Impact and Effectiveness of 10 and 13-Valent Pneumococcal Conjugate Vaccines on Hospitalization and Mortality in Children Aged Less than 5 Years in Latin American Countries: A Systematic Review

Lucia Helena de Oliveira¹ *, Luiz Antonio B. Camacho², Evandro S. F. Coutinho², Martha S. Martinez-Silveira³, Ana Flavia Carvalho⁴, Cuauhtemoc Ruiz-Matus¹, Cristiana M. Toscano⁵

¹ Immunization Unit/FGL, Pan American Health Organization, World Health Organization (PAHO), Washington DC, United States of America, ² Department of Epidemiology and Quantitative Methods in Health, National Public Health School (ENSP), Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil, ³ Library, Gonçalo Moniz Institute, Oswaldo Cruz Foundation (Fiocruz), Salvador, Bahia, Brazil, ⁴ Vaccine Advocacy and Education, Sabin Vaccine Institute, Washington DC, United States of America, ⁵ Institute of Tropical Pathology and Public Health (IPTSP), Federal University of Goias (UFG), Goiânia, Goiás, Brazil

Abstract

Background

Several Latin American and Caribbean (LAC) countries have introduced pneumococcal conjugate vaccine (PCV-10 or PCV-13) in their routine national immunization programs.

Objectives

We aimed to summarize the evidence of PCV impact and effectiveness in children under 5 years old in the LAC Region.

Methods

We conducted a systematic review of the literature on impact or effectiveness of PCVs on deaths or hospitalizations due to invasive pneumococcal disease (IPD), pneumonia, meningitis and sepsis. We searched Medline, WoS, Lilacs, Scopus, Central and gray literature published in any language from 2009 to January 2016. We included studies addressing the outcomes of interest in children in the target age group, and with the following designs: randomized trials, cohort or case-control, interrupted time series with at least three data points before and after the intervention, and before-after studies. Screening of citations, data extraction, and risk of bias assessment were conducted in duplicate by independent reviewers, according to the study protocol registered on PROSPERO. Descriptive analysis of the effectiveness measurements and sensitivity analysis were conducted. Effectiveness is reported as 1-OR or 1-RR for case control or cohort/clinical trials, and as percent change of disease incidence rates for before-after studies.
Results

We identified 1,085 citations, 892 from databases and 193 from other sources. Of these, 22 were further analyzed. Studies were from Brazil, Chile, Uruguay, Argentina, Peru and Nicaragua. Effectiveness ranged from 8.8–37.8% for hospitalizations due to X-ray confirmed pneumonia, 7.4–20.6% for clinical pneumonia, and 13.3–87.7% for meningitis hospitalizations, and 56–83.3% for IPD hospitalization, varying by age, outcome definition, type of vaccine and study design.

Conclusions

Available evidence to date indicates significant impact of both PCV-10 and PCV-13 in the outcomes studied, with no evidence of the superiority of one vaccine over the other on pneumonia, IPD or meningitis hospitalization reduction in children under 5 years old.

Introduction

Pneumococcal diseases are infections caused by Streptococcus pneumoniae (S. pneumoniae or pneumococcus), which is considered the most common vaccine-preventable bacterial etiology of pneumonia, causing approximately 18% of cases in children globally [1]. Worldwide, it was estimated that 14.5 million cases (uncertainty range 11.1–18.0 million) of severe pneumococcal disease occurred each year, resulting in approximately 826,000 deaths (582,000–926,000) [2]. In Latin America and Caribbean (LAC) countries pneumococcus was estimated to cause 12,000–28,000 deaths, 182,000 hospitalizations, and 1.4 million clinic visits annually, in 2009 [3, 4].

The World Health Organization (WHO) in 2012 recommended the introduction of pneumococcal conjugate vaccines (PCV) in childhood immunization programs with high priority to countries with mortality rate > 50 deaths/1000 births in children under 5 years of age [5]. The Pan American Health Organization’s (PAHO) Technical Advisory Group (TAG) on vaccine-preventable diseases also recommended in 2011 the introduction of PCV into the Expanded Program on Immunization (EPI) of countries in the American Region [6].

Since 2009 countries in LAC Region have been among the first developing countries to introduce PCVs into their EPIs [7]. As of May 2016, 29 LAC countries and territories were using PCV-10 or PCV-13 with schedules consisting of vaccine doses given at ages 2, 4, and 6 months without a booster dose (3+0), or primary PCV doses administered at ages 2 and 4 months with a booster at age 12–18 months (2+1). Some countries also provided a single catch-up dose to children aged 12–23 months in the year of the vaccine introduction [8].

PCV-10 and PCV-13 were licensed mostly on the basis of comparative immunogenicity with PCV-7, and as such, studies on vaccine efficacy or effectiveness were not available at the time of its initial licensure [5]. Notwithstanding, since the introduction of PCV-10 and PCV-13 in LAC, preliminary evidence suggested that these vaccines were promising in reducing illness and deaths due to S. pneumoniae [8].

The analysis of variation in the magnitude of the protective effect of PCV vaccines across study settings may be informative of the factors that influence their performance in immunization programs. This systematic review aims at summarizing the evidence of the impact and effectiveness of PCVs on hospitalization and mortality due to pneumonias, meningitis, and invasive pneumococcal disease (IPD) in children less than 5 years old in LAC.
Methods

The study protocol was registered in PROSPERO under registration number CRD4206032693 (available at http://www.crd.york.ac.uk/PROSPERO/DisplayPDF.php?ID=CRD42016032693). (S1 Appendix)

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. (S2 Appendix)

Literature Search

A systematic literature review was performed to identify all available data from published and unpublished studies conducted in Latin America and Caribbean, on the effects of PCV on hospitalization and mortality in children younger than 5 years of age. Details of the search terms and methods are presented in S3 Appendix. Electronic searches were conducted in the following databases: Medline (PubMed), Scopus, Web of Science, Literatura Latino Americana e do Caribe em Ciências da Saúde (Lilacs), Cochrane Central Register of Controlled Trials (Central), as well as the grey literature, unpublished literature, and selected congress and conference proceedings and annals. There was no restriction regarding languages. Full strategies for grey, unpublished and supplementary searches are presented in S4 Appendix.

