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Impact of Pertussis on the Italian population: analysis of hospital discharge records in the period 2001-2014

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ABSTRACT

Objectives

The study aimed to analyze and update the impact of pertussis on the Italian population by evaluating pertussis-related hospital admissions in the period 2001-2014.

Design or methods

Hospital Discharge Records (HDR) were provided by the National Archive of HDR data of the Ministry of Health. Only hospitalizations included in the primary diagnosis were evaluated. Significant trends over the considered years were assessed as average annual percent changes (AAPC) applying the Joinpoint model.

Results

A total of 7,102 hospital admissions for pertussis (main diagnosis) were registered; the trend of hospitalizations progressively decreased from >1/100,000 inhabitants in the years 2001-2004 to 0.64/100,000 inhabitants in 2014. A great part of hospitalizations (63.6%) involved subjects <1 year of life; almost 20% of cases were registered in the age class 5-14 years. The Joinpoint analysis showed a statistically significant variation in some age classes.

Conclusions

Even if this study shows a decreasing trend in the number of pertussis-related hospitalizations, the impact of the disease in Italy in terms of hospital admissions continues to be relevant, especially in the <1 year age class. Pertussis therefore continues to be, in Italy as well as in other European countries, an important public health issue.

Keywords: pertussis; burden; vaccination; pertussis-related hospitalization; hospital discharge record.

Introduction

Pertussis is a respiratory infection caused by *Bordetella pertussis*, an endemic bacteria in all countries, transmitted to susceptible individuals via droplets and highly contagious; it affects all age groups but tends to be responsible for severe clinical pictures in children, particularly infants (Kilgore at al., 2016; Edwards and Decker, 2013).

It represents a worldwide important cause of childhood morbidity and mortality and, despite high vaccine coverage achieved in many parts of the world, it continues to be a public health issue (Edwards and Decker, 2013).

In infants pertussis may have severe features, such as apnoea and cyanosis (World Health Organization, 2015a) while in adolescents and adults the disease is milder and it may have atypical features (Guiso et al., 2011a), making them a potential source of infection for susceptible children (World Health Organization, 2015a).

In the pre-antibiotic and pre-vaccination era, child morbidity and mortality were very high(Mattoo and Cherry, 2005).

Both whole cell (wP) and acellular (aP) pertussis vaccines have a high level of safety, efficacy and effectiveness (Halperin BA and Halperin SA, 2011); however aP vaccines may be less effective than the highest-efficacy wP vaccines (World Health Organization, 2015a). A recent study compared the immunity response induced by the acellular and whole cell vaccines. After the primary vaccination cycle, the immune response was similar in aP- and wP-immunized children, while the Tdap booster vaccination induced lower humoral and cellular responses in children who were immunized with aP-vaccine compared with those vaccinated with wP-vaccine (van der Lee S, 2018).

Although vaccination has been associated with a significant decrease in both incidence and mortality, pertussis continues to be one of the most relevant vaccine preventable infectious

diseases, being still a major cause of death in children <1 year of life, too young to have already received all their primary doses of pertussis vaccine or those whose delay the immunization (Halperin BA and Halperin SA, 2011; Saadatian-Elahi et al., 2016). According to a recent review (Domenech de Celle`s et al., 2016), the incidence of pertussis in the world is characterized by both spatial and temporal variability. In Europe, the notification rate has increased since 2011 (5.5/100,000 inhabitants) and 2012, the last epidemic year (11.6/100,000 inhabitants and 42,525 notifications) (Tant et al., 2015; European Centre for Disease Prevention and Control, 2016). In 2016, the notification rate was 10.77 cases /100,000 inhabitants, for a total of about 50,000 cases (Stefanelli et al., 2018) and in 2017 the confirmed European cases were 42,242 with a notification rate of 9.38/100,000 inhabitants (European Centre for Disease Prevention and Control, 2019).In Italy the incidence of pertussis has significantly decreased along with increasing immunization coverage rates. In the epidemic year 2012 the notification rate has been 0.82/100,000 (European Centre for Disease Prevention and Control, 2016) and the last avalaible data (2017) shown 964 notifications and a notification rate equal to 1.59/100,000 inhabitants (European Centre for Disease Prevention and Control, 2019).

Extensive immunization has exerted an immunological pressure on *Bordetella pertussis* and has been followed by a relevant change of the epidemiology of this disease (Gabutti et al., 2008).

Noteworthy, the immune protection conferred by both natural infection and vaccination is not long-lasting; the decline in immunity occurs 4-12 years after vaccination. Therefore, in recent years it has been observed a resurgence of pertussis, due to a progressive decrease of immunity, in particular for acellular vaccines (Klein et al., 2012). As shown by a study on the seroprevalence of IgG antibodies against pertussis toxin in Italy, the limited duration of immune protection conferred by natural disease as well by vaccination leads to an increased

circulation of infection even in adulthood (Fedele et al, 2017). With the introduction of vaccination programs, pertussis disease has shifted to older age groups, thus involving adolescents and adults.

