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Vaccine preventable invasive bacterial diseases in Italy: A comparison between the national surveillance system and recorded hospitalizations, 2007–2016

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ABSTRACT

Background: Vaccine-preventable invasive bacterial diseases (IBDs) caused by *Neisseria meningitidis* (*Nm*), *Streptococcus pneumoniae* (*Sp*), and *Haemophilus influenzae* (*Hi*) have been notified in Italy since 2007 without assessing reporting completeness.
Methods: Our study compared the number of cases of IBDs identified from the Italian Hospital Discharge Records (HDRs), using specific diagnostic ICD-9-CM codes, with those notified to the National Surveillance System (NSS) from 2007 to 2016. A multinomial logistic regression model was used to impute the aetiology of all discharges with a diagnosis of unspecified bacterial meningitis.
Results: Over a 10-year period, 14,243 hospital discharges with diagnosis of IBD were estimated in Italy (12,671 with specified aetiology and 1,572 with imputed aetiology). Among those, 2,513 (17.6%) were caused by *Nm*, 10,441 (73.3%) by *Sp*, and 1289 (9.1%) by *Hi*. Most invasive meningococcal diseases were coded as meningitis (72.3%), while *Hi* and *Sp* were more frequently coded as septicaemia (51.6% and 60.4%, respectively). The highest mean annual incidence rate was found for IBD caused by *Sp* (1.74 per 100,000), followed by *Nm* (0.42 per 100,000) and by *Hi* (0.21 per 100,000). Comparing NSS with HDR data, we found an initially high underreporting of all IBDs, and particularly for *Hi*. Data from the two systems overlapped in more recent years, due to an improved reporting completeness. The increasing IBD incidence observed in NSS data was not confirmed by HDR data trends, although with pathogen-related differences with *Hi* cases rising in both data sources, suggesting that is mainly due to an improved disease notification rather than to a true incidence increase.
Conclusions: Comparing surveillance data with other data sources is useful to better interpret observed trends of notifiable diseases.

1. Introduction

In line with other countries of the European Union (EU) [1], vaccine-preventable invasive bacterial diseases (IBDs) caused by *Neisseria meningitidis (Nm)*, *Streptococcus pneumoniae (Sp),* and *Haemophilus influenzae (Hi)*, hereby vaccine preventable IBD (VP-IBD), have been included since 2007 in an enhanced surveillance system in Italy coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) [2]. This system is laboratory-based and, by definition, cases are notified only if *Nm*, *Sp*, or *Hi* are isolated or identified from normally sterile sites (e.g. blood, cerebrospinal fluid or pleural/peritoneal/pericardium/synovial fluid) [3]. Data on demographic and clinical characteristics, as well as vaccination history of each reported case, are also collected. Pathogens are characterized and monitored over time, in order to assess whether prevailing serogroups/serotypes change among the general population and/or in specific age groups. These data are analysed taking into account current immunization policies, in order to identify outbreaks and the emergence/re-emergence of serotypes/serogroups that are not vaccine-preventable.

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As reported by the European Centre for Disease Prevention and Control (ECDC), IBDs are relatively rare conditions in the European Union (EU), however incidence rates differ notably across countries, pathogens, and age groups. In 2015, the EU mean incidence rate (per 100,000 population) was 0.6 for invasive meningococcal disease (IMD), higher among infants and young children [4], 5.5 for invasive pneumococcal disease (IPD), higher among infants and adults aged 65 years or over [5], and 0.7 for invasive *Haemophilus influenzae* disease (IHD), with peaks among infants under 1 year and in the elderly [6].

The incidence of VP-IBD due to the three pathogens has been consistently lower in Italy compared with the mean incidence in the EU. However, increasing trends in the number of reported cases have been observed in the period 2007–2016, with yearly case counts more than doubling, from 745 in the year 2007 to 1,834 in 2016 [7,8]. The increase, not attributable to ongoing outbreaks, except for one IMD outbreak in Tuscany in 2015–2016 [9], is supposed to be mainly due to improved completeness of surveillance data. However, this interpretation had not been verified and no study had quantified the possible underreporting of VP-IBDs to the National Surveillance System (NSS). To assess the completeness of the NSS and better interpret the observed trends, the number of VP-IBD cases notified to this surveillance system between 2007 and 2016 was compared with the number of Italian Hospital Discharge Records (HDRs) reporting a diagnosis compatible with a VP-IBD in the same time period.

2. Methods

2.1. Data sources

2.1.1. Hospital discharge records

The Italian hospital information system, established in 1995, routinely collects data on all hospital discharges in public and private hospitals and covers 100% of hospital admissions in Italy [10]. It systematically collects both demographic and clinical information, including primary diagnosis and up to five secondary diagnoses, primary and secondary diagnostic/therapeutic procedures, type of discharge, hospital length of stay. Diagnoses and procedures are coded using the "International Classification of Diseases, 9th Revision, Clinical Modification" (ICD-9-CM). The data are sent by hospitals to the Regional Health Authority that, before transmission to the Ministry of Health, is responsible of data quality verification.

