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MODEL FOR THE ESTIMATION OF SOCIETAL COSTS FOR PERTUSSIS IN ITALY

Abstract. Objectives. To estimate age-specific costs associated with pertussis in Italy and the related Societal burden in the last decade (2006-2015), starting from available epidemiological data and healthcare charges. **Methods**. Age-specific data on notified pertussis cases were corrected to account for under-notification and hospitalization rates were estimated based on Italian data in the same period. Complications (pneumonia, seizures, and encephalopathy) rates were derived from a US study and adjusted. Assuming all complications are hospitalized, hospitalization-without-complications rates were estimated as a difference. The remaining part was considered outpatient cases. For outpatient, general practitioner (GP) consultations and antibiotics prescription rates were taken from a Dutch study. National DRG tariffs were used for inpatients; GP consultation cost was estimated from an Italian study and antibiotics (erythromycin, clarithromycin, and azithromycin) cost was estimated based on dosage units necessary to cover a full cycle of therapy, considering the formulations available on the Italian market. The Societal impact is measured in term of days of daily activities lost: globally (scenario 1) or medical-related (scenario 2). Age-specific values for days lost were obtained from an Italian study. **Results**. The estimated average direct medical cost ranges from €77 to €1,488 and is highest for infants. Average indirect costs (scenario 1) accounts for 70% of total costs and are lowest for adolescents. The estimated Societal burden amounts to, considering both direct and indirect costs, € 3.74 million per year for pertussis and to € 73.55 million for rotavirus, despite the similar cost per episode. **Conclusions**. The high level of vaccination coverage attained since 2000 has played a key role in diminishing both the incidence of the disease and the related burden for Society, as shown from the comparison with the burden associated with rotavirus.

Keywords. Pertussis, Cost-of-Illness, Societal burden, Italy

1. INTRODUCTION

A report issued by World Health Organization in 2001 (WHO 2002) estimated that, globally, there are 50 million cases of pertussis and 300,000 deaths every year, mostly among infants, in whom the risk of severe morbidity and mortality is highest. In addition, recent reports have noted an increase in the incidence of pertussis among adolescents and adults, in whom it is a considerable source of cough illness.
Several authors have reviewed the epidemiology of pertussis over a long period of time to describe the disease trends and to investigate the role of factors that may affect these trends (Clark *et al.* 2012; Hellenbrand *et al.* 2009; Jackson and Rohani 2014; Rohani and Drake 2011).These studies have focused on the epidemiology of

pertussis since the introduction of the immunization in the mid-1940s and have investigated factors potentially involved in the resurgence of pertussis, including increased awareness, diagnosis, and reporting, changes in vaccine composition or schedule, waning immunity, and evolution of the bacteria.

In addition to understanding the epidemiology and health burden of Bordetella pertussis infection and disease, it is also important to recognize the economic burden it poses.

1.1 Italian background

In Italy, recommendations for pertussis immunization were released in 1961, when whole cell vaccines became available. Nevertheless, vaccination coverage increased substantially only after the introduction of acellular pertussis vaccines in 1995 and, even further, after 2002, when the vaccine started to be offered free of charge by all Italian regions (Rota *et al.* 2005).

Based on routine surveillance data, Italy is currently a low incidence country and outbreaks or incidence peaks have been rarely reported after the achievement of a high immunization coverage (Gonfiantini *et al.* 2014).

The primary objective of this study was to estimate age-specific costs associated with the disease in Italy and describe, based on these results, the burden the Society had to bear in the last decade (2006-2015) because of pertussis.

2. METHODS

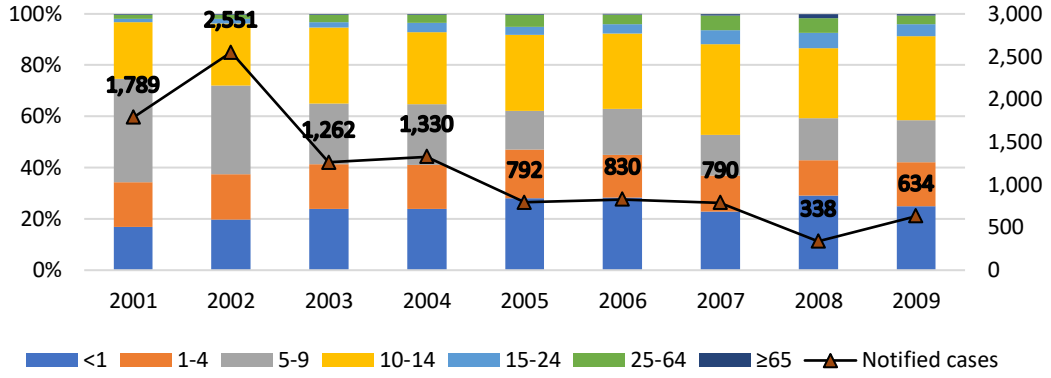
A micro-simulation model was developed, starting from available epidemiological data and healthcare charges associated with pertussis episodes, to estimate age-specific costs and burden of disease. All the costs, expressed in euros, were inflated to 2016 using the inflation rates for Italy (Eurostat 2018).