Inclusion and exclusion criteria

We included studies carried out in LAC countries made available (published or presented) between January 2009 and January 2016, without language limitation, with the following study designs: randomized trials, observational studies including cohort and case-control, and quasi-experimental studies including before-after and interrupted time series.

To be eligible for review, studies had to target children aged less than five years of either sex. The study focused on the commercially available pneumococcal conjugate vaccines—PCV-10 and PCV-13—and considered any immunization schedule: 2 primary doses plus a booster (2+1) or 3 primary doses with or without a booster (3+1 or 3+0), with or without catch-up. The outcomes of interest were deaths or hospitalizations due to IPD, pneumonia, meningitis and sepsis. Secondary outcomes, such as serotype specific disease, adverse events, immunogenicity (antibody levels) and nasopharyngeal carriage were considered complementary information. All cause deaths and hospitalizations were not considered as study outcomes.

The following exclusion criteria were considered: cross-sectional studies, case series and case reports as well as studies that only reported data before or after PCV introduction but not for both periods. Interrupted time series studies were included only if they presented data on a minimum of two data points before and after the intervention. For both before-after and time series studies, we excluded those in which only the number of cases were presented, without denominator information or incidence estimates presented. Studies specifically targeted at children with sickle cell disease, HIV-infection or conditions known to affect immune response were not eligible. Studies that considered only disease of selected serotypes, adverse events, immunogenicity (antibody levels), nasopharyngeal carriage, and all-cause mortality and hospitalization as primary outcomes; and studies assessing nosocomial infections were excluded.

Study Selection

Citations were screened by two independent reviewers in a two-step approach. Titles and abstracts were first reviewed for duplication and inclusion criteria. Duplicates were excluded and full text of those papers meeting inclusion criteria were obtained for completion of
screening on their eligibility. Screened articles were categorized as potentially eligible, unclear, or excluded. Citations on which eligibility reviewers disagreed were discussed or assessed by a third reviewer. Reasons for excluding studies were recorded. (S5 Appendix) Authors of studies were contacted when required due to uncertainties or difficulties in decision. Inter-rater agreement (proportion agreement and Kappa statistic) was assessed.

Data collection and Assessment of Study Quality
Data extraction was done independently by three reviewers, working in pairs, using abstraction forms developed specifically for this systematic review, by study design: cohort, case-control, before-after and time-series.

As recently proposed to assess impact studies, to avoid multiple counting of reports from the same study group on data originated from the same study protocol, population or information system were grouped for extraction, and reported as a single study [9].

Data extracted included country, funding and ethical issues, study design, intervention details (vaccine used, vaccination schedule, changes in vaccine type), study setting and period, data source, baseline information on study population, case definition and diagnostic criteria, data ascertainment methods, methods for data analysis, and main results including descriptive result and impact assessment results, corresponding confidence limits when available, and any results from sub-group analyses. Additional information on control and ascertainment of exposure for case-control studies and information on loss to follow-up for cohort studies were obtained.

All studies were independently assessed for quality considering the items of structured quality scoring systems as checklists. Data elements of the Newcastle-Ottawa Scale (NOS) [10] were used to address potential sources of bias in case-control and cohort studies, the National Institutes of Health (NIH) checklist for before-after studies [11], and a modified version of Ramsey et al. criteria [12] for time-series studies.

Disagreements between reviewers were assessed and the major sources of divergence discussed until agreement was reached. When disagreement was not resolved, a third reviewer was used as an arbitrator.

Data analysis
This paper presents data on effects of PCV on a variety of outcomes. As such, study results are presented by the following outcomes: pneumonia, meningitis, and invasive pneumococcal disease. As pneumonia studies included different case definitions, results were further grouped by the following categories: X-ray confirmed pneumonia (consolidated), and clinical pneumonia (including broad pneumonia definitions based on ICD10 codes J12-J18 when using secondary data sources, and cough and fever as case definition when primary data from surveillance was used).

A descriptive analysis of study characteristics including design, country, type and schedule of PCV introduced, data source, and endpoints considered was conducted. All results were stratified by age groups as presented by authors.

For all studies, the main measure of interest was the vaccine effect in reducing the outcome of interest. In case control and cohort studies, this was reported as odds-ratio (OR) and relative risk (RR), and the resulting effectiveness was estimated as 1-OR or 1-RR. For time series studies, the effect was reported as either the % reduction in rates when modeling observed rates against predicted rates of disease, or resulting from a percent change in incidence rates when comparing the post and pre-vaccination periods.
In before-after studies, vaccine effects were reported as % change in rates (incidence or mortality rate reduction). Studies reporting only number of cases were excluded from the analysis as it was not possible to determine the impact of the vaccine as a rate reduction. When possible, we calculated the percent change in rates using a systematic method in which all data points in the pre and post intervention period were considered, and the intervention year was excluded from the analysis. Percent change was calculated as \((\text{pre PCV incidence rate} - \text{post PCV incidence rate}) / \text{pre PCV incidence}) \times 100$. We conducted all analysis using Stata 10.0 (StataCorp. 2007. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP.).

The level of risk of bias in study analysis was assessed for each study expanding on the structured assessment using published scales and checklists [11–13]. Internal validity of each study was evaluated considering six methodological domains [14]: selection of study participants, exposure and outcome variable measurement, design-specific sources of bias, control of confounding, statistical analyses, and conflict of interest.