Another significant phenomenon is the confirmation, through the surveillance systems, of *B. pertussis* strains that do not express pertactin (contained in the vaccine). This condition is thought to contribute to the occurrence of epidemic outbreaks registered throughout the world in recent years (Lam et al., 2014).

It is believed that pertussis is widely underestimated in Italy, as well as in other countries, because the passive surveillance system has some critical issues such as under-notification, under-diagnosis and delay in notification. Besides, laboratory diagnosis is not always requested and most of the cases occurring in adolescents and adults with atypical presentation are not recognized (Guiso et al., 2011b). Laboratory confirmation and differential tests between Bordetella species are helpful to conferm diagnosis (Stefanelli et al, 2019) and to contrast the under-notification and under-diagnosis.

The aim of this study has been to analyze and update the impact of pertussis on the Italian population by evaluating pertussis-related hospital admissions in the period 2001-2014.

Methods

The Hospital Discharge Record (HDR) was officially established in 1991 with the aim of providing a summary of the main information contained in the medical record (Decree of the Ministry of Health of 28 December 1991).

HDRs represent the information gathering tool for each patient discharged by public and private hospital and contains information on clinical and organizational aspects of hospitalization (Decree of the Ministry of Health of 28 December 1991) and are coded by the International Classification of Disease, 9th Revision, Clinical Modification Coding System (ICD9-CM), currently used in Italy.

All anonymous HDRs data were provided by the National Archive of HDR data of the Ministry of Health; for this type of retrospective study formal consent was not required. This survey is not based upon animal or human clinical study nor patient data. Anyway, the research was performed protecting any personal data accordingly to the Helsinki Declaration and to the Italian law (Legislative Decree of 30 June 2003).

Only hospitalizations included in the primary diagnosis and containing the following ICD9-CM diagnosis codes were evaluated: 033.0 (pertussis caused by *Bordetella pertussis*), 033.1 (pertussis caused by *Bordetella parapertussis*), 033.8 (pertussis caused by other specified organisms), 033.9 (pertusiss caused by unspecified organisms) and 484.3 (pneumonia in pertussis). The patient identification code was not requested.

Data processing was performed through the Microsoft Excel 2007 Software. The calculation of rates was performed using the resident population data available for each considered year in the National Statistics Institute (ISTAT) website.

Significant trends over the considered years were assessed as average annual percent changes (AAPC). This is a summary measure of the trend over a given fixed interval that is computed as a weighted average of the annual percent change (APC) emerging from the joinpoint model, using weights equating to the length of the APC interval. If an AAPC lies entirely within a single joinpoint segment, the AAPC is the same as the APC for that segment (Kim et al., 2000).

Results

In the studied period (2001-2014) a total of 7,102 hospital admissions for pertussis (main diagnosis) were registered in the database provided by the Ministry of Health.

The trend of hospitalizations showed a peak in 2002, when 15.1% (1,074 hospitalizations) of all hospitalizations observed in the studied time interval occurred. The rate of hospitalizations

had obviously the same trend and progressively decreased from values >1/100,000 inhabitants in the years 2001-2004 to 0.64/100,000 inhabitants in 2014 (Figure 1).

In the study period, the overall annual pertussis hospitalization rate was 0.87 per 100,000 inhabitants showing a significant reduction trend [AAPC: -7.5% (95% CI: -10.1; -4.8)]. The age group with the highest hospitalization rate regarded children under 1 year of age. During the studied period this age group showed an average annual rate of 59.7 per 100,000 inhabitants, shifting from 67.1 in 2001 to 57.4 in 2014 with a significant reduction trend [AAPC: -4.9% (95% CI: -8.0; -1.7)] and peaking in 2002 with 118.7 hospitalizations per 100,000 populations. The peak in 2002 was highlighted for all age classes considered. In the last three years, the trend of pertussis hospitalization rate for children up to 15 years of age reversed even if it isn't statistically significant in all the age class considered; the more relevant increase concerned the children under 1 year of age for which the rate of hospitalization rose from 41.6 per 100,000 in 2011 to 57.6 per 100,000 inhabitants in 2014 (APCC 10.9, CI95%: -6.2 – 31.1, not significant). Overall, the distribution pattern of hospitalization stratified by age group resulted quite similar during the studied period (Figure 2).

Taking into account the different ICD9-CM diagnosis codes used, 60.4% of the admissions during the period considered were pertussis caused by unspecified organisms, 31.2% pertussis caused by *Bordetella pertussis*, 3.4% pertussis caused by *Bordetella parapertussis*, 2.7% pertussis pneumonia and 2.3% pertussis caused by other specified organisms. As we do not have additional data concerning laboratory tests, we are unsure why in many cases 033.8 or 033.9 was coded. For both diagnoses, pertussis caused by non-specified organisms and pertussis caused by *Bordetella pertussis,* the trend of the percentage of hospitalizations is similar with two peaks, one in children <1 year of age and a lower one in the 5-14 years age class.

