidence on MMR vaccination in relation to timing of doses, number of doses, programme effectiveness. Current evidence supports a two-dose MMR programme. at 12-15 months, & at school entry 4-6 years of age. Outlines measures that assist in developing a successful programme.	Good.
13.	B¨ottiger M, Forsgren M. *Twenty years' experience of rubella vaccination in Sweden: 10 years of selective vaccination (of 12-year-old girls and of women postpartum) and 13 years of a general two-dose vaccination.* Vaccine 1997; 15(14): 1538-44 (abst)	Review of effectiveness of Sweden's move from rubella immunisation in schoolgirls & susceptible women to a two dose MMR vaccination programme	Sweden first country to adopt two dose MMR vaccination programme (at 18 months and 12 years) - since 1982 Data shows a dramatic drop in susceptible pregnant women from 12% in 1975 to below 2% in 1994 No case of CRS since 1985	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
Vaccine Safety and Side Effects				
1.	American Academy of Pediatrics (Red Book): *Report of the committee on infectious diseases*. Peter G, ed. 24th ed. Elk Grove Village, Il. 1997.	Recommendations by expert committee based on scientific literature	Potential adverse effects & contraindications listed	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Department of Health, United Kingdom *Immunisation Against Infectious Disease ("The Green Book")*: HMSO 1996.	Recommendations by expert committee based on scientific literature	Potential adverse effects & contraindications listed	Good
3.	National Health & Medical Research Council, Australia. *The Australian immunisation handbook*. 5th Ed 1997.	Recommendations by expert committee based on scientific literature	Potential adverse effects & contraindications listed	Good
4.	Watson JC; Hadler SC; Dykewicz CA; Reef S; Phillips L. *Measles, Mumps, and Rubella - Vaccine Use and Strategies for Elimination of Measles, Rubella, & Congenital Rubella Syndrome & Control of Mumps:* Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1998 May 22; 47(RR-8): 1-57.	Evidence based review on available data on many issues related to MMR including vaccine safety.	Review of all evidence on causal relationship between MMR vaccination & various adverse events by expert committees. Current evidence only establishes a causal relation between MMR vaccination & anaphylaxis, thrombocytopenia, febrile seizures, & acute arthritis. No basis of evidence for a causal to autism and other chronic diseases. Side effects very rare after revaccination, i.e. with a second dose of MMR vaccine	Good.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
5.	Peltola H, et al. *The elimination of indigenous measles, mumps & rubella from Finland by a 12-year, two-dose program.* N Engl J Med 1994; 331:1397-402.	Multiple study types (surveillance & RCT) 1.5 million vaccinations over 12 yrs	Minimal side effects (ITP 3.3, Feb Fit 7, Urticaria 0.6 per 100,000). No deaths or permanent sequelae.	Good
6.	Isaac D, Menser M. *Measles, mumps, rubella and varicella. In Modern Vaccines - Current Practice and New Approach.* A Lancet Review 1990; pg. 50-58, Hodder & Stoughton, London.	Review of scientific literature.	Gives rates of side effects due to vaccine as compared to natural infections. Marked reduction of CNS related infections due to measles or mumps. Other side effects mild and of low frequency.	Poor
7.	Davis RL, Marcuse E, Black S, et al. *MMR2 immunisation at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunisation in the vaccine safety data link project.* Pediatrics 1997; 100(5): 767-771.	Case control study Very large sample size, good documentation & follow up.	Attempts to provide data on timing of 2nd dose of MMR. Ease of access (younger) versus minimising the impact of waning immunity (older). Side effects significantly (but marginal in terms of number) higher in-group given vaccine later. No firm decision resulting from study.	Poor Fair.
8.	Griffin MR, et al. *Risk of seizures after measles, mumps, rubella immunization.* Pediatr 1991; 88(5): 881-885.	Retrospective cohort study comprising > 18,000 children under the age of 3 years	No episodes of encephalopathy after the first dose of MMR vaccine Very few seizure events. Relative risk of seizures after MMR vaccine 2.1 (95% CI 0.7-6.4)	Fair
9.	Kimura M, Kuno-Sakai H, Yamazaki S, et al.	Nationwide surveillance of 4 MMR vaccines -	Standard MMR, Takeda MMR, Kitasato MMR, Biken MMR vaccines compared. Rates of various	Good to fair.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	Adverse events associated with MMR vaccines in Japan. Acta Paediatr Jpn 1996; 38(3): 205-11 (abst)	1255 participating pediatricians, 38,203 registered recipients of MMR vaccines	complications (e.g. virologically confirmed aseptic meningitis, convulsions, fever) documented for each vaccine. Higher rate of aseptic meningitis noted with Urabe Am 9 mumps virus (Biken MMR vaccine).	
10.	Nicoll A, Elliman D, Ross E. *MMR vaccination and autism 1998.* BMJ 1998; 316:715-6.	Editorial (expert opinion)	Review the data recently published on autism & MMR. no evidence of a causal link highlights the potential damage by limited data.	Poor
11.	Fasano MB, et al. *Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine*. J Pediatr 1992; 120(6): 878-881.	Prospective clinical trial (single arm) of 140 children with documented egg allergy.	The data indicates that 97.5% of children with allergy to eggs can safely receive MMR vaccine.	Fair
12.	Stewart BJA, Prabhu PM. *Reports of sensorineural deafness after measles, mumps, and rubella immunisation.* Arch Ds Child 1993; 69:153-154.	Case series based on national surveillance.	9 cases reports, 3 of which unrelated to MMR. Incidence of adverse events << incidence of sensorineural hearing loss and hence indicates that this possible association is simply by chance.	Poor
Cost Effectiveness				
1.	Frenkel LD. *Routine immunisation for American children in the 1990s.* Ped Cli N Am 1990; 37(3): 531-547.	Review of scientific literature.	Average lifetime cost of congenital rubella syndrome is between US$ 200,000 to 4,000,000.	Poor
2.	White CC, Koplan JP, Orenstein WA. *Benefits, risks and costs of immunization for measles, mumps and rubella.* Am J Public Health 1985; 75(7): 739-44. (Abst)	Cost-benefit analysis using 1983 figures (one year estimates)	Compared actual & estimated morbidity, mortality, & costs attributable to measles, mumps, & rubella with having or not having a MMR immunization program. Without vaccination program, disease costs $1.4 billion. Expenditures for immunization, vaccine administration costs & costs associated with vaccine reactions, totaled $96 million. Cost-benefit ratio for the MMR immunization program	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
			is approximately 1:14.	
3.	Riviere M, et al. *Economic benefits of a routine second dose of combined measles, mumps and rubella vaccine in Canada*. Can J Infect Dis 1997; 8(5): 257-264.	Detailed cost-benefit analysis. Extensive use of various data sources to arrive at estimate.	Estimated cost benefit ratio 1:6.34 for the ministry of health & 1:3.25 to the society (i.e. a savings of US $6.34 for every dollar spent for the ministry of health and US $3.25 for the society). The cost benefit ratio of a two-dose rubella immunisation programme has been estimated as 1:23.	Good.
4.	*Advances in Global Measles Control and Elimination*: Summary of the 1997 International Meeting. MMWR July 24, 1998 / 47(RR11); 1-23.	Summarises the many cost-saving measures for measles immunisation.	Many cost analyses mentioned. Clear statement of the cost-effectiveness of programs to control measles - either by attempts to increase the coverage of a single dose of measles (beyond 95%) or interrupt measles transmission by a two-dose strategy	Fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
5.	Hatziandreu EJ, Brown RE, Halpern MT. *A cost benefit analysis of the MMR vaccine*. Final report prepared for National Immunization Program, CDC & Prevention. Arlington, VA: Center for Public Health Research & Evaluation, Battelle Memorial Institute, 1994. (Quoted data)	Recent CDC cost-benefit analysis. report.	Overall cost benefit ratio of MMR vaccination 1:1443.	Fair

HAEMOPHILUS INFLUENZAE VACCINE

1. BACKGROUND

Haemophilus influenzae virus was first isolated during the 1889 pandemic by Richard Pfeiffer from the blood and CSF of young children with meningitis. It requires blood factors X and V for growth, and hence its name. The first purified polysaccharide (PRP) vaccine was licensed in USA in 1985. However, this vaccine is only of historical significance since its role has been supplanted by the development and licensure of PRP protein conjugate vaccines (Plotkin, 1999)

2. INTRODUCTION

Haemophilus influenzae is a respiratory pathogen of humans causing infections ranging from asyptomatic colonisation of the upper respiratory tract to serious invasive disease. It is an important pathogen for children causing considerable morbidity mortality and health care expense, both worldwide (Dept. of Health, UK.1997; National Health and Medical Research Council, Australia, 1997; Plotkin, 1999) and locally (Choo, 1990; Lyn, 1988; Lee, 1997; Thong, 1983; Puthucheary, 1984; Rohani, 1997).

Most Haemophilus influenzae infections involve asyptomatic infections or colonization, followed subsequently by mucosal infections and invasive disease. Mucosal infections such as otitis media, sinusitis and bronchitis occur frequently, but they do not cause bacteremia.

Invasive disease is associated with encapsulated strains of the organism, there being six capsular serotypes, designated *a-f*. Colonisation by *type b* organisms, however, is infrequent ranging from 2-5% of children in the vaccine era (Department of Health, UK.1997). Invasive disease is characterised by dissemination of bacteria to the blood stream and subsequently to other sites (Plotkin, 1999). Meningitis is the most common invasive Hemophilus influenza type B (Hib) infection, followed by pneumonia, septicaemia, cellulitis, septic arthritis and osteomyelitis Meningitis, frequently accompanied by septicaemia, accounts for approximately 60% of all cases (Dept. of Health, UK.1997; National Health and Medical Research Council, Australia, 1997; Puthucheary, 1984; Thong, 1983; Lee, 1997; Choo, 1990).

Meningitis and other invasive infections are common in children aged 3 months to 3 years, and approximately half these occur in infants less than 12 months (Department of Health, UK.1997; National Health and Medical Research Council, Australia, 1997; Adegbola 1996). Most cases of Hib meningitis in Malaysia occurred in children under 12 months of age and it was rarely encountered beyond 5 years of age (Thong 1983; Puthucheary,

1984). The disease is rare under 3 months of age (Rohani, 1997). Maternally transmitted Hib antibodies may have provided partial protection for Hib infection. Hence, the reason it is uncommon in infants of less than 3 months.

The mode of transmission is presumably from person to person by direct contact or inhalation of droplets of respiratory tract secretions containing organisms. Invasive disease results when Hib organisms spread to other sites, normally through the blood stream (National Health and Medical Research Council, Australia, 1997).

2.1 Incidence Worldwide

The reported incidence in of Hib disease Australia is 500 cases under 8 years per year, with about 10-15 deaths, and 20-40 suffering permanent neurological damage (National Health and Medical Research Council, Australia, 1997). In the United Kingdom, the incidence of invasive disease is 34 per 100,000 under the age of 5 years (Department of Health, UK, 1997). The figures in both these countries were reported before the implementation of the immunization programme. A retrospective hospital based report of the incidence of cases with meningitis in India indicates a rate of 75-100 per 100 000 in children less than 5 years of age (John, 1998). A prospective study in Gambia reported an incidence of 73 per 100 000 children less than 5 years of invasive disease, but a rate of 274 per 100 000 in children less than 1 year with 222 per 100 000 children having Hib Meningitis (Adegbola 1996).

2.2 Local Incidence

Most (> 90%) invasive Haemophilus influenzae infections are caused by *type b* (Department of Health, UK.1997; National Health and Medical Research Council, Australia, 1997; Lee, 1997; Puthucheary, 1984; Thong, 1983; Rohani MY 1997). In two local studies, the incidence of type b disease was 52.2% and 86.1% (Rohani, 1997; Thong 1983). Local hospital based studies have identified Hib to be the most common organism in childhood meningitis, after the neonatal period (Puthucheary, 1984; Lee, 1997; Lyn, 1988; Choo, 1990; Hussain, 1998; Khairuddin, 1999). A large survey involving 7 major hospitals in 1994–1995 revealed the incidence of *Haemophilus influenzae* infection to be 150 per 100 000 with the incidence of pneumonia and meningitis being equal (Rohani, 1997). However, the true incidence may be difficult to ascertain because successful isolation is only possible in a small proportion of cases (Hussain HI 1997).

2.3 Morbidity and Mortality

The mortality for Hib meningitis locally is estimated to be approximately 9% (Choo, 1990; Tee, 1995; Puthucheary, 1984; Thong, 1983) and at least 30% are left with permanent neurological sequelae. These include cerebral palsy, epilepsy, intellectual and developmental handicap, deafness, blindness, hydrocephalus and behavioral abnormalities (Tee, 1995) In the UK before the introduction of the vaccination programme, the mortality rate was reported at 4-5 % with 8-11% having permanent neurological sequelae

3. TECHNICAL FEATURES OF VACCINES

The first generation Hib vaccines, consisting of purified polysaccharide (PRP) from the Hib capsule, were found not to be effective in children under the age of 18 months. However, the second-generation Hib vaccines, which consist of PRP chemically, linked to a variety of carrier proteins, (conjugated) have been shown to be not only immunogenic, but also highly effective over (> 95%) in protecting young children from invasive Hib disease. The carrier protein used in conjugate Hib vaccine ensures a good antibody response to the Hib capsular polysaccharide, but there is no significant antibody response to the carrier protein (National Health and Medical Research Council, Australia, 1997).

There are four types of different vaccines

i. PRP – outer membrane protein conjugate vaccine (PRP – OMP).
   In this vaccine, median lengths of PRP are linked to components of the outer membrane vesicles of serogroup B *Neisseria meningitidis*.

ii. PRP – tetanus toxoid conjugate vaccine (PRP-T).
   In this vaccine, large polysaccharide polymers are linked to tetanus toxoid carrier.

iii. PRP – Hib oligosaccharide conjugate vaccine (HbOC).
   Very short PRP repeat units are linked to CRM_{197}, which is a non-toxic mutant of diphtheria toxin.

iv. PRP – diphtheria toxoid conjugate vaccine (PRP-D). In this vaccine, median lengths of PRP are linked to a diphtheria toxoid carrier.

The 2 Hib conjugates that are presently available in Malaysia are:

- PRP-OMP (Pedvac Hib) – *Merck & Co.*
- PRP-T (Act Hib) – *Pasteur Marieux*

Conjugate vaccines should be stored at 2-8°C. They must not be frozen. The dose of Hib vaccine is 0.5mls, administered by deep subcutaneous or intramuscular injection. Primary immunization begins at 2 months of age (National Health and Medical Research Council, Australia, 1997, Department of Health, UK, 1997).

PRP-OMP is given in three doses - 2 doses at 2-month intervals followed by the third dose at 12-15 months of age. The first and second dose must be of the same vaccine, while the third dose may be any conjugated vaccine (American Academy of Pediatrics, 1997).

PRP-T is administered in four doses, with three doses at 2-month intervals, followed by the fourth dose at 12-15 months of age. The first three doses must be of the same vaccine while the fourth dose may be any conjugated vaccine (American Academy of Pediatrics, 1997).

4. METHDOLOGY

An electronic search of MEDLINE database using various keywords, and year limits was carried out. In addition, three country immunisation handbooks (USA, UK, Australia) WHO reports, Ministry of Health reports and. other important references were obtained from various sources. The keywords used and the year limits were as follows:

Key words used for search and years searched

a. Haemophilus influenza type b vaccine, 1990– 2000
(85% relevancy but would include articles on Influenza virus)
b. Haemophilus and Malaysia, 1970-2000
c Haemophilus influenzae type b and cost, 1966 - 2000

The results are summarized below:

- Total electronic (Medline) search = 278
- Relevant titles (pertaining to Hib vaccines & in English & in humans) = 121
- Abstracts reviewed = 88
- Full papers reviewed = 21
- Papers not available (abstracts used) = 51
- Books and reports reviewed (sections used) = 4

5. RESULTS

5.1 Vaccine Efficacy

The efficacy of the conjugate Hib vaccine has been demonstrated in large field trails in Finland, the United States and in the UK. The efficacy exceeds 95% in infants immunised from 2 months of age (Department of Health, UK, 1997). In Gambia Hib conjugate vaccines prevented 21% episodes of severe pneumonia in vaccine recipients (Mulholland, 1998). In Chile PRP-T vaccination prevented 2.5 episodes of pneumonia per 1000 children per year (Levine, 1999). In a review of 11 previous studies (2 of them

RCT) immunisation with three doses of PRP-T vaccine at 2,3,4 or 2,4,6 months, was shown to be highly immunogenic, where 98-100% of infants had geometric mean antibody titre (GMC) of > 0.15 μgm/l after the 3rd dose (Fritzell, 1992).

5.1.1 Type of vaccine

The American of Academy of Pediatrics considers that PRP-T, HbOC and PRP-OMP are likely to be equivalent in the protection achieved against Hib disease, after completing the recommended primary series of two or three doses (AAP, 1993). The protective superiority of any one of the three vaccines PRP-T, PTP-OMP and HbOC has not been demonstrated (Capeding, 1996; Granoff, 1992; Holmes, 1993). Clinical efficacy studies indicate PRP-OMP, PRP-T and HbOC vaccines are suitable for prevention of Hib disease in infants and children (Claesson, 1991; Decker, 1992; Fritzell, 1992; Booy, 1992; Eskola, 1992; Greenberg, 1994; Parke, 1991; Booy, 1994; Mulholland, 1997; Booy, 1997).

In randomized trials of Hib vaccines, PRP-T had the highest GMC followed by HbOC and PRP-OMP (Decker, 1992; Capeding, 1996; Capeding, 1998). The mean avidity - a measure of the functional affinity of serum antibody to bind to antigen - of antibody elicited by PRP-T was intermediate, being lower than HbOC but higher than PRP-OMP (Schlesinger, 1992). In India, PRP-T showed good immunogenicity with 97% seroconversion (Acharya, 1995). PRP-T conjugate vaccine was able to elicit a protective immune response in children who had low or immeasurable PRP antibody levels after a systemic Hib infection (Berthet, 1998). In a large randomized control trial in Gambia involving 42 848 infants receiving either DPT mixed with PRP-T or DPT alone, it was shown that the efficacy of the vaccine for the prevention of all invasive disease after three doses was 95% and efficacy of two or three doses in preventing Hib pneumonia was 100%. An important finding of this study was the high degree of efficacy shown by the vaccine for the prevention of Hib pneumonia (Mulholland, 1997). Smaller studies with PRP-T have shown an efficacy of 98-100% (Booy, 1997; Booy R 1994). Analysis of cases by ethnic groups consistent with the racial mix of UK suggests that PRP-T vaccine is protective for all racial groups in the UK (Booy, 1997).

In another randomized trial, antibody response to PRP-OMP was higher after the first dose compared to other Hib vaccines, but the levels were not significantly different after 3 doses (Granoff, 1992; Bulkow, 1993; Capeding, 1998).

PRP-D was shown to have low immunigenicity in studies done in USA (Decker, 1992) but was shown to be 90% efficacious in field trials involving a large Finnish cohort. This is possibly due to wide differences in vaccine efficacy in different ethnic groups (Eskola, 1992). Protection may also vary with the age of immunization since the vaccine is less immunogenic in younger infants. Thus in Finland, where relative few cases occur in the first year (28%), a vaccine of lesser immunogenicity may perform better, than in the UK, among Eskimos in Alaska, or in Gambia where 44%, 67% and 84% respectively of Hib occur by 1 year (Booy, 1994).

5.1.2 Dosage

In Chile, the use of fractional and a two dose regimens showed adequate serological response and immunological memory at 13-15 months. This has the potential to lower the cost of immunization of infants in developing countries (Lagos, 1998).

In a study in the UK, with PRP-T in an accelerated immunization schedule (2,3 and 4 months) without booster, there was persistence of satisfactory concentration (92%> 0.15um/ml) of antibody to 4.5 years (Heath, 1997). The impressive efficacy of PRP-T given in infancy and virtual disappearance of the disease in the UK, suggest that the booster dose may not required for a population where high vaccination coverage (>90%) is achieved (Booy, 1997). In Finland, antibody levels were maintained 18 months after the primary immunization (Carlson, 1996). However, in American studies at 12 months of age, the antibody concentration had decreased approximately three to six fold compared with the respective peak concentrations, therefore, a booster dose of a conjugate vaccine is recommended at 12-15 months (AAP 1993)

5.1.3 Combination of vaccines

Effective immunization of children against multiple disease is best tackled by giving several antigens in one injection. The preparation of the single injection could be done either during manufacture of vaccines or immediately before administration, since some authorities recommend that the first dose of both Hib conjugate and DPT vaccines be given at the same time (2-6 months) (Department of Health UK, 1997; National Health and Medical Research Council, Australia, 1997). Their suitability to be administered in combination has been tested. Administration of premixed DTP (acellular) and Hib conjugate(PRP-T) and IPV affects the immune response significantly where the antibody levels were significantly lower (Eskola 1996). Other studies showed similar findings but the antibody concentration was considered to be protective for invasive Hib disease (Scheifele, 1993; Goldblatt, 1999; Pichichero 1997). In Taiwanese infants combining the vaccines (DTaP and PRP-T) did not show any clinically significant immunological interaction (Lee, 1999). Adverse event rates were, however, low when using DTaP and PRP-T (Eskola, 1996; Scheifele, 1993; Lee, 1999). Concurrent administration of PRP-T vaccine with DTwP (whole cell) vaccine, either in the same syringe or at different sites, interfered with antipertussis responses to a primary series of immunizations. Although the clinical significance of this antagonism is uncertain, these data underscore the caution required in decisions to add new vaccines to existing immunization regimens (Clemens, 1992). In other studies, PRP-T and DPwT vaccines combined in a single syringe performed satisfactorily with minimal side effects (Scheifele, 1993; Acharaya, 1995; Levine, 1996; Kaplan, 1994; Kurkila, 1996; Watemberg, 1991; Ferreccio, 1991; Avendano, 1993; Miller, 1995; Barra, 1993).

5.2 Program Effectiveness

The efficacy of Hib vaccine in prevention of invasive Hib disease in the community ranges from 90–98% (Adegbola, 1998; Booy, 1997; Takala, 1994; Dept. of Health, UK.1997; National Health and Medical Research Council, Australia, 1997).

Country	Year Hib Vaccination Introduced	Type of Disease Surveyed	Percentage decline in incidence	Surveillance Program Year Surveyed
Scandinavia (Petola, 1999)	1998-1993	Invasive Hib disease	95%	1996
Finland (Takala 1994)	1986	Hib epiglotitis	94%	1992
USA (Black SB 1992) (AAP, 1997)	1988	Hib invasive disease	94% 95%	1991
U. K (Dept of Health)	1992	Invasive Hib infection < 1 year	96%	1995
Australia (NHMRC)	1993	Invasive Hib disease	90%	1995

As seen in the table above, a review of the introduction of national Hib vaccine in various countries showed a decline in incidence of Hib ranging from 90%–96%.

5.3 Safety

Adverse reactions to Hib conjugate vaccines are few. Pain, redness, swelling at infection site occurs in approximately 5-25% of recipients. These symptoms are mild and last for less than 24 hours. Systemic reactions such as fever and irritability are infrequent (Department of Health, UK, 1997; National Health and Medical Research Council, Australia, 1997; American Academy of Pediatrics, 1997; Vadheim, 1993; Fritzell, 1992: Mulholland, 1994; Booy, 1992; Usonis, 1999, Scheifele, 1993). When conjugate vaccines are administered during the same visit that DPT is given, the rates of systemic reactions do not differ from those observed when only DPT vaccine is administered (Watemberg, 1991, Mulholland, 1994; Fritzell, 1992). The incidence of local effects of the PRP-T mixed with DPT in the same syringe was the same except for tenderness, which was more frequent in those given the mixed vaccine (Scheifele, 1993).

