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# Pediatric disease burden and vaccination recommendations: Understanding local differences

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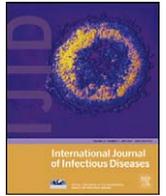
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## Review

## Pediatric disease burden and vaccination recommendations: understanding local differences<sup>☆</sup>

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## ABSTRACT

**Background:** Diphtheria (D), tetanus (T), pertussis (P), hepatitis B (HepB), invasive *Haemophilus influenzae* type b (Hib) disease, and measles cause substantial global morbidity and mortality.

**Methods:** This unique review highlights geographic differences in disease burden across certain countries in the African, Americas, Mediterranean, South-East Asian, and Western Pacific World Health Organization (WHO) regions, and relates this to vaccination coverage and local vaccine recommendations using the authors' countries as illustrations.

**Results:** Substantial differences were observed in the incidence of these diseases and in vaccination coverage between the countries studied. Disease incidence often reflected inadequate surveillance, but also variable or poor vaccination coverage. Vaccination coverage against HepB was particularly low in the African and South-East Asian WHO regions; vaccination coverage against invasive Hib disease was low in these regions and in the Eastern Mediterranean and Western Pacific WHO regions. Vaccination schedules within some countries in these regions do not include, or have only recently included, vaccinations against HepB and Hib disease. The use of DTWP–HepB–Hib (diphtheria, tetanus, whole-cell pertussis, HepB, Hib) combination vaccines has now been adopted by some countries to help increase vaccination coverage.

**Conclusions:** Vaccination coverage and vaccination schedules vary markedly between the countries studied, often according to the resources available. DTWP–HepB–Hib combination vaccines represent a cost-effective option, with the potential to substantially reduce the burden associated with these diseases by increasing coverage and compliance.

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### 1. Introduction

Diphtheria, tetanus, pertussis, hepatitis B (HepB), invasive *Haemophilus influenzae* type b (Hib) disease, and measles are all serious childhood diseases that are associated with significant levels of morbidity and mortality. The reported incidence of these diseases varies across countries and regions, as does the proportion of cases reported to result in death (Table 1).<sup>1–14</sup> It is believed that there is a large amount of under-reporting of these diseases, partly

<sup>☆</sup> The information given here was presented at the Quinvaxem Advisory Board meeting at the 13<sup>th</sup> International Congress on Infectious Diseases, Kuala Lumpur, Malaysia, June 19, 2008.

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**Table 1**

Global reported incidence, estimated actual global incidence and prevalence, and mortality of diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b (Hib) disease, and measles<sup>1–14</sup>

Disease	Global reported incidence (cases/year)	Estimated actual global incidence/prevalence	Mortality	Data sources
Diphtheria	7088	Unknown	5–10% (20% in those <5 years of age)	CDC 2008 <sup>1</sup>
Tetanus	16 628	Incidence: 1 million	~11%	WHO 2010 <sup>2</sup> Bleck 2005 <sup>3</sup> CDC 2008 <sup>4</sup>
Pertussis	152 535	Incidence: 17.6 million	~1.6%	WHO 2010 <sup>5</sup> WHO 2005 <sup>6</sup> WHO 2008 <sup>7</sup>
Hepatitis B	914 000	Prevalence: 350–360 million	600 000/year <sup>a</sup>	WHO 2004 <sup>8</sup> WHO 2008 <sup>9</sup> WHO 2008 <sup>10</sup>
Hib disease	3 million	Unknown	386 000/year	WHO 2005 <sup>11</sup> WHO 2006 <sup>12</sup>
Measles	281 972	Unknown	1–5% (developed countries); up to 25% in certain countries	WHO 2009 <sup>13</sup> WHO 2008 <sup>14</sup>

Data relate to 2007 or latest available data, unless otherwise stated. CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

<sup>a</sup> Includes chronic consequences of hepatitis B.

due to the poor access to healthcare for many individuals in developing countries. There is also a lack of surveillance, or weak surveillance programs. For example, although the documented global annual incidence of tetanus was 16 628 cases in 2008,<sup>5</sup> the actual incidence is believed to be closer to 1 million cases per year.<sup>3</sup> This is also the case with pertussis, for which the reported annual incidence is 151 586,<sup>7</sup> whereas it has been estimated that approximately 17.6 million cases occur each year.<sup>6</sup> Difficulty in detection may also affect disease reporting. Although millions of people are known to develop invasive Hib disease every year (2 200 000 estimated cases with 325 000–500 000 deaths per year worldwide),<sup>15</sup> it is difficult to diagnose as it causes a range of illnesses, sometimes with non-specific symptoms, and confirmation by laboratory testing may be expensive and can be challenging, requiring special agar and sera, and staff trained in and equipped for diagnosis. It is likely, therefore, that the estimated incidence of invasive Hib disease and the numbers of cases and mortalities are underestimates, and many of those infected die without the disease being diagnosed or reported.