Most hospitalizations (6,457 cases; 90.9% of all hospitalizations) were ordinary admissions (general ward) and 645 (9.1%) were day-hospital admissions. Females were more represented than men (53.3% vs. 46.7%) [statistically significant AAPC Female: -7,4% (CI95%: -10,6; -4,6) Male: -7.4 (CI95%: -10.1 – -4.7), Figure 3].

Noteworthy, hospitalization was urgent in 78.4% of cases and the urgency is greater in the first age class than in all the others. The duration of stay was less than one week for most admissions (73.8%) (Figure 4). The mean was 5.77 (5.67-5.89), the median was 5 days (5%-95% boundaries: 5% 1 days and 95%: 14 days).

Most hospitalized patients were discharged at home (90.2%), followed by voluntary dismissal in 7.06% of cases; nine patients died (0.13%), aged between 61 and 94 and just in one case <1 year of age, 2 patients (0.03) were discharged at a health care provision, 23 patients (0.32) were discharged at home with activation of home care, 150 patients (2.11) were transferred to another acute care institution, 10 patiens (0.14) were transferred to the same institution for another type of hospitalization or other hospitalization regimen, 1 patient (0.01) was transferred to a rehabilitation institute.

The analysis of hospitalizations stratified by geographical area showed a wide range of hospitalization rates in different regions; the highest rates were registered in Sicily, Apulia and Campania (3.79, 3.76 and 3.74/100,000 in 2002, respectively), in Sardinia (3.29/100,000 in 2004) and in Valle d'Aosta (4.74/100,000 in 2012) (Table 1).

Discussion

This study investigated the impact of pertussis in Italy in terms of hospitalization, thus assessing the most serious cases of the disease. The rate of hospitalization during the studied period ranged between 1.23/100,000 inhabitants in 2001 and 0.64/100,000 inhabitants in 2014 (Figure 1).

As expected, the rate of hospitalization in <1 year-old children was particularly high (59.4/100,000). These data confirm that pertussis continues to be a major public health problem for the most vulnerable subjects, such as unvaccinated or not completely immunized infants and children, possibly exposed to adolescents and adults who act as an often unidentified source of infection (Zamir et al., 2015).

The age distribution of pertussis detected in this study is in line with the one reported in the scientific literature. In a study conducted in Israel in 2015, <1 year-old children showed a 5-fold higher notification rate than the other age groups (96/100,000 inhabitants) and were the most involved age group in hospitalization (Zamir et al., 2015).

This scenario agrees with what was reported in Australia in 2011, where pertussis was reported three times more frequently in children than in the general population. In particular, 1-2 months of age children showed a notification rate 3.5 times higher than the one registered in 3-11 months-old children (Foxwell et al., 2011).

A study in Catalonia showed an incidence rate of pertussis (1.56/100,000 inhabitants / year) and a hospitalization rate (0.85/100,000 inhabitants in the period 2004-2008) (Crespo et al., 2011). This later increased in recent years (1.01/100,000 inhabitants in period 2012-2013) (Crespo et al., 2015). The proportion of hospitalizations compared to the notifications was equal to 31.5%. More than half of the notified cases of illness (52.9%) and 93.7% of admissions occurred in <1 year-old children, confirming also in this geographical area the greater involvement of this age group.

Taking into account the notifications (Figure 1S, Supplementary Material) (European Centre for Disease Prevention and Control, 2016; European Centre for Disease Prevention and Control, 2017; Epicentro, 2018a) and hospital admissions registered in Italy in the period 2001-2014, the proportion of hospitalizations compared to notifications has been equal to 54.45%.

This value could be likely related to the quite high under-notification of the disease. A recent study supports this evaluation showing that Italian physicians rarely suspect pertussis in adult or in elderly patients with long-lasting cough and usually request a diagnostic test (Gonfiantini et al., 2013).

The poor use of laboratory tests as confirmation of a suspected infection caused by *Bordetella pertussis* lowers the possibility of diagnosis in patients of all ages with an atypical presentation of the illness and contributes to under-notification and under-diagnosis (Gonfiantini et al., 2014; Crespo et al., 2015). In Sweden only 2% of all laboratory confirmed hospitalized pertussis cases are above one year and younger than 20 year of age; in our study there could be a limit in the evaluation of hospitalizations considering the absence of laboratory diagnosis (Aronsson et al, 2018).

It should also be noted that in Italy, in recent years, there has also been a decrease in vaccine coverage (VC) rate for pertussis; in fact, while in 2007-2008 a VC of 96.7% was achieved, in 2014 VC felt to 94.6%, reaching the minimum value of 93.3% in 2015 (Figure 1S Supplementary Material) (Epicentro, 2018b). However, an improvement in VC is occurring both in childhood and adolescence as effect of the vaccination requirement (Ministero della Salute, 2018; Law 31 July 2017 N.119).