5.4 Cost Implications

Invasive disease caused by Haemophilus Influenzae type b vaccination is associated with serious neurological sequalae and mortality. The cost of Hib disease in the 1988 USA birth cohort would be $2.546 billion without a vaccination program. If 60% of these children are vaccinated at 18 months, savings would amount to $207.1 million, with 3.57/1 benefit-to-cost ratio (Hay, 1990). In Australia, the direct costs of invasive Hib infection would be $10.2 million. Even with a worst-case scenario, an immunisation programme at 6, 12, 18 months would become cost saving if indirect costs of death were included (Mc Intyre, 1994). Cost benefit analyses have shown similar cost-saving benefits in other countries (Asensi, 1995; Midani, 1995; Hussey, 1995; Trollfors, 1994; Levine, 1993; Garpenholt, 1998; Ginsburg, 1993). Two studies had shown that cost and benefit are in balance (Jimenez, 1999; Martens, 1991).

6. CONCLUSIONS

There is sufficient evidence of the effectiveness, safety and cost effectiveness of H influenzae type b immunization. In addition, there is good evidence to support the use of a combination of vaccines. There is inconclusive evidence on the need for a booster dose.

7. RECOMMENDATIONS

It is recommended that all children be immunised with H influenzae type b vaccine at approximately 3, 4 and 5 months of age, to coincide with the visit for DPT OPV vaccination.

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Greenwood Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants [published erratum appears in Lancet 1997 Aug 16; 350(9076): 524] Lancet 1997 Apr 26; 349(9060):1191-7

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9. EVIDENCE TABLE
Hib

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
Vaccine efficacy				
1.	Claesson BA, Schneerson E Persistence of serum antibodies elicited by Hib-T conjugate vaccine in infants. (22) Pediatr Inf DisJ, 1991, 10 (8); 560-4	Monitoring antibody levels 85 children Follow up: 18 months	PRP-T vaccine given at 3,5,12 months. Antibody levels monitored until 18 months after last does. Antibody level > 0.15 ugm/ml; after 1 dose: 81%; after 2 doses: 99%; 18 months after 3rd dose: 97%	Poor (Abstract)
2.	Decker MD, et al Comparative trial in infants of 4 Conjugate Hib Vaccines (24) J of Pediatr 1992 120 (2) 184-89	Double-Blind Randomized Trial 293 children Follow up: 1 month after 3rd dose.	4 Hib vaccines administered randomly at 2,4,6 months of age. Antibody levels monitored 1 month after each dose. Mean antibody levels after 3 injections PRP-OMP - 1.14 ugm/ml PRP-T - 3.64 ugm /ml HbOC - 3.08 ugm /ml PRP-D - 0.28 ugm /ml All 4 vaccines safe for primary vaccination during infancy. PRP-D - low immunogenicity	Good
3.	Fritzell.B;Plotkin S Efficacy and safety of a Hib capsular polysaccharide – tetanus protein conjugate vaccine. (28) J of Pediatr 1992, 121(3) 355-62	Analysis 11 previous studies with PRP-T 2 RCT more than 100,000	Vaccine administered at 2,3,4 months of age or 2,4,6 months. Antibody levels > 0.15 ugm/ml After 2 doses: 69-100% After 3 doses: 98-100% 2 cases of Invasive Hib disease between 1st and 2nd doses.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
4.	Capeding MR; Nohynek H; Pascual LG; Kayhty H; Sombrero LT; Eskola J; Ruutu *The immunogenicity of three Haemophilus influenzae type B conjugate vaccines after a primary vaccination series in Philippine infants* Am J Trop Med Hyg 1996 Nov; 55(5): 516-20	Randomized 174 infants receive one of the 3 Hib vaccines or into a control group GMC measured one month after 3rd dose	*Differences in the GMC three doses were significant (P < 0.0001);* GMC was highest for PRP-T 6.62 umg/ml HbOC 1.9 umg/ml PRP-OMP 1.06 umg/ml control group 0.11 umg/ml All three Hib conjugate vaccines were immunogenic after three primary doses among Philippine infants	Good (Abstract)
5.	Booy R; Taylor SA; Dobson SR; Isaacs D; Sleight G; Aitken S; Griffiths H; Chapel H; Mayon-White RT; Macfarlane JA *Immunogenicity and safety of PRP-T conjugate vaccine given according to the British accelerated immunisation schedule* Arch Dis Child 1992 Apr; 67(4): 475-8	Monitoring antibody levels 107 infants given PRP-T concurrently with diphtheria, pertussis, tetanus, and polio vaccines at 2, 3, and 4 months of age GMC 1 month after 3rd dose	GMC increased from 0.09 umg/ml to 5.01 umg/ml after three immunisations. 98% of children had antibody concentrations consistent with protection (greater than or equal to 0.15 micrograms/ml).	Poor Abstract
6.	Holmes SJ; Fritzell B; Guito KP; Esbenshade JF; Blatter MM; Reisinger KS; Keyserling HL; Rothstein EP; Bernstein HH; Feldman S; et al *Immunogenicity of Haemophilus influenzae type b polysaccharide-*	A multicenter, randomized control trial 484 Infants were vaccinated at 2, 4, and 6 months of age with one of three lots of PRP-T. A control group received H	There were no significant differences in the geometric mean antibody concentration after three doses of PRP-T or HbOC (8.3 vs. 7.7 μgms/mL), 95% and 91%, respectively, of infants had greater than 1.0 microgram/ml of antibody.	Good (Abstract)

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	tetanus toxoid conjugate vaccine in infants Am J Dis Child 1993 Aug; 147(8): 832-6	influenzae type b oligomers conjugated to CRM197 (HbOC)		
7.	Eskola J; Peltola H; Kayhty H; Takala AK; Makela PH Finnish efficacy trials with Haemophilus influenzae type b vaccines J Infect Dis 1992 Jun; 165 Suppl 1:S137-8	cohort 58000 infants vaccinated with PRP-D at 3, 4, and 6 months of age	The PRP-D vaccine (polysaccharide conjugated to diphtheria toxoid) was 90% efficacious	Fair (Abstract)
8.	Greenberg DP; Vadheim CM; Partridge S; Chang SJ; Chiu CY; Ward JI Immunogenicity of Haemophilus influenzae type b tetanus toxoid vaccine in young infants. The Kaiser-UCLA Vaccine Study Group J Infect Dis 1994 Jul; 170(1): 76-81	prospective, randomized, double-blind PRP-T against Hep B vaccine 10,317 infants 4 months follow up	Geometric mean concentrations of total anticapsular antibody were 0.08, 0.79, and 5.29 micrograms/ml after the first, second, and third doses, respectively.	Good (Abstract)
9.	Parke JC Jr; Schneerson R; Reimer C; Black C; Welfare S; Bryla D; Levi L; Pavliakova D; Cramton T; Schulz D; et al J Clinical and immunologic responses to Haemophilus	Case control 77 infants receiving injections at 3, 5, 7, and 18 months of age. (Hib-TT) Control 10 infants	Hib antibody level rose to 0.55 μgm/ml, and each subsequent injection elicited a statistically significant rise in the geometric mean. The percentage of vaccinees with Hib antibody levels greater than 0.15 μgm/ml serum was 75.5% after the first, 97.4% after the second, and 100% after the third Hib-TT injection. It fell to 90.9% at 18	Fair (Abstract)

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	influenzae type b-tetanus toxoid conjugate vaccine in infants injected at 3, 5, 7, and 18 months of age. Pediatr 1991 Feb; 118(2): 184-90	receiving DPT	months of age but rose again to 100% after the fourth injection. Control infants only had nondetectable levels after the second injection.	
10.	Booy R; Hodgson S; Carpenter L; Mayon-White RT; Slack MP; Macfarlane JA; Haworth EA; Kiddle M; Shribman S; Roberts JS; et *Efficacy of Haemophilus influenzae type b conjugate vaccine PRP-T* Lancet 1994 Aug 6; 344(8919): 362-6	Controlled community intervention study PRP-T was offered to infants addition to the standard DPT to an accelerated 2, 3, and 4 month schedule 2 years follow up	None of the infants given three doses had developed Hib infection, whereas 11 infections occurred in the control population (vaccine efficacy 100%, 95% CI 80-100%). Follow-up of study has shown only 1 vaccine failure in an infant and no invasive infections in those older than 1 year (average age 22 months).	Good
11.	Mulholland K; Hilton S; Adegbola R; Usen S; Oparaugo A; Omosigho C; Weber M; Palmer A; Schneider G; Jobe K; Lahai G; Jaffar S; Secka O; Lin K; Ethevenaux C; Greenwood *Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants* Lancet 1997 Apr 26; 349(9060): 1191-7	Double -blind randomised trial 42,848 infants were randomly allocated the PRP-T mixed with DTP, or DTP alone Followed up between 5 and 36 months.	The efficacy of the vaccine for the prevention of all invasive disease after three doses was 95% (PRP-T vaccine 1, controls 19 [95% CI 67-100]) Efficacy of two or three doses in preventing Hib pneumonia was 100%	Good
12.	Granoff DM; Anderson EL et al Differences in immunogenicity of 3 Hib conjugate vaccines in infants (34)	Randomized Inmmunogenicity trial 458 infants Efficacy of 3 Hib vaccines (PRP-OMP, PRP-T and HbOC)	Antibody level was significantly higher after 1 dose of PRP-OMP After 3 doses, level of antibody response was not significantly different in the 3 vaccines.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	J of Pediatr 1992, 121(2) 187-94	compared. Antibody assay after 1-month post administration at 2,4, and 6 months of age.		
13.	NHMRC *The Australian Immunisation hand book* 6th edition National Health and Medical Research Council 1997	*Review of clinical trials*	PRP chemically linked (conjugated) to a variety of carrier proteins have been shown to be not only immunogenisc highly effective (over95%) in protecting young children from invasive Hib disease	Good
14.	Booy R; Heath PT; Slack MP; Begg N; Moxon ER *Vaccine failures after primary immunisation with Haemophilus influenzae type-b conjugate vaccine without booster* Lancet 1997 Apr 26; 349(9060): 1197-202	National surveillance report all cases of invasive H influenzae infection in children who had received at least one dose of Hib-conjugate vaccine.	164 reports of invasive infection in the study period, 43 were considered true **vaccine** failures. The estimated overall efficacy for three doses of PRP-T was 98.1% (95% CI 97.3-98.7%).	Fair
15.	Lagos R,Valenzuela M T, Levine O Economisation of vaccination against H. influenzae type b: a randomized trial of immunogenicity of fractional dose and two	*Randomized control trail Comparing fractional doses (one half and one third), two dose and standard*	For PRP-T all 4 regimens resulted in adequate serological response With PRP-CRM one half and one third doses were as effective as the full dose in eliciting PRP antibody. The two dose PRP-CRM regimen was the least immunogenic Fractional doses Of PRP-T and PRP-CRM vaccines can stimulate adequate antibody in 91-100% of the immunised infants	Good

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	dose regimens Lancet, Vol.351 (9114) May 16 1998 1472-1476	*three dose regimens for PRP-T and PRP-CRM* *I year follow up*		
16.	Carlson RM; Claesson BO.A; Lagergard T Serum antibodies against Hib and Tetanus at 2.5 years of age: A follow up of two different regimens of infant vaccination Sand J Infect Dis 519-523 1996	*Randomised trial of PRP-T and PRP-OMP and two difffrent regimen of tetanus vaccination* *2.5 years folluow up*	Hib and tetanus antibodies were well maintained 18 months after primary vaccination PRP-T 93% antibody levels $\geq$ 15 μgm/ml PRP-OMP 80% antibody levels $\geq$ 15 μgm/ml	Good
17.	Acharya D; Desai A; Nanavaty N; Pandit A; Patel V; Shah J; Shendurnikar N; Singh S; Taneja A; Vani S. *Evaluation of immunogenicity and tolerance of single dose haemophilus influenzae type B (PRP-T) vaccine*. Indian Pediatr 1995 Oct; 32(10): 1077-82	Multicenter open parallel group Group 1 PRP-T alone Group 11 PRP-T and DPT	Prevaccination antibody levels > 0.15 mcg/ml in 56.3% in Group I 35.7% in Group II. Post-seroconversion was seen in 97% in Group 1 100% in Group II The **vaccine** was well tolerated	Fair (Abstract)
18.	Capeding MR; Nohynek H; Kayhty H; Pascual LG; Sunico ES; Tamundong AA; Ruutu P *Antibody responses of three Haemophilus influenzae type b conjugate vaccines after one, two and three doses in*	? randomized 102 infants 3 months follow up	Differences in the GMC after the primary series were significant: GMC was highest for PRP-T (4.0), followed by HbOC (1.6) and PRP-OMP (1.1)	Fair (Abstract)

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	Filipino children. Vaccine 1998 May-Jun; 16(9-10): 1004-8			
Safety				
1.	Green Book Immunisation against Infectious Disease Department of Health Welsh Office Scottish Office of Health DHSS (North Ireland) 1996	Review of clinical trials Post licensure surveillance	• Swelling and redness at injection site: 10% • No increase in incidence of febrile convulsions compared to controls. • No increase in adverse reactions when combined with DPT Non replicating bacterial capsular antigens	Good
2.	National Health and Medical Research Council Australia The Australian Immunisation hand book 6th edition 1997	*Review of clinical trials* *Post licensure surveillance*	• Swelling and redness at injection site: 5% • No increase in adverse reactions when combined with DPT	Good
3.	Red Book Report of the Committee on Infectious Disease 24th edition 1997	Review of clinical trials Post licensure surveillance	• Pain, redness and/or swelling occur in approximately 25% but these are mild and last for 24 hours • No increase in adverse reactions when combined with DPT	Good
4.	Vadheim CM; Greenberg DP; Partridge S; Jing J; Ward JI Effectiveness and safety of a Haemophilus influenzae type b conjugate vaccine (PRP-T) in young infants. Kaiser-UCLA Vaccine Study Group. Pediatrics 1993 Aug; 92(2): 272-9	Randomized double blind controlled trial. 10317 infants Parental reports *Follow-up : 3 months* *PRP-T/DPT* *HepB/DPT*	• Swelling and redness: 12 - 18 % • Tenderness: 57 % • Fever > 102 ^{o} F: 5.5% • Five seizure episodes vs. three in controls.	Good
5.	Fritzell B; Plotkin S Efficacy and safety of a	Review of controlled trials	DPT and PRP-T given simultaneously. Redness and swelling: 9.8 – 12.4%; Tenderness: 42 %;	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	Hib polysaccharide tetanus protein conjugate vaccine 1992. J Pediatr 1992 Sep; 121(3): 355-62	Active monitoring 7 900 children	Fever > 39 ^{o} C 4.5 – 5.7%; Seizure: 5 infants; Tremors: 1 infant; Hypotonia – hyporesponsive episode: 2 infants; Well within the limits observe red for DPT given alone	
6.	Mulholland EK; Byass P; Campbell H; Fritzell B; Greenwood AM; Todd J; Greenwood BM *The immunogenicity and safety of Haemophilus influenzae type b-tetanus toxoid conjugate vaccine in Gambian infants*. Ann Trop Paediatr 1994; 14(3): 183-8	Randomised 131 infants were recruited and randomized into three groups to receive PRP-T at 1 and 3 months (group A), PRP-T at 2 and 4 months (group B) or no PRP-T (group C).	No serious side effects were observed and the rate of adverse reactions was consistent with the concurrent administration of diphtheria-tetanus-pertussis (DPT) vaccine.	Good (Abstract)
7.	Booy R; Taylor SA; Dobson SR; Isaacs D; Sleight G; Aitken S; Griffiths H; Chapel H; Mayon-White RT; Macfarlane JA Immunogenicity and safety of PRP-T conjugate vaccine given according to the British accelerated immunisation schedule. Arch Dis Child 1992 Apr; 67(4): 475-8	107 infants The PRP-T vaccine was given concurrently with DPT and polio vaccines at 2, 3, and 4 months of age.	No serious adverse reactions were observed and there was no increase in the incidence of expected minor side effects.	Poor Abstract

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
8.	Usonis V; Bakasenas V *Does concomitant injection of a combined diphtheria-tetanus-acellular pertussis - hepatitis B virus - inactivated poliovirus vaccine influence the reactogenicity and immunogenicity of commercial Haemophilus influenzae type b conjugates vaccines?* Eur J Pediatr 1999 May; 158(5): 398-402	549 healthy infants at 3, 4.5 and 6 months of age (Hib) conjugate vaccines (Hiberix, ActHib, Pedvax, HibTITER) administered concomitantly but in the opposite thigh with a candidate DPT-acellular pertussis-hepatitis B-inactivated poliovirus vaccine	Local reactions were mild, but different between the four groups, **a tetanus conjugate** Hib **vaccine** showing the fewest reactions. All local reactions resolved without sequelae. There was no apparent general reaction.	Good Abstract
9.	Watemberg N; Dagan R; Arbelli Y; Belmaker I; Morag A; Hessel L; Fritzell B; Bajard A; Peyron L *Safety and immunogenicity of Haemophilus type b-tetanus protein conjugate vaccine, mixed in the same syringe with diphtheria-tetanus-pertussis vaccine in young infants* Pediatr Infect Dis J 1991 Oct; 10(10): 758-63	Randomised 112 infants received DTP-PRP-T or DTP-placebo mixed immediately before immunization in the same syringe.	The addition of PRP-T to DTP did not increase the rate of local or systemic reactions.	Good (Abstract)
10.	Scheifele D; Barreto L; Meekison W; Guasparini R; Friesen **B** *Can Haemophilus influenzae type b-tetanus toxoid conjugate vaccine be combined with diphtheria toxoid-pertussis vaccine-tetanus toxoid?* CMAJ 1993 Oct 15; 149(8): 1105-12	Multicenter randomized control trail Infants given PRP-T and DPT either mixed in single syringe or separate syringe bilateral injections	Local adverse effects of the PRP-T **vaccine** were infrequent and mild (e.g., redness was noted in 5.9% of cases and the area of redness was more than 2.5 cm in diameter in 0.8%). The incidence rate of local effects of the DPT-containing **vaccines** was the same in the two groups except for tenderness, which was more frequent in the group given the mixed **vaccine** (26.6% v. 17.9%, $p < 0.001$).	Good (Abstract)

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
11.	Miller MA; Meschievitz CK; Ballanco GA; Daum RS Safety and immunogenicity of PRP-T combined with DTP: excretion of capsular polysaccharide and antibody response in the immediate post-vaccination period. Pediatrics 1995 Apr; 95(4): 522-7	Randomised control trials DPT/PRP-T combined DPT and PRP-T separately DPT and HbOC separately All received oral polio 150 infants 5 month follow-up	Combining PRP-T and DTP produced a combination vaccine associated with a slight increase in the rate of erythema and swelling but with similar immunogenicity of the vaccine components and oral polio vaccine.	Good (Abstract)
Cost Effectiveness				
1.	Jimenez FJ, Guallar-Castillon P, Rubio Teres C, Guallar E. Cost benefit analysis of H. Infuenzae type b vaccination in children in Spain. Pharmacoeconomics 1999 Jan; 15(1) 75-83	Cost benefit analysis 5 year period 384,883 infants	• Benefit-to- cost- ratio 0.89/1. • This ratio would be >1 in regions of highest incidence of the disease. Economic returns would be at of a similar magnitude as its expense. Decision to implement should not be based only on economic factors	*Good* (Abstract)
2.	Garpenholt O; Silfverdal SA; Levin LA. Economic evaluation of general childhood vaccination against H. Influenzae type b in Sweden Scand J Infect. Dis 1998; 30(10:5-10)	Cohort studies comparing with historical cohort 0-4yr old children	Analysis shows that it is cost saving if indirect cost is included. General childhood Hib vaccination is cost effective public health intervention in Swedish society	Fair (Abstract)

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	Asensi F; Otero MC; Perez- Tamarit D, Miranda j; Pico L; Neito A Economic aspects of a general vaccination against invasive disease caused by H. Influenzae type b (hib) via the experience of the Children's Hospital La Fe Valencia Spain Vaccine 1995 Nov 13(16), 1563 –6	Retrospective 100 cases of invasive Hib disease Cost analysis was done to compare cost of care and a vaccination program	Mean annual cost of care + economic valuation of loss of life 205 million pesetas. Cost of vaccinating (4 doses) infants in the region 84 million pesetas(max) Hib vaccination would be profitable even if not quantifying the cost of loss of life This is without taking into account the fact that the emotional, family and social serious disturbance would also be avoided due to hospitalisation, sequalae and deaths caused by the disease	Good (Abstract)
4.	De Campora E; Pizzuti R Use of the economic evaluation in the comparison of different vaccination programs against H. Influenzae type b disease Ann Ig 1995 Sept- Oct; 7 (5): 329-38	Compares several vaccination strategies in terms of cost benefit, cost effectiveness and cost utility	Highest benefit could be obtained performing mass vaccination in the age gp 0-5 years.	Fair (Abstract)
5.	Midani S; Ayob EM; Rathore MH. *Cost effectiveness of H. Infuenzae type b conjugate vaccine program in Florida* J Fla Med Assoc 1995 Jun 82(6): 401-2	Cost effectiveness were investigated and three periods compared Immunisation with hib vaccine started during Period III	Cost per year of Hib disease Period I 1984-1988 $27.84 million Period II 1989-1990 $15.95milion Period III 1991-1992 $0.88 million The greatest saving was realised between periods I and III Hib immunisation is cost effective and significant savings would more than pay for the cost of the program	Good (Abstract)

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
6.	Hussey GD; Lasser ML; Reekie WD *The cost benefit s of a vaccination programme for H. Influenzae type b disease*. S Afr Med J 1995 Jan 85:85(1): 20-5	Cost benefit analysis on birth cohort of 46,537 comparing the disease cost and the cost of vaccination	the absence of vaccination the estimated economic cost nge R10.7 million –R11.8 million; cost of introducing ccination - R8.3 million. Had the vaccine been ministered to the 1992 cohorts benefits would have ceeded cost by between R2.4 million and R3.5 million	Good (Abstract)
7.	Mc Intyre P; Hall J , Leeder S An economic analysis of alternatives for childhood immunisation against H Influenza type b disease. Aust J Public Health 1994 Dec 18 (4): 394-400	Cost benefit analysis on birth cohort of 250,000 comparing the disease cost and the cost of vaccination	Without immunisation direct cost would be $10.2 million Even under the worst case scenario an immunisation program at 6, 12, 18 months became cost saving if indirect cost of death were included	Good (Abstract)
8.	Harris A, Hendrie D, Bower C, Payne J, de Klerk N, Stanley F,. *The burden of H influenza type b disease in Australia and an economic appraisal of the vaccine PRP-OMP* Med J Aust 1994 Apr 18: 160(8); 483-8	Extent of the disease and cost sequelae was based medical records. Cost benefit analysis was used to predict cost of the implementation of an vaccination program with PRP-OMP at 2,4 and 12 months over a 5 year period	The vaccination program would decrease deaths per year from 19 to 2 and severe disability from 46 to 21 cases. The incremental cost per quality adjusted life year is $1965 compared to $5047 of a single vaccine at 18 months	Good (Abstract)
9.	Trollfors B Cost benefit analysis of general vaccination against Haemophilus influenzae	Cost benefit analysis incidence and prognosis of epiglottises and meningitis from a retrospective	Annual cost was SEK72 million (including values of life lost) Cost of the immunization program would be SEK45 million	Good (Abstract)