2.1.2. The Italian national surveillance system for VP-IBD

Laboratory confirmed VP-IBD cases are reported by clinicians and laboratory staff in hospitals to local health authorities and to the ISS [2]. Isolates/samples are sent for further characterization/advanced diagnostics to Regional Reference Laboratories and/or to the National Reference Laboratory at the ISS. Data on each patient and on the pathogen causing the disease (e.g. species, serogroup/serotype) are routinely collected by Local Health Units and transferred to the ISS and to the Ministry of Health. Information on vaccine introduction, vaccine coverage, and most frequent serogroups/serotypes circulating in Italy is given in Supplement 1.

2.2. Identification of VP-IBD cases from hospital discharge records

We selected hospital discharges due to VP-IBD on the basis of the following ICD-9-CM codes as indicated in primary or secondary diagnoses:

- Invasive Meningococcal Disease:
  - meningitis – 036.0 "Meningococcal meningitis";
  - septicaemia/bacteremia – 036.0 "Meningococcemia";
  - other invasive meningococcal forms – 036.X (i.e., any digit code, but 0 and 2).
- Invasive Pneumococcal Disease:
  - meningitis – 320.1 "Pneumococcal meningitis", or 041.2 "Pneumococcus infection in conditions classified elsewhere and of unspecified site" if associated with 320.7 "Meningitis in other bacterial diseases classified elsewhere" or with 320.8X "Meningitis due to other specified bacteria";
  - septicaemia/bacteremia – 038.2 "Pneumococcal septicemia", or 041.2 "Pneumococcus infection in conditions classified elsewhere and of unspecified site" if associated with 038.8 "Other specified septicemias" or with 038.9 "Unspecified septicemia", or 041.2 "Pneumococcus infection in conditions classified elsewhere and of unspecified site" if associated with 790.7 "Bacteremia";
  - other invasive pneumococcal disease – 481 "Pneumococcal pneumonia" if associated with 790.7 "Bacteremia", 567.1 "Pneumococcal peritonitis", or 041.2 "Pneumococcus infection in conditions classified elsewhere and of unspecified site" if associated with 681.X "Cellulitis and abscess of finger and toe" or with 682.X "Other cellulitis and abscess" (cellulitis), or with 464.3X "Acute epiglottitis" (epiglottitis), or with 420.X "Acute pericarditis" (pericarditis), or with 711.0X "Pyogenic arthritis" (septic arthritis), or with 730.X "Osteomyelitis periostitis and other infections involving bone" (osteomyelitis).
- Invasive *Haemophilus influenzae* Disease:
  - meningitis – 320.1 "Haemophilus meningitis" or 041.5 "*Hemophilus influenzae* infection in conditions classified elsewhere and of unspecified site" if associated with 320.7 "Meningitis in other bacterial diseases classified elsewhere" or with 320.8X "Meningitis due to other specified bacteria";
  - septicaemia/bacteremia – 038.41 "*Haemophilus Influenzae* septicemia" or 041.5 "*Hemophilus influenzae* infection in conditions classified elsewhere and of unspecified site" if associated with 038.8 "Other specified septicemias" or with 038.9 "Unspecified septicaemia" or with 790.7 "Bacteremia";
  - other invasive *H. infuenzae* forms – 482.2 "Pneumoniae due to *Haemophilus Influenzae*" if associated with 790.7 "Bacteremia", or 041.5 "*Hemophilus influenzae* infection in conditions classified elsewhere and of unspecified site" if associated with 567.X "Peritonitis and retroperitoneal infections" (peritonitis), or with 681.X "Cellulitis and abscess of finger and toe" or with 682.X "Other cellulitis and abscess" (cellulitis), or with 464.3X "Acute epiglottitis" (epiglottitis), or with 420.X "Acute pericarditis" (pericarditis), or with 711.0X "Pyogenic arthritis" (septic arthritis), or with 730.X "Osteomyelitis periostitis and other infections involving bone" (osteomyelitis).

2.3. Imputation of VP-IBDs among HDRs for "meningitis due to unspecified bacterium"

Preliminary exploratory analyses highlighted that 22% of all bacterial meningitis in the HDRs were reported only as ICD-9-CM code 320.9: "meningitis due to unspecified bacterium". We therefore decided to capture all HDRs with any code for bacterial meningitis (i.e., *Nm, Sp, Hi, other Streptococcus, Staphylococcus, Mycobacterium tuberculosis, Listeria monocytogenes*, other specified bacteria) with the aim of reclassifying HDRs with the 320.9 code using a multiple imputation approach [11,12]. In the statistical analysis section, we describe how this multiple imputation was

performed. Details of the ICD-9-CM codes selected to identify other bacterial meningitis are reported in Supplement 2.

