Childhood pneumococcal disease burden in Argentina

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ABSTRACT

Objectives. *To understand the disease burden of pneumococcal disease (PD), a major cause of childhood morbidity and mortality in Argentina, and to draw a baseline against which the need for and effectiveness of vaccination with pneumococcal conjugate vaccines might be measured.*

Methods. *A Markov model was constructed to estimate incidence and mortality rates of PD—meningitis (MEN), bacteremia/septicemia (BACT), pneumonia (PNEU), acute otitis media (AOM)—among a hypothetical, birth cohort of 750 000 Argentine infants born in 2006–2015. A systematic review of the literature was performed to select and incorporate input parameters. Life years and costs in 2006 US$ were expressed as both undiscounted and discounted.*

Results. *The number of PD episodes estimated to occur over a 10-year period in the hypothetical birth cohort were: MEN, 225; BACT, 2 841; PNEU, 2 628; and AOM, 2 066 719. Chronic sequelae of MEN could be expected to cause neurological damage in 43 children and severe hearing issues in 28. Results indicate that there would be 78 PD-related deaths in the cohort (29% due to MEN; 54%, BACT; and 17%, PNEU). The undiscounted life-expectancy for individuals in the birth cohort was estimated to be 72.4 years (29.0 years discounted). Mean, undiscounted, lifetime costs attributed to PD for each child of the cohort totaled US$ 167 (US$ 151 discounted), imposing a total, cohort cost-burden of more than US$ 126 million (US$ 113 million discounted).*

Conclusions. *The study shows that PD imposes a significant health and economic burden on the Argentine population. This information is essential for assessing the potential health and economic impact of introducing pneumococcal conjugate vaccine into the national immunization schedule.*

Key words Meningitis, pneumococcal; pneumococcal infections; pneumococcal vaccines; cost-benefit analysis; Argentina.

Pneumococcal disease (1) is a major cause of childhood morbidity and mortality worldwide. Infections caused by *S. pneumoniae* are the most common cause of vaccine-preventable deaths among children less than 5 years of age in Latin America (2) and worldwide (3, 4). Epidemiologic studies carried out in Latin America (5–8) and Argentina (9–12) support these reports, underscoring the importance of the health impact of PD.

The quality and availability of epidemiological data are very heterogeneous, both among and within Latin American countries. In general, there is better information regarding invasive pneumococcal diseases (IPD), specifically meningitis (MEN), than noninvasive pneumococcal diseases, such as nonbacteremic pneumonia (PNEU) and acute otitis media (AOM). Given the known efficacy (13)

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and recent data regarding the effectiveness (14–19) of pneumococcal conjugate vaccines in preventing PD in children, it is important to understand the burden and the incidence of preventable PD in Argentine children. This information is essential for assessing the potential health and economic impact of introducing pneumococcal conjugate vaccination into the national immunization schedule. The wider use of new pneumococcal conjugate vaccines over the next few years may represent an important advance in countries that can afford it. For example, the introduction of routine, conjugate pneumococcal immunization of infants in the United States (20) has produced a 60–90% reduction in the IPD incidence rate among children under 2 years of age.

Vaccines available differ mainly in the serotype coverage (all include the seven serotypes covered by the first FDA-approved vaccine, Prevnar®-4, 6B, 9V, 14, 18C, 19F, and 23F). A 9-valent vaccine adds serotypes 1 and 5; a 11-valent, serotypes 3 and 7Fm; and the 13-valent, 19A and 6A.

Although there have been some studies evaluating IPD in Argentina (9–11) and neighboring countries (5), there are no studies assessing the disease burden of all PDs (IPD and non-invasive pneumococcal diseases) nor the economic burden in Argentine children. The objective of the present study was to estimate, using a Markov model, the childhood burden of PD in Argentina, from an epidemiologic and economic perspective. This study can serve as a basis for projecting what the benefits of each of the available pneumococcal conjugate vaccines might be.