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	type b in Sweden Scand J Infect Dis 1994; 26(5) 611-4	studies	General vaccination of infants against hib is cost effective saves life's and reduces human suffering	
10.	Ginsburg GM, Kassis I, Dagan R *Cost benefit analysis of Haemophilus influenzae type b vaccination programme in Israel.* J Epidemiol Community Healt 1993 Dec; 47 (6): 485-90	Cost benefit analysis between 3 and 4 doses Hib prevention programmes	The 4 dose programme would yield a benefit / ratio of 1.26:1 when benefits of reduction in mild and sever neurological sequelae The ratio is 1.45/1 when indirect benefits of reduction in work absences and mortality are included & 0.29/1 for health services alone. Benefits would exceed cost to society. Cost of the programme exceed the benefits to the health services alone	Good (Abstract)
11.	Levine OS Ortiz E, Contreras R, Lagos R, Vail P Cost benefit analysis for the use of H. Influenzae type b conjugate vaccine in Santiago, Chile Am J Epedimiol 1993 Jun 1; 137(11): 1221-8	Cost benefit analysis on base model over 10 year period	Vaccination would prevent 1229 cases of Hib invasive disease. The benefit/cost ratio 1.66/1 Net discounted savings $403,225	Good (Abstract)
12.	Martens LL, ten Valden GH, Bol P *Cost and benefits of vaccination against Haemophilus influenzae type b* Ned Tijdschr Geneeskd 1991 Jan 5; 135(1): 16-20	Cost effective analysis Some elements are in the analysis are uncertain-price, schedule and method of administration.	Cost and benefit would be in balance	Poor (Abstract)
13.	Hay WJ; Daum RS; Cost benefit analysis of H. Influenzae type b prevention: conjugate	Cost benefit analysis on the use of PRP-D and HbOC for children less than 18 months	Economic cost of Hib disease in USA birth cohort would be $2.546 billion If 60% of the children are vaccinated at 18 months savings would amount to 207.1 million with 3.57/1 benefit-to-cost ratio	Good abstract

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	vaccination at 18 months of age Pediatr Infect Dis j. 1990 Apr; 9(4) 246-52		Vaccination at 18 months of age is sufficiently efficacious so that the cost of vaccination would more than offset by decreased medical care cost for treating Hib disease	
Program Effectiveness				
1.	Takala AK; Peltola H; Eskola J *Disappearance of epiglottises during large-scale vaccination with Haemophilus influenzae type B conjugate vaccine among children in Finland* Laryngoscope 1994 Jun; 104(6 Pt 1): 731-5	National Surveillance before and after introduction of Hib-conjugate vaccination in Finland, with coverage of 94% to 98% of infants.	In 1987 through 1992, the proportion of vaccinated children increased steadily while the incidence of Hib epiglottises decreased from 50 to 60 cases seen annually in 1985 and 1986 to 2 cases in 1992.	Fair (Abstract)
2.	Booy R; Heath PT; Slack MP; Begg N; Moxon ER Vaccine failures after primary immunisation with Haemophilus influenzae type-b conjugate vaccine without booster Lancet 1997 Apr 26;349(9060):1197-202	National surveillance report all cases of invasive H influenzae infection in children who had received at least one dose of Hib-conjugate vaccine.	164 reports of invasive infection in the study period, 43 were considered true **vaccine** failures. The estimated overall efficacy for three doses of PRP-T was 98.1% (95% CI 97.3-98.7%).	Fair
3.	Adegbola RA, Mulholland EK, Secka O, Jaffar S, Greenwood BM. *Vaccination with a Haemophilus influenzae type b conjugate vaccine*	Survey of 1000 children aged 1-2 years for 4 consecutive years Children were vaccinated	Carriage was significantly lower among children fully vaccinated with Hib/PRP-T given with DTP (4.4%; 95% confidence interval [CI], 3.8%-5.7%) than among children fully vaccinated with DTP alone (11.0%; 95% CI, 8.9%-	Good (Abstract)

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	reduces oropharyngeal carriage of H. influenzae type b among Gambian children. J Infect Dis. 1998 Jun; 177(6): 1758-61	with Hib/PRP-T and DTP or DTP alone at ages 2, 3, and 4	13.0%) (Protective effect adjusted by year = 60%; 95% CI, 44%-72%; P < .001).	
4.	Red Book - Immunisation Against Infectious Disease Department of Health Welsh Office Scottish Office of Health DHSS (North Ireland) 1996	Recommendation by expert committee based on scientific literature	96% reduction in invasive Hib infection for children under 1 year after introduction of the immunisation	Good
5.	NHMRC Australian Immunisation hand book 6th edition National Health and Medical Research Council 1997	Recommendation by expert committee based on scientific literature	90% reduction in invasive Hib infection for children under 5 years after introduction of the immunisation	Good
6.	Black SB; Shinefield HR Immunization with oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine on a large health maintenance organization population: extended follow-up and impact on Haemophilus influenzae disease epidemiology. The Kaiser Permanente Pediatric Vaccine Study Group. Pediatr Infect Dis J 1992 Aug; 11(8):610-3	Post licensure survey Compared with pre licensure prospective study	94% reduction in disease incidence in this age group from that observed in the years 1984 to1987	Fair (Abstract)

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
7.	Petola H; Aavitsland P; Hansen KG; Jonsdotir KE. *Prospective five-country analysis of the impact of four different H. Influenzae type b conjugates and vaccination strategies in Scandinavia*. J Infect Dis. 1999 Jan; 179(1): 223-9	Retrospective and prospective data	Prior to vaccination the incidence of cases in Scandinavia 49 per 100000 per year in 0-4 year olds Vaccination introduced 1989-1993 95% effectiveness	Good (Abstract)

VARICELLA ZOSTER VACCINE

1. INTRODUCTION

Varicella-zoster virus infections are rapidly emerging as the most common vaccine-preventable illness in several developed countries that have in place, successful measles and rubella control programs. Yet, varicella-zoster infections are popularly viewed as a nuisance disease; accumulating evidence however indicates that such infections may yet result in not-inconsequential morbidities and cause fatalities. It is to be acknowledged however, that whereas the introduction of vaccination programmes was to essentially prevent death either directly (e.g. smallpox, diphtheria vaccines) or indirectly (e.g. rubella vaccine in children to prevent fetal disease), varicella vaccination is essentially a strategy to decrease disease morbidity, thereby improving quality of life. Hence, an assessment of the benefits of varicella vaccination is best viewed by its impact on quality-of-life measures, rather than by traditional yardsticks of vaccine benefits.

1.1 Disease Pattern

The Varicella-zoster virus (VZV) causes two distinct clinical syndromes, varicella (chickenpox) and herpes zoster (HZ). Like other childhood exanthemas, varicella is exclusively a human disease; animal or insect reservoirs are not known to exist (Centers for Disease Control and Prevention, 1999).

Primary infection by VZV results in varicella (chickenpox), a vesicular exanthema that is spread through respiratory aerosols that inoculate a susceptible host's conjunctivae and upper respiratory tract. A low-grade primary viremia occurs 4-6 days after infection, followed by a secondary larger viremia 10-12 days after infection that results in cutaneous infection. On the average, the rash appears 14 days after infection (Gershon, 1998).

After an incubation period of 14–16 days, fever occurring concurrently with rashes heralds the onset of disease (Gershon, 1998). The characteristic rash appears in crops over the next 5-6 days in an essentially central distribution (trunk, scalp and face) and usually progresses rapidly from macules to papules, vesicles, pustules and crusts. Crops of lesions in different stages of evolution may be seen, numbering usually between 250 to 500 (Balfour, 1990). Shallow herpetiform ulcers may also occur in the mucosae of the upper respiratory tract and the rectum/vagina. The height and course of fever closely parallels the progression of rash and a subject is usually ill from 5-7 days in uncomplicated infection (Gershon, 1998). Clinical examination is often sufficient for diagnosis.

The most common complication in children is secondary bacterial infection of skin (Preblud, 1986). Most infected healthy children have minimal extracutaneous complications. Acute, often self-limited, cerebellar ataxia may occur in up to 1/4000 infected children (Guess, 1986). Varicella encephalitis is a more serious, albeit less common, complication; pneumonia (Policy Analysis Inc, 1994) and hepatitis (Plotkin, 1985) are the other two important complications (CDC, 1996). With widespread public awareness, the incidence of Reye's syndrome related to salicylate use in varicella infection has declined dramatically (CDC, 1989).

Varicella is highly contagious (Centers for Disease Control and Prevention, 1999) with secondary attack rates among susceptible contacts, of 90%. An infected subject is contagious beginning 1-2 days before onset of rash until 4-5 days later, when all lesions have crusted (CDC, 1996).

Sub clinical primary infection is rare (American Academy of Pediatrics, 1997; National Health & Medical Research Council, Australia, 1997), while repeat cases of varicella are unusual in immunocompetent individuals (Gershon, 1984; Junker, 1991; Terada, 1996); sub clinical reinfection is, however, common and often boosts antibody titers (Arvin, 1983; Gershon, 1982; Gershon, 1990).

As opposed to the apparently benign course of disease in healthy children, certain patient populations are at especial risk for severe or complicated varicella (CDC, 1997; Choo, 1995; Gogos, 1992; Brunell, 1992; Joseph, 1988; Preblud, 1986):

1. Susceptible immunocompetent individuals like fetuses or newborns (Enders, 1994; Gershon, 1994; Pastuszak, 1994; Centers for Disease Control and Prevention, 1999; Brunella, 1981; Dworsky, 1980), pregnant women, adolescents and young adults (> 16 years old), and children living in crowded conditions (e.g., day-care centers) (Aebi, 1996; Vugia, 1996; Diez, 1999; Doctor A, 1995; Peterson, 1996; Kuter, 1991; White, 1991).
2. Immunodeficient individuals.
   Severe varicella infection often develops in immunodeficient individuals referred to as progressive varicella (Krugman, 1992). These include patients receiving radiation therapy or/and chemotherapy for malignant diseases, individuals with congenital immune deficiencies involving cell-mediated immunity, those with the Human Immunodeficiency Virus infection, and patients on high-doses of steroids and other cytotoxic agents (Jura, 1989).

1.2 Incidence

Varicella infection is not a notifiable illness in Malaysia, and, coupled with the essentially self-limiting disease course in most children that often does not necessitate contact with a doctor (Joseph, 1988), means that accurate estimates of disease incidence are not available. Experience in the United States indicates that disease incidence approximates the birth-cohort (CDC, 1996; Plotkin, 1985) resulting in an annual incidence of 4 million, of whom approximately 10% seek medical attention (Guess, 1986) while in the UK; 1/3rd seek treatment (Joseph, 1988). 0.3% of varicella-infected

individuals would require hospitalization. In tropical countries, the number of susceptible immune-naive adults is higher (Lin, 1996; Barzaga, 1994; Garnett, 1994; Ooi, 1992; Kositanont, 1985; Venkitaraman, 1984; Sinha, 1976; Maretic, 1963). With the exception of the children less than a year old, severe varicella is more likely to occur in infected adolescents and young adults (Gershon, 1998; Guess, 1986).

2. TECHNICAL FEATURES OF VACCINE

The varicella vaccine is a live-attenuated vaccine using the Oka virus strain, isolated originally in the early 1970s from the vesicular fluid of an infected healthy child, and maintained by serial passage in cultures of human embryonic lung fibroblasts, embryonic guinea-pig cells and human diploid cells (WI-38) (Oka/Merck varicella vaccine product monograph, 1997). The Oka strain was subsequently licensed to several pharmaceutical companies (see below) resulting in vaccines that differ in viral dose, the number of passages in human diploid cells and stabilizer constituents (Gershon, 1998). The following vaccines are currently licensed for use in Malaysia:

Vaccine type	Characteristics
VARIVAX (Merck & Co. Inc.)	The present lot (1991) has 2 900 – 9 000 Plaque Forming Units (PFUs). Marketed as a lyophilized preparation (stored frozen at -20°C) with a reconstituting fluid (may be refrigerated); 0.5 ml is administered **subcutaneously**. It has been extensively studied. Usually costed at US$ 35 in most studies
VARILIX (SmithKline Beecham Biological)	Approximately 600 – 1200 PFUs (Andre, 1984; Varis 1996). Added stabilizers that facilitate storage at 4-8°C. Extensive field data not available.

Other manufacturers include Pasteur-Merieux-Connaught (France) and Biken (Japan). Since the Merck vaccine preparation has been, the most extensively studied, subsequent references would refer to the Oka/Merck vaccine preparation (unless otherwise stated).

2.1 Vaccine Administration

2.1.1 independently administered

Varicella vaccine is administered in healthy children between 12 months – 12 years, universally in a single dose, 0.5 ml, subcutaneous. In healthy susceptible individuals, 13 years of age and above, two doses of 0.5 ml each are administered subcutaneously, 4-8 weeks apart.

2.1.2 Administered with other childhood vaccines

Varicella vaccine can be administered with MMR in separate syringes, simultaneously at different anatomical sites, or administered mixed together in the same syringe. It can also be administered concomitantly with DPT/OPV/Hib (separate syringes).

3. METHODOLOGY

An electronic search of MEDLINE database using various keywords, and year limits was carried out. In addition, three country immunisation handbooks (USA, UK, Australia) The Centers for Disease Control and Prevention Mortality and Morbidity Weekly Reports, and. other important references were obtained from various sources. The keywords used and the year limits were as follows:

(a) Varicella/Chickenpox 1960 - 2000
(b) Varicella Vaccine 1970 – 2000
(c) Malaysia and Chickenpox 1966 – 2000
(d) Malaysia and Immunisation 1966 – 2000

The results are summarized below:

- Total electronic (Medline) search = 221
- Relevant titles (pertaining to Varicella vaccines) = 117
- Abstracts reviewed = 57
- Full papers reviewed = 8
- Abstracts not available for review = 32
- Books and reports reviewed (sections used) = 10

4. RESULTS

4.1 Vaccine Efficacy

Vaccine efficacy needs to be discussed from several aspects.

4.1.1 Short-term immunity

(a) Immunogenicity

Seroconversion rates ranging from 90–99% in an overall study population of 6889 susceptible healthy children 12 months – 12 years, have been observed in several studies within 4–6 weeks of vaccination, over a wide range of viral doses (300 – 17000 PFUs) and manufacturing processes (White, 1991; Arbeter, 1986; Weibel, 1985;Asano 1983). Seroconversion was assessed using VZV glycoprotein-based ELISA (gpELISA) or the Fluorescent Antibody to Membrane Antigen (FAMA) techniques. While no reliable immune correlates exist, geometric mean titers above 1:5 as assayed by gp-ELISA appear to be protective. However, commercially available assays are insensitive in detecting post-vaccination seroconversion (Gershon, 1992).

Seroconversion rates appear to be significantly less in adolescents and healthy adults (1648 adolescents and adults, 15-55 years of age), necessitating two doses of the vaccine to achieve 90% seroconversion (Kuter, 1995). Further, geometric mean titer following two-dose exposure is around 1:6, half of what is seen in post-vaccinated healthy children (White, 1991). Apart from this, the vaccine dose significantly influences seroconversion rates, the higher the viral dose, and the higher the seroconversion rate. Most current vaccine preparations have viral doses ranging between 500 to 3 500 PFUs (Watson, 1993; Rothstein, 1997). Further, higher vaccine doses are associated with lower rates of breakthrough varicella (Varis, 1996, Gershon, 1995)

(b) Protective efficacy

Most published long-term follow up studies indicate that following household exposure, up to 80% of vaccinated children are protected from all forms of varicella infection, giving a disease attack rate in the vaccinated population of 15-20% as compared to the 80-90% attack rate in susceptible household contacts (Kuter, 1991; White, 1991). Up to 98% of vaccinated children are protected from severe varicella (Kuter, 1991; White, 1991). Breakthrough varicella in vaccinated household contacts is significantly milder with fewer than 50 cutaneous lesions, lower median febrile spikes and shorter disease duration of 5 days, referred to as Mild Varicella-like syndrome, MVLS (Gershon, 1996; White, 1992).

4.1.2 Long-term immunity

Of more than 200 immunized healthy children followed up over 4-6 years, 95% showed persistent antibody levels to varicella (Clements, 1995; Watson, 1994; Kuter, 1991). In one study, 97% vaccinees demonstrated appropriate CMI 5-6 years post-immunization. A similar response is seen in adolescents and young adults in 20-year follow-up studies in Japan (Asano, 1996; Asano, 1994; Asano, 1985).

Long-term protective efficacy is dose-dependent and is observed at gpELISA VZV antibodies of more than 10 units at 6 weeks post-vaccination, and may be ensured by administering two doses of vaccine 4-8 weeks apart (Watson, 1995; Watson, 1994). Breakthrough varicella infections post-vaccination occur at a constant rate of 0-4% per year, with no increased incidence over time (Krause, 1995). The incidence of Herpes Zoster in vaccinated children, which may reflect waning CMI following potential post-vaccination latent VZV infection, is not increased (Guess, 1985).

Long-term antibody persistence has to be viewed with caution, since continued circulation of wild-type VZV may result in periodic immune boosts without overt infection (Asano, 1996). The long-term protective efficacy of the varicella vaccine cannot be unequivocally established, until widespread vaccine coverage interrupts wild-type VZV transmission. A study of 16 vaccinated children with no further exposure to wild- or vaccine-type VZV for 5 years still demonstrated persistent VZV antibodies and skin reactions to VZV (Gershon, 1998). It is probable that persistence or even escalation of VZV antibody titers post-vaccination may be due to recurrent endogenous reactivation

of the vaccine-stain virus, rather than by subclinical infection following exposure to the wild-type VZV.

These studies indicate that humoral and cellular immunity persists for several years following vaccination, thereby conferring continued protection.

4.2 Vaccine Tolerability and Safety

The Varicella vaccine is essentially well tolerated with the most common complaints being pain and redness at the injection site, and post-vaccination rashes (MMWR, 1999). It has been found that 3-5% of vaccinated subjects may develop a generalized rash, but vaccine virus transmissibility is unusual in these circumstances (Clements, 1996). In most instances, it results in subclinical or very mild infection (Gershon, 1995; Hughes, 1994; Diaz, 1991; Tsolia, 1990; Weibel, 1984). Only three well-documented cases of vaccine-virus transmission to susceptible contacts, resulting in varicella, have been reported, occurring in immunized subjects who developed a post-vaccination rash. (American Academy of Pediatrics, 2000)

In the short follow-up available, inadvertent vaccination of pregnant women (especially 3 months or less before pregnancy) has not resulted in any newborn with the Congenital Varicella Syndrome. A case-report of a pregnant woman at 5-6 weeks gestation exposed to her vaccinated 12-month infant who developed rashes – the pregnancy was terminated but fetal tissue analysis by PCR did not reveal VZV infection (Salzman, 1997).

However, as mentioned, vaccinated individuals appear to have a lowered risk of HZ in short-term follow-ups (Hardy, 1991).

4.3 Cost Implications

Extrapolation from limited locally-available data and data from neighbouring countries like Singapore, Thailand, Philippines indicate that the annual disease incidence rate would be in the neighbourhood of 300 000 cases per year, assuming a birth rate of 2.5%, a population of 20 million and a lower attack rate of about 70% in tropical-climate countries. Thus, an estimated 1000 – 2000 hospitalizations of all ages may be expected annually. Further, about 2.5 million individuals above 15 years may be expected to be still susceptible to varicella. Extrapolation of data from the United States would indicate that between 6-10 previously healthy individuals probably die every year because of varicella-related complications. The mortality figures may be higher locally as a result of higher disease incidence among individuals > 15 years, and furthermore, this age group is more likely to develop varicella-related complications. Therefore, as a vaccine-preventable cause of mortality, varicella may rank only next to Hemophilus *influenza*e-related deaths. Further, individuals with varicella are expected to experience significant disease-related morbidity (Gomez, 1992).

With the introduction of the varicella vaccine universally among infants, the disease incidence would be expected to be reduced by 75-80% and the incidence of severe varicella reduced by 95% (Preblud, 1985). As a result 250 000 cases can be averted annually, including 600 – 700 hospitalizations and 7 deaths of chickenpox (Scuffham, 1999). The vaccine will also be expected to eliminate or reduce the incidence of Herpes Zoster (Arvin, 1996)

4.3.1 Economic impact of vaccination

A study of the economic impact of vaccination would need to consider the various possible strategies:

***Strategy I*: Universal immunization 12 months – 12 years old (one-dose) ± catch-up vaccination in susceptible adolescents ≥ 13 years (two doses)**

Several studies have indicated that the introduction of a universal varicella vaccination programme in these children reduces health care costs (Preblud 1985, Sullivan-Bolyai 1987, Huse 1994, Lieu 1994, Strassels 1997, Markham 1999, Scuffham, 1999, Schuffham 1999, Diez-Domingo 1999, Coudeville 1999, Beutels 1996). Most of these analyses emphasise the importance of including societal costs like work loss for caregivers, in cost computations and not merely consider direct savings alone. In addition, cost computations have been shown to be directly affected by vaccine price, discount rates and vaccine coverage (Scott, 1997).

The issue of catch-up vaccination of susceptible adolescents and young adults ≥ 13 years following universal immunization in 12 months – 12 years old, has not been extensively evaluated. Beutels et al (1996) demonstrated that when a strategy of universal vaccination of 12 month – 12 year olds is considered together with an 11-year catch-up vaccination in susceptible adolescents, net savings were highest. In addition, this strategy was the most feasible from an organizational point of view. The identification of susceptible adolescents either from the medical history or by serology may be difficult, since a history of chickenpox is not always reliably obtained. It was found in one study, that almost 50% of children whose parents were uncertain of a history of varicella tested seropositive to VZV (Jerant, 1999; Lieu, 1998).

***Strategy II*: Targeted vaccination**

Vaccination can be targeted to various groups as follows:

(a) Vaccination of all susceptible individuals adolescents ≥ 12 years

In this strategy, all individuals above 12 years with a negative history of varicella are vaccinated, and may be introduced as a school health elective vaccination programme as practiced by health-care providers in Japan. However, limited vaccine coverage will mean that herd immunity will not be attained since vaccine virus transmission is minimal. In addition, the incidence of childhood varicella with its attendant morbidity will not be affected, while the elective vaccination of adolescents may pose organizational problems that may inflate costs (Krause, 1995). If only direct costs are considered, it is an

economically viable option with the most vulnerable population of varicella-susceptibles being immediately protected (Scuffham, 1999). Though feasible from a strictly economic point of view, the cost per case averted is less than that observed by implementing a universal vaccination programme in 12 months-12 year olds (Scuffham, 1999;Beutels, 1996; Lieu, 1995). It has been suggested that susceptibility to varicella is best determined by serologic testing and presumptive vaccination of all adolescents is not economically viable (Lieu, 1995)

(c) Vaccination of highly-susceptible populations:
The routine vaccination of children with leukemia when well and into maintenance therapy may be a cost-effective option (Buda, 1996).

4.3.2 Cost-considerations of introducing universal varicella vaccination in Malaysia
The licensed Oka/Merck varicella vaccine (VARIVAX) costs about RM 50 per dose (personal communication, *Merck Sharp & Dohme* [*Malaysian Branch*]). Vaccination of children may be considered initially at 2 points: one at the age of 12-18 months (expected population 500,000) and the other at the age of 12 years (expected susceptible population 200 000; 2 doses). This would be expected to incur a cost of RM 50 million (or RM 165 per case averted) annually. However, this amount may be reduced to RM 25 million (RM 85 per case averted and RM 17 000 per averted hospitalization), if vaccine prices decrease, or if only 12-18 month olds are vaccinated

5. CONCLUSIONS

(a) There is sufficient evidence that the live-attenuated varicella vaccine confers significant seroprotection, attenuate breakthrough infections that do occur and prevent severe/progressive varicella effectively. Concerns still remain over the possibility of waning immunity over time, especially when the frequency of subclinical booster infections due to wild-type VZV decreases following its decreased transmission with increasing vaccine coverage. In short-term follow-ups, no increased incidence of herpes zoster has been noted.

(b) The evidence suggests that susceptible adolescents who work in high-risk settings like day care and health centers should be vaccinated with two doses of the vaccine, 4-8 weeks apart.