2.4. Statistical analysis

We extracted all the Italian national HDRs between January 1st, 2005 and December 31st, 2016. We considered each HDR as a hospitalization event unless the same patient was found having experienced more than one hospital admission during the same period, in this case only the first one was included. An exception to this general rule was represented by re-admissions within 48 h after the previous discharge that were due to transfers between hospitals. These re-admissions, being a continuation of a single hospitalization event, were managed accordingly. Following this classification, we excluded all hospitalization events occurring in the years 2005 and 2006, in order to exclude patients with sequelae from previous IBDs discharged from 2007 to 2016 with codes indicating prior disease.

In order to reclassify HDRs with ICD-9-CM code 320.9, a multivariable multinomial logistic regression model [13] was used to calculate adjusted relative risk ratios for possible predictors of meningitis due to different pathogens. To this aim, we investigated the effect of seasonal, demographic factors and intra-country geographical variations, since previous studies have shown that class of age, temperature and geographical area were associated with invasive bacterial disease occurrence [14,15]. The following variables were included: age group at hospital admission (11 age groups: newborns <1 month of life, children 1–12 months of age, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–59 and ≥60 years old), gender, nationality (i.e., Italian, non-Italian), geographical area of residence (northern, central or southern Italy as defined by the Italian National Bureau of Census), month of hospital admission and year of hospital discharge. All those variables significantly ($p < 0.05$) improved the goodness of fit of the model according to the log-likelihood ratio test. In order to quantify the accuracy of the model, the area under the multiclass receiver operator characteristics curve (AUC) with 95% confidence interval was considered, using a procedure based on kernel density estimation through a bootstrap method with 100 iterations [16,17]. Following this, the multiple imputation method was used to reclassify the "meningitis due to unspecified bacterium" (i.e. each HDR with ICD-9-CM code 320.9) based on case-specific characteristics. This approach, essentially an iterative form of stochastic imputation (based on the previously identified variables), uses the distribution of the observed data to estimate missing information (in this case the pathogen causing the meningitis). This procedure generates multiple (200 in this analysis) imputations of the missing outcome that were then summarized considering the median value, and the 3th and 97th percentiles as a measure of uncertainty [12]. The estimated outcome for each HDR was then used in the analysis, and the median value was added to the frequency of IBD hospitalization events for each specific pathogen.

The number of discharges (identified and imputed) by pathogen were summarized by calendar year, by age group, and by geographical area (i.e., northern, central, and southern Italy, based on the Italian National Bureau of Census - ISTAT, www.demo.istat.it – classification). We calculated the yearly IBD incidence rates by pathogen, using population statistics from ISTAT, and compared these rates and case counts with those reported by the NSS for all IBDs in the same time-period. NSS data were derived from the official reports [7,8]. Descriptive data on meningitis due to other bacteria, as well as the results of the multinomial multivariable logistic regression model are provided in Supplementary Tables S1 and S2a-b.

Statistical analysis was performed using the Stata software, version 13 (Stata Cooperation, College Station, Texas, USA).

3. Results

3.1. Vaccine preventable invasive bacterial diseases

We identified 12,671 hospital discharges with a diagnosis compatible with IBD due to *Nm*, *Sp*, and *Hi* (5,567 with at least meningitis, 6,860 with at least septicaemia, and 1,051 with other invasive conditions) between 2007 and 2016 in Italy. Most VP-IBDs were caused by *Sp* (9430, 74.4%), followed by *Nm* (2,067, 16.3%) and by *Hi* (1,174, 9.3%) (Table 1). IMD presented mainly as meningitis (1,370, 66.3%), whereas the most common clinical presentation of IPD and HID was septicaemia/bacteraemia (5,388, 57.1% and 779, 66.4% respectively). Of all VP-IBDs cases, 5.3% (674/12,671) were diagnosed with both meningitis and septicaemia. Of those 262 (38.9%) were caused by *Nm*, 393 (58.3%) by *Sp* and 19 (2.8%) by *Hi*. The combination of the two syndromes was more frequently found among cases of IMD 12.7% (262/2,067), followed by IPD 4.2% (393/9,430), and IHD 1.6% (19/1,174). IMD cases declined during the 2007–2013 period, then subsequently increased, whereas IPD and IHD remained quite stable until 2014 and 2011, respectively, increasing thereafter.

