A POST-MARKETING SURVEILLANCE STUDY OF A COMBINED DIPHTHERIA, TETANUS, WHOLE-CELL PERTUSSIS, AND HEPATITIS B VACCINE IN THE PHILIPPINES

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Abstract. As part of a vaccination program which included about 30,000 children, 1,036 children were actively followed up to assess the reactogenicity of a combined DTPw-HB vaccine (Tritanrix™-HB) under routine conditions. Vaccinations were given in accordance with the WHO schedule at 6, 10, and 14 weeks of age. Over 98% of the study population completed the course of 3 vaccinations. Local and systemic reactions to the vaccine were mostly mild and transient, and almost all had resolved by 3 days after vaccination. The most common systemic reactions were irritability, restlessness, and unusual crying. Only 3 infants had fever of ≥40ºC after any vaccination. No serious adverse events were reported during the study. Most health workers taking part in the study thought that combined vaccines were better than separate vaccinations. Overall, these results show that the combined DTPw-HB vaccine used in the study was well tolerated and accepted under conditions of normal use.

INTRODUCTION

Infectious diseases are the leading cause of death worldwide, and are also responsible for a huge burden of morbidity. Their impact varies widely among countries: in 1997, infectious and parasitic diseases were responsible for 43% of deaths in developing countries, but just 1% of deaths in developed countries (WHO, 1998). Vaccines are among the most effective weapons against infectious disease, and effective vaccination programs can lead to dramatic decreases in mortality (Hinman, 1998). One of the most spectacular successes of vaccination was the global eradication of smallpox in 1980, after a campaign that began in 1967. However, there is still much to be done in implementing effective vaccination programs. The WHO has estimated that at least two million deaths among children under five years old could be prevented each year using existing vaccines (WHO, 1998).

Consequently, the WHO, through its Expanded Programme on Immunization (EPI), is active in promoting wider vaccine coverage (WHO, 1997). The EPI was founded in 1974, and originally included vaccinations against polio, diphtheria, tetanus, pertussis, tuberculosis, and measles. More recently, hepatitis B has been added to the EPI vaccines, and the WHO now recommends universal childhood vaccination against hepatitis B (WHO, 1996). Hepatitis B is a widespread disease: more than two billion people worldwide have evidence of past or current hepatitis B infection, and more than 350 million are chronic carriers of the virus (WHO, 1998). Many chronic carriers of hepatitis B virus develop cirrhosis and hepatocellular carcinoma, leading to substantial mortality (Ikeda *et al*, 1998; Kew *et al*, 1997; Schwabe and Stremmel, 1998). There is evidence from Taiwan, where a nationwide program of hepatitis B vaccination began in 1984, that such vaccination can be effective in reducing both the number of carriers and the incidence of hepatocellular carcinoma (Chang *et al*, 1997; Lee and Ko, 1997). Similar beneficial effects have been found in Italy (Da Villa *et al*, 1998).

A drawback of vaccination programs that include coverage against a wide range of diseases is that such programs would involve large numbers of injections. A common strategy to reduce the number of injections needed is the use of combination vaccines, in which a single injection contains more than one vaccine (Choo and Finn, 1999; CDC, 1999). Combination vaccines in widespread use include diphtheria, tetanus, and pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine. There are many advantages to combining vaccines in this way: not only does it reduce discomfort for patients by sparing them multiple injections, but it also reduces costs. Reduced costs come from many factors, such as fewer clinic visits, fewer syringes and needles, and a reduced requirement for cold storage of vaccines (Weniger *et al*, 1998). Moreover, when vaccinations are given separately there is greater scope for missed doses (Ferson *et al*, 1997), so combination vaccines can also increase compliance, and hence the overall

effectiveness of vaccination programs.

The DTP combination vaccine is an ideal partner for combining with hepatitis B vaccines, because it is already established in most immunization programs and so is in widespread use (Díez-Domingo *et al*, 1998; CDC, 1996), with global coverage estimated to exceed 80% (WHO, 1999). Combining hepatitis B vaccination with DTP would therefore facilitate high coverage, and this strategy has been endorsed by the WHO (1996).