(c) Universal varicella vaccination of all children between 12 months and 12 years of age with catch-up vaccination in susceptible individuals ≥ 13 years old (susceptibility determined serologically) has been shown to be cost-effective

6. RECOMMENDATIONS

In view of the high cost of universal vaccination of all infants, in the presence of competing vaccination alternatives like the introduction of universal H. influenzae

vaccination and the universal introduction of the MMR vaccine, it is recommended that varicella vaccination this be deferred to a later date.

8. REFERENCES

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8. EVIDENCE TABLE
VARICELLA ZOSTER VACCINE

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
Vaccine Efficacy				
1.	Johnson C, Rome L, Stancin T, Kumar Humoral immunity and clinical re-infections following varicella vaccine in healthy children Pediatrics 1989 84 418-421	A 3-year study of 140 vaccinees (all healthy children, Oka/Merck varicella vaccine) assessing persistence of the VZV antibody (assessed by the modified FAMA assay) at 6 weeks, one year and three years post-vaccination.	Antibody titers fell sharply after the 6-week post-vaccination peak but plateau-ed after 1 year to hover at between 6-10 Geometric Mean Titers 85% of vaccinees (113/133) were exposed to household varicella, 6% had breakthrough varicella; breakthrough disease was milder.	Fair
2.	Watson B, Gupta R, Randall R, Starr S Persistence of cell-mediated and humoral immune responses in healthy children immunized with live attenuated varicella vaccine J Infect Dis 1994 169 197-199	A cohort of 214 healthy seronegative children vaccinated with various doses of the Oka/Merck varicella vaccine were followed up to determine persistence of VZV-specific lymphocyte proliferation and VZV antibodies (gp-ELISA)	At 6 years: (a) 94% vaccinees (of 140 tested) had positive VZV-specific lymphocyte response (b) 95% (of 214 tested) had positive gp-ELISA VZV antibody titers with a geometric mean of 30.2	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	Johnson CE, Stancin T, Fattlar D et al A long-term prospective study of varicella vaccine in healthy children Pediatrics 1997 100 761-766	10-year prospective study; all sronegative children; the research group (n=143) received one dose of the Oka/Merck varicella vaccine (950 pfus) & the standard group received the vaccine production lots (doses 1145 to 3265 pfus). Humoral antibody persistence and breakthrough varicella infections studied at 6 and 10 years.	Important conclusions emerging from this study: (a) Vaccine protective efficacy similar over a range of viral doses (950 to 3265 pfus) (b) Breakthrough varicella occurs at a constant rate (2-3% vaccinees per year) (c) The peak VZV titer (as measured by FAMA) at 6-weeks post vaccination (> 8) is predictive of protection from modified varicella infection breakthrough	Good to fair
4.	Asano Y Varicella vaccine: The Japanese experience J Infect Dis 1996 174 S310-313	An open-label study of the efficacy of the Oka/Biken varicella vaccine with follow-up of ~2.5 million children (Japan & South.Korea) over 6-years (1987-1993).	(a) Well-tolerated vaccine (7% reported minor symptoms) (b) Seroconversion at 4 weeks post-vaccination 91.5% (c) Of those vaccinated and subsequently exposed to varicella, only 2% developed breakthrough illness over a 6-year period (d) Breakthrough illness was generally mild (e) Persistence of humoral and cell-mediated immunity ≥ 10 years post-vaccination	
5.	Asano Y, Suga S, Yoshikawa T et al Experience and reason: Twenty-year follow up of protective immunity of the Oka live varicella vaccine	Follow-up investigation of long-term efficacy (~20 years) of varicella vaccination in a cohort of children and adolescents (n=244) derived from the	2/100 varicella exposures among the cohort of vaccinees resulted in breakthrough varicella; both were significantly mild. 100% of all tested among this cohort (n=26) retained protective VZV antibody titers and delayed-type skin reactivity to VZV antigen. Some of those tested had higher antibody levels at 20 years post-	

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	Pediatrics 1994 94 524-526	above.	vaccination as compared to 10 years post-vaccination.	
6.	White CJ Clinical trials of varicella vaccine in healthy children Infect Dis Clin North Am 1996 10 595-608	A compilation of work done by several investigators worldwide + several independent trials by the author.	Notes that vaccinees numbered close to 100 million at the time of writing with the following observations: (a) Vaccine efficacy ranged between 65 – 100%. Vaccine efficacy depended on the intensity of exposure to varicella and the vaccine viral dose. (b) The vaccine was generally well tolerated. (c) Breakthrough varicella infections are generally milder (MVLS) (d) Waning immunity does not appear to be a clinical problem Overall disease rates are expected to fall in most countries and consequent morbidity and mortality expected to fall.	Good.
7.	Clements DA, Armstrong CB, Ursano AM Over five-year follow-up of Oka/Merck varicella vaccine recipients in 465 infants and adolescents Pediatr Infect Dis J 1995 14 874-879	Open-label study of the Oka/Merck varicella vaccine monitoring seroconversion rates and breakthrough disease among individuals 12 months to 17 years old.	(a) Good post-vaccine seroconversion rates; overall 94%. Seroconversion rates depend on vaccine viral dose (85% with a 950pfu lot and 100% with a > 3000 pfu lot (b) 5-10 year breakthrough varicella incidence 18% (c) Severity of breakthrough disease milder.	Fair grade of evidence.
8.	Kuter BJ, Weibel RE, Guess SH, Matthews H, Morton DH, Neff BJ, Provost PJ, Watson BA, Starr SE, Plotkin SA Oka/Merck varicella vaccine in healthy children: final report of a 2-year	Double-blind placebo-controlled trial of the Oka/Merck varicella vaccine 956 children, 1-14 years old	(a) Vaccine efficacy 100% in the 1st varicella season (b) 2nd varicella season: 22 cases of varicella; 1 in vaccinee, 21 in placebo (c) Estimated overall vaccine efficacy 98% (d) Follow-up of vaccinees: 95% remained varicella-free at the end of 7 years (e) Breakthrough infections were milder	

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	efficacy study and 7-year follow-up studies Vaccine Vol. 9, Sept 1991, 643-647			
9.	Arbeter A, Starr SE, Plotkin SA Varicella vaccine studies in healthy children and adults Pediatrics 78 (supp) 1986 748-756	Summary of various clinical trials examining vaccine immunogenicity and the need for booster vaccination in seropositive individuals	(a) Seroconversion rates at 94-100% (b) Antibody persistence at 95-100% over 3 to 4 years. (c) Protective efficacy at > 90% (d) Post-exposure vaccination effective only if higher viral dose selected. (e) Minimal vaccine reactions (f) No increase in Herpes Zoster in vaccinees.	
10.	Weibel R, Neff BJ, Kuter BJ Live attenuated varicella vaccine: Efficacy trial in healthy children N Engl J Med 1984 310 1409-1415	Double-blind placebo controlled efficacy trial of the efficacy of the Oka/Merck varicella vaccine in 914 seronegative individuals 1 to 14 years old; 468/914 received the vaccine.	(a) 94% of vaccinated individuals had detectable VZV antibodies 8 weeks after vaccination. (b) Over a nine-month surveillance period post-vaccination, 39 cases of varicella occurred - all in the placebo-treated children, giving a < 1-year vaccine protective efficacy of 100% (c) The vaccine was well tolerated.	
11.	Gershon AA, Steinberg S, LaRussa P et al NIAID Collaborative Varicella Vaccine Study Group Immunization of	Open label study of varicella vaccination in 187 susceptible adults.	(a) Seroconversion was 82% after one dose and 94% after two doses. (b) Protection after household exposure noted in 56% of those exposed; breakthrough illness was significantly milder (average 24 vesicles) (c) 25% of initial-response vaccinees eventually lost	

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	healthy adults with live attenuated varicella vaccine J Infect Dis 1988 158 132-137		detectable VZV antibodies, but still appeared partially protected. (d) All vaccinees were protected from severe chickenpox. (e) All vaccinees tolerated vaccination well.	
12.	Takahashi M, Kamiya H, Baba K Clinical experience with Oka live varicella vaccine in Japan Postgrad Med 1985 61 61-67	Open-label study of the efficacy of the varicella vaccine in children with acute leukemia and related hematological malignancies. Simultaneously assessed vaccine response in children with non-malignant diseases (1500) and in healthy children (4000)	(a) Children with acute leukemia may be vaccinated safely when all cytotoxic therapy is suspended for 2 weeks (1-week prior to and 1 week following vaccination) and when cell-mediated immunity (as assessed by phytohemagglutination response) is normal. (b) The vaccine is immunogenic in most such subjects, but a higher percentage (11%) were noted to develop varicella on exposure as compared to healthy subjects Vaccination in children with non-malignant illnesses and healthy children conferred good protection over a 7-10 year follow-up.	
13.	Bergen RE, Diaz P, Arvin A The immunogenicity of Oka/Merck varicella vaccine in relation to infectious varicella-zoster virus and relative viral antigen content J Infect Dis 1990, 162, 1049-1054,	Different vaccine viral doses of the Oka/Merck varicella vaccine were compared (950, 1140, 1145) by evaluating the initial seroconversion rate and T-lymphocyte proliferation (for cell-mediated immunity) percentages.	The higher dose vaccines were more immunogenic; immunogenicity appeared related to the vaccine viral antigen content rather than the dose of the whole attenuated vaccine virus.	Fair.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
14.	Varis T, Vesikari T Efficacy of high titer live attenauted varicella vaccine in healthy young children J Infect Dis 1996 174 S330-334	Randomised allocation of various vaccine dose/preparations to 513 10-30 month children (one or two lots of a high-titer vaccine; one or two lots of a partially heat-inactivated vaccine [i.e. low-titer] and a placebo) and examining seroconversion and breakthrough disease.	(a) Seroconversions were high (99-100%) in both the high and low titer groups. (b) The lower-titer groups had a significantly higher breakthrough varicella infection rate over follow-up (~2.5 years)	

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Programme Effectiveness And Population Acceptability				
1.	Krause P, Klinman DM Efficacy, immunogenicity, safety and use of live attenuated chickenpox vaccine J Pediatr 1995 127 518-525	Review of scientific literature, systematically examining vaccine efficacy, immunization practices, safety issues and probable impact of universal childhood varicella vaccination.	Several issues raised: (a) The current vaccine viral dose of the Oka/Merck varicella vaccine (2900-900 pfus) confers a 93% protective efficacy. The 1000-1625 pfu lots (1987) had a protective efficacy of 66-77% per year over a two-year follow-up (b) Unequivocal analysis of long-term vaccine efficacy is limited by the booster effect of subclinical wild-type VZV re-infection. (c) Universal childhood varicella vaccination may shift disease incidence to involve the higher-age groups, especially if universal vaccine coverage is not widespread and waning of immunity occurs. (d) Vaccination of immunocompromised individuals and adolescents > 12 years with negative varicella	Good

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			antibodies is attractive, but will not result in herd immunity and decrease in death and morbidity among unvaccinated children. (e) Post-licensure studies to be undertaken to study change in varicella rates in 5 cohorts of 8000 vaccinated children over 15 years, especially examining seropersitence and anamnestic boosters due to sub clinical VZV reinfection.	
2.	Watson B, Boardman C, Laufer D et al Humoral and cell-mediated immune responses in healthy children after one or two doses varicella vaccine Clin Infect Dis 1995 20 316-19	Immune responses to varicella vaccination among healthy children after one or two doses of the Oka/Merck vaccine compared.	Cell-mediated and humoral immune responses at 1 year better with the two dose approach (3 months apart)	Fair
3.	Rothstein EP, Bernstein HH, Ngai AL, Cho I, White CJ Dose titration study of live attenuated varicella vaccine in healthy children J Infect Dis 1997 175 444-447	A study to assess the effect of prolonged storage on vaccine immunogenicity and safety comparing the marketed vaccine (3625 pfus) with the partially heat-inactivated vaccine (1125 or 439 pfus); antigen content was similar in all three vaccines preparation.	(a) Higher dose resulted in higher GMT of antibodies (gp ELISA) at 6 weeks. (b) These differences were maintained at 1-year post-vaccination.	Fair.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
4.	Kuter BJ, Ngaiu A, Patterson CM et al *Safety, tolerability and immunogenicity of two regimens of Oka/Merck varicella vaccine (Varivax) in healthy* adolescents and adults Vaccine 1995 13 967-972	Multicenter trial of varicella vaccination in 757 healthy adolescents and adults (13-54 years old) comparing two regimens of the Oka/Merck varicella vaccine (two doses 4 weeks apart or eight weeks apart)	Differences in seroconversion rates were not significant between the two regimens (Injection I 72-78%, injection II 99%).	Good
5.	Gershon AA, Steinberg SP *Live attenuated varicella vaccine: protection in healthy adults compared with leukemic children. National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group.* J Infect Dis 1990 Apr 161:4 661-6	Open-label study to examine immunogenicity and protective efficacy of the varicella vaccine in healthy adults (n=26) and children with leukemia (n=102)	Though both adults and children had serological responses with a single vaccine dose that were not different from vaccination in healthy children, the intensity of the immune responses were lower (both humoral and cell-mediated) among leukemic children and adults. Breakthrough varicella did not occur at a higher rate in both these groups (protective efficacy 80-90%)	Fair
6.	Arbeter AM, Baker L, Starr SE, Plotkin SA The combination measles, mumps, rubella and varicella vaccine in healthy children Dev Biol Stand 1986 65 89-93	Comparison of the quadrivalent vaccine (MMRV) versus the MMR + V schedule in 15-17 month olds	Both groups recorded 100% seroconversion rates and similar mean antibody titers to all 4 viral components; no difference in adverse events between the two groups; no differences noted in varicella breakthrough rates.	Fair
7.	Brunell PA, Novelli VM, Lipton SV, PollockB	Prospective study comparing seroconversion	(a) Seroconversion rates were similar in both groups and protective levels persisted 1 year later.	Fair

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	Combined vaccine against measles, mumps, rubella and varicella Pediatrics 1988 Jun 81:6, 779-84	responses to a quadrivalent vaccine combining measles, mumps, rubella and varicella as against these vaccines administered separately	(b) Protective efficacy towards varicella was similar in both groups. Vaccine reaction rates were not increased if all 4 vaccines were combined.	
8.	Reuman PD, Sawyer MH, Kuter BJ, Matthews H Safety and immunogenicity of concurrent administration of measles-mumps-rubella-varicella and PedvaxHIB vaccines in healthy children twelve to eighteen months. The MMRV Study Group Pediatr Infect Dis J 1997 Jul 16:7 662-667	Random allocation of healthy susceptible children, 12-18 months old (n= 294) to two groups: MMRV + Conjugated Hib vaccine (PedvaxHIB) vs MMR + PedvaxHIB + Oka/Merck varicella vaccine 6 weeks later. Seroconversion rates (at 6 weeks), antibody persistence (at 1 year) and magnitude of antibody responses studied.	Seroconversion rates and antibody persistence to all 4 viral antigens were similar in both groups. However, significantly lower GMTs for VZV antibodies noted in the MMRV group as compared to the MMR + V group Similar adverse event rates in both groups.	Good
9.	Shinefield HR, Black SB, Staehle BO, Adelman T, Ensor K, Ngai A, White CJ, Bird SR, Matthews H, Kuter BJ Safety, tolerability and immunogenicity of concomitant injections in	Prospective randomized study of immune response, antibody persistence, adverse events and breakthrough varicella in two groups of children 12-23 months old (n=609) receiving two	Again, VZV antibody GMTs were lower in the concomitant administration group though seroconversion rates, antibody persistence at 1-year and varicella breakthrough rates were similar in both groups. Seroconversion rates, antibody persistence and antibody titers to measles, mumps and rubella were similar in both groups. The MMR + TETRAMUNE combination resulted in a significant incidence of fever.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	separate locations of M-M-R II, VARIVAX and TETRAMUNE in healthy children vs. concomitant injections of M-M-R II and TETRAMUNE followed six weeks later by VARIVAX Pediatr Infec Dis J 1998 Nov 17:11 980-5	vaccine schedules: A = Concomitant MMR + TETRAMUNE (DPT/Hib conjugated) + Oka/Merck varicella vaccine (separate injection site) vs. B = MMR + TETRAMUNE + Oka/Merck varicella vaccine given 6 weeks later		
10.	White CJ, Stinson D, Staehle B, Cho I, Matthews H, Ngai A, Keller P, Eiden J, Kuter B999 Measles, mumps, rubella and varicella combination vaccine: safety and immunogenicity alone and in combination with other vaccines given to children. Measles. Mumps, Rubella, Varicella Vaccine Study Group Clin Infect Dis 1997 May 24:5 955-31	Presents findings of two concurrent trials involving 812 children, 12 months – 3.5 years old: (a) MMRV vaccine vs. MMR+V (all at the same injection site. (b) MMRV + DT acellularP + OPV vs MMR + DtaP + OPV and Varicella vaccine (Oka/Merck) given 6 weeks later	All vaccinees recorded similar seroconversion rates; no significant differences in the adverse event rates. Again, peak VZV titers were lower with the MMRV vaccine than with the varicella vaccine administered separately (in a different syringe).	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
11.	Watson B, Seward J, Yang AR, Witte P, Lutz J, Chan C, Orlin, Sandra MSN, Levenson R Post-exposure effectiveness of varicella vaccine Pediatrics 2000 Jan 105:1 84-8	A prospective observational study of the efficacy of varicella vaccination in an institution where susceptible inmates (negative history for varicella) received the varicella vaccine (Oka/Merck, > 1000 pfus) following exposure to two index cases with chickenpox. Post-exposure vaccination was within 36 hours.	42/67 (62%) of vaccinees were children < 13 years; None developed typical varicella. Vaccine was 92.5% effective for prevention of any disease and 100% effective for prevention of moderate-severe disease among vaccinees<13 years old.	Fair
12.	Izurieta HS, Strebel PM, Blake PA *Post licensure effectiveness of varicella vaccine during an outbreak in a childcare center* JAMA, 1997 Nov 278:18, 1495-9	Retrospective cohort study of the incidence of varicella among susceptible vaccinated children who were exposed to a 15-week l varicella outbreak in a day-care center in DeKalb county, Georgia, USA and were vaccinated post-exposure	14% of vaccinated children developed varicella as against 88% of unvaccinated children, giving a vaccine efficacy of 86% against all forms of disease and 100% protection against moderate-severe disease. Breakthrough varicella illness was less severe in the vaccinated cohort. Respiratory illnesses in the vaccinated cohort were observed to result in lesser vaccine efficacy.	Fair
13.	LaRussa P., Steinberg S., Gershon A.A. *Varicella Vaccine for immunocompromised children: results of collaborative studies in the United States*	Open label study of varicella vaccine safety and efficacy when administered to children (n= 575, USA and	Vaccine noted to be safe, immunogenic and effective. A major side-effect was a post-vaccination varicelliform rash in ~50% of vaccinees 1 –month post-immunization.;	Fair.

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	and Canada (Varicella Vaccine Collaborative Study) J Infect Dis 1996 174 Supp3 S 320-3	Canada) with leukemia in remission. Steroids stopped 1 week before and 2 weeks after vaccination.	40% of those with rash needed acyclovir. Vaccine decreased varicella incidence post-exposure to 14% with breakthrough illness being merely mild varicella.	
14.	Baba K., Yabuuchi H., Takahashi M., Gershon A.A., Ogra P.L. Seroepidemiologic behavior of varicella zoster virus infection in a semi closed community after introduction of VZV vaccine J Pediatr 1984 Nov 105:5 712-6	A study of the incidence of measles and varicella prior to (1950-75) and following introduction (10years) of the measles and varicella vaccine in a semi closed institution with infants and children in Osaka, Japan.	(a) The incidence of varicella outbreaks was not reduced despite introduction of routine varicella vaccination & despite maintaining a high rate (~75%) of immune individuals annually over the years following routine varicella vaccination. (b) This was in contrast to the measles incidence following introduction of routine vaccination with only one outbreak in the 9 years following vaccination as compared to 9 outbreaks in the 24 years preceding vaccination.	
15.	Broyer M, Tete MJ, Guest G, Gagnadoux MF, Rouzioux C *Varicella and zoster in children after kidney transplantation; long-term results of vaccination* Pediatrics 1997 Jan 99:1, 35-39	An open label study of the efficacy of varicella vaccination to all prospective renal allograft recipients; 704 children and adolescents studied.	(a) VZV antibodies were detectable in 62% and 42% of vaccinees at 1- and 10-years post-vaccination. (b) The incidence of varicella was significantly lower in vaccinees (12% versus 45% in non-vaccinated subjects). (c) Breakthrough disease severity in vaccinated subjects less with no deaths among vaccinees (3 deaths among non-vaccinated subjects) (d) Breakthrough varicella coincided with disappearance of VZV antibodies. (e) Vaccinated subjects had a lower incidence of herpes zoster (7% versus 38% infected with wild-type varicella). (f) Varicella vaccination did not impact on graft survival/function.	Good
16.	Newman RD, Taylor JA Reactions of pediatricians to the recommendations for universal varicella	Questionnaire survey on self-reported adherence to the 1995 AAP and ACIP varicella vaccination	42% of responders followed a policy of universal varicella immunization. Adherence to recommendations prompted by belief in vaccine efficacy in eliminating potentially serious disease complications (especially varicella	Poor

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	vaccination Arch Pediatr Adolesc Med 1998 Aug 152:6 792-6	recommendations, among pediatricians in the state of Washington, USA and to determine factors that influence guideline adherence	encephalitis) and decreasing parental work loss because of childhood varicella. Non-adherence to guidelines often due to perceptions that varicella vaccination does not confer long-lasting immunity.	
17.	Freeman VA, Freed GL Parental knowledge, attitudes and demands regarding a vaccine to prevent varicella Am J Prev Med 1999 Aug 17:2 153-5	Questionnaire survey of parental knowledge and attitudes towards the varicella vaccine	(a) 75% of parents were aware of the availability of the varicella vaccine, mainly via non-medical literature. (b) 13% of respondents had already obtained the varicella vaccination for their children. (c) 25% intended to get it but 50% were undecided. (d) The strongest influencing factor was their doctor(s)' recommendations Insufficient information regarding the vaccine was the often-cited reason for parental indecision regarding the vaccine.	
18.	Holmes SJ, Rees S, Hadler SC, Williams WW, Wharton M Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices Morb Mort Wkly Rep 1996 45 (RR-11)	Evidence-based review of varicella disease epidemiology and associated morbidity, vaccine properties and formulation of vaccination guidelines based on available evidence	Recommends universal varicella vaccination for individuals < 13 years of age and for at-risk susceptible adults/adolescents ≥ 13 years old. Universal vaccination best carried out at 12-18 months age along with the MMR vaccine at separate sites using separate syringes. At time of report preparation, vaccine contraindicated in individuals with immunosuppressive illnesses/therapy.	Good.
19.	Galil K, Mootrey Gp, Seward J, WhartonM *Prevention of varicella: Update Recommendations of the Advisory Committee on Immunization Practices (ACIP)*	Updated recommendations for varicella vaccination	(a) Recommends that all day-care entry children have received the varicella vaccine (b) Post-exposure administration of the varicella vaccine in outbreaks situations, to susceptible contacts within 3-5 days of exposure (c) Again, strongly recommends that all susceptible ≥ 13	Good

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	Morb Mort Wkly Rep 1999 48 (RR-6)		years be vaccinated if in high-risk environments (d) Special recommendations for vaccination of HIV-infected children (ClassI, CD4 > 25%) and immunocompromised subjects	
20.	American Academy of Pediatrics *Varicella Vaccine Update* Pediatrics 2000 105(1) 136-141	Discussion of vaccine efficacy, effect on disease epidemiology with universal childhood vaccination, cost-effectiveness, and vaccination recommendations.	Recommends universal immunization of all children < 13 years old and all susceptible adolescents (negative history of varicella) at middle-school entry. Endorses the ACIP recommendations for varicella vaccination.	Good;
21.	Halloran ME Epidemiologic effects of varicella vaccination Infect Dis Clin North Am, 1996 Sept 10:3, 631-655	Projections on perceived epidemiological shifts in varicella disease incidence with introduction of a routine vaccination strategy with data derived from published literature.	Implementation of vaccination programme likely to result in a shift in age-distribution of varicella to higher-age groups – yet overall morbidity and disease incidence is expected to reduce. Catch-up vaccination programmes in older children may be able to decrease the age-shift in disease, until such time that routine vaccination is well established. At 97% coverage, endogenous varicella transmission is expected to be virtually eliminated.	Good.
Vaccine Safety and Side-Effects				
1.	Salzman MB, Sharrar R, Steinberg S, La Russa P Transmission of varicella-veccine virus from a healthy 12 month old child	Case-report of potential vaccine virus transmission from a vaccinee (12-month old healthy boy) who had developed 30 varicelliform skin lesions	Anecdotal report. Accompanying editorial discusses potential reasons for the vaccine-induced rash in the child; he had atopic dermatitis and using a moderately potent topical steroid cream. The mother underwent a therapeutic abortion and there was no evidence of viral infection of the fetus.	Poor

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	to his pregnant mother J Pediatr 1997 131 151-154	24 days post-vaccination to his pregnant mother (early gestation) who developed 100 lesions, 16-days later.		