2.1 Reported cases

Data on notified pertussis cases in Italy from 2001 to 2009 were obtained from the Ministry of Health, which collects notifications from the Surveillance System for Infectious Diseases in Italy (MdS). For the same period, information on the age

percent distribution for the younger (0-14) was obtained from an article reviewing the epidemiology of pertussis in Italy in the last century (Gonfiantini *et al.* 2014) (Fig. 1) summarizes this information.

Figure 1. Age-distribution and number of reported cases of pertussis cases in Italy, 2001-2009



The Italian Surveillance system is passive, universal, mandatory and based on notifications. As a consequence, it is affected by limitations such as under-notification, under-diagnosis, and delay of notification. Moreover, pertussis incidence is under-estimated as many cases in adolescents, young adults, and adults are not identified because of their atypical clinical characteristics and the lack of lab assessment. Lab diagnosis and ad hoc epidemiological studies are not easily performed due to logistic and diagnostic issues (Guiso *et al.* 2011). Gonfiantini and colleagues (2014) found high under-notification in Italy when comparing incidence figures from a sentinel surveillance system with routine reports. Similar results have been reported for Poland (Stefanoff *et al.* 2014). To account for this issue, notified data were adjusted for the factors reported in Table 1.

Table 1. Age-specific under-notification correction factors

Age-class	Correction factor
<1	1.8
1-4	11.8
5-9	9.2
10-14	12.9
15-24	52.3
25-64	77.2
≥65	102.7

2.2 Hospitalization

Data on pertussis hospitalization (primary and secondary diagnoses) in Italy from 2001 to 2009 were obtained from an article analyzing the Italian hospital discharge database (Gabutti *et al.* 2012). Age-specific adjusted hospitalization rates were then estimated, as reported in Table 2.

Table 2. Age-specific hospitalization rates, corrected to account for under-reporting

Age-class	Hospitalization rate
<1	95.40%
1-4	3.09%
5-9	2.50%
10-19	2.09%
≥20	3.08%

2.2.1 Complications

The most frequent complication observed in children with pertussis is pneumonia, which occurs in 6% of cases. Other complications include sinusitis, otitis media, viral and bacterial superinfections, nutritional deficiencies resulting from repeated vomiting and neurologic complications, which are due mostly to hypoxia during coughing spells and apnea (Heininger *et al.* 1997)

In 1990 it was estimated that 50,000 children worldwide experienced long-term neurologic complications of pertussis (Ivanoff and Robertson 1997) and in the late 1990s, it was reported that 0.9 per 100,000 pertussis cases were complicated by encephalopathy (CDC 2002).

The risk of complications is higher among infants than among older children and adolescents. In a prospective case series in Germany, Heininger and colleagues (1997) report that the rate of complications among infants less than 6 months of age was 24%, as compared with 5% among older children.

Gonfiantini and colleagues (2014) report that during the last century, in Italy, pertussis mortality progressively decreased and reached so low numbers that from 1995 to 2001, only one pertussis death per year was reported and no deaths have been reported since 2002.

Given this, the present model considers the following complications: pneumonia, seizures, and encephalopathy.

In the absence of Italian data, assuming that complications rates are similar among similar countries, age-specific complication rates were then obtained from a study summarizing the characteristics and trends in reported cases of pertussis for the years 1980-1989 in the United States (Farizo *et al.* 1992). These rates were then adjusted in order to account for under-reporting (see section 2.1). Assuming that all pertussis cases with complications are hospitalized, age-specific hospitalization-without-complications rates were computed as the difference between the hospitalization rates (see section 2.2) and the sum of adjusted complication rates.

For last, age-specific percentages of outpatient cases were defined as the remaining part of patients. The estimated rates are reported in Table 3.

Table 3. Age-specific rates

Age-class	Hospitalized patients				Outpatients
	Pneumonia	Seizures	Encephalopathy	No complications	
<1	12.06%	1.67%	0.50%	81.17%	4.60%
1-4	1.04%	0.18%	0.03%	1.84%	96.91%
5-9	0.54%	0.10%	0.04%	1.82%	97.50%
10-19	0.22%	0.03%	0.01%	1.84%	97.91%
≥20	0.03%	0.01%	0.01%	3.03%	96.92%

2.2.2 Day Hospital

In Italy, according to Gabutti and colleagues (2012), pertussis hospitalizations treated in day hospital represent 10% of all hospitalizations (primary diagnosis) for pertussis.