In the Philippines, the Maternal and Child Health Service (MCHS) of the Department of Health takes responsibility for implementing the WHO EPI. The MCHS undertook this post-marketing surveillance study to assess the tolerability and acceptability of a combined DTPw-HB vaccine (Tritanrix™-HB, SmithKline Beecham Biologicals) under conditions of routine use. Such studies are important to investigate vaccines or drugs under "real-life" conditions, in addition to the controlled situation of a clinical trial.

MATERIALS AND METHODS

Ethics

The study was approved by the Ethics Review Committee of the Maternal and Child Health Services (MCHS) of the Department of Health before any patients were enrolled, and was conducted in accordance with the Declaration of Helsinki (Hong Kong revision, 1989) and the Good Clinical Practice guidelines in force at the time. The parents or guardians of all subjects gave written informed consent to participate.

Study population, trial design, and vaccines

The study population consisted of about 1,000 children who were actively followed up within a program of vaccination aimed at 30,000 children. Children were vaccinated as part of the program if they were aged 6 weeks to 11 months and had no previous DTP or hepatitis B vaccination, clinical AIDS, hypersensitivity to vaccines previously taken, or illness needing hospitalization. Forty midwives were trained for the study (20 in Tacloban and 20 in Davao), and the children whom they vaccinated were included in the active follow-up.

The study had an open, observational design, intended to represent conditions of normal use of the vaccine. All children in the study received the same treatment, with a combined DTPw-hepatitis B vaccine (Tritanrix™-HB, SmithKline Beecham Biologicals). Vaccinations were given as intramuscular injections into the left thigh. The study aimed to use the WHO-recommended schedule of 6, 10, and 14 weeks of age, although children up to the age of 11 months at the first dose were eligible to participate. Whatever the age at the first vaccination, doses were separated by intervals of approximately 4 weeks.

Data collection

Study midwives and parents of the infants were asked to answer structured questionnaires about common local reactions and general symptoms 30 minutes after dose administration, and in the evening and at 1, 2, and 3 days following each of the three doses. Serious medical incidents were reported to the study coordinators or admitted to the nearest government hospitals. Local reactions were rated as follows: redness and swelling (absent, 1-5 mm, 5-10 mm and > 10 mm in diameter), and pain [absent (none), light reaction to touch (mild/minor), cries or protests to touch (moderate), and cries when the limb is moved (severe)]. General symptoms were scored as follows: fever (temperature was categorized as < 37.0, 37.0-37.4, 37.5-37.9, 38.0-39.9, and > 40ºC), irritability [(child behaves as usual (none), child is periodically more irritable than usual but has normal activity (mild), prolonged crying and refuses to play (moderate), and persistent crying and can't be comforted (severe)]. Intensity of diarrhea, loss of appetite (eating/drinking less than usual), and unusual crying (high pitch cries) were scored as follows: absent (none), easily tolerated (mild), causes sufficient discomfort to interfere with daily activities (moderate), and prevents normal everyday activities and necessitates medical advice (severe). In addition, midwives and parents were asked to answer questionnaires concerning acceptability of the vaccine. Midwives were asked to compare the combined vaccines with separate DTPw and HB vaccines on 7 items, namely: ease of flexibility of vaccination schedule, ease of preparing the vaccine before injection, ease of vaccine injection, lessens use of material resources, less time used for vaccination, reaction of patient after vaccination, patient compliance to vaccination, and effectiveness of the vaccine. For each item, the midwives were asked to specify whether they thought separate vaccines were better, combined vaccines were better, or they were both the same. Parents were asked whether they thought it was necessary for their children to be vaccinated, and to specify reasons if not.

Statistical methods

Every single immunization for which reaction data were available was included in the analysis. If no result was recorded on the form for a given reaction and observation time, the reaction was considered to be absent at that time. Data are presented descriptively; no statistical hypotheses were tested.

Summary statistics were generated with SPSS for Windows, Version 7.5.