Together, these vaccine-preventable diseases cause a substantial disease burden affecting populations worldwide, particularly in developing countries. Once any of these diseases is contracted, treatment options can be extremely limited, particularly for measles, pertussis, and HepB, with most treatments focused on providing symptomatic relief. Therefore, the most effective strategy to combat these diseases is disease prevention, particularly through vaccination. Vaccination has been shown to be one of the most effective public health interventions worldwide,<sup>16</sup> through which a number of serious childhood diseases have been successfully eradicated. For example, as a result of vaccination, polio has now been eradicated from the Americas (in 1994), the Western Pacific (in 2000), and the European World Health Organization (WHO) regions (in 2002).<sup>17</sup>

The WHO recommends vaccination against a number of serious infectious diseases, including diphtheria,<sup>18</sup> tetanus,<sup>19</sup> pertussis,<sup>6</sup> HepB,<sup>8</sup> invasive Hib disease,<sup>12</sup> and measles<sup>20</sup> for all children, and against pneumococcal disease, yellow fever, and rotavirus disease for children in some areas as part of their Expanded Program on Immunization (EPI). However, many infants and children still die every year from diseases that could be prevented by implementing the WHO vaccination recommendations.<sup>21</sup> It has been shown that approximately 27 million infants are not vaccinated against common childhood diseases, such as measles or tetanus. As a result, 2–3 million children will die annually from easily preventable diseases, and many more will fall ill.<sup>22</sup>

Developing countries can find the implementation of vaccination programs challenging and may not have the financial resources available to incorporate new vaccines into their schedules. The availability of cost-effective combination vaccines could make the implementation of complex schedules more achievable, through a number of economic and logistical benefits, including time gains in administration and throughout the supply chain,<sup>23</sup> as well as through enhancing timeliness and compliance in schedule completion.<sup>24</sup> Vaccination has the additional benefit of decreasing the inequity brought about by inaccessibility of medical care to the poor. For the local communities, providing vaccination brings benefits in terms of reduced morbidity, greater productivity, and improved economic savings and gains.<sup>25</sup>

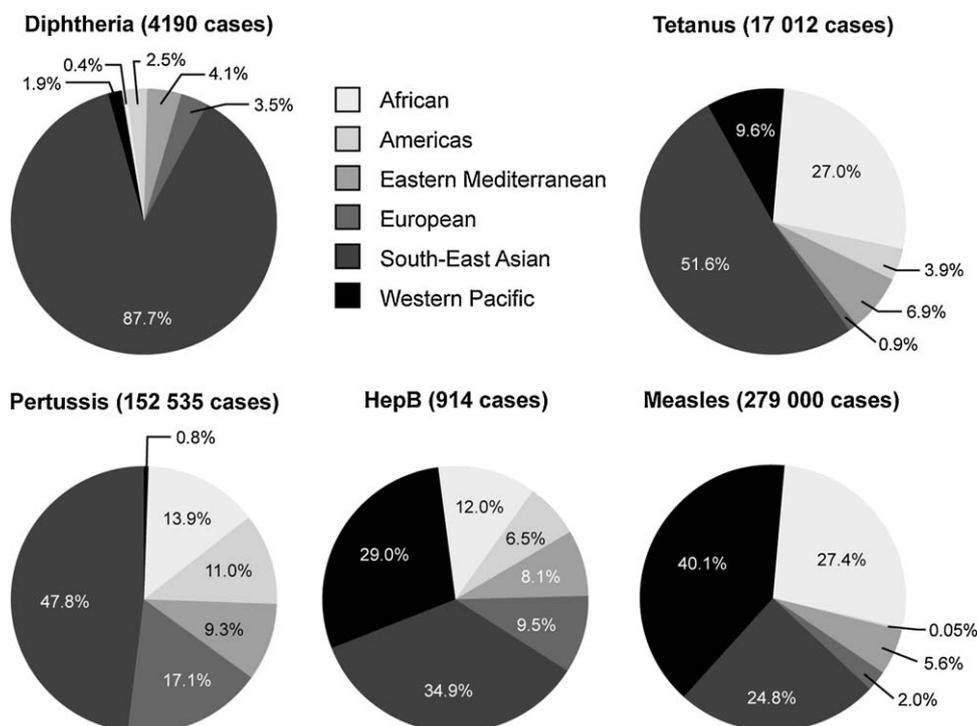
The aim of this review is to provide an insight into disease burden, vaccination recommendations, and vaccination coverage across a range of geographical regions. The review is based on discussions from an experts' meeting of pediatricians from several different countries and regions. The broad geographical and socioeconomic spread of the countries that are represented allows a balanced analysis of the current situation; this may be particular to the country of origin of the meeting attendees rather than to the WHO region.

