

## Costs of *Bordetella pertussis* in tertiary hospitals of Argentina

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### ABSTRACT

The National Immunization Commission and the National Program for the Control of Vaccine-Preventable Diseases (*Programa Nacional de Control de Enfermedades Inmunoprevenibles, ProNaCEI*) updated the immunization policy in relation to *Bordetella pertussis* (BP) in 2009 in order to improve the control of this disease in accordance with international recommendations. To evaluate the financial impact of this new immunization policy, we must first know the cost on the health system of having a hospitalized or outpatient child infected with BP.

The objective of this study was to describe the profile of costs of hospitalized or outpatient children with laboratory-confirmed BP infection in three hospitals of Argentina. This was a prospective study of the cost of BP in the period between December 2010 and March 2012.

**Results.** The total cost for the entire cohort was 1 170 663.32 ARS (236 497.64 USD); direct medical costs were 1 124 052.31 ARS (227 081.27 USD); indirect costs and out-of-pocket expenses were 46 611 ARS (9416.6 USD). From this data, it is possible to conclude that the total average cost per patient was 10 546.52 ARS (95% CI: 9009-13 840) (2130.60 USD, 95% CI: 1820-2795), the direct medical cost per patient was 10 126.6 ARS (95% CI: 8607-13 171) (2045.77 USD, 95% CI: 1738-2660), and the indirect plus out-of-pocket costs (transportation and extras) were 419.92 ARS (95% CI: 344.7-565.3) (84 USD, 95% CI: 69-115).

**Conclusion.** The cost of a hospitalized child with confirmed BP is 10 546.52 ARS (95% CI: 9009-13 840) (2130.60 USD, 95% CI: 1820-2795). Direct non-medical costs and overhead costs account for 4% of the total cost, amounting to 419.91 ARS per family (84 USD, 95% CI: 69-115), approximately an 8% of an average salary.

**Key words:** *Bordetella pertussis*, costs, cost analysis, immunization.

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### INTRODUCTION

*Pertussis* or whooping cough is an acute infectious disease of the lower respiratory tract caused by *Bordetella pertussis* (BP). *Pertussis* means violent cough (Sydenham, 1679), name which describes the main feature of this disease.<sup>1</sup>

In Argentina,<sup>2</sup> as in developed

countries,<sup>3</sup> the re-emergence of this infection has been observed, with an increase in the incidence and death rates, especially in newborns and infants younger than 6 months old.<sup>4</sup>

In 2011, the Ministry of Health of Argentina reported a total of 70 deaths among infants, all younger than 3 months old; most of them were either not immunized or partially immunized which is to be expected in this age group (in Argentina, as per the vaccination schedule, the first dose should be administered at 2 months old).<sup>5</sup> One of the hypotheses is that these children get infected from their school aged or adolescent siblings or from their parents,<sup>6</sup> who play a fundamental role in the transmission of this disease.

The National Advisory Committee on Immunization and the National Program for the Control of Vaccine-Preventable Diseases (*Programa Nacional de Control de Enfermedades Inmunoprevenibles, ProNaCEI*) updated the Argentine immunization policy in 2009,<sup>7,8</sup> based on the epidemiological scenario and with the aim to control this disease in accordance with international guidelines.<sup>9,10</sup> Children younger than 7 years old receive whole-cell vaccines combined with other antigens, depending on their age.

For children older than 7 years old, acellular vaccines which contain antigenic components of *Bordetella pertussis* are used, which create immunogenicity with a lower rate of adverse events. Currently, immunization is provided to 11 year old children (2009), to healthcare staff who are in contact with children (2010), to parents of preterm newborn

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infants with a birth weight of less than 1500 g (2010), and to pregnant women with a single dose as of gestational week 20 (2011). In relation to the latter strategy, if it is not possible to administer the vaccine during pregnancy, the mother should be immunized in the post-partum period and before her baby is 6 months old. Such strategy can be less effective, but given the epidemiological context, achieving protection in the first months of life is critical.

These changes in the national immunization program were implemented to achieve a reduction in the number of cases, especially among younger infants, and they require a high immunization coverage.

