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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

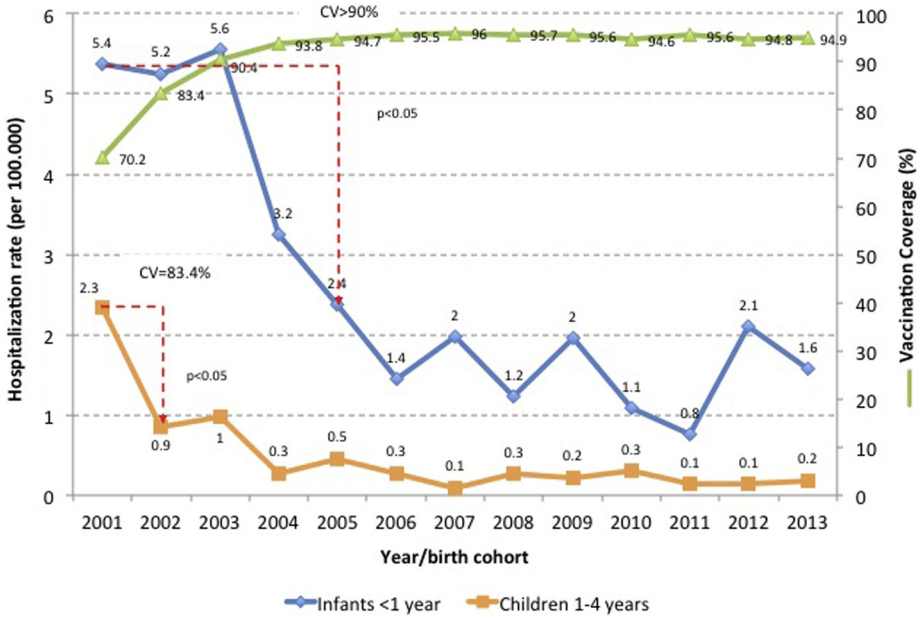

Fig. 1. Hospitalization rates for invasive *H. influenzae* disease in infants <1 year and children 1–4 years, Italy, 2001–2013. Vaccination coverage at age 24 months in the same period [13].

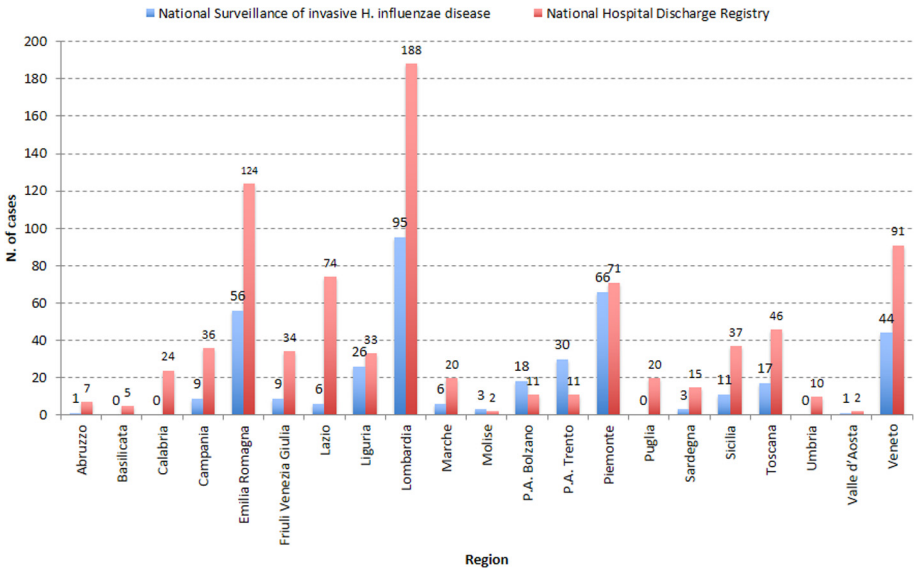

Fig. 2. Number of hospitalizations and number of cases reported to the National Surveillance of invasive *H. influenzae* disease, by Italian region, 2007–2013.

b (estimated hospitalization rate 0.18 × 100,000). Lombardia had the highest number of discharge records (188/≈9,795,000 inhabitants), with an estimated 23 cases that could be attributable to serotype b (Fig. 2).