3.2. Predictive factors for bacterial meningitis due to a specific pathogen

Multinomial logistic regression was used to evaluate predictive factors, based on demographic and clinical characteristics, associated with meningitis caused by *Nm* and *Hi* compared to *Sp*, with the aim of reclassifying cases that did not have a specified bacterial pathogen in the diagnostic codes. Supplementary Table S2 shows the main characteristics of the bacterial meningitis cases reported in the HDR in the period 2007–2016 in Italy. In summary, children <5 years of age (22.7%) and 15–24 year-olds young adults (20.9%) were the most affected by meningitis caused by *Nm*. Most cases due to *Sp* (41.7%) or *Hi* (36.7%) were ≥65 year old, followed by 45–64 year old adults (30.5% and 25.6%, respectively). In addition, children <5 years accounted for 7.9% of IPD, while infants <1 year accounted for 8.7% of IHD. Infants <1 year were the most affected by meningitis due to *Streptococcus* spp. other than *Sp* (33.5%) and *Staphylococcus* spp. (7.6%), together with adults aged 25–44 years and elderly (27.5% and 42.2%, respectively). The majority of cases was registered in northern Italy, and among males. As indicated in Supplementary Tables S2a-b, all the characteristics reported above were significantly associated with the specific bacteria. The classification accuracy of the model was very good, indicated by an AUC of 0.82 (95% confidence interval 0.73–0.90). Considering *Sp* meningitis as reference, new-borns admitted during the first month of life showed a higher risk of *Hi* meningitis [relative-risk ratio (RRR): 3.43] compared with children aged from 1 month to 1 year. Teenagers (RRR 5.33) and young adults up to 24 years (RRR 4.56) were at higher risk for *Nm* meningitis compared with *Sp* meningitis. Females showed an increased risk of meningitis by *Nm* (RRR 1.19). Living in central or southern Italy, as compared with the north of Italy, was associated with a higher risk for *Nm* meningitis (RRR 1.31 centre, 1.36 south). Compared to *Sp*, the risk of bacterial meningitis due to *Hi* was higher during summer months.

3.3. Comparison between hospital discharge records and national surveillance system

Table 2 and Figs. 1–3 show the number of IBD cases caused by *Nm*, *Sp*, and *Hi* reported to the NSS, and those identified by the HDR, during the period 2007–2016. Cases identified by HDRs (with a specified diagnostic code corresponding to a VP-IBD) including

Table 1
Vaccine-preventable invasive bacterial diseases, Italy 2007–2016.

Year	*Neisseria meningitidis*				*Streptococcus pneumoniae*				*Haemophilus influenzae*			
	Meningitis	Septicaemia	Other	IMD	Meningitis	Septicaemia	Other	IPD	Meningitis	Septicaemia	Other	IHD
2007	162	93	50	257	409	453	102	924	40	52	3	93
2008	144	90	46	239	357	489	123	932	37	55	2	93
2009	181	78	33	250	355	505	71	904	38	63	3	102
2010	116	68	34	190	370	484	80	903	46	85	9	135
2011	146	62	36	211	403	496	48	907	39	61	2	100
2012	119	54	28	172	350	490	52	859	34	82	3	116
2013	106	53	30	157	377	559	55	941	39	71	2	111
2014	108	63	34	176	357	524	45	878	39	90	6	133
2015	138	58	37	196	414	671	33	1,064	35	98	7	137
2016	150	74	34	219	426	717	40	1,118	32	122	3	154
2007–2016	1,370	693	362	2,067	3,818	5,388	649	9,430	379	779	40	1,174

Data were extracted from Hospital Discharge Records.
Diagnosis of meningitis and septicaemia were not mutually exclusive. Septicaemia included bacteraemia.
IMD, Invasive meningococcal disease; IPD, Invasive pneumococcal disease; IHD, Invasive *Haemophilus influenzae* disease.
IMD included meningitis, septicaemia and other (bacteremic pneumonia, cellulitis, epiglottitis, peritonitis, pericarditis, arthritis, osteomyelitis).
ICD-9-CM diagnosis codes for IMD: 036.X meningococcal infections (036.0 meningitis, 036.2 meningococcemia).
ICD-9-CM diagnosis codes for IPD: 320.1 or [041.2 & (320.7 or 320.8X)] meningitis, 038.2 or [041.2 & (038.8 or 038.9)] or (041.2 & 790.7) septicaemia, 481 & 790.7 bacteremic pneumonia, 041.2 & (681.X or 682.X) cellulitis, 041.2 & 464.3X epiglottitis, 567.1 peritonitis, 041.2 & 420.X pericarditis, 041.2 & 711.0X arthritis, 041.2 & 730.X osteomyelitis.
ICD-9-CM diagnosis codes for IHD: 320.0 or [041.5 & (320.7 or 320.8X)] meningitis, 038.41 or [041.5 & (038.8 or 038.9)] or (041.5 & 790.7) septicaemia, 482.2 & 790.7 bacteremic pneumonia, 041.5 & (681.X or 682.X) cellulitis, 041.5 & 464.3X epiglottitis, 041.5 & 567.X peritonitis, 041.5 & 420.X pericarditis, 041.5 & 711.0X arthritis, 041.5 & 730.X osteomyelitis.

Table 2
Number of cases and incidence rates of vaccine-preventable invasive bacterial diseases, Italy 2007–2016.