In order to assess the financial impact of these new strategies, and in accordance with the recommendations made by the Pan American Health Organization through the ProVac initiative,<sup>11</sup> it is necessary to know the cost on the health system of having a hospitalized or outpatient child infected by *Bordetella pertussis*. It is recommended that these pieces of evidence are included in data to be analyzed as part of decision making processes regarding the most adequate strategies in Argentina. This study provides information which was unavailable at the time of proposing the new guidelines.

There are no multicenter studies conducted in Argentina evaluating the cost of BP, but it is estimated that the cost per case could be relevant because all children with cyanosing cough, reprises or apnea are eligible for hospitalization, and younger children even require to be hospitalized in neonatal or pediatric intensive care units.<sup>12,13</sup> Moreover, laboratory techniques, additional exams and invasive therapeutic procedures are conducted for diagnostic purposes.

The objective of this study was to describe the cost profile of hospitalized or outpatient children with laboratory-confirmed BP infection in three tertiary hospitals of Argentina.

## MATERIAL AND METHODS

This was a prospective study of the cost of *Bordetella pertussis* in three tertiary pediatric hospitals of Argentina (Hospital de Niños Ricardo Gutiérrez, Hospital Municipal Materno Infantil de San Isidro Dr. Gianantonio, and Hospital de Niños Víctor J. Vilela, Rosario, Province of Santa Fe) over a period between December 2010 and March 2012. For this study, children seeking care in the participating sites and meeting the criteria

for suspected *Bordetella pertussis* infection were selected.

**Infants younger than 6 months old:** any acute respiratory tract infection with at least one of the following symptoms: apnea, cyanosis, inspiratory stridor, cough with vomiting, or paroxysmal cough.

**Children older than 6 months old and younger than 11 years old:** cough for 14 or more days accompanied with one or more of the following symptoms: paroxysmal cough, inspiratory stridor, or cough with vomiting, with no other apparent cause.

**Children older than 11 years old:** persistent cough for 14 or more days with no other symptoms.

All these children had a polymerase chain reaction assay for BP using the multitarget real-time method in real time for regions IS 481, pTxS1, hIS 1001, pIS 1001.<sup>14</sup>

If the assay was positive, children were included in the study for follow-up after the informed consent was signed.

An epidemiological card was developed for each child; the following data were included: identification, personal history, number of healthy household members and number of household members with BP-compatible symptoms, personal history of immunization, presence of prematurity, malnutrition or chronic disease, characteristics of the clinical presentation of the case, antibiotic prescription patterns, medical visits, length of stay in the hospital, diagnostic procedures, and clinical course. In addition, parents were asked about the expenses resulting from their visit to the hospital and any discount on their salaries due to absenteeism so as to be able to assess overhead costs, transportation and out-of-pocket expenses.

The unit cost of each resource was obtained based on the values established by the National Register of Medical Practices of the Ministry of Health of the Autonomous City of Buenos Aires,<sup>15</sup> and antibiotic costs were obtained from the pharmacopeia called Manual Farmacéutico.<sup>16</sup> To establish the price of medications, a 40% discount was included as per hospital procurement agreements. This study was conducted in the society's perspective, and costs are stated in Argentine pesos (ARS) with an exchange rate of 1 US dollar (USD)= 4.95 ARS.

Missing data were set off using conditional imputation with the mean sample value, according to Gray, et al.'s recommendations.<sup>17</sup>

The study lasted one year, so no discount was applied.

### Ethical considerations

The study was approved by all Institutional Ethics Committees and was subsidized by the Ministry of Health of Argentina through the Argentine Society of Pediatrics. Analysis of results Mean, standard deviation (SD), median and interquartile range of clinical variables were calculated using the Epi Info software, version 6.0, while the confidence intervals of proportions were calculated with the OpenEpi 2.2.1 software.<sup>18</sup>

Costs were calculated based on an Excel model designed for this aim where the following data were introduced: resources used, unit costs, overhead costs, and out-of-pocket expenses for each patient enrolled in the study. Calculations included total cost for each patient, total cost of all cases, and average cost per patient, all caused by BP.