RESULTS

Patients studied

A total of 1,036 infants entered the active follow-up part of the study, 483 females (46.6%) and 535 males (51.6%) (sex was not recorded for 18 (1.7%) infants). Mean (range) age, length, and weight were 8.4 weeks (6-51) weeks, 56.8 (19-95) cm, and 4.7 (2.7-5.3) kg. All infants included in the active follow-up received the first dose, of whom 1,024 (98.8%) and 1,019 (98.4%) received the second and third doses respectively. Thus a total of 17 infants (1.6%) failed to complete the course of vaccinations.

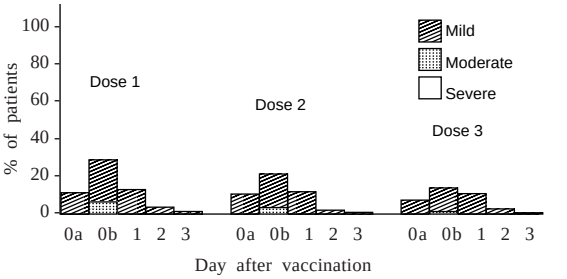
Local reactions

After the first vaccination, 487 (46.7%) infants experienced at least one local reaction (pain, redness, or swelling), of which the majority were mild. The frequency and severity of symptoms declined substantially during the 3 days following each vaccination, and were also lower after subsequent vaccinations (Fig 1-3).

Systemic reactions

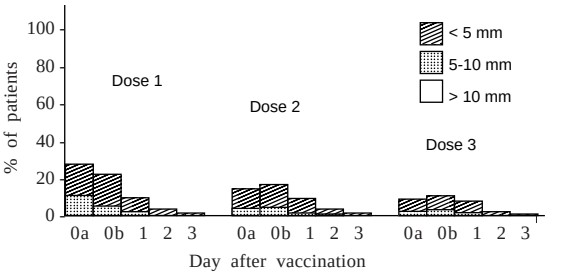
The solicited systemic reactions showed a similar pattern to the local reactions, in that they were mostly mild and transient, and were generally present in fewer than 1% of subjects by day 3 (Table 1). Most general symptoms had the highest frequency on the evening of the day of vaccination. There was a tendency for fewer symptoms to be reported after each successive dose. The most common symptoms were irritability and unusual crying, which had incidences of respectively 21.1% and 20.3% on the evening of the first dose, and of 17.8% and 18% after the second dose.

Fig 4 shows the incidence of fever after each dose. Most infants had slightly raised temperature on the evening of each vaccine dose, but the fever



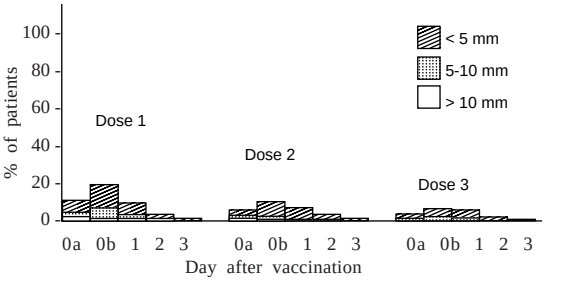
0a = within 30 minutes after vaccination, Ob = evening of day of vaccination

Fig 1–Incidence and severity of pain at the injection site.



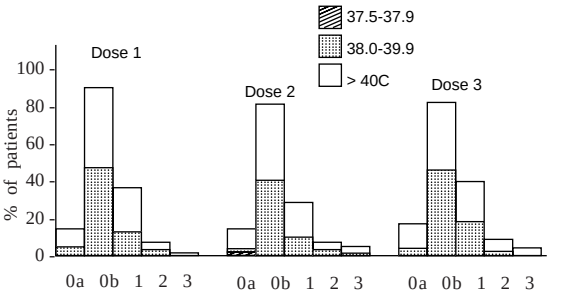
0a = within 30 minutes after vaccination, Ob = evening of day of vaccination

Fig 2–Incidence and extent of redness at the injection site.



0a = within 30 minutes after vaccination, Ob = evening of day of vaccination

Fig 3–Incidence and extent of swelling at the injection site.



0a = within 30 minutes after vaccination, Ob = evening of day of vaccination

Fig 4–Incidence of fever.

Table 1
Percentage incidence of solicited systemic symptoms.