It is our hope that this unique review will help to facilitate implementation of vaccination support that is tailored to local needs, and will play a part in increasing vaccination coverage by promoting greater awareness of current challenges. Such improvements in vaccination coverage are essential to control disease outbreaks, and reduce the morbidity and mortality associated with vaccine-preventable childhood diseases.

## 2. Regional variation in disease burden

While global statistics provide a useful overview of disease burden, examination of regional variations across the countries studied reveals clear differences in geographical distributions for diphtheria, tetanus, pertussis, HepB, and measles (Figure 1).<sup>8,26–33</sup> The vast majority of diphtheria cases occur in the South-East Asian WHO region; this region also has the greatest proportion of tetanus, pertussis, and HepB cases. The greatest proportion of measles cases are found in the Western Pacific WHO region.

The distribution of cases appears much clearer when countries are classified as developed or developing, with the vast majority of cases of diphtheria (99.0%), tetanus (99.2%), pertussis (71.5%), and measles (98.8%) occurring in developing countries.<sup>34</sup> Indeed, more than 95% of measles cases occur in countries that have both a per



**Figure 1.** Distribution of cases of diphtheria, tetanus, pertussis, and measles (2007 data), and for hepatitis B (HepB) (2002 data) by World Health Organization region.<sup>8,26–33</sup>

capita gross national income of less than US\$1000 and an inefficient healthcare system.<sup>13</sup> The situation is similar for HepB; approximately three-quarters of the HepB cases in 2002 occurred in the African, South-East Asian, and Western Pacific WHO regions.<sup>8</sup>

There is also a notable geographical split with regard to the burden of disease. Invasive Hib disease remains one of the most significant challenges in developing countries, where Hib pneumonia is more common than Hib meningitis.<sup>11</sup> The challenge of making a definitive diagnosis, particularly in developing countries, results in a significant underestimation of the impact of Hib disease. In particular, it can be difficult to make a diagnosis of Hib pneumonia in children, as low levels of bacteremia lead to the majority of blood samples appearing negative. In Latin American countries, before Hib vaccination was more widely introduced, the most common diagnosis was of meningitis. More recently, the WHO evaluated the evidence from probe trials and other high-quality estimates, and recommended that the burden of invasive Hib disease is sufficient to warrant introduction of Hib vaccine for all children, and that a lack of local data should not be a reason to delay the introduction of the vaccine.<sup>12</sup> This approach also applies to other vaccines, such as those for the prevention of invasive pneumococcal disease.<sup>35</sup>

These data illustrate how regional and socioeconomic factors affect the incidence and mortality rates of these common vaccine-preventable childhood diseases. Both the quality of reporting, in terms of the completeness of information and laboratory confirmation, and its quantity, as many regions have inadequate surveillance, are currently limited. In order to more fully understand the degree of regional variation, we sought to bring together representatives from key countries to derive a best estimate of disease burden by country.

### 3. Disease burden by country and region

The incidence of diphtheria, tetanus, pertussis, HepB, Hib disease, and measles for the authors' and contributors' countries is

shown in Table 2.<sup>33,36–44</sup> This direct comparison reveals large variations in reported disease incidence, not only between different WHO regions (e.g., for HepB in the Americas region compared with the South-East Asian region), but also between the countries within each WHO region (e.g., for measles between Egypt and Iran).

Of particular note, invasive Hib disease appears to be uncommon in Egypt, and the vaccine is still not included in the national immunization programme.<sup>45</sup> Pakistan has one of the highest reported incidences of this disease in the region, with an annual incidence of approximately 1 in every 100 children. Similarly, there is a relatively low incidence of HepB in Thailand, while Bangladesh, in the same region, has one of the highest HepB incidences of the countries studied here (Table 2).<sup>33,38,39,41–43</sup>

Conversely, among the highest burdens of HepB can be found in South-East Asia and the Philippines, where the incidence is as high as 10–12% of the population.<sup>46</sup> The reduced incidence seen in Thailand was brought about by the introduction of a first dose of HepB vaccine at birth. This birth dose was also introduced in the Philippines in 2007; however, only administration of the second and third doses (at 6 and 14 weeks) will ensure adequate protection from disease in the longer term.

While some countries have succeeded in reducing the incidence and subsequent burden of individual diseases, no country in this study has successfully achieved good control of all the targeted diseases – diphtheria, tetanus, pertussis, HepB, Hib disease, and measles. In Argentina, for example, which is free from reported diphtheria, childhood HepB, and measles, pertussis remains a significant burden, with a mortality rate of 3.5% in pertussis patients <12 months of age (A. Gentile, personal communication, 2008). The high incidence of Hib disease in Pakistan results in an estimated 25 000 disease-associated deaths per year,<sup>47</sup> neonatal tetanus has a mortality rate of up to 11.6 per 1000 live births,<sup>48</sup> and approximately 2% of the population is reported to be positive for HepB.<sup>38</sup>

Many factors, including population density and hygiene standards, have a significant influence on disease incidence.