4. Discussion

The epidemiological characteristics of Hib disease have markedly changed since the introduction of highly effective Hib conjugate vaccine in the countries using it, regardless of their levels of development and economic status [11,12]. At least 2 doses of Hib vaccine are required to achieve high effectiveness, up to 98% (95% CI: 89–100%) against Hib meningitis and to 100% (95% CI: 64–100%) against invasive disease [20].

Before the introduction of universal Hib vaccination in Italy, the incidence of invasive disease caused by *H. influenzae* type b in children aged <5 years increased from 2.5 × 100,000 in 1994 to 4.5 × 100,000 in 1998 [8,21], a trend most probably attributable to the implementation of an active laboratory-based surveillance of invasive *H. influenzae* disease in some Italian regions in 1997. An excellent disease control was achieved following the inclusion of the Hib vaccine 2 + 1 schedule in the National Immunization Program in 1999 [18].

Assuming the hospitalization rate for invasive *H. influenzae* disease as a proxy of incidence, as the disease is so severe that all patients are expected to show up in the hospital, a marked decline was observed between 2001–2013 (Fig. 1), following the implementation of hexavalent vaccines in Italy. This decline correlated over time with the vaccine coverage trend for 3 doses of Hib

vaccine that increased from 54.7% in 2000 to 83.4% in 2002 and achieved more than 95% since 2011 [13]. As a consequence, the incidence of cases registered during this entire period in Italy was steadily lower than the incidence reported to The European Surveillance System (TESSy) for the year 2014 by all 30 EU/EEA (European Union/European Economic Area) Member States taken together [22]. A recent study including data on invasive *H. influenzae* disease reported to ECDC during 2007–2014 from 12 EU/EEA countries (41% of the total EU/EEA population; year of Hib vaccine introduction ranging from 1992 to 2001; 3-dose vaccination coverage >90% during the study period) showed a sustained low notification rate for Hib and continued decreasing infection trend in all age groups. Although this reduction has been greatest among children <5 years of age, almost 1 in 5 cases is still caused by Hib, a disease preventable by vaccination [23].

In 1998, Coen et al. estimated a value of 70% as critical threshold of vaccination coverage among children <1 year of age required to eradicate Hib infection [24]. Data from the Veneto region of Italy suggested that levels below this threshold could substantially reduce the incidence of Hib invasive disease. In this region, during 1997–1999, a coverage of 26% for primary vaccination in children 1 year of age plus a 31–53% catch-up coverage in children 1–4 years of age resulted in a 91% reduction of Hib disease in children <5 years of age [25]. In our study, the hospitalization rates for invasive *H. influenzae* disease among infants declined significantly (-55%) when Hib vaccine coverage achieved more than 90%. Similar significant reduction (-60%) was observed among children 1–4 years when coverage at 24 months increased from 70.2% to 83.4% (Fig. 1), documenting herd effect in older (unvaccinated) children.

Moreover, our hospital admissions analysis showed higher rates of *H. influenzae* invasive disease ($1.6 \times 100{,}000$ infants and $0.2 \times 100{,}000$ children 1–4 years in 2013) than seen in IBD surveillance ($0.8 \times 100{,}000$ infants and $0.1 \times 100{,}000$ children 1–4 years in 2013) [15,16]. Some regions (Lombardia, Emilia Romagna, Veneto and Friuli-Venezia Giulia) showed a 50% discrepancy in hospitalization and surveillance reporting (Fig. 2), despite they are among those regions that are deemed to have more solid regional surveillance systems and seem less prone to under-reporting or under-diagnosis compared to other geographical areas [26]. IBD surveillance data 2016 showed that a group of seven regions (representing 43% of the Italian population and including the four aforementioned) provided 75.7% of all invasive *Haemophilus influenzae* disease notifications with an incidence of $0.41 \times 100{,}000$, approximately double than the national one ($0.23 \times 100{,}000$) [16]. These differences suggest that use of data for only microbiologically confirmed cases might underestimate incidence of *H. influenzae* disease, complicating efforts to understand its occurrence and burden, particularly when the evaluation of vaccination programmes need timely, reliable incidence data.

