



Invasive *Haemophilus influenzae* Infections after 3 Decades of Hib Protein Conjugate Vaccine Use

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SUMMARY *Haemophilus influenzae* serotype b (Hib) was previously the most common cause of bacterial meningitis and an important etiologic agent of pneumonia in children aged <5 years. Its major virulence factor is the polyribosyl ribitol phosphate (PRP) polysaccharide capsule. In the 1980s, PRP-protein conjugate Hib vaccines were developed and are now included in almost all national immunization programs, achieving a sustained

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decline in invasive Hib infections. However, invasive Hib disease has not yet been eliminated in countries with low vaccine coverage, and sporadic outbreaks of Hib infection still occur occasionally in countries with high vaccine coverage. Over the past 2 decades, other capsulated serotypes have been recognized increasingly as causing invasive infections. *H. influenzae* serotype a (Hia) is now a major cause of invasive infection in Indigenous communities of North America, prompting a possible requirement for an Hia conjugate vaccine. *H. influenzae* serotypes e and f are now more common than serotype b in Europe. Significant year-to-year increases in nontypeable *H. influenzae* invasive infections have occurred in many regions of the world. Invasive *H. influenzae* infections are now seen predominantly in patients at the extremes of life and those with underlying comorbidities. This review provides a comprehensive and critical overview of the current global epidemiology of invasive *H. influenzae* infections in different geographic regions of the world. It discusses those now at risk of invasive Hib disease, describes the emergence of other severe invasive *H. influenzae* infections, and emphasizes the importance of long-term, comprehensive, clinical and microbiologic surveillance to monitor a vaccine's impact.

KEYWORDS *Haemophilus influenzae*, Hib, conjugate vaccine, immunization, epidemiology, nontypeable *H. influenzae*

INTRODUCTION

Haemophilus influenzae is a fastidious Gram-negative coccobacillus, requiring two accessory growth factors, X factor (hemin) and V factor (NAD). *H. influenzae* is restricted to humans, colonizing the nasopharynx and to a lesser extent the conjunctivae and genital tract (1). It is differentiated into six capsular types (a to f) according to its capsular polysaccharide structure. Other strains do not have a capsule and are classified as nonencapsulated or nontypeable *H. influenzae* (NTHi). The most virulent serotype is *H. influenzae* type b (Hib), and its capsule, composed of polyribosyl ribitol phosphate (PRP), is the predominant virulence determinant. Studies on unvaccinated individuals in Finland found that serum anti-PRP immunoglobulin G (IgG) antibody concentrations of $\geq 0.15 \mu\text{g/ml}$ correlated with a lower incidence of Hib meningitis (2, 3). Additional studies determined that serum anti-PRP IgG antibody levels of $\geq 0.15 \mu\text{g/ml}$ provide short-term protection against invasive Hib disease, but long-term protection requires concentrations of $\geq 1.0 \mu\text{g/ml}$ (4). It is now 30 years since Hib protein conjugate vaccines were first licensed, and since then, Hib immunization has been incorporated into almost all national immunization programs (NIPs) globally. Wherever Hib protein conjugate vaccines have been introduced and high coverage has been achieved, there has been a profound and sustained decline in the incidence of invasive Hib disease (5–11). This review starts by examining the impact of Hib protein conjugate vaccines during these 3 decades and the consequent changes in the worldwide epidemiology and disease burden of Hib and other invasive *H. influenzae* infections. The emergence of NTHi and other *H. influenzae* non-b serotypes as important invasive pathogens is emphasized. The increased incidences of NTHi invasive infections in vulnerable patient populations where infection is associated with high rates of morbidity and mortality and of *H. influenzae* type a (Hia) as a major cause of invasive disease in Indigenous groups in North America are highlighted. Finally, we conclude that the changing epidemiology of invasive *H. influenzae* infection emphasizes the importance of continuing surveillance and the possible need for developing new vaccines to control these emerging non-b infections.

GLOBAL BURDEN OF *H. INFLUENZAE* DISEASE PRIOR TO ROUTINE Hib PROTEIN CONJUGATE VACCINE IMMUNIZATION

Before the introduction of routine immunization with Hib protein conjugate vaccines, Hib was the most important cause of bacterial meningitis in young children (12, 13). It was also a major cause of pneumonia globally, resulting each year in a conservative estimate of 1.76 million episodes of severe pneumonia in children aged <5 years and 80% of all invasive Hib infections in this age group (5).

More than 90% of cases of invasive Hib infection were in children aged <5 years, and 60% of cases of Hib meningitis were in infants <12 months of age (14). These proportions varied across the world, with approximately 50%, 40%, and 55% of Hib meningitis cases in the World Health Organization (WHO) American, European, and Western Pacific Regions occurring in <12-month-old infants, respectively (15). In high-mortality regions, including Africa and Asia, the proportion of Hib meningitis in <12-month-old infants was approximately 80% (15). Prior to the introduction of Hib infections protein conjugate vaccines in the United Kingdom, most cases of invasive *H. influenzae* were due to Hib and affected young children, with only about 10% of all invasive Hib infections occurring in adults (16). Similarly, in Finland, 9.5% of invasive Hib infections and 3% of Hib meningitis cases were in individuals aged ≥ 10 years (17). In contrast, while only approximately 10% of invasive *H. influenzae* cases in the United Kingdom were from NTHi, two-thirds of these infections involved adults, especially those ≥ 65 years of age (16).

Prior to the introduction of routine Hib vaccination, the incidence of Hib meningitis in children aged 0 to 4 years in the United States was 54/100,000 per year (range, 19 to 69/100,000) (5, 18). However, much higher rates of Hib meningitis in this age group of 150 to 450/100,000 per year were reported in Indigenous populations residing in Alaska (19), Northern Canada (20), and Central and Northern Australia (5, 21). Hib meningitis had a mean case fatality ratio (CFR) of 14%, ranging from approximate values of 5% in Europe to 28% in Africa (15). The second highest CFR was in South East Asia (17%), followed by the Eastern Mediterranean Region (12%), the Region of the Americas (11%), and the Western Pacific Region (6%) (15).

In a meta-analysis of the outcomes of bacterial meningitis in high-income countries (22), long-term sequelae following Hib meningitis were observed in 26% of survivors, manifesting as sensorineural hearing loss (10%), spasticity (5%), intellectual impairment (6%), and epilepsy (6%). Additionally, survivors might develop functionally important behavioral disorders, neuropsychologic impairment, or auditory dysfunction adversely affecting academic performance (5, 23). In contrast, long-term sequelae following Hib meningitis were seen in 38% of survivors in The Gambia (24). Twenty-nine percent of Navajo Indian children suffered long-term sequelae (25), notably intellectual impairment (24%), severe hearing loss (5%), spasticity (7%), and seizures (12%). Among Alaska Native infants, 29% suffered motor deficits and 7% developed hydrocephalus (26). Age is also an important factor in determining outcome of meningitis (27), and the higher rates of adverse sequelae in Indigenous children and in Africa may have resulted from a higher proportion of cases occurring in infants <12 months of age in these communities. Additional potential factors contributing to adverse outcomes might also include poor access to medical care, delayed diagnosis and treatment, and in African children comorbidities such as malaria, malnutrition, and human immunodeficiency virus (HIV) infection.

Hib vaccine probe studies used data from randomized controlled trials (RCTs) to estimate the underlying burden of disease from Hib pneumonia by measuring the difference in incidence of pneumonia between vaccinated and unvaccinated children. These vaccine probe studies were conducted in The Gambia (28), Lombok in Indonesia (29), and Santiago in Chile (30). They suggested that Hib was an important cause of bacteremic and nonbacteremic pneumonia in young children (Fig. 1) in low- and middle-income countries (LMICs) and likely the most common presentation of Hib disease globally. Subsequent analyses provided an estimated annual global incidence of Hib pneumonia in unvaccinated children of 1,304/100,000 children aged <5 years (31). Other studies in children from Papua New Guinea and Indigenous children in the Northern Territory of Australia estimated the incidence of Hib pneumonia to be 2,860/100,000 and 225/100,000 children <5 years of age, respectively (32, 33).

Unvaccinated HIV-infected children are at particularly high risk of invasive Hib disease in comparison to unvaccinated children from the same region but who are HIV negative (relative risk, 5.9; 95% confidence interval [CI], 2.7 to 12.6) and where pneumonia was also a more common presentation than meningitis (34, 35). In a pneumococcal vaccine trial in South Africa, bacteremic Hib pneumonia was the most common

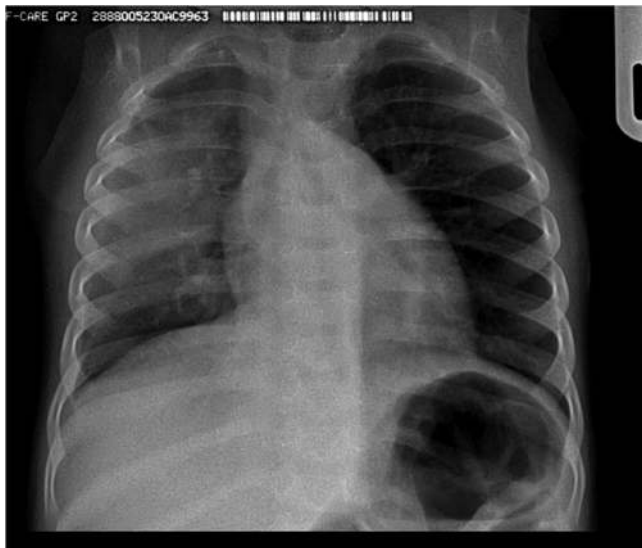


FIG 1 Posteroanterior chest radiograph of an 11-month-old infant showing right-sided pneumonia caused by *H. influenzae* type b (copyright 2020 Grant Mackenzie).

presentation of invasive Hib disease (34, 35). The incidence of Hib pneumonia in HIV-positive infants aged <1 year was 822/100,000 compared to 48/100,000 in HIV-negative infants (relative risk, 18.0; 95% CI, 6.9 to 47.1) (34). In addition to patients with HIV, patients with asplenia, sickle cell disease (SCD), and possibly malignancies were also at a higher risk of developing invasive Hib infections (18).

Hib was also the most common cause of acute epiglottitis, which usually presented in older children aged 2 to 4 years, but it was rarely seen in Indigenous children in Australia (36) or in Native Alaskan and Canadian Inuit children (19), where the greatest burden of invasive *H. influenzae* disease was found in those aged <18 months. Other manifestations of invasive Hib infection include bacteremia without a focus of infection, orbital and periorbital cellulitis, facial cellulitis, and skeletal infections (1). The annual incidence of all invasive Hib disease before the introduction of Hib vaccine ranged from 67 to 131/100,000 in the United States (18), 58/100,000 in Australia (37), 52/100,000 in Finland (38), 24 to 36/100,000 in the United Kingdom (16), 34/100,000 in Israel (39) and 18.8/100,000 in children aged <5 years in Japan (40).

Hib POLYSACCHARIDE VACCINE

The original Hib vaccine was a PRP plain polysaccharide vaccine. A large field trial recruiting 100,000 children aged 3 months to 5 years in Finland demonstrated an age-dependent response to PRP but failed to show any impact on nasopharyngeal carriage and therefore no interruption of transmission (17). The PRP vaccine did not induce protective levels of anti-PRP antibodies in children aged <18 months, but it was 90% efficacious in those aged \geq 18 months. Polysaccharides are T-cell-independent antigens which lead primarily to IgM responses with little isotype switching to IgG antibody in infants aged <18 months. Plain polysaccharide vaccines fail to induce immunologic memory and also fail to elicit a booster response on repeated exposure (2, 41).

Hib PROTEIN CONJUGATE VACCINES

To address the reduced immunogenicity of polysaccharide vaccines in infants, conjugated protein-polysaccharide (glycoconjugate) vaccines were developed (Fig. 2).

Antibody responses to proteins are T cell dependent and can be elicited from a very young age, resulting in high-affinity antibodies with isotype switching, affinity maturation, and the generation of immunologic memory. Subsequent exposure to the

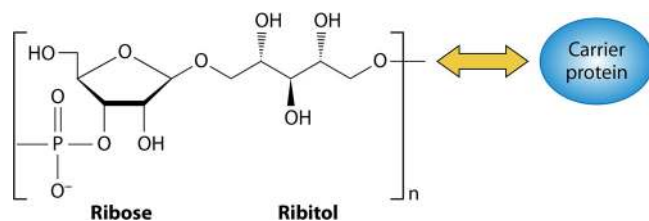


FIG 2 Cartoon illustrating Hib conjugate vaccine. Polyribosyl ribitol phosphate (PRP) [composed of repeating units of 5-D-ribitol-(1→1)-β-D-ribose-3-phosphate] covalently linked to a carrier protein (chemical structure kindly provided by Neni Nurainy, Biofarma, Indonesia).

antigen results in a significant booster response. Hib PRP-protein conjugate vaccines, which activate a T-cell-dependent response with high levels of protective antibodies in infants from 2 months of age, were developed in the late 1980s (42). Hib nasopharyngeal carriage is reduced in those who are vaccinated, thereby interrupting transmission of Hib to susceptible unvaccinated children and adults (i.e., herd protection) (43). Initially, four different monovalent Hib protein conjugate vaccines were produced. Different carrier proteins, various lengths of PRP saccharide, and different protein-poly-saccharide conjugation techniques were used. The four protein carriers were tetanus toxoid (PRP-TT), diphtheria toxoid (PRP-D), *Neisseria meningitidis* outer membrane complex (PRP-OMP), and a nontoxic mutant *Corynebacterium diphtheriae* protein CRM₁₉₇ (PRP-CRM). The Hib protein conjugate vaccines had different immunologic properties, resulting in different antibody titers, avidity maturation, rapidity of response, and idiotypic expression of the antibody response following vaccination (44–47). A double-blind RCT of the four Hib protein conjugate vaccines administered at 2, 4, and 6 months found that only 29% of infants achieved the putative long-term protective concentration of Hib antibodies ($\geq 1 \mu\text{g/ml}$) after three doses of PRP-D, compared with 55%, 75%, and 83% of infants who had received PRP-OMP, PRP-CRM, and PRP-T, respectively (48). The PRP-OMP vaccine stimulated the highest antibody concentration after the first dose in infants aged as young as 2 months (49), with 57% of infants achieving an antibody concentration of $\geq 1.0 \mu\text{g/ml}$ at age 4 months. However, PRP-OMP did not produce significant increases in antibody concentration when further doses of vaccine were administered at 4 and 6 months of age. Despite this, PRP-OMP was the first vaccine used in Indigenous populations in North America and Australia, where a high burden of disease existed in very young infants (19, 20, 33). Over time, PRP-D was withdrawn, and Hib protein conjugate vaccines have since been incorporated into a range of combination bivalent (Hib/meningococcal serogroup C [MenC]), pentavalent (diphtheria-tetanus-acellular pertussis [DTaP]/inactivated poliovirus [IPV]/Hib), and hexavalent (DTaP/IPV/Hib/hepatitis B [HepB]) vaccines.