Year	*Neisseria meningitidis*					*Streptococcus pneumoniae*					*Haemophilus influenzae*				
	N. cases		Incidence rates			N. cases		Incidence rates			N. cases		Incidence rates		
	NSS	Adj HDR	NSS	Adj HDR	95% CI	NSS	Adj HDR	NSS	Adj HDR	95% CI	NSS	Adj HDR	NSS	Adj HDR	95% CI
2007	183	319	0.31	0.54	0.52–0.56	524	1,075	0.89	1.82	1.78–1.86	38	109	0.06	0.18	0.17–0.20
2008	180	296	0.30	0.50	0.47–0.52	691	1,046	1.16	1.75	1.72–1.78	49	106	0.08	0.18	0.17–0.19
2009	187	312	0.31	0.52	0.50–0.54	738	1,022	1.23	1.70	1.67–1.73	54	117	0.09	0.19	0.18–0.21
2010	149	228	0.25	0.38	0.36–0.40	848	998	1.41	1.65	1.63–1.68	70	148	0.12	0.25	0.24–0.26
2011	152	261	0.25	0.43	0.41–0.45	750	1,011	1.24	1.67	1.64–1.70	49	112	0.08	0.18	0.17–0.20
2012	137	211	0.23	0.36	0.34–0.38	815	949	1.37	1.60	1.57–1.63	63	126	0.11	0.21	0.20–0.23
2013	172	188	0.29	0.31	0.30–0.33	977	1,033	1.64	1.73	1.70–1.76	78	122	0.13	0.20	0.19–0.22
2014	164	212	0.27	0.35	0.33–0.36	955	962	1.57	1.58	1.56–1.61	106	143	0.17	0.24	0.23–0.25
2015	189	234	0.31	0.38	0.37–0.40	1,250	1,150	2.06	1.89	1.87–1.91	131	145	0.22	0.24	0.23–0.25
2016	232	252	0.38	0.42	0.40–0.43	1,462	1,195	2.41	1.97	1.95–1.99	140	161	0.23	0.27	0.26–0.28
2007–2016	1,745	2,513	0.29	0.42	0.41–0.42	9,010	10,441	1.50	1.74	1.73–1.75	778	1,289	0.13	0.21	0.21–0.22

NSS, National Surveillance System; Adj HDR, Hospital Discharge cases with invasive bacterial disease including also imputed unspecified bacterial meningitis (see Methods and Supplement 2). Confidence intervals refer to adjusted rates.
HDR data were extracted from Hospital Discharge Records; Italian population data were obtained from ISTAT database (www.demo.istat.it). Incidence rates are expressed per 100,000 population.

imputed VP-IBDs and notified cases are presented. At the beginning of the study period, the number of IMD cases reported to the NSS was consistently lower than the relevant HDR (Fig. 1). This difference declined in more recent years when the number of cases identified by the two systems were very similar. The time trend of the cases was substantially different, with a quite stable trend of IMD reported to the NSS and a declining trend for hospitalizations from HDR. IPD trends were also different with a steep rise in the number of cases reported to the NSS in the study period and a relatively stable trend of HDR, with a slight increase in 2015–2016. At the beginning of the study period, the trend of IPD (Fig. 2) showed a higher number of cases reported through the HDR compared to the number reported to the NSS. This difference progressively decreased until 2013, when the number of cases reported through the HDR became lower than the number reported to the NSS. This was true also considering HDR cases obtained after combining notified and imputed IPD cases in 2015 and 2016.

IHD cases rose in both data sources with evidence of a more clear increasing trend following 2011, although NSS reported cases increased more steeply throughout the study period. Differences in IHD counts between the two data sources were more evident at the beginning of the study period and progressively decreased in time, almost coinciding in 2016 (Fig. 3). According to the data reported in Table 1, the rise observed by using the HDR was due to an increasing number of cases presenting with septicaemia.

Table 2 shows the number of cases and the incidence rates (IR) per year of VP-IBD by pathogen, obtained from the NSS and HDR (including cases estimated by multiple imputation from unspecified meningitis). In line with Figs. 1–3, the IR of HDR cases was often higher than the IR of NSS reported cases, with IR estimates obtained from the two registries becoming closer in the most recent years. Specifically, the highest mean annual IR (per 100,000 population) was detected for IBD due to *Sp* (1.50 from NSS and 1.74 from adjusted HDR), followed by those caused by *Nm* (0.29 from NSS and 0.42 from adjusted HDR) and by *Hi* (0.13 from NSS and 0.21 from adjusted HDR).

Stratifying VP-IBD by clinical presentation (i.e. meningitis and septicaemia/other), we observed that the highest proportion of cases reported to the NSS, as compared to the HDR, were classified as meningitis, both for *Nm* (92.8%) and *Hi* (72.8%). Conversely, NSS cases presenting with septicaemia/other exceeded those recorded in HDR database for *Sp* (103.3%) (Table 3). Classification by age