**Table 2**Incidence per 100 000 individuals of diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b disease, and measles in countries within different World Health Organization regions<sup>29</sup>

WHO region and country	Diphtheria	Tetanus	Pertussis	HepB <sup>a</sup>	Hib <sup>a</sup>	Measles	Data source(s)
African South Africa	~0 (5 cases in 2007; 1 case in 2008)	~0 (21 cases in 2007)	~0 (3 cases in 2007)	~1 (485 cases in 2007)	~0.04 (24 cases in 2007)	~0.2 (114 cases in 2007)	Republic of South Africa Department of National Health 2005 <sup>36</sup>
Americas Argentina	0	0–0.2 (neonatal tetanus: 0 cases; all tetanus: 6 cases)	3.8–6.5	0	0.05	0	WHO 2008 <sup>33</sup> Boletín Epidemiológico Anual 2006 <sup>37</sup>
Eastern Mediterranean Egypt	0	0.05	0	...	...	2.2	WHO 2008 <sup>33</sup>
Iran	0.045	0.015	0.37	...	...	0.19	WHO 2008 <sup>33</sup>
Pakistan	0.01	0.45	0.16	1.7–5.5% positive for HepB	893 (children 0–4 years of age)	1.7	WHO 2008 <sup>33</sup> Ali et al. 2009 <sup>38</sup> Nizami et al. 2006 <sup>39</sup>
Saudi Arabia	0.01	0.03–0.11	0.14–0.27	18.2	1.08	3.41–18.8	Ministry of Health, Saudi Arabia 2006 <sup>40</sup> WHO 2008 <sup>33</sup>
South-East Asian Bangladesh	0.05	0.14–0.65	0.05	~6700 (currently 9–13 million of population infected)	No clear consensus	1.84	WHO 2008 <sup>29</sup> Liver Foundation of Bangladesh 2006 <sup>41</sup>
Sri Lanka	0	0.23	0	...	...	0.23	WHO 2008 <sup>33</sup>
Thailand	<0.01	0.21	0.04	6.9	3.8 in children under 5 years of age for meningitis only	6.1–6.2	Rerks-Ngarm et al. 2004 <sup>42</sup> Bureau of Epidemiology, Thailand 2007 <sup>43</sup> WHO 2008 <sup>33</sup>
Western Pacific Philippines	0.04–0.05	0.02	0.02 (0.6 among children)	6.8 among children	94.6 (children under 5 years of age)	0.6	Limcangco et al. 2000 <sup>44</sup> [Ref. 44?] WHO 2008 <sup>33</sup>

Data relate to 2007 or latest available data, unless otherwise stated. HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; WHO, World Health Organization.<sup>a</sup> Ellipses indicate no data available.

Factors such as access to healthcare and presence of concomitant illnesses affect the morbidity and mortality rates associated with these diseases. In addition, vaccination coverage may have a significant impact. The findings presented here are also dependent on appropriateness of surveillance and reporting, which is known to be poor in some areas.

#### 4. Regional variations in vaccination coverage and recommendations

Vaccines for inclusion in national programs are recommended by the WHO Expanded Program on Immunization (EPI). However, these recommendations are not universally adopted, which may lead to discrepancies in vaccination coverage between and within countries.

##### 4.1. Vaccination coverage

In the WHO African and South-East Asian regions, low uptake of DTP3 vaccination (the third dose of diphtheria, tetanus, and pertussis combination vaccine, to complete the primary vaccination course) among infants (those <1 year of age) results in an estimated vaccination coverage of <75% (Figure 2),<sup>2,34</sup> which is well below the WHO target of 90%.<sup>49</sup> Vaccination coverage for the third dose of HepB and measles-containing vaccine (MCV1) are also low in Africa and South-East Asia (Figure 2).<sup>2,14,34</sup> In the Eastern Mediterranean, South-East Asian, and Western Pacific WHO regions, the estimated vaccination coverage for Hib in infants is very low (0–16%). Vaccination coverage for HepB among infants is also low in the African and South-East Asian WHO regions (Figure 2).<sup>2,34</sup> The low vaccination coverage against HepB and Hib disease in these regions, therefore, represents a significant healthcare gap, especially given the high burden of HepB in countries such as Bangladesh, and of invasive Hib disease in countries such as Iran and Pakistan.<sup>33,38,39,41</sup> (Table 2).