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
2.	Watson BM, Piercy SA, Plotkin SA, Starr SE Modified chickenpox in children immunized with the Oka/Merck varicella vaccine Pediatrics 1993 91 17-22	Prospective cohort-based study of the nature of breakthrough chickenpox or vaccine-induced varicella (rash developing 4-6 weeks post-vaccination) in 2163 children vaccinated with the Oka/Merck varicella vaccine since 1981 (8y)	164/2163 children developed varicella (7.5%, 8% of whom had failed to seroconvert after vaccination), 2-96 months (median 44 months) post-vaccination. The clinical manifestations were noted to be less severe, with 54% being asymptomatic except for a rash, median number of lesions of 18, median duration of school misses of 2 days and median time to complete healing of 5 days. Secondary attack rates in households of vaccinated children with breakthrough varicella were 12% and secondary cases had disease severity similar to the index case.	Good
3.	Diaz PS, Au D, Smith S et al Lack of Transmission of the Live-attenuated Varicella Vaccine Virus to Immunocompromised Children after immunization of their	Susceptible well siblings (n=37) of children with hematological and solid tumors in remission for > 3 months (n=30) were vaccinated	(a) No evidence of vaccine virus transmission from vaccinated healthy child to contact sibling with malignancy (b) No virus shedding or isolation from respiratory sites. (c) No subclinical varicella infection in vaccinee contacts (d) Late breakthrough varicella infection in 4/37	Good to fair

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments Grade of Evidence
	siblings Pediatrics 1991 87 166-170		vaccinees, with transmission to 3 of their immunocompromised contacts; however varicella in these immunocompromised contacts was mild.	
4.	Tsolia M, Geshon AA, Steinberg SP, Gelb L *Live attenuated varicella vaccine: evidence that the virus is attenuated and the importance of skin lesions in transmission of varicella-zoster virus. National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group.* J Pediatr 1990 116 184-189	Examination of the biological behaviour of the vaccine varicella virus by studying the occurrence of vaccine-induced varicella among healthy contacts of leukemic children with breakthrough vaccine-induced varicella following immunization with the live-attenuated vaccine.	88 susceptible contacts of 156 leukemic children with post-vaccination varicella: (a) 17% (15) seroconverted (b) 11 (73%) had an accompanying rash (median no. of lesions, 38) (c) None of the infected contacts had systemic symptoms (d) Infected contacts were protected during later exposures to natural varicella (e) Transmission from vaccinees to contacts depends on the intensity of the post-vaccination rash.	Good to fair
5.	Hardy IB, Gershon AA, Steinberg SP The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia N Engl J Med 1991 325 1545-1550	Case-control study examining the risk of zoster in vaccinated leukemic subjects, to investigate concerns that zoster incidence may increase in vaccinated individuals.	(a) Zoster documented in 13 of 548 vaccinated leukemic children over a 4-year follow-up (2.4%). (b) The incidence-rate for zoster was 0.86 /100 patient years in this cohort as compared to a matched cohort of healthy children who had natural varicella infection (2.46/100 patient years). (c) Zoster in vaccinated leukemic subjects occurs more commonly in subjects who develop a post-vaccination rash (or have breakthrough natural varicella infection) and is associated with biological evidence of decreased cell-mediated immunity.	Good

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Cost Effectiveness				
1.	Markham MH, Darville T Morbidity and cost of vaccine-preventable varicella in previously healthy children in Arkansas J Ark Med Soc 1999 Dec 96:7, 260-2	Retrospective study to assess morbidity and costs due to varicella-related hospitalizations	55 hospitalizations over a year in the 19 counties of Arkansas, 192 patient day, ¼ million dollars in costs.	
2.	Shepard DS, Walsh JA, Kleinau E, Stansfield S, Bhalotra S Setting priorities for the Children's Vaccine Initiative: a cost-effectiveness approach Vaccine 1995 13:8 707-14	An analysis of various cost-effectiveness models that may help select the most cost-effective strategies in childhood vaccination in developing countries; cost-benefit analyses also considered; 13 candidate vaccines considered. Five best vaccination strategies considered based on US $/Quality-adjusted Life Years saved (cut-off < 25)	The five best vaccination strategies noted were: (a) early administration of the measles vaccine (b) Alternatively a two-dose measles vaccine schedule (c) Tetanus toxoid for pregnant women (especially the slow-release form) (d) Improved typhoid vaccine (e) Hepatitis B with DPT vaccine	

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3.	Strassels SA, Sullivan SD Clinical and economic	Review of published literature	Disease-related direct and indirect costs estimated at $ 400m/year. From the health payers' viewpoint, every	Good to Fair.

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	considerations of vaccinating against varicella Pharmacotherapy 1997 17:1, 133-9		dollar invested would result in $0.9 return if universal varicella vaccination is implemented. If considered form a societal viewpoint, every dollar invested results in $5.4 saved	
4.	Lieu TA, Black SB, Rieser N, Ray P, Lewis EM, Shinefield HR The cost of childhood chickenpox: parents' perspective Pediatr Infect Dis J 1994 Mar 13:3 173-7	Cohort-based analysis of medical costs and indirect costs as a result of childhood varicella in 179 families	(a) 2/3rds of mothers and 1/3 rd of fathers missed work as a result of chickenpox in their children (US $ 183 / case) (b) Non-prescription medicines also resulted in costs ($ 12.5 per case) (c) School exclusion policies meant that children stayed home three times longer than they actually needed to.	
5.	Preblud SR, Orenstein WA, Koplan JP et al A benefit-cost analysis of a childhood vaccination programme Postgrad Med J 1985 61 17-22	On of the first studies to assess varicella vaccination as a cost-effective measure. Data sourced from published literature and models constructed	3 million varicella cases estimated to occur yearly in the US without a vaccination programme, with ~ 350,000 physician visits and > 4500 hospitalizations per year Incidence expected to be decreased to 78% with vaccine introduction; disease-related morbidity and work losses expected to reduce. Projected returns of US$ 7 for every dollar invested in routine varicella vaccination.	fair
6.	Lieu T, Cocchi S, Black S et al Cost-effectiveness of a routine varicella vaccination program for U.S.children JAMA 1994 271 375-381	Assesses cost-effectiveness of a routine varicella vaccination strategy based on costs and medical intervention statistics form the Kaiser Permanente Medical Care, (California, USA) Programme and allied studies. Vaccine cost estimated at $ 35, administration costs at $ 5-10.	Similar conclusion as Preblud & associate study; savings of more than $5 for every dollar invested in routine vaccination. Costs savings obvious when indirect cost also considered. From the healthcare payer's perspective, programme cost would be US $ 2 per case averted or $ 2500 per life-year saved.	Good

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7.	Huse DM, Meissner C, Lacy MJ, Oster G Childhood vaccination against chickenpox: An analysis of benefits and costs J Pediatr 1994 124 869-874	Cost-effectiveness analysis model with data based from the US Estimates of physician visits, prescription drugs, hospitalization costs from the National Heath Interview Survey and the National Hospital Discharge Survey. Vaccine cots estimated at $35 per dose.	32 physician visits / 100 cases of varicella estimated for patients between 1-15 years with 16/10,000 cases hospitalized. 95 visits/100 cases of varicella estimated for patients between 16-25 years with 60/10,000 cases hospitalized. Average work loss (parental) for cases in children between 5-12 years estimated at $103 (3.7 days home stay). Average work loss (patient) for patients 18-25 years estimated at $75 per day (duration 5.5 days). Universal varicella vaccination expected to result in net savings of ~ 6.5 million per year	Good
8.	Scuffham PA, Lowin AV, Burgess MA The cost-effectiveness of varicella vaccine programs for Australia Vaccine 1999 Oct 18:5, 407-15	Cost-effectiveness study to assess three vaccination strategies compared to a no-vaccination policy, using only direct health-care costs: strategy I – universal vaccination of all infants; strategy II- vaccination of all adolescents; strategy III – all infants + catch-up vaccination of adolescents without a history of varicella for the first 11 years. Simulation over a 30-year period	Average cost per case of chickenpox averted for strategies I, II, II were $ 64, $ 530 and $ 418 respectively. Universal vaccination of infants noted to be most cost-effective; potential to avert 4.4 million cases, 13,500 hospitalizations and 30 fatalities over a 30-year period. Cost computations most sensitive to vaccine price and discounting rates. Problem of poor negative predictive value of a negative history of chickenpox necessitates pre- testing; this cuts down cost savings.	

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9.	Schuffham P, Devlin N, Eberhart-Philips J, Wilson-Salt R The cost-effectiveness of introducing a varicella vaccine to the New Zealand immunization schedule Soc Sci Med 1999 Sep 49:6 763-79	Cost-effectiveness analysis of adding a varicella vaccine to the New Zealand immunization schedule. A cohort of 15-month olds considered; costs simulated for a 30-year period. Simulation design to mimic the phasing-in effects of routine varicella vaccination before being universally implemented.	Direct health cost would return 0.67 NZ$ for every dollar invested. Societal cost inclusion resulted in a savings of NZ$ 2.79 per dollar invested with 2 million dollars saved in indirect losses, compared to the estimated 1 million dollars needed to cover 80% of 15-month olds. Total costs savings amounted to 47 dollars per child vaccinated.	Good.
10.	Beutels P, Clara R, Tormans G, van Doorslaer E, Van Damme P Costs and benefits of routine varicella vaccination in German children J Infect Dis 1996 Nov Supp 3 S335-41	Cost-effectiveness analysis comparing three strategies to a no-vaccination approach: strategy I – vaccination of all 15-month olds, strategy II – vaccination of all susceptible 12-year olds; strategy III; childhood vaccination + catch-up vaccination. Both direct and indirect costs were analyzed.	If only direct costs considered, vaccination of susceptible adolescents as ascertained by a negative serology deemed most cost-effective. When indirect costs considered, childhood vaccination + a limited catch-up vaccination strategy for susceptible adolescents (for a period of 11 years) resulted in highest net savings (DM 4.72 per case averted, DM 6915 per life-year saved) – after 12 years, the first strategy was recommended.	Good
11.	Diez-Domingo J, Ridao M, Latour J, Ballester A, Morant A A cost-benefit analysis of routine varicella vaccination in Spain	Cost-benefit analysis using a Markov decision model with data derived from a limited prospective study of 150 children.	Direct costs from disease were noted to be lower than the cost from vaccination. However, indirect cost considerations showed that universal childhood vaccination could result in cost-savings of 2627 pesetas per vaccinated child (returns of 1.6 peseta per peseta	Fair

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	Vaccine 1999 Mar 17:11-12 1306-11		invested in the vaccination programme). Cost analyses sensitive to vaccine price, discounting rates.	
12.	Coudeville L, Paree F, Lebrun T, Sailly J The value of varicella vaccination in healthy children: cost-benefit analysis of the situation in France Vaccine 1999 17:2 142-151	Cost-benefit analysis derived from two models (a) Prospective observational study (b) Epidemiological model Looks into societal and patient costs and studies vaccination coverage rates to estimate costs	Varicella administered with MMR determined to the most cost-effective option ensuring maximal coverage. Also shows that a higher coverage rate ensures maximal protection, offsetting costs incurred by a wide vaccine coverage	Fair .
13.	Lieu TA, Finkler JJ, Sorel ME, Black SB, Shinefield HR Cost-effectiveness of varicella serotesting versus presumptive vaccination of school-age children and adolescents Pediatrics 1995 may 95:5 632-8	Decision analysis model based on published literature; hypothetical cohorts of school-age children and adolescents considered; presumptive vaccination versus selective vaccination (seronegatives) considered	(a) Presumptive vaccination more cost-effective in school-going children. Previous history of chickenpox had a high positive-predictive value for seropositivity (b) Presumptive vaccination of adolescents not cost-effective; serotesting further increases costs.	
14.	Gayman J A cost-effectiveness model for analyzing two varicella vaccination strategies Am J Health Syst Pharm 1998 Dec 55:24 Supp 4 S4-8	Cost-effectiveness model to assess a programme of varicella vaccination in at-risk susceptible adults – two strategies considered: vaccinate all OR vacciante only seronegative employees.	Model supported the screen-then vaccinate strategy with cost savings of ~ $50 per employee. Cost of preventing one employee exposure was estimated at $775 while cost of preventing one employee infection was estimated to be $ 15 000.	Fair study

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
15.	Buda K., Tubergen D.G., Levin M.J., *The frequency and consequences of varicella exposure and varicella infection in children receiving maintenance therapy for acute lymphoblastic leukemia*	Retrospective study to determine costs incurred for treating varicella exposure (& infection) in children with ALL on maintenance therapy and project probable impact of instituting routine varicella vaccination during maintenance Rx	Varicella exposures: 10/100 patient years; varicella disaese 4.6/100 patient years Considerable costs: US $ 470 / varicella exposure; $ 7450/ varicella infection Varicella vaccination expected to reduce costs by 80%	Fair
16.	Tenenburg AM, Brassard JF, Lieu JV, Drusin ML Varicella vaccination for health care workers at a University Hospital: an analysis of costs and benefits Infect Control Hosp Epidemiol 1997 18 405-411	Retrospective study determining (a) Number of employees susceptible to varicella thro' seroanalysis (b) Number of varicella exposures and infection (c) Work loss as a result of varicella (d) Costs projections if varicella vaccination introduced	40 exposures to varicella over one year, 72% involving those who were susceptible Substantial expenses when infected employees reprieved and replacement workers employed. Projected varicella vaccination of seronegatives workers potentially cost-effective	Fair.
17.	Nettleman MD, Schmid M Controlling varicella in the healthcare setting: the cost-effectiveness of using varicella vaccine in	Cost-effectiveness analysis based on a Markov-based decision analysis format. Input data derived from literature.	Universal vaccination of health care workers with varicella deemed to result in net cost savings of RM 59 per person. Interestingly, selected vaccination after serotesting noted to be not as cost-effective since serotesting offsets cost savings.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	healthcare workers Infect Control Hosp Epidemiol 1997 Jul 18:7 504-8			
18.	Smith WJ, Jackson LA, Watts DH, Koepsell TD *Prevention of chickenpox in reproductive-age women: cost-effectiveness of routine prenatal screening with postpartum vaccination of susceptibles* Obstet Gynecol 1998 Oct 92:4 535-45	Targeted vaccination in at-risk cohorts: A cost-analysis model considering immediate postpartum vaccination of reproductive-age women following (a) serotesting only those with negative h/o varicella OR (b) serotesting all pregnant women	Selected serotesting of all pregnant women with a negative history of varicella and vaccinating them in the immediate postpartum period found to be a cost-effective model, especially if seropositivity is relatively high among adults: $ 1126 per varicella averted; the strategy is expected to prevent ~50% of future varicella infections in the susceptible cohort	Fair

PNEUMOCOCCAL VACCINE

1. INTRODUCTION

Pneumococcal infections result in 1 million children dying annually worldwide, the majority being from developing countries. In developed countries, elderly adults are a high-risk group for invasive pneumococcal infections. There is increased susceptibility to these infections in individuals with HIV infection, sickle-cell disease and a variety of chronic organ failures.

Pneumococcal infections refer to those infections caused by Streptococcus pneumoniae. These may be broadly categorized into asymptomatic colonization, pneumococcal otitis media and pneumococcal pneumonia, and invasive pneumococcal disease (bacteremia, meningitis).

Nasopharyngeal colonization is especially frequent in children, may occur as early as at 2 months of life, and are highest in children less than 5 years, especially in crowded environs like day-care centers (Hendley, 1975). In a local study of 355 nasopharyngeal specimens from children 1 month to 6 years of age in Kota Bharu, Kelantan, a 10% carrier rate was noted. However, the population of children studied was hetereogenous, including hospitalized children and children attending pediatric clinics who may have reduced carrier rates due to concomitant antimicrobial therapy (Malik, 1998). While asymptomatic nasopharyngeal colonization may not necessarily lead to invasive disease, prolonged carriage serves as a reservoir for antimicrobial-resistant S. pneumoniae strains, thereby facilitating their transmission. An effective pneumococcal vaccine would be able to eliminate or reduce carrier rates.

Otitis media is estimated to afflict nearly 60% of children by the age of 1 year (Klein, 1989). S. pneumoniae is estimated to account for nearly 30-50% of middle-ear fluid positive otitis media (Bluestone, 1992). While there are no locally available data on the incidence of childhood otitis media, assuming a conservative incidence rate of 0.5 case/child less than 2 years/year (Karma, 1985), nearly 500 000 cases of otitis media may be expected. Otitis media is a disease with significant morbidity, the most feared complication being hearing loss because of conductive deafness. While antimicrobial therapy has been effective in preventing acute mastoiditis following acute otitis media, it is less effective in preventing the complications of tympanic perforation, otorrhea and progression to otitis media with effusion (Rosenfeld, 1995). The widespread use of antibiotics, even though having a modest impact on the disease course, has resulted in enhancing perpetration of antimicrobial resistant pneumococcal strains and significant cost-burdens (Kaplan, 1997; McCracken 1995). A vaccine would be able to decrease the incidence of pneumococcal otitis media.

While an etiological diagnosis of childhood pneumonia is difficult, indirect evidence of the importance of bacterial infections in childhood pneumonia can be seen in moderate-severe acute lower respiratory infections where infant mortality was reduced by 20% and 25% in children aged less than 5 years (Sazawal, 1992). Studies using lung aspiration in children in developing countries have consistently shown that most cases of severe pneumonia are caused by S. pneumoniae (serotypes 1, 5, 6B, 14, 18C, 19F, 23F) or Hemophilus influenzae (Ikeogu, 1988; Shann, 1986). S. pneumoniae accounted for nearly a third of the isolates from lung aspirates in children with pneumonia. Further, S. pneumoniae often tends to secondarily complicate primary viral pneumonias in children (Korppi, 1989).

In Malaysia, results of the Second National Morbidity Survey (1996) indicate that Acute Respiratory Infections (ARI) are the leading cause of childhood morbidity (< 5 years) accounting for two-third of all childhood hospitalizations and the 6th principal cause of death in government hospitals in Malaysia (331 deaths among children < 12 years old in 1997, resulting in a case-fatality rate of 3.1%). In 1992, 36.4% of deaths in infants and 18.2% of deaths among children 1-5 years old were due to Acute Respiratory Infections (ARI Strengthening Program in Malaysia 1998). It is therefore reasonable to speculate that at least a third of the cases of ARI (~ 4000, 1997) and two-thirds of the fatalities due to ARI (~200, 1997) may be attributable to S. pneumoniae infection. Attempts to prevent pneumococcal pneumonia by vaccination are clearly indicated.

Data on the incidence of invasive pneumococcal disease (bacteremia) is less forthcoming. Detection and prompt treatment of S. *pneumoniae* bacteremia in children is important since some case-series quote figures as alarmingly high as 20% (*Jaffe DM 1994*). Pneumococcal meningitis is a serious illness as shown by a recent meta-analysis of 9 studies involving 122 children indicating that illness in 1 of 6 affected children will either be complicated by mental retardation, seizure disorder or paresis/spasticity; deafness may occur in up to 1 in 4 children – half of them being severe (Baraff LJ, 1993). Mortality rates of between 20-30% have also been reported (Choo KE, 1990). In a large prospective 5-year study in Finland, 15% of blood-culture positive febrile illness in otherwise healthy children (< 16 years) was due to S. pneumoniae (Saarinen, 1995). The incidence rates for invasive pneumococcal disease varied from 24 (Finland), through the 50s-60s (USA, New Zealand, Israel) to 240 (The Gambia) per 100000 children < 5 years – that is at least 10 times the incidence rate of 2.9 per 100 000, reported for H. influenzae (Loughlin, 1995). Invasive disease is more common in infants than in older children, with an average mortality rates ranging from 1.3% (Finland) to up to 6 % (Israel, West Africa).

In the absence of direct data, therefore, it is not unlikely that the incidence-rate of pneumococcal bacteremia in Malaysia is at least at 30/100 000 children < 5 years (that means, at least 750 cases per year of invasive pneumococcal bacteremia that may potentially be complicated by meningitis) – nearly 15-20 deaths (2% mortality) may result annually. These projections are conservative and make allowance for a probable widespread local practice of early antimicrobial therapy of the febrile child that is known to decisively decrease complications from pneumococcal bacteremia. It is to be noted that in a 1-year local study of pneumococcal isolates from blood, CSF and other body fluids (65% involving children less than 2 years old), serotypes 1, 6B, 19B, 19F and 23F were most commonly encountered (especially serotypes 1 and 19B) (Rohani MY, 1999).

In summary, the burden of pneumococcal disease in childhood in Malaysia is high. At least 500 000 cases annually of otitis media in children < 2 years, with 25 000 of these progressing to chronic otorrhea; 4000 cases annually of childhood acute respiratory infections, 200 of which result in death; and 750 cases of pneumococcal bacteremia yearly resulting in between 15-20 deaths, may be expected.

There are two other issues concerning S. *pneumoniae* infections that need to be considered:

(a) The increasingly widespread problem of antimicrobial resistance of S. pneumoniae:
Increased use of oral antibiotics coupled with poor compliance to prescribed antibiotic regimens have resulted in the emergence of penicillin-resistant and penicillin non-susceptible strains that demonstrate one or more alterations of the cell-wall, the prevalence

in Malaysia being between 7-9% for penicillin non-susceptible strains and about 1.1% for erythromycin resistance (*Rohani MY, 1999*). However, 23% of pneumococcal isolates from Singapore and 57.9% from Thailand were observed to be pencillin-nonsusceptible. It is believed that penicillin-resistant clones may soon be widely prevalent in the South East Asian region (*Song JH, 1999*).

(b) Increased susceptibility of specific patient populations to invasive pneumococcal disease:

Patients with decreased phagocytic function absent splenic clearance mechanisms and deficient antibody production in response to pneumococcal capsular polysaccharides are at especial risk of invasive pneumococcal infection. Thus, healthy infants and young children due to their immune-naive state and children with functional and anatomic asplenia, human immunodeficiency virus infection, hematologic and non-hematologic neoplasms on chemotherapy, recipients of solid-organ and bone-marrow transplants, nephrotic syndrome and other chronic renal diseases and chronic liver disease are at increased risk of serious pneumococcal disease. Further, disruptions in anatomic barriers may also predispose to invasive pneumococcal disease – this is seen in children with osteomeningeal breach resulting in cerebrospinal fluid leak who are at increased risk of recurrent pneumococcal meninigitis.