Day	Day 0 30 minutes			Day 0 evening			Day 1			Day 2			Day 3		
Dose	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Irritability															
None	95.3	96.4	96.4	79.0	82.2	87.5	89.2	90.2	91.7	97.6	97.7	97.7	99.5	99.2	99.1
Mild	3.8	3.1	2.9	17.1	15.5	10.7	9.3	8.7	7.3	1.8	2.1	2.0	0.5	0.6	0.8
Moderate	1.0	0.3	0.7	3.8	2.1	1.8	1.4	1.1	1.0	0.6	0.3	0.3	0.0	0.1	0.1
Severe	0.0	0.2	0.0	0.2	0.2	0.0	0.2	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0
Diarrhea															
None	99.8	99.4	99.0	98.6	98.5	97.8	98.6	98.5	98.1	98.9	99.6	98.7	99.5	99.8	99.5
Mild	0.2	0.5	0.4	1.0	1.3	1.2	1.0	1.3	0.9	0.8	0.1	0.9	0.3	0.0	0.4
Moderate	0.0	0.1	0.5	0.4	0.2	1.0	0.2	0.2	1.0	0.2	0.3	0.4	0.1	0.2	0.1
Severe	0.0	0.0	0.1	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0
Loss of appetite															
None	99.5	98.9	99.3	94.8	94.3	97.4	97.0	96.7	97.6	99.1	98.7	99.1	99.6	99.7	99.5
Mild	0.5	0.9	0.2	4.2	5.5	1.7	2.7	0.9	1.9	0.8	1.1	0.8	0.3	0.2	0.4
Moderate	0.0	0.2	0.5	0.9	0.2	0.9	0.3	0.4	0.5	0.1	0.2	0.1	0.1	0.1	0.1
Severe	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Restlessness															
None	97.8	96.2	96.8	84.7	85.5	90.1	92.2	91.8	93.6	97.7	98.3	97.5	99.3	99.5	99.6
Mild	1.5	3.6	2.8	11.6	13.1	8.7	6.6	7.9	5.6	1.7	1.5	2.4	0.5	0.4	0.4
Moderate	0.7	0.2	0.4	3.7	1.4	1.2	0.9	0.3	0.8	0.3	0.2	0.1	0.2	0.1	0.0
Severe	0.0	0.0	0.0	0.1	0.0	0.0	0.4	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0
Unusual crying															
None	95.8	94.3	94.5	79.7	81.9	88.3	90.3	90.2	92.8	97.3	97.9	98.2	99.2	96.4	99.4
Mild	3.6	4.9	4.6	15.1	14.9	9.9	7.6	8.8	6.3	2.5	1.9	1.5	0.8	2.9	0.4
Moderate	0.6	0.7	0.9	4.5	3.0	1.8	1.7	1.0	0.7	0.1	0.3	0.3	0.0	0.7	0.2
Severe	0.1	0.1	0.0	0.7	0.1	0.0	0.3	0.0	0.2	0.1	0.0	0.0	0.0	0.0	0.0

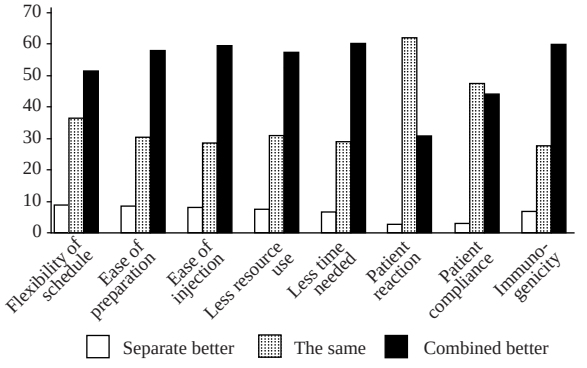


Fig 5–Preferences of health workers.

was generally mild and transient: only 3 infants had temperature ≥40ºC at any time, and most infants' temperatures had returned to normal by day 3.

No serious adverse events were reported during the study.