Although DTP coverage is generally good in the Philippines, protection of infants against neonatal tetanus through vaccination of pregnant mothers has been relatively low, with poor vaccine uptake following politically inspired claims that the tetanus toxoid component would induce miscarriage, despite adequate and reliable data to the contrary.<sup>50</sup> Coverage is now improving, and 2006 data suggest that 64% of infants were protected.<sup>51</sup>

Even where national vaccination coverage is above the WHO target, the local situation can vary considerably. For example, in

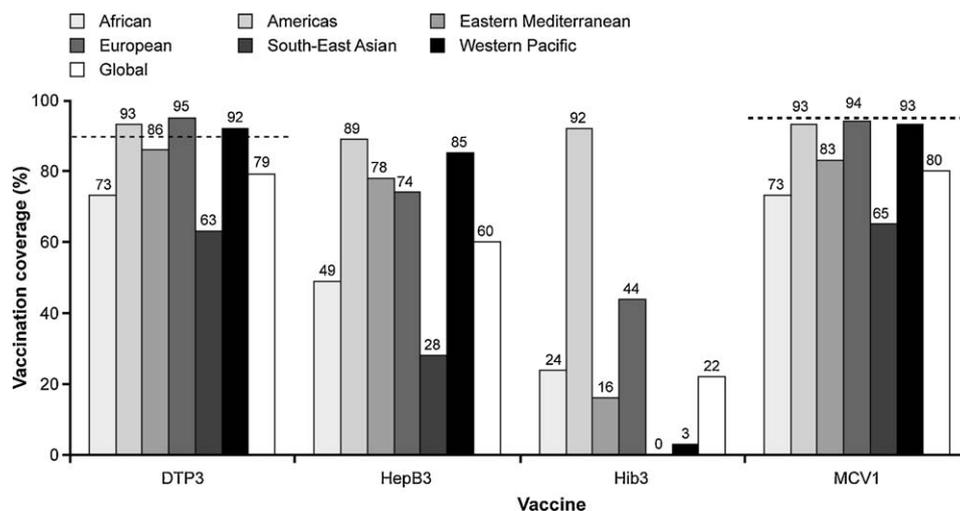
2008 in the Western Cape region of South Africa, coverage for a range of childhood vaccinations was reported as 53.2% by 18 months of age,<sup>52</sup> whereas far higher vaccination coverage was observed on a national level. Poor vaccination coverage, whether locally or across a WHO region, has been proven to lead to outbreaks of disease and epidemics; this was observed in Argentina, where an outbreak of pertussis resulted in an increase in reported cases from 976 in 2004, to 2060 in 2005, and 1607 in 2006.<sup>34</sup> Measles outbreaks have also been reported in specific communities where vaccine uptake was low in Germany, northern Italy/Austria, Switzerland (Tyrol), and the USA,<sup>53–56</sup> as well as in the UK following a period of parental concern over the safety of the measles, mumps, and rubella (MMR) vaccine.<sup>33,57</sup>

##### 4.2. Vaccination recommendations

Examination of the variation in vaccination recommendations between countries and regions provides an insight into the priorities of vaccination programs, and how the implementation of vaccination programs may be improved.

Recommended vaccination schedules for individual countries (Table 3)<sup>33</sup> highlight substantial variations between countries and regions in the timing and number of doses of the vaccines that are recommended.<sup>58</sup> For example, in some countries, only three doses of DTP are recommended, whereas others recommend that five or six doses be administered, including toddler, pre-school, and adolescent boosters. Also, for HepB vaccination, some countries recommend administering doses according to the EPI recommendation of 6–10–14 weeks, whereas others recommend that this vaccine be given at 2–4–6 months, with or without a dose at birth. In many cases, however, details of vaccination goals are not available and so meaningful comparisons are difficult. Moreover, details of how vaccination goals are implemented or achieved are either not publicly known or do not exist for some countries.

It is notable that for some countries, the incidence of certain diseases (Table 2) is higher than would be expected from the vaccination schedules shown in Table 3.<sup>33</sup> This may be partly due to low vaccination coverage (Table 4)<sup>33</sup> and to the vaccination recommendations within these countries. For example, in the Philippines, the birth dose of HepB vaccine was not included in the recommended vaccination schedule until 2007, which may partly account for the high childhood incidence of HepB. A measles elimination program was started by the Philippines Department of Health in 2004, vaccinating all children 9 months to 8 years of age,



**Figure 2.** Estimated vaccination coverage among infants <1 year of age, for the third dose of vaccines against diphtheria, tetanus, and pertussis (DTP3), hepatitis B (HepB3), and *Haemophilus influenzae* type b (Hib3), and for the first dose of measles-containing vaccine (MCV1), by World Health Organization (WHO) region.<sup>2,34</sup> Dotted lines indicate WHO targets, where applicable.