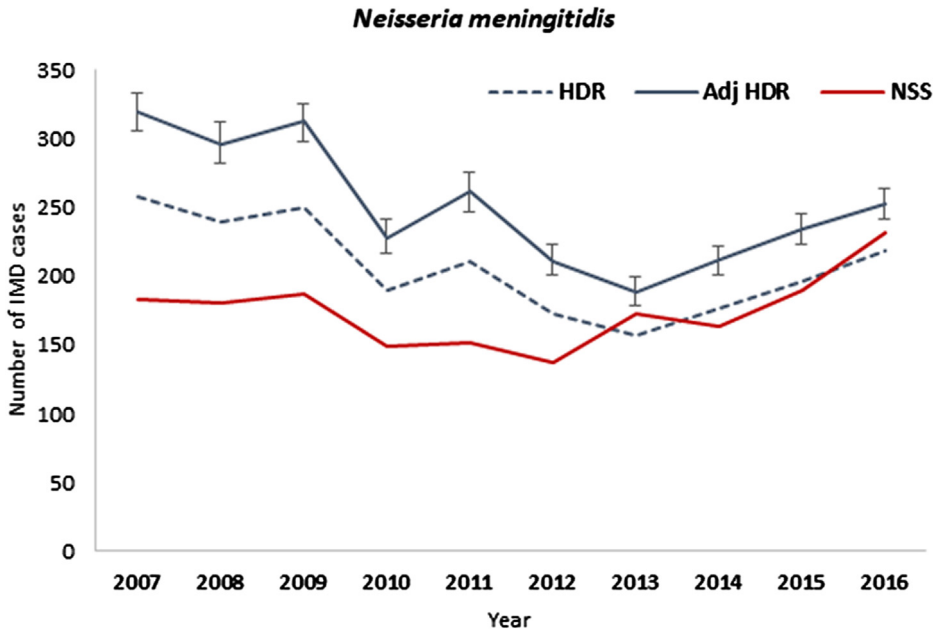

Fig. 1. Invasive meningococcal disease, Italy 2007–2016. Comparison between unadjusted/adjusted HDR and NSS. NSS, National Surveillance System; HDR, Hospital Discharge Records; Adj HDR, Adjusted HDR including imputed unspecified bacterial meningitis.

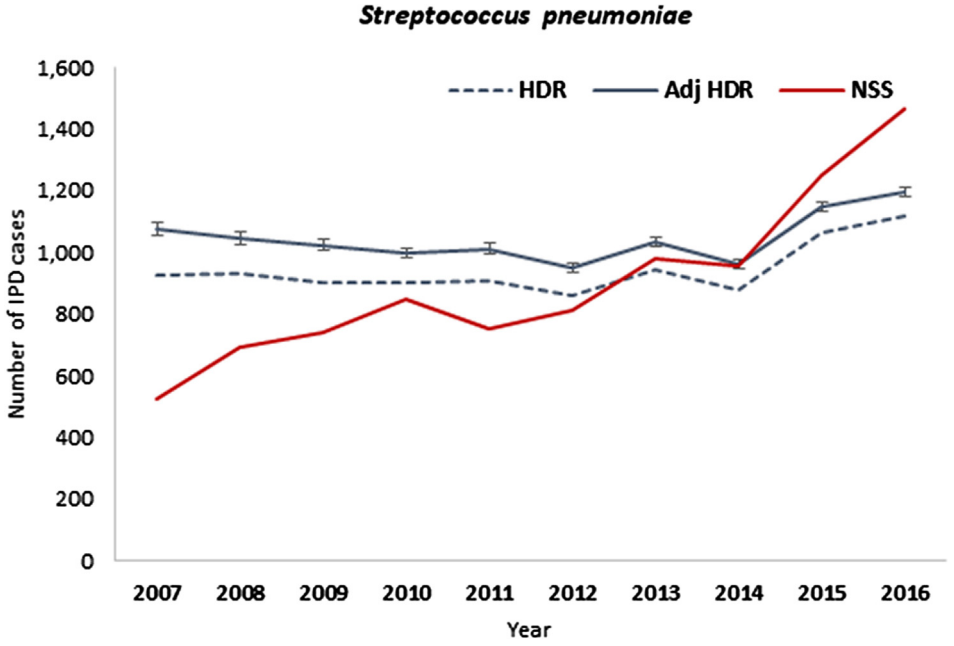

Fig. 2. Invasive pneumococcal disease, Italy 2007–2016. Comparison between unadjusted/adjusted HDR and NSS. NSS, National Surveillance System; HDR, Hospital Discharge Records; Adj HDR, Adjusted HDR including imputed unspecified bacterial meningitis.

groups (0–14, 15–64 and ≥65 years) showed that the highest percentage of cases reported to the NSS, as compared to the adjusted HDR, was found for patients 0–14 years old, both for *Nm* (77.0%) and *Hi* (71.2%), whereas the highest value was found for patients aged 65 years and over for *Sp* (91.4%) (Table 3). Of note, values just over 50% were found for the elderly, both for *Nm* and *Hi*. Northern Italy showed the highest levels of reporting completeness, while low values were detected for the southern Regions, particularly for *Hi* (15.7%) and *Sp* (33.6%).

Overall, in the entire study period 2007–2016, NSS cases of VP-IBD were respectively 91% and 81% of those obtained by unadjusted and adjusted (by multiple imputation) HDR data, indicating a good level of reporting completeness. Specifically, IMD cases reported to the NSS were 84% and 69%, IPD cases were 96% and 86%, and IHD cases were 66% and 60% of those unadjusted/adjusted from HDR, respectively.