For the 95% confidence interval of the average cost per patient, a probabilistic bootstrapping analysis with 10 000 simulations was done using the R 2.15.0 software (Vanderbilt University, Nashville Tennessee, USA, R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>).

### RESULTS

In the period between December 2010 and February 2012, 856 suspected cases of whooping cough were detected in the three reference hospitals. Nasopharyngeal secretion samples were obtained from 817 patients and tested for *Bordetella pertussis* genetic material. Out of all suspected cases, 39 were not tested because the sample was scarce; 123 cases (123/778; 16%) were confirmed and 112 patients were hospitalized.

*Table 1* describes the most relevant demographic and clinical characteristics of confirmed cases requiring hospitalization. Out of the total number of patients included in the three sites, 10 (9%; CI: 5.5-18.48) required treatment in intensive care units, and 6 died (5.3% of confirmed cases).

*Table 2* describes the patterns related to average use of medical resources and SD per patient, plus median and interquartile range. *Table 3* describes the patterns related to antibiotic prescription, administration and costs for the hospitalized population. *Table 4* provides details on overhead costs and out-of-pocket expenses. In relation to total costs analyzed, direct medical

TABLE 1. Relevant demographic and clinical characteristics of confirmed cases requiring hospitalization

Demographic and clinical variables	Cases (n= 112)
Average age (months) and SD (Median and interquartile range)	4.56 (5.35) 3 (1-5)
Females	50%
Patients with prematurity	10.1% (5.4-16.8)
Patients with malnutrition	2.7% (0.7-7.3)
Patients with chronic disease	8.5% (4.2-15)
Patients with complete immunization scheme against BP (as per age)	75% (62.3-86.5)
Duration of cough in days (mean and SD) (Median and interquartile range)	10.6 (9.2) 7 (4-15)
Number of consultations due to symptoms (mean and SD) (Median and interquartile range)	0.4 (0.9) 0 (0-1)
Number of household members (mean and SD) (Median and interquartile range)	4.7 (22) 4 (3-6)
Patients with fever (%)	39% (30.8-49)
Leukocyte count (mean and SD) (Median and interquartile range)	22 831 (13 489) 18 800 (12 700-28 300)
Number of lymphocytes in blood differential (mean and SD) (Median and interquartile range)	58.9% (16) 62.5 (49-71)
Patients with chest x-ray showing a lung condition as per treating physician	99% (95.6-99.9)

costs accounted for 96%, and indirect costs for 4%, result which is shown in *Table 5*.

The total cost for the entire cohort was 1 170 663.32 ARS (236 497.64 USD); direct medical costs were 1 124 052.31 ARS (227 081.27 USD); overhead costs and out-of-pocket expenses were 46 611 ARS (9416,36 USD). From this data, it is possible to conclude that the total average cost per patient was 10 546.52 ARS (95% CI: 9009-13 840) (2130.60 USD, 95% CI: 1820-2795), direct medical cost per patient was 10 126.6 ARS (95% CI: 8607-13 171) (2045.77 USD, 95% CI: 1738-2660), and overhead plus out-of-pocket costs (transportation

and extras) were 419.92 ARS (95% CI: 344.7-565.3) (84 USD, 95% CI: 69-115).

## DISCUSSION

*Bordetella pertussis* infection is one of the vaccine-preventable diseases that is most difficult to control.<sup>19</sup>

Several causes can be provided as an explanation for these hurdles and for the re-emergence of this disease. BP is transmitted in the catarrhal stage, when there is still no diagnosis made; many of the patients are school aged children or adolescents with atypical symptoms,

