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Impact of *Haemophilus influenzae* type b conjugate vaccination on hospitalization for invasive disease in children fifteen years after its introduction in Italy

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ABSTRACT

In Italy, Hib conjugate vaccine was introduced for infants in 1999 and included in the DTaP-HBV-IPV-Hib combination in 2001, with an uptake of 83.4% in 2002, >90% by 2005, and >95% by 2011. We estimated the impact of Hib vaccination on hospitalizations for *H. influenzae* invasive disease in children <5 years.

Age-specific hospitalization rates and hospitalization risk ratios (HRRs) with 95%CI during 2001–2013 were calculated performing time-series analysis. The number of cases reported to the national surveillance of invasive bacterial diseases was compared to the number of hospitalizations between 2007–2013.

Hospitalization rates declined from 2.3 in 2001 to 0.9 × 100,000 in 2002 (HRR = 0.4, 95%CI = 0.3–0.6, $p < 0.05$) among children 1–4 years and from 5.4 in 2001 to 2.4 × 100,000 in 2005 (HRR = 0.4, 95% CI = 0.2–0.9, $p < 0.05$) among infants.

During 2007–2013: 401 cases were reported, 242 were typed, 12.4% were by serotype b; 861 hospital admissions were recorded. Applying the percentage of typed b strains retrieved from the surveillance to the number of hospitalizations for invasive *H. influenzae* disease, an estimated 107 episodes could be attributable to serotype b.

These findings provided reassuring data on the impact of Hib vaccination on the burden of hospitalization for invasive disease in Italian children.

1. Introduction

Haemophilus influenzae is an infectious bacterium cause of meningitis, pneumonia, epiglottitis and other severe infectious diseases (such as septic arthritis, cellulitis, purulent pericarditis, and bacteremia). Both capsulated (types a, b, c, d, e, or f) and non-capsulated *Haemophilus influenzae* can cause invasive disease primarily among children under five years of age and immunosuppressed patients [1,2]. In the absence of vaccination plans, capsulated *Haemophilus influenzae* type b (Hib) has undoubtedly the highest incidence [3].

The first Hib conjugate vaccines were developed in the late 1980s [4]. Since that time Hib vaccines were widely used in most industrialized countries and demonstrated high safety and efficacy. Near elimination of *H. influenzae* meningitis has been documented after vaccine introduction [5]. In the USA, where Hib vaccines were introduced into routine use first, the average annual incidence rate of invasive Hib disease in children aged <5 years remained below the *Healthy People 2020* (U.S. Department of Health and Human Services) goal of 0.27 × 100,000 throughout 2000–2012 and reached 0.19 × 100,000 in 2014 [6]. In European countries, in 2012, the notification rate of confirmed cases of invasive *Haemophilus influenzae* disease due to all serotypes was 0.49

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per × 100,000 population (comparable to the rates observed between 2008 and 2011) and 0.97 × 100,000 children under five years of age. Serotype b infections have remained constantly low [7].

In Italy, Hib monovalent vaccine was licensed in 1995 [8], although vaccination was voluntary. It was included in the National Immunization Program in 1999 with a 2p + 1 schedule at 3, 5, and 11 months of age [9,10]. Vaccination coverage at age 24 months was estimated at 19.8% for the 1996 birth cohort and increased to 53.1% for the 1998 birth cohort [11,12]. Since 2001, the DTaP-HBV-IPV-Hib combined vaccine has being used with an estimated vaccination coverage that was 83.4% in 2002, more than 90% by 2005, and more than 95% by 2011 [13].

In the first years of vaccine introduction, from 1997 to 2002, an active laboratory-based surveillance of invasive *H. influenzae* disease was implemented in some Italian regions (Piemonte, Liguria, Toscana, Campania, and Puglia). Later, from 2003 to 2006, cases of *H. influenzae* meningitis were collected nationally as a part of a passive reporting system of bacterial meningitis. Since 2007, data on cases of *H. influenzae* invasive disease are routinely reported to the National Surveillance of Invasive Bacterial Disease (IBD) [14–16].

Since when Hib vaccination was introduced, the incidence of confirmed invasive *H. influenzae* disease in children <5 years declined from 5 × 100,000 in 1997 to 0.07 × 100,000 in 2009; beginning in 2006, the rate has remained at, or less than, 0.12 × 100,000, with around half of the cases identified as non-typeable strains and very few as type b [17,18].

This work aimed at estimating the burden of hospitalization for invasive *H. influenzae* disease in children <5 years fifteen years after vaccine introduction.