METHODS

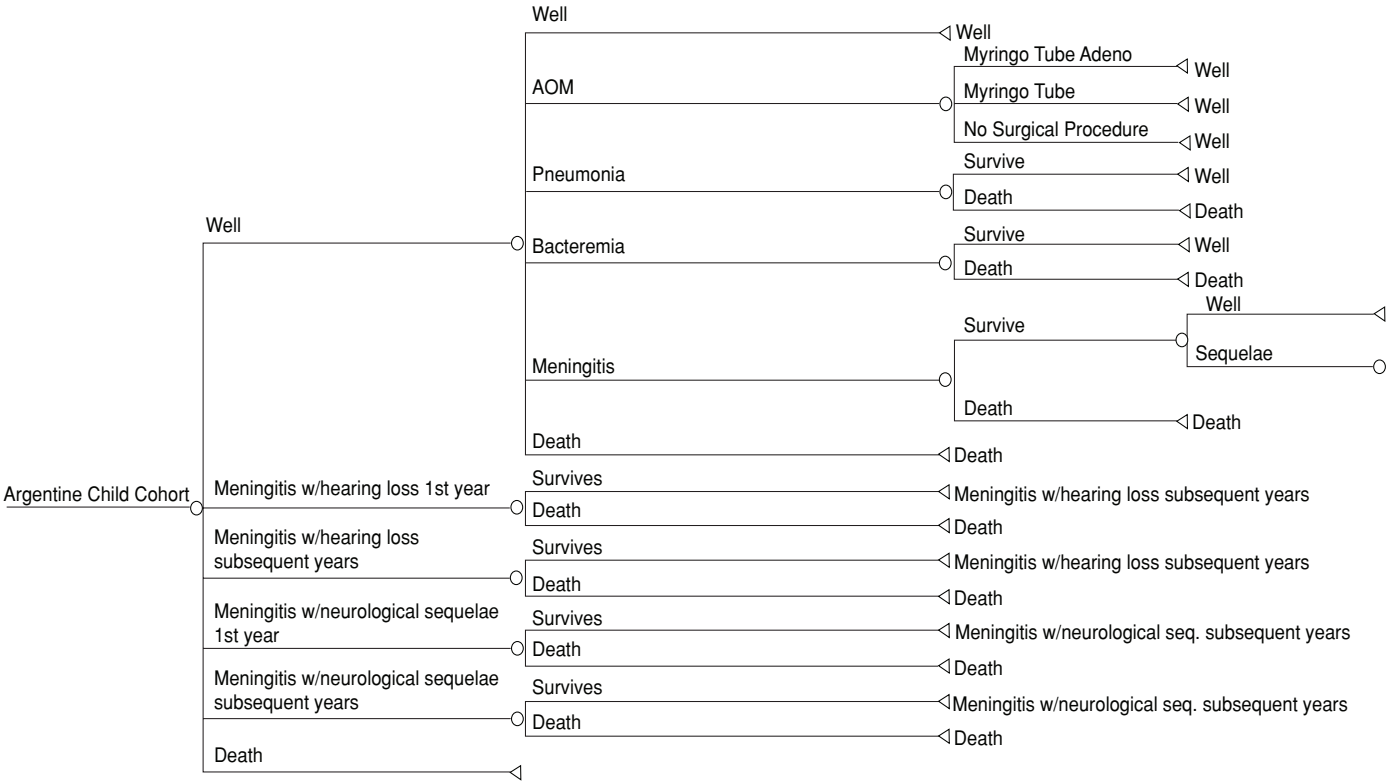
Model structure

A Markov model (Figure 1) was constructed to derive disease burden. Markov models are a subtype of decision-analytic models widely used in decision analysis and economic evaluations. Briefly, they simulate the long-term evolution of the selected health problem. So, patients spend their lives in different health states according to the elapsing time (in cycles of a certain duration) and probabilities of "transitioning" from one health state to another (21). In this case, the main health states modeled were MEN, BACT, PNEU, AOM, and deaths from PD in a birth cohort of 750 000 Argentines hypothetically born in 2006–2015, during the first 10 years of life. Neurological and hearing sequelae from meningitis were also modeled, as were AOM sequelae (through myringotomy rates); however, bacteremia was assumed to have no sequelae. Transition probabilities within 6-month cycles were incorporated. These were calculated by converting annual probabilities to rates and then to 6-month probabilities, assuming an exponential function. Estimates of life expectancy and mortality were based on 2006 data reported by the Dirección Nacional de Estadísticas Sociales y de Población (National Institute on Statistics and Population, INDEC) (22). Following recommendations of the Washington Panel (23), a 3% discount rate was used for the base-case analysis, although undiscounted results are also reported.