**Table 3**  
Recommended vaccination schedules for diphtheria, tetanus, and pertussis, hepatitis B, *Haemophilus influenzae* type b disease, and measles in countries within different World Health Organization regions<sup>29</sup>

WHO region and country	DTP	HepB	Hib <sup>a</sup>	Measles
African				
South Africa	6, 10, 14 weeks; 18 months	6, 10, 14 weeks	6, 10, 14 weeks; 18 months <sup>b</sup>	9, 18 months
Americas				
Argentina	2, 4, 6, 18 months; 6 years	Birth; 2, 6 months <sup>c</sup>	2, 4, 6, 18 months <sup>b</sup>	1, 6 years
Eastern Mediterranean				
Egypt	2, 4, 6, 18 months	2, 4, 6 months	...	12 months (as MMR)
Iran	2, 4, 6, 18 months; 4–6 years	Birth; 2, 6 months	...	12 months; 4–6 years
Pakistan	6, 10, 14 weeks	6, 10, 14 weeks <sup>p</sup>	6, 10, 14 weeks (2008 onwards) <sup>c</sup>	9 months
Saudi Arabia	2, 4, 6 months (as DTP–HepB–Hib); 18 months (as DTP–Hib); 4–6 years	Birth; and 2, 4, 6 months (as DTP–HepB–Hib)	2, 4, 6 months (as DTP–HepB–Hib); 18 months (as DTP–Hib)	9 months (2008 onwards); 1, 4–6 years
South-East Asian				
Bangladesh	6, 10, 14 weeks	6, 10, 14 weeks	...	38 weeks
Sri Lanka	2, 4, 6, 18 months; 5 years <sup>d</sup>	2, 4, 6 months	2, 4, 6 months (2008 onwards) <sup>c</sup>	9 months; 3 years
Thailand	2, 4, 6 months; 1.5–2, 4–6 years	Birth; 2, 6 months; or birth (HepB only); 2, 4, 6 months (as DTP–HepB)	...	9–12 months; 4–6 years
Western Pacific				
Philippines	6, 10, 14 weeks	Birth; 6, 14 weeks	...	9, 18 months

Data relate to 2007 or latest available data, unless otherwise stated. WHO, World Health Organization; DTP, diphtheria, tetanus, pertussis; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; MMR, measles, mumps, and rubella vaccine.

<sup>a</sup> Ellipses indicate no data available.

<sup>b</sup> Included as a multi-component vaccine with DTP.

<sup>c</sup> Included as part of DTP–HepB–Hib vaccination from 2008.

<sup>d</sup> Vaccination at 5 years of age only includes DT.

resulting in a significant reduction in measles-associated morbidity and mortality. The target of eliminating measles by 2010 is likely to be achieved in the Philippines. Although measles is included in the recommended vaccination schedules of most countries, vaccinations against mumps and rubella (individually or as part of the measles and rubella (MR) or MMR combination vaccine) are not recommended in Bangladesh, Pakistan, the Philippines, or South Africa, and in Sri Lanka, there is no recommendation for vaccination against mumps. In the Philippines, although rubella vaccination is included in the EPI, this has not yet been implemented.

For various reasons, including lack of local evidence, lack of awareness, or lack of resources, many countries still do not include Hib vaccination in their recommended vaccination schedules. This is despite the relatively high burden of disease in some of these countries, e.g., Iran. However, the inclusion of Hib vaccination from

2008 onwards as part of a DTP–HepB–Hib vaccine in Pakistan and Sri Lanka should help to reduce the high burden of this disease in these countries. The adoption of Hib vaccine is accelerating in the poorest countries, with the vast majority planning to introduce the vaccine with support from the Global Alliance for Vaccines and Immunisation (GAVI) in 2009 and 2010. Many lower-middle income countries still have not made the decision to adopt the vaccine, mainly due to cost concerns. Following the development of the Child Survival Strategy to meet Millennium Development Goal 4 of reducing infant and childhood mortality, plans have been announced to include vaccination against Hib disease in the Philippines, although the date of introduction is unknown. In addition to the promotion of good nutrition, and a clean and safe water supply, the introduction of new and underutilized vaccines, particularly against pneumonia (including Hib), is one of the major interventions for child survival.<sup>59</sup>

**Table 4**  
Official 2007 country estimates of vaccination coverage (%) by antigen for diphtheria, tetanus, and pertussis, hepatitis B, *Haemophilus influenzae* type b disease, and measles-containing vaccine for countries within different World Health Organization regions<sup>29</sup>

WHO region and country	DTP1 <sup>a</sup>	DTP3 <sup>b</sup>	HepB1 <sup>c,d</sup>	HepB3 <sup>e</sup>	Hib3 <sup>d,f</sup>	MCV	MCV2 <sup>d</sup>
African							
South Africa	99	97	...	97	97	83	69
Americas							
Argentina	94	96	79	92	96	99	91
Eastern Mediterranean							
Egypt	98	98	...	98	...	97	97
Iran	99	99	99	97	...	97	97
Pakistan	90	83	...	83	...	80	...
Saudi Arabia	97	96	96	96	96	96	...
South-East Asian							
Bangladesh	98	87	...	87	...	85	...
Sri Lanka	99	98	...	98	...	98	97
Thailand	99	98	99	96	...	96	94
Western Pacific							
Philippines	90	87	9	88	...	92	...