The pattern of this underreporting is a complex mix of factors, including availability and use of appropriate diagnostic services, reporting practices by physicians, and the operation of the surveillance system itself [27]. A possible explanation of the significant differences in reporting practices between Italian regions could lie, as seen in other studies, in a lack of feedback on the outcome of notification activities, perceived by clinicians as no useful action has been taken, leading to further apathy about the process [28].

Estimates for Italy would suggest that there could be still 12.4% of subjects admitted to hospital with serotype b disease. This occurrence has been observed in other countries with effective Hib vaccination programmes, showing the importance of ongoing vaccine development and deployment to ensure child health [29]. In France, where routine Hib vaccination was introduced in 1993, the proportion of type b isolates decreased markedly between 1991–1992 (80%) and 1995–2007 (16%). During the 1999–2007 post-vaccine period, no case of invasive Hib infection was identified in fully vaccinated children; more than half of the cases diagnosed in children up to age 15 years occurred in those not appropriately vaccinated for their age [30]. In Finland, where universal Hib vaccination was introduced since 1986, serotype b accounted for 8% of isolates from *H. influenzae* meningitis cases reported during 2004–2014 [31].

Some limitations could have affected our analysis. Using data from hospital discharge database is known to have limitations such as sensitivity and specificity of the coding, differences in coding habits over space and mainly time. In this study, the more than twice higher estimation of *H. influenzae* disease incidence through hospital data than seen in IBD surveillance raises the issue of the specificity of the hospital data (mainly due to lack of serotyping information) and not only of the poor sensitivity of the IBD surveillance. On the other hand, we could have lost several cases because a number of the discharge records are coded as meningitis or septicaemia due to unspecified bacterium, as showed in a recently published study on meningococcal meningitis burden in Italy [27].

Another limitation is the absence of data on vaccination status of cases in both national hospital discharge database and IBD surveillance available data, making our evaluation of the remaining occurrence of Hib in children fairly weak. Moreover, both hospitalization and surveillance data were provided on an anonymous basis, making the absence of record-verification of vaccination status a major study limitation.

In Italy, as in the rest of Europe [22], most invasive *H. influenzae* infections are currently caused by non-capsulated *H. influenzae* strains [11,18,32,33] and there is still no evidence of serotype replacement following the introduction of routine Hib vaccination [22].

Our study, despite its limitations, provided reassuring data on the sustained success of serotype b vaccination on the burden of hospitalization due to invasive disease in children in Italy. Maintaining high vaccination coverage for combined vaccines and enhancing continuous surveillance are however essential [22].

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Conflict of interest

Domenico Martinelli reports grants and non-financial support from Sanofi Pasteur MSD, GSK, and Pfizer, outside this work. Paolo Bonanni reports grants and personal fees from Pfizer, grants and personal fees from GSK, personal fees from Novartis, grants and personal fees from Sanofi Pasteur MSD, personal fees from Sequiros. Susanna Esposito reports grants from DMG, GSK, Pfizer, Sanofi Pasteur MSD, Valeas, Vifor and was involved in advisory boards from GSK and Sanofi Pasteur MSD. Elisabetta Franco reports reimbursement for participation to meetings and advisory boards from GSK and Sanofi Pasteur MSD without any personal fee. Giancarlo Icardi reports grants from Sanofi Pasteur MSD, GSK, Novartis, and Pfizer for taking part to advisory boards, expert meetings, for acting as speaker and/or organizer of meetings/congresses and as principal investigator and chief of O.U. in RCTs. Gianvincenzo Zuccotti reports grants from Sanofi Pasteur MSD, GSK, Novartis, Pfizer for taking part to advisory boards and expert meetings. Rosa Prato has served in advisory committees related to Hib vaccine for Sanofi Pasteur MSD. She also reports grants, personal fees and non-financial support from Sanofi Pasteur MSD, Pfizer, and GSK, outside this work.

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