4. Discussion

The present study had the aim to compare VP-IBDs cases from two data sources (NSS and HDR) over a 10-year period in Italy. The comparison suggests that NSS data are affected by underreporting, which differs by pathogen and calendar year. HDR data

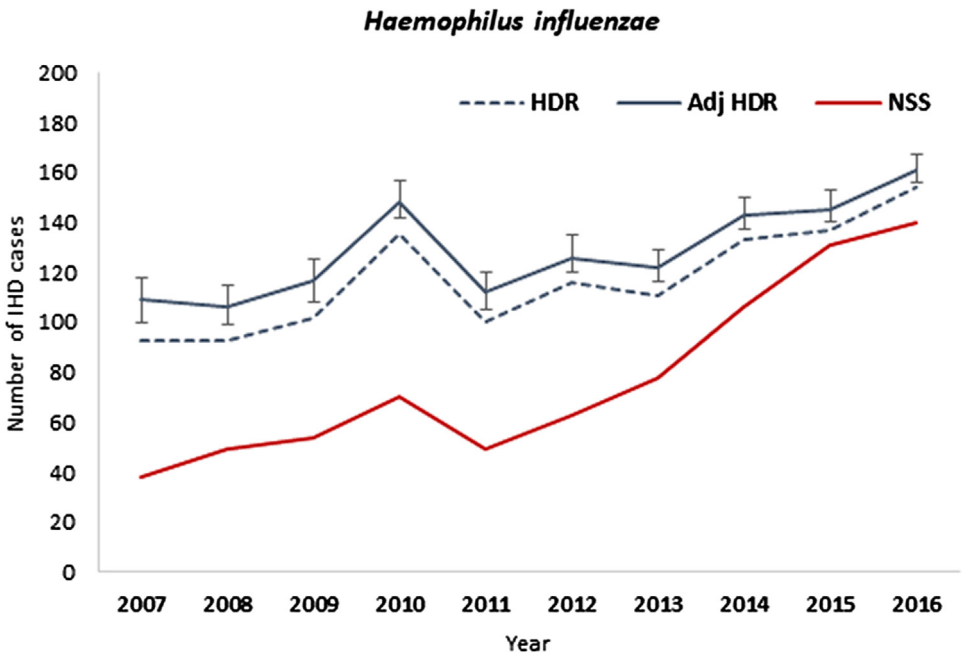

Fig. 3. Invasive *haemophilus influenzae* disease, Italy 2007–2016. Comparison between unadjusted/adjusted HDR and NSS. NSS, National Surveillance System; HDR, Hospital Discharge Records; Adj HDR, Adjusted HDR including imputed unspecified bacterial meningitis.

Table 3
Comparison of vaccine-preventable invasive bacterial diseases reported by the Italian National Surveillance System and those obtained by the Italian Hospital Discharge Records by class of age and geographical area, Italy 2007–2016.

VP-IBD	NSS	HDR	NSS/HDR (%)	Adj HDR	NSS/Adj HDR (%)
Neisseria meningitidis	1,745	2,067	84.4	2,513	69.4
Meningitis	1,271	1,370	92.8	1,815	70.0
Septicaemia/other	469	697	67.3	–	–
Class of age (years)					
0–14	747	805	92.8	970	77.0
15–64	837	997	84.0	1,243	67.3
>64	161	265	60.8	300	53.7
Geographical area					
North	999	1,038	96.2	1,212	82.4
Centre	388	522	74.3	626	62.0
South	358	507	70.6	675	53.0
Streptococcus pneumoniae	9,010	9,430	95.5	10,441	86.3
Meningitis	3,193	3,818	83.6	4,826	66.2
Septicaemia/other	5,797	5,612	103.3	–	–
Class of age (years)					
0–14	1,024	1,002	102.2	1,132	90.5
15–64	3,214	3,594	89.4	4,086	78.7
>64	4,772	4,834	98.7	5,223	91.4
Geographical area					
North	7,817	6,659	117.4	7,156	109.2
Centre	711	1,604	44.3	1,849	38.5
South	482	1,167	41.3	1,436	33.6
Haemophilus influenzae	778	1,174	66.3	1,289	60.4
Meningitis	276	379	72.8	496	55.6
Septicaemia/other	497	795	62.5	–	–
Class of age (years)					
0–14	136	170	80.0	191	71.2
15–64	275	373	73.7	431	63.8
>64	367	631	58.2	667	55.0
Geographical area					
North	660	813	81.2	864	76.4
Centre	86	195	44.1	221	38.9
South	32	166	19.3	204	15.7

NSS, National Surveillance System; HDR, Hospital Discharge Records; Adj HDR, Hospital Discharge Records with a diagnosis of invasive bacterial diseases including those imputed as part of the unspecified bacterial meningitis. According to NSS reports, VP-IBD cases diagnosed with both meningitis and septicaemia have been classified as meningitis.

were used as reference because this data source covers 100% of all hospital admissions.