For what concerns hospitalized patients, the model considers all cases with complications and infants (i.e. <1 years old) cases with no complications as treated with ordinary hospitalization. For older inpatients cases with no complications, the percentage of day hospital cases was defined so that the ratio between day hospital cases and total hospitalized cases is 10%.

2.3 Outpatients

The number of general practitioner consultations (GP) per pertussis case and the proportion of patients receiving antibiotics were estimated from a previous study on

the disease burden of pertussis in the Netherlands (de Greeff *et al.* 2009) as reported in Table 4 and Table 5, respectively.

Table 4. Age-specific distribution of the number of gp consultations

Number GP consultations	0-9	≥10
1	3%	2%
2	39%	42%
3	38%	41%
4	19%	13%
5	2%	1%

Table 5. Age-specific percentage of outpatients treated with antibiotics

Age-class	% treated with antibiotics
<1	73%
1-9	69%
10-19	45%
20-44	61%
≥45	56%

For hospitalized cases, the model assumes no GP consultations and no antibiotics consumption, besides those received in the hospital.

3. COSTS CALCULATION

3.1 Direct medical costs

National Diagnosis-Related Group (DRG) tariffs (MdS 2013) were used to estimate costs related with hospitalized case: pneumonia [DRG 89, 90, 91], seizures [DRG 26, 562, 563], encephalopathy [DRG 22], ordinary hospitalization without complications [DRG 96, 97, 98] and day hospital [DRG 96, 97, 98] costs used in the model are reported in Table 6.

Table 6. National DRG tariffs

Age-class	Pneumonia	Seizures	Encephalopathy	Ord. Hosp. w/o complications	Day Hospital
<18	€ 1,948	€ 1,729	€ 2,989	€ 1,538	€ 185
≥18	€ 3,558	€ 3,289		€ 1,832	€ 197

For what concerns outpatients, even if theoretically the cost of a GP consultation is null, as, in Italy, the National Health Service remunerates GPs mainly on a capitation basis, the model follows the opportunity-cost approach, according to which the value of resources is defined by the benefit foregone when selecting one therapeutic alternative over the next best alternative use. Thus, in the model the cost of a GP consultation is estimated on the basis of Garattini and colleagues (2003) as the mean between the cost of office and home visits weighed for their respective frequencies.

Since a timely laboratory confirmation of pertussis diagnosis is problematic, administering an antibiotic on the basis of a clinical diagnosis is the practice. Antibiotics eradicate Bordetella pertussis from the airway but limit the severity of disease only if started in the catarrhal phase (Tozzi *et al.* 2005). The standard treatment of pertussis has been a full dose of erythromycin. More recently, many national agencies have tended to encourage the use of other macrolides such as clarithromycin and azithromycin.

Thus, the antibiotics considered in the model are erythromycin, clarithromycin, and azithromycin. The distribution of patients among these macrolides therapy, shown in Table 7 was obtained from a Canadian study documenting the morbidity of pertussis in adolescents and adult cases (De Serres *et al.* 2000).

Table 7. Distribution of patients treated with antibiotics among different therapies

Macrolides therapy	% of treatment
Erythromycin	55%
Clarithromycin	36%
Azithromycin	9%

The cost for each antibiotic treatment was estimated on the basis of dosage units necessary to cover a full cycle of therapy (see **Error! Reference source not found.**). The calculation takes into account the different formulations available on the Italian market and the specific dosage for adult and pediatric patients. The price of package – for those formulations not patented their reference price is considered – net of mandatory discounts (AIFA 2006a; 2006b) was obtained from the Italian Medicines Agency reimbursement lists (AIFA 2017); while the dosage from the summary of product characteristics of each active substance.

Table 8. Length and cost per cycle of antibiotic therapy

Antibiotics	Cycle	Cost per cycle
Erythromycin	10 days	€ 12.37
Clarithromycin	14 days	€ 15.89
Azithromycin	3 days	€ 6.70

3.2 Indirect costs

For what concerns indirect costs, the model estimates the social impact of pertussis in terms of loss of days of daily activities by one parent, if the person is less than 12 years old or by the person itself otherwise.

In the model, the age of the person who has to stay at home is estimated as the mean of the average age of fathers and mothers at birth (ISTAT 2015) plus the age of the infected person.