IMPACT OF Hib PROTEIN CONJUGATE VACCINES ON INVASIVE Hib DISEASE

The inclusion of Hib glycoconjugate vaccines in NIPs has led to a significant and sustained decline in invasive Hib disease across all age groups, through direct and indirect (herd) protection (50, 51). Routine use of Hib protein conjugate vaccine has consistently reduced the incidence of invasive Hib disease by $\geq 90\%$ in high-income countries (51). The inclusion of Hib protein conjugate vaccines in the NIPs of low and middle-income countries has been generally much slower than its introduction in high-income countries. This was due to several factors, including limited local data on the burden of Hib infections as a result of high rates of antimicrobial therapy before specimen collections for culture and difficulties in growing this fastidious organism, as well as the associated vaccine costs (14). By 2004, few low-income countries had adopted Hib vaccines. The World Health Organization (WHO) and the Global Alliance for Vaccines and Immunization (GAVI) sought to address this problem in several ways. Vaccine probe studies (28–30) and the WHO Hib rapid assessment tool (HibRAT) (52)

provided a prompt and timely assessment of Hib disease burden in many countries. In 2005, the GAVI Alliance established the Hib Initiative to accelerate the introduction of Hib protein conjugate vaccine into GAVI-eligible countries (53). In 2006, the WHO advocated the global introduction of Hib protein conjugate vaccines (54), enabling GAVI-eligible countries to apply for Hib vaccine introduction without needing to generate data on local disease burden. For GAVI-eligible countries, free vaccine was initially provided through the GAVI Alliance with cofinancing guidelines offering a financial commitment to cover vaccine costs until 2015, together with a small copayment by each country to address concerns regarding the long-term sustainability of the program. As a result of these endeavors, the number of countries implementing Hib immunization increased from 89/193 (46%) in 2004 to 158/193 (82%) in 2009 (55). As of 2020, all countries in the world, except China and the Russian Federation (where Hib vaccine is recommended for certain risk groups), have included Hib protein conjugate vaccines in their routine NIPs (see Tables 1 to 6).

A substantial reduction in Hib disease burden has been seen wherever the vaccine has been used. In an updated analysis of data from the year 2000, Hib was estimated to have caused approximately 8.13 million (uncertainty range [UR], 7.33 to 13.2 million) cases of serious disease and 371,000 deaths (UR, 247,000 to 527,000) per year in children aged <5 years (31). Between 2000 and 2015, the estimated global burden of Hib meningitis, pneumonia, and nonpneumonic bacteremia in HIV-negative children aged <5 years had declined to 340,000 cases (UR, 196,000 to 669,000) and 29,800 deaths (UR, 18,600 to 41,100) (56). From 2000 to 2015, Hib-related deaths declined by 90% (UR, 78% to 96%) (56). Most Hib deaths occurred in just four countries, India (15,600 deaths; UR, 9,800 to 21,500), Nigeria (3,600 deaths; UR, 2,200 to 51,000), China (3,400 deaths; UR, 2,300 to 4,600), and South Sudan (1,000 deaths; UR, 600 to 1,400) (56).

CURRENT EPIDEMIOLOGY OF INVASIVE *H. INFLUENZAE* DISEASE

The burden of invasive Hib disease is limited currently to a small number of countries where Hib immunization is either not freely available or has been incorporated only recently into the NIP. Reducing invasive Hib disease to the lowest possible level depends on maintaining high vaccine coverage and maintaining good surveillance systems for Hib disease.

Initially, concerns were raised that other capsulated serotypes of *H. influenzae* might occupy the ecologic niche formerly occupied by Hib and emerge as significant causes of invasive disease once Hib vaccination had been introduced. In general, this has not happened in many parts of the world, with an important exception of the Indigenous communities of North America, where Hia is an emerging pathogen (57, 58). There has also been a slight increase in invasive *H. influenzae* serotype e (Hie) and *H. influenzae* serotype f (Hif) cases in Europe (9, 59). In contrast, the numbers of cases of invasive NTHi infections have increased significantly in multiple regions of the world (60, 61). In the following sections, the current epidemiology in the different WHO-designated regions is described (Fig. 3) (62).

Region of the Americas

All countries in the WHO Region of the Americas have introduced Hib vaccine. In 2020, the average coverage of three doses of Hib vaccine was 85% (63).

The data on individual countries in the Region of the Americas are shown in Table 1.

North America. Hib was a major cause of invasive bacterial infection in young children in the United States and Canada before the introduction of Hib vaccine. Population-based surveillance studies in the United States and Canada reported 10,000 to 20,000 cases annually of Hib meningitis and other serious invasive infections, with a CFR of 3% to 5% and long-term sequelae in as many as 25% of meningitis survivors (8). Much higher incidence rates of invasive Hib disease were observed in Alaska Native (64), White Mountain Apache (65), and Navajo Indian (66) children, with reported annual incidence rates of 700/100,000, 214/100,000, and 254/100,000 children aged <5 years, respectively. In North America, Hib infection occurred at a younger age

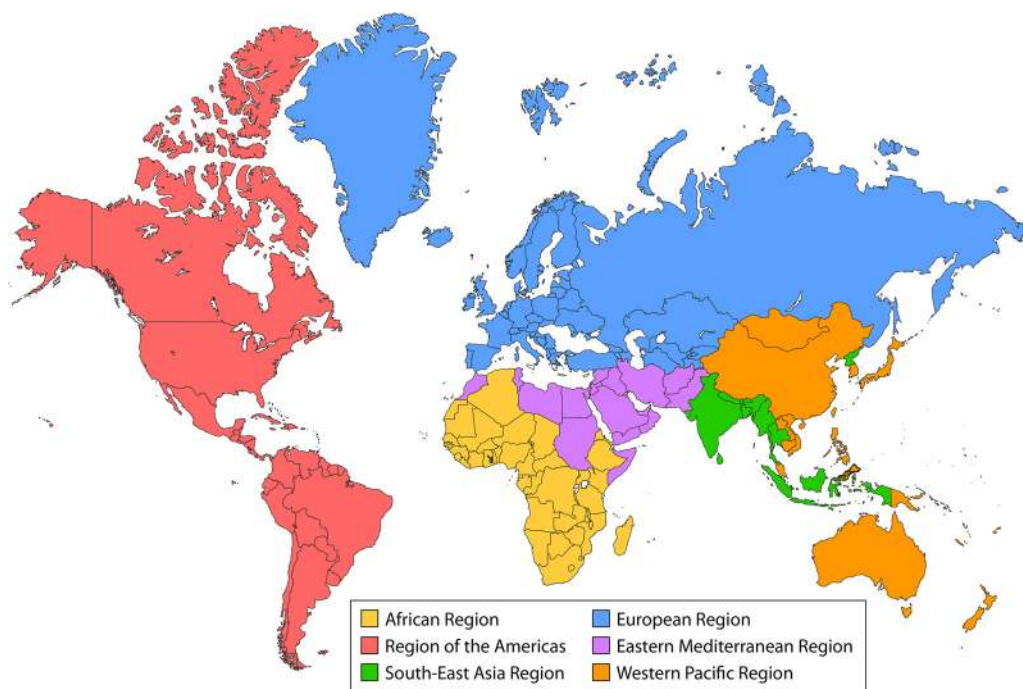


FIG 3 The six designated World Health Organization regions.

in Indigenous than non-Indigenous children. The peak incidence of Hib meningitis in Navajo children was at age 4 to 8 months (66), and that in White Mountain Apache children was at 4 to 7 months of age (65). In Alaska Native children, 23% of cases were in infants aged <6 months (64), whereas in North American non-Indigenous children, the peak rate of Hib meningitis was at 6 to 11 months of age (8). Although most cases in North American Indigenous children presented with meningitis, CFRs in Navajo Indian and Alaska Native children were lower than in the U.S. general population, 4% and 3% versus 5%, respectively (8, 64, 66). However, 16% of Navajo children who survived meningitis suffered neurologic sequelae (66). Carriage of Hib in Indigenous children began at a very young age (66), with asymptomatic carriers acting as a major reservoir and source of disease transmission.

Hib immunization was initiated in Alaska in 1991 using PRP-CRM and then changed to PRP-OMP, as this vaccine elicited protective antibody levels after a single dose (49). The incidence of invasive Hib disease in Alaska Native children aged <5 years fell from 309.4/100,000 in 1980 to 1991 to 18.3/100,000 in 1992 to 1995 (67). The PRP-OMP vaccine was used in Alaska until 1996, when it was replaced by a combination vaccine with a PRP-CRM component. Cases of Hib disease in rural Alaska Native children increased over the next year to 91.1/100,000 children aged <5 years, and in 1997, Alaska adopted a sequential Hib vaccine policy for Alaska Native children, with an initial dose of PRP-OMP and PRP-CRM for the rest of the schedule. In 2001, Alaska reintroduced a schedule using PRP-OMP alone or a combined hepatitis B/PRP-OMP vaccine (67). Although Hib disease is largely controlled, the rate of disease in this age group is still higher among rural Alaska Native children (5.4/100,000) than in non-Native Alaska and other non-Indigenous U.S. children (0.09/100,000) (67, 68).

In 1990, Hib protein conjugate vaccine was added to the routine infant immunization program in the United States (69). The program had a dramatic impact, and by 1995, invasive Hib disease incidence in children aged <5 years had declined by more than 95% (8). Ongoing active surveillance of invasive *H. influenzae* disease has continued in the Active Bacterial Core (ABC) surveillance sites coordinated by the Centers for Disease Control and Prevention (CDC). This surveillance system encompasses a

TABLE 1 Implementation of Hib vaccine in countries of the WHO Region of the Americas^a

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached ≥50%
Antigua and Barbuda	2000	Yes	DTwP/Hib/HepB	2, 4, 6 mo	99	2001
Argentina	1997	Yes	DTwP/Hib/HepB DTaP/Hib/HepB/IPV	2, 4, 6, 15–18 mo 2, 4, 6 mo for premature neonates	86	1999
The Bahamas	1998	Yes	Hib DTaP/Hib/HepB/IPV	Special cases 2, 4, 6 mo (private sector)	86	1999
			DTwP/Hib/HepB DTwP/Hib	2, 4, 6 mo 15 mo		
Barbados	2000	Yes	DTwP/Hib/HepB DTaP/Hib/HepB/IPV (infants of HIV ⁺ mother)	2, 4, 6 mo 2, 4, 6 mo	90	2002
Belize	2001	Yes	DTwP/Hib/HepB	2, 4, 6 mo	98	2001
Plurinational State of Bolivia	2000	Yes	DTwP/Hib/HepB	2, 4, 6 mo, 18–23 mo, 4 yrs	75	2000
Brazil	1999	Yes	DTwP/Hib/HepB Hib	2, 4, 6 mo Special population	80	2000
Canada	1986	Yes	DTaP/Hib/HepB/IPV	2, 4, 6, 18 mo	96	1996
Chile	1996	Yes	DTaP/Hib/HepB/IPV	2, 4, 6, 18 mo	96	1996
Colombia	1998	Yes	DTwP/Hib/HepB	2, 4, 6 mo	92	1998
Costa Rica	1998	Yes	DTaP/Hib/HepB/IPV	2, 4, 6, 15 mo	94	1999
Cuba	1999	Yes	DTwP/Hib/HepB Hib (children of HepB ⁺ women)	2, 4, 6, 18 mo 2, 4, 6, 18 mo	99	1999
Dominica	2006	Yes	DTwP/Hib/HepB	2, 4, 6 mo	99	2007
Dominican Republic	2002	Yes	DTwP/Hib/HepB	2, 4, 6 mo	79	2003
Ecuador	2003	Yes	DTwP/Hib/HepB	2, 4, 6 mo	85	2003
El Salvador	2002	Yes	DTwP/Hib/HepB	2, 4, 6, 15–18 mo	81	2002
Grenada	2000	Yes	DTwP/Hib/HepB	6–8 wks, 4–6 mo	94	2001
Guatemala	2006	Yes	DTwP/Hib/HepB	2, 4, 6 mo	86	2005
Guyana	2001	Yes	DTwP/Hib/HepB	2, 4, 6 mo	99	2001
Haiti	2012	Yes	DTwP/Hib/HepB	6, 10, 14 wks	51	2013
Honduras	2000	Yes	DTwP/Hib/HepB	2, 4, 6 mo	87	2000
Jamaica	2003	Yes	DTwP/Hib/HepB Hib (<5 yrs; scheduled splenectomy, HIV ⁺ , immunodeficiencies, and not fully vaccinated)	6 wks, 3 mo, 6 mo After 1 yr	96	2004
Mexico	1999	Yes	DTaP/Hib/HepB/IPV	2, 4, 6, 18 mo	82	2000
Nicaragua	1999	Yes	DTwP/Hib/HepB	2, 4, 6 mo	98	1999
Panama	2000	Yes	DTaP/Hib/HepB/IPV DTwP/Hib	2, 4, 6 mo 18 mo	88	2001
Paraguay	2002	Yes	DTwP/Hib/HepB Hib (<5 yrs; scheduled splenectomy, HIV ⁺ , immunodeficiencies, and not fully vaccinated)	2, 4, 6 mo 1st contact and 2 mo later	86	2003
Peru	2005	Yes	DTwP/Hib/HepB Hib (if pentavalent contraindicated)	2, 4, 6 mo 4, 6 mo	88	2004 (introduced in part of the country)
Saint Kitts and Nevis	2000	Yes	DTwP/Hib/HepB	4, 6 mo	97	2001
Saint Lucia	2002	Yes	DTwP/Hib/HepB	2, 4, 6 mo	92	2003
Saint Vincent and the Grenadines	2003	Yes	DTwP/Hib/HepB	2, 4, 6 mo	97	2005

(Continued on next page)

TABLE 1 (Continued)

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached $\geq 50\%$
Suriname	2005	Yes	DTwP/Hib/HepB	2, 4, 6 mo	77	2005
Trinidad and Tobago	1999	Yes	DTwP/Hib/HepB Hib (given to children born overseas who are over the age for pentavalent)	2, 4, 6 mo >12 mo	93	2000
United States	1991	Yes	DTaP/Hib/HepB/IPV Hib	2, 4, 6, 12 mo 2, 4, 6, 12 mo	91	1995
Uruguay	1994	Yes	DTwP/Hib/HepB Hib (if pertussis contraindicated)	2, 4, 6, 15 mo 2, 4, 6, 15 mo	94	1997
Bolivarian Republic of Venezuela	2000	Yes	DTwP/Hib/HepB	2, 4, 6, 18 mo, 5 yrs	64	2002

^aAnnual birth cohort, 14.7 million. Children aged <5 years, 73.3 million. Eighty-five percent of target population was immunized with three doses of Hib (Hib3) in 2019 (based on WHO-UNICEF estimates) (63). NIP, national immunization program. Abbreviations of vaccine antigens: D, diphtheria; T, tetanus; aP, acellular pertussis; wP, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B virus surface antigen; IPV, inactivated poliovirus.

population of over 42 million in five states and five metropolitan areas across the United States (70). It showed that invasive Hib disease continued to decline, and from 2009 to 2015, only 77 cases of invasive Hib disease were reported from the ABC sites, with a median patient age of 49 years (68). Of the 77 cases, only 23 (29.9%) occurred in children of <5 years of age, and in the 22 with available clinical information, nine presented with meningitis, six with bacteremic pneumonia, three with bacteremia, and four with other presentations. Only five (21.7%) of the children had been age appropriately vaccinated, including two aged 3 months who were eligible for only their first vaccine dose. None had reported underlying comorbidities. Of the remaining 54/77 (70.1%) Hib patients of >5 years of age, 9 (16.7%) were aged 5 to 17 years, 28 (51.9%) were 18 to 64 years, and 17 (31.5%) were ≥ 65 years of age.

The ABC surveillance network also reported that between 2009 and 2015, there were 545 cases of invasive *H. influenzae* infection in children aged <5 years, with an incidence of 2.84/100,000 children <5 years and 8.45/100,000 infants aged <1 year (68). Of the 317 cases in infants <1 year, 140 (44.2%) were in the first month of life, and of these, 127/140 (90.7%) were in the first week of life, with 109/127 (77.9%) presenting at birth. Most who developed infection in the first month of life were preterm and low-birthweight infants, and 113 (80.7%) of these infections were from bacteremia, with 111 (98.5%) caused by NTHi. The incidence of invasive *H. influenzae* infection was substantially higher in Alaska Native and American Indian children (15.19/100,000 children <5 years and 34.36/100,000 infants <1 year of age) (68). In these children, infections with non-b serotypes, principally Hia, had the highest incidence. During 2009 to 2015, the risk of invasive *H. influenzae* infection in U.S. adults of ≥ 65 years increased with age, with incidences of 3.48/100,000, 4.65/100,000, 6.48/100,000, 8.56/100,000, and 13.56/100,000 in those aged 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 85 years, and ≥ 85 years, respectively (68). Most infections in ≥ 65 -year-old patients were caused by NTHi (79.3%) or non-b serotypes (19.9%; with serotype f the most frequent). Only 0.08% of cases were due to Hib. Bacteremic pneumonia was the most common presentation in this age group (73.4%), and 74.0% had at least one underlying comorbidity. The overall incidence of invasive *H. influenzae* disease was 1.70/100,000 population, with a CFR of 14.5%. NTHi had a higher incidence (1.22/100,000) and CFR (16%) than Hib (0.03/100,000 and 4%, respectively) and non-b capsulated (0.45/100,000 and 11%, respectively) *H. influenzae* serotypes.