Search strategy for parameter incorporation

Input parameters were selected following a strategic and systematic review of

FIGURE 1. Markov model structure used for the estimation of pneumococcal disease burden among a hypothetical, birth cohort of 750 000 Argentine infants, 2006–2015



all available sources including: (a) literature published in January 1990–June 2007 (Medline, LILACS, EMBASE, CCCTR, CRD); (b) abstracts from the local, regional, and international conferences held by Argentina's major scientific associations; (c) bibliographies of relevant papers; (d) bibliography provided by local pediatric infectious disease specialists and epidemiologists; and (e) modified-Delphi expert panels for parameters that were not found with steps (a) through (d), mainly for local clinical management strategies and resource use for each PD.

Currency

Costs are expressed in discounted 2006 United States dollars (US$, discount rate 3%) (23), although undiscounted costs are also presented. The conversion rate used was US$ 1 = 3.04 Argentine pesos. For the present analysis, the base-case analysis was performed from a societal perspective.

Epidemiological data sources

Meningitis. National statistics from the Ministry of Health's *National Epidemiological Bulletin 2000–2001* (24) for birth–10 years of age were used to estimate meningitis incidence (Table 1). Data for children under 2 years of age were supplemented by a previously reported study (10). It was assumed that all meningitis episodes resulted in hospitalization, with a 10.17% mortality rate. This estimate was based on the weighted average of mortality data from three local studies (25–27).

Long-term sequelae. To estimate the prevalence of neurological and hearing sequelae following a meningitis episode, local as well as international literature were used. As a conservative estimate, and in keeping with other studies (28–32), it was assumed that those who survived an acute episode with a sequelae would have a mortality rate similar to that of the general population.

Hearing sequelae. There is enormous variability in the literature regarding the incidence of hearing sequelae, ranging from 4% (25) to 30% incidence (33, 34). Since this study focused on severe hearing sequelae needing special education and cochlear implants, an intermediate figure of 14% was used.

Neurological sequelae. Local data (25, 27) were used to estimate global incidence of motor and epileptic neurological sequelae. For the base-case analysis, 19.8% of the patients with meningitis were assumed to have neurological sequelae, of which half were assumed to be motor, and half, epileptic.

Pneumococcal bacteremia and septicemia

To estimate the number of bacteremia/septicemia episodes (Table 1), local data from a population-based study done in Córdoba were used (10, 11). Since that study included children birth–2 years of age, and no local data in older children were available, the relative decrement in incidence for the subsequent years (2–10 years of age) was extrapolated by averaging data from four other studies (28–30, 32). To estimate bacteremia-related mortality, local epidemiological data reporting bacteremia hospitalization rates (10), and mortality rates in those hospitalized were used (26). These produced estimates that 11.8% of children with bacteremia are hospitalized (10), and of these, 12.5% do not survive (26). We assumed no mortality among ambulatory patients.

Pneumococcal pneumonia

The search strategy used in this study retrieved two population-based studies that evaluated the incidence of pneumonia: one in children up to 2 years of age (10, 11), and the other, in children up to 5 years (9). These studies defined probable bacterial pneumonia as: a child with clinical symptoms of pneumonia and a compatible chest film. Since incidence data came from four different cities, a weighted average was used to determine mean incidence rates.

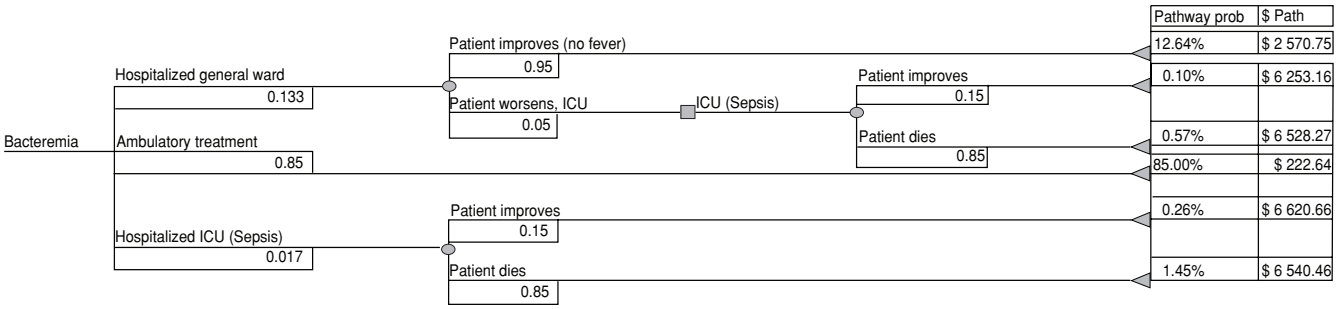
No local data on pneumonia incidence in children more than 5 years of age was found; therefore, the same methodology, explained above for bacteremia, was followed to estimate these values (Table 1). Again it was assumed that no deaths occurred in the ambulatory setting. Based on Ruvinsky et al., it was estimated that