Concerning the number of days lost (De Serres *et al.* 2000) the model assumes that the distribution of those 12-17 years old also applies to younger (see Table 9 and 10). Finally, age-specific values for the loss of a day of daily activities were obtained from an Italian study estimating the societal costs of lost production in Italy (Pradelli and Ghetti 2017).

Table 9. Distribution of days lost – adolescents – scenario 1

# of days lost - <18 years	
Mean number of days lost	5
No days lost	22%
1-5 days	53%
6-10 days	17%
≥11 days	9%

Table 10. Distribution of days lost – adults – scenario 1

# of days lost - Adults	
Mean number of days lost	7
No days lost	33%
1-5 days	36%
6-10 days	13%
11-15 days	7%
≥16 days	10%

For what concerns the estimated number of days lost, in the model, there is also another, more conservative, scenario.

For outpatients, it is assumed a loss of a quarter of daily activities for every GP consultation by one parent, if the person is less than 12 years old or by the person itself otherwise. On the other hand, for inpatients, it is assumed a loss of a full day for day hospital and a loss equal to the length of hospital stay for those treated with ordinary hospitalization. Data on age-specific lengths of hospital stay, as reported in Table 11, were derived from an article examining demographics, case fatality rate, resource use and costs of hospital care related to pertussis in the US from 1996 to 1999 (O'Brien and Caro 2005).

Table 11. Age-specific length of hospitalization

Age-class >>>	**<1**	**1-11**	**≥12**
Mean length of hospital stay [days]	6	3.7	3.4
Median	4.5	3	3
Range (min, max)	1	1	1
	110	10	11

4. PROBABILISTIC SENSITIVITY ANALYSIS

A probabilistic sensitivity analysis (PSA) was performed in order to account for uncertainty in the parameters.

While the micro-simulation takes into account the variability in the population, the PSA allows considering the uncertainty on key parameters and its effect on the estimated outcomes. This is obtained by a two-level Montecarlo simulation: the

inner loop (10,000 iterations) is the patient-level simulation, which is averaged and repeated 1,000 times (outer loop) to perform PSA on key model parameters.

In the absence of reliable data on the uncertainty of model parameters, standard deviation was set at 10% of their mean value, and adequate distributions were attributed according to the type of data (i.e. gamma or weibull distributions for age, number of days lost and length of hospital stay and beta distributions for probabilities). For conjugate probabilities (i.e. the probabilities of developing pneumonia, seizures, encephalopathy, of being hospitalized without complications or of being an outpatient, etc.) Dirichlet distributions were used.

The parameters on which the PSA was conducted and their distributions are presented in Table 12.

Table 12. Parameters and distributions for PSA

Variable	Expected value	Distribution	Alfa (1) o Lambda (2)	Beta (1) o K (2)
Distr. cases < 1 year				
Pneumonia	12.06%	Dirichlet		
Seizures	1.67%			
Encephalopathy	0.50%			
Hospitalization w/o complications	81.17%			
Outpatients	4.60%			
Distr. cases 1-4 years				
Pneumonia	1.04%	Dirichlet		
Seizures	0.18%			
Encephalopathy	0.03%			
Hospitalization w/o complications	1.84%			
Outpatients	96.91%			
Distr. cases 5-9 years				
Pneumonia	0.54%	Dirichlet		
Seizures	0.10%			
Encephalopathy	0.04%			
Hospitalization w/o complications	1.82%			
Outpatients	97.50%			
Distr. cases 10-19 years				
Pneumonia	0.22%	Dirichlet		
Seizures	0.03%			
Encephalopathy	0.01%			
Hospitalization	1.84%			

w/o complications				
Outpatients	97.91%			
Distr. cases ≥ 20 years				
Pneumonia	0.03%	Dirichlet		
Seizures	0.01%			
Encephalopathy	0.01%			
Hospitalization w/o complications	3.03%			
Outpatients	96.92%			
Age distribution of cases				
< 1	3.02%	Dirichlet		
1-4	15.67%			
5-9	12.83%			
10-14	27.31%			
15-19	6.75%			
20-29	5.63%			
≥30	28.80%			
Distr. # GP consultations < 10 years				
1	2.80%	Dirichlet		
2	38.80%			
3	37.80%			
4	18.80%			
5	1.80%			
Distr. # GP consultations ≥ 10 years				
1	2.20%	Dirichlet		
2	42.20%			
3	41.20%			
4	13.20%			
5	1.20%			
Distr. antibiotics				
Erythromycin	55.00%	Dirichlet		
Clarithromycin	36.00%			
Azithromycin	9.00%			
% treated with antibiotics				
< 1	73.00%	Beta	26.27	9.72
1-9	69.00%	Beta	30.31	13.62
10-19	45.00%	Beta	54.55	66.67
20-44	61.00%	Beta	38.39	24.54
≥45	56.00%	Beta	43.44	34.13
Day Hospital rate ≥ 1	26.52%	Beta	73.21	202.84
Age of parent at birth	33.50	Gamma	100	0.335
# days lost < 18 years	5.00	Gamma	0.69	5.41