From 2002 to 2015, the estimated overall incidence of invasive *H. influenzae* infections in the United States increased by 2% per year (68, 71). The annual incidence of NTHi and Hia invasive infections increased by 3% and 13%, respectively. The incidence

of all other non-b serotypes declined or remained the same. The NTHi and Hia infection CFRs were 16.1% and 8.3%, respectively. Among the non-b encapsulated serotypes, Hia affected predominantly children <5 years of age, Hif had the highest overall incidence (0.27/100,000), and Hie exhibited a high CFR (18.4%). While Hid was detected rarely, its CFR (50.0%) was the highest recorded.

(i) Invasive *H. influenzae* disease and HIV. From 2017 to 2018, invasive NTHi infections in HIV-infected men who had sex with men increased in metropolitan Atlanta, Georgia (72). The incidence of invasive NTHi infection in HIV-positive individuals (41.7/100,000) in 2017 to 2018 was significantly greater than that in HIV-positive individuals from 2008 to 2016 (9.9/100,000; $P < 0.001$) and in those without HIV from 2008 to 2018 (1.1/100,000; $P < 0.001$). Comparing NTHi infections in 2017 to 2018 to those in 2008 to 2016, HIV-positive adults aged 18 to 55 years with NTHi infection in 2017 to 2018 were significantly more likely to be male (94% versus 49%; $P < 0.001$), African-American (100% versus 53%; $P < 0.001$), and to have septic arthritis (35% versus 1%; $P < 0.001$) than HIV-negative adults with NTHi infection in 2008 to 2016. Whole-genome sequencing confirmed two distinct but genetically related clonal lineages of NTHi. Among 38 cases of NTHi infection in persons with HIV, 32 (84%) lived in close geographic proximity, while all were male African-Americans with a median age of 34.5 years and 31 (82%) reported having sex with men.

(ii) Invasive *H. influenzae* infections and sickle cell disease. There is an increased risk of invasive infections caused by encapsulated bacteria, including Hib, in children with sickle cell disease (SCD). Before the introduction of Hib conjugate vaccine, children with SCD in the United States had a 4-fold increased risk of developing Hib bacteremia (73). In a Kenyan study of bacteremic episodes in children with SCD, 13/108 (12%) were due to Hib (74). In Africa, children with invasive Hib infections had 13-times-higher odds of having SCD (75).

In the United States, antibiotic prophylaxis and Hib and pneumococcal conjugate vaccines have led to a marked decline in the overall rates of invasive infections in SCD, including Hib infections. A retrospective review of the medical records of 815 children with SCD at the Children's Hospital of Philadelphia conducted from 2000 to 2010 in the era of Hib conjugate vaccination did not find a single case of Hib bacteremia (76). In one study in a pediatric tertiary care center in Atlanta, Georgia, there were eight episodes of *H. influenzae* bacteremia over a 17-year period (2000 to 2017): 5 Hif, 2 NTHi, and 1 Hia (77). Seven of the eight infections occurred in children aged <5 years, with an incidence of 1.6/1,000 person-years in this age group. Although uncommon, the possibility of non-Hib *H. influenzae* bacteremia should therefore also be considered in children with SCD.

(iii) Strain replacement: Hia in the United States. In the pre-Hib vaccine era, Hia as a cause of invasive *H. influenzae* disease was overshadowed by Hib, and epidemiologic data on Hia disease prior to 2000 are very limited. However, during the last decade, Hia has been recognized increasingly as a clinically significant pathogen causing severe disease and high CFRs in certain geographic areas and populations (58). Based on experiments with an infant rat septicemia model (78), Hia was found to be the second most virulent serotype after Hib (79). Indeed, Hia and Hib share many similarities: both serotypes cause invasive disease preferentially in young children, and both pathogens are characterized by serious infections, including meningitis, bacteremic pneumonia, and septic arthritis (58). Whereas at present invasive Hia disease is extremely uncommon in Europe or Asia, it has been reported consistently from Alaska, the North American Arctic, Western Canada, North Western Ontario, Manitoba, and South Western parts of the United States, where Indigenous people comprise a high proportion of the population, with concerning trends toward increasing incidence rates in some of these regions (58, 80). Hia has emerged as a significant pathogen in Utah (81, 82) and North and South Dakota (83). In a study in Utah from 1998 to 2008, 28% of all invasive *H. influenzae* disease in children aged <5 years was due to Hia, while just 18% was from Hib. Fifty percent of the Hia cases presented as meningitis. However, unlike

in other parts of North America, Hia and Hib did not occur predominantly in American Indian children in these states. A recent study from Utah described 51 cases of invasive Hia disease in children over the 10-year period from 2007 to 2017 (82). Meningitis was the most common clinical presentation (53%), with pneumonia and septic arthritis each accounting for 14% of cases; 43% of children required admission to an intensive care unit, and one child died (82).

The incidence of invasive Hia disease in the United States has been increasing by an average of 11.1% annually, from 0.05 to 0.14/100,000 population overall between 2008 and 2017 (84). The overall greatest burden of disease was observed in Alaska Native and American Indian children, with an estimated incidence of 8.29/100,000 in those aged <5 years, compared to 0.49/100,000 in those <5 years of age in all other races combined; for infants <1 year of age, the incidence rates were 17.78/100,000 and 1.28/100,000, respectively (84).

The highest incidence rates of invasive Hia disease have been reported from Alaska, where no Hia disease was identified before 2002, but since then, the incidence has been increasing annually by an average of 4.9% (85) and outbreaks have occurred, with the biggest disease burden borne by Alaska Native children (86). The average annual incidence rates of invasive Hia disease in Alaska Native children were 27.74/100,000 in those aged <5 years and 82.39/100,000 in infants aged <1 year (2008 to 2017) (84). Between 2002 and 2014, 42% of pediatric Hia cases in Alaska presented as meningitis with a high prevalence of unfavorable outcomes, including death (11%) or neurologic sequelae (14%) (87). All but two of 36 (94%) affected children were Alaska Natives, and 32 (89%) were <18 months of age (87).

From 2011 to 2015, review of the medical records of 169 patients with Hia infection in the ABC sites demonstrated the severity of invasive Hia disease: 96.0% were admitted to hospital, 25.3% required ventilatory support, 47.5% needed intensive care, and 6.2% died during hospitalization (88). In children aged <1 year, meningitis was the most common clinical presentation (71.4%). Overall, 17.7% of patients had adverse sequelae following discharge from hospital, as did 17.8% 1 year after the onset of the infection. Patients with meningitis had the highest proportion of sequelae (48.5%), including deafness and developmental and/or speech delay, with all adverse outcomes documented in children aged <5 years (88).

(iv) Strain replacement: Hia in Canada. In Canada, the highest incidence rates of invasive Hia are reported from the Nunavut and Nunavik territories in Northern Canada, which are populated mainly by Inuit people, where Hia epidemiology is very similar to that in Alaska. In these Canadian territories, Hia affects mainly young Indigenous children, has severe clinical presentation, such as meningitis with high CFRs, and causes outbreaks when the incidence can reach 300/100,000 in children aged <1 year (80, 89). In addition, Hia disease has been reported consistently from northern parts of the Canadian provinces of Manitoba, Ontario, and Quebec, regions largely inhabited by Indigenous peoples (58, 80, 90). Thus, invasive Hia disease is now prevalent in populations of North American Indigenous people, where several outbreaks have occurred since 2002, although sporadic cases have been reported from countries outside this continent. The emergence of Hia as a significant cause of invasive disease has prompted moves to develop a conjugated Hia vaccine (91), which if effective could prevent the high rates of morbidity and mortality seen with invasive Hia disease in addition to saving health care systems millions of dollars in both acute and long-term care (91).

Latin America and the Caribbean

Before Hib protein conjugate vaccines were introduced, the estimated incidence rate in children aged <5 years in 16 countries of this region for Hib meningitis was 35/100,000, and for all invasive Hib disease, it was 60/100,000 (92). The first country in Latin America to introduce large-scale immunization with Hib protein conjugate vaccines was Uruguay in 1994 (93). By 2006, all countries and territories in this region, except Haiti (94), had incorporated Hib vaccines into their NIPs (Table 1). Haiti

subsequently introduced pentavalent vaccine (diphtheria-tetanus-whole-cell pertussis [DTwP]/HepB/Hib) in 2012 (95). As in other regions, cases of Hib meningitis have declined substantially with the use of Hib vaccines (96). Surveillance in four countries suggested that high vaccine coverage resulted in a low incidence of Hib meningitis and low rates of Hib nasopharyngeal carriage in countries that used a three-dose primary course with (Uruguay and Argentina) or without (Colombia and Chile) a booster dose in the second year of life (93). In Mexico, a cross-sectional study (97) undertaken in 2007 found that only 40% to 50% of 110 children aged 12 to 23 months of age had anti-PRP antibody titers of $>1\mu\text{g/ml}$, the putative concentration required for long-term protection, despite 92% of these children having been fully immunized with three doses of Hib combination vaccine given at 2, 4, and 6 months of age. As a result, Mexico introduced a booster dose of an acellular pertussis pentavalent vaccine (DTaP/Hib/IPV) in 2007 (97).

Strain replacement: Hia in Central and South America. Hia infections have also been recorded in several Caribbean and South American countries, including Colombia, Venezuela, Argentina, and Cuba, with most reports coming from Brazil (80). Routine Hib immunization was introduced in Brazil in 1999. The incidence rates of Hia meningitis increased 8-fold, from 0.02/100,000 person-years in 1996 to 0.16 cases/100,000 person-years in 2000 (98). In Paraguay, invasive Hib infections in children <5 years of age declined following the introduction of Hib vaccine but was associated with an increase in invasive NTHi infections in older children and adults (99).

European Region

Almost all nations in the WHO European Region have included Hib vaccine in their recommended NIPs. In the Russian Federation, Hib vaccines are recommended for certain risk groups but are not yet included in the NIP. In 2019, the average coverage of three doses of Hib vaccine in the WHO European Region was 85% (100). It was estimated that the incidence of all invasive Hib infections in the WHO European Region in 2000 was 304/100,000 (UR, 274 to 491) in children aged <5 years (31). By 2015, the estimated incidence had declined to 41/100,000 (UR, 37 to 67) in children aged <5 years (56). These two studies only reported data on invasive Hib infections and did not analyze data on infections due to NTHi or other serotypes.

The data for individual countries in the European Region are shown in Table 2.

Invasive *H. influenzae* infections in Western Europe. The mean annual incidence of Hib meningitis among children <5 years of age in Europe was 23/100,000 before Hib vaccination was implemented (101). By 2005, all countries in the European Union (EU) and European Economic Area (EEA) had introduced Hib vaccine (Table 2). In 2018, the overall incidence of all invasive *H. influenzae* infections in the EU/EEA had declined to 0.8/100,000 population, with the highest incidence in infants <1 year of age (4.0/100,000) and adults >65 years of age (2.4/100,000) (102). NTHi accounted for 78% of infections overall. The most common serotype was Hif. From 1996 to 2006, surveillance of invasive *H. influenzae* infections in Western Europe was undertaken by the European Union Invasive Bacterial Infection Surveillance (EU-IBIS) network (funded by the European Commission DG SANCO) (9, 103). In 2007, coordination of the network was transferred to the European Centre for Disease Prevention and Control (ECDC) (103). Data from this network collected from 1996 to 2006 (9) and from 2007 to 2014 (10) have been reported separately. Between 1996 and 2006, 14 countries reported 10,081 cases of invasive *H. influenzae* infection, and serotype data were reported for 9,117 (80.5%) of the isolates: 44% were due to NTHi, 28% were Hib, and 7.9% were from other capsulated serotypes. Some isolates were “non-Hib” but were not fully serotyped, and others were not submitted to the reference laboratory. By 2006, national reference laboratories in 14 European countries with an annual denominator population of 150 million persons routinely serotyped all invasive *H. influenzae* isolates (9).

From 2007 to 2014, 12 European countries reported 10,624 cases of invasive *H. influenzae* infection (10). Serotyping data were reported for 8,781 (83%) isolates. A total of 6,853 (78%) were NTHi, 828 (9%) were Hif, 239 (3%) were Hie, and 811 (9%) were

TABLE 2 Implementation of Hib vaccine in countries of the WHO European Region^a

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached ≥50%
Albania	2009	Yes	DTwP/Hib/HepB	2, 4, 6 mo	99	2009
Andorra	1999	Yes	DTaP/Hib/HepB/IPV	2, 4, 12 mo	98	1999
Armenia	2009	Yes	DTwP/Hib/HepB DTaP/Hib/HepB/IPV	6, 12, 18 wks 18 mo	92	2011
Austria	1994	Yes	DTaP/Hib/HepB/IPV	2, 4, 11 mo	85	1999
Azerbaijan	2011	Yes	DTwP/Hib/HepB	2, 3, 4 mo	94	2012
Belarus	2018	Yes	DTwP/Hib/HepB Hib	2, 3, 4 mo 1–4 yrs	91	2018
Belgium	1993	Yes	DTaP/Hib/HepB/IPV	8, 12, 16 wks, 15 mo	97	1999
Bosnia and Herzegovina	2008	Yes	DTaP/Hib/IPV	2, 4, 10 mo (3, 4, 18, 24 mo in Republic of Srpska/Brcko District)	62	2005
Bulgaria	2010	Yes	DTaP/Hib/HepB/IPV DTaP/Hib/IPV	2, 3, 4 mo 2, 3, 4, 18 mo	92	2010
Croatia	2002	Yes	DTaP/Hib/HepB/IPV	2, 4, 6, 18 mo	94	2002
Cyprus	2001	Yes	Hib	2, 4, 6, 12–18 mo	92	2003
Czech Republic	2001	Yes	DTaP/Hib/HepB/IPV	3, 5, 11 mo	97	2002
Denmark	1993	Yes	DTaP/Hib/IPV	3, 5, 12 mo	97	1993
Estonia	2005	Yes	DTaP/Hib/HepB/IPV Hib (for children with contraindication for pertussis)	3, 4, 5, 6 mo, 2 yrs 3, 4, 6 mo, 2 yrs	91	2006
Finland	1986	Yes	DTaP/Hib/IPV	3, 5, 12 mo	91	1992
France	1992	Yes	DTaP/Hib/HepB/IPV	2, 4, 11 mo	95	1998
Georgia	2010	Yes	DTaP/Hib/HepB/IPV	2, 3, 4 mo	94	2010
Germany	1990	Yes	DTaP/Hib/HepB/IPV	2, 3, 4, 11–14 mo	92	1991
Greece	2000	Yes	Hib (in various combination vaccines)	2, 4, 6, 15–18 mo	99	1997
Hungary	1999	Yes	DTaP/Hib/IPV	2, 3, 4, 18 mo	99	1999
Iceland	1989	Yes	DTaP/Hib/IPV	3, 5, 12 mo	91	1991
Ireland	1992	Yes	DTaP/Hib/HepB/IPV Hib (plus all high-risk groups)	2, 4, 6 mo 13 mo	94	1997
Israel	1994	Yes	DTaP/Hib/IPV	2, 4, 6, 12 mo	98	1994
Italy	1999	Yes	DTaP/Hib/HepB/IPV	3, 5, 11 mo	95	2000
Kazakhstan	2008	Yes	DTaP/Hib/HepB/IPV DTaP/Hib/IPV	2, 4 mo 3, 18 mo	97	2009
Kyrgyzstan	2009	Yes	DTwP/Hib/HepB	2, 3, 5 mo	94	2010
Latvia	1994	Yes	DTaP/Hib/HepB/IPV DTaP/Hib/IPV (infants who receive monovalent HepB due to HepB risk from mother)	2, 4, 6, 12–15 mo 2, 4, 6 mo	99	1999
Lithuania	2004	Yes	DTaP/Hib/IPV	2, 4, 6, 18 mo	92	2005
Luxembourg	1994	Yes	DTaP/Hib/HepB/IPV DTaP/Hib/IPV	2, 3, 13 mo 4 mo	99	1997
Malta	1996	Yes	DTaP/Hib/HepB/IPV	6–8 wks, 3, 4, 18 mo	97	1997
Monaco	1992	Yes	Hib	2, 4, 11 mo	99	1999
Montenegro	2006	Yes	DTaP/Hib/IPV Hib	9, 17, 23 wks 18 mo	86	2006
Netherlands	1993	Yes	DTaP/Hib/HepB/IPV	2, 3, 4–11 mo	94	1997
North Macedonia	2008	Yes	DTaP/Hib/HepB/IPV DTaP/Hib/IPV	2, 6 mo 3, 5, 18 mo	92	2009
Norway	1992	Yes	DTaP/Hib/HepB/IPV	3, 5, 12 mo	97	1996