TABLE 2. Patterns of medical resource use

Resource and unit cost n = 112	Mean and SD Median and interquartile range	Costs (mean and SD) (ARS)
Visits to the emergency room	2.6 (2.5) 1 (1-3)	273 (262.5)
Chest X-rays	1.9 (4) 1 (1-1)	110 (232)
Length of hospital stay in medical	6.5 (4) 6 (4-8)	7475 (4600)
Length of hospital stay (ICU)	14.2 (14.8) 10.5 (4-20)*	26 980 (12 160)
Blood count	1.6 (2.6) 1 (1-1)	35.2 (57.2)
Blood gases	1.5 (5.9) 0 (0-50)**	48 (188.8)
Blood culture	1.5 (1.2) 0 (0-6)**	87 (69.6)
Lumbar taps	0.07 (0.2) 0 (0-1)	4 (11.6)
Liver Function Tests	0.5 (2.2) 0 (0-15)	29 (127.6)
Follow-up visit	0.9 (0.7) 1 (1-1) *	34 (26.6)

\* Average days of hospitalization in ICU: only for the population admitted to the ICU; n = 10.

\*\* For values with an interquartile range of 0, only the range was provided.

ICU: Intensive care unit.

TABLE 3. Patterns related to antibiotic prescription, administration and costs

Antibiotic	Proportion of patients receiving the antibiotic (%)	Total grams administered (g)	Total costs (ARS)
Clarithromycin J01FA09	89	61.4	1197
Azithromycin J01FA10	1.8	0.3	9
Erythromycin J01FA01	8	29	151
Cefotaxime J01DD01	8	1.9	891
Ceftriaxone J01DD04	3.6	3	96

a late diagnosis and the resulting inadequate treatment; epidemiological measures taken for managing those who are in contact with these patients are also untimely, thus favoring the transmission of the disease.

Another cause for BP re-emergence is the accumulation of susceptible individuals, because BP does not result in life-long immunity and because the antibodies conferred by the vaccine do not last long (five years after receiving the complete immunization scheme, a clinically significant loss of antibodies has been observed).<sup>20-22</sup>

In relation to this issue, acellular vaccine effectiveness and immunity duration have been under study given the recent outbreaks in USA (California and Seattle) in school children who received complete immunization schemes.

Studies published in Argentina<sup>12,13,23</sup> have had a higher proportion of cases in infants younger than 6 months old, and these data are consistent with the findings of our study.

The most severe cases were also found in this age group, as described in the bibliography, because younger newborn infants have not completed their immunization due to their age and also because they have less capacity to produce an immune response.<sup>23-25</sup>

Fatal cases accounted for 5.8% of cases in our study, similar to the values published in other Argentine studies.<sup>12,13,23</sup>

In terms of the immunization status, 23% of children (average number for the three hospitals)

had an incomplete immunization for their age, consistent with the data previously published by Romanin, et al. for Hospital de Niños Ricardo Gutiérrez in the City of Buenos Aires<sup>26-27</sup> and updated in 2012 with a multicenter study in primary healthcare facilities and tertiary care sites.

It is worth underscoring such information because one of the critical components for BP prevention and management is to maintain high rates of vaccine coverage in infants and children.<sup>28</sup>

BP cost studies are rare in Latin America, but they are available in North America<sup>29-31</sup> and Europe.<sup>32,33</sup> Most of them highlight that the estimations of BP direct medical costs depend on age: they are higher in infants younger than 1 year old because this age group usually requires hospitalization, as mentioned above.

In our study, the average age was 4.5 months old, and direct medical costs were 2045.77 USD. The study conducted in the USA by Lee, et al. in 2000 estimated that BP direct medical costs were 2822 USD for children younger than 2 years old, and in this group, hospitalization accounted for 75% of the total cost.<sup>30</sup>

O'Brien (2005) had a more representative population sample and estimated that for infants younger than 1 year old, the cost amounted to 9580 USD.<sup>31</sup>

In our study, hospitalization-related direct medical costs accounted for 96% of total costs. This is probably because our study focused on tertiary care hospitals, where there is a lower

TABLE 4. *Overhead costs and out-of-pocket expenses*

Resource and unit cost *	Patients hospitalized in the internal medicine unit n = 102 (mean and SD)	Patients hospitalized in the intensive care unit n = 10 (mean and SD)
Transportation expenses	65.8 (62.5)	106 (69.5)
Discount for absenteeism (father)	101 (247.8)	282.7 (660.7)
Discount for absenteeism (mother)	48.7 (173.3)	105.3 (297.7)
Additional expenses	148.7 (93.7)	459 (724.2)

\* In ARS.