# days lost ≥ 18 years	7.00	Gamma	0.37	14.48
Length of hospital stay [days]				
< 1	6	Weibull	0.37	0.62
1-11	3.7	Weibull	0.07	1.97
≥ 12	3.4	Weibull	0.10	1.78

Note: 1 – for beta and gamma distributions, 2 – for weibull distributions

In addition, in order to account for uncertainty in the parameters of the gamma and weibull distributions, these were further sampled from bivariate normal distributions, with mean equal to the value of parameters in the base case (as reported in the previous table) and assuming a standard deviation of 10% of their mean value and a correlation coefficient of -0.5. This last assumption was dictated by the fact that, by definition, the parameters of the gamma distribution are inversely proportional.

5. RESULTS

The model simulates a population of 10,000 pertussis patients whose age distribution (see Table 12) was estimated on the data on notified pertussis cases in Italy from 2003 (i.e. the first year after vaccination was offered free of charge by all Italian regions) to 2015, obtained from European Centre for Disease Prevention and Control (ECDC) and corrected in order to account for under-reporting (see section 2.1). The results of the probabilistic sensitivity analysis are reported in Table 13.

Table 13. Age-specific estimates of direct medical costs and indirect costs per pertussis case

Age-specific estimates of direct medical costs and indirect costs per pertussis case			
	Medical costs	**Indirect costs – Sc. 1**	**Indirect costs – Sc. 2**
< 1 year	€ 1,488 (48.36)	€ 382 (67.01)	€ 844 (196.87)
1-4 years	€ 104 (10.80)	€ 340 (48.84)	€ 73 (3.48)
5-9 years	€ 94 (10.29)	€ 360 (41.63)	€ 76 (2.23)
10-14 years	€ 77 (5.60)	€ 155 (14.48)	€ 30 (0.98)
15-19 years	€ 87 (11.97)	€ 101 (11.50)	€ 17 (0.59)
20-29 years	€ 102 (13.31)	€ 299 (35.76)	€ 40 (1.80)
≥ 30 years	€ 93 (6.91)	€ 439 (44.52)	€ 59 (1.32)
Total	**€ 135 (24.78)**	**€ 302 (35.16)**	**€ 75 (13.05)**

Note: Data presented as mean (sd)

Direct medical costs are those costs that focus exclusively on health care resource utilization. For pertussis, this would include such things as hospitalizations, emergency room/physician visits, laboratory tests, and medications. Typically the direct costs of pertussis are higher in infants, for whom the disease burden is considerably greater and hospitalization is more common (Caro *et al.* 2005).

The average medical costs associated with pertussis range from € 77 to € 1,488 per patient and, as expected, these are particularly relevant for infants, where about 95% of cases are hospitalized and about 12% develop pneumonia as a complication.

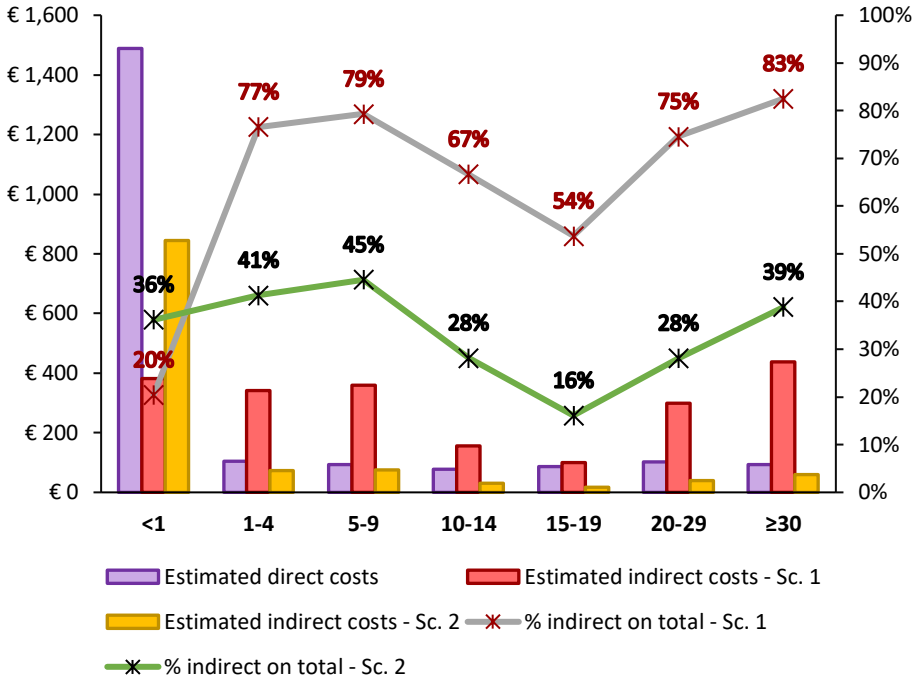
The indirect costs of pertussis are those incurred as a consequence of the illness, even though no direct expenditure has occurred. These include costs associated with time diverted from normal activities (e.g. as a consequence of visits to the general practitioner) and reduced work productivity, both of which may be caused by either individual illness or illness in a family member. Indirect costs can be expected to be relatively higher in adult cases, in whom illness is most directly linked to time lost from paid work activities, but can also be high for cases in infants and young children, where working parents are required to stay at home to care for their children (Lee and Pichichero 2000).