2. TECHNICAL FEATURES

Anticapsular antibodies against the pneumococcal capsule are protective. The 14- and later, the 23-valent polysaccharide vaccine have been around for nearly 25 years and have limited immunogenicitry in children between 2-5 years, a group at highest risk for invasive pneumococcal disease. The conjugated pneumococcal vaccine, in a series of injections, has been demonstrated to protect normal infants from invasive pneumococcal infections, episodes of lobar pneumonia and acute otitis media caused by vaccine serotypes (Rubin, 2000). The23-valent pneumococcal vaccine has an overall protective efficacy of between 60-70%. The protective efficacy of the polysaccharide vaccine is poor in children < 2 years old and individuals with HIV infection. The healthy elderly and elderly with chronic diseases benefit most from the polysaccharide vaccine (Butler JC, 1997).

The new generation of conjugate vaccines (with 7-11 serotypes bound to a protein carrier) results in a T-cell mediated immune response that may ensure protection in children < 2 years old, and the vaccine has the potential to result in widespread immunity through a herd effect (WHO, 1999). Conjugate vaccine preparations have better immonogenicity, due to the ability to produce a T-cell dependent response with anamnestic responses to revaccination, and it also decreases nasopharyngeal carriage rates and thus, decreases disease transmission. Conjugated vaccines will first find their use in vaccinating immunocompromised patients (Nuorti, 1997). It is estimated that the 7-valent conjugate pneumococcal vaccines could potentially prevent 86% of bacteremia, 83% of meningitis and 65% of otitis media cases, and that protection could be enhanced by immunity to cross-reactive serotypes.

3. METHODOLOGY

An electronic search of MEDLINE database using various keywords, and year limits was carried out. In addition, three country immunisation handbooks (USA, UK, Australia) WHO report, Ministry of Health reports and other important references were obtained from various sources. The keywords used and the year limits were as follows:

a. Pnemococcus vaccine 1990 – 2000
b. Streptococcus pneumoniae and Malaysia 1970 - 2000
c. Haemophilus influenzae type b and cost 1966 - 2000

4. RESULTS

4.1 Vaccine Efficacy

The 14- and later, the 23-valent polysaccharide vaccine have been around for nearly 25 years and have limited immunogenicitry in children between 2-5 years (Rubin LG, 2000). The WHO reports that the 23-valent pneumococcal vaccine has an overall protective efficacy of between 60-70%. The protective efficacy of the polysaccharide vaccine is poor in children < 2 years old and in individuals with HIV infection. However, the new generation of conjugate vaccines (with 7-11 serotypes bound to a protein carrier) results in a T-cell mediated immune response that may ensure protection in children < 2 years old; the vaccine has the potential to result in widespread immunity through a herd effect (World Health Organization, 1999). A study in infants found that the immunogenicity of pneumococcal capsular polysaccharide antigens was variable, differing with different serotypes, and inducing a T-cell independent immune response that results in poor persistence of immunity. It was suggested that pneumococcal capsular polysaccharide vaccine needs to be probably conjugated to a protein carrier to recruit a T-cell mediated mechanism, similar to the experience with the Hemophilus influnzae conjugate vaccine (Cadoz M, 1998).

Another study in schoolchildren using a 14-valent PPV found that while vaccine antibody responses were two-fold following revaccination but local reactions were severe, and the immunogenicity of serotype 6 capsular polysaccharide preparations was consistently poor (Lawrence EM, 1983). A smilar study assessing antibody responses post-vaccination in children found a poor immune response although there was a better immune response in older children. This study too reiterates the poor vaccine efficacy in children < 2 years (Temple K, 1991). A study in 827 children ranging from 3 months to 6 years found that an overall protective efficacy estimated at 58%, which was better in children older than 2 years (Makela PH, 1980). Another case control study confirms poor vaccine efficacy in infants with poor antibody response to vaccine serotypes after the 1st and 2nd doses and rapid deterioration of antibody titers (Koskela M, 1986). A study on the effect of two PPV formulations on nasopharyngeal carriage rate in 200 infants found that the vaccine appears to be poorly effective in infants, and it is uncertain whether elimination of carrier state will prevent invasive pneumococcal disease (Wright PF, 1981). Another review also recognizes the poor vaccine efficacy in prevention of pneumococcal disease in children (Douglas RM, 1979).

4.1.1 Efficacy of conjugated vaccine

The conjugated pneumococcal vaccine has been demonstrated to protect normal infants from invasive pneumococcal infections, episodes of lobar pneumonia and acute otitis media caused by vaccine serotypes Anticapsular antibodies against the pneumococcal capsule are protective. A study of the vaccine in 25 children found that the vaccination was well tolerated, and concluded that the vaccine is safe and immunogenic in young infants, however, requires at least 2-3 vaccination doses (Ahman H, 1996). Studying the vaccine in 60 children, it was found that, all children demonstrated an immune response and antibody titers did not wane over the next 12 months. Pneumococcal polysaccharide vaccine induced a greater anamnestic response in children primed with the conjugate vaccine compared to those primed with the plain PPV and a greater response was seen with the 23F than with the 6B serotype. It was concluded that vaccine serotype is a major determinant of vaccine immunogenicity (O'Brien KL, 1996). A review of laboratory isolates found that the overall vaccine efficacy was 57% with a higher efficacy in immunocompetent individuals (75%), moderate protective efficacy in those with an absent spleen (77%), and that vaccination may provide protection for at least 9 years after the initial vaccination (Butler JC, 1993). The immonegenicity of the conjugated vaccine this vaccine was further confirmed in a study of 212 infants (Rennels MB, 1998). A study on the immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine found that there were significant antibody responses to all vaccine serotypes and decrease in nasopharyngeal carriage (Mbelle N, 1999). In a study of 37,868 children, the vaccine efficacy for prevention of invasive disease was 97.4% with a 73% reduction in severe pneumonia, and 66.7% decrease in incidence of suppurative otitis media was (Black S, 2000). An evaluation of 2 large scale trials demonstrated a 94% efficacy against invasive pneumococcal disease and the conjugate vaccines also appeared effective against childhood pneumonia and otitis media (Shinefield HR, 2000).

4.1.2 Efficacy in selected populations

Pneumococcal polysaccharide vaccination is recommended in selected categories of immunocompetent persons above 2 years old, those with chronic illnesses (cardiovascular & pulmonary diseases, diabetes mellitus, chronic liver disease and CSF leaks), persons with anatomic or functional asplenia (concurrently with penicillin chemoprophylaxis) and those in special environments like in institutionalized care. Revaccination is recommended in young children who are expected to have declining antibody titers. It has also been reported that conjugate vaccine preparations have better immonogenicity, ability to produce a T-cell dependent response with anamnestic responses to revaccination and decreases nasopharyngeal carriage rates and thus, decrease disease transmission (Nuorti PJ, 1997). There have also been other reports that the pneumococcal polysaccharide vaccine is not beneficial in children since it does not prevent otitis media in infants and young children. The vaccine is recommended in patients with homozygous sickle-cell disease and post-splenectomy patients, but not in immunocompromised patients. The conjugate vaccine is said to have great potential in preventing invasive childhood pneumococcal disease and otitis media (Wang EL, 1998). A meta-analysis of 9 randomized studies studying vaccine efficacy (23-valent PPV) in preventing all proven/ presumed pneumococcal pneumonia or proven/presumed pneumococcal pneumonia caused by vaccine serotypes found that there is poor protection against pneumonia (irrespective of cause) in the general population and in children < 2 years old, whilst it is efficacious in post-splenectomy patients and patients with sickle-cell anemia (Bacle A, 1997). An indirect cohort analysis of vaccine efficacy in immunocompromised groups found that overall vaccine efficacy (vaccination across all ages) was estimated to be 36%, with the lowest vaccine efficacy in both normal and

immunocompromised children 2-10 years old (vaccine efficacy ≤ 0%), while vaccine efficacy was best at ages above 10 years (Broome CV, 1980).

Examining the efficacy in selected populations, in patients with bacteremic illness, the vaccine protective efficacy was estimated at 64%, and noted that vaccination in moderate immunosuppressed states like Hodgkin's disease, multiple myeloma, immunoglobulin deficiency, was not protective (Bolan G, 1986). An evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infections found that the overall protective efficacy of the was at 67%, the vaccine being most protective (70%) in the moderate-risk category i.e. moderately impaired immunity secondary to conditions like chronic renal disease on dialysis and in severe or mild immune impairment, the vaccine protective efficacy was 0% (Shapiro ED, 1984). Extending this review from1984-1990, the overall vaccine efficacy was 57% over a 3-year period post-vaccination, with a vaccine efficacy of only 21% in immunocompromised patients, and the vaccine efficacy progressively waned over time (Shapiro ED, 1991).

4.1.3 Otitis media

A RCT of 1237 children from 6-54 months old failed to reveal consistent or significant protective efficacy of the vaccine against otitis media (Douglas RM, 1984). A study in 179 patients found no significant vaccine efficacy in prevention of otitis media among infants (Sloyer JL, 1981). A case control study concluded that although immunization with pneumococcal vaccine appeared to reduce the number of episodes of acute otitis media due to serotypes contained in octavalent vaccine, the clinical experience of the children was not favourably affected by this vaccine (Teele DW, 1981). However, a study on children aged between 6-60 months concluded that while the vaccine had no effect on children under 2 years old, it might be a useful aid in preventing recurrent attacks of otitis media in children between 2 and 5 years of age (Rosen C, 1984). Examining the effect of the vaccine on otitis media prone children, it was found that the response to vaccination is equally poor in all children, irrespective of whether they have a history of frequent attacks of acute otitis media. (Kalm O, 1986).

4.1.4 Other disease states

A comparative study of the immunogenicity of PPV in selected at-risk children with nephrotic syndrome, recurrent asthma and splenectomized children found lower vaccine immunogenic intensity in the high-risk group of children was noted (Lee JH, 1995).

A study in 43 in **splenectomized** children recommends revaccination in selected post-splenectomy patients who have low anti-pneumococcal antibody titers 5 years after primary vaccination (Konradsen HB, 1990). Another study in 59 post-splenectomy patients recommends delayed (14 days) vaccination in patients post-splenectomy to obtain best functional antibody activity (Shatz DV, 1998).

There is also no convincing data on the efficacy of the pneumococcal polysaccharide vaccine in **sickle cell disease** (Overturf GD, 1999). Another study concludes recommends a combination of the pneumococcal polysaccharide vaccine and penicillin to prevent invasive pneumococcal infection in young children with sickle cell homozygous disease (Babiker MA, 1986). Penicillin prophylaxis has been found to be superior to pneumococcal polysaccharide vaccination in sickle cell disease children, at least until the age of 3 years (Johm AB, 1984). In splenectomised children, vaccination was found to be protective against invasive pneumococcal disease (Konradsen HB, 1991).

There is limited efficacy data of the 23-valent pneumococcal polysaccharide vaccine in **HIV**-infected individuals, but however, vaccination is recommended as a "something better than nothing" option vaccine (Keller DW, 1995). However, another review does not recommend routine PPV vaccination in HIV-infected persons since vaccine efficacy has been found to be poor in HIV-infected persons compared to vaccination in healthy persons, and recommends large-scale trials to resolve the role of PPV-vaccination in HIV-infected patients (Jain A, 1995). The antibody titers in vaccinated HIV children were found to be not significantly higher than those of unvaccinated HIV-infected children and healthy children (Arpadi SM, 1994). Another study of 20 recently diagnosed HIV patients found no significant antibody responses between cases and controls at 4 weeks and 6 months post-vaccination (Weiss PJ, 1995). In a study of HIV infected individuals, the HIV clinical status did not appear to influence vaccine response for a given CD4 count (Rodriguez-Barradas MC, 1992). A study of post pneumococcal vaccination (23-valent) antibody responses found that there is rapid waning of antibody levels resulting in only short-term immunity (Nielsen H, 1998). Antibody response following vaccination was also lower in HIV-infected subjects and again the low-responder HIV-infected subjects had faster waning of protective antibody levels, while revaccination did not boost response as compared to non-infected controls (Rodriguez-Barradas MC, 1996).

A study of the protective effect of PPV in death secondary to **acute respiratory infections** (ARI), noted an efficacy of 59% in preventing ARI deaths in children less than 5 years old, with an overall reduction of ~20% in mortality attributable to vaccination (Riley ID, 1986). Another study found that the vaccine efficacy in protecting children < 5 years old from moderate-severe acute lower respiratory infection (ALRI) was 28%, while there was no effect on the incidence of mild ALRI (Lehmann D, 1991).

A study in 40 children and young adults with chronic **renal diseases** found that PPV vaccination induces only short-term immunity in children (Fuchshuber A, 1996). Another study of 21 renal transplant recipients found that vaccine titers did not decline within 12 weeks post-vaccination (Kazancioglu R, 2000). In 25 children with steroid-responsive nephrotic syndrome, following PPV vaccination, antibody titers were found to decline rapidly, especially in those patients who relapsed (Spika JS, 1986).

In children with **acute lymphocytic leukemia,** vaccine response was noted to be suboptimal with protective antibody titers in only two serotypes in most patients (Feldman S, 1985). A study in children receiving **bone marrow transplantation** (BMT) found that immune response to vaccine was noted in only 20-30% of patients receiving vaccine between 6months-1 year post-bone mBMT and 50% in children vaccinated between 1-2 years post-BMT, so that the highest risk groups mounted the poorest response to vaccination (Avanzini MA, 1995). A study of 45 patients in cirrhosis and liver transplantation found that PPV vaccine is ineffective and thus routine PPV vaccination is not recommended (McCashland TM, 2000).

4.2 Safety

A report from the Advisory Committee on Immunization Practices in CDC, Atlanta, USA indicates that the pneumococcal polysaccharide vaccine is generally a safe vaccine as a results of a meta-analysis of nine RCTs where local reactions were seen in about a third 1/3rd of 7531 vaccinees and no severe febrile or anaphylactic reactions were observed (Nuorti PJ, 1997). A consensus on Pneumococcal Vaccine from Belgium indicate that the most

commonly observed adverse effect following vaccination was local pain and erythema, and that moderate-severe adverse events wer noted in < 1% of vaccinees (Belgian Society for Infectiology and Clinical Microbiology, Belgian Society for Pulmonology, Scientific Society of General Physicians, 1996).

4.3 Cost Implications

A cost effectiveness analysis of pneumococcal vaccination strategies found that cost savings were influenced by vaccine efficacy, disease burden in specific population groups and unit vaccine cost, and concludes that adult vaccination is the most cost-effective approach (Gable CB, 1997 Plans Rubio P, 1995; Patrick KM, 1981). Another cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children postulates that vaccination of healthy infants would prevent 12 000 cases of meningitis and bacteremia, 53 000 cases of pneumonia and 1 million episodes of otitis media and 116 deaths could be averted in a year, that could be translated into cost savings of US $ 342 million in medical (direct) costs and US$415 million in work-loss and other indirect costs (Lieu TA, 2000). Examining the cost-benefits, it has been predicted that immunization with a conjugate pneumococcal vaccine would be expected to save 222 lives per million vaccinated children annually, resulting in nett direct costs of $0.08 to $2.42 per child, and when indirect costs of illness are considered, the vaccine is cost-saving (Hueston WJ, 2000).

5. CONCLUSIONS

There is sufficient evidence that 23-valent Pneumococcal Polysaccharide Vaccine is poorly immunogenic in infants and young children, does not decrease nasopharyngeal carrier rates or reduce the frequency of otitis media episodes in vaccinees.

The vaccine is effective in patient populations especially susceptible to invasive pneumococcal infection like those who have undergone splenectomy. Regular revaccinations every 3-5 years in patients post-splenectomy has been demonstrated to be safe and effective.

There is insufficient evidence of the efficacy of the vaccine in patients with HIV infection, children with nephrotic syndrome, recipients of solid-organ or bone-marrow transplants, patients with solid/hematological neoplasms and patients with chronic renal or liver diseases.

There is sufficient evidence of efficacy of the new 9-11 valent conjugate pneumococcal vaccines in decreasing childhood pneumococcal disease, including otitis media and pneumonia; in addition, by decreasing nasopharyngeal carriage, the vaccine will help interrupt disease transmission. Cost-effective estimations also support introduction of the conjugate vaccine as universal primary immunization in infants.

The vaccine is generally well tolerated and is essentially free of serious local and systemic side effects.

6. RECOMMENDATIONS

Pneumococccal Polysaccharide Vaccine is not recommended for the routine vaccination of healthy infants and young children. It is recommended for vaccination in patients undergoing splenectomy.

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8. EVIDENCE TABLE
PNEUMOCOCCAL VACCINE

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
Vaccine Efficacy				
1.	Rubin LG *Pneumococcal vaccine* Pediatr Clin Nort Am 2000 47:269-285	Review of available literature	Anticapsular antibodies against the pneumococcal capsule are protective. The 14- and later, the 23-valent polysaccharide vaccine have been around for nearly 25 years and have limited immunogenicitry in children between 2-5 years, a group at highest risk for invasive pneumococcal disease. The conjugated pneumococcal vaccine, in a series of injections, has been demonstrated to protect normal infants from invasive pneumococcal infections, episodes of lobar pneumonia and acute otitis media caused by vaccine serotypes.	Good
2.	*WHO: Pneumococcal vaccines: World Health Organization position paper* Can Commun Dis Rep 1999 25:150-151	Review of available literature	(a) The23-valent pneumococcal vaccine has an overall protective efficacy of between 60-70%. (b) Protective efficacy of the polysaccharide vaccine is poor in children < 2 years old and individuals with HIV infection. (c) The healthy elderly and elderly with chronic diseases benefit most from the polysaccharide vaccine. The new generation of conjugate vaccines (with 7-11 serotypes bound to a protein carrier) results in a T-cell mediated immune response that may ensure protection in children < 2 years old; the vaccine has the potential to result in widespread immunity through a herd effect.	Poor

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	Nuorti PJ, Butler JC, Breiman RF *Prevention of Pneumococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP*) CDC MMWR 1997 46:RR-8 1-24	Review of available literature.	(a) Recommends pneumococcal polysaccharide vaccination in selected category of immunocompetent persons above 2 years old: otherwise healthy adults ≥ 65 years old, persons aged between 2-64 years with chronic illnesses (cardiovascular & pulmonary diseases, diabetes mellitus, chronic alcoholism, chronic liver disease and CSF leaks), persons aged 2-64 years with anatomic or functional asplenia (concurrently with penicillin chemoprophylaxis) and persons aged 2-64 years in special environments (e.g., institutionalized). (b) Less persuasive recommendations in immunocompromised patients, since vaccine efficacy has not been unequivocally proven in this group of patients. Patients with HIV infection need to be vaccinated early in their disease course. (c) Recommends revaccination in young children who are expected to have declining antibody titers. (d) Conjugate vaccine preparations have their better immonogenicity, ability to produce a T-cell dependent response with anamnestic responses to revaccination and decreases nasopharyngeal carriage rates and thus, decrease disease transmission. Conjugated vaccines will first find their use in vaccinating immunocompromised patients.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
4.	Wang EL *Canadian Task Force on Preventive Health Care: Pneumococcal vaccine* (Updated) 1998	Review of the available literature.	(a) The pneumococcal polysaccharide vaccine is not beneficial in children. The vaccine does not prevent otitis media in infants and young children. (b) Recommends the vaccine in patients with homozygous sickle-cell disease and patients post-splenectomy. (c) Does not recommend vaccination in immunocompromised patients. (d) Recommends vaccination in all immunocompetent healthy adults >55 years old. (e) Potential of the conjugate vaccine in preventing invasive childhood pneumococcal disease and otitis media and demonstarted cost-effectiveness of a vaccination programme.	Good
5.	Douglas RM, Riley ID Pneumococcal disease and its prevention with polyvalent pneumococcal vaccine – a review Aust NZ J Med 1979 9:327-338	Review of available literature	Pneumococcus is a major pathogen in childhood otitis media, invasive disease and adult pneumonia. Recommends vaccine in adults > 50 years with chronic systemic diseases, alcoholics, splenectomized individuals and in disadvantaged groups (as the Aborigines). Recognizes poor vaccine efficacy in prevention of pneumococcal disease in children	Fair
6.	Overturf GD Infections and immunizations of children with sickle-cell disease Adv Pediatr Infect Dis 1999 14:191-218	Review of available literature.	Sickle-cell disease (SCD) patients have dysfunctional humoral immunity and opsonophagocytic function (including hyposplenism), predisposing them to invasive infection by polysaccharide-encapsulated organisms. No convincing data exist on the efficacy of the pneumococcal polysaccharide vaccine in SCD. Penicillin prophylaxis however has been well documented to be protective in SCD patients in many clinical trials. Increasing penicillin resistance of S. pneumoniae and problems of compliance with penicillin	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
			prophylaxis will mean that the new conjugate pneumococcal vaccine may be a better prophylactic option in SCD patients.	
7.	Babiker MA Prophylaxis of pneumococcal infection in sickle-cell disease by the combined use of vaccination and penicillin Ann Trop Med 1986 6:179-181	Prospective cohort-based study Follow-up -over 4 years.	Assessing the combined efficacy of PPV + penicillin prophylaxis in preventing pneumococcal infection in children (2-5 years) with homozygous sickle-cell disease (n=40). Revaccination boosters were given 2-yearly. Penicillin was administered as oral therapy (Pen-V, 12-hourly, n=24) or as 4-weekly IM benzathine-penicillin. (a) 12 episodes of bacteremial sepsis over 160 patient –years noted compared to a historical cohort (without prophylaxis) that reported 15 episodes of bacteremia over 44 patient-years. (b) 2 of the 12 episodes were due to S. pneumoniae compared to 8 of a5 in the historical cohort. Remaining bacteremial episodes were due to gram-negative bacteria. (c) 1 of the 2 S. pnemoniae bacteremial episodes in the cohort was in a child who was non-compliant to penicillin prophylaxis. (d) Compliance was significantly better in the group administered IM benzathine penicillin (92%) than in the oral penicillin group (40%). IM benzathine was administered during clinic visits. Recommends a combination of the pneumococcal polysaccharide vaccine and penicillin to prevent invasive pneumococcal infection in young children with SS homozygous disease. Benzathine penicillin IM appears a better mode of penicillin prophylaxis.	Fair Limitations: (a) S. pneumoniae seroytypes not ascertained in breakthrough infections; if vaccine serotypes isolated, then vaccine efficacy would have been poor in these young children (b) Concurrent comparisons with children of other ages with SS disease or with a control group to study whether penicillin necessary despite vaccination would be ideal.
8.	Konradsen HB; Henrichsen J Pneumococcal infections in splenectomized children are	Retrospective review	Retrospective review of the incidence of invasive pneumococcal disease in vaccinated splenectomized children 0-15 years old over a 9-year period (1979-1987) compared to a historical cohort of unvaccinated splenectomized similarly-	Poor Poor study design Indications for splenectomy not detailed,