In the present study, most hospitalizations lasted about a week, accordingly to another study conducted in Piedmont in 2013. Besides, the authors of this study underlined the usefulness of vaccination for mother during the post-partum period and for other family members with close contact with the baby, called cocoon strategy, as they could be a potential source of infection; they believed that cocoon strategy could reduce the transmission of the disease and consequently also of the pertussis-related hospitalizations, in particular in <1 year of age children (Meregaglia et al., 2013). However, in recent years this strategy has not been implemented because of the difficulties in achieving high levels of vaccination coverage in

family contacts (this strategy could be effective provided that a large number of contacts is immunized) and some cost –effectiveness assessments not always favorable. A study conducted in the USA, in fact, recognized the vaccination in pregnancy with a dose of dTap (diphtheria, tetanus, acellular pertussis with a reduced antigen content) as more cost-effective than the cocoon strategy (Terranella et al., 2013) and also WHO considers vaccination of pregnant women as more cost-effective than "cocoon strategy" (World Health Organization 2015b).

In accordance with what is reported in the literature, a booster dose of acellular pertussis vaccine is strongly recommended in order to overcome the decline in immunity. A booster dose is strongly recommended in adolescents as well as every ten years in adults/elderly using the combined dTap vaccine, which has been approved for use in children older than 4 years of age (Gabutti et al., 2012; Calendario vaccinale per la vita, 2018; Vittucci et al., 2016). The introduction of booster doses could have impacted on hospitalizations in the 5-14 age group, shown in our results (Figure 2S Supplementary Material).

Nowadays, pertussis immunization in pregnancy is strongly recommended in both the USA and United Kingdom and has been recently included in the National Immunization Plan in Italy; the objective of this intervention is the prevention of pertussis infection in infants (Centers for Disease Control and Prevention, 2018; Abu Raya et al., 2015; Gabutti et al., 2015; Gabutti et al., 2017; Makis et al., 2017).

The present study has some limitations. As a matter of fact, we evaluated pertussis-related hospitalizations and thus we have considered only the most severe cases of the disease. Besides, this observational study evaluated pertussis admissions (pertussis caused by *Bordetella pertussis*, *Bordetella parapertussis*, other specified organisms, unspecified organisms and pertussis pneumonia) referring exclusively to the main diagnosis inserted in

the HDR database. This has certainly been a conservative approach and could have implied the loss of some cases included in the HDR database as secondary diagnosis.

The patient identification code was not requested so we are not able to identify if any patient was readmitted and to estimate the duration of stay of repeated hospitalizations.

Conclusions

Even if this study shows a decreasing trend in the number of pertussis-related hospitalizations, the impact of the disease in Italy in terms of hospital admissions continues to be relevant, especially in the <1year age class. This impact is actually even greater taking into account under-notification and under-diagnosis. Pertussis therefore continues to be, in Italy as well as in other European countries, an important public health issue, that could even worsen as vaccine coverage rates are decreasing. It is therefore necessary to strengthen prevention activities against this relevant infectious disease by acting on multiple levels, improving the epidemiological surveillance, increasing the use of laboratory diagnostics for suspected cases, optimizing vaccine interventions already in place by improving vaccine coverage rates and supporting the use of already recommended booster doses in all age groups.

Acknowledgements

HDRs were provided by the National Archive of SDO data, Ministry of Health, General Directorate of Healthcare Planning, VI Office.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

Hospital discharge records are available at the National Archive of HDRs data, Ministry of Health, General Directorate of Healthcare Planning, VI Office.

Authors' contributions

All Authors have made a substantial contribution to the conception, design, analysis and interpretation of data, drafting the article and revising it critically for intellectual content; all Authors approve the final version of the manuscript.

Ethics approval and consent to participate

HDRs were provided by the National Archive of SDO data, Ministry of Health, General Directorate of Healthcare Planning, VI Office. For this type of retrospective study formal consent is not required; any personal data was protected accordingly to the Helsinki Declaration and to the Italian law.

Conflict of interest statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. GG received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Seqirus, Sanofi Pasteur, Merck Italy and Pfizer for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials. VB received grants from Sanofi Pasteur MSD, GSK Biologicals SA, Novartis, Pfizer, Seqirus, Merck Italy, and Sanofi Pasteur for taking part to advisory boards, expert meetings, for acting as speaker and/or organizer of meetings/congresses, outside this work. SC received grants from Pfizer, Seqirus, Merck Italy, for taking part to advisory boards, for attending to congresses, outside this work. FB, PK and AS have no conflicts to disclose.

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Figure Captions

Figure 1. Absolute number and hospitalization rate per 100,000 inhabitants in the studied period (2001-2014).