The results of the model are in line with what expected: indirect costs (scenario 1) are much higher for infants, young children, and adults than for adolescents.

For what concerns indirect costs, the model simulates two different scenarios. The second scenario has more conservative assumptions and, consequently, indirect costs are in general much lower with respect to the other scenario, with the exception of infants. This is due to the fact that the mean length of hospital stay for these patients may be also very long (up to 110 days). Therefore, valuing the number of days spent in the hospital, the estimated burden in this age-class is much higher than in the other scenario.

A graphical representation of the estimates obtained is given in Figure 2. For infants, medical costs are much higher than indirect ones, while the opposite holds true for all the other age-classes, considering the indirect costs of the first scenario. In the other scenario, indirect costs are always lower than direct costs, for every age-group.

Figure 2. Economic results of the simulation



5.1 Estimated burden in Italy, 2006-2015

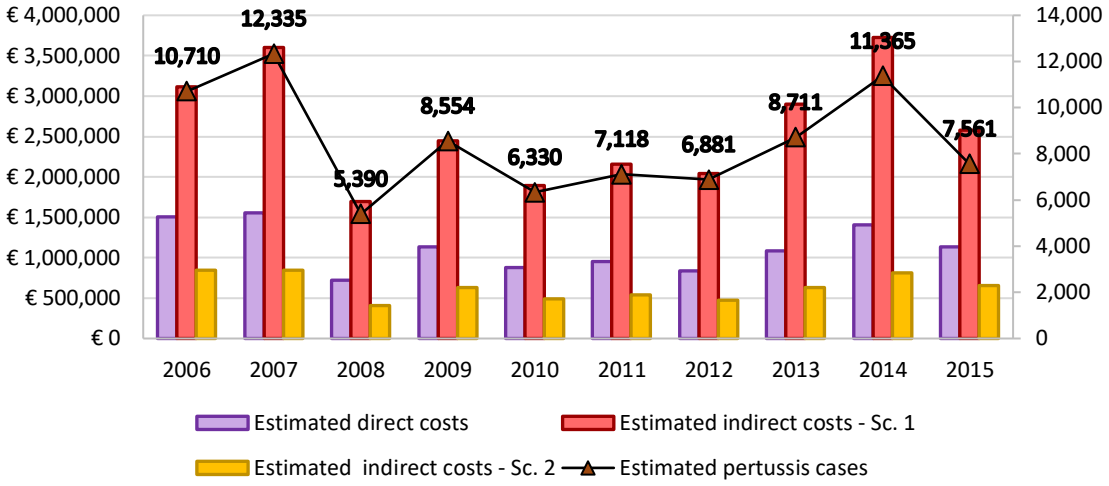
Data on the incidence of pertussis in Italy in the last decade (2006-2015) (ECDC) were corrected in order to account for under-reporting (see section 2.1).

With these data and the age-specific costs per pertussis case presented above (see Table 13), the burden the Society had to bear, in the last decade, because of pertussis amounts to, considering only direct medical costs, about € 11 million, corresponding to € 1.11 million per year. This result shows that annual costs for pertussis in Italy are still considerable and do not substantially deviate from those estimated for the Netherlands (approximately € 1.77 million) (de Greeff *et al.* 2009).

Pertussis in infants was responsible for 33% of these costs. The 1-4-year olds, 5-9-years olds, 10-14-year olds, 15-19-year olds, 20-29-year olds and ≥30-year olds accounted in for respectively 12%, 8%, 15%, 5%, 4% and 23% of the total direct medical costs.