Results are reported as intervals of VE by endpoint (pneumonia, meningitis, IPD) and age group. Estimates of VE on hospitalization and mortality are presented separately. A posteriori, we defined the following age groups for which results are reported: <12m, 12-23m, 2-23m, 12-35m, 0-35m, 24-35m, 24-47m, 24-59m, <48m, and <60m. Further, combined results including all age groups < 2 years, the most important target age group for PCV, are presented.

Sensitivity analysis was conducted to assess the impact of excluding studies which included pneumonia inpatients and outpatients combined, and selected outlier estimates from studies with significant potential for bias.

**Results**

A total of 1,085 references were identified and 33 were eligible for data extraction. They comprised 18 full reports and 15 abstracts and posters, reporting on 22 individual studies (Fig 1). Of the 33 references, 11 were multiple reports of the same studies. An additional 2 pairs of studies [15, 16] reported on the same population and surveillance data, but used different methods for data analysis. In one case, two studies by the same authors [17, 18] reported on cases from the same area/health services in overlapping periods, but differed in approach (individual vs. aggregate data) and reference group (unvaccinated group with concurrent follow-up data vs. surveillance data from population long before PCV was available). Also related in their dataset were the matched case-control study by Domingues et al. [15] and the ancillary study by Verani et al. [16], based on cases only (vaccine-type and vaccine related cases) compared to non-vaccine-type disease (“indirect cohort method”).

Of the 22 studies that met the inclusion criteria 5 were only available as poster/abstract. Studies were conducted in Argentina, Brazil, Chile, Nicaragua, Peru and Uruguay, with more than half of them being from Brazil. No study from the Caribbean countries was included. Most studies were published/presented in 2014–2016 (91%). PCV-10 was assessed in most of the studies (68%), and the predominant dosing schedules, regardless of vaccine type, were 3+1 and 2+1 (95%). A variety of endpoints, study designs and data sources were considered. Pneumonia was the most frequent endpoint of interest, and no study evaluating sepsis as an individual outcome was included in this review. Before-after was the most common study design, and surveillance the most common data source used in the reported studies (Table 1). A total of 6 studies analyzed mortality: 2 evaluated PCV impact on pneumococcal meningitis deaths [19, 20], 2 evaluated impact on all-cause deaths [21, 22], and 3 analyzed deaths due to pneumonia [22–24].

The variety of study designs and methods used in the studies made it inappropriate to conduct a meta-analysis.
PCV effectiveness on pneumonia hospitalizations and deaths

Thirteen of the studies included in this review evaluated PCV effectiveness on pneumonia (Table 2). Among those studies, 8 evaluated pneumonia hospitalizations only [17, 18, 21, 22, 25–28], 4 evaluated both hospitalized and outpatient pneumonia combined [24, 29–31] two evaluated both pneumonia hospitalizations and deaths [22, 24], and one evaluated only pneumonia deaths [23]. Among the 13 studies, there were 5 interrupted times series [21, 23–25, 32], 6 before-after [17, 27–30], 1 cohort [18] and 1 case-control study [22].

Fig 1. Flowchart: process of study selection.

doi:10.1371/journal.pone.0166736.g001
Hospitalization rates for pneumonia in 13 studies varied widely (29.2 to 2880 per 100,000 and 321 to 6,440 per 100,000 person-years), mainly by outcome (inpatients only vs. inpatients and outpatients combined), and age subgroups (Table 2).

| Characteristics          | n (Total 22) | %  |
|--------------------------|--------------|----|
| Publication Type         |              |    |
| Full report              | 17           | 77 |
| Abstract                 | 5            | 23 |
| Publication Year         |              |    |
| 2012                     | 1            | 5  |
| 2013                     | 1            | 5  |
| 2014                     | 9            | 41 |
| 2015                     | 7            | 32 |
| 2016                     | 4            | 18 |
| PCV product              |              |    |
| PCV-10                   | 15           | 68 |
| PCV-13                   | 7            | 32 |
| Dosing schedules         |              |    |
| 2+1                      | 9            | 41 |
| 3+0                      | 1            | 5  |
| 3+1                      | 12           | 55 |
| Country                  |              |    |
| Argentina                | 3            | 14 |
| Brazil                   | 12           | 55 |
| Chile                    | 2            | 9  |
| Nicaragua                | 1            | 5  |
| Peru                     | 1            | 5  |
| Uruguay                  | 3            | 14 |
| Endpoint*                |              |    |
| Pneumonia                | 12           | 55 |
| X-ray confirmed          | 5            | 23 |
| Clinically confirmed     | 6            | 27 |
| Both                     | 1            | 5  |
| IPD                      | 5            | 23 |
| Meningitis               | 5            | 23 |
| Study Type               |              |    |
| Before-after             | 11           | 50 |
| Time series analysis     | 7            | 32 |
| Case control             | 2            | 9  |
| Cohort                   | 1            | 5  |
| Indirect cohort*         | 1            | 5  |
| Data sources             |              |    |
| Surveillance             | 16           | 73 |
| Secondary hospitalization data | 6 | 27 |