Figure 2. Trend of hospitalizations stratified by age class and year (AAPC: average annual percent changes).

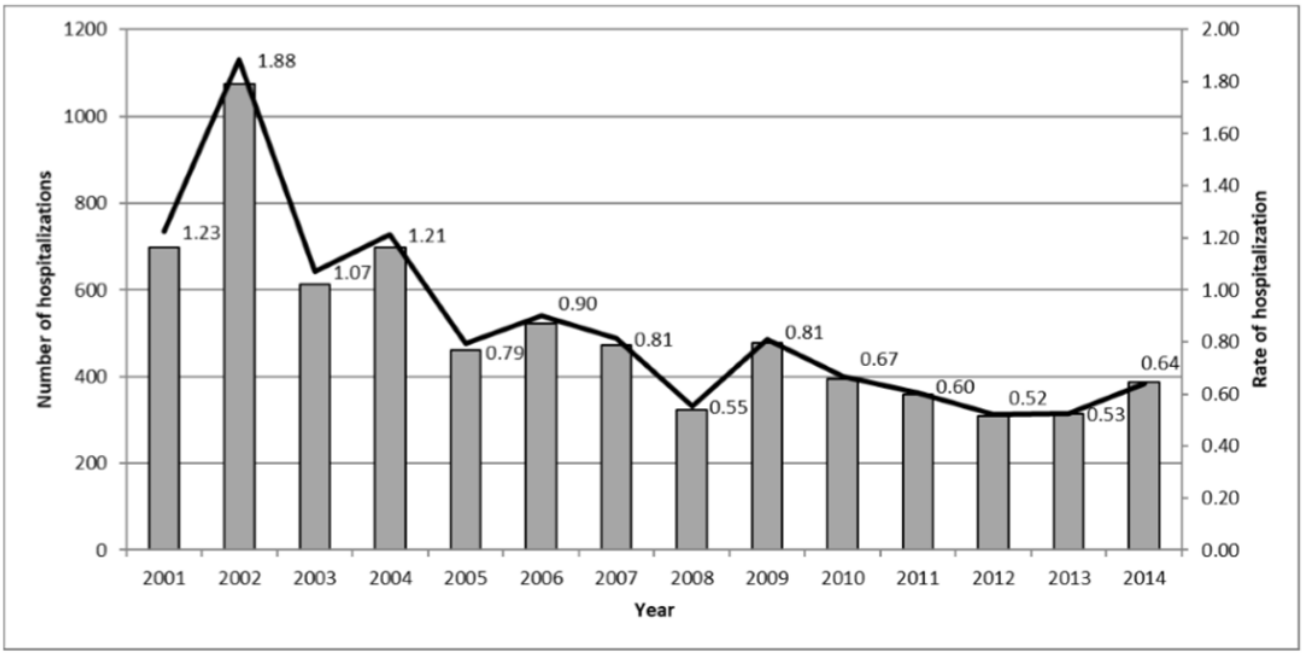
Figure 3. Trend of hospitalizations stratified by gender.**Figure 4.** Italian hospitalizations in the studied period (2001-2014) stratified by length of stay.