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	preventable Acta Paediatr Scand 1991 80:423-427		aged children over an earlier 8-year period (1969-1978)..None of the vaccinated and splenectomized children developed invasive pneumococcal disease as against 4% in the historical non-vaccinated cohort group. Vaccinated splenctomized subjects did not receive regular penicillin prophylaxis; defined antibiotic therapy (antibiotics in case of fever) was practised instead.	but vaccine efficacy may be lower in immunocompromised children undergoing splenectomy.
9.	Johm AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR Prevention of pneumococcal infection in children with homozygous sickle-cell disease Br Med J (Clin Res Ed) 1984 288:1567-1570	Case-control study	Study of efficacy of a regimen of pneumococcal polysaccharide vaccination (14-valent) alone in 242 children (6 months – 3 years) with homozygous sickle-cell disease (SCD) versus unvaccinated SCD children on penicillin prophylaxis alone (study over 5 years) The vaccine group experienced 11 pneumococcal infections, 10 of which were by vaccine serotypes (type 23 being the commonest vaccine serotype isolated). Most infections noted in children vaccinated when less than 1 year old. In contrast, no pneumococcal isolated noted in the penicillin-only group; significantly, this group experienced 4 episodes of pneumococcal infections within a year of stopping penicillin. Penicillin prophylaxis is superior to pneumococcal polysaccharide vaccination in SCD children, at least till the age of 3 year	Poor
10.	Keller DW, Breiman RF Preventing bacterial respiratory infections among persons infected with human immunodeficiency virus. Clin Infect Dis 1995 21 (suppl) S77-S83	Review of available literature.	HIV-infected patients experience more frequent and recurrent pneumococcal respiratory infections. Recommends early administration of 23-valent pneumococcal polysaccharide vaccine in HIV-infected individuals despite acknowledging that efficacy data are limited. Speculates that antiretroviral therapy may improve vaccine immunogenicity.No data available at time of writing, on revaccination in HIV-infected subjects. PPV vaccination recommended in HIV-	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
			infected individuals as a “something better than nothing” option, since efficacy data are not remarkable	
11.	Jain A, Jain S, Gant V Should patients positive for HIV receive pneumococcal vaccine? BMJ 1995 310:1060-1062	Review of available literature.	HIV-infected individuals have a 100-times increased risk of developing invasive pneumococcal infection. Vaccine efficacy is poor in HIV-infected persons compared to vaccination in healthy persons.. Does not recommend routine PPV vaccination in HIV-infected persons. Recommends large-scale trials to resolve the role of PPV-vaccination in HIV-infected patients	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
PROTECTIVE EFFICACY OF THE PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV) IN AN UNSELECTED POPULATION				
1.	Bacle A, Diot P, Lemarie E. Anti-pneumococcal vaccine: justifications and results. Rev Pneumol Clin 1997 53:128-137	Meta-analysis of 9 randomized studies	Meta-analysis of 9 randomized studies studying vaccine efficacy (23-valent PPV) in preventing all proven/ presumed pneumococcal pneumonia or proven/presumed pneumococcal pneumonia caused by vaccine serotypesBest vaccine response noted in the population at lowest risk of invasive disease. (a) Poor protection against pneumonia (irrespective of cause) in the general population and in children <2 years old. (b) Modest efficacy in adults at especial risk (> 65 years, institutionalized and/or with cardiopulmonary diseases). (c) Efficacy in post-splenectomy patients and patients with sickle-cell anemia. May be used in children (d) Inconclusive data on revaccination.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
2.	Broome CV, Facklam RR, Fraser DW Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine N Engl J Med 1980 303:549-552	cohort analysis.	An indirect cohort analysis of vaccine efficacy in immunocompromised groups by comparing serotypes of pneumococcal isolates (n=35) from blood and CSF of vaccinated immunocompromised patients with serotypes of S. pneumoniae isolates from unvaccinated healthy individuals. The hypothesis was that vaccine serotype isolates should be decreased in vaccinated subjects. Proportion of vaccine serotypes isolated not different in the vaccinated and unvaccinated groups. (a) Overall vaccine efficacy (vaccination across all ages) was estimated to be 36%. (b) Lowest vaccine efficacy in children 2-10 years old (vaccine efficacy ≤ 0%). (c) Surprisingly, in immunocompromised individuals with highest risk of invasive pneumococcal disease, vaccine efficacy was also estimated at ≤ 0%. (d) Vaccine efficacy was best at ages above 10 years (60%). Selected vaccination of at-risk adults appears superior to universal vaccination.	Fair, Did not specifically assess vaccine protection in splenectomised subjects.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	Wright PF, Sell SH, Vaughn WK, Andrews C,McConnell KB, Schiffman G Clinical studies of pneumococcal vaccines in infants: efficacy and effect on nasopharyngeal carriage. Rev Infect Dis 1981 3 (suppl):S108-112	Open-label study 200 infants.	Open-label study of effect of two PPV formulations on nasopharyngeal carriage rate in 200 infants. (a) Vaccination did not affect nasopharyngeal carriage rate. (b) Vaccine serotype-specific antibodies did not correlate with nasopharyngeal carrier state at all titers of antibodies. (c) Pneumococcal bacteremia incidence not altered after vaccination in infants; vaccine serotype noted in 1 of 4 bacteremic illnesses in these 200 infants. Vaccine appears to be poorly effective in infants. Uncertain whether elimination of carrier state will prevent invasive pneumococcal disease.	Poor level of evidence
4.	Koskela M, Leinonen M, Haiva VM, Timonen M, Makela PH First and second dose antibody responses to pneumococcal polysaccharide vaccine in infants Pediatr Infect Dis 1986 5:45-50	double-blind placebo-controlled study	Open-label study of antibody responses to PPV immunization schedule after one (at 7 months) and two doses (at 13 months) in infants as compared to controls. Poor antibody response to vaccine serotypes after the 1st and 2nd doses; rapid deterioration of antibody titers noted. Confirms poor vaccine efficacy in infants.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
5.	Lawrence EM, Edwards KM, Schiffman G, ThompsonJM, Vaughn WK, Wright PF Pneumococcal vaccine in normal children: primary and secondary vaccination Am J Dis Child 1983 137:846-850	Case-control study 52 healthy children 2-5 years of age.	Study of antibody responses and tolerabilty PPV revaccination using a vaccine component strength was 50 mcg per vaccine serotype; a 14-valent PPV was used. A simultaneous control group received saline injections as placebo during primary vaccination Vaccine antibody responses were two-fold following revaccination but local reactions were severe; immunogenicity of serotype 6 capsular polysaccharide preparation was consistently poor.	Fair study Revaccination interval was not looked at critically. No correlations were made between antibody titers and clinical protection. Higher adverse events probably due to capsular polysaccharide dose.
6.	Cadoz M Potential and limitations of polysaccharide vaccines in infancy Vaccine 1998 16:1391-1395	Review	To assess efficacy of polysaccharide vaccine in infants. Infants are at especial risk of invasive pneumococcal disease. Immunogenicity of pneumococcal capsular polysaccharide antigens variable, differs with different serotypes and induces a T-cell independent immune response that results in poor persistence of immunity. Pneumococcal capsular polysaccharide vaccine needs to be probably conjugated to a protein carrier to recruit a T-cell mediated mechanism, similar to the experience with the Hemophilus influnzae conjugate vaccine.	Good
7.	Temple K, Greenwood B, Inskip H, Hall A, Koskela M, Leinonen M Antibody response to pneumococcal capsular polysaccharide vaccine in African children Pediatr Infect Dis J 1991 10:386-390	Open-label study	Study assessing antibody responses post-vaccination in 2 groups of children (between 2-9 months and between 5-10 years). Poor immune response; noted to only selected serotypes Better immune response in older children. Reiterates poor vaccine efficacy in children <2 years	Poor

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
8.	Mufson MA Antibody response of pneumococcal vaccine: need for booster dosing? Int J Antimicrob Agents 2000 14:107-112	Review of available literature	While the 23-valent PPV, covering 90% of the most pathogenic pneumococcal serotypes, is immunogenic in most immunocompetent persons (including elderly adults), protective antibody titers rapidly decline within 1-month post-vaccination to pre-vaccination levels. Booster doses are noted to be effective only in immunocompetent adults, not in children and immunocompromised subjects. Recommends regular revaccination for adult high-risk patients and the elderly (>80 years).	Good.
9.	Makela PH, Sibakov M, Herva E, Henrichsen J, Luotenen J, Timonen M, Leinonen M, Koskela M, Pukander J, Pontynen S, Gonroos P, Karma P Pneumococcal vaccine and Otitis media Lancet 1980 13:547-551	827 children (3 months – 6 years) were randomly assigned to receive either a 14-valent PPV or a control vaccine (Hib vaccine) following 1 attack of acute otitis media.	(a) Immune responses were poor in children ≤ 6 months old. Reasonably satisfactory immune response was noted in children older than 6 months, except to serotype 6. (b) No clinical protection against recurrent otitis media was seen in infants ≤ 6 months old or to serotype 6 pneumococci –related otitis media. (c) In children older than 6 months, significantly fewer attack rates caused by vaccine serotypes (except serotype 6) were noted in the 6 months after vaccination. (d) Overall protective efficacy was estimated at 58% and was better in children older than 2 years. (e) Of note, vaccine protective efficacy was not noted to be enhanced by previous attacks of pneumococcal otitis media.	Good Limitation: short follow-up of vaccinated children. It may be argued that the protective efficacy could have waned over time.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
10.	Sloyer JL, Ploussard JH, Howie VM Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama Rev Infect Dis 1981 3 (suppl) S19-S23	Case-control study. 179 infants 2-year follow-up.	179 infants were randomly assigned to receive either a target serotype PPV (covering 8 serotypes commonly associated with otitis media) or a control 7-valent vaccine with non-pathogenic serotypes. Incidence of otitis media due to the target serotypes were assessed in both groups. For infants > 12 months old, the incidence of otitis media due to target serotypes did not differ in the targeted and control groups. (a) In infants vaccinated when ≤ 12 months old (n=66), 22/33 episodes of otitis media were due to target serotypes; target vaccinated infants experienced 13 of these 22 episodes. (b) Progression to a otitis-prone state (≥ 6 episodes) was seen in 4 target-vaccinated and 13 control-vaccinated infants. No significant vaccine efficacy in prevention of otitis media among infants was noted.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
11.	Teele DW; Klein JO; Bratton L; Fisch GR; Mathieu OR; Porter PJ; Starobin SG; Tarlin LD; Younes RP *Use of pneumococcal vaccine for prevention of recurrent acute otitis media in infants in Boston. The Greater Boston Collaborative Otitis Media Study Group* Rev Infect Dis 1981 3 Suppl:S113-18	Double-blind randomized study 124 children	Study of protective efficacy of a 8-valent pneumococcal vaccine (with serotypes most commonly associated with Acute Otitis Media, AOM) against AOM compared to a control 7-valent vaccine (with non-pathogenic pneumococcal serotypes) in children 5-21 months old (a) Recipients of the octavalent vaccine experienced significantly less AOM due to serotypes contained in the octavalent vaccine than did children who received the control vaccine. (b) However, their clinical experience with AOM was not different. Both groups of children were equally likely to experience at least one episode of AOM after vaccination (70% for octavalent vaccine and 78% for heptavalent vaccine). (c) The mean numbers of episodes of AOM after vaccination also were similar (2.1 for octavalent vaccine and 2.3 for heptavalent vaccine). Similarly, the period of effusion in the middle ear after pneumococcal AOM was identical for both groups. Although immunization with pneumococcal vaccine appeared to reduce the number of episodes of AOM due to serotypes contained in octavalent vaccine, the clinical experience of the children was not favourably affected by this vaccine.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
12.	Rosen C, Christensen P, Henrichsen J, Hovelius B, Prellner K *Beneficial effect of pneumococcal vaccination on otitis media in children over two years old* Int J Pediatr Otorhinolaryngol 1984 7:239-246	Double-blind trial 415 children 2-year follow-up period.	Study of protective efficacy of a 14-valent pneumococcal vaccine in children aged 6-60 months, matched for age, history of otitis media and environment in decreasing frequency of acute otitis media. (a) The total incidence of acute otitis media was reduced during the 2-year follow-up period by 24% among those vaccinated between the ages of 2 and 5. (b) Recurrent episodes of otitis media decreased by 49% (c) Protective efficacy was demonstrable during the first post-vaccinational year, but not when more than 1 year had lapsed after the vaccination. These findings suggest that, while the vaccine had no effect on children under 2 years old, it may be a useful aid in preventing recurrent attacks of otitis media in children between 2 and 5 years of age.	Good Available data are confusing - larger trials showed poorer protective efficacy.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
13.	Douglas RM, Miles HB *Vaccination against Streptococcus pneumoniae in childhood: lack of demonstrable benefit in young Australian children* J Infect Dis 1984 149:861-869	double-blind randomized placebo-controlled trial 1273 healthy children Follow-up > two years	A double-blind randomized placebo-controlled trial to assess protective efficacy of a 14-valent pneumococcal polysaccharide vaccine administered to healthy children, 6-54 months old (n=1273, saline placebo). Different vaccine dosage regimens used for children ≤ 2 years old and > 2 years old. Follow-up was over two years, assessing frequency of respiratory and ear infections through home-based and medical records.Data from diaries and medical and hospital case notes failed to reveal consistent or significant benefits in those who received the vaccine. In the first 16 months after immunization, recipients of placebo experienced an average of 0.69 episodes of otitis media per child, compared with 0.63 in recipients of vaccine. Recipients of vaccine had no consistent reduction in days of respiratory morbidity, antibiotic consumption, hospitalization, or visits to a physician, when compared with recipients of placebo.	Good. .

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
14.	Kalm O, Prellner K, Freijd A, Rynnel-Dagoo *Antibody activity before and after pneumococcal vaccination of otitis-prone and non-otitis-prone children*. Acta Otolaryngol 1986 101:467-74	Case control study	The antibody activity of the IgM class and subclasses of IgG and IgA against pneumococcal bacteria of types 3, 6A and 19F was studied before and after administration of a pneumococcal vaccine (Pneumovax) in a group of children with recurrent acute otitis media (rAOM) and in groups of non-otitis-prone childrenOnly occasionally was there a significant rise in antibody activity after vaccination in any of the groups. There was no difference in the response to vaccination between rAOM children and healthy children. However, rAOM children exhibited lower antibody activities in most Ig subclasses against pneumococcus type 6A--a common causative agent in AOM--before as well as after vaccination compared with the healthy children. The results indicate that the response to vaccination is equally poor in all children, irrespective of whether they have a history of frequent attacks of acute otitis media. Further, in contrast to healthy children, the rAOM children seem to have an inability to mobilize antibodies in response to infections with some pneumococcal types.	Poor level of evidence Specific deficits in ability to mount immune responses may predispose some children to rAOM; this is not reversed by vaccination.
15.	Riley ID, Lehmann D, Alpers MP, Marshall TF, Gratten H, Smith D Pneumococcal vaccine prevents death from acute lower-respiratory-tract infections in Papua New Guinean children Lancet 1986 2:877-881	Double-blind placebo controlled trial	Study of PPV protection from death (secondary to Acute Respiratory Infections, ARI) in vaccinated children (6 months to 5 years) versus controls Vaccine efficacy noted at 59% in preventing ARI deaths in children less than 5 years old; in a subgroup of children < 2 years old (especial risk from pneumococcal disease), protective efficacy at 50%. Overall reduction in mortality attributable to vaccination at ~20%.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
16.	Lehmann D; Marshall TF; Riley ID; Alpers MP Effect of pneumococcal vaccine on morbidity from acute lower respiratory tract infections in Papua New Guinean children. Ann Trop Paediatr 1991 11:247-257	Randomized double-blind controlled trial	To assess impact of introduction of the 14-valent pneumococcal vaccine on incidence of Acute Lower Respiratory Infection (ALRI) in children < 5 years old. Morbidity from ALRI was assessed. Children were recruited in 5 separate cohorts, 4 months apart. (a) Overall vaccine efficacy in protecting children from moderate-severe ALRI was a modest 28%; this was a significant protection when mortality from modest-severe ALRI was considered. Vaccination had no effect on mild ALRI incidence. (b) Vaccine effect was greatest in the cohort of children at risk of developing moderate-severe ALRI during an epidemic situation. It was therefore in children at the most vulnerable age in times of greatest incidence of disease that the vaccine had its most potent effect. (c) Vaccine efficacy was probably influenced by incidence of disease by vaccine serotypes, immune response of susceptible children to specific pathogenic serotypes and pre-vaccination specific immune status. The study raises the question: How does the vaccine confer protection in children < 2 years whose immune response to vaccine serotypes is known to be poor? It is speculated that a modest immune response may yet attenuate disease severity in children; further non-capsular cell wall antigens contaminating vaccine preparations may result in protective immunity too.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
PROTECTIVE EFFICACY OF THE PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV) IN SELECTED POPULATION GROUPS				
1.	Lee JH, , Kang JH, Henrichsen J, Konradsen HB, Jang SH, Shin HY, Ahn HS, Choi Y, Hessel L, Nam SW Immunogenicity and safety of a 23-valent pneumococcal polysaccharide vaccine in healthy children and in children at increased risk of pneumococcal infection Vaccine 1995 13:1533-1536	21 healthy children assessed 4 weeks post-vaccination.	Open-label study of a single dose of the 23-valent PPV immunogenicity in selected at-risk (26 splenectomized, 48 with nephrotic syndrome, 24 with recurrent asthma) and healthy Korean children (n=21). Representative capsular-specific antibody responses assessed 4 weeks post-vaccination. (a) Good first-dose response in all healthy children with increase in Antibody Geometric Mean Titers (Ab-GMT) of 2.6 at 4 weeks. (b) Mean Ab-GMT titers lower in the at-risk population (c) Vaccine well tolerated with minor local injection-related symptoms in 41% of vaccinees Lower vaccine immunogenic intensity in high-risk groups noted. Open-label study with small numbers but instructive. Did not assess persistence of immune response.	Fair

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
2.	Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR Pneumococcal Polysaccharide Vaccine efficacy: An evaluation of current recommendations JAMA 1993 270:1826-1831	Indirect cohort analysis over a 14 year period 2837 individuals,	Comparing proportion of pneumococcal infections caused by vaccine serotypes in vaccinees as compared to unvaccinated individuals from 1978-1992 through records of pneumococcal isolates (from blood and/or CSF) in selected hospital laboratories; (a) Overall vaccine efficacy (preventing infection by vaccine serotype) was 57% (b) Efficacy was higher in immunocompetent individuals (75%) (c) Best efficacy outcomes in elderly subjects with chronic cardiac or pulmonary disease and diabetes. (d) Protective efficacy in subjects with absent spleen (congenital/post-operative/functional) moderate: 77% (e) Efficacy was not a function of time, being 71% and 80% 5 and 9 years post-vaccination (f) Vaccine efficacy not assessed in more severely immunodepressed groups (chronic renal failure, chronic alcoholism, liver cirrhosis, multiple myeloma, sickle-cell disease) as numbers were too small. (g) Notes that vaccination may provide protection for at least 9 years after initial vaccination.	Fair

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	Bolan G, Broome CV, Facklam RR, Plikaytis BD, Fraser DW, Schlech WF Pneumococcal vaccine efficacy in selected populations in the United States Ann Intern Med 1986 104:1-6	Indirect cohort analysis over a 6-yaer period.	Looking at distribution of serotypes of S. pneumoniae in isolates from blood and CSF among vaccinated and unvaccinated subjects from 1978-1984. Based on a CDC hypothesis that pneumococcal infections in vaccinated subjects should be less frequently due to vaccine serotypes than in unvaccinated subjects.In patients with bacteremic illness, the vaccine protective efficacy was estimated at 64%. Efficacy did not vary with age. PPV efficacy was 61% in adults >65 years old, either in the presence or absence of underlying disease (diabetes and cardiopulmonary disease). Study excluded children<2 years old and subjects with moderate immunosuppressed states (Hodgkin's disease, multiple myeloma, immunoglobulin deficeiency) but noted that vaccination in the latter groups was not protective.	Fair. Possible bias in study design since based on a retrospective review of laboratory isolates that may not be representative.
4.	Shapiro ED, Clemens JD *A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infections* Ann Intern Med 1984 101:325-330	Case-control study (n=90/90)	Assessing vaccination status in two groups: cases with pneumococcal infection as against uninfected controls. The hypothesis was that frequency of vaccination should be higher in uninfected controls as compared to infected cases if the vaccine is deemed protectiveVaccine protective efficacy was assessed at 67% overall. The vaccine was most protective (70%) in the moderate-risk category (moderately impaired immunity secondary to chronic alcoholism, diabetes mellitus, chronic renal disease on dialysis and congestive heart failure). In subjects with severe or mild immune impairment, the vaccine protective efficacy was 0%	Good to fair

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
5.	Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, Adair RK, Clemens JD The protective efficacy of polyvalent pneumococcal polysaccharide vaccine N Engl J Med 1991 325:1453-1460	case-control over a 6-year period (n=1054).	An expansion of the above from1984-1990 ascertaining vaccination status in cases with invasive pneumococcal disease versus matched controls. Isolates of S. pneumoniae were further serotyped. Overall vaccine efficacy for serotypes included in the vaccine was 57% over a 3-year period post-vaccination. Vaccine efficacy was only 21% (protection status similar to unvaccinated subjects) in immunocompromised patients. Vaccine efficacy in adults ≥ 85 years was only 46%. Vaccine efficacy progressively waned over time.	Good.
6.	Arpadi SM, Back S, O'Brien, Janoff EN Antibodies to pneumococcal capsular polysaccharides in children with human immunodeficiency virus infection given polyvalent pneumococcal vaccine J Pediatr 1994 125:77-79	Case-control study (n=11).	Assessing antibody titers to representative serotypes post vaccination in vaccinated HIV children versus unvaccinated HIV children and unvaccinated healthy subjects HIV-infected vaccinees did not have significantly higher antibody titers as compared to unvaccinated HIV-infected children and healthy children. Small sample size is a major weakness. A concurrent arm comparing vaccination in HIV-infected adults should have been created to eliminate age as a confounder. A cohort of vaccinated healthy controls should have been (alternatively) included.	Fair

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
7.	Weiss PJ, Wallace MR, Oldfield EC, O'Brien J, Janoff EN Response of recent human immunodeficiency virus seroconverters to the pneumococcal polysaccharide vaccine and Hemophilus influenzae type b conjugate vaccine J Infect Dis 1995 171:1217-1222	Case-control format (n=20).	Studying antibody response to the 23-valent PPV in recently diagnosed HIV patients (illness<18 months, n=20) versus healthy controls Equivalent antibody responses between cases and controls at 4 weeks and 6 months post-vaccination. Small numbers studied but suggests that vaccination of HIV-infected individuals early in the disease course ensures adequate vaccine protective efficacy. Limited by small numbers and the short-term follow-up.	Poor
8.	Rodriguez-Barradas MC, Musher DM, Lahart C, Lacke C, Groover J, Watson D, Baughn R, Cate T, Crofoot G Antibody to capsular polysaccharides of Streptococcus pneumoniae after vaccination of human immunodeficiency virus-infected subjects with 23-valent pneumococcal vaccine J Infect Dis 1992 165:553-556	Case control	Post-vaccination antibody response to 5 representative serotypes studied in two groups of HIV infected individuals: I, with CD4 count ≤ 500/cu.mm and II, with CD4 count > 500. Responses compared to simultaneously vaccinated healthy controls. HIV-infected individuals with lower counts exhibited a poor vaccine immune response (24%). Vaccine responses among HIV-infected individuals with CD4 counts >500 and healthy controls were similar (~75%). HIV clinical status did not appear to influence vaccine response for a given CD4 count. Recommends that HIV-infected individuals be administered PPV early in disease course (when CD4 >500) to obtain optimal immune responses.	Good Fails to study persistence of immunity in vaccinated HIV-infected subjects as compared to healthy controls.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
9.	Nielsen H, Kvinesdal B, Benfield TL, Lundgren JD, Konradsen HB Rapid loss of specific antibodies after pneumococcal vaccination in patients with human immunodeficiency virus-1 infection Scand J Infect Dis 1998 30:597-601	Cohort-based	Study of post pneumococcal vaccination (23-valent) antibody responses in 103 asymptomatic/mildly asymptomatic patients with HIV-infection (a) Two-thirds of vaccinated patients showed significant increase in IgG to capsular polysaccharides, 4 weeks post –vaccination. (b) However, antibody titers declined to pre-vaccination levels 12-months post-vaccination. While vaccination early in the course of HIV infection is recommended, rapid waning of antibody levels results in only short-term immunity.	Fair
10.	Rodriguez-Barradas MC, Groover JE, Lacke CE, Gump DW, Lahart CJ, Pandey JP, Musher DM IgG antibody to pneumococcal capsular polysaccharide in human immunodeficeincy virus-infected subjects: persistence of antibody in responders, revaccination in non-responders and relationship of immunoglobulin allotype to response. J Infect Dis 1996 713:1347-1353	Open-label study.	Study of antibody titers over time following vaccination with a 23-valent PPV in HIV-infected subjects (a) Antibody response following vaccination lower in HIV-infected subjects as compared to non-infected controls. (b) Responders however demonstrate similar IgG titers post-vaccination as responding non-infected subjects (c) High-level HIV-infected responders (IgG≥ 1mcg/ml post vaccination) showed similar IgG titers 1 and 2 years post-vaccination as non-infected high-responder subjects. (d) Low-responder HIV-infected subjects had faster waning of protective antibody levels; revaccination did not boost response.	Poor