WHO, World Health Organization; DTP, diphtheria, tetanus, pertussis; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; MCV, measles-containing vaccine.

<sup>a</sup> First dose of DTP vaccine.

<sup>b</sup> Third dose of DTP vaccine.

<sup>c</sup> First (birth) dose of HepB vaccine.

<sup>d</sup> Ellipses indicate no data available.

<sup>e</sup> Third dose of HepB vaccine.

<sup>f</sup> Third dose of Hib vaccine.

In the majority of the authors' countries included in this study, vaccination recommendations are made by a national committee of governmental advisers or by the ministry of health. In most cases, vaccination is then funded by the government, although this can be facilitated by local government in some countries (e.g., the Philippines). In Sri Lanka, vaccinations are partly funded by the government, in conjunction with the EPI and GAVI Alliance. The GAVI Alliance provides support for vaccine financing to 72 countries with low gross national product, including Pakistan, as does the United Nations Children's Fund (UNICEF) in Bangladesh.

Although many countries provide funding for vaccination, there are several factors that may prevent vaccination coverage reaching targets. For example, in South Africa, the falling number of nurses restricts the implementation of vaccination recommendations. This has led to a growing private market in South Africa and in other countries such as Bangladesh. In the Philippines, vaccines not included in the EPI recommendations must be paid for by the patient, which is likely to have a detrimental effect on vaccine uptake. About 10–15% of recommended childhood vaccinations, including Hib vaccine, are provided through private clinics, together with other non-EPI vaccines (L. Bravo, personal communication, 2008).

#### 4.3. Summary

All of the authors' countries recommend vaccination against diphtheria, tetanus, pertussis, and measles. Although vaccination against HepB is recommended in all of the authors' countries, this has only recently been implemented in many countries, and the absence of a birth dose is reflected in high incidence rates of HepB among children in some countries. Vaccination against invasive Hib disease is still not recommended in all countries, and requires private funding in some countries; however, it has recently been introduced to some countries with a high Hib disease burden. It should also be noted that pneumococcal conjugate vaccine is being introduced as part of GAVI Alliance initiatives to prevent pneumococcal infection.

The introduction of pentavalent vaccines, currently used in Saudi Arabia, and recently introduced in Argentina, Pakistan, and Sri Lanka, allows cost-effective vaccination against HepB and Hib disease as an add-on to the existing DTP vaccination. The use of whole-cell pertussis (wP) vaccines (i.e., DTWP–HepB–Hib) makes the vaccines more affordable than their acellular pertussis (aP) counterparts, and the suitability of these vaccines in the implementation of EPI vaccination programs contributes to a reduction in Hib disease in countries such as Argentina, where they have been introduced.

## 5. Discussion

Vaccination programs have successfully reduced disease burden in developing countries. In the Gambia, for example, the incidence of invasive Hib disease per 100 000 children <5 years of age decreased from approximately 60 cases in 1990–1993 to 0 cases in 2002 following the introduction of Hib vaccination.<sup>60</sup> More recently, similar success has been seen in Uganda following vaccine introduction, where Hib meningitis incidence dropped from 88 cases per 100 000 children <5 years of age in the year before vaccine introduction to 13 cases within 4 years, and to almost zero in the fifth year. In Uganda, it is now estimated that Hib vaccine prevents some 28 000 cases of Hib pneumonia and Hib meningitis, 5000 deaths, and 1000 severe Hib-meningitis sequelae each year.<sup>61</sup> However, the issue remains that surveillance is still poor in many countries, and vaccination coverage for some key pediatric vaccines is lower in some countries than recommended by the WHO. Substantial differences have also been reported

between official and survey-based measures of vaccine coverage, indicating that coverage may not be as great as reported figures suggest.<sup>62</sup> Moreover, in many countries within the Eastern Mediterranean and South-East Asian WHO regions, recommended vaccines have not been incorporated into national programs. The information brought together here shows that a clear correlation exists between the adoption of a given vaccine into the national schedule, vaccine coverage, and disease incidence, reinforcing the case for widespread pediatric vaccination to reduce the burden of disease.