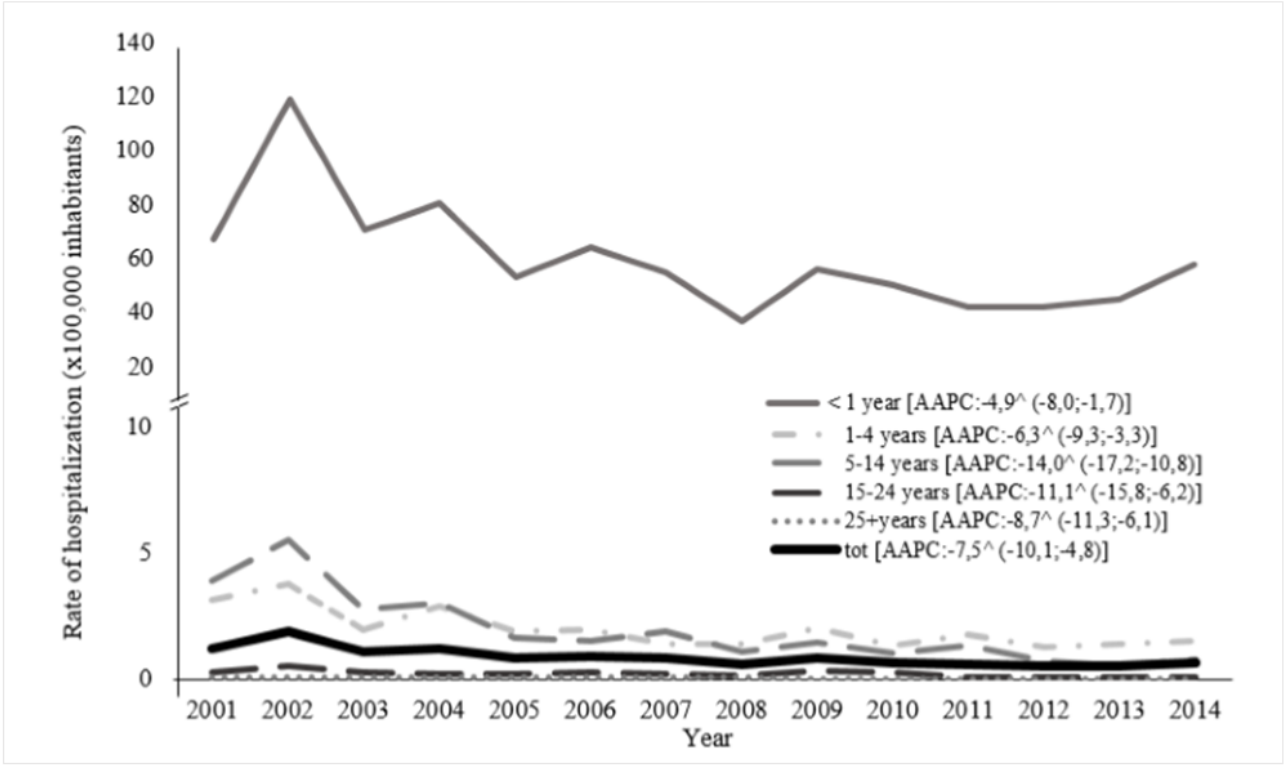
Supplementary material captions

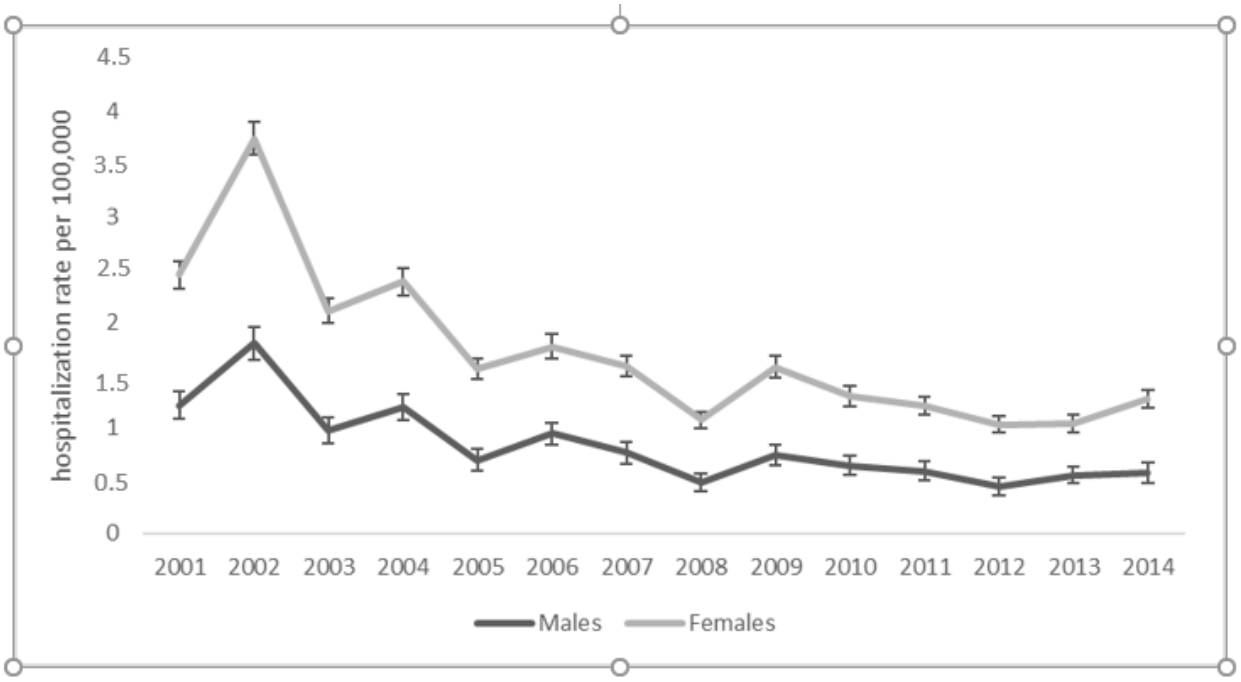
Table 1. Hospitalization rate by region and year (2001-2014).

Figure 1S. Pertussis: notifications and vaccine coverage in Italy in the period 2001-2015 (Epicentro, ECDC).

Figure 2S. Trend of hospitalizations in the 5-14 year age group in the period 2001-2014.