(Continued on next page)

TABLE 2 (Continued)

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached $\geq 50\%$
Poland	2007	Yes	DTaP/Hib/IPV (infants who receive HepB monovaccine due to HepB risk from mother)	7–8 wks, 3–4, 5–6, 16–18 mo	95	2007
			Hib	2, 3–4, 5–6, 16–18 mo		
Portugal	2000	Yes	DTaP/Hib/HepB/IPV	2, 6 mo	99	1998
			DTaP/Hib/IPV	18 mo		
Republic of Moldova	2009	Yes	DTwP/Hib/HepB	2, 4, 6 mo	92	2010
Romania	2010	Yes	DTaP/Hib/HepB/IPV	2, 4, 11 mo	86	2011
Russian Federation		NO	DTaP/Hib/HepB/IPV	3, 4.5, 6, 18 mo	Risk groups	
			DTaP/Hib/IPV	3, 4.5, 6, 18 mo		
			Hib	3, 4.5, 6, 18 mo		
San Marino	1996	Yes	DTaP/Hib/HepB/IPV; Hib (risk groups)	3, 5, 11 mo	91	1991
Serbia	2006	Yes	DTaP/Hib/IPV	8, 10, 14 wks, 18 mo	96	2007
Slovakia	2000	Yes	DTaP/Hib/HepB/IPV	2, 4, 10 mo	96	2000
Slovenia	2000	Yes	DTaP/Hib/HepB/IPV; Hib (risk groups)	3, 4, 5, 6, 18 mo	93	2001
Spain	1998	Yes	DTaP/Hib/HepB/IPV	2, 4, 11 mo	94	1998
Sweden	1992	Yes	DTaP/Hib/HepB/IPV	3, 5, 12 mo	97	1991
Switzerland	1990	Yes	DTaP/Hib/HepB/IPV	2, 4, 6, 15–24 mo	95	1998
			DTaP/Hib/IPV	2, 4, 6, 15–24 mo		
			Hib	2, 4, 6, 15–24 mo		
Tajikistan	2008	Yes	DTwP/Hib/HepB	2, 3, 4 mo	96	2009
Turkey	2006	Yes	DTaP/Hib/IPV	2, 4, 6, 18 mo	98	2007
Turkmenistan	2010	Yes	DTwP/Hib/HepB	2, 3, 4 mo	99	2010
Ukraine	2006	Yes	DTwP/Hib/HepB	2, 4, 12 mo	39	2008, then declined
United Kingdom	1992	Yes	DTaP/Hib/HepB/IPV	8, 12, 16 wks	94	1993
			Hib/MenC	1 yr		
Uzbekistan	2009	Yes	DTwP/Hib/HepB	2, 3, 4 mo	98	2009

^aAnnual birth cohort, 11.1 million. Children aged <5 years, 56.4 million. Seventy-nine percent of target population was immunized with three doses of Hib (Hib3) in 2019 (based on WHO-UNICEF estimates) (100). NIP, national immunization program. Abbreviations of vaccine antigens: D, diphtheria; T, tetanus; aP, acellular pertussis; wP, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B virus surface antigen; IPV, inactivated poliovirus; MenC, meningococcal serogroup C.

Hib. By 2014, the notification rates for invasive Hib in children aged <1 year and 1 to 4 years had declined to 0.65/100,000 and 0.18/100,000, respectively (10). The notification rates for all invasive *H. influenzae* infections gradually increased from 0.27/100,000 in 1999 to 0.56/100,000 in 2014, driven by increases in the incidence of NTHi and to a lesser extent by non-b capsulated serotypes, following the introduction of Hib vaccine. The incidence of invasive *H. influenzae* infections in adults aged ≥ 65 years increased from 0.53/100,000 in 1999 to 1.55/100,000 in 2014. Invasive NTHi infections occurred more frequently in older patients than Hib infections (median age, 58 years versus 5 years [$P < 0.0001$]) and were associated with a higher CFR (12% versus 4% [$P < 0.001$]). Invasive NTHi infections also occur in neonates, where the increased CFR of NTHi compared to that of Hib was especially marked (17% versus 3% [$P < 0.001$]) (104). Non-b serotypes were almost exclusively Hif (72%) and Hie (21%) with an overall CFR of 9%.

The United Kingdom. In 1992, the Hib protein conjugate vaccine was introduced in the United Kingdom, with a 2-, 3-, and 4-month schedule and no booster in the second year of life (105). Simultaneously, a catch-up program offered Hib vaccine to all children aged <4 years. There was a rapid and sustained decline in invasive Hib disease in children <5 years of age from 23.8/100,000 in 1991 to 1992 to 1.8/100,000 in 1993 to 1994. The decline in the vaccinated age group was soon followed by a decline in other age

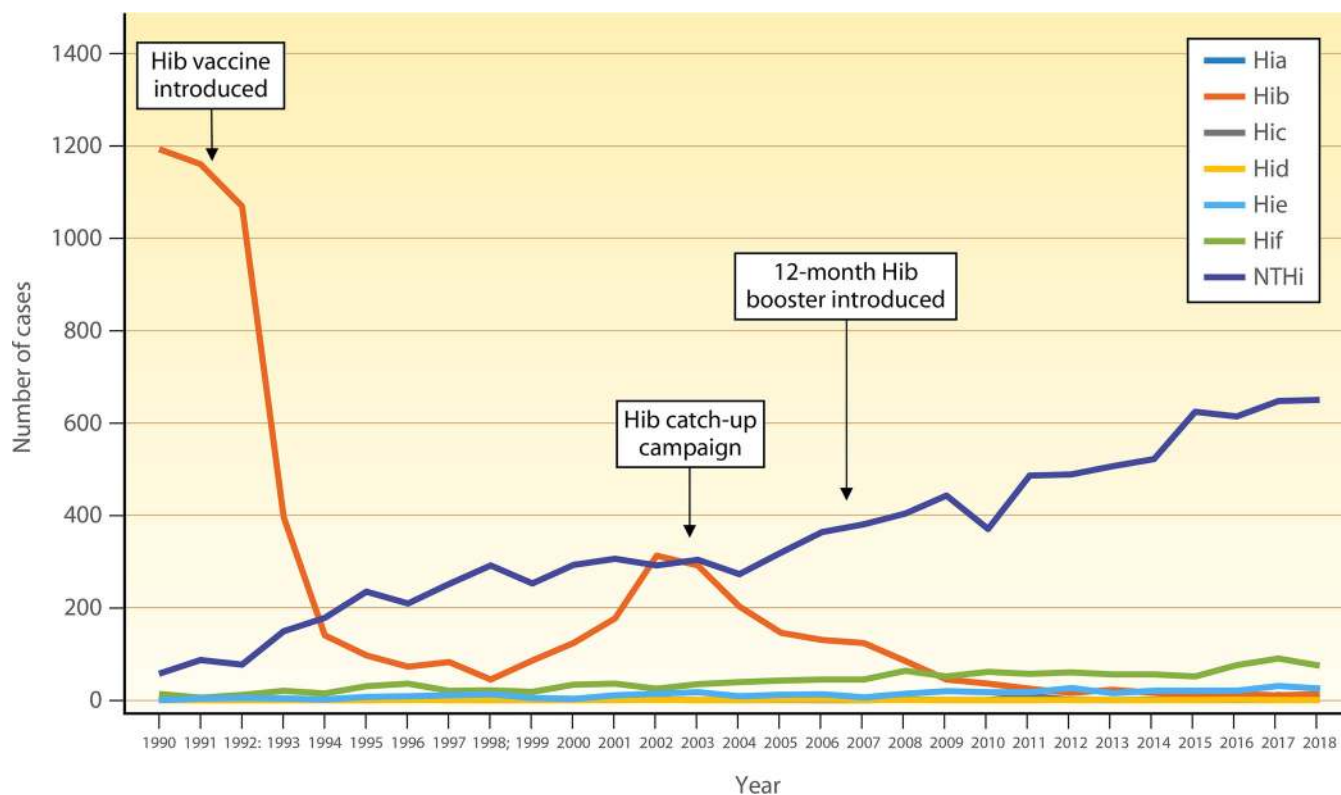


FIG 4 Number of cases of invasive *Haemophilus influenzae* infections in England, 1990 to 2018, by serotype (unpublished data from Public Health England, with permission from Shamez Ladhani).

groups through herd protection (106). This continued until 1998, when the estimated incidence of Hib disease in children aged <5 years was 0.63/100,000 (106). However, after 1999, cases of invasive Hib infection in children increased (107), with 134 cases in children aged <5 years in 2002 compared with 22 cases in 1998 (Fig. 4) (0.63/100,000 in 1998 to 4.60/100,000 in 2002) (105).

There were several reasons for this resurgence (105). First, immunization in infancy resulted in a lower than expected vaccine effectiveness (VE), which was also lower than the VE in children who had been given one dose of Hib vaccine at an older age in the catch-up program. The VE in those immunized in infancy declined over time, reaching zero after 1 year. This became apparent only after the direct and indirect protection provided by the catch-up program had waned. By 1998, all children aged <5 years had only received Hib vaccine in infancy. Next, a shortage of the combination vaccine used in the United Kingdom at that time, which had a whole-cell pertussis component (DTwP/Hib) resulted in utilization of an alternative combination vaccine containing an acellular component (DTaP/Hib). This vaccine was given to approximately 50% of infants (108). The Hib component of some DTaP/Hib vaccines can be less immunogenic, particularly when administered in an early, accelerated schedule, as was the case in the United Kingdom (109). A third possible reason was the introduction of meningococcal group C protein conjugate vaccine (MenC) in 1999, which was coadministered with the Hib vaccine. The MenC vaccine used was mainly CRM based, and there is evidence that the MenC/CRM vaccine given with DTaP/Hib also reduces the immunogenicity of the Hib component (110).

Control of the resurgence was achieved by providing a single dose of Hib vaccine to all children aged 6 months to 4 years in 2003. In 2004, a booster dose at 12 months of Hib vaccine was added to the NIP. This resulted in a prompt decline in incidence of Hib infections (4.60/100,000 in 2002 to 1.1/100,000 in children aged <5 years in 2004) (111). In 2007, there was a second campaign administering a preschool booster to

children who were too old for the 12-month booster but too young for the campaign in 2003. These actions led to a further decline in Hib disease, with only six cases reported in the United Kingdom for the period 2007 to 2010 (105). The United Kingdom experience indicated that protective levels of serum anti-PRP antibodies at the time of nasopharyngeal acquisition of Hib are necessary to prevent infection and that immunologic memory alone will not prevent colonization. By giving a booster dose of vaccine in the second year of life, serum anti-PRP antibody titers are maintained above the protective threshold in children <5 years of age.

In contrast, between 2001 and 2010, there were annual increases in England and Wales of 11.0% and 7.4% in Hif and Hie infections, respectively. Hif incidence was 0.09 (95% CI, 0.07 to 1.10)/100,000 persons, and Hie incidence was 0.03 (95% CI, 0.02 to 0.04)/100,000 persons in 2009 to 2010, with the majority of cases occurring in infants and older adults (59). There were 1,275 invasive *H. influenzae* infections reported in 2009 to 2010, comprising 715 (56.1%) NTHi, 99 (7.8%) Hif, 69 (5.4%) Hib, and 33 (2.6%) Hie cases. In the remaining 359 (28.2%) cases, the serotype was unknown.

Of the 132 cases of Hif and Hie infection, 25 (18.9%) were in children aged <15 years (59). Ten of these 25 cases (7 Hif, 3 Hie) were in previously healthy infants aged <1 year, nine of whom had meningitis and the one remaining infant had Hif septic arthritis. Of the three infant cases of Hie meningitis, one died and the two survivors had long-term sequelae. All seven infants with Hif infection survived without sequelae. At the other end of the age spectrum, approximately half of the cases (52 Hif, 14 Hie) occurred in adults of ≥ 65 years of age. In contrast to the infants, 50/52 (96.2%) adults aged ≥ 65 years with Hif infections had underlying comorbidities (including 11 with cancer), and their most frequent presentation was pneumonia (35/50 [70%]), followed by sepsis (9/50 [18%]). The CFR in these patients was 54% (27/50). Similarly, 13/14 (93.9%) patients aged ≥ 65 years with Hie infections had comorbidities, and again pneumonia (10/14 [71.4%]) was the most common presentation. There were no cases of Hie or Hif meningitis in adults ≥ 65 years of age. Eight of the 14 Hie patients aged ≥ 65 years (57.1%) died. Hie and Hif invasive infections are comparable to invasive NTHi infections by generally presenting as pneumonia in older adults with underlying comorbidities. However, Hie causes more cases of meningitis and has a higher CFR than Hif.

From 2012 to 2016, a low incidence of invasive Hib disease in all age groups was reported in England (0.05/100,000 population), with just 67 cases of Hib reported (112). In contrast, during this period, there were 2,451 cases of NTHi (85.0%), 274 (9.5%) of Hif, and 85 (2.9%) of Hie invasive disease. There were only four cases of Hia and just two cases of *H. influenzae* serotype d (Hid). Indeed, the incidence of NTHi increased 10-fold, from 0.12/100,000 in 2012 to 1.2/100,000 in 2016. Hia caused only five invasive infections in England from 2008 to 2015 but caused 10 infections in the 12 months between December 2016 and December 2017 (113). More recent data (2017 to 2018) from England (114) reported that 76.7% of all invasive *H. influenzae* infections were due to NTHi, and Hif was the most prevalent capsulated serotype (8.3%). Other capsulated serotypes caused 2.7% (Hie), 1.2% (Hib), and 0.8% (Hia) of the invasive *H. influenzae* infections.

Rest of Western Europe. In a detailed analysis of 4,044 invasive *H. influenzae* infections in Germany, in 2001 to 2016, NTHi caused 1,545/1,902 (81%) infections (115). Among the capsulated strains, 69% were Hif and 17% were Hib. Moreover, NTHi and Hif infections in those aged <5 years and ≥ 60 years, respectively, and ampicillin resistance in NTHi increased significantly after the introduction of Hib vaccine. Data for 2017 to 2018 (116) reported that 84.5% of invasive infections were due to NTHi. Hif was the most prevalent capsulated serotype (9.8%), followed by Hib and Hie (2.4% each) and Hia (0.5%).