Despite vaccination recommendations, the pediatric disease burden remains high in many regions. Hepatitis B and Hib disease contribute substantially to this disease burden in the Eastern Mediterranean and South-East Asian WHO regions. Unfortunately, many of the regions with the highest disease burden are associated with very low levels of diagnosis and disease surveillance. This problem is more common in the Eastern Mediterranean, South-East Asian, and Western Pacific WHO regions, where there is a need for improved surveillance, to capture data accurately and assess the magnitude of the disease burden. Here, sentinel surveillance carried out on a widespread basis by local organizations could provide invaluable information about disease incidence, which would help to establish the true burden of disease in many developing countries. Surveillance needs to be of a high quality, however, to help avoid the potential for decision-making based on incomplete or potentially misleading results. Models, such as recent global disease burden models for Hib, pneumococcus, and measles, may be required to establish a truer picture of disease burden. Such models provide country-level estimates and take into account probe studies or other regional information where local data are insufficient.

There is also a large degree of variation between countries in terms of vaccination recommendations. These variations are often driven by lack of resources, and can lead to confusion regarding regional vaccination priorities. In addition, with increasing numbers of diseases for which vaccinations are recommended, vaccination programs become complex and can be challenging to implement, leading to sub-optimal vaccination coverage.

The incorporation of new vaccines into already complex schedules can prove challenging to healthcare providers, particularly in areas of developing countries and in regions with isolated populations. An increased number of injections, both in total and per visit, can lead to distressed patients and parents, which may deter parents from attending clinic visits, and therefore may act to reduce compliance with vaccination schedules.<sup>63,64</sup> An example of the number of vaccinations that may be required can be drawn from the USA, where the vaccination schedule for children ≤2 years of age increased from five injections and four sets of oral drops in 1983, to 20 injections in 2003.<sup>65</sup> Parents often express concern about the number of injections per visit received by their children.<sup>63</sup> However, scheduling additional vaccination visits to reduce the number of injections per visit increases time and costs, burdens healthcare staff, and may risk the success of a vaccination program by increasing the likelihood of missed visits.<sup>64</sup>

The use of combination rather than separately administered vaccines may facilitate the implementation of complex vaccination programs. Combination vaccines have been proven to offer comparable or even superior immunogenicity to separate administration of individual components,<sup>66</sup> and have also been shown to lead to higher compliance rates, and therefore more complete vaccination coverage, since fewer clinic visits and injections are required.<sup>24,67–69</sup> A time and motion study carried out in India using a fully liquid combination vaccine also identified significant savings throughout the whole supply chain, as well as time savings at the facility level compared with lyophilized vaccines requiring reconstitution. This translated into economic savings

which could be key in countries with limited economic resources.<sup>23</sup>

Additionally, combination vaccines that include the wP component offer additional cost savings over those that include the aP component.<sup>6</sup> A number of studies have compared wP- with aP-containing vaccines, and found some wP vaccines may provide greater protection than some aP vaccines,<sup>70</sup> and that the wP component does not adversely affect the immune response to Hib.<sup>71</sup> Moreover, recent data from Rieber and colleagues suggest that wP vaccines may produce more effective priming of B cell memory and, therefore, offer better long-term protection – a major goal in the future improvement of pertussis vaccines.<sup>72</sup> Whole-cell pertussis vaccines can be more reactogenic than aP vaccines; recent comparative studies have shown that although local adverse reactions are less frequent with the aP-containing vaccine compared with wP, there is no significant difference in systemic reactions except for fever, and that wP combination vaccines have an acceptable safety and tolerability profile.<sup>73</sup> By virtue of the combination of efficacy, tolerability, and cost-effectiveness, the WHO recommends that wP combination vaccines should be the vaccines of choice in regions where resources may be limited.<sup>6</sup> These factors will be key in expanding vaccine coverage into the developing countries highlighted here, where there remains a significant unmet need.

By the end of 2008, it was estimated that over 50 million children had been vaccinated with DTwP-based pentavalent vaccine, with 49 countries now eligible for GAVI Alliance support.<sup>74</sup> This is a significant increase over figures reported for 2007, at which time 28 million children had received pentavalent vaccine across 39 countries.<sup>75</sup> Focused efforts to inform countries of the burden of disease, benefits of vaccination, and availability of vaccine and financial support have helped to drive the increase in vaccine uptake. The availability of the vaccine in a fully liquid formulation has also been a significant factor in increasing uptake.<sup>74</sup> Of 29 countries that applied to the GAVI Alliance for help in strengthening their vaccination systems in 2007, 20 requested support in obtaining pentavalent vaccines. Of these, 16 (80%) expressed a preference for a fully liquid vaccine, indicating that it is the favored option, particularly in countries of limited means.<sup>76</sup>

This review has highlighted considerable geographical variance in the burden of childhood disease and vaccination coverage in the countries studied. Combination vaccines that are cost-effective have the potential to increase vaccination coverage against common childhood diseases, and reduce their substantial disease burden. They may also enhance the implementation of vaccination programs and release budget for the incorporation of additional vaccines into existing programs, further extending vaccination coverage and reducing the substantial morbidity and mortality associated with vaccine-preventable diseases.

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