Number of hospitalizations
Rate of hospitalization
Year
1200
1000
800
600
400
200
0
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
1.23
1.88
1.07
1.21
0.79
0.90
0.81
0.55
0.81
0.67
0.60
0.52
0.53
0.64


Rate of hospitalization (x100,000 inhabitants)
140
120
100
80
60
40
20
10
5
0
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year
< 1 year [AAPC:-4,9^ (-8,0;-1,7)]
1-4 years [AAPC:-6,3^ (-9,3;-3,3)]
5-14 years [AAPC:-14,0^ (-17,2;-10,8)]
15-24 years [AAPC:-11,1^ (-15,8;-6,2)]
25+years [AAPC:-8,7^ (-11,3;-6,1)]
tot [AAPC:-7,5^ (-10,1;-4,8)]


4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
hospitalization rate per 100,000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Males
Females

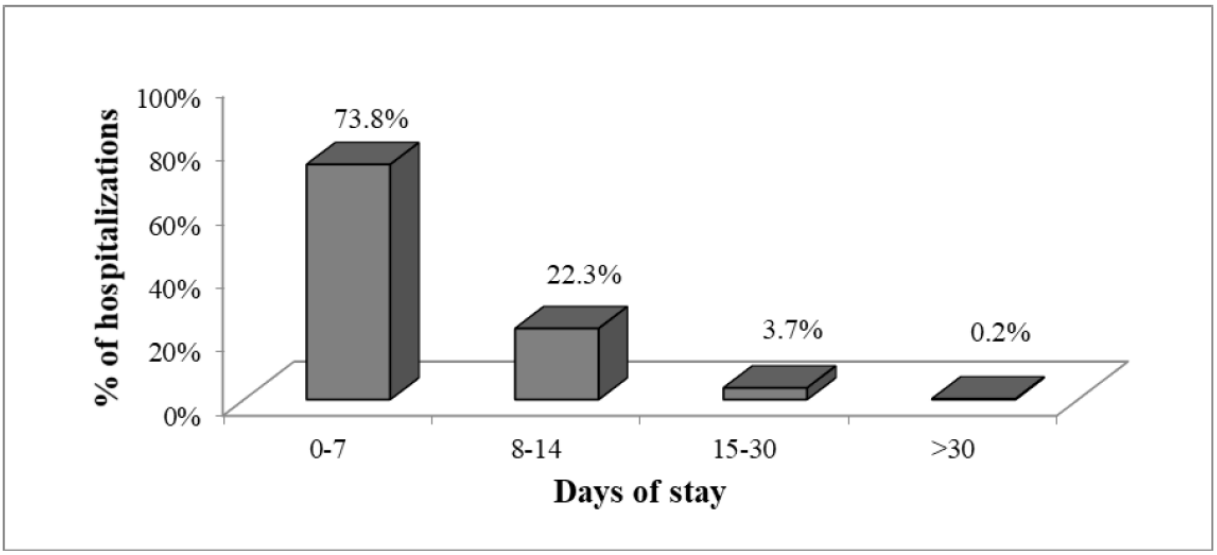

% of hospitalizations
100%
80%
60%
40%
20%
0%
73.8%
22.3%
3.7%
0.2%
0-7
8-14
15-30
>30
Days of stay

Table 1. Hospitalization rates by region and year (2001-2014).

Hospitalization rate/ 100,000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Piedmont	1.45	1.16	0.71	0.82	0.39	0.74	0.39	0.75	0.56	0.45	0.36	0.32	0.11	0.34
Val d'Aosta	2.51	0.00	0.00	0.00	0.00	1.61	0.80	0.00	3.15	0.00	0.78	4.74	1.56	0.00
Lombardy	1.25	0.80	0.34	0.62	0.48	0.60	0.57	0.26	0.47	0.22	0.28	0.35	0.29	0.37
Autonomous Province of Bolzano	1.30	2.37	0.00	0.85	3.35	1.24	1.44	0.40	2.00	0.20	0.39	1.39	1.18	0.19
Autonomous Province of Trento	1.89	1.26	0.41	1.43	1.81	0.20	0.79	0.78	0.58	0.38	0.00	0.57	0.57	0.56
Veneto	1.06	1.41	0.72	0.78	0.28	0.49	0.40	0.17	0.20	0.37	0.32	0.14	0.29	0.65
Friuli Venezia Giulia	0.17	0.34	0.34	0.17	0.17	0.25	0.16	0.00	0.16	0.32	0.24	0.00	0.16	0.00
Liguria	1.78	1.08	1.02	1.14	0.63	1.37	0.50	0.56	0.87	0.80	0.43	0.83	1.15	0.50
Emilia Romagna	0.83	0.93	0.52	0.86	0.46	0.55	0.52	0.14	0.65	0.61	0.65	0.48	0.30	0.52
Tuscany	0.83	1.20	0.60	0.93	0.50	0.30	0.49	0.33	0.73	0.72	0.35	0.38	0.68	0.43
Umbria	0.85	1.69	0.60	1.06	0.93	0.69	1.03	0.00	0.00	0.67	0.33	0.34	0.00	0.22
Marche	1.43	1.43	0.47	0.40	0.86	0.65	0.26	0.45	0.51	0.45	0.64	0.26	0.00	0.52
Lazio	0.88	1.25	0.99	2.00	0.80	1.07	1.04	0.50	1.17	0.81	0.51	0.73	1.04	1.31
Abruzzo	0.79	2.14	0.86	0.47	0.46	1.53	0.99	0.30	0.45	0.45	0.67	0.31	0.30	0.30
Molise	1.56	3.12	1.56	0.31	0.93	0.31	0.00	0.00	1.56	0.00	0.00	0.00	0.32	0.00
Campania	1.54	3.74	1.17	1.35	1.28	2.02	1.28	0.77	1.19	0.67	0.74	0.62	0.71	0.56
Apulia	1.24	3.76	2.58	2.18	1.08	0.84	1.13	0.81	1.13	1.03	0.76	0.54	0.86	1.22
Basilicata	0.50	0.84	1.01	0.50	0.34	0.17	0.85	0.17	0.68	0.34	0.34	0.52	0.35	0.17
Calabria	1.79	2.54	2.04	1.14	0.55	1.15	0.45	0.40	0.85	0.90	0.55	1.02	0.36	0.25
Sicily	1.57	3.79	2.92	1.96	1.91	1.42	1.59	1.73	1.65	1.69	1.94	1.08	0.92	1.30
Sardinia	1.41	1.72	0.73	3.29	0.73	0.18	1.45	0.72	0.24	0.54	0.48	0.24	0.24	0.42
Italy	1.22	1.88	1.07	1.2	0.78	0.89	0.80	0.54	0.79	0.65	0.59	0.52	0.53	0.64