TABLE 5. *Cost percent distribution*

Direct costs: 96%	Overhead costs: 4%
Hospitalization in the medical unit: 69%	Transportation expenses: 0.6%
Hospitalization in the ICU: 23%	Discount for absenteeism (mother): 0.5%
Medical visits: 3%	Discount for absenteeism (father): 1.1%
Antibiotics: 1%	Additional expenses: 1.8%

number of outpatient consultations and because most patients since they are younger than 6 months old are hospitalized at an early stage.

It is believed that hospitalization of adolescents and adults with whooping cough is infrequent; however, some studies have documented that up to 7.5% of 10-19 year old individuals and 5.7% of >20 year old individuals with whooping cough do require hospitalization.<sup>29,30</sup> No reliable data are available in Argentina regarding this aspect.

In relation to the length of stay, some authors have proposed that the longest stay make take place in patients older than 50 years old and in infants younger than 1 year old, as evidenced in the study by Gil, et al. where the mean length of hospitalization was 8.7 and 9.4 days, respectively.<sup>32</sup> In our study, the average stay in the internal medicine unit was 6.5 days, and results are similar to those observed by Lee, et al. and O'Brien in infants younger than 1 years old in the USA.<sup>30,31</sup>

Direct non-medical costs and overhead costs are only 4% of total costs, and correspond to 419.91 ARS (84 USD) per family, approximately 8% of an average salary (5194 ARS for the third quarter of 2011, according to INDEC, the Statistics and Censuses Institute of Argentina).<sup>34</sup>

In the study by Rowensztein, et al.<sup>35</sup> on respiratory disease costs in 2004, the total transportation expenses were 41.92 ARS (8 USD). When compared to our results of 69 ARS (14 USD) per family, as an average, and adjusted for inflation, our observations seem to indicate that expenses are lower than in Hospital Garrahan.

It should be noted that this value highly depends on the distance travelled by families from their house to the medical facility, and this situation can lead to a significant interinstitutional variability.

Regarding overhead costs, the study of Lee conducted<sup>27</sup> in 69 families (87 cases confirmed for *Bordetella pertussis*) in New York showed that parents missed 6 working days (1-35 days) in average to look after their sick children. This meant a loss of 767 USD and an average of 1.7 or 0.7 days used to take their children to medical consultation or to the emergency room, respectively. In addition, most parents (58%) who were not absent from their jobs indicated that their work performance had decreased (25-99%).

In our population, absenteeism-related expenses were in average 35 USD, which is extremely low when compared to other published studies. However, if compared to data obtained

by Rowensztein, et al.,<sup>35</sup> the discount due to absenteeism suffered by both parents was 32 USD, but these authors explain that more than 50% of the population seeking care in the hospital and interviewed were poor and destitute.

It should be pointed out that both hospitals possibly provide care to very-low-income populations who have a high unemployment rate, thus reducing absenteeism-related costs.

This study has some weaknesses, such as not including the cost of the polymerase chain reaction diagnostic assay, because the purpose of the study was to only consider costs of confirmed cases.

If the PCR cost is included, which is 125 ARS (25 USD) according to the register, the total cohort cost would be 1 186 038.32 ARS (239 603.70 USD), accounting for 1.2% of all BP costs.

The number of cases found at each site was not uniform, and the total cost analysis is probably more representative of the site with the higher number of confirmed cases. Finally, the number of outpatient consultations per confirmed case may have been under-recorded in this study because, as explained before, assessment was done in tertiary hospitals.

Results of this study will help to improve BP-related evidence and lead to an enhanced assessment of immunization strategies, basis of decision making in healthcare policies.

## CONCLUSIONS

A hospitalized child with confirmed BP represents a cost of 10 546.52 ARS (95% CI: 9009-13 840) (2130.60 USD, 95% CI: 1820-2795).

Direct non-medical costs and overhead costs account for 4% of total costs, and correspond to 419.91 ARS per family (84 USD, 95% CI: 69-115), approximately 8% of an average salary. ■

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