TABLE 1. Annual incidence of various pneumococcal diseases (Meningitis, Bacteremia, Pneumonia), as well as pneumococcal Acute Otitis Media (P-AOM, proportion of children who suffer it and number of episodes), Argentina

Year of life	Meningitis[a] (cases per 100 000 persons)	Bacteremia[b] (cases per 100 000 persons)	Pneumonia[c] (cases per 100 000 persons)	Proportion of children with P-AOM[d]	Mean number of episodes in children with P-AOM
1st	16	98	108	0.23	1.94
2nd	2	98	92	0.22	1.86
3rd	2	32	29	0.15	1.71
4th	2	29	30	0.16	1.91
5th	2	25	19	0.16	1.67
6th	1	18	15	0.14	1.62
7th	1	18	14	0.11	1.33
8th	1	17	13	0.10	1.33
9th	1	17	13	0.08	1.33
10th	1	17	12	0.07	1.33

[a] Data from the *National Epidemiological Bulletin*, 2000–2001 (20).
[b] Data was from Tregnaghi et al. (10) and Tregnaghi et al. (11) for children up to 2 years of age. The subsequent relative decrement in incidence up to the age of 10 years was extrapolated.
[c] Denotes probable bacterial pneumonia cases, defined as patients with clinical symptoms and a compatible chest film (9–11).
[d] Derived from all-cause AOM incidence data multiplied by 0.374 (the proportion of AOM cases due to pneumococcal infection) (36, 37).

FIGURE 2. Clinical management pathway of a disease state (example): Bacteremia. The number below each path name is the probability of the event's occurrence; Pathway prob is the probability of each clinical pathway, Argentina, 2006–2015



67% of pneumonia episodes result in hospitalization, and of these, 0.74% do not survive (9). Local data sources were used to estimate pneumococcal-specific pneumonia burden (35). To estimate probable pneumococcal-specific pneumonia incidence, these values were multiplied by 0.128 (pneumonias shown to have bacterial etiology among children with pneumonia), and then by 0.39 (those shown to be pneumococcal among bacterial pneumonias) (35, 36). Final values are shown in Table 1.

Pneumococcal AOM

Epidemiological data for AOM was extracted from a population-based cohort study (37), from which we derived the data for our model (Table 1), using a similar approach to Beutels et al. (38). To estimate pneumococcal-specific AOM burden, a weighted average of incidence data was derived from local AOM studies (36) with a value of 0.374 (95%CI: 0.343–0.404) for the proportion of AOM cases due to pneumococcal infection. This value was then used to find the pneumococcal-specific AOM incidence from all-cause AOM incidence data (Table 1) (37). As in other published studies, long-term AOM sequelae were not included (29–32).

Resource use and costs

Clinical management pathways were constructed using information from a systematic review of the literature and from modified Delphi panels. These clinical pathways represent the usual/routine care for the different pneumococcal diseases in Argentina. An example of the clinical management pathway for bacteremia is shown in Figure 2. Unit costs were obtained from the Health Care Cost Database, an independent reference source for tariffs in the different health subsectors (39). Drug costs were obtained from 2006 national drug prices (40). Where necessary, costs were adjusted using the health care component of the consumer price index of Argentina (41). Some cost parameters not reported in the aforementioned sources were obtained by surveying local health systems (i.e., for myringotomy, adenoidectomy, cochlear implant-related acute and long-term costs, special education, and rehabilitation). In the sensitivity analysis, we tested a range of 50%–150% for the base-case cost values.

Sensitivity analysis

Extensive one-way sensitivity analyses were performed. The parameters explored included AOM incidence, mortality rates, hospitalization rates, neurological and hearing sequelae rates, episodes, and procedure costs. The parameters, their ranges, and sources are shown in the Table 2.