* One study may consider more than one endpoint
* Also denominated case-only study by some authors

doi:10.1371/journal.pone.0166736.t001
| First Author, year | Country | Vaccine | Study design | Case definition | Data source | Age* groups | Years of baseline data | Baseline measure (Rates p. 100,000) | Years of post PCV introduction data | Percent change/effectiveness | Statistical Significance (95% CI or p-value) |
|-------------------|---------|---------|--------------|----------------|-------------|--------------|------------------------|-------------------------------|---------------------------------|-------------------------------|-----------------------------------------------|
| Afonso, 2013 [25] | Brazil (5 capitals) | PCV-10 | Interrupted time series | ICD10 codes J12-18 | Secondary Hospitalization Data | 2-24m Jan05-Aug11 | Belo Horizonte 164.3 | 40 | 27.4–50.9 | 140 | 37.6 | 22.7–49.6 |
| Suarez, 2016 [24] | Peru | PCV-10 | Interrupted time series | ICD10 codes J12-18 – (inpatients and outpatients) | Secondary Data | <12m Jan06-Dec08 | 58.0 | 2 | 20.6 | 10.9–29.5 |
| Becker-Dreps, 2013 [33], 2014 [21] | Nicaragua (León Department) | PCV-13 | Interrupted time series | X-ray confirmed pneumonia | Hospital population based surveillance | <12m Jan08-Dec10 | 6440a | 2 | 33 | 25–41 |
| Diaz, 2016 [22] | Chile | PCV-10 | Nested case control | ICD10 codes J13-18 | Secondary Hospitalization Data | 2-23m 2010/2012 | 13,210 cases and 52,840 controls | 2b | 20.7 | 17.3–23.8 |
| Hortal, 2014 [17] | Uruguay (2 municipalities) | PCV-13 | Before-after | X-ray confirmed pneumonia | Hospital population based surveillance | <12m 2001–2004 | 2604a | 4 | 8.8 | NS |
| Hortal, 2014 [54], 2015 [19] a | Uruguay (2 municipalities) | PCV-13 | Cohort | X-ray confirmed pneumonia | Hospital population based surveillance | 0-35m 2010a | 1048a vaccinated; 5679b non vaccinated | 3b | 84.6 | NR |
| Sgambatti, 2014 [28], 2016 [35] | Brazil (Goiania municipality) | PCV-10 | Before-after | X-ray confirmed pneumonia | Hospital based surveillance | <12m 2007–2009 | 678.8 | 3 | 25.3 | 24.6–26.1 |

(Continued)
| First Author, year | Country | Vaccine | Study design | Case definition | Data source | Age * groups | Years of baseline data | Baseline measure (Rates p. 100,000) | Years of post PCV introduction data | Percent change/effectiveness | Statistical Significance (95% CI or p-value) |
|-------------------|---------|---------|--------------|----------------|-------------|--------------|----------------------|--------------------------------------|-------------------------------------|----------------------------------|----------------------------------------|
| Scotta, 2014 [27], Pinto, 2013, [36] | Brazil | PCV-10 | Before-after | ICD10 codes J12-J18 | Secondary Hospitalization Data | 24-35m | 100.9 | 7.4 | 7.1–7.8 |
| Gentile, 2014 [38], 2015 [30], 2015 [37] | Argentina (Pilar municipality) | PCV-13 | Before-after | X-ray confirmed pneumonia (inpatients and outpatients) | Hospital population based surveillance | <12m | 2002–2009 | 2 | 10.4 | NR |
| Gentile, 2014 [38], 2015 [30], 2015 [37] | Argentina (Pilar municipality) | PCV-13 | Before-after | X-ray confirmed pneumonia (inpatients and outpatients) | Hospital population based surveillance | <12m | 2003–2005 | 1922 A | 44.6 | 24.6–59.3 |
| Gaiano; 2013 [29], Vizzotti, 2014 [39], 2014 [40] | Argentina | PCV-13 | Before-after | Clinical pneumonia—(inpatients and outpatients) | Secondary data | <12m | 2011 | 2880 | 28.06 | 26.5–29.6 |
| Rearte, 2015 [31] ABSTRACT ONLY | Argentina (Concordia municipality) | PCV-13 | Before-after | X-ray confirmed pneumonia (inpatients and outpatients) | Hospital population based surveillance | <60m | 2002–2005 | 732 | 50.7 | 33–64 |
| Andrade, 2015 [26] POSTER ONLY | Brazil | PCV-10 | Interrupted time series | ICD-10 codes J12-J18 | Secondary Hospitalization Data | 2-23m | 2005–2009 | Not shown | 16.6 | 1.0–32.1 |
| Rearte, 2015 [31] ABSTRACT ONLY | Argentina (Concordia municipality) | PCV-13 | Before-after | X-ray confirmed pneumonia (inpatients and outpatients) | Hospital population based surveillance | 2-23m | 2005–2009 | Not shown | 16.6 | 1.0–32.1 |
| Minamisava et al., 2014 [23] ABSTRACT ONLY | Brazil | PCV-10 | Interrupted time series | Death due to pneumonia (ICD10 codes J12-J18) | Mortality Information System | 2-23m | 2005–2009 | Not shown | 15.5 | -7.2–38.2 |

* Age groups with results of interest for this study; % VT-PCV-13; $ rates per person-years
$ #: Start of case detection
$ #: duration of follow-up/case detection
$ #: This study reports on the same data/study population as the above (Hortal, 2014) [17] using different study method and considering 2010–2013 as opposed to 2009–2012 post-vaccine period data in the analysis

doi:10.1371/journal.pone.0166736.t002
All included studies on pneumonia hospitalization and deaths reported 35 effectiveness estimates in different age subgroups. When we consider all the above reports on PCV-10 and PCV-13 effectiveness (VE), regardless of outcome, age group, data source and study methodology, VE point estimates varied from a lower 7.4% to 84.6%. Some of the estimates had very wide confidence intervals (Fig 2), whereas two studies [18, 27] presented only point estimates. Another study did not present confidence intervals but reported statistical significance (p-values or "NS") [17]. Of note, VE on X-ray confirmed hospitalized pneumonias reported by Hortal et al. [17] using before-after analysis varied from 8.8 (non-significant) in the <12-month age group to 37.8% (p-value < 0.001) in the 12–23 month group. However, estimates using a cohort study design analyzing data obtained by the same surveillance system

![Fig 2. Vaccine effectiveness (%; 95% confidence interval*) against pneumonias clinical and X-Ray/consolidated, by vaccine, group of age, and hospitalization or death. * Effectiveness estimates and 95% CI are presented in black for studies assessing hospitalized pneumonia, and in light gray for studies assessing combined pneumonia inpatient and outpatients as endpoints. Two studies with no available confidence intervals were not plotted: Hortal et al.[17]; Scotta et al.[27] Countries: ARG (Argentina); BRA (Brazil); CHI (Chile); NIC (Nicaragua); PER (Peru); URU (Uruguay). doi:10.1371/journal.pone.0166736.g002](image)
in the same study population found VE estimates of 84.6% (95% CI not reported) for the <3 year age group. [18]

When results are stratified by the different pneumonia case definitions, regardless of age subgroup, PCV-10 and PCV-13 effectiveness estimates for clinical pneumonia varied from 7.4% to 49.3%, whereas for consolidated (X-ray confirmed) pneumonia VE ranged from 8.8% to 84.6%.