Acceptability to health workers and parents

Health workers taking part in the study were asked to rate their preferences for combined or separate vaccinations on the following items: ease of flexibility of vaccination schedule, ease of preparing the vaccine before injection, ease of vaccine injection, lessens use of material resources, less time used for vaccination, reaction of patient after vaccination, patient compliance to vaccination, and effectiveness of the vaccine. For each item, respondents were asked to specify whether they thought separate vaccines were better, combined vaccines were better, or they were both the same. On most items, the majority of respondents thought that combined vaccines were better (Fig 5). For all items, fewer than 10% of respondents thought that separate vaccines were better.

The parents/guardians of the infants in the study were asked whether they thought it was necessary for children to be vaccinated. The overwhelming majority (96.5%) replied that they thought it was, thus showing that acceptability of vaccinations among parents was high.

DISCUSSION

The strength of this post-marketing surveillance study is that it was done under conditions that were as close as possible to normal use of the vaccine, without the exclusion of subjects or burden of extra procedures that would typically be found in a controlled clinical trial. For that reason, and owing to the large number of subjects included, the study provides excellent data on the tolerability of the vaccine, which should be a realistic guide to what can be expected from the vaccine in routine use.

The main finding from the study was that the combined DTPw-HB vaccine was well tolerated and accepted by infants and parents. Reactions to the vaccine, both local and systemic, were of the kind that are normally expected after vaccination with DTPw, and were mostly mild and transient. In particular, the incidence of severe systemic reactions to the vaccine was very low (< 1% for all solicited symptoms). In addition, in children who experienced adverse reactions to the combined vaccine, the study provides reassurance that such reactions are likely to subside within 3 days of the vaccination. A further illustration of the good tolerability of the vaccine is that no serious adverse events were reported after more than 3,000 doses.

This study also found that combination vaccines were well accepted by health workers, fewer than 10% of whom expressed a preference for separate vaccines on any of the criteria by which they were asked to judge the vaccines. Moreover, almost all parents of children in the study said they thought that immunization of their children was necessary.

Although this study, owing to its naturalistic design, did not have a control group, the incidence of adverse reactions to the DTPw-HB vaccine used in this study compares favorably with historical control data for DTPw vaccination alone (Cody *et al*, 1981; Gustafsson *et al*, 1996). This suggests that the addition of hepatitis B vaccine to the DTPw vaccine does not lead to important increases in reactogenicity. Other studies, in a variety of ethnic groups and populations, have also investigated the reactogenicity of the DTPw-HB combination, and have also found no increased reactogenicity either in comparison with DTPw and HB vaccinations given separately, or with the historical control data for DTPw vaccination alone (Díez-Delgado *et al*, 1997; Poovorawan *et al*, 1997; Chiu *et al*, 1998; Papaevangelou *et al*, 1995; Usonis *et al*, 1996; Prikazsky and Vandepapeliére, 1999).

The immunogenicity of the combination of DTPw-HB used in this study has also been extensively investigated. Studies using a variety of schedules have found it to be highly immunogenic, with hepatitis B seroprotection rates after 3 doses at or close to 100% (Díez-Delgado *et al*, 1997; Chiu *et al*, 1998; Papaevangelou *et al*, 1995; Usonis *et al*, 1996; Poovorawan *et al*, 1997; Prikazsky and Vandepapeliére, 1999).

In conclusion, this study has shown that Tritanrix-HB was well tolerated and accepted under conditions of normal use in a post-marketing surveillance study including more than 1,000 infants. The infants vaccinated in this study began their vaccinations at ages between 6 weeks and 11 months, and should be a true reflection of those vaccinated in everyday practice. Together with data from other studies showing the excellent immunogenicity of this combination vaccine, these results give added confidence that Tritanrix-HB can be used as part of routine immunization programs, and will help to achieve the WHO's aim of universal infant vaccination against hepatitis B.

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REFERENCES

Centers for Disease Control and Prevention (CDC). Status report on the childhood immunization initiative: national, state, and urban area vaccination coverage levels among children aged 19-35 months – United States. 1996. *MMWR* 1997; 46:657-64.

Centers for Disease Control and Prevention (CDC). Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). *MMWR* 1999; (RR-5): 1-16.

Chang MH, Chen CJ, Lai MS, *et al*. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997; 336: 1855-9.