RESULTS

The projected epidemiological data, resource use and costs, and life expectancy burden of PD are shown in Table 3. Briefly, the values for PD episodes in the first 10 years of life were MEN: 225; BACT: 2 841; PNEU: 2 628; and AOM: 2 066 719. Chronic sequelae of MEN included 43 children with neurological damage and 28 with significant hearing sequelae.

Seventy-eight deaths in the cohort were attributable to PD with 29% due to MEN, 54% to BACT, and 17% to PNEU. The undiscounted life-expectancy was estimated to be 72.445 years (29.039 years discounted). These values translate to 5 533 years of life lost due to PD. Mean undiscounted lifetime costs, attributable to PD for each child in the cohort, total US$ 167.43, imposing a total cohort cost burden of US$ 125.5 million. The corresponding discounted costs were US$ 151.25 and US$ 113.4 million, respectively. AOM-specific costs, which were the largest source of costs, included surgical costs from a projected 147 077 AOM-related procedures (85% of which were myringotomies with tubes, totaling US$ 31 735 992; 15% were myringotomies with additional adenoidectomies, totaling US$ 9 240 759).

PD-related costs of each event-episode were calculated through the clinical pathway analysis with each resource use and its unit cost, as shown in Table 4.

Sensitivity analysis

Life-expectancy was most sensitive to variability at the discounted rate (Table 5). When undiscounted, life expectancy was 72.4 years. Discounting at a rate of 3% resulted in a life expectancy of 29.0 years, whereas a discount rate of 6% resulted in a life expectancy of 16.5 years. The variables that had the most influence on the total cost were: non-surgical AOM cost; AOM incidence; myringotomy cost; probability of myringotomy with tubes in AOM; discount rate; and probability of pneumococcal etiology in AOM (Table 5). All of the aforementioned parameters varied the base-case value of lifetime cost-per-child by more than 5%. The analysis was robust for all other variables in the ranges tested.

DISCUSSION

Despite using a model with conservative estimates of disease burden as input data, this study shows that PD imposes

TABLE 2. Parameters used for sensitivity analysis, their ranges and sources, in a study of the pneumococcal disease (PD) burden in a hypothetical cohort of 750 000 children, Argentina, 2006–2015

	Range of parameters		
	Minimum	Maximum	Source
Relative risk of IPD[d] reduction	0.827	0.999	Black et al. (13)
Relative risk of pneumonia reduction	0.044	0.34	Black et al. (13)
Relative risk of AOM[e] reduction	0.041	0.097	Black et al. (13)
Relative risk of myringotomy reduction	0.117	0.35	Black et al. (15)
AOM incidence	0.7	1.3	± 30%[a]
Meningitis mortality rate	0.05	0.15	± 50%[a]
Bacteremia mortality rate	0.06	0.18	± 50%[a]
Pneumonia mortality rate	0.0035	0.015	± 50%[a]
Bacteremia hospitalization rate	0.071	0.308	Tregnaghi et al. (10)
Pneumonia hospitalization rate	0.54	0.8	± 50%[a]
Probability of hearing sequelae post meningitis	0.04	0.3	Abate et al. (25) McIntyre et al. (34) Baraff et al (33)
Probability of neurological sequelae post meningitis	0.095	0.285	± 50%[a]
Probability of pneumococcal etiology in pneumonia	0.0328	0.064	[b]Melegaro et al. (32) + 50%[a,c]
Probability of pneumococcal etiology in AOM	0.343	0.404	SAP AOM consensus (36)
Probability of myringotomy, tubes and adenoidectomy	0.00535	0.01605	± 50%[a]
Meningitis — episode cost	2052.97	6158.91	± 50%[a]
Hospitalized bacteremia — episode cost	1597.82	4793.46	± 50%[a]
Ambulatory bacteremia — episode cost	111	334	± 50%[a]
Pneumonia — episode cost	1342	4027	± 50%[a]
Non surgical AOM — episode cost	61	183	± 50%[a]
Severe hearing sequelae — annual costs	1353.085	4059.255	± 50%[a]
Motor sequelae — annual costs	3187.085	9561.255	± 50%[a]
Epileptic sequelae — annual costs	2278.995	6836.985	± 50%[a]
Myringotomy — intervention costs	384	1153	± 50%[a]
Myringotomy with tubes — intervention costs	0.03025	0.09075	± 50%[a]
Myringotomy adenoidectomy — intervention costs	634	1903	± 50%[a]
Cost — discount rate	0	0.06	Weinstein et al. (23)
Life years — discount rate	0	0.06	Weinstein et al. (23)

[a] Authors' assumption.
[b] Source for minimum value.
[c] Source for maximum value.
[d] IPD: invasive pneumococcal diseases.
[e] AOM: acute otitis media.