From 2016 to 2018, there were 231 cases of invasive *H. influenzae* infection in Finland (117), with an annual incidence of 1.3 to 1.6/100,000 population. Most of the cases were caused by NTHi (79.2%), followed by Hif (12.6%), Hib (3.5%), and Hie (3.0%).

All Hie infections, 86% of Hif infections, and 63% of Hib infections occurred in adults aged 27 to 79 years of age.

In Italy, the annual incidence of invasive *H. influenzae* disease in 2017 to 2018 was 0.28/100,000 population, with an incidence of 0.77/100,000 in children aged <5 years (118). Most of the cases were due to NTHi (76.1%), with 11.5% and 4.6% caused by Hib and Hif, respectively.

In a Swedish Arctic region, between 1986 to 1991 and 2010 to 2015, invasive *H. influenzae* infections declined by 89.1% ($P < 0.01$) from 41/100,000 to 1.1/100,000, respectively, including *H. influenzae* meningitis by 95.3% ($P < 0.01$; 28 to 1.1/100,000) and “all-cause” bacterial meningitis by 82.3% ($P < 0.01$; 37 to 3.4/100,000) in children aged 0 to 4 years following the introduction in 1992 of infant Hib vaccination (119).

In Portugal, 260 invasive *H. influenzae* isolates received from 2011 to 2018 were characterized (120): NTHi, 206 (79.2%); Hib, 35 (13.5%); Hif, 8 (3.1%); Hia, 7 (2.7%); and Hie, 4 (1.5%). The NTHi strains were isolated mainly from adults (161/260 [78.2%]), especially among those ≥ 65 years of age (103/161 [64.0%]), whereas 56.3% of *H. influenzae* infections in children were due to NTHi. Most of the capsulated strains causing infection were from preschool-aged children (35/54 [64.8%]): 25 Hib, 7 Hia, 2 Hif, and 1 Hie. Six cases of Hib infection were in infants too young to have received the Hib vaccine, 15 were aged 10 months to 5 years, and 4 were older (6 to 16 years). All seven cases of Hia infection occurred in children aged <2 years and were isolated from 2016 onwards.

Persistence of Hib infections and Hib vaccine failures. Bajanca-Lavado et al. (121) reported on 29 cases of Hib infection identified in Portugal between 2010 and 2018. Half of the cases occurred in 2017 to 2018, and 72% were in preschool-aged children. Eighteen were Hib vaccine failures: three were infants, seven were aged between 13 and 47 months, and eight were ≥ 4 years of age. Only one child had an underlying comorbidity.

In France, a country with high Hib vaccine coverage (95% to 98% over the last decade) (122), the number of invasive Hib cases almost doubled in 2018 from <10 per year in previous years (123). Most cases were in children aged <5 years, and there were at least 10 vaccine failures. After a change in the Hib immunization program from 3 + 1 to 2 + 1 doses in 2013, mean anti-PRP IgG titers were lower and peaked at 6 to 11 months rather than at 2 years of age, as seen with a 3 + 1 schedule. Antibody titers also declined to <1 $\mu\text{g/ml}$ at a much younger age (4 to 5 years versus 20 years).

Eastern Europe and Central Asia. Data on invasive Hib disease incidence in Eastern Europe and Central Asia are limited. The data that exist suggest that the prevaccine incidence was low. For example, Hib meningitis incidence in children aged <5 years in Bulgaria and Moscow was 6.7/100,000 (124) and 5.7/100,000, respectively (125). One factor contributing to low incidence figures is the high proportion of culture-negative cases of purulent meningitis, possibly reflecting prior antimicrobial therapy or limited laboratory capacity. One approach, advocated by the WHO, is to allocate culture-negative cases to bacterial pathogens in the same proportions as microbiologically confirmed cases (52). Using this approach, Griffiths and colleagues (126) adjusted the incidence of Hib meningitis prior to introducing Hib conjugate vaccine in Belarus and Uzbekistan upwards to 10.8/100,000 and 18.7/100,000, respectively. In 2006, Ukraine was the first country in Eastern Europe to incorporate Hib protein conjugate vaccine into its infant NIP. Between 2007 and 2009, hospitalized children <2 years of age in Ukraine with radiographically confirmed pneumonia were significantly less likely to have been immunized with Hib vaccine than age-matched controls (51% of cases versus 67% of controls [$P < 0.001$]) (127). A retrospective study in a tertiary hospital in Budapest, Hungary, undertaken between 2004 and 2017 identified 34 adult invasive *H. influenzae* infections (128). Most cases presented as pneumonia (62%) due to NTHi (79%), followed by Hif (11%), Hia (5%), and Hib (5%). One-third of patients were aged ≥ 65 years with underlying comorbidities, including cardiovascular disease, diabetes mellitus, and malignancy.

TABLE 3 Implementation of Hib vaccine in countries of the WHO Eastern Mediterranean Region^a

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached ≥50%
Afghanistan	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	66	2009
Bahrain	1998	Yes	DTaP/Hib/HepB/IPV DTwP/Hib/HepB Hib (for SCD, asplenia, post-BMT, and post-cancer chemotherapy)	2, 4 mo 6, 18 mo <5 yrs	99	1998
Djibouti	2007	Yes	DTwP/Hib/HepB	6, 10, 14 wks	85	2008
Egypt	2014	Yes	DTwP/Hib/HepB Hib	2, 4, 6 mo 2, 4, 6 mo (previous adverse reaction after pertussis vaccination)	95	2014
Islamic Republic of Iran	2014	Yes	DTwP/Hib/HepB Hib	2, 4, 6 mo 2, 4, 6 mo (previous adverse reaction after pertussis vaccination)	99	2015
Iraq	2012	Yes	DTaP/Hib/HepB	2, 4, 6 mo	84	2013
Jordan	2001	Yes	DTaP/Hib/HepB/IPV Hib	3, 4, 5 mo 3, 4, 5 mo	89	2001
Kuwait	1998	Yes	DTwP/Hib/HepB	2, 4, 6, 18 mo	91	1998
Lebanon	2003	Yes	DTwP/Hib/HepB	2, 4, 6, 18 mo	85	2003
Libya	2007	Yes	DTaP/Hib/HepB/IPV DTaP/Hib/IPV	2, 4, 6 mo 18 mo	73	2007
Morocco	2007	Yes	DTwP/Hib/HepB	2, 3, 4 mo	99	2007
Oman	2001	Yes	DTaP/Hib/HepB/IPV DTwP/Hib/HepB; Hib (immunocompromised)	2, 4 mo 6 mo	99	2002
Pakistan	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	75	2009
Qatar	1996	Yes	DTaP/Hib/HepB/IPV DTwP/Hib/HepB	2, 4 mo 6 mo	98	1997
Saudi Arabia	2002	Yes	DTaP/Hib/HepB/IPV	2, 4, 6 mo	96	2002
Somalia	2013	Yes	DTwP/Hib/HepB	6, 10, 14 wks	42	
Sudan	2008	Yes	DTwP/Hib/HepB	6, 10, 14 wks	93	2008
Syrian Arab Republic	2001	Yes	DTwP/Hib/HepB	8, 16, 24 wks, 18 mo	54	2001 (fell to <50% after 2012)
Tunisia	2011	Yes	DTwP/Hib/HepB	2, 3, 6 mo	92	2012
United Arab Emirates	1999	Yes	DTaP/Hib/HepB/IPV DTwP/Hib/HepB DTaP/Hib/IPV; Hib (high-risk groups)	2, 4 mo 6 mo 18 mo	99	1999
Yemen	2005	Yes	DTwP/Hib/HepB	6, 10, 14 wks	73	2006

^aAnnual birth cohort, 17.3 million. Children aged <5 years, 85.3 million. Eighty-two percent of target population was immunized with three doses of Hib (Hib3) in 2019 (based on WHO-UNICEF estimates) (129). Abbreviations of vaccine antigens: D, diphtheria; T, tetanus; aP, acellular pertussis; wP, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B virus surface antigen; IPV, inactivated poliovirus. NIP, national immunization program; SCD, sickle cell disease; BMT, bone marrow transplant.

Eastern Mediterranean Region

All countries in the WHO Eastern Mediterranean Region have introduced Hib vaccine. In 2019, the average coverage of three doses of Hib vaccine was 82% (129). Data on individual countries are shown in Table 3. Reports on invasive Hib disease before Hib vaccination was initiated are limited to a few countries (130). Pre-vaccine data from Egypt showed that Hib was the most common cause of meningitis (39%) in children <6 years of age with a CFR of 27% (131). In Jordan, 32% of cases of bacterial meningitis in children aged 2 months to 12 years were due to *H. influenzae*, with 95% of Hib meningitis occurring in children <2 years of age (132). In Qatar, a pre-vaccine study

recorded the incidence of bacterial meningitis as 2.24/100,000, with the highest rate observed in infants aged <1 year and where Hib accounted for 24% of cases (133). In Pakistan, a prospective study of bacterial meningitis in children conducted in 2004, before Hib vaccines were introduced (134), estimated incidences of Hib meningitis of 7.6/100,000 in children <5 years of age and 38.1/100,000 in children aged <1 year. In Saudi Arabia, Hib meningitis incidence was 16.9/100,000 in those aged <5 years but with marked regional variation (135). Pre- and postvaccine introduction incidence data are available in this region only from Oman. Before Hib vaccines were introduced in Oman, their highest incidence of Hib meningitis was in infants aged <1 year (23/100,000 in 1999). After Hib immunization was introduced in 2001, the incidence declined to 4/100,000 by 2003 (130). All countries in this region have now introduced Hib vaccines, with Bahrain being the first country, in 1998, and Egypt and Iran the last, in 2014.

Currently, there are few data on the emergence of NTHi or non-b serotypes of *H. influenzae* causing invasive disease in this region.

African Region

Hib conjugate vaccines have been introduced into the NIPs of all 47 member states in the WHO African Region, and the average coverage of three doses of Hib vaccine was 73%, with wide variation between countries (136). Data on individual countries are shown in Table 4. The Gambia introduced the Hib protein conjugate vaccine in 1997, being the first African country to do so. Several other African countries followed suit, although 15 years elapsed before all countries in the region had introduced the vaccine. An important study in The Gambia established Hib as a significant cause of pediatric pneumonia, something that had not been appreciated previously (28). This trial showed vaccine efficacy of 21% against radiographic pneumonia, 36% efficacy against hypoxic pneumonia, and 95% efficacy against invasive Hib disease. Before The Gambia introduced routine Hib vaccination, Hib meningitis incidence was 297/100,000 in infants <1 year of age and 60/100,000 in children aged <5 years (137).

The GAVI Alliance and the Hib Initiative have been major players in providing subsidized vaccines for low-income countries in Africa. All studies from African countries indicate that with the sole exception of South Africa, Hib vaccination has led to a >90% decline in Hib meningitis or invasive disease. However, in South Africa, 5 years after vaccine introduction, Hib disease rates were only reduced approximately 65% in the <1-year age group (11), and a decade after Hib vaccination was implemented, cases were reported to have increased from 0.7 to 1.3/100,000 in children aged <5 years (138). To some extent, the increase was due to low vaccine coverage and waning immunity of a 3-dose primary schedule without a booster, with Hib vaccine failure occurring in both HIV-positive and -negative children. South Africa introduced enhanced surveillance of invasive *H. influenzae* infections in 1999 following the introduction of Hib vaccination (138). During the first 10 years of Hib immunization, there was no significant increase in other capsulated serotypes or NTHi (138). From 2003 to 2009, 135/263 (51%) cases of invasive Hib disease occurred in fully immunized children and 55% of the Hib vaccine failures were in children aged ≥ 18 months (138). South Africa introduced an 18-month booster dose of Hib vaccine in 2009 in a pentavalent vaccine (DTaP/Hib/IPV). Invasive Hib disease in infants aged <1 year then declined significantly from 5.2 cases/100,000 in 2010 to 1.6 cases/100,000 in 2017 ($P < 0.001$) and remained <0.2/100,000 in children aged 1 to 4 years from 2013 to 2018 (139).

In 2018, the ongoing surveillance program in South Africa (GERMS) identified 327 cases of invasive *H. influenzae* infection, of which 201 provided isolates for typing (139). Seventeen percent (34/201) were Hib, and 64% (129/201) were NTHi. There were 25 isolates (12%) of other capsulated serotypes. Hib isolates were more likely than NTHi isolates to be from cases of meningitis (8/34 [24%] versus 15/129 [12%], $P = 0.01$). The highest incidence of invasive *H. influenzae* infection (all types) was in children aged <5 years, with a second peak in adults aged 25 to 44 years. NTHi incidence was

TABLE 4 Implementation of Hib vaccine in countries of the WHO African Region^a

Country	Yr of Introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached ≥50%
Algeria	2008	Yes	DTaP/HepB/Hib/IPV	2, 4, 12 mo	91	2008
Angola	2006	Yes	DTwP/HepB/Hib	2, 4, 6 mo	53	2010
Benin	2005	Yes	DTwP/HepB/Hib	6, 10, 14 wks	76	2006
Botswana	2011	Yes	DTwP/HepB/Hib	2, 3, 4 mo	95	2011
Burkina Faso	2006	Yes	DTwP/HepB/Hib	8, 12, 16 wks	91	2006
Burundi	2004	Yes	DTwP/HepB/Hib	6, 10, 14 wks	93	2004
Cameroon	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	67	2009
Cabo Verde	2010	Yes	DTwP/HepB/Hib	2, 4, 6, 18 mo	97	2011
The Central African Republic	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	47	
Chad	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	50	
Comoros	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	91	2009
The Congo	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	79	2009
Côte d'Ivoire	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	84	2009
The Democratic Republic of the Congo	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	57	2009
Equatorial Guinea	2013	Yes	DTwP/HepB/Hib	6, 10, 14 wks	53	2016
Eritrea	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	95	2008
Ethiopia	2007	Yes	DTwP/HepB/Hib	6, 10, 14 wks	68	2008
Gabon	2010	Yes	DTwP/HepB/Hib	6, 10, 14 wks	70	2010
The Gambia	1997	Yes	DTwP/HepB/Hib	2, 3, 4 mo	88	1998
Ghana	2002	Yes	DTwP/HepB/Hib	6, 10, 14 wks	97	2002
Guinea	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	45	2009 (<50% in 2014)
Guinea-Bissau	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	84	2009
Kenya	2001	Yes	DTwP/HepB/Hib	6, 10, 14 wks	92	2002
Lesotho	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	87	2009
Liberia	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	74	2008
Madagascar	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	79	2008
Malawi	2002	Yes	DTwP/HepB/Hib	6, 10, 14 wks	95	2002
Mali	2007	Yes	DTwP/HepB/Hib	6, 10, 14 wks	77	2008
Mauritania	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	81	2009
Mauritius	2006	Yes	DTaP/HepB/Hib/IPV	6, 10, 14 wks, 18 mo	97	2006
Mozambique	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	88	2009
Namibia	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	87	2010
Niger	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	81	2009
Nigeria	2012	Yes	DTwP/HepB/Hib	6, 10, 14 wks	57	2016
Rwanda	2002	Yes	DTwP/HepB/Hib	6, 10, 14 wks	98	2002
Sao Tome and Principe	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	95	2010
Senegal	2005	Yes	DTwP/HepB/Hib	6, 10, 14 wks	93	2006
Seychelles	2010	Yes	DTwP/HepB/Hib	3, 4, 5 mo	99	2010
Sierra Leone	2007	Yes	DTwP/HepB/Hib	6, 10, 14 wks	95	2007
South Africa	1999	Yes	DTaP/HepB/Hib/IPV	6, 10, 14 wks, 18 mo	77	2000
South Sudan	2014	Yes	DTwP/HepB/Hib	6, 10, 14 wks	49	
Eswatini (Swaziland)	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	90	2009
Togo	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	84	2009
Uganda	2002	Yes	DTwP/HepB/Hib	6, 10, 14 wks	93	2004
The United Republic of Tanzania	2009	Yes	DTwP/HepB/Hib	6, 10, 14 wks	89	2009
Zambia	2004	Yes	DTwP/HepB/Hib	6, 10, 14 wks	88	2004
Zimbabwe	2008	Yes	DTwP/HepB/Hib	6, 10, 14 wks	90	2008

^aAnnual birth cohort, 35.7 million. Children aged <5 years, 170.2 million. Seventy-three percent of target population was immunized with three doses of Hib (Hib3) in 2019 (based on WHO-UNICEF estimates) (136). NIP, national immunization program. Abbreviations of vaccine antigens: D, diphtheria; T, tetanus; aP, acellular pertussis; wP, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B virus surface antigen; IPV, inactivated poliovirus.

highest in infants, with a second peak in adults aged >65 years (2.9/100,000 and 0.3/100,000, respectively) (Fig. 5).