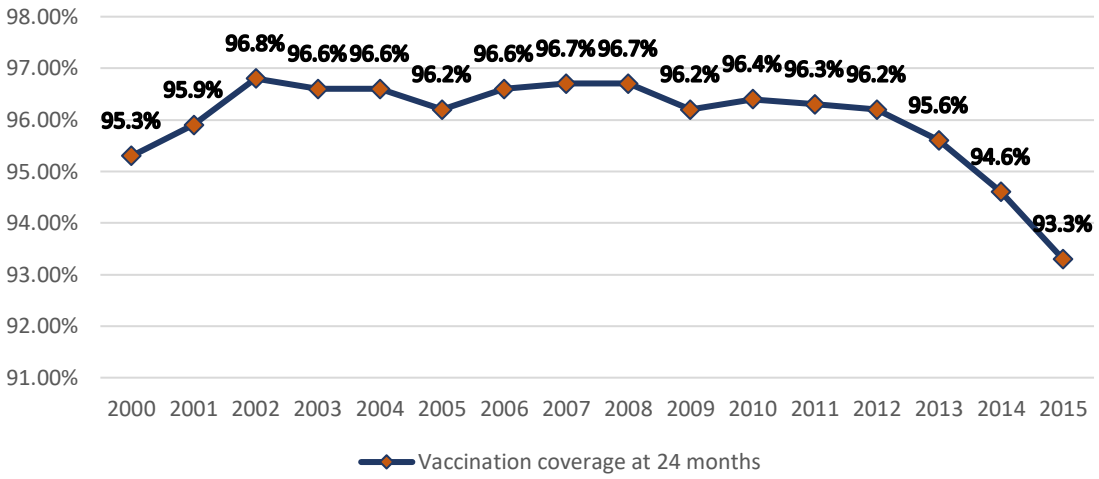
Considering also indirect costs, the mean annual burden rises to € 3.74 million (70% of which is due to indirect costs) in the first scenario and to € 1.75 million (where indirect costs amount to 36% of the total costs) in the more conservative one.

Figure 3. Estimated economic burden and estimated number of pertussis cases in Italy, 2006-2015



In order to account also for vaccination coverage, data were obtained from Istituto Superiore di Sanità (ISS). Figure 4 reports the level of vaccination coverage for pertussis at 24 months attained in Italy since 2000. Data do not show a clear trend: despite the vaccination coverage is almost constant since 2000, the burden has dropped in 2008 and peaked again in 2014, following a decrease in the vaccination coverage started between 2012 and 2013.

Figure 4. Pertussis vaccination coverage at 24 months in Italy, 2000-2015



In order to compare the annual burden of pertussis with that of other vaccine-preventable pediatric diseases, we took data from the REVEAL (Rotavirus Gastroenteritis Epidemiology and Viral Types in Europe Accounting for Losses in Public Health and Society) study; a prospective, multicenter, observational study of acute gastroenteritis in children <5 years of age in selected areas of 7 European countries (Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom) that collected and analyzed data for each country for a 12-month period (1 October 2004 - 30 September 2005). For Italy, Padua was the selected study area (Van Damme *et al.* 2007; Giaquinto *et al.* 2007a; 2007b).

The estimated cost per episode of confirmed rotavirus gastroenteritis amounts to € 691 (considering both direct and indirect costs) (Giaquinto *et al.* 2007a), which is in line with the cost per pertussis episode estimated by the model for a person <5 years of age: € 690 (scenario 1). Notwithstanding this, in Italy, the estimated yearly burden of pertussis amounts to € 3.74 million while that of rotavirus to 73.55 million (Giaquinto *et al.* 2007b).

6. DISCUSSION

From the findings of a comprehensive review of the literature (Caro *et al.* 2005), performed by the Global Pertussis Initiative to uncover data that quantify the economic burden of pertussis, it emerged that the cost of pertussis is highly variable. One important aspect is whether pertussis-related complications, such as pneumonia and encephalopathy, develop. According to published German estimates (Tormans *et al.* 1998), an uncomplicated case of pertussis is estimated to produce direct costs of € 210, whereas a case requiring hospitalization will be considerably more expensive, incurring an average direct cost of € 1700. Pertussis-related pneumonia has been estimated to increase the direct cost to € 3940, and cases leading to encephalopathy were estimated at € 5170.

It also emerged that estimates of direct costs vary according to age, being highest in infants. A US study estimated the direct costs of pertussis at US$ 2822 for infants (0-23 months), US$ 308 for children (2-12 years), US$ 254 for adolescents (13-18 years) and US$ 181 for adults (19 years of age or older) (Lee and Pichichero 2000).