In Italy, no study has been performed at a national level aimed at evaluating the possible underreporting to the NSS of VP-IBD. In a previous study combining different health data sources in the Lazio Region, evaluating the reporting of bacterial meningitis from 2001 to 2005, it was estimated that just around 50% of the cases were reported to the surveillance system [18]. In a more recent study conducted in Veneto Region, reporting completeness of IMD was evaluated using different data sources, combined surveillance system (CSS) and HDR, resulting in 63% of cases recorded by both information sources, 18% only by the CSS and 19% only in the HDR [19].

In our study, although underreporting to the national surveillance was found, a good agreement between the two institutional information systems for VP-IBD was observed, particularly in more recent years. Indeed, several initiatives have been implemented to improve the notification rate. This includes defining a more sensitive laboratory diagnosis for confirmation, training and awareness raising initiatives targeting the specialists involved, as well as recommendations for public health practitioners and health managers. Moreover, since 2013 data from the national surveillance system have been also integrated with data from the Regional infectious disease notification systems. The number of cases notified yearly to the NSS, over time proportionally increased compared with the hospitalizations recorded in the HDR, from 57% in 2007 to 92% in 2016 for IMD and from 35% to 87% for IHD, respectively. Of note, for IPD the percentage ranged from 49% in 2007 to 99% in 2014, while in 2015 and 2016 the cases reported to the NSS exceeded those recorded in the HDR. The possibility of coding errors and inappropriate discharge diagnosis are more likely in the hospital records, whereas this is not expected to occur in the national surveillance system, where all the cases are laboratory-confirmed.

Study findings indicate that the NSS could not be exhaustive as a unique source of information because it failed to identify approximately 20% of VP-IBD cases. Specifically, the proportion of the notified diseases to NSS out of the adjusted HDR cases was 69% for *Nm*, 86% for *Sp* and 60% for *Hi*. This partiality in data availability can make the interpretation of case count and incident trends more difficult. In our study, the steep rise in IBD incidence observed in NSS data was not confirmed by HDR data trends and, also considering pathogen-related differences with *Hi* cases increasing in both data sources, was consistently linked to a more pronounced underreporting at the beginning of the study period. This suggests that the steep rise in the number of reported IBD cases is mainly due to an improved disease notification rate rather than to a true incidence increase. Comparing surveillance data with another data source in this case was useful to better interpret the trends observed through surveillance alone.

Notwithstanding these limitations, only the NSS can provide accurate information on the microbiological characteristics of the invasive pathogens by serogroups and serotypes. This information allows us to monitor changes in serogroup/serotype distribution due to the immunization policies and to promptly detect outbreaks, driving immunization interventions. Moreover, continued enhanced VP-IBD surveillance is essential for assessing the long-term effectiveness of vaccination by age, also considering evolving vaccination policies.

We also should consider some limitations when using HDR data for this comparison. HDR data have the limit of ICD-9 diagnostic codes, which are not based on specific case definitions, and the diagnostic criteria used in the clinical practice are sometimes not extremely accurate if no added value in terms of clinical case-management is expected. Therefore, HDR are not necessarily accurate for identifying specific diagnosis and can be also affected by underreporting, as observed for pneumococcal disease in 2015 and 2016. In this setting, physicians' reporting needs to be improved in order to ensure a better and more extensive diagnosis, for instance adding bacteraemia to a diagnosis of pneumococcal pneumonia. Indeed, taking into account only meningitis cases due to *Sp*, NSS and HDR data almost overlapped. Further, more than 20% of all bacterial meningitis hospital discharges in the study period had the ICD-9-CM diagnostic code 320.9 "meningitis due to unspecified bacterium". However, in order to have more accurate estimate of meningitis by bacterial agent, multivariable multinomial logistic regression model and multiple imputation technique were used to reclassify unspecified meningitis recorded in the HDR by specific pathogen.

5. Conclusions

Efficient and reliable surveillance systems are fundamental for monitoring disease trends and outbreaks. They provide essential data for decision-making processes, public health policies, planning of intervention measures and healthcare services. However, most notification systems are affected by some degree of underestimation. Several efforts could be implemented to reduce underreporting and aimed at strengthening surveillance procedures, as implementing automated, electronic laboratory-based reporting and training, raising awareness among clinicians, microbiologists, public health specialists and other key partners in notifiable disease reporting. Finally, the adoption on a routine basis of the evaluation of surveillance systems, also through the review of hospital discharge registries for case-finding, could be a valid support to improving the quality of surveillance data [20–21]. In conclusion, both sources should be considered for comprehensive knowledge of the epidemic dynamics useful to prevention strategies planning and public health decision-making.

6. Authors' contributions

PS, GR and PP conceived the initial idea and the study design. PP, SB and FL performed the statistical analyses. PP, SB FL, and FR drafted the manuscript. AP and MC critically revised the manuscript. PS is the coordinator of the Italian National Surveillance System for VP-IBD and critically revised the manuscript. PS, AP, MC are responsible of the National reference laboratory of *Nm*, *Sp*, and *Hi*, respectively. All authors revised and approved the manuscript.

7. Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.047.

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