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
11.	Abildgaard N, Nielsen JL Pneumococcal septicemia and meningitis in vaccinated splenectomized adult patients Scand J Infect Dis 1994 26:615-617	Retrospective survey	Study of the occurrence of invasive pneumococcal disease in splenectomized adults following vaccination (over a 15-year period since vaccination introduced in 1978). Many adults were also immunocompromised (eg. Hodgkin's disease on chemotherapy4 episodes of S. pneumoniae septicemia noted; all were with non-vaccine serotypes. Indirect evidence of vaccine efficacy post-splenectomy despite the immunocompromised state.	Poor
12.	Konradsen HB, Pedersen FK, Henrichsen J Pneumococcal revaccination in splenectomized children Pediatr Infect Dis J 1990 9:258-263	Prospective cohort-based study post-vaccination.	Assessing need for revaccination in splenectomized children (n=43) following primary 14-valent PPV vaccinations. Pre-primary vaccination antipneumococcal antibody levels to all 14 capsular polysaccharide antigens were measured; antibody levels were further measured at 4 weeks and 5 years Post-splenectomized children who had lower pre-primary vaccination anti-pneumococcal antibody titers also demonstrated declining titers 5 years following vaccination, necessitating revaccination. Re-vaccination induced a good immune response and was well tolerated. Recommends revaccination in selected post-splenectomy patients who have low anti-pneumococcal antibody titers 5 years after primary vaccination.	Poor.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
13.	Shatz DV, Schinsky MF, Pais LB, Romero-Steriner S, Kirton OC, Carlone GM Immune responses of splenectomized trauma patients to the 23-valent vaccine at 1 versus 7 versus 14 days after splenectomy J Trauma 1998 44:760-765	Case control	Study to determine the optimal timing of PPV administration following emergent post-trauma splenectomy in 59 consecutive patients; assessment by determining immune responses by antibody titers and opsonophagocytic activity of antibodies induced. Immune responses compared to healthy vaccinated controls. (a) Post-vaccination antibody titers (IgG ELISA) were similar in splenectomized patients (at all post-operative intervals) and controls. (b) However, functional opsonophagocytic activity was best (similar to controls) in patients vaccinated 14-days after splenectomy. Recommends delayed (14-days) vaccination in patients post-splenectomy to obtain best functional antibody activity.	Good Limited by small numbers in each group.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
14.	Fuchshuber A, Kuhnemund O, Keuth B, Lutticken R, Michalk D, Querfeld U Pneumococcal vaccine in children and young adults with chronic renal disease Nephrol Dial Transplant 1996 11:468-473	Cae series	Open-label study of immune response 1, 6 and 12 months following vaccination with the 23-valent PPV in 40 children and young adults with various chronic renal diseases (idiopathic nephrotic syndrome, chronic renal failure, chronic renal failure on dialysis and post-transplantation); 23 of these 40 patients were in addition revaccinated 1 year later. Good immune response was defined as a 4-fold rise in postvaccination antibody titers to a level >200. (a) 83% of vaccinees showed an appropriate response 4 weeks post-vaccination. (b) Waning of immune status noted with Ab levels declining to 68% after 6 months and 48% after 1 year. (c) Following revaccination, 50% showed a rise in Ab titers, only to be followed by a decline in titers 6 months later. Revaccination was well tolerated. PPV vaccination induces only short-term immunity in children with chronic renal diseases.	Fair Limited by small numbers and absence of a concurrent control group.
15.	Kazancioglu R, Sever MS, Yuksel-Onel D, Eraksoy H, Yildiz A, Celik AV, Kayacan SM, Badur S. Immunization of renal transplant recipients with pneumococcal polysaccharide vaccine Clin Transplant 2000 14:61-65	Prospective study (n=13).	Assessing PPV efficacy (single-dose, IM, 23-valent) in 21 patients with well-functioning renal allografts. PPV was administered at least 2 months after operation. Patients were stratified as receiving double (n=8) or triple immunosuppressive therapy. Antibody titers were higher at 6 and 12 weeks post-vaccination in 20 of the 21 patients. Titers were similar in both double and triple immunosuppressive therapy groups. Vaccine titers did not decline within 12 weeks post-vaccination.	Poor No controls were included; numbers were small. Long-term immune persistence was not investigated; clinical efficacy not assessed.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
16.	Spika JS, Halsey NA, Le CT, Fish AJ, Lum GM, Lauer BA, Schiffman G, Giebink GS Decline of vaccine-induced antipneumococcal antibody in children with nephrotic syndrome Am J Kidney Dis 1986 7:466-470	Cohort-based prospective study. 25 patients	Patients with steroid-responsive nephrotic syndrome were studied for persistence of antipneumococcal capsular polysaccharide antibody (at 1, 6 and 12 months) following vaccination with a 14-valent PPV and during relapse of their disease. Non-relapsers (group I) were compared to those who had at least one relapse (sera obtained during remission, group II) (a) Following vaccination, antibody titers declined; rate of decline was faster for group II (b) By 1 year, 50% of patients had non-protective titers to 5 of the 14 vaccine serotypes. (c) Patients who relapsed after being vaccinated had low mean antibody titers (< 300 ng AntibodyN/ml) in their sera. Data indicate that antibody titers decline rapidly in patients with steroid-sensitive nephrotic syndrome vaccinated with PPV, especially in patients who relapse. Decline in antibody titers is non-uniform and varies for various capsular serotypes. Weakness of the study includes its small numbers, short follow-up, lack of a control group and lack of clinical efficacy data.	Poor

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
17.	Feldman S, Malone W, Wilbur R, Schiffman G Pneumococcal vaccination in children with acute lymphocytic leukemia Med Pediatr Oncol 1985 13:69-72	Prospective cohort-based study 63 children.	Assessing antibody response to vaccination with 14-valent PPV in 63 children with ALL (46 vaccinated 1, 3 or 6 months following initial induction remission, 15 vaccinated 4-6 weeks following completion of 2.5 years of therapy and 2 vaccinated at time of diagnosis). Vaccine response was noted to be suboptimal in all three groups of patients. Protective antibody titers (≥ 300 ng specific IgG/ml) were noted for only two serotypes in most (>50%) patients, 6 months following vaccination.	Fair
18.	Avanzini MA, Carra AM, Maccario R, Zecca M, Pignatti P, Bonetti F, De Stefano P, Locatelli F Antibody response to pneumococcal vaccine in children receiving bone marrow transplantation J Clin Immunol 1995 15:137-144	Observational study 53 children	Open-label study off PPV efficacy (23-valent preparation) administered in 53 pediatric patients, 6 months after allo/auto-logous bone-marrow transplantation. Efficacy assessed by measuring total pneumococcal IgM and IgG titers and IgG subclasses.Response to PPV vaccine was best in children receiving vaccine 2 years or more after BMT. Immune response to vaccine noted in only 20-30% of patients receiving vaccine between 6mo-1 year post-BMT and 50% in children vaccinated between 1-2 years post-BMT. Hence, time after BMT influenced response to vaccine. Hence, the highest risk groups mounted the poorest response to vaccination. Part of the poor response may be due to the delayed recovery of B-cell function post-BMT.	Fair to good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
19.	McCashland TM, Preheim LC, Gentry MJ Pneumococcal vaccine response in cirrhosis and liver transplantation J Infect Dis 2000 181:757-760	Case-control study	Assessing antibody response to vaccination with the 23-valent PPV in 45 patients with liver cirrhosis awaiting liver transplantation and in 13 age-matched controls. (a) Control subjects had higher IgG responses to all serotypes; vaccinated patients showed mainly IgA and IgM responses. (b) IgA and IgM titers in patients declined rapidly compared to controls, so that all anti-pneumococcal polysaccharide antibody titers were at pre-vaccination levels in patients 3 months after transplantation. Does not recommend routine PPV vaccination in patients undergoing liver transplantation.	Fair. Small numbers

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
EFFICACY OF THE NEW CONJUGATED PNEUMOCOCCAL POLYSACCHARIDE VACCINE (C-PPV)				
1.	Butler JC Epidemiology of pneumococcal serotypes and conjugate vaccine formulations Microb Drug Resist 1997 3:125-129	Review	National surveillance data over 16 years (1978-1994) (from the CDC, Atlanta, US) to identify pneumococcal serotypes most commonly associated with infection (bacteremia, meningitis, otitis media) in young children (<6 years). Aims to determine whether the new 7-valent conjugate PPV covers a major proportion of these serotypes.78% of these infections were accounted for by the seven serotypes (14, 6B, 19F, 18C, 23F, 4 & 9V) contained in the 7-valent conjugate vaccines. Estimates that this 7-valent conjugate pneumococcal vaccine could potentially prevent 86% of bacteremia, 83% of meningitis and 65% of otitis media cases; protection could be enhanced by immunity to cross-reactive serotypes. Further noted that 80% of the penicillin-nonsusceptible pneumococcal isolates between 1992-1994 belonged to the 7-valent conjugate serotype.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
2.	Ahman H, Kayhty H, Tamminen P, Vuorela A, Malinoski F, EskolaJ Pentavelent pneumococcal conjugate oligosaccharide conjugate vaccine PncCRM is well tolerated and able to induce an antibody response in infants Pediatr Infect Dis J 1996 15:134-139	Case control	Assessment of antibody responses to a pneumococcal conjugate vaccinse (Oligosaccharides derived from capsular polysaccharides of serotypes 6B, 14, 18C, 19F & 23F, 10 mcg each, conjugated to a nontoxic mutant diphtheria toxin CRM197). 25 control sera from unvaccinated children were simultaneously assessed. Anti-pneumococcal polysaccharide antibosy levels were assessed by ELISA. Three doses of the vaccine were administered (2, 4, 6 months). Significant increase in antibody titers to all 6 oligosaccharides noted after the 2^{nd} and 3^{rd} vaccine doses. Specific IgG titers to vaccine serotypes higher in vaccinated infants than in age-matched sera form control unvaccinated infants. Vaccination was well tolerated. Concludes that the vaccine is safe and immunogenic in young infants; immunogenicity requires at least 2-3 vaccination doses.	Fair

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	O'Brien KL, Steinhoff MC, Edwards K, Keyserling H, Thoms ML, Madore D. Immunologic priming of young children by pneumococcal glycoprotein conjugate but not polysaccharide vaccines Pediatr Infect Dis 1996 15:425-430	Case control	Assesses the kinetics of pneumococcal IgG in children (18-30 months old, n=60) who received one dose of an experimental bivalent (6B, 23F) pneumococcal polysaccharide vaccine conjugated to CRM197 protein carrier. 1/3rd of these children subsequently received a booster PPV (including 6A & 23F) 11-20 months later. A control group primed with an experimental bivalent non-conjugated vaccine and later revaccinated similarly was included. (a) Following primary vaccination, all children demonstrated an immune response and antibody titers did not wane over the next 12 months. (b) Pneumococcal polysaccharide vaccine induced a greater anamnestic response in children primed with the conjugate vaccine (13- to 40-fold increases in IgG titers) compared to those primed with the plain PPV (2- to 4-fold increase). (c) While primary conjugate vaccine immune response resulted in elevations of only the IgG1 subclass, secondary immunizations resulted in both IgG1 and IgG2 elevations. (d) A greater response was seen with the 23F than with the 6B serotype. 2 important conclusions therefore made: (a) The conjugated vaccine results in an anamnestic response after revaccination since primary immune response to C-PPV is by a T-cell dependent mechanism unlike with plain PPV. Vaccine serotype is a major determinant of vaccine immunogenicity.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
4.	Rennels MB, Edwards KM, Keyserling HL, Reisinger KS, Hogerman DA, Madore DV, Chang I, Paradiso PR, Malinoski FJ, Kimura A Safety and immunogenicity of heptavelent pneumococcal vaccine conjugated to CRM197 in United States infants. Pediatrics 1998 101:604-611	RCT 212 children	212 healthy 2-month old infants were equally randomized to receive 4 consecutive doses (2, 4, 6 and 12-15 months of age) of C-PPV (7-valent, conjugated to CRM197), and a control conjugated meningococcal vaccine. Other vaccines concurrently administered were OPV/DPT, TT and/or DTP/Hemophilus influenzae b vaccine conjugated to CRM197 (HbOC) (when at 2-6 months) and MMR and/or Hib at 12-15 months old. Antibody levels to each of the vaccine serotypes were measured by ELISA after each dose. (a) The C-PPV was well tolerated with a lower frequency of local injection-site problems than the DPT/HbOC vaccine. Local reactions did not increase with revaccination. Fever incidence and severity was similar in case and control groups and mat have been contributed by simultaneously administered DPT/HbOC (b) After 3 doses of C-PPV, 92-100% of children gad antibody titers above 0.15 mcg/ml; 50-90% had higher antibody levels against specific serotypes. (c) Brisk anamnestic response noted with booster immunization at 12-15 months indicate immunity is T-cell mediated. Indicates safety and immunogenicity of conjugated vaccine in infants.	Good. Choice of vaccine serotypes may make usefulness of the vaccine geographically limited.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
5.	Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine J Infect Dis 1999 180:1171-1176	Double-blind randomized placebo-controlled study 500 infants	Examining the safety, immunogenicity and impact on nasopharyngeal carriage of a nonavalent conjugated vaccine; vaccine was administered at ages 6, 10 and 14 weeks. (a) Vaccine was well tolerated; no serious systemic or local side effects were reported. (b) Significant antibody responses to all vaccine serotypes noted in all vaccinated infants, 4 weeks after the 3rd dose. (c) Vaccination appeared to simultaneously enhance antibody response to the diphtheria toxoid and the Hemophilus influenzae Polyribitol Phosphate antigens. (d) Nasopharyngeal carriage of vaccine serotypes decreased by half (36% to 18%) at age 9 months but carriage of non-vaccine serotypes increased (from 25 to 36%). (e) Carriage of penicillin-resistant and cotrimoxazole-resistant pneumococci was significantly reduced 9 months after vaccination compared to controls.	Good. .

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
6.	Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, Elvin L, Ensor KM, Hackell J, Siber G, Malinoski F, Madore D, Chang I, Kohberger R, Watson W, Austrian R, Edwards K Efficacy, safety and immunogenicity of a heptavelent pneumococcal conjugate vaccine in children, Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000 19:187-195	Double-blind 3-year trial	To assess the efficacy, safety and immunogenicity of the Wyeth-Lederle Heptavalent CRM197 conjugated pneumococcal vaccine (C-PPV) against a control group (receiving the meningococcus type C CRM197 conjugate). 37,868 children randomly assigned 1:1 to receive C-PPV or the meningococcal vaccine. C-PPV was administered at 2, 4 and 6 months and a booster dose was administered at between 12-15 months. Primary outcome: protection against invasive disease caused by vaccine serotype. Secondary outcome: protection against all pneumococcal invasive disease, impact on clinical otitis media, impact on severe and frequent otitis media including effect on ventilatory-tube placement. (a) 39 of 40 invasive disease caused by vaccine serotype occurred in the control group. Vaccine efficacy for prevention of invasive disease was therefore estimated at 97.4%. By adopting an intent-to-treat analysis, vaccine efficacy was estimated at 93.9%. (b) No simultaneous observation of an increase in invasive disease caused by non-vaccine serotypes. (c) A 73% reduction in severe pneumonia (radiographic diagnosis of a large area of lobar consolidation) was noted; vaccination reduced the overall incidence of pneumonia (any opacity on a radiograph) by a third. However, physician visits for pneumonia were reduced by only 11%, since 'pneumonia' was a clinically defined entity in this study. (d) Otitis media incidence as assessed by office visits decreased by ~9%. There was a 9.3% decrease in the incidence of 'frequent otitis media'. (e) Vaccination reduced need for tympanostomy tube placements in severe otitis media by 20%. If a serotype-specific analysis was adopted, vaccine efficacy in decreasing incidence of suppurative otitis media was 66.7% The study had to be halted by early 1999 when it became apparent to study investigators that the placebo group was demonstrating a significantly higher incidence of invasive disease; the investigators then vaccinated all children enrolled in the study.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
7.	Shinefield HR, Black S *Efficacy of pneumococcal conjugate vaccines in large scale field trials*. Pediatr Infect Dis J 2000 19:394-397	Review of data from trials on cojugate pneumococcal vaccines.	(a) Small trials noted to have shown conjugate vaccines to induce good immune responses in young children (< 5 years old) following primary and booster vaccination. (b) Also noted to be immunogenic in immunodeficient patients. (c) Evaluates the results of 2 large scale trials of the conjugate vaccine (California & Finland) – these trials demonstrate a 94% efficacy against invasive pneumococcal disease (d) Conjugate vaccines also appear effective against childhood pneumonia and otitis media.	Poor

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
Vaccine Safety				
1.	Nuorti PJ, Butler JC, Breiman RF Prevention of Pneumococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP) CDC MMWR 1997 46:RR-8:1-24	Review of available literature.	(a) Notes that the pneumococcal polysaccharide vaccine is generally a safe vaccine. Mild local injection-site side-effects lasting <48h seen in up to 50% vaccinees. (b) Moderate (fever and myalgias) and severe side effects (local – induration; systemic – anaphylaxis) reported but rarely seen. Severe local reactions preclude vaccine administration intradermal vaccine administration. (c) Presents results of a meta-analysis of nine RCTs where local reactions were seen in ~1/3rd of 7531 vaccinees and no severe febrile or anaphylactic reactions were observed. (d) Notes that one study observed a transiently increased viral replication following vaccination in HIV-infected patients; no associated deterioration in clinical status, findings not noted in other trials of vaccination in HIV-infected subjects and similar responses seen in HIV-infected patients receiving other inactivated vaccines (tetanus toxoid). (e) Vaccine observed safe to be administered with other vaccines.	Good.

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
2.	The Belgian Society for Infectiology and Clinical Microbiology, the Belgian Society for Pulmonology, the Scientific Society of General Physicians.	Review of available literature.	(a) Notes that the most commonly observed adverse effect following vaccination was local pain and erythema. Moderate-severe adverse events (fever, myalgia and severe local reactions as induration) was noted in < 1% of vaccinees. (b) Anaphylaxis may occur in less than 1 / 200,000	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
	Consensus on Pneumococcal Vaccine Acta Clin Belg 1996 51:350-356		vaccinees. (c) Early revaccination results in more pronounced local adverse reactions – hence early revaccination (within 3 years post-vaccination) is not recommended.	
Cost-Effectiveness Of Pneumococcal Vaccination Program				
1.	Gable CB, Botteman M, Savage G, Joy K The Cost Effectiveness of Pneumococcal Vaccination Strategies Pharmacoeconomics 1997 12:161-174	Review	epidemiology & economic factors determining cost-effectiveness of various pneumococcal vaccination strategies using the polysaccharide vaccine. Cost savings influenced by vaccine efficacy, disease burden in specific population groups and unit vaccine cost. Concludes that vaccination of the elderly (>65 years, vaccination of high-risk immunocompetent patients <65 years and vaccination in patients with HIV/AIDS represent the most cost-effective approaches. Per-patient vaccination costs may be reduced through mass targeted vaccination programs.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
2.	Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, Miller MA, Shinefield HR *Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children.* JAMA 2000 283:1460-1468	Review	Evaluation of projected health and economic impact of routine conjugate pneumococcal vaccination of healthy infants and young children in the United States, A vaccination program included a 3-dose primary vaccination schedule (2, 4, 6 months) + a booster (at 12-15 months) and a single-dose catch-up vaccination in children 2-5 years old. (a) Vaccination of healthy infants would be expected to prevent 12 000 cases of meninigitis and bacteremia, 53 000 cases of pneumonia and 1 million episodes of otitis media annually; 116 deaths annually could be averted a year. This would translate into cost savings of US $ 342 million in medical (direct) costs and US$415 million in work-loss and other indirect costs. (b) Net societal cost savings would be observed if the vaccine cost were less than US$ 46 per dose. (c) At a cost price of US$ 58 per dose, infant vaccination would cost US$ 80 000 per life year saved, US$ 3 200 per pneumonia case prevented, US$ 15 000 per bacteremia episode prevented, US$ 280 000 per meningitis case prevented and US$ 160 per otitis media episode averted. (d) Cost-effectiveness of a catch-up vaccination program in children 2-5 years old would depend on the disease burden in this population and the effect of herd immunity induced by the infant vaccination program. Concludes that the conjugate vaccine immunization of young infants and children has the potential to be cost-effective, especially if per-dose vaccine costs decrease.	Good

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
3.	Hueston WJ, Mainous AG, Brauer N Predicting cost-benefits before programs are started: looking at conjugate vaccine for invasive pneumococcal infection J Community Health 2000 25:23-33	Review	An analysis to predict the net financial impact of the emerging medical program of universal childhood vaccination with a conjugate pneumococcal vaccine and to determine key variables that will influence program costs and benefits. Analysis was made using existing available datas looking at vaccine impact on invasive pneumococcal disease; otitis media and pneumonia were omitted from analysis due to scarce data on epidemiology of these two diseases. Immunization with a conjugate pneumococcal vaccine would be expected to save 222 lives per million vaccinated children annually. Analysis of direct cost (projected immunization cost – savings from reduced illness) indicates that such a program would result in net direct costs of $0.08 to $2.42 per child. When indirect costs of illness are considered, the vaccine is cost saving. Cost-savings due to vaccination is influenced by disease incidence and cost of vaccine (preparation + administration).	Good;
4.	Plans Rubio P, Garrido Morales P, Sallares Samarti L The cost-effectiveness of pneumococcal vaccination in Catalonia. Rev Esp Salud Publica 1995 69:409-417	Assessment of cost-effectiveness of vaccination of healthy adults >65 years old with the pneumococcal polysaccharide vaccine using data from disease epidemiology and known vaccine efficacy.	The cost of a vaccination program in adults > 65 years old would entail annual cost of 2800 million pesetas (~US$ 25 million). Cost-effectiveness of vaccination of adults > 65 years was estimated at 3360 pesetas (US$ 30) per incremental life-year gained or 6463 pesetas (US$ 50) per QALY. A program of vaccination among healthy adults> 65 years was the most cost-effective when compared to vaccination in other age group cohorts. Some benefit was also noted	Fair;

No	*Author, Title, Journal, Year*	*Study Type, Sample Size, Follow-up*	*Characteristics & Outcome*	*Comments Grade of Evidence*
			for vaccination in adults aged 45-65 years. Concludes that a program of vaccination of healthy adults is the most cost-effective.	
	Patrick KM, Woolley FR A cost-benefit analysis of immunization for pneumococcal pneumonia JAMA 1981 245:473-477	Review	Assessment of impact of a pneumococcal vaccination program on a population subset under a health maintenance organization. Retrospective data on average costs associated with episodes of pneumonia were gathered along with data on disease burden in population and vaccine efficacy. Concluded that a selective immunization of healthy adults > 50 years old and adults < 50 years old and with chronic predisposing diseases resulted in net cost-benefits.	Fair.

Appendix

LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic reviews.
2	Good	Large sample of RCT
3	Good to fair	Small sample of RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN

THE FOLLOWING HTA REPORTS ARE AVAILABLE ON REQUEST:

REPORT	**YEAR**
1. LOW TEMPERATURE STERILISATION	1998
2. DRY CHEMISTRY	1998
3. DRY LASER IMAGE PROCESSING	1998
4. ROUTINE SKULL RADIOGRAPHS IN HEAD INJURY PATIENTS	2002
5. STROKE REHABILITATION	2002
6. MEDICAL MANAGEMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA	2002
7. CHILDHOOD IMMUNISATION	2002