2. Material and methods

Hospitalization records for invasive *H. influenzae* disease stratified according to age groups (infants aged <1 year and children aged 1–4 years) were provided by the Office of National Hospital Discharge Registry (HDR) for the period 2001–2013 [19]. HDR contains information about each patient discharged from public and private hospitals and includes data related to both clinical and organizational aspects of hospitalization. Records include demographic information, dates of admission and discharge, diagnoses (one main and up to five secondary diagnoses) and therapeutic procedures performed during the hospitalization, type of admission (1-day admission / ordinary admission), and in-hospital mortality. Clinical information is coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM).

An invasive *H. influenzae* episode was defined as ICD9-CM code 320.0 "Meningitis due to *H. influenzae*" or 038.41 "Septicemia due to other gram-negative organisms – *H. influenzae*" or 041.5 "Bacterial infection in conditions classified elsewhere and of unspecified site – *H. influenzae*" if associated with code 320.8 (Other specified meningitis), 790.7 (Bacteremia), or 038.9 (Unspecified septicemia). These ICD9-CM codes were scanned across discharge diagnoses in each child record for any mention of these diseases.

The proportion of 1-day admissions, in-hospital mortality (number of admissions reporting the code "Died" / total number of admissions), the proportion of admissions reporting one or more comorbidities (ICD9-CM codes for congenital anomalies, immunodeficiency, HIV, cardiovascular disease, tumour, etc., as main or secondary diagnosis), and the proportion of discharge records reporting an ICD9-CM code for "Disorders relating to short gestation and low birthweight" were calculated.

Outcome-specific Poisson regression was used for time series analysis to assess annual hospitalization rates and hospitalization risk ratios (HRRs), together with 95% confidence interval (95% CI). Statistical analyses were performed in STATA (version 14; StataCorp, College Station, TX, USA).

Assuming the hospitalization rate for invasive *H. influenzae* disease as a proxy of incidence, the time series were evaluated in light of the vaccination coverage rates achieved in children <24 months during the examined period [13].

Moreover, in order to assess the size of under-reporting for invasive *H. influenzae* disease, cases (all age groups) reported to the national surveillance of IBD [15,16] during 2007–2013 were compared to the number of hospitalizations recorded in the same period, by year and Italian region.

Because hospital discharge records lack serotyping information, the distribution of *H. influenzae* serogroups detected by laboratory-based IBD surveillance was applied to the total number of hospitalizations in order to estimate the number of cases attributable to serotype b.

The study protocol was approved by the Institutional Review Board at the Apulian Regional Observatory for Epidemiology (PROT:121/OER/2016, March 30, 2016). The study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was not obtained from participants because both hospitalization and surveillance data were provided and analysed anonymously.

3. Results

Between 2001 and 2013, a total of 183 (62% males) and 140 (56% males) hospitalizations for invasive *H. influenzae* disease were recorded among infants aged <1 year and children aged 1–4 years, respectively. The proportion of 1-day admissions was 5% (9/183) among infants and 21% (29/140) among children. The in-hospital mortality rate was 1% (2/183 admission) among infants and 2% (3/140) among children. Infants hospitalized for invasive *H. influenzae* reporting an ICD9-CM code for a chronic condition were 9% (17/183; 12 with congenital anomalies, three with cardiovascular disease, two with immunodeficiency – HIV not included). The proportion of children aged 1–4 years with comorbidities was 6% (8/140; three reporting congenital anomalies, three cardiovascular disease, one immunodeficiency – HIV not included, one tumour). The proportion of infants reporting disorders relating to short gestation and low birthweight was 7% (13/183). Over the study period, a significant decline of hospitalization rates was observed among children 1–4 years between 2001 and 2002 (from 2.3 to 0.9 × 100,000; HRR = 0.4, 95% CI = 0.3–0.6, $p < 0.05$). Similar significant reduction was seen among infants between 2001 and 2005 (from 5.4 to 2.4 × 100,000; HRR = 0.4, 95% CI = 0.2–0.9, $p < 0.05$) (Fig. 1).

During 2007–2013, 401 cases (all age groups) of invasive *H. influenzae* disease due to both encapsulated and non-typeable strains were reported to the IBD national surveillance. Among the 242 (60.3%) strains typed, serotype b accounted for 12.4% of isolates. Lombardia reported the highest number of notifications (95 cases/≈9,795,000 inhabitants, according to 2013 census figures) [15,16], therefore the estimated number of cases that could be attributable to serotype b was 12. Four regions (Basilicata, Calabria, Puglia, and Umbria, amounting in all to ≈7,470,000 inhabitants) reported zero cases (Fig. 2). In the same period, a total of 861 hospitalizations for invasive *H. influenzae* disease were recorded in the national HDR. Applying the percentage of 12.4% typed b strains retrieved from the IBD surveillance to the total number of hospitalizations for invasive *H. influenzae*, we obtained an estimated 107 episodes that could be attributable to serotype

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