



Review

Haemophilus influenzae type b conjugate vaccines – A South African perspectiveAdele Visser^{a,*}, Anwar Hoosen^b^a Department Medical Microbiology, Division Clinical Pathology, University of Pretoria, National Health Laboratory Services, Tshwane Academic Division, South Africa^b Department Medical Microbiology, University of Pretoria, National Health Laboratory Services, Tshwane Academic Division, South Africa

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ABSTRACT

Introduction of Hib vaccine is known to positively impact on reduction of both morbidity and mortality in children less than 5 years of age. Incorporation of this vaccine into a National EPI, however, does come at a significant cost, which is especially important in non-GAVI funded countries. Compounded reduction in response in certain patient populations and possible indication of booster doses further impacts on cost-benefit analyses. Despite these issues, South Africa has supplied Hib vaccine as part of the National EPI in the form of a combination vaccine, Pentaxim®, which combines Hib with Diphtheria, Tetanus, acellular Pertussis (DTP) and Poliomyelitis since 2009. Prior to this, another combination vaccine was utilized containing Hib and DTP. This has subsequently lead to a significant reduction in invasive Hib disease post-introduction, therefore largely justifying utilization.

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1. Introduction

Historically, *Haemophilus influenzae* type b (Hib) was considered the most common severe invasive infection in children younger than 5 years of age [1,2] in industrialized countries [3], causing in excess of 8 million serious infections worldwide [4]. The peak incidence among unvaccinated individuals varies from 6 to 7 months in developing countries [5], to slightly older in developed countries [6]. Hib-related mortality is attributed to meningitis and pneumonia, but invasive disease may also present as epiglottitis, osteomyelitis, septic arthritis, septicemia, cellulitis and pericarditis [6]. Worldwide studies conducted prior to the introduction of Hib vaccines amongst almost 4000 patients showed that in excess of 90% of patients presented with one of six clinical syndromes. Of these, meningitis accounted for more than half, but other clinical manifestations included bacteremic pneumonia, epiglottitis, septicemia, cellulitis and osteoarticular disease (with septic arthritis more common than osteomyelitis) [7]. Invasive disease represented only part of the clinical implication, as meningitis is often complicated with hearing impairment, seizure disorders, cognitive and developmental delay, and various other permanent neurological sequelae [8]. Introduction of Hib vaccination has had a major impact on invasive disease in both developing [9–12] and industrialized countries [7,13,14] despite the fact that disease epidemiology differs in these settings (Table 1).

South Africa was the first African country to introduce Hib vaccine as part of the National Expanded Program on Immunization

(EPI) in 1999 [15]; the estimated coverage in 2004 was 92% [6]. Comparison of pre- and post-vaccination burden of diseases data is not possible as a national laboratory-based surveillance system for invasive Hib disease was established simultaneously with the introduction of Hib vaccine in 1999 [15]. However, a study from Cape Town in the pre-immunization era performed at an academic hospital reported an incidence rate of invasive Hib disease of 169 and 47 per 100,000 population for children less than 1 and less than 5 years of age, respectively [17]. Based on the national laboratory-based surveillance (which yields only a fraction of the real burden) reported rates of invasive Hib disease in the first year following vaccination were 6.2 and 1.9 per 100,000 population in less than 1 year and less than 5 years old, respectively. Over the period of 2000–2004 rates of invasive Hib disease decreased significantly, by 65% and 71% in less than 1 year old and less than 5 year old [16], indicating the impact of the Hib vaccine introduction in 1999.

Since 2003, the laboratory surveillance system become an active system including enhanced surveillance conducted at sentinel sites in each of the 9 provinces; detection rates of invasive Hib disease remains low, but from 2003 to 2009 the detection rate increased from 0.7 to 1.3 cases per 100,000 population in children less than 5 years old. Most of these cases were in fully vaccinated children (primary series of 3 doses at 6, 10 and 14 weeks of age) [18]. These findings supported the decision to add since November 2010 a booster dose of Hib at 18 months of age as part of the a new pentavalent vaccine [18].

The World Health Organization (WHO) Strategic Advisory Group of Experts recommended worldwide implementation of Hib vaccination, in 2006. They further stated exception from this only if “robust epidemiologic evidence exists of low disease burden, lack of benefit, or overwhelming impediments to

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Table 1

Differential epidemiology of Hib disease in Africa versus the Americas described in children younger than 5 years of age and expressed per 100,000 population.

	African population		American population	
Age of disease	6–7 months [6]		12 months [5]	
Clinical features (number of cases) [12]	Meningitis	46 (31–52)	Meningitis	25 (16–30)
	Pneumonia	1724 (1574–2817)	Pneumonia	510 (466–834)
Death rate	60 (40–85)		11 (7–15)	

Adapted from Ref. [4].

implementation” [19]. Despite convincing evidence collected over more than twenty years, indicating vaccine efficacy [20,21], only 42% of children worldwide had received this vaccine by 2010 [22]. Two main obstacles have been cited for this; firstly the lack of accurate epidemiological data due to various practical issues surrounding disease identification (discussed in text) and secondly, the high vaccine cost [23].