In sensitivity analysis, disregarding the outlier estimate reported by Hortal [18], VE for X-ray confirmed pneumonia ranged from 8.8% to 57.9%. In further sensitivity analysis, including only studies assessing hospitalized pneumonia (effectiveness estimates and CI presented in black in Fig 2), and disregarding estimates for combined pneumonia inpatient and outpatient endpoints [24, 29–31] (presented in light gray in Fig 2), VE ranged from 7.4% to 49.3%. Finally, VE estimates reported by Afonso et al. [25] with a very short follow-up period after PCV introduction were also identified as outliers prone to biases. When these results were excluded, ranges of VE were 7.4%-20.6% for clinical pneumonia, and 8.8%-37.8% for X-ray confirmed (consolidated) pneumonia.

When only effectiveness estimates from the studies included in sensitivity analyses were stratified by vaccine type, for clinical pneumonia outcome, VE varied from 7.4 to 20.6% among the various age subgroups. Those results concern studies conducted in sites using PCV-10 (n = 4) as studies from sites using PCV-13 did not fulfill the criteria above for sensitivity analysis (i.e., assessing only pneumonia hospitalizations). When X-ray confirmed pneumonia (consolidated) outcome was considered, estimates varied from 11.9% to 25.3% for PCV-10 (n = 6), and from 8.8 to 37.8% for PCV-13 (n = 2). Estimates for both PCV vaccines in either pneumonia outcome fell under overlapping 95% confidence limits (Fig 2).

Given the great diversity of age subgroups in the reports (Table 2; Fig 2), stratification resulted in overlapping categories with wide VE ranges: 8.8%-78.9% in children aged <24 months; 1.6%-53.3% in children aged >24 months; and 12.6%-84.6% in children from mixed age subgroups (data not shown). Within age subgroups VE varied by types of outcome and study designs but the numbers were too small to allow further stratification.

VE for pneumonia caused by vaccine-type serotypes [15] were not considered in this review as effectiveness estimates for pneumonia were pooled together with those for bacteremia.

All three studies that assessed PCV impact on pneumonia mortality [22–24] showed substantial decline in rates after PCV introduction (Table 2; Fig 2). However, 2 of these studies reported very wide confidence intervals [22, 24], and one reported non-significant estimates [23]. Two studies also assessed pneumonia mortality as a secondary outcome: Diaz et al. [22] estimated PCV-10 VE for all-cause mortality at 38.8% (95% CI, 23.7%-44.3%) in a nested case control study; Becker-Dreps [21] estimated PCV-13 VE at 33% (95% CI 20%-43%), acknowledging that the number of pneumonia related deaths was too small to explain the reported reduction in infant mortality (138/10,000 child-years).

Analysis of effectiveness for combinations of dosing schedules and catch-up doses was not performed, due to the existing methodological variation among studies, already referred to.

**PCV effectiveness on meningitis hospitalizations and deaths**

Five studies addressed PCV effectiveness against pneumococcal meningitis, all of which were conducted in Brazil, where PCV-10 is used. They comprised four before-after [19, 20, 41, 42], and one case-control study [15]. Hospitalization rates before intervention reported in the before–after studies were higher among younger children, varying from a lower 0.83/100,000 in children aged 2–3 years [20] to 14.85/100,000 in infants <1 year old [19]. (Table 3)

Considering all reports on PCV-10 effectiveness regardless of age group, VE point estimates varied from 13.3% to 87.7% (Table 3). The highest reported VE was 87.7% against meningitis
| First Author, year | Country | Vaccine | Study design | Case definition | Data source | Age groups* | Years of baseline data | Baseline measure (Rates p. 100,000) | Years of post PCV introduction data | Percent change/effectiveness | Statistical Significance (95% CI or p-value) |
|--------------------|---------|---------|--------------|----------------|-------------|-------------|------------------------|-----------------------------------|-----------------------------------|----------------------------------|----------------------------------|
| Domingues, 2014 [15, 43], Verani, 2015 [16] | Brazil | PCV-10 | Case-control | Pneumococcal meningitis | National laboratory surveillance; Controls: National birth registry | 2m–53.1m | 2010<sup>a</sup> | 158 cases and 1,219 controls | 2.7<sup>b</sup> | 87.7<sup>*</sup> | 61.4–96.1<sup>*</sup> |
| Grando, 2015 [20] | Brazil | PCV-10 | Before-after | Pneumococcal meningitis | National passive surveillance system | <12m | 2007–2009 | 7.38 | 2 | 36.6 | NR |
| | | | | | | 12-23m | 2.14 | 61.2 | NR |
| | | | | | 24-36m | 0.83 | 13.3 | NR |
| Hirose, 2015 [19] | Brazil | PCV-10 | Before-after | Pneumococcal meningitis | National passive surveillance system | <12m | 1998–2009 | 14.85 | 2 | 62.8 | <0.001 |
| | | | | | 12-23m | 1.86 | 51.6 | <0.001 |
| | | | | | 0-23m | 6.21 | 59.9 | <0.001 |
| Azevedo, 2015 [41] POSTER ONLY | Brazil | PCV-10 | Before-after | Pneumococcal meningitis | Hospital based surveillance | 0-2 yrs | 2008–2010 | 4.23 | 3 | 48 | -9–75 |
| | | | | | 0-23m | 1.92 | 75.5 | <0.001 |
| Liphaus, 2012 [42] POSTER ONLY | Brazil | PCV-10 | Before-after | Pneumococcal meningitis | National passive surveillance system | <24m | 2001–2009 | 10.2 | 1 | 50 | p<0.001 |