In addition, a large-scale US study focusing on the societal costs (medical and nonmedical, excluding antibiotics to treat contacts) of pertussis in adolescents and

adults found that mean direct medical costs in a cohort of 1679 adolescents (10-17 years old) and 936 adults (18 years old or older) were $242 and $326, respectively (Lee *et al.* 2004).

In this model, estimates of direct costs are much lower. Indeed, an uncomplicated case of pertussis is estimated to produce direct costs of € 58, whereas a case requiring hospitalization will be producing an average direct cost of € 1,471. Pertussis-related pneumonia has been estimated to increase the direct cost to € 2,015, and cases leading to encephalopathy were estimated at € 2,989. Age-specific estimates of direct costs are reported in Table 13.

Although charges for medical consumption differ across countries and exchange rates may fluctuate, hampering direct comparison of costs, the costs per case also depend on the estimated level of underreporting and the direct medical costs considered. For instance, the presented model includes neither specialist consultation, nor laboratory tests, nor cough medicine, nor vaccination costs.

Published data relating to the indirect costs of pertussis are less available than those for direct costs, but those available strongly suggest that, from a societal perspective, the indirect costs of pertussis and its management are substantial, particularly for working parents and working adults with pertussis. Indeed the economic consequences of pertussis in terms of reduced work productivity and absence from work likely match or exceed direct health care costs (Caro *et al.* 2005).
For instance, the estimate that, in the period 2006-2015 in Italy, indirect costs accounted for 70% of the total burden for pertussis is in line with the finding that the overall indirect costs associated with 87 cases of pertussis totaled US$ 107,025, equaling 73% of the total costs (Lee and Pichichero 2000).
For what concerns vaccination coverage, with the introduction in the Italian market of whole-cell vaccine, pertussis incidence showed a decreasing trend, although immunization coverage was still very low. When acellular vaccines replaced whole-cell ones, vaccine coverage increased dramatically and, within few years, incidence felt to so low figures that since 2002 epidemic cycles have been less clearly identifiable (Gonfiantini *et al.* 2014).
Bearing in mind that the estimated cost per episode for a person <5 years of age is almost identical for rotavirus and pertussis, the almost twenty-times higher annual Societal burden for rotavirus can be ascribed to the fact that this disease has a very low vaccination coverage. Vaccination is not mandatory yet and immunization policies still differ among regions.

This study has several limitations and I acknowledge there are still uncertainties around the proposed estimates of disease burden and assumptions on health care utilization. Concerning the number of pertussis cases, as said, passive surveillance systems, based on notifications, suffer from under-notification; I tried to overcome this issue correcting the available data. Regarding resources consumption, I neither collected data prospectively on the actual consumption of healthcare resources nor I collected information on the indirect costs, so that I had to rely on available data. For what concerns complications, I did not have access to Italian data, therefore I had to rely on US ones. The same holds true for data regarding the number of GP consultations, the percentage of outpatients cases treated with antibiotics, the number of days lost and the length of hospital stays.

7. CONCLUSION

The analysis presented in this article estimated age-specific costs associated with pertussis in Italy and the burden of pertussis the Society had to bear in the last decade (2006-2015). The results show that the average medical costs associated with pertussis range from € 77 to € 1,488 per patient and that these are particularly relevant for infants. Furthermore, the annual direct medical costs for pertussis in Italy are still considerable (approximately € 1.11 million) and do not substantially deviate from those estimated for the Netherlands (approximately € 1.77 million) (de Greeff *et al.* 2009).

The high level of vaccination coverage attained since 2000 has played a key role in diminishing both the incidence of the disease and the related burden for Society. Indeed, even though the estimated cost per episode of confirmed rotavirus gastroenteritis, amounting to € 691 (Giaquinto *et al.* 2007a), is in line with that of a pertussis episode, estimated in € 690, the annual societal burden associated with rotavirus gastroenteritis is almost twenty-times higher: € 3.74 million against 73.55 million (Giaquinto *et al.* 2007b).

The results highlighted the importance of indirect costs, representing 70% of total costs. Different studies suggest that the indirect economic burden of pertussis is substantial because of the economic expenditures required to care for ill family members, the prolonged recovery from illness and the consequential time lost from work.

Although the available studies provide some estimates of medical resource use and data on work time lost due to illness, a complete picture of the economic burden of pertussis is lacking. Major obstacles to the accurate assessment of the costs of pertussis are that the true incidence of pertussis is subject to considerable uncertainty, the severity and cost consequences of unreported and undiagnosed cases are unknown, and costs by the severity of symptoms have not been fully investigated.

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