TABLE 3. Estimated incidence of pneumococcal disease (PD) in the first 10 years of life, and related resource use, costs, and life expectancy among a hypothetical cohort of 750 000 children, Argentina, 2006–2015

	Base-case value (for the first 10 years of life)	Total costs (in 2006 US$)
Meningitis episodes	225	304 901
Neurological sequelae	43	2 776 150
Severe hearing sequelae	28	1 240 996
Bacteremia episodes	2 841	627 270
Pneumonia episodes	2 628	2 328 746
Children with AOM	1 225 297	NA
Number of AOM episodes[a]	2 066 719	118 294 388
Lifetime cost per child	$151[b]	167
Total Costs	$113 438 487[b]	125 572 451
Deaths	78	NA
Life expectancy (life years)	72.445 (29.039[b])	NA

[a] AOM episodes include both ambulatory and surgical acute events and their costs.
[b] Discounted at a rate of 3%.

a significant health and economic burden on the population of Argentina. For example, the estimate of the health and economic burden attributable to meningitis relied on source data that is known to be an underestimate of actual burden (i.e., meningitis incidence). This implies that the overall health and economic burden from PD in Argentina could be greater still than that which is presented here.

As reported in a previous study (32), AOM-related parameters were the most influential to PD disease burden due to the high prevalence of AOM. Our results confirm that AOM and AOM-related procedures, together with pneumonia, accounted for the greatest proportion of health and cost burden from PD.

Although we found several local data sources to evaluate the burden of pneumococcal disease, the available data regarding the etiology of AOM are not very detailed. This is a limitation our study shares with most other pneumococcal disease-burden studies (32, 42). The best local data available on the pneumococcal etiology of AOM was provided by a Consensus of AOM and Pneumonia from the Sociedad Argentina de Pediatría (Argentine Society of Pediatrics). Because this data was based on a few site-specific studies, not a nationally representative sample, sensitivity analysis was performed on these values to illustrate the range of results that could be expected and to provide a basis to evaluate their relative importance.

The burden of bacterial pneumonia in Argentina from our study is also likely an underestimate. Using the technology available for this study, pneumococcal pneumonia cases were identified by

TABLE 4. Unit costs for pneumococcal-related acute events (meningitis, bacteremia, pneumonia, Acute Otitis Media (AOM)) and chronic states (motor, epileptic, or hearing sequelae), Argentina, 2006

Acute events	Cost per episode (in 2006 US$)
Meningitis	1 351
Bacteremia (outpatient)	73
Bacteremia (inpatient)	1 052
Pneumonia	883
Non-surgical AOM episode	40
Surgical AOM	278
Chronic health states	**Annual costs (in 2006 US$)**
Motor sequelae[a]	6 374
Epileptic sequelae[b]	4 558
Severe hearing sequelae[c]	2 706

[a] Estimated as the impact of long-term sequelae with their inherent costs each year from physician visits, lab tests, imaging tests, drugs, special education, rehabilitation, caregiver time, and travel.
[b] Plus costs due to wheelchair use and orthotic devices.
[c] Plus costs due to cochlear implants and their maintenance.

TABLE 5. Sensitivity analysis for the two main outcomes of pneumococcal disease (PD) in a hypothetical cohort of 750 000 children: life expectancy and mean discounted lifetime costs per child; and epidemiological and resource use, related uncertainty, Argentina, 2006–2015

Parameter varied	Range of life expectancy (life years)		Difference (life years)
	Lowest parameter value	Highest parameter value	
Discount rate	72.450	16.463	55.9986
Meningitis mortality rate	72.451	72.449	0.002
Bacteremia hospitalization rate	72.451	72.443	0.008
Bacteremia mortality rate	72.452	72.448	0.004
Pneumonia mortality rate	72.450	72.448	0.002
Rate of pneumococcal etiology in bacterial pneumonia	72.450	72.449	0.001
	Range of lifetime cost per child (in 2006 US$)		Percent variation of lifetime costs
	Minimum	Maximum	
Non-surgical AOM[a] cost	105	198	±31
AOM incidence	108	194	±28
Myringotomy cost	132	170	±13
Probability of myringotomy with tubes in AOM	135	167	±11
Discount rate	138	167	±10
Probability of pneumococcal etiology in AOM	140	163	±8

[a] Acute Otitis Media.

chest x-ray and a positive blood culture. However, recent studies in South Africa indicate that the sensitivity of chest x-rays for the diagnosis of pneumonia underestimates the burden of pneumococcal pneumonia by as much as 63% (43). In addition, burden attributable to pneumococcal-specific pneumonia relies on the use of positive blood cultures for diagnosis (35), which are known to have a low yield.