Figure 1S. Pertussis: notifications and vaccine coverage in Italy in the period 2001-2015.

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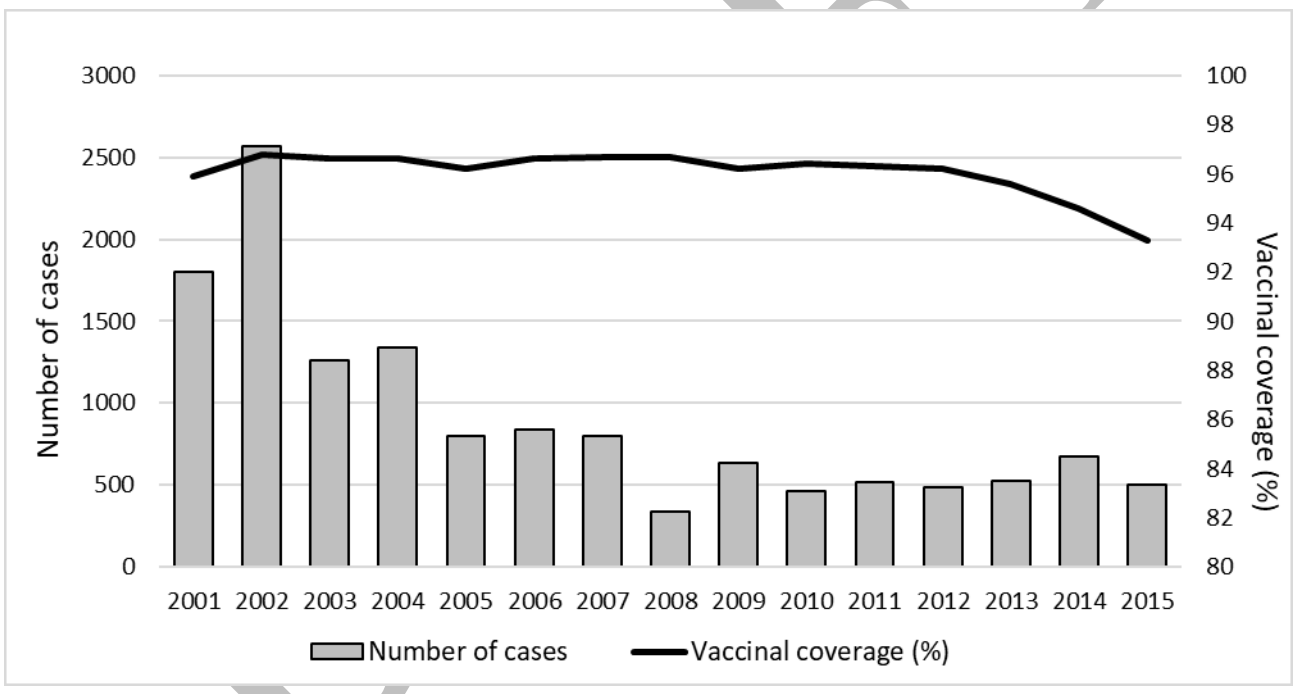

Figure 2S. Trend of hospitalizations in the 5-14 year age group in the period 2001-2014.