Chiu HH, Huang LM, Lee PI, Safary A, Lee CY. Diphtheria, tetanus and whole cell pertussis vaccine combined with hepatitis B vaccines: a comparison of two doses (10 μg and 5 μg). *Pediatr Infect Dis J* 1998; 17: 206-11.

Choo S, Finn A. Pediatric combination vaccines. *Curr Opin Pediatr* 1999; 11: 14-20.

Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics* 1981; 68: 650-60.

Da Villa G, Piccinino F, Scolastico C, Fusco M, Piccinino R, Sepe A. Long-term epidemiological survey of hepatitis B virus infection in a hyperendemic area (Afragola, southern Italy): results of a pilot vaccination project. *Res Virol* 1998; 149: 263-70.

Díez-Domingo J, Pereiro Berenguer I, Ferrer Salvà A, *et al*. The coverage of vaccines systematically administered and of a vaccine against *Haemophilus influenzae* type b prior to its inclusion in the vaccinal calendar in the Valencian Community. *An Esp Pediatr* 1998; 49: 568-70.

Díez-Delgado J, Dal-Ré R, Llorente M, González A, López J. Hepatitis B component does not interfere with the immune response to diphtheria, tetanus and whole-cell *Bordetella pertussis* component of a quadrivalent (DTPw-HB) vaccine: a controlled trial in healthy infants. *Vaccine* 1997; 15: 1418-22.

Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med* 1996; 334: 349-55.

Ferson MJ, McKenzie KA, Macartney-Bourne F. Fragmentation of scheduled visits and missed doses among infants receiving multiple injected vaccines. *Aust N Z J Public Health* 1997; 21: 735-8.

Hinman AR. Global progress in infectious disease control. *Vaccine* 1998; 16: 1116-21.

Ikeda K, Saitoh S, Suzuki Y, *et al*. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol* 1998; 28: 930-8.

Kew MC, Yu MC, Kedda MA, Coppin A, Sarkin A, Hodkinson J. The relative roles of hepatitis B and C viruses in the etiology of hepatocellular carcinoma in southern African blacks. *Gastroenterology* 1997; 112: 184-7.

Lee CL, Ko YC. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics* 1997; 99: 351-3.

Papaevangelou G, Karvelis E, Alexiou D, *et al*. Evaluation of a combined tetravalent diphtheria, tetanus, whole-cell pertussis and hepatitis B candidate vaccine administered to healthy infants according to a three-dose vaccination schedule. *Vaccine* 1995; 13: 175-8.

Poovorawan Y, Theamboonlers A, Sanpavat S, Chumdermpadetsuk S, Safary A, Vandepapeliére P. 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; 17: 301-8.

Prikazsky V, Vandepapeliére P. Clinical comparison of a combined diphtheria-tetanus-whole-cell pertussis-hepatitis B vaccine with separate administration of DTPw and hepatitis B vaccines in infants. *J Paediatr Child Health* 1999; 33 (suppl 1): S122

Schwabe RF, Stremmel W. The natural course of hepatitis B and hepatitis C virus infection. *Schweiz Rundsch Med Prax* 1998; 87: 1403-7.

Usonis V, Bakasenas V, Taylor D, Vandepapelière P. Immunogenicity and reactogenicity of a combined DTPw-hepatitis B vaccine in Lithuanian infants. *Eur J Pediatr* 1996; 155: 189-93.

Weniger BG, Chen RT, Jacobson SH, *et al*. Addressing the challenges to immunization practice with an economic algorithm for vaccine selection. *Vaccine* 1998; 16: 1885-97.

World Health Organization (WHO). The children's vaccine initiative and the global programme for vaccines and immunization: recommendations from the special advisory group of experts, Part I. WER 1996; 71: 261-6.

World Health Organization (WHO). Imaginative ways of raising immunization coverage. *EPI Update* 1997; 32: 1-5.

World Health Organization (WHO). The World Health Report 1998: Life in the 21st Century – A vision for all. World Health Organization, Geneva, 1998.

World Health Organization (WHO). Vaccines and Biologicals Annual Report, 1998. World Health Organization, Geneva, 1999.