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RESEARCH ARTICLE

Impact of 13Valent Vaccine for Prevention of Pneumococcal Diseases in Children and Adults at Risk: Possible Scenarios in Campania Region

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ARTICLE HISTORY

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Abstract: ***Background*:** Pneumonias are the most frequent infectious diseases, characterized by a high prevalence especially among children and adults at risk. The socio-economic impact caused by *Streptococcus pneumoniae* is evaluated in terms of morbidity, death rate and hospitalizations.

***Objective*:** The aim of the study was to demonstrate the potential economic advantages by implementation of an active anti-pneumococcal 13-valent vaccine strategy in Campania region (Southern Italy) in two different categories of subjects, children (aged 0-12), and adults (aged 50-79) at risk (hypertension, nephropathies, COPD and heart diseases)

***Methods*:** Vaccination costs were compared with costs necessary to treat avoidable diseases in the presence and absence of a vaccination program.

***Results*:** Offering anti-pneumococcal 13-valent vaccine to the paediatric population was quantified as saving one million euros for Italian national health service in two years. In addition, offering anti-pneumococcal vaccine to adults at risk would generate a return of around 29 million euros.

***Conclusion*:** In both cases, offering anti-pneumococcal 13-valent vaccine was proven to be a helpful political health strategy, not only in consideration of a reduction of cases but also in view of the favourable economic impacts.

Keywords: Pneumococcal disease, 13-valent vaccine, budget impact analysis, *Streptococcus pneumoniae*, bacterium, etiologic agent.

1. INTRODUCTION

Streptococcus pneumoniae is a Gram-positive bacterium widely common in the general population. It is able to colonize the mucosa of the upper airways and it could cause infections, even serious, such as sinusitis, otitis, pneumonia and meningitis [1, 2]. In the last decades, to fight the significant increase of the infections, several vaccine formulas have already been available, capable of assuring high levels of protection in both paediatric population (around 90%) and in adult subjects at risk of, or affected by specific diseases [3-6].

Anti-pneumococcal vaccination shows a good performance in at least 80% of healthy adults, with a rate of efficiency slightly lower for elderly people, but acceptable in subjects affected by chronic diseases [7, 8]. Furthermore, an excellent safety profile has been demonstrated, also when it is administrated in conjunction with other vaccines [9, 10]. A wide availability of anti-pneumococcal vaccines would not only reduce cases of infection/disease, but would also protect the remaining population due to the reduced circulation of the etiologic agent [11-13]. The socio-economic impact of diseases caused by *Streptococcus pneumoniae* is evaluated in terms of excess of morbidity, mortality and hospitalizations [14-18]. World Health Organization (WHO) estimates that there are at least 1.6 million deaths annually caused by *S. pneumoniae*, with 1 million of these among children below 5 years [19].

Pneumonias are the most frequent infectious disease, characterized by a high prevalence especially among children, adults at risk and elderly people, with clinical heterogeneity and variable severity [20]. Several studies estimated that incidence varies among countries, but, as reported in recent years, it is clear that the number of cases and mortality increase significantly due to pneumonia with age.

Pneumonia represents the most frequent cause of death from pneumococcal infection and this has a considerable impact on health systems all over the world [21, 22]. In the

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Table 1. Costs in Euros of anti-pneumococcal and *S.pneumoniae* pathologies vaccination.

Costs	Amount (€)	Source
Vaccine	42,58	Price for AASSLL
Vaccine operator	4,12	ISTAT
Vaccination	140*	Estimated elaboration*
Otitis:	30,59	Lucioni, 1999
- Paediatric visit	18,54	Retail price
- Clavulanic acid + amoxicillin	12,05	
Pneumonia:	1.868,54	Istat
- Paediatric visit	18,54	DRG Campania
- Recovery	1.850	
Meningitis	10.696	Lucioni, 1999

absence of adequate vaccination strategies, it will determine an inevitable negative impact on related health system costs in the near future [20-24].

Prevenar 13® is currently the most utilized conjugated anti-pneumococcal vaccine in our country, considering the high immunogenicity and safety demonstrated over the years [16]. Considering the remarkable epidemiological, clinical and economic relevance of pneumococcal diseases in different ages, especially in paediatric and adults-at-risk subjects, European Medical Agency (EMA) approved and extended the use of Prevenar 13® for individuals of all ages between April 2010 and June 2013. In fact, today PVC13 is commonly referred to as the anti-pneumococcal vaccine "for life". http://www.ema.europa.eu

Despite the most recent national vaccine plans, we underline the clinical efficiency of anti-pneumococcal vaccine in the prevention of infections due to *Streptococcus pneumoniae* in subjects of all ages. Up to now, there is a condition of 'absence of right', so offering such a vaccine is not included or covered by any national regulations [25, 26]. On the other hand, this situation could be an opportunity to reorganize the entire system of vaccination policies in the various local health units around the country, in an attempt to improve the efficiency of the offering [27].