2. Development of Hib conjugate vaccines

Development of the first polysaccharide Hib vaccines started in the 1970s with the only field studies performed in Finland [24]. This was achieved by utilizing the polyribosylribitol phosphate (PRP) subunits of the bacterial capsule [25]. This vaccine showed an 90% efficacy (95% confidence interval of 55–98%) specifically in children older than 18 months [24]. Efficacy in younger children is markedly lower due to the T-cell independent nature of the vaccine response. These formulations were only licensed for use in the United States (US) [26], Canada [27] and parts of Saudi Arabia [28], where more than 10 million doses were administered from 1985 to 1989 in the US alone [13]. By the late 1980s, conjugate vaccines were being developed against Hib disease, and following this, combination formulations were developed containing these Hib conjugate vaccines [29]. These conjugate vaccines were proven to be superior to PRP vaccines as the PRP-only vaccines were poorly immunogenic in children under the age of 18 months [24], lacked a booster response [30] and did not show any reduction in nasal carriage [31]. This was by and large due to the T-cell-independent nature of the immune response to polysaccharides. Based on disease epidemiology where severe infection is typically noted in younger children, an alternative was needed to improve immunogenicity in this target group [6]. The first Hib conjugate vaccine introduced to the market was a diphtheria toxoid conjugate (PRP-D), thereafter altered to the mutant diphtheria toxin conjugate (PRP-HbOC) [7]. Later on, conjugates were developed containing the outer membrane protein of *Neisseria meningitidis* (PRP-OMP) and tetanus toxoid (PRP-T) [32,33] (Table 2). The first vaccines to be commercially produced were formulated as PRP-HbOC, PRP-D or PRP-OMP and effectiveness was established by extensive clinical trials [34]. Subsequently, PRP-T formulations were produced and efficacy and licensing were based on demonstrating equivalent serum antibody levels compared to PRP-OMP and PRP-HbOC. Of note, most formulations currently utilized, conjugate to tetanus

toxoid, as the conjugation technology is not protected by patent laws [6]. PRP-D formulations are no longer in clinical use as these vaccines have been shown to have inferior effectiveness, especially in high prevalence disease populations [35].

In December 2007, a voluntary recall of specific Hib conjugate vaccine lots (PRP-OMP Pedvax HIB® and Combax®) by Merck & Co., Inc. (West Point, USA) indirectly lead to generalized reduction in vaccine coverage. The recall was purely precautionary following identification of *Bacillus cereus* in vaccine manufacturing equipment [36], and subsequent surveillance did not reveal any contaminated vaccine lots [37] or clinical cases of vaccine-associated *B. cereus* infection to recipients [36]. Subsequent recommendations were to simply omit use of the booster dose, but to continue vaccination otherwise. Despite this, a generalized reduction in vaccine coverage was noted. This finding highlights the importance of clearly communicated guidelines once a change in national policy is necessary [38].

3. Cost, distribution and delivery

Hib vaccine is more expensive than most of the other EPI vaccines. Costs were estimated to be as much as seven times that of measles, polio, Bacillus Calmette–Guérin (BCG), diphtheria, tetanus and pertussis vaccine in 2005 [23] but current prices are 3 to 9 times the cost (S. Phoshoko, Personal communication). By the end of 2004, the WHO reported that only ten countries in Africa included Hib conjugate vaccine as part of their EPI. These countries are Burundi, The Gambia, Ghana, Kenya, Madagascar, Malawi, Rwanda, South Africa, Uganda and Zambia [39]. However, the current state of Hib vaccine use in Africa seems promising as only Equatorial Guinea, Nigeria, Tunisia, Botswana and Somalia are not including Hib in their routine EPI [40]. In January 2000, the Global Alliance for Vaccines and Immunization (GAVI) was launched, with the mission statement, to provide access to vaccines to the 70 poorest countries in the world [41]. Subsequently, this was expanded to the poorest 76 countries [23,42]. The strategy aims to provide these vaccines through collaboration between the WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation, donor governments, international development and finance organizations, the pharmaceutical industry, as well as from the developing countries themselves [41]. By the end of 2010, an additional 91 million children had received a full course of Hib vaccines, they would otherwise not have had access to [43]. One of the requirements for GAVI support is proof of burden of disease [44]. This has been an issue in the past in the Indian subcontinent, where inadequate surveillance data existed to motivate for provision of vaccines [45]. Fortunately, this has fueled research in this field, confirming mortality due to Hib meningitis to be as high as 11% with 30% of survivors suffering subsequent major neurological sequelae [45].

Despite formal inclusion in the respective EPI's, vaccine coverage varies significantly from as low as 50% (Madagascar) [39] and more recently, Central African Republic (58%), to 99% in Burkina Faso [46]. Evaluation of rates of invasive Hib disease is dependent on National Surveillance systems. Several countries do not make use of this, and those who do, report significantly variable rates. These vary from no reported cases (Congo, Gambia, Guinea-Bissau,

Table 2

Conjugate vaccines developed to improve immunogenicity of Hib vaccines.

	Subunit utilized	Licensing
<i>Corynebacterium diphtheriae</i>	Modified non-toxic fragment of diphtheria toxin (PRP-HbOC) Diphtheria toxoid (PRP-D)	Vaccine efficacy clinical trials [14,34]
<i>Neisseria meningitidis</i>	Outer membrane protein (PRP-OMP)	Vaccine efficacy clinical trials [14]
<i>Clostridium tetani</i> [34]	Tetanus toxoid (PRP-T)	Equivalence studies [31,32]

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