* Age groups with results of interest for this study

<sup>a</sup>: Start of case detection

<sup>b</sup>: Duration of follow-up/case detection

doi:10.1371/journal.pone.0166736.t003
caused by serotypes included in PCV-10 in children aged <5 with an age-appropriate PCV-10 schedule [15].

Most studies reported effectiveness against pneumococcal meningitis of all serotypes for <12m, 12-23m, and younger than 2 years. Two studies reported on VE for children < 12 months of age, ranging from 36.6% [20] to 62.8% [19]. Lower VE effectiveness was reported for children aged 24-36m (13.3%) [20]. Effectiveness estimates ranged from 48% to 59.9% among studies reporting on children < 2 years of age [19, 41, 42].

As showed in Fig 3, higher effectiveness on pneumococcal meningitis hospitalizations and deaths are reported for children < 12 months of age. One study considered individuals aged 5 years and more (including adults and elderly) as a comparator group of individuals not targeted by PCV [41]. Data from a reference hospital showed small and non-significant decrease in pneumococcal meningitis in this age group, as opposed to a significant decrease of 48% for overall and 77% for vaccine-type pneumococcal meningitis in children aged <2 years three months.
years after PCV introduction. As observed in Table 3 and Fig 3, most studies reporting on vaccine effectiveness against meningitis did not report 95% confidence intervals for the estimated effectiveness measure.

Two studies addressed pneumococcal meningitis mortality [19, 20] and reported similarly high VE estimates ranging from 65–77.3% in children < 12 months to 56.8–68.4% in children aged 12–23 months.

Estimates of serotype-specific PCV-10 effectiveness against meningitis were reported by some authors, mainly as proportion of cases before and after vaccine introduction. In addition, most of such studies reported on a small number of cases with serotype data. In Paraná State, Brazil, Hirose et al. [19] reported on number of cases of pneumococcal meningitis due to PCV-10 serotypes in children less than 2 years old before and after PCV introduction. The proportion of cases due to PCV-10 serotypes was reduced from 76% of 187 cases in pre-vaccine period to 47% of 15 cases in the post-vaccine period. In a reference hospital in Salvador, Brazil [41] a 73% reduction in PCV-10 serotype cases was observed in 2011–2013, for serotypes 14 (10 cases in the pre PCV to 2 cases in the post PCV period), 19F (4 to 1) and 6B (5 to 2). Cases by 18C and 9V did not occur during post-PCV-10 period. Serotype 19A was isolated in only 3 cases before and 1 after PCV-10.

**PCV effectiveness on Invasive Pneumococcal Disease (IPD) hospitalizations**

Four studies addressed invasive pneumococcal disease (IPD) hospitalizations [15, 32, 44, 45], none of which analyzed IPD mortality. Reported baseline IPD rates ranged from 3.9 (predicted rates based on time-series modelling for children aged 2–4 years) to 68.7 (children < 2 years old in Uruguay) per 100,000 children (Table 4).

Reported VE against all-type IPD was generally high regardless of age, ranging from -14.7% to 66.0% (Table 4, Fig 4). Disregarding the outlier estimate by Andrade et al. [32], VE varied from 34.7% to 66.0%. Effectiveness was even higher for vaccine-types IPD, as reported by Domingues et al. [15] in a case-control study in Brazil, and Garcia Gabarrot et al. [44] in a before-after study in Uruguay (Table 4; Fig 4). Results from Domingues et al. [15] were corroborated by Verani et al. [16], based on the same study but with an indirect cohort design, which reported an adjusted VE of an age-appropriate PCV-10 schedule against type-specific pneumococcal IPD of 73.9% (95%CI 41.9%-88.3%), and 72.8% (95%CI 44.1%-86.7%), respectively, for children with up-to-date schedule, and one or more PCV doses. VE against vaccine-related types was 64.8% (95%CI 15.3%-85.4%), and 61.3% (95%CI 14.5%-82.5%), respectively, for children with up-to-date schedule, and one or more PCV doses [16].

Both interrupted time series studies conducted in Chile [45] and Brazil [32] showed a decreasing trend after PCV introduction in children aged < 2 years contrasting with non-decreasing trend in rates in age groups not targeted by PCV. That resulted in consistently high VE in both studies (Table 4).

Estimates of PCV-10 effectiveness against IPD caused by individual serotypes were reported by some authors, but were mostly based on the comparison of the number of cases when comparing pre- and post-vaccine periods. A study in Chile [45] reported important decrease in serotype specific pneumococcal IPD after PCV-10 introduction in children under 2 years of age, particularly for serotypes 4 (5 cases in the pre-PCV to 0 cases in the post-PCV period), 19F (15 to 1), 23F (11 to 1), 14 (74 to 14), 6B (20 to 6), 18C (12 to 5), and 1 (11 to 2). Serotype 19A cases decreased from 13 to 8. Similarly, in Uruguay [44], important reductions of serotype specific IPD cases were reported after PCV-13 introduction in children aged < 5 years, for serotype 14, and serotype 5. Small decreases were observed for the other PCV-13 serogroups,
Table 4. Characteristics of studies reviewed with invasive pneumococcal disease as endpoint.