In contrast to South Africa, long-term surveillance in Kenya has demonstrated the effectiveness of a 3-dose primary schedule of Hib vaccine and no booster dose in the

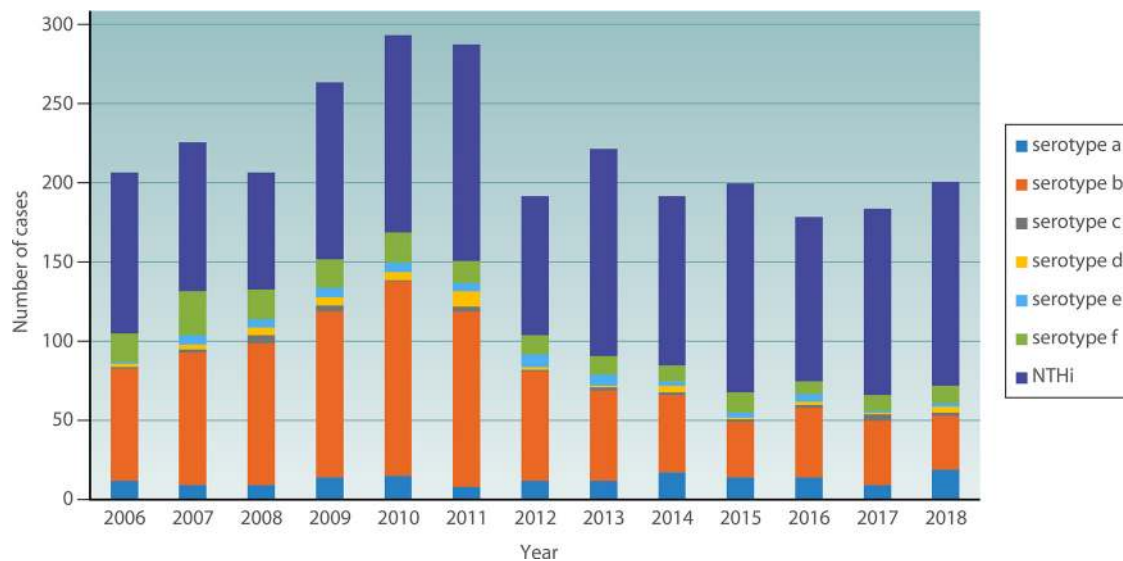


FIG 5 Number of cases of invasive *Haemophilus influenzae* infection, by serotype, reported to National Institute of Communicable Diseases (NICD), South Africa, 2006 to 2018 (from GERMS-SA Annual Reports, 2006 to 2018, with permission from Anne von Gottberg, NICD, Johannesburg, South Africa) (139, 227–237).

second year of life (140, 141). In Kenya, there has not been an increase in invasive infections by other serotypes or NTHi (140). The reasons why a booster dose is necessary to achieve control in some settings but not in others remain unclear (see discussion below).

The Gambia also uses a 3-dose primary series of Hib immunization without a booster dose. This resulted in excellent control of invasive Hib disease for 14 years after the vaccine was introduced, with consistently high coverage, low carriage rates, and high levels of protective antibodies (142). In order to measure the impact of pneumococcal conjugate vaccine introduction, surveillance for meningitis, sepsis, and pneumonia was established in Eastern Gambia (in Basse in 2008 and in Fuladu West in 2011). This surveillance identified increased Hib infections in Eastern Gambia between 2011 and 2013, despite high vaccine coverage. In 2013, the annual incidences of invasive Hib disease in this region were 90/100,000 in infants aged <1 year and 26/100,000 in children <5 years of age (143). The primary reasons for Hib infection were vaccine failure (39%) and onset of infection in infants before receipt of two doses of Hib vaccine (39%). At least two doses of Hib vaccine are required for high vaccine effectiveness ($\geq 85\%$) (144). HIV infection did not appear to be a factor (143). The surveillance in Eastern Gambia identified 57 cases of invasive *H. influenzae* infection: 24 (42%) Hib, 17 (30%) NTHi, 10 (18%) Hia, 2 Hic, Hid, Hie, or Hif, 2 isolates that failed to grow on subculture, and 2 isolates that could not be retrieved. Fourteen of the Hib infections (58%) were cases of meningitis, whereas NTHi presented principally as bacteremic pneumonia (12/17 [71%]). The CFRs were 17% (4/24) for Hib and 21% (5/17) for NTHi (143). It is also noteworthy that molecular studies of lung aspirate specimens collected in The Gambia more than 10 years after the introduction of Hib vaccines indicate that *H. influenzae* (mostly NTHi) may still cause up to 23% of cases of radiographic pneumonia. In this study, there was sufficient DNA for full multilocus sequence typing in 4/12 samples, with 3 samples yielding NTHi, whereas 1 sample in a child with HIV contained Hib (145).

Data on pediatric bacterial meningitis have been generated in 26 Sub-Saharan African countries by the WHO's Invasive Bacterial Vaccine-Preventable Diseases Surveillance Network (IB-VPD) (146–154). During 2011 to 2016, 1,670/49,844 (3.3%) meningitis cases in children aged <5 years were laboratory confirmed, of which *H. influenzae* (232/1,670 [13.9%]) was the least common organism identified (146). While most were Hib infections,

cases of Hia, Hic, Hie, and NTHi were also reported. Interestingly, Boni-Cisse et al. noted that NTHi had become a significant cause of meningitis in Côte d'Ivoire (154).

Several West African countries participating in the IB-VPD network reported bacterial meningitis cases in children aged <5 years in the years 2010 to 2016. In Lomé, Togo, there were 23 cases of *H. influenzae* meningitis, and 20 of the isolates were available for serotyping. There were 9 cases of Hib meningitis, with the number declining by year, with only 1 case in 2015, while 2/2 cases of Hic occurred in 2012 and 5/7 cases of Hie were in 2015 (151). In Nigeria, 19/153 (12%) pediatric bacterial meningitis cases were due to *H. influenzae* (150). Serotyping was performed on 16/19, with Hib being the predominant serotype (11/16, 69%). In contrast to the findings in Togo, the number of Hib isolates increased from one in 2012, two in 2013, to eight in 2016. Hia and Hic caused three and two infections, respectively, in 2015 (150). In Senegal, *H. influenzae* was responsible for 10/115 (9%) of cases, with serotyping data available for five cases. Hib was the causative serotype in 4/5 (2 in 2014 and 2 in 2016). There was also one case of Hic (148). In The Gambia, *H. influenzae* was responsible for 11/69 cases of meningitis (15.9%), with Hib causing 6/11 (54%) cases (149). In Ghana, 5/73 (6.8%) microbiologically confirmed cases of bacterial meningitis were caused by *H. influenzae*: 1 Hib, 1 Hic, 2 Hie, and 1 NTHi (152). It is of note that although Hib vaccine was introduced in The Gambia and Senegal in 1997 and 2005, respectively, Hib continues to cause pediatric bacterial meningitis, albeit at a low rate. Although the number of cases is small, the identification of Hia, Hic, and Hie as causative agents of pediatric bacterial meningitis underlines the importance of continuing surveillance and serotyping of isolates.

In Sub-Saharan Africa, in countries with a high prevalence of SCD and low rates of Hib vaccine coverage, invasive Hib infections remain one of the most frequent causes of bacteremia in children with SCD (155). Improving uptake of Hib vaccine should result in a significant decline in invasive Hib infections in these children. However, SCD children will remain at potential risk of bacteremia from non-type b strains.

Apart from South Africa and The Gambia, countries in Sub-Saharan Africa using schedules of three primary doses of Hib vaccine and no booster dose have not seen a resurgence of invasive Hib infection. A lack of robust surveillance in many countries may mask potential limitations of the vaccine's impact in populations with high HIV prevalence or limited vaccine coverage. To fully appreciate the ongoing burden of Hib meningitis in Africa, surveillance using molecular methods is needed. The difficulty of making an etiologic diagnosis of pneumonia may also mask the role of NTHi and Hib as ongoing causes of pneumonia with consolidation. There are only limited data on other *H. influenzae* serotypes or NTHi. With respect to Hib disease, the primary challenges for NIPs in Sub-Saharan Africa are optimizing the timeliness of the primary series of doses and increasing coverage in displaced or migrating subpopulations.

South East Asia Region

Hib immunization was introduced throughout the WHO South East Asia Region after 2009. An exception was Thailand, where although Hib vaccine had been added to the NIP in 2019 as a 3-dose primary course without a booster dose, the vaccine had been available in the private market since the late 1990s. In 2019, the average coverage of three doses of Hib vaccine in the South East Asian Region was 89%, although rates between countries are highly variable (156). Data for individual countries in the region are shown in Table 5. Data on the incidence of invasive disease and pneumonia across the region are limited. In 1998, Miller (157) estimated that there were 135,000 deaths annually due to Hib and 92% of these occurred in three countries in this WHO region: India, Bangladesh, and Indonesia. In India, most deaths were from meningitis and pneumonia (158), although the incidence of severe Hib pneumonia is most likely to have been substantially underestimated (159). This is probably true for other countries in the region. The reported incidence rates for Hib meningitis vary widely from an estimate of 9.5/100,000 in Thailand (160) to 75 to 100/100,000 in children aged <5 years in India (161), and there are no reliable data for the incidence of pneumonia and bacteremia or sepsis. However, it is likely that the true incidence of meningitis

TABLE 5 Implementation of Hib vaccine in countries of the WHO South East Asia Region^a

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached ≥50%
Bangladesh	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	98	2009
Bhutan	2011	Yes	DTwP/Hib/HepB	6, 10, 14 wks	97	2012
Democratic People's Republic of Korea	2012	Yes	DTwP/Hib/HepB	6, 10, 14 wks	97	2013
India	2015	Yes	DTwP/Hib/HepB	6, 10, 14 wks	89	2016
Indonesia	2014	Yes	DTwP/Hib/HepB	2, 3, 4, 18 mo	79	2015
Maldives	2013	Yes	DTwP/Hib/HepB	2, 4, 6 mo	99	2013
Myanmar	2012	Yes	DTwP/Hib/HepB	2, 4, 6 mo	91	2013
Nepal	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	91	2011
Sri Lanka	2008	Yes	DTwP/Hib/HepB	2, 4, 6 mo	99	2010
Thailand	2019	Yes	DTwP/Hib/HepB	2, 4, 6 mo	ND	ND
Timor-Leste	2012	Yes	DTwP/Hib/HepB	6, 10, 14 wks	83	2013

^aAnnual birth cohort, 33.8 million. Children aged <5 years, 169.7 million. Eighty-nine percent of target population immunized with three doses of Hib (Hib3) in 2019 (based on WHO-UNICEF estimates) (156). NIP, national immunization program; ND, no data. Abbreviations of vaccine antigens: D, diphtheria; T, tetanus; wP, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B virus surface antigen; IPV, inactivated poliovirus.

reported for Thailand may also have been underestimated due to antimicrobial use prior to admission and before blood or cerebrospinal fluid samples for culture were collected (160, 162).

In India, with the largest population of any country in this region, the decision was made to introduce Hib immunization in 2011, but by 2015, only 8 of 29 Indian states had initiated Hib immunization in the public sector. Therefore, given the recent introduction of the vaccine, the earlier availability of the vaccine through the private sector, the widespread use of antibiotics, and the lack of access to reliable diagnostic laboratories, it is very difficult to determine the impact of Hib immunization on the epidemiology of *H. influenzae* disease in this region. A study modeling the national, regional, and state-level burden of Hib infections in children throughout India from 2000 to 2015 (163) estimated that Hib deaths in children aged <5 years fell from 82,600 (UR, 52,300 to 112,000) to 15,600 (UR, 9,800 to 21,500), representing an 81% decline in death rates. The mortality rate varied between states, with Uttar Pradesh (9,300 [UR 5,900 to 12,700]) and Odisha (1,100 [UR, 700 to 1,500]) reporting the highest number of deaths in 2015. It is of note that Hib mortality had declined before nationwide implementation of Hib conjugate vaccine, reflecting child survival trends in India (164) as a result of improved maternal and child health provision throughout the country. Introduction of Hib vaccine in several states corresponded with a more rapid reduction in morbidity and mortality associated with Hib infection (163). The recent establishment of hospital-based sentinel surveillance for invasive bacterial diseases in India (HBSSPIBD) (165) will be of great benefit in determining the local impact of Hib and pneumococcal conjugate vaccine immunization programs.

Generally, there are few data on the impact of introducing Hib vaccines on invasive *H. influenzae* disease in the WHO South East Asian Region. Two sentinel studies have demonstrated that the burden of invasive Hib disease should be reduced after Hib vaccine has been used in NIPs for many years. The first, a large vaccine probe trial conducted in Lombok, Indonesia, reported a significant reduction in Hib meningitis incidence, but it did not prevent pneumonia in children <5 years of age (29). This study also revealed that contrary to the previously widely held belief, the incidence of Hib disease was high in the region and potentially the incidence of vaccine-preventable clinical meningitis was as much as 158/100,000, while vaccine-preventable pneumonia was 1,467/100,000 (29). The second was a case-control study in children aged <2 years from Bangladesh, where preventable fractions of radiographically confirmed pneumonia and Hib meningitis were 17% (95% CI, 10% to 38%) and 89% (95% CI, 28% to 100%), respectively, when community controls were used and 35% (95% CI, 13% to

52%) and 93% (95% CI, 53% to 100%), respectively, when controls were recruited from hospitals (166). To date, there are no published data on the impact of Hib immunization on bacteremic pneumonia in this region.

Given the relative lack of data, it is important that surveillance networks are established not only to monitor the impact of vaccination on Hib disease but also to monitor the effect on *H. influenzae* epidemiology, given the resurgence of disease by non-type b strains seen elsewhere in Europe, North America, and Australia.

Western Pacific Region

According to the WHO, the Western Pacific Region has an annual birth cohort of almost 24 million, with 121 million children aged <5 years. Both Australia and New Zealand incorporated Hib vaccine in their NIPs in 1993 and 1994, respectively. However, other countries within the region have included Hib vaccines in their NIPs only within the last 10 to 15 years. The notable exception is China, which so far has not adopted Hib vaccines for its 17 million infants born annually. In China, Hib vaccines are available in the private market, with only approximately 55% coverage for the full immunization schedule (167). Consequently, despite 19/26 countries reporting $\geq 90\%$ completion rates of the third Hib vaccine dose during infancy, in 2019 just 24% of infants in this WHO region received three primary doses of Hib vaccine by 1 year of age (168).