This study supports the hypothesis that an active offering of an anti-pneumococcal vaccine is an important health-related political choice supported not only by clinical efficiency data, but also by results regarding economic return, with reference to results obtained during several studies conducted in Campania region [28, 29].

2. MATERIALS AND METHODS

Budget impact analysis (BIA) was applied in two different work hypotheses.

2.1. First Hypothesis

We estimated, through a budget impact analysis (BIA), time required for an economic return for the National Health System derived from an active offering of the conjugated vaccine 13-valent to newborns in Campania region in 2009 (about two years).

First of all, we estimated the incidence of the 3 principal pneumococcal diseases expected in the paediatric population (otitis, pneumonia and meningitis) in the presence and absence of a vaccination program. Data was deduced from the studies results by Esposito S, La Torre G and Pavia M [30-32]. Then we estimated the cost of treating every single case of otitis, pneumonia and pneumococcal meningitis, with reference to studies conducted on these issues by Lucioni [33], Giorgi-Rossi [34], Colombo [35] and Berto [36]. This cost was multiplied for the number of estimated events in the two hypothesised scenarios. Subsequently, we calculated the cost of vaccination (local health unit's price of medicine + hourly cost of operator) and the expense for the entire immunization program (Table **1**).

The potential economic advantages of the active offering of Prevenar 13® to all newborns in the region were estimated for each year considering the difference between the costs to be sustained for the number of cases of avoidable pneumococcal diseases in vaccinated subjects and those in the non vaccinated subjects.

2.2. Second Hypothesis

We estimated savings obtainable by an active offering of an anti-pneumococcal vaccine to the population aged 50-79 at risk of diabetes, hypertension, nephropathies, COPD and heart conditions (about 1 million of individuals in the region) due to a budget impact analysis (BIA).

The impact of PCV vaccination programs was compared with a no-vaccination scenario. The analyses were performed on the resident population in Campania on January 1 2009, as reported by the National Institute for Statistics (IstitutoNazionale di Statistica, ISTAT), without considering sex and origin [37]. Considering the average national coverage for the last influenza immunization program in Italy in elderly people, vaccination coverage of the targeted cohorts was supposed to be 60% [38].

Table 2. Number of cases (%) of Spn pathologies estimated in case of presence and absence of vaccination programs.

	With Vaccination Program	Without Vaccination Program
	Number of cases (%)	Number of cases (%)
Otitis	23.878 (40%)	29.848 (50%)
Pneumonia	896 (1,5%)	2.985 (5%)
Meningitis	3 (0,05%)	59 (0,1%)
Total	24.777	32.892

Table 3. Costs in Euros for pneumococcal pathologies with presence or absence of a vaccination program and advantage attainable through active offer to paediatric population.

COSTS (€)						
VACCINATION		FIRST YEAR		SECOND YEAR		Costs at the end of the two years
		With vaccination	Without vaccination	With vaccination	Without vaccination	
		8.363.410	-	-	-	8.363.410
Disease	Otitis	730.428,02	913.050,32	730.428,02	913.050,32	365.244,6
	Pneumonia	1.674.211,84	5.577.218,192	1.674.211,84	5.577.218,192	7.806.012,70
	Meningitis	32.089,77	631.064,00	32.089,77	631.064,00	1.197.948,46
Obtainable economic benefit		-	-	-	-	**1.005,796**

*59.696 children

Community-Acquired Pneumonia (CAP) incidence was considered about 3.34% [39]. The clinical outcome of the analysis was hospitalized pneumococcal CAP cases in adult population (50-79 y). Data were obtained from the hospital discharge forms (Scheda di Dimissione Ospedaliera, SDO) of respiratory departments which participate in the training regional network [40]. During the years 2010-2011, 18.965 CAP cases were reported in these SDOs.

Considering that the overall rate of CAP due to *S. pneumoniae* is about 40%, the number of pneumococcal CAP per year among reported cases was estimated to be 3.793 [41].

Considering previous studies, the vaccine efficacy against pneumococcal pneumonia was assumed to be 87.5%, so this value was used to calculate the number of avoided cases for each vaccination strategy [38, 42-44].

Expected cases were corrected for the global mortality rate, as obtained from 2010 ISTAT data [45].

The economic model was based on the difference between the costs sustained with (vaccine plus treatment for expected cases) and without (only expected cases) a vaccination program.

The cost of the vaccine was 42.5 Euro per dose; the cost of a CAP case due to *S. pneumoniae* was assumed to be the average of costs for complicated and non-complicated pneumonia cases, equal to €3.809 [46]. Costs were updated to a rate of 3%.

3. RESULTS

3.1. First Hypothesis

In such a case, the number of cases (%) of diseases caused by *S. pneumoniae*, in the presence and absence of vaccination programs (Table **2**) is estimated. After that, three possible scenarios were hypothesized:

In the first case, supposing that the entire regional population in the year 2009 would be vaccinated, the cost of the vaccination program would be € 8,363,410.00. Conversely, at the end of the two-year period under consideration, obtainable clinical benefits (fewer cases of otitis, meningitis and pneumonia) would provide the opportunity to overthrow the costs due to these diseases, with a quantifiable economic advantage of about 1 million euros (Table **3**).

