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Ten Years of Hib Vaccination in Tunisia : Epidemiological Trends and Emerging Challenges

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ABSTRACT

Background: Haemophilus influenzae type b (Hib) was historically a leading cause of bacterial meningitis and pneumonia among young children worldwide. Tunisia introduced Hib conjugate vaccination in 2002 as part of the pentavalent vaccine. Ten years after vaccine implementation, epidemiological surveillance revealed changing disease patterns and emerging challenges.

Methods: A retrospective, multicenter analysis of national surveillance data was conducted from 2012 to 2022. Laboratory-confirmed cases of invasive H. influenzae infections were reviewed. Incidence trends, demographic characteristics, vaccination status, and the distribution of non-b serotypes were analyzed.

Results: Hib disease incidence declined by 80% compared with pre-vaccination levels, yet sporadic cases persisted, particularly after 2018. Non-type b strains became increasingly prevalent. Vaccine coverage remained high (>90%) nationally but showed regional disparities.

Conclusions: The Tunisian Hib vaccination program achieved sustained reduction in invasive Hib disease, but surveillance data indicate the emergence of non-b H. influenzae strains and possible vaccine-related challenges. Continuous monitoring and immunization program strengthening remain essential.

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Introduction

Haemophilus influenzae type b (Hib) was once one of the leading causes of bacterial meningitis and pneumonia in children under five years of age [1]. Prior to vaccine introduction, Hib was estimated to cause over eight million serious illnesses and approximately 371,000 child deaths globally each year [2]. The introduction of Hib conjugate vaccines in the 1990s dramatically reduced the incidence of invasive Hib disease in high- and middle-income countries [3].

In Tunisia, Hib conjugate vaccine (as part of the pentavalent DTP-HepB-Hib formulation) was introduced into the National Immunization Program (NIP) in 2002. Since then, vaccination coverage has exceeded 90% in most governorates [4]. Early post-introduction surveillance demonstrated a significant decline in Hib meningitis, confirming the program's success [5].

However, a decade later, the epidemiological landscape of H. influenzae infections appears to be evolving. Several reports from the National Observatory of New and Emerging Diseases (ONMNE) and regional hospitals have documented sporadic Hib cases, even among fully vaccinated children, as well as an increasing number of invasive infections caused by non-type b (non-b) strains [6]. Similar trends have been observed globally, suggesting possible serotype replacement or the emergence of nontypeable H. influenzae (NTHi) as significant pathogens [7].

The objective of this study is to analyze ten years of surveillance data on invasive H. influenzae infections in Tunisia following Hib vaccine introduction. We aim to (1) describe long-term epidemiological trends; (2) assess the distribution of Hib and non-b serotypes; (3) evaluate vaccination status among confirmed cases; and (4) identify emerging challenges for public health and immunization strategies.

Materials and Methods

Study Design and Population

A retrospective, multicenter observational study was conducted from January 2012 to December 2022. Data were extracted from the National Surveillance Network for Invasive Bacterial Diseases (ONMNE), which includes 23 sentinel hospitals across Tunisia. Children aged 0–15 years admitted with suspected bacterial meningitis, pneumonia, or sepsis were eligible. Laboratory-confirmed H. influenzae infections were included if isolates were recovered from normally sterile body fluids (blood, cerebrospinal fluid, pleural fluid, or synovial fluid) or detected by polymerase chain reaction (PCR).

Case Definitions
A confirmed Hib Case was defined as a patient with clinical signs compatible with invasive disease and H. influenzae type b isolated or detected by PCR. **Non-b cases** were defined similarly but included other serotypes (a, c, d, e, f) or nontypeable strains.

Laboratory Methods
Specimens were processed using standard bacteriological procedures. Cultures were performed on chocolate agar supplemented with X and V factors. Identification was confirmed by oxidase testing and API NH® (bioMérieux). Serotyping was done by slide agglutination using type-specific antisera and confirmed by PCR when available. Antimicrobial susceptibility testing followed CLSI guidelines [8]. Quality assurance was coordinated by the National Reference Laboratory for Meningitis Pathogens (Institut Pasteur de Tunis).

Vaccination Data
Vaccination status was verified using child health cards, hospital records, and national immunization registries. A child was considered "fully vaccinated" after receiving three doses of Hib-containing vaccine according to the NIP schedule (2, 3, and 6 months).

Statistical Analysis
Annual incidence rates were calculated per 100,000 population under five years of age using data from the National Institute of Statistics [9]. Temporal trends were assessed using Poisson regression. Differences between categorical variables were analyzed with the chi-square test, and continuous variables with Student's t-test. Analyses were performed using SPSS version 27.0 (IBM Corp., USA). A p-value <0.05 was considered statistically significant.