The data for individual countries in the region are shown in Table 6. In 2015, in the Western Pacific Region, there were an estimated 370,000 cases of invasive Hib disease and 3,800 deaths (56). This compares with estimates of 1.5 million cases and 27,200 deaths in the year 2000 for this region (31). Meanwhile, the proportion of Hib-related deaths in the region attributed to China has almost doubled from 40% in 2000 to 74% in 2015 (56). Data on *H. influenzae* disease incidence in China are limited, although one study estimated that 29% of pediatric pneumonia was due to Hib (169). One study in Hefei City estimated that 30% to 50% of bacterial meningitis was from Hib, with an annual incidence of Hib meningitis of 10.4/100,000 in children aged <5 years (170), whereas the incidence of all invasive Hib infections in Hong Kong was estimated to be 2.7/100,000 (171). In contrast, neighboring Mongolia, which introduced Hib vaccines in 2000, has had a 93% reduction in Hib meningitis cases and no Hib-related deaths since 2012 (6, 56). The annual incidence of Hib meningitis in Mongolia declined from 28/100,000 in children aged <5 years in 2002 to 2005 to 2/100,000 in 2008 to 2010 ($P < 0.0001$) (6).

Following the introduction of Hib vaccine into the Australian NIP in 1993, annual invasive Hib disease rates declined from 40 to 60/100,000 in non-Indigenous children aged <5 years in 1993 to 0.07/100,000 in 2010 and from 580/100,000 in Indigenous children aged <5 years to 1.4/100,000 over the same time period (172). Recent surveys have not found a subsequent increase in replacement disease by encapsulated non-b strains (173, 174). A review of 238 invasive *H. influenzae* cases in South Australia and the Northern Territory between 2001 and 2011 reported an annual incidence rate in the Indigenous population of 9.0/100,000 compared to 0.7/100,000 in non-Indigenous people (173). Indigenous children aged <5 years had the highest rates of invasive *H. influenzae* disease. This included Hia, whose annual incidence of 10.5/100,000 was stable and outranked that of Hib, NTHi, and other non-b serotypes in this age group. Another recent review of 737 invasive cases from the state of Queensland found that the incidence of Hib and encapsulated non-b strains between 2000 and 2013 did not change significantly (174). The highest observed rates for encapsulated types were for Hia and Hib in Indigenous populations. However, across age groups, invasive NTHi infections predominated year-to-year and the incidence increased significantly during the study. The highest annual disease incidence rates for NTHi of 14.8 and 16.5/100,000 were in infants and in those aged >90 years, respectively.

In 2018, the age of administration of the Hib booster dose in Australia was moved from 12 months to 18 months (7). To assess the likely impact of this change, incidence rate ratios (IRR) and vaccine failure trends were calculated using Hib case surveillance

TABLE 6 Implementation of Hib vaccine in countries of the WHO Western Pacific Region^a

Country	Yr of introduction	NIP	Formulation in 2019	Schedule in 2019	Coverage of Hib3 in 2019 (%)	Yr in which coverage reached ≥50%
Australia	1993	Yes	DTaP/Hib/HepB/IPV Hib	2, 4, 6 mo 18 mo	95	1997
Brunei Darussalem	2002	Yes	DTaP/Hib/HepB/IPV Hib	2, 4, 6 mo 1 yr	99	2002
Cambodia	2010	Yes	DTwP/Hib/HepB	6, 10, 14 wks	92	2010
China		No				
Cook Islands	2009	Yes	DTaP/Hib/HepB	6 wks, 3, 5 mo	98	2009
Fiji	1997	Yes	DTwP/Hib/HepB	6, 10, 14 wks	99	1997
Japan	2011	Yes	Hib	2, 3, 4 mo, 1 yr	98	2011
Kiribati	2008	Yes	DTwP/Hib/HepB	6, 10, 14 wks	95	2008
Lao People's Democratic Republic	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	68	2010
Malaysia	2002	Yes	DTaP/Hib/HepB/IPV	2, 3, 5, 18 mo	98	2004
The Marshall Islands	1998	Yes	DTaP/Hib/IPV Hib	2, 4, 12 mo 2, 4, 12 mo	72	2002
Federated States of Micronesia	1996	Yes	Hib	2, 4, 12 mo	64	2000
Mongolia	2005	Yes	DTwP/Hib/HepB	2, 3, 4 mo	99	2006
Nauru	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	96	2009
New Zealand	1994	Yes	DTaP/Hib/HepB/IPV Hib	6 wks, 3, 5 mo 15 mo	91	1997
Niue	1998	Yes	DTaP/Hib/HepB/IPV Hib	6 wks, 3, 5 mo 15 mo	99	2000
Palau	1998	Yes	Hib	2, 4, 6 mo	93	1998
Papua New Guinea	2008	Yes	DTwP/Hib/HepB	1, 2, 3 mo	35	2009
The Philippines	2012	Yes	DTwP/Hib/HepB	6, 10, 14 wks	65	2013
The Republic of Korea	2013	Yes	DTaP/Hib/IPV Hib	2, 4, 6 mo 12–15 mo	98	2014
Samoa	2007	Yes	DTwP/Hib/HepB	6, 10, 14 wks	58	2009
Singapore	2013	Yes	DTaP/Hib/IPV	3, 4, 5, 18 mo	96	2013
Solomon Islands	2008	Yes	DTwP/Hib/HepB	6, 10, 14 wks	94	2008
Tonga	2005	Yes	DTwP/Hib/HepB	6, 10, 14 wks	99	2005
Tuvalu	2009	Yes	DTwP/Hib/HepB	6, 10, 14 wks	92	2009
Vanuatu	2011	Yes	DTwP/Hib/HepB	6, 10, 14 wks	90	2011
Vietnam	2010	Yes	DTwP/Hib/HepB	2, 3, 4 mo	89	2010

^aAnnual birth cohort, 23.2 million. Children aged <5 years, 119.8 million. Twenty-four percent of target population was immunized with three doses of Hib (Hib3) in 2019 (based on WHO-UNICEF estimates) (168). NIP, national immunization program. Abbreviations of vaccine antigens: D, diphtheria; T, tetanus; aP, acellular pertussis; wP, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B virus surface antigen; IPV, inactivated poliovirus.

scheme data from 2000 to 2017, where 153/345 (44%) cases were in children born after 2000, and 51/153 (33%) occurred in Indigenous Australian children. The IRR for Indigenous children was 8.34 (95% CI, 5.83 to 11.79) in comparison with non-Indigenous children with no evidence of a decline over these years. There was also no evidence of an increase in vaccine failures during the study period. Between 2000 and 2017, invasive Hib disease declined by 55%, with a persistent marked disparity between Indigenous and non-Indigenous children (7). These results indicate the need to monitor any potential impact of moving the booster dose to 18 months of age, particularly in Indigenous children.

After Hib vaccine introduction in New Zealand, hospital admissions for Hib meningitis and epiglottitis in children aged <15 years decreased sharply (175). From 1993 to 1995, meningitis rates declined by 82% from 8.63/100,000 in 1993 to 1.58/100,000 in 1995. Epiglottitis rates fell similarly by 87% from 3.67/100,000 in 1993 to 0.48/100,000 in 1995. In the period between 1991 and 2014, annual invasive Hib disease rates in this age group fell to as low as 0.12/100,000. There was a similarly declining trend in Hib bacteremia hospitalization rates (175). Moreover, hospitalization rates for Indigenous Māori and non-Māori children for Hib disease were comparable.

In Japan, Hib vaccine was introduced on a voluntary basis in 2008 and was then incorporated into the NIP in 2013. Active population-based surveillance of culture-proven pediatric invasive *H. influenzae* infections was conducted from 2008 to 2017 in 10 prefectures in Japan (approximately 23% of the total Japanese population) (176). Over the 10 years of the study, 566 cases of invasive *H. influenzae* infection, including 336 meningitis cases, were identified. From 2013 to 2017, invasive *H. influenzae* infections among children <5 years of age declined by 93% (IRR, 0.07; 95% CI, 0.05 to 0.10; $P < 0.001$) compared with cases in 2008 to 2012. The annual incidence of invasive *H. influenzae* disease in children <5 years of age declined from 12.5/100,000 in 2012 to 0.9/100,000 in 2017 (176). However, since 2014, in the post-Hib vaccine era, NTHi and Hif invasive infections have been identified in children <5 years of age. NTHi is now the major cause of invasive *H. influenzae* disease in Japan (177).

WHO IS NOW AT RISK OF INVASIVE Hib DISEASE?

In countries that have established infant NIPs, including Hib protein conjugate vaccine, invasive Hib infections are no longer a major cause of bacterial meningitis in young children, but cases of invasive Hib disease do still occur. Collins and colleagues investigated the epidemiology of all cases of invasive Hib disease in England and Wales from 2009 to 2012 (178). The incidence of invasive Hib disease in children aged <5 years was 0.06/100,000 (two cases) compared with an incidence of 35.5/100,000 prior to routine Hib immunization. All 106 cases of invasive Hib infection that occurred between 2009 and 2012 were followed up. The median age at disease onset was 49.4 years (interquartile range, 16.9 to 67.5). Seventy-three percent of the cases occurred in adults, presenting with pneumonia (56%), many of whom had underlying comorbidities (77%): chronic heart disease ($n = 17$, particularly in those of >65 years of age) and chronic lung disease ($n = 17$, mainly among those of >45 years of age) being the most frequently reported. The Hib-associated mortality was 9.4% (10/106). Data from the United States show a similar pattern (68). Between 2009 and 2015, the ABC surveillance sites identified 77 patients with invasive Hib disease whose median age was 49 years (interquartile range, 4 to 62). Of the 54 adults, 37 (82.2%) presented with bacteremic pneumonia, with underlying comorbidities in 62.9%, including chronic obstructive pulmonary disease (COPD), chronic heart disease, diabetes, and obesity. The shift of invasive Hib disease from young children to adults could be due to the absence of natural boosting from exposure to Hib organisms before Hib vaccines were introduced (179).

There is an increased risk of invasive Hib disease in patients with primary immunodeficiency disorders (e.g., agammaglobulinemia, early complement component deficiencies), those with anatomical or functional asplenia, those with HIV infection, and patients undergoing radiotherapy or chemotherapy for malignancy or post-hematopoietic stem cell transplantation (180). In the United States, a single booster dose of Hib vaccine is recommended for these high-risk groups whenever a primary course has not been completed (180). Hib vaccination is not recommended for HIV-infected adults.

IS A BOOSTER DOSE OF Hib VACCINE NEEDED?

Evidence of waning immunity following the introduction of a primary immunization series, without a booster dose, prompted three countries, the United Kingdom, South Africa, and Mexico, to add a booster dose. Worldwide, 50/83 high-income countries, as defined by the World Bank (181), recommend a booster dose at 11 to 18 months. In contrast, booster doses are used only by 19/56 upper middle-income countries and 5/50 lower middle-income countries. All 29 low-income countries employ a 3-dose primary series of Hib vaccine (at 6, 10, and 14 weeks of age) without a booster dose, as recommended by the WHO Expanded Program on Immunization (EPI) schedule (182) and adopted by the Vaccine Alliance (GAVI) (183) when it began supporting Hib vaccine introduction in the poorest countries globally in 2000. In many countries, Hib vaccine is included in a pentavalent or hexavalent vaccine, and the existing schedule for

diphtheria, tetanus, and pertussis vaccine (DTP) has often been a deciding factor in the timing of Hib vaccination.

A meta-analysis of 20 RCTs, which had been conducted in 15 countries (United States, Canada, Chile, Guatemala, Belgium, Austria, Germany, Greece, France, Sweden, Netherlands, Turkey, The Gambia, Niger, China) compared different Hib vaccination schedules (3 + 0, 3 + 1, and 2 + 1) and different intervals between the primary schedule and the primary and booster dose schedule (184). There was no difference between the schedules in terms of prevention of invasive Hib disease, clinical effectiveness, or immunologic response. The authors concluded that a two-dose primary schedule plus a booster (2 + 1), 3 + 1, and 3 + 0 schedules all protected against Hib infection and that the choice would depend on the local epidemiology. Three doses in the first 6 months of life would be more appropriate when the greatest burden of Hib infection is in the first year of life, as in Sub-Saharan Africa. In countries where the burden of infection occurs at a later age, the third dose could be given in the second year of life. Where there had been a resurgence of infection following the use of a 3 + 0 schedule, as in the United Kingdom, then a fourth dose as a booster in the second year of life may be required. A further meta-analysis of RCTs reported that 3- and 2-dose primary immunization courses of Hib vaccine in infancy showed similar vaccine efficacies (185). A 3-dose primary schedule had a vaccine efficacy of 82% compared to 79% for a 2-dose primary series. A systematic review and meta-analysis of observational data (144) considered the number of doses of vaccine, age at which the vaccination schedule was initiated, the interval between doses, and coadministration with other vaccines in the NIP. The authors concluded that ≥ 2 doses of Hib vaccine are needed to achieve high levels of effectiveness ($>85\%$) and a booster could be beneficial, especially if the primary course was incomplete, but there were insufficient data to clearly show superiority of any particular schedule. A modeling study estimated that a primary series plus a booster dose within 1 year would result in greater reduction in the incidence of Hib disease than a primary series without a booster dose (186). However, this assumed high vaccine coverage of 90 to 100%, which has not yet been achieved in many countries. The model also looked at delaying the booster dose for 2 years after the primary vaccination series and found that this had little impact on direct vaccine-induced protection against invasive Hib disease in children who have received Hib vaccine (186). A study in four South American countries (93) concluded that high Hib vaccine coverage resulted in a sustained low incidence of Hib meningitis and nasopharyngeal carriage of Hib with a three-dose primary series of Hib vaccine with or without a booster dose of vaccine in the second year of life.

Children with HIV may, however, require a booster dose of Hib vaccine. In a systematic review of Hib infection in HIV-infected children (35), the effectiveness of one or more doses of Hib vaccine was 55% (95% CI, 5% to 80%) in HIV-positive children and 91% (95% CI, 79% to 96%) in HIV-negative children.

It is unclear why a booster dose appears to be necessary in some settings but not in others. Among the factors that may be of importance are the type of vaccine used. Almost all countries now use combination vaccines which include Hib and either a whole-cell or acellular pertussis component. Some DTaP/Hib vaccines were reported to be associated with reduced Hib immunogenicity, but the clinical significance of this finding is unclear. Almost all countries currently using a Hib-acellular pertussis combination vaccine do include a booster dose in their schedule, but this may reflect national income rather than issues with the vaccine. Use of DTaP/Hib or DTaP/Hib/IPV does not significantly alter the immunogenicity and antibody functionality of the individual vaccine components (187), and in Germany, the use of DTaP-Hib combination vaccines produced protective levels of anti-PRP antibodies and high VE (188). The protein carrier used for the Hib component does not appear to be a factor. Tetanus toxoid (TT)-conjugated Hib vaccine has been adopted widely by low-income countries, both in those with sustained control, such as Kenya (141), and in others with evidence

of waning immunity, such as The Gambia (143), so this seems to be an unlikely explanation.

It is difficult to determine the long-term impact of a primary immunization series without a booster dose in countries where high-quality population-based surveillance is not in place and sustained high coverage over a prolonged period has not yet been achieved.

The impact of changes to the timing of a booster dose has been reported from France, where a 3 + 1 schedule of Hib vaccine was used from 1992 to 2012, with vaccine given at 2, 3, and 4 months and a booster dose at 16 to 18 months. In 2013, the schedule was changed to a 2 + 1 schedule, with a 2-dose primary course at 2 and 4 months plus a booster dose at 11 months. In 2018, cases of invasive Hib disease increased, with several examples of vaccine failure in children aged <5 years (123). This 2 + 1 schedule was associated with a decline in anti-PRP antibodies to <1 $\mu\text{g/ml}$ by the age of 4 to 5 years. Although these are only preliminary data, it does suggest that a booster dose administered in the second year of life rather than before the first birthday may achieve sustained high levels of anti-PRP antibodies.

