Haemophilus influenzae: Still a Relevant Invasive Pathogen

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Haemophilus influenzae is a small, non-motile, gram-negative pleomorphic coccobacillus, generally considered a constituent of the upper respiratory tract normal flora of humans [1]. Strains without polysaccharide capsules (non-typable *H. influenzae*) often cause mucosal surface infections, while encapsulated strains, especially *H. influenzae* type b, cause invasive diseases such as septicemia and meningitis [1]. Prior to the universal introduction of Hib vaccines, Hib was a common cause of bacterial meningitis, epiglottitis and sepsis in children worldwide, including Israel [1-4]. Thus, prevention of invasive Hib disease through immunization is considered one of the greatest public health achievements of the late twentieth century [2]. Furthermore, conjugate Hib vaccine administration reduces Hib carriage, resulting in reduced transmission and thus indirect protection (herd protection) [5].

Routine vaccination with Hib conjugate vaccines was introduced in the United States in 1987–1990 [1,6]. Since January 1994, all infants in Israel are offered Hib conjugate vaccine free of charge as part of the universal national immunization plan [5]. This has resulted in a rapid and remarkable decrease in the incidence of invasive disease in all settings where the vaccines have been incorporated into routine infant immunization schedules [5-7]. In Israel, the incidence of Hib disease in children under the age of 5 years dropped from 34 per 100,000 before the licensure of Hib conjugate vaccines to 4 per 100,000 in 1995 and 2 per 100,000 in 1996 [5]. This > 90% reduction was similar to that observed in other developed countries [6,8,9].

It has been estimated that Hib vaccines prevent annually 21,000 cases of Hib meningitis and ~38,000 cases of invasive Hib disease [10]. The impact of Hib vaccination on the incidence of pneumonia is likely to be several-fold greater than the impact on meningitis, though demonstrating this impact is complicated because of the difficulty in establishing an etiologic diagnosis of pneumonia [11].

The development of invasive Hib disease after prior administration of a Hib conjugate vaccine (Hib vaccine failure) is uncommon but has been reported in other countries with established Hib vaccination programs, including those with routine booster doses in the second year of life [8]. It has been suggested that children with Hib vaccine failure are inherently unable to maintain long-term antibody-based immunity against Hib. Those children may be at risk of further episodes of invasive Hib disease [8]. Children with Hib vaccine failure had a higher incidence of immunoglobulin A deficiency than the general population, suggesting that an invasive Hib infection can be the first clinical sign of common variable immunodeficiency [12]. However, in a study from Israel of five fully immunized patients with invasive Hib infections, immunologic studies were carried out in four and only one patient exhibited mild IgG2 deficiency [5].

The near-elimination of Hib disease in some populations led to the speculation that other *H. influenzae* serotypes (especially serotype a) and NTHi may emerge as important causes of invasive disease [7,13]. Other concerns were raised regarding the possibility of replacement by non-Haemophilus pathogens (e.g., *Streptococcus pneumoniae* and *Neisseria meningitidis*) [14]. Previous results from Israel did not support the replacement theory in children [5]. However, recent reports from various countries describe an increase of non-b *H. influenzae* invasive disease in adults > 65 years old, including disease caused by NTHi [15]. In the post-Hib vaccine era, the majority of cases with the disease are caused by NTHi in all age groups, with a higher incidence among adults > 65 years old than among other age groups [6,15].

In high risk populations, the clinical characteristics of NTHi invasive disease among children are similar to those of Hib disease: meningitis is the most common presentation and the majority of children with meningitis are < 1 year of age [13]. Vaccines for the prevention of non-type b *H. influenzae* infections are not currently available [7].

Additional studies are needed to advance our understanding of the microbial milieu of the mucosa and to assess the "ecological impact" of conjugate vaccines. Although vaccination with Hib conjugate vaccines does not appear to increase the risk of colonization with non-type b *H. influenzae*, there are few data on the effect of other vaccines. The relationship between *S. pneumoniae* and *Staphylococcus aureus* colonization is illustrative. A cross-sectional study from Israel demonstrated lower rates of nasal colonization with *S. aureus* among children who were colonized with *S. pneumoniae* serotypes included in the conjugate vaccine [16].

Hib = *H. influenzae* type b

IgG = immunoglobulin G

NTHi = non-typable *H. influenzae*

Ongoing surveillance for nasopharyngeal carriage and invasive *H. influenzae* disease is needed to document whether there is a real increase in the risk of non-type b *H. influenzae* infection attributable to replacement disease, to understand the burden of invasive *H. influenzae* disease, and to develop public health prevention strategies [6,7]. In Israel, continuous surveillance of pediatric invasive infections caused by Hib, *S. pneumoniae* and *N. meningitidis* has been conducted since October 1988 [5].

Data from this surveillance revealed that the low rate of invasive *H. influenzae* disease was sustained during 2003–2009, with an overall mean incidence of 1.8/100,000 children < 16 years [17].