Results
Overall Incidence and Trends
Between 2012 and 2022, 482 laboratory-confirmed H. influenzae infections were recorded nationwide. Among them, 176 (36.5%) were due to Hib and 306 (63.5%) to non-b strains. The incidence of Hib meningitis in children under five declined from 0.9 per 100,000 in 2012 to 0.18 per 100,000 in 2022, representing an 80% reduction compared with the pre-vaccine era (5.2/100,000 during 1998–2001) [10].

A modest resurgence was observed after 2018, with localized clusters in the southern and central regions (Sidi Bouzid, Gafsa, and Kairouan). The increase corresponded to periods of temporary vaccine stock-outs (2018–2019) and the COVID-19 pandemic (2020–2021), when routine immunization coverage dropped below 85% in some districts [11].

Demographic Characteristics
The median age of Hib patients was 11 months (interquartile range : 7–18 months). Most cases (62%) occurred in infants under one year old, and 85% in children under two. Boys represented 54% of cases. Geographical analysis showed a higher incidence in central and southern Tunisia compared with coastal regions.

Clinical Manifestations
Among confirmed Hib infections, meningitis was the most common clinical presentation (68%), followed by pneumonia (21%), sepsis (9%), and other focal infections (2%). The overall case-fatality rate was 14.7% for Hib meningitis and 8.3% for other invasive forms. Neurological sequelae (hearing loss, motor deficits) were documented in 16% of survivors.

Vaccination Status and Vaccine Failures
Of 176 Hib cases, 52 (29.5%) were fully vaccinated, 37 (21.0%) partially vaccinated, and 87 (49.5%) unvaccinated or with unknown status. The annual number of cases among fully vaccinated children remained low but increased slightly after 2018 (from 3 cases/year to 6 cases/year). Most vaccine failure cases occurred in children aged 7–18 months and were associated with severe disease. Investigation of these cases did not reveal major cold chain breaches, but detailed serological follow-up was limited.

Emergence of Non-b Strains
Non-b H. influenzae strains became increasingly dominant, accounting for 63.5% of all isolates after 2018. Type a (Hia) represented 14%, type f 11%, type e 9%, and nontypeable strains 27%. Non-b infections were more frequently associated with pneumonia (43%) and occurred in slightly older children (median age: 2.4 years).

Molecular characterization (available for 97 isolates) showed genetic diversity among non-b strains, with several belonging to globally circulating sequence types (ST-23, ST-367, ST-422) [12].

Discussion
This ten-year review confirms the long-term success of the Hib conjugate vaccine in Tunisia, with sustained reduction in invasive Hib disease. The initial decline following vaccine introduction mirrors trends observed in neighboring countries such as Morocco and Egypt [13,14]. However, several evolving epidemiological patterns warrant attention.

Persistence and Resurgence of Hib
Although Hib incidence remains low, the reappearance of sporadic cases since 2018 underscores the need for vigilance. Temporary drops in vaccine coverage and logistic issues (stock-outs, delayed doses) likely contributed to this pattern [15]. Moreover, disruptions due to the COVID-19 pandemic had measurable effects on routine immunization programs globally, including in North Africa [16].

Vaccine failures, though rare, were observed and could be multifactorial. Waning antibody levels, genetic variability in vaccine strains, or host immune deficiencies may play a role [17]. Continued serological monitoring and assessment of booster strategies could help sustain long-term protection.

Emergence of Non-B and Nontypeable Strains
A significant finding of this study is the increased proportion of infections due to non-b H. influenzae. Similar trends have been reported in the post-Hib vaccine era in Europe, North America, and Asia [18,19]. Non-b strains, especially Hia and Hif, are now recognized as important causes of invasive disease, particularly in indigenous and low-resource populations [20].

The mechanisms driving this shift remain unclear but may involve ecological niche replacement following Hib suppression, improved diagnostic sensitivity, or naturally fluctuating strain prevalence [21]. Importantly, current Hib vaccines do not protect against these emerging serotypes, highlighting the need for broader conjugate formulations.

Programmatic and Public Health Implications
The success of Hib vaccination in Tunisia demonstrates the effectiveness of sustained national immunization programs. However, regional disparities in vaccine uptake and health infrastructure persist. Strengthening surveillance, ensuring uninterrupted vaccine supply, and reinforcing cold chain

management are key priorities [22].

Enhanced laboratory capacity, including molecular serotyping and genome sequencing, will enable better understanding of H. influenzae strain evolution and antimicrobial resistance trends [23]. Periodic impact evaluations, integrating clinical, microbiological, and immunological data, are essential for guiding vaccine policy.

Conclusions

Ten years after the introduction of Hib vaccination in Tunisia, the burden of Hib disease remains dramatically reduced, confirming the vaccine's long-term impact. Nevertheless, the emergence of non-b H. influenzae strains, sporadic vaccine failures, and regional inequities in vaccine coverage pose new challenges.

Sustained surveillance, laboratory strengthening, and research into next-generation conjugate vaccines covering multiple serotypes are crucial to consolidate achievements and prevent future resurgence of invasive Haemophilus influenzae disease.

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