INVASIVE NONTYPEABLE *H. INFLUENZAE* DISEASE

Few reports exist describing the epidemiology of non-Hib disease prior to routine Hib immunization. A prospective, enhanced population-based surveillance of all invasive *H. influenzae* infections, conducted in six regions in England and Wales over the 2 years before routine Hib immunization was introduced, indicated that the majority (approximately 90%) were caused by Hib, while approximately 10% were due to nontypeable *H. influenzae* (NTHi) (16). Other serotypes of *H. influenzae* accounted for <1% of invasive infections. Twenty-three percent of NTHi cases were in children <5 years of age, and 62% occurred in adults, including 39% in adults aged >65 years. The annual attack rate of NTHi was 14.9/100,000 in neonates and 0.39/100,000 in those >65 years of age. Bacteremia without a detectable focus was the predominant presentation of invasive NTHi disease, being present in 37% of cases, while pneumonia accounted for 27% and meningitis for 12% of cases.

When Hib protein conjugate vaccines were first introduced in the early 1990s, there was concern that as these vaccines reduced nasopharyngeal carriage of Hib, other *H. influenzae* serotypes might replace Hib in the vacated ecological niche in the nasopharynx and cause more invasive disease. Indeed, as described above, NTHi is now responsible for the majority of invasive *H. influenzae* disease in every age group in countries where Hib vaccination programs are well established (60, 68, 189, 190). This is most probably due to multiple factors, such as the increased number and survival of preterm and extremely preterm infants (111), the increasing number of patients with underlying chronic medical disorders and immunocompromising conditions, and an aging population (60, 191).

Between 1992 and 2006, the Health Protection Agency in the United Kingdom coordinated surveillance data from Europe and other regions as part of the EU-IBIS program (9, 103). The incidence of invasive NTHi infections increased from 0.22/100,000 population in 1996 to 0.28/100,000 in 2006, a small but statistically significant increase of 3.5% (95% CI, 2.1% to 5.2%) year-to-year in 14 countries (9). Overall, 97% of invasive non-b *H. influenzae* infections were caused by NTHi (9). Since 2007, European data collation has been undertaken by the ECDC (192). In 2008 and 2009, the overall incidence of invasive NTHi disease from 29 reporting countries was 0.41/100,000 and 0.36/100,000, respectively, with higher incidence rates reported in Sweden (1.78/100,000 and 1.58/100,000, respectively) and Norway (1.58/100,000 and 1.48/100,000, respectively) than in other European countries. The increase in NTHi infections was particularly notable among adults aged ≥ 60 years (10). In Italy during 2017 to 2018, the majority of invasive *H. influenzae* infections were caused by NTHi (76.1%) (118). Similar increases in NTHi infections have been reported from other European countries, including Greece (193), Germany (194), England (114), Poland (195), and Finland (117).

NTHi is now the major cause of invasive *H. influenzae* disease in all age groups in the United States, with a substantial disease burden, particularly in neonates, pregnant/postpartum women, and older adults (196). Surveillance in the CDC ABC sites from 2009 to 2015 reported that the highest incidence (1.22/100,000) and highest CFRs (16%) were for NTHi compared to Hib (0.03/100,000 and 4%, respectively) and other capsulated serotypes (0.45/100,000 and 11%, respectively) (68). The incidence of all invasive *H. influenzae* disease had increased by 16%, compared with that in 2002 to 2008, driven by increases in NTHi and Hia disease (68). The highest incidence rates of invasive NTHi disease were in children aged <1 year (3.18/100,000) and those aged >65 years (4.47/100,000). These age groups also had the highest CFRs (68).

NTHi Infections in Neonates and Pregnancy

Early-onset neonatal NTHi infections are well described in studies from Europe (197–199), the United States (200), and Australia (201), with an incidence of 0.9/100,000 (95% CI, 0.9 to 1.6) in infants born at term rising to 342/100,000 (95% CI, 234 to 483) in infants born at <28 weeks gestation (104, 197, 199, 202) accounting for approximately 5% of all neonatal sepsis episodes (104). The European EU-IBIS study reported a 10-fold-higher incidence of invasive NTHi disease than with Hib in neonates, with 81% of cases occurring in the first 7 days of life (9). Neonatal NTHi sepsis develops rapidly (usually within the first 24 h after birth) and has a fulminant course with a CFR of 19%, especially in preterm infants. Each additional gestational week reduced the CFR by 21% (OR, 0.79; 95% CI, 0.69 to 0.90). NTHi can colonize the female genital tract, and an ascending infection can cause both maternal and fetal infection, with maternal sepsis, septic abortion, preterm delivery, and increased complications during labor as possible consequences (196, 198, 203). In the EU-IBIS study, for example, NTHi caused more infections in women than in men aged 25 to 44 years, and there may be an increased risk of invasive NTHi infection in women of childbearing age. Between 2008 and 2017, the ABC surveillance network identified NTHi invasive infection in 390 women of childbearing age. Of these, 86/390 (27.8%) were pregnant or postpartum. Pregnant/postpartum women were also more likely to have NTHi bacteremia than nonpregnant women of childbearing age (91% versus 56.1%; $P < 0.001$) and less likely to have ≥ 1 underlying comorbidity (31.4% versus 67.7%; $P < 0.001$). Three mother/infant pairs with invasive NTHi at delivery were identified. The neonatal isolate had the same sequence type as that of the corresponding maternal isolate (196). Of the 188 neonates with invasive NTHi infection identified in this study, 152 (81%) were diagnosed in the first 24 h of life and 134 (71%) were preterm. The average annual incidences among neonates and preterm infants were 43/100,000 and 320/100,000, respectively.

There is increasing evidence that NTHi invasive infection in early pregnancy may be associated with fetal loss, but as this diagnosis relies on postmortem placental and fetal samples, it is likely to be underrecognized. In a retrospective survey of all postmortem samples at <24 weeks gestation, NTHi was identified in 20% of cases with histologically confirmed chorioamnionitis and matched fetal and placental samples (198).

NTHi Infections in Older Adults

In countries with mature Hib vaccination programs, the median age at onset of invasive *H. influenzae* disease has now moved from early childhood to late adulthood, since the majority of invasive infections are now due to NTHi, which has a median age at disease onset of approximately 60 years (9). The majority of invasive NTHi cases in children (40% to 70%) and adults (60% to 80%) are seen in those with underlying comorbidities, notably chronic respiratory disease and impaired immunity (104, 204–206). While only 38% of cases in a recent Swedish study had identified comorbidities (207), one-third of patients in that study were aged >80 years. Interestingly, the authors found B-cell immunity disorders, including chronic lymphatic leukemia and multiple myeloma, to be common among patients with invasive NTHi, suggesting that humoral immunity may have an important protective role to play (207). The authors also speculated that immunosenescence with age-related decline in B-cell function

might explain the increasing incidence of invasive NTHi infections. Nevertheless, NTHi invasive disease can also occur in previously healthy individuals.

The clinical presentation of invasive NTHi disease varies with age. While meningitis is more commonly seen in older infants and children, it is uncommon in adults. Overall, pneumonia is the most frequent presentation, with invasive NTHi disease and NTHi pneumonia incidence increasing with age, particularly in older adults with underlying respiratory tract comorbidities, such as COPD and emphysema (204, 208). Other clinical presentations, such as epiglottitis (once a characteristic of invasive Hib disease) and skeletal and soft tissue infections, are uncommon, but cholecystitis (209) and urolithiasis (210) appear to be a particular feature of invasive NTHi infection in adults. The morbidity rate of invasive NTHi infections is high in older adults. In a Swedish study, 48% of 101 invasive NTHi cases developed severe sepsis or septic shock and 20% required intensive care (207).

In the United States, 4,683 cases of invasive NTHi disease were reported from 2008 to 2017 in the ABC surveillance system (196). The overall average annual incidence of invasive NTHi infection was 1.29/100,000, with an overall CFR of 15.6% and considerable variation between different age groups. While in children aged <1 year the average annual incidence was 5.94/100,000, with a CFR of 8.3%, in adults aged ≥ 80 years the average annual incidence was 10.08/100,000, with a CFR of 25.2%.

Several studies have reported that invasive NTHi infection causes significant mortality, with CFRs of 12% to 22% (196, 204, 211). Moreover, CFRs for invasive NTHi disease have also been reported to be higher in studies with an extended follow-up after the initial NTHi infection, suggesting that NTHi may preferentially target those in poor health who, even if they survive the initial infection, may subsequently succumb to their underlying illness. The 28-day CFR for invasive NTHi disease in the Swedish study was 8%, but 1 year postinfection, it had risen to 29% (207).

In countries with limited surveillance, or where serotyping of clinical isolates is incomplete, detecting an increase in NTHi infections will be difficult. Several factors may be responsible for the increase in NTHi infections, and it is possible that all have contributed to some extent. One possible explanation is strain replacement disease following the successful implementation of Hib immunization programs, although the evidence for this is limited (212). In England and Wales, invasive NTHi infections in children aged <15 years increased by 3% to 4% per year from 1994 to 2008, but there was no detectable effect on NTHi epidemiology during the resurgence of invasive Hib infections from 2000 to 2003 (111). It is also well described that vulnerable populations, such as preterm infants, older adults, and individuals with underlying cardiac and respiratory comorbidities, malignancy, and immunosuppression, are particularly susceptible to invasive NTHi infection (111). In recent years, medical advances have increased the survival rates for these groups, resulting in a larger number of individuals susceptible to invasive NTHi infections. Other possible reasons for the increase may be the result of increased awareness of NTHi infections, alterations in clinical practice, and improved diagnostic testing, including the use of automated blood culture systems and molecular typing of isolates, together with more comprehensive epidemiologic surveillance.

NTHi Vaccine Strategies

In marked contrast to capsulated *H. influenzae* strains, NTHi strains are highly heterogeneous and there is no obvious vaccine candidate (191). One outer membrane protein, protein D, is highly conserved and produced by almost all strains (213). It is the protein carrier for eight of the pneumococcal polysaccharide antigens in the 10-valent pneumococcal protein conjugate vaccine (Synflorix; GlaxoSmithKline). Use of an 11-valent prototype of this vaccine resulted in a 35.3% reduction in NTHi acute otitis media in children (214), but to date, the licensed vaccine has failed to show any significant effectiveness against invasive NTHi infections and has no effect on carriage (215). A multicomponent NTHi vaccine, containing protein D, protein E, and a fusion protein of another surface-exposed protein, PilA, is under investigation as a possible vaccine to

prevent NTHi infections in adults with COPD (216). Other routes of vaccine administration have also been under consideration. Oral NTHi vaccination has been proposed for patients with recurrent exacerbations of COPD. A Cochrane review (217) concluded that oral administration of an NTHi vaccine did not yield consistent reductions in NTHi-mediated exacerbations but did demonstrate a significant reduction in the number of antibiotic courses prescribed. Subject age and gender were significant confounding factors in these studies (218).

Invasive Disease and *Haemophilus quentini*

Albritton et al. described a "cryptic genospecies of *Haemophilus* biotype IV" isolated from genitourinary tract specimens (219). Quentin et al. (220) further investigated these strains, which have been designated *Haemophilus quentini*. These strains can be differentiated from other NTHi strains by DNA hybridization, 16S rRNA gene sequencing, and multilocus enzyme electrophoresis (221). There have been case reports of *H. quentini* as a cause of neonatal bacteremia (222) and bacteremia in an adult with multiple myeloma (223). *H. quentini* has also been isolated from urine and urethral cultures in adult males (224). Between 2016 and 2018, the Public Health Ontario laboratory in Toronto identified seven cases of invasive *H. quentini* infection (225). Two of the isolates were from neonates, three were from adult females of childbearing age (2 were known to be pregnant), and one was from an elderly female. There was also an atypical *H. quentini* biotype III from an elderly male with varices. *H. quentini* strains were identified as nontypeable, biotype IV, possessed *sodC*, and lacked *fucK*, with detection of the *H. quentini*-specific 16S rRNA gene and near-full-length 16S rRNA gene sequencing, tests which require referral to a reference laboratory. Given the need for testing not generally available in routine diagnostic laboratories, *H. quentini* may well be an under-recognized pathogen in adults, especially in pregnant women (225).

CONCLUSIONS

The sustained low incidence of invasive Hib infection in all age groups in all countries that have introduced Hib protein conjugate vaccine illustrate the remarkable success of routine Hib vaccination programs that have provided both direct and indirect protection to vaccine recipients and their communities, respectively (226). Vaccine failures in fully immunized children are rare, and Hib vaccines are safe and well tolerated. The coverage of the third dose of Hib vaccine ranges from 76% in the WHO African and European Regions (100, 136) to 82% in the Eastern Mediterranean Region (129) and to 87% in the Region of the Americas and South East Asian Region (63, 156). The overall coverage in the Western Pacific Region is only 23% (168), reflecting that China has yet to include Hib vaccines in their NIP. Most invasive Hib cases now occur mainly in older adults with underlying comorbidities. The continuing identification of cases of invasive Hib disease stresses the importance of maintaining Hib immunization with high rates of coverage in all countries to ensure that this pathogen does not reemerge as an important agent of serious pediatric infections.

In the prevaccine era, NTHi was an infrequent cause of invasive infection, but it is now acknowledged as the major contributor to invasive *H. influenzae* disease in countries with good surveillance mechanisms and full typing capabilities. The low rates of invasive NTHi infections reported in some countries is more likely due to the low proportion of strains referred to reference laboratories and highlights the need to improve ascertainment of such cases. NTHi infections occur predominantly in infants, particularly neonates, older adults, those who are immunosuppressed or who have underlying comorbidities, and women of childbearing age. Several studies have shown an increased burden of NTHi in these vulnerable individuals, resulting in frequent intensive care admission, high CFRs, and many sequelae in those who survive the infection. The reporting rate of NTHi infections in neonates is particularly striking, with most cases presenting as early-onset sepsis, especially in those born preterm where maternal infection has induced early labor and preterm delivery. Furthermore, NTHi infections in neonates are likely to be underestimated, although the increasing notification

rates in this age group suggest an increasing awareness and reporting of these infections. NTHi immunization of pregnant women could protect both the mother and her baby. However, the development of an NTHi vaccine is difficult because of the genetic diversity of unencapsulated NTHi strains needing identification of multiple vaccine targets. Despite these challenges, investigations of potential NTHi vaccine candidates are ongoing.

Hia has emerged as a serious problem among the Indigenous populations of North America, to the extent that an Hia conjugate vaccine may be required to control these infections. In contrast, Hif is now the most frequently isolated capsulated serotype of *H. influenzae* causing invasive disease in the European Region, but the number of cases remains relatively small. Hie infections have also been recognized increasingly, principally in the European Region. Like NTHi, both Hie and Hif often target the elderly, and a high proportion of cases occur in patients with underlying comorbidities. Hie appears to be more virulent than Hif.

Hib conjugate vaccines were the first glycoprotein vaccines developed. The use of these vaccines over the last 30 years has proven extremely successful, to the extent that young pediatricians in high-income countries may never see cases of acute epiglottitis or acute meningitis caused by Hib. Valuable lessons have been learned about the use of these glycoprotein vaccines, which have aided the development of this type of vaccine for other major bacterial pathogens, including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Salmonella enterica* serovar Typhi. The changing epidemiology of invasive *H. influenzae* infections, exemplified by the increasing incidence of Hia in Indigenous populations in North America and NTHi globally, together with alterations in the age groups affected, emphasizes the importance of ongoing surveillance. National Reference Centers, with sufficient resources, should establish comprehensive epidemiologic and microbiologic surveillance of all *H. influenzae* serotypes and NTHi infections, with accurate identification and typing of invasive isolates using molecular methods together with data on age groups affected, underlying comorbidities, risk factors, clinical presentations, and outcomes of the infections. Such systems should be implemented both before and for many years after a new vaccine has been introduced to establish its potential impact. Continuous surveillance is essential to inform future vaccination strategies and to detect vaccine “escape mutants” or replacement disease and vaccine failures. Indeed, as Hib disease has declined, surveillance systems have identified the increasing importance of NTHi, and in some regions of non-b serotypes, so that these species may themselves become future vaccine targets.

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