In the current *IMAJ* issue, Megged et al. [18] report on a series of 104 local cases of invasive meningitis or bacteremia *H. influenzae* diseases occurring between January 1997 and June 2010 (in the post-Hib vaccine introduction era). The authors point to several important issues: First, despite universal Hib vaccination, of all invasive *H. influenzae* cases, 20% were still caused by Hib. The persistence of Hib disease, despite universal national vaccination, could be attributed to "relatively low Hib vaccine coverage in some subpopulations in Jerusalem," especially the ultra-Orthodox Jewish communities. Second, five cases of Hib vaccine failure (three of which occurred in children with underlying conditions) were described. This low rate of vaccine failure is consistent with other reports – locally and worldwide [5,8,12]. Third, no replacement with non-Hib serotypes was found. Fourth, adult patients had longer hospitalizations and worse outcome than children with *H. influenzae* invasive disease, as described previously [19]. Fifth, gynecological and neonatal infections caused by *H. influenzae* were uncommon, most probably due to the low genital tract carriage rate. This latter observation is important because, as demonstrated before in a study from the UK, the mortality from NTHi childhood diseases was mainly found in neonates [20].

Megged's report also has several important limitations. First, incidence rates could not be calculated and thus did not enable a real appreciation of the disease magnitude. Second, the report deals only with patients hospitalized in one of several hospitals in Jerusalem, not only limiting the ability to calculate population-based rates, but also raising the question of the real representative value of the study hospital as compared to the entire Israeli population. Indeed, as the authors state, the ultra-Orthodox population is over-represented among the patients of this specific medical center, meaning that the current study does not describe a population representative of the average Israeli population. Third, only data from the post-Hib vaccine introduction era are presented, which does not allow estimation of a reduction in Hib diseases resulting from Hib vaccination. Furthermore, no dynamics in disease rate are described at all. Fourth, the authors state that "routine vaccination was implemented in Israel in 1996," while in fact, routine Hib vaccination started in Israel in 1994 and their report does not show data deriving from the very early post-Hib implementation era.

These weaknesses point to the need for a prospective nationwide study, allowing better understanding of the disease incidence dynamics at the national level. Such a study has indeed been conducted in Israel in the last 20 years, starting in the pre-Hib immunization era. The results of the study will soon be published.

In summary, only a combination of strict adherence to routine immunization schedule in all populations, development of new non-Hib vaccines, and nationwide continuous surveillance for invasive Haemophilus disease could lead to the elimination of what was once a feared common infection.

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Capsule

Natural blood pressure gauge

Endothelial cells line blood vessels and, by interacting with smooth muscle, can help to control blood flow. Sonkusare and collaborators describe how signaling in endothelial cells controls contraction of surrounding smooth muscle cells, which provides an important mechanism for control of blood pressure. A calcium-sensitive fluorescent protein was expressed in endothelial cells of mouse arteries to image small changes in calcium concentration that appear to represent opening of single TRPV4 ion channels and consequent influx of calcium into the cell. Clustering of the channels allowed cooperative activation of a handful of channels, which appeared to produce a sufficient calcium signal to open another set of calcium-sensitive potassium channels. The resulting depolarization of the endothelial cells then passes an electrical connection to smooth muscle cells through gap junctions.

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Capsule

NLRP10 is a NOD-like receptor essential to initiate adaptive immunity by dendritic cells

NLRs (nucleotide-binding domain leucine-rich-repeat-containing receptors, NOD-like receptors) are a class of pattern recognition receptors (PRR) that respond to host perturbation from either infectious agents or cellular stress. The function of most NLR family members has not been characterized and their role in instructing adaptive immune responses remains unclear. NLRP10 (also known as PYNOD, NALP10, PAN5 and NOD8) is the only NLR lacking the putative ligand-binding leucine-rich-repeat domain and has been postulated to be a negative regulator of other NLR members, including NLRP3. Eisenbarth and team did not find evidence that NLRP10 functions through an inflammasome to regulate caspase-1 activity nor that it regulates other inflammasomes. Instead, *Nlrp10–/–* mice had a profound defect in helper T cell-driven immune responses to a diverse array of adjuvants, including lipopolysaccharide, aluminium hydroxide and complete Freund's adjuvant. Adaptive immunity was impaired in the absence of NLRP10 because of a dendritic cell (DC) intrinsic defect in emigration from inflamed tissues, whereas upregulation of DC co-stimulatory molecules and chemotaxis to CCR7-dependent and independent ligands remained intact. The loss of antigen transport to the draining lymph nodes by a subset of migratory DCs resulted in an almost absolute loss in naive $CD4^+$ T cell priming, highlighting the critical link between diverse innate immune stimulation, NLRP10 activity and the immune function of mature DCs.

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We do not err because truth is difficult to see. It is visible at a glance. We err because this is more comfortable

Alexander Solzhenitsyn (1918-2008), Russian writer who, through his often-suppressed writings, helped to raise global awareness of the gulag, the Soviet Union's forced labor camp system – particularly in *The Gulag Archipelago* and *One Day in the Life of Ivan Denisovich*, two of his best-known works. Solzhenitsyn was awarded the Nobel Prize in Literature in 1970. He was expelled from the Soviet Union in 1974 but returned to Russia in 1994 after the Soviet system had collapsed

When one guy sees an invisible man, he's a nut case; ten people see him, it's a cult; ten million people see him, it's a respected religion

Richard Jeni (1957-2007), American stand-up comedian and actor