| Author, year | Country | Vaccine | Study design | Case definition | Data source | Age * groups | Years of baseline data | Baseline measure (Rates p. 100,000) | Years of post PCV introduction data | Percent change/effectiveness | Statistical Significance (95% CI or p-value) |
|--------------|---------|---------|--------------|-----------------|-------------|--------------|------------------------|--------------------------------------|-------------------------------------|----------------------------------|---------------------------------------------|
| Valenzuela, 2014 [45], ISPC, 2015 [46] | Chile | PCV-10 | Interrupted time series | Spn² isolated from normally sterile fluids | National Reference Laboratory | 0–35m | 2007–2010 | 24.6 | 2012 | 56.9 | Not available |
| Garcia Gabarrot, 2014 [44] | Uruguay | PCV-13 | Before-after | Spn isolated from normally sterile fluids | National Reference Laboratory | <24m | 2003–2007 | 68.7; 24.8¹ | 2009–2012 | 66.0; 75.0¹ | 46–79; 39–90¹ |
| Domingues, 2014 [15, 43] Verani, 2015 [16] | Brazil | PCV-10 | Case control | Spn isolated from normally sterile fluids | Cases: National laboratory surveillance; Controls: National birth registry | 2–53.1m | 2010¹ | 316 cases and 1,219 controls | 2.7² | 83.8² | 65.9–92.3² |
| Andrade, 2015 [47] 2016[32] | Brazil | PCV-10 | Interrupted time series | Spn isolated from normally sterile fluids | National Notifiable Diseases Surveillance System; National reference laboratory | 2–23m | Jan. 2008—Dec. 2009 | 20.9³ | Jan. 2011 Dec. 2013 | 44.2 | 15.8–72.5 |

* Age groups with results of interest for this study
¹ VT-PCV-13
²a: Start of case detection
²b: Duration of follow-up/case detection
³: Predicted rates based on time-series modeling
⁴ S. pneumonia
⁵ Verani et al. [16] reports similar VE estimates. As the authors report on the same study using different data analysis, results for Verani et al. [16] are not included in the table.

* VT-PCV-13
¹a: Start of case detection
¹b: Duration of follow-up/case detection
¹: Predicted rates based on time-series modeling
²: S. pneumonia
³ Verani et al. [16] reports similar VE estimates. As the authors report on the same study using different data analysis, results for Verani et al. [16] are not included in the table.

doi:10.1371/journal.pone.0166736.t004

Impact and Effectiveness of PCV on Hospitalization and Mortality in Children: A Systematic Review

PLOS ONE | DOI:10.1371/journal.pone.0166736 December 12, 2016 15 / 25
except for serogroup 3 and 4, which showed modest increase, and 19A, which did not change substantially.

Two studies conducted in Brazil [15, 32] estimated VE for specific serotypes. In a case-control study, Domingues et al. [15] reported VE of 87.7% (95% CI 60.8–96.1%) for serotype 14 (72 cases), 82.8% (95% CI 23.8%-96.1%) for 6B (32 cases) and 82.2% (95% CI 10.7%-96.4%) for 19A (26 cases). For serotypes 3, 6A and 23F, the effectiveness was not statistically significant. Effectiveness against IPD due to PCV-7 serotypes was 83.2% (95% CI 64.7%-92.1%). No cases of disease due to serotypes 1 or 5, and only one due to 7F, were enrolled.

Andrade et al. [32] by means of a time series analysis, found that, overall, PCV-10 type IPD declined 41.3% (p-value <0.001), mostly in children aged 2–23 months, while PCV-13 minus PCV-10 types increased by 62.8% in all age groups (p-value <0.001). This increase was mostly significant in children under 5-year of age.

**Risk of bias assessment**

An inventory of potential for bias was detailed for all studies included in the review (S1 and S2 Tables). Of three studies based on individual data [15, 18, 22], one cohort study on PCV-13 did not address potential selection bias and confounding, and presented only a crude measure of association [18], indicating an unexpected high VE for consolidated pneumonia. In the case-control study by Domingues et al. [15], IPD was defined by the detection of S. pneumoniae, which enhanced specificity of case definition. However, the authors acknowledged that case ascertainment took place in a small number of hospitals with the laboratory capacity for pneumococcal identification. Moreover, case detection of IPD via surveillance system resulted
in over-representation of meningitis, despite being the least common invasive syndrome. Selection of controls is a major challenge and there is no “ideal” control group for case-control studies. Neighborhood controls appeared a reasonable and efficient approach in that study conducted in a developing country [48, 49]. A study by Verani et al. [16], ancillary to the case-control study, used the “indirect cohort method” to control for biases in ascertainment between cases and controls and obtained results similar to the main study. Exposure (vaccination status) was ascertained from written documentation (vaccination cards). This source was considered reliable and allowed the classification as up-to-date for PCV-10 if the number of valid doses was greater than or equal to the number recommended for the age at hospital admission or reference date. Confounding was addressed by matching on age and by multivariate analysis of major confounders, but residual confounding was acknowledged by the authors. Finally, the case-control study by Diaz et al. [22] was nested in a birth cohort and thus protected against selection bias. Nonetheless, children from the year before introduction of PCV-10 were mostly all unvaccinated, which might have led to misclassification of vaccination status.