As with AOM, local data on the pneumococcal etiology of pneumonia provided by the Sociedad Argentina de Pediatría's (Argentine Society of Pediatrics) Consensus of AOM and Pneumonia, which was used due to the lack of national data (36). Sensitivity analysis was used to show the robustness of the results.

Recent studies have shown that the burden of pneumonia may be higher than previously thought due to the lack of a validated, sensitive, and specific test for confirming the pathogen-specific bacterial etiology of pneumonia (43). A study in the United States reported that only 2% of the all-cause pneumonia admissions of children less than 2 years of age were coded as pneumococcal pneumonia in 1997–2004, underscoring the problems associated with accurate diagnosis (44).

The introduction of pneumococcal vaccines is poised to change the landscape of PD. In fact, although pneumococcal pneumonia was the diagnosis in only 2% of children less than 2 years of age, the same study reported a 39% reduction in all-cause pneumonia admission rates for that group since introduction of the pneumococcal conjugate vaccine (PCV) (44). Additionally, a randomized controlled trial in South Africa of infants immunized with a PCV showed that the vaccine prevents 31% (95%CI: 15–43%) of pneumonias associated with any of seven respiratory viruses in hospitalized children (45). Our study provides an estimate of the childhood PD burden in Argentina before vaccine introduction. It is important to have incidence data from geographical areas of interest, or from an epidemiologically similar area, in order to improve evidence-based policy decision-making and provide the foundation for local economic studies (46).

In conclusion, pneumococcal-related disease imposes a significant health and economic burden on Argentine children. The knowledge of this prevaccination disease-burden is critical for the evaluating the potential impact of available preventive strategies, such as the pneumococcal conjugate vaccine.

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Carga por enfermedad neumocócica en niños de Argentina

RESUMEN

Objetivos. Analizar la carga que provoca la enfermedad neumocócica (EN), una importante causa de morbimortalidad infantil en Argentina y establecer una línea de base a partir de la cual se pueda medir la necesidad y la eficacia del uso de vacunas antineumocócicas conjugadas.

Métodos. Se elaboró un modelo de Markov para estimar las tasas de incidencia y mortalidad por meningitis (MEN), bacteremia/septicemia (BACT), neumonía (PNEU) y otitis media aguda (AOM) asociadas con la EN, en una cohorte hipotética de 750 000 niños nacidos en Argentina entre 2006 y 2015. Se realizó una revisión sistemática para seleccionar los parámetros de entrada y utilizarlos en el modelo. Los resultados se expresaron en años de vida y costos en dólares estadounidenses (US$), con descuento y sin descuento.

Resultados. Los episodios de EN que se estima ocurrirían en un período de 10 años en la cohorte hipotética serían 225 MEN, 2 841 BACT, 2 628 PNEU y 2 066 719 AOM. Las secuelas crónicas de las MEN podrían causar daños neurológicos en 43 niños y trastornos auditivos graves en 28. Estos resultados indican que en esta cohorte habría 78 muertes asociadas con la EN (29% por MEN, 54% por BACT y 17% por PNEU). La esperanza de vida sin descuento estimada para los niños de la cohorte fue de 72,4 años (con descuento de 29,9 años). Los costos promedio sin descuento atribuidos a la EN por cada niño de la cohorte durante toda la vida fueron de US$ 167 (con descuento de US$ 151), lo que provocaría un costo total para la cohorte de más de US$ 126 millones (con descuento de US$ 113 millones).

Conclusiones. Estos resultados demuestran que la EN impone una carga sanitaria y económica significativa a la población argentina. Esta información es esencial para evaluar el posible impacto sanitario y económico de la introducción de la vacuna conjugada antineumocócica en el programa nacional de vacunación.

Palabras clave Meningitis neumocócica, infecciones neumocócicas, vacunas neumocócicas, análisis costo-beneficio, Argentina.