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 protest 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
Table 1
Percentage incidence of solicited systemic symptoms.

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 0 afternoon</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Irritability</td>
<td>None</td>
<td>95.3</td>
<td>96.4</td>
<td>96.4</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>3.8</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.0</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.0</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>None</td>
<td>99.8</td>
<td>99.4</td>
<td>99.0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.2</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.0</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>None</td>
<td>99.5</td>
<td>98.9</td>
<td>99.3</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.5</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.0</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
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<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Restlessness</td>
<td>None</td>
<td>97.8</td>
<td>96.2</td>
<td>96.8</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.5</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.7</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Unusual crying</td>
<td>None</td>
<td>95.8</td>
<td>94.3</td>
<td>94.5</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>3.6</td>
<td>4.9</td>
<td>4.6</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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.

Fig 5—Preferences of health workers.

was generally mild and transient: only 3 infants had temperature ≥40°C at any time, and most infants’ temperatures had returned to normal by day 3.
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; Papeavangelou 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; Papeavangelou 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.

ACKNOWLEDGEMENTS

The authors would like to thank all CHO’s, MHOs, DHOs, PHNs and midwives who made the study possible, and all the parents who agree to participate. Thanks are also due to: Dr Juanita Basilio, Dr Joselito Vital, Dr Luzviminda Garcia at the Maternal and Child Health Service; Dr Avelino C Grospe, Dr Salvador O Estrera, Dr Eden A Wales, Ms Evelyn Hausac, Dr Migel Oppus, Dr Azuencna Dayanghirang, Ms Armi Capili at the Regional Health Department (Region XI, Davao City); Dr Alfredo Perez, Dr Lilia Arteche, Dr Fidelita Dico, Ms Emile Buot, Dr Rogelio Daya, Dr Alicia Nebrija, Dr Edgardo Daya, Dr Felicidad Sales, Dr Reynerio Tan, Dr Josefina Balderian, Dr Nemia Sangrano at the Regional Health Department (Region VIII, Tacloban City).
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