In the second case, coverage for 80% of newborns was considered, with a consequential potential return in economic terms of € 804,635 at the end of two years. This latter hypothesis considered the vaccination of half the paediatric population in the year 2009: also, in this case, a quantifiable advantage of € 502,897 would be achieved after only two years (Table **4**).

3.2. Second Hypothesis

Because of the processing of epidemiological data, we estimated the number of expected pneumonias in the presence and absence of a vaccination program in subjects at risk aged 50-79 during the period under consideration. Particu-

Table 4. Achievable economic benefit at the end of the two years with active offer of vaccine to 50% and 80% of paediatric population.

% Coverage for Vaccinated People	Number of Vaccinated Subjects	Vaccination Cost	Cost of Avoidable Pathologies	Obtainable Economic Benefit
80%	47.756	6.690.728	7.495.363	804.635,00
50%	29.848	4.181.705	4.684.602	502.897,00

Table 5. Vaccination program costs, costs to be sustained with and without a vaccination program (vaccination costs + costs for treatment of expected casesfor subjects at risk aged 50-79 and Budget Impact Analysis (BIA).

1° YEAR	2° YEAR	3° YEAR	4° YEAR	5° YEAR	TOTAL
Vaccination costs					
€ 25.321.482	€ 483.568	€ 505.692	€ 542.146	€ 570.471	€ 27.423.359
Costs to be sustained with vaccination program					
€ 26.767.386	€ 2.011.272	€ 2.111.999	€ 2.230.071	€ 2.341.038	€ 35.461.965
Costs to be sustained without vaccination program					
€ 11.597.535	€ 12.252.844	€ 12.882.597	€ 13.538.112	€ 14.196.539	€ 64.467.625
Budget Impact Analisys					
+€ 15.169.851	-€ 10.241.572	-€ 10.770.598	-€ 11.307.841	-€ 11.855.501	-€ 29.005.660

larly, expected pneumonias in the first case would be around 509, compared to 4,083 estimated in the second case, with a reduction of 3,574 cases. Subsequently, the design of the study allowed quantification in economic terms of the vaccination program and costs for expected diseases in the two prospected scenarios. In the first approximation, we found that in the first year, the cost that must be sustained to vaccinate all adults at risk aged 50-79 (60% of them) was € 25,321,482, which is about twice the cost needed to treat expected cases of pneumonia in the absence of a vaccination program. Thanks to the vaccination strategy, after some obvious, expected, costs during the first year, we found a saving at the end of the second year due to the reduction of cases of pneumonia (Table **5**).

4. DISCUSSION

Diseases due to *Streptococcus pneumoniae* are a relevant and current health issue that represents one of the most relevant causes of morbidity and mortality in Italy [1, 2].

Only by appropriate preventive measures - specific vaccination strategies - the quality of life of patients can be improved and the number of cases can be reduced.

A prevention approach is fundamental: it moves from “expectation medicine” to “initiative medicine”. It is very important to create a multidisciplinary network.

National vaccine plans exist as guidelines or opportunities to plan strategies on behalf of Public Healthcare organizations to promote health [25, 26].

It must also be stressed that today there is much difference between mandatory and optional vaccinations.

The latest National Vaccine Plan promotes the anti-pneumococcal vaccination strategy for all individuals in the nation.

In past years, the aspect of the cost-effectiveness of vaccinations has been addressed with "ad hoc" analysis. A strategy is considered efficient only if it is also effective, according to recognized high-level scientific evidence.

CONCLUSION

This study demonstrates how a vaccination strategy can generate economic savings [28, 29].

The analysis has two important limits: 1) it does not consider indirect costs; 2) it considers only 5 years. This strategy could represent a sustainable and savings-producer health policy.

LIST OF ABBREVIATIONS

BIA = Budget Impact Analysis

WHO = World Health Organization

EMA = European Medicine Agency

COPD = Chronic Obstructive Pulmonary Disease

AUTHOR’S CONTRIBUTIONS

Alessandro Sanduzzi, Angelo Canora and Marialuisa Bocchino were involved in the concept and design of the

study. Patrizia Belfiore, Giorgio Liguori and Renato Liguori acquired the data. Patrizia Belfiore, Giorgio Liguori, Renato Liguori and Alessandro Sanduzzi were responsible for the analyses of the data. Patrizia Belfiore, Giorgio Liguori, Renato Liguori and Alessandro Sanduzzi interpreted the results. All Authors were involved in drafting and critically revising the manuscript and approved the final version. I.P. is the guarantor of this manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data sets generated during and/or analyzed during the current study are not publicly available due to ethical consideration but are available from the corresponding author on reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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