Before-after and ITS were the most common study designs in this review (11 studies) (Tables 2, 3 and 4), which was not surprising, as nationwide implementation of PCV in public funded immunization programs made non-exposed individuals rare and special. But those study designs are inherently vulnerable to aggregation bias, and to confounding by epidemiological and health care setting changes concomitant to vaccination. Among ITS and before-after studies, two [28, 30] presented data on potential confounders. Five studies [21, 23, 25–27, 32] included other diseases without plausible association to PCV as a comparator, and in two of them estimates of effectiveness against a pneumococcal disease were “adjusted” for the change in the comparator. In 5 studies [17, 21, 41, 44, 45] age groups not targeted by PCV were analyzed either as comparators or to assess the indirect effect of the vaccine. Two ITS studies of pneumonia used proper seasonality modeling and time trend analysis (one clinical pneumonia [25] and one consolidated pneumonia [21] with inpatients and outpatients pooled together) but had short post-vaccination periods (1 year). Short periods of observation added to the limitations of some studies. Pre-vaccination periods ranged from 2 to 12 years (median: 4 years), although one study based its effectiveness assessment on rates of the year before PCV introduction [29]. Most studies [20, 21, 24, 25, 27, 30–32, 41, 42, 44, 45] considered a transition period (usually, the year of PCV introduction), which were excluded from analysis by some, or included either in pre-vaccination or post-vaccination by others.

Selection bias was an issue rarely addressed in the studies even in those based on passive surveillance, hospital and laboratory surveillance, or sentinel surveillance systems. Only one of them acknowledged the changed approach to diagnosis engendered by PCV implementation [32].

Vaccination coverage was presented in ten studies [17, 19, 20, 24, 25, 27, 28, 30, 32, 44], for descriptive purposes only, except one [25] study in which discrepancies of effectiveness across cities were attributed to the proportion of vaccinated subjects.

**Discussion**

To our knowledge this is the first systematic review of the impact and effectiveness of the 2 currently commercially available pneumococcal conjugate vaccines (PCV-10 and PCV-13) in LAC countries. The thorough review of the literature allowed assessment of PCV impact and effectiveness on the most relevant clinical syndromes of pneumococcal disease, which lead to hospitalization and mortality in children under 5 years old. In this review, pneumonia was the most frequently targeted clinical presentation by the studies, which showed high incidence
rates. Studies in this review showed that PCV had both direct and indirect effects on the three clinical syndromes most relevant for hospitalization, in all different age-groups, schedules, countries, and study designs, except for very few instances in untargeted age groups [50]. A positive impact of PCV-10 was also shown in a review of studies conducted in Brazil on hospitalizations and deaths from pneumonia and IPD [51].

The studies selected in our review were carried out in countries using the vaccination schedule 2+1, except Brazil which used 3+1 and Nicaragua, 3+0[8]. Brazil has since switched to a 2+1 schedule, which is also currently used in all countries in the Region where PCV has been implemented, except for 4 countries which are supported by GAVI. A recent systematic review showed that all schedules mentioned above reduced clinical and radiologically confirmed pneumonia [52, 53]. Therefore we decided to analyze the impact and effectiveness studies without any distinction of vaccine schedule established in the countries.

We selected pneumonia and IPD hospitalizations and deaths as study outcomes, which are relevant in terms of disease burden and severity, and for which there are available data sources for impact assessment. These are the most commonly measured disease outcomes in countries with PCV impact studies [9].

A variety of case definitions and endpoints for pneumonia assessment were used in the included studies. It is known that the sensitivity of pneumonia diagnosis and the estimated effectiveness of PCV on pneumonias vary according to the endpoint and case definition considered [54]. This affected data analysis and synthesis, by which results were analyzed by grouping studies with similar pneumonia endpoints. We observed higher VE when X-ray confirmed pneumonia was considered as opposed to clinical pneumonia, which considered generic clinical endpoints or diagnosis as coded by ICD-10 codes. Markedly high PCV-13 VE estimates were disclosed by two studies included in this review, in which bias and confounding had not been properly managed [18, 30]. This finding of our review is consistent with the literature where that specific end points and case definitions showed a more accurate VE on pneumonias due to pneumococcus. Moreover nonspecific and generic endpoints presented lower VE since these diagnoses likely include other pneumonias caused by pathogens other than pneumococcus [52, 53].

Four of the 12 studies that evaluated pneumonia hospitalizations considered combined endpoint of pneumonia inpatients and outpatients [24, 29–31]. These studies reported higher effectiveness rates when compared to studies assessing pneumonia inpatients only. Whereas some authors describe larger effects of PCV on pneumonia hospitalization when compared to ambulatory visits [55], selected studies have reported the opposite [56, 57]. As such, considering that the expected effectiveness could be different when including outpatients in the outcome of interest (in addition to hospitalized patients with pneumonia), we opted to conduct sensitivity analysis excluding these studies [24, 29–31], which resulted in more accurate VE estimates with a smaller range of values.

Effectiveness estimates were consistently high for meningitis and IPD when compared to other outcomes, reaching 56.8–83.8%. Other authors have found similar findings, as reported by a recent systematic review on the impact of PCV in pediatric older children in low and middle income countries [58]. This is likely due to high specificity of laboratory confirmed pneumococcal meningitis and IPD, as reported by studies conducted in high-income countries [59, 60].

Several studies reported on serotype-specific PCV effectiveness, and some authors acknowledged the small number of type-specific IPD cases and low representativeness of reported cases as an important limitation to demonstrating type specific VE [32, 45]. As expected, data on specific serotypes in studies included in this review were scarce as serotype was not one of the outcomes targeted by this review. The available data did not indicate that enough cases of
serotypes 3, 6A and 19A had been averted to allow PCV-13 to show any advantage. Moreover, as fluctuations in the frequency of the serotypes can occur without selective pressure of vaccines, and considering limitations in study design and small number of cases, it is not possible to attribute increases in non-vaccine serotypes to the reduction in vaccine-type circulation in a vaccinated population as pointed out by Hirose et al. [19]. Reduction of carriage is fundamental to determine indirect and direct effects of pneumococcal vaccination with conjugate vaccines and it was highlighted in a systematic review where the reduction of risk on IPD due to 19A was discussed [61]. Additionally for robust conclusions it is important that countries implement surveillance, at least, to monitor the frequency of vaccine-type and non-vaccine type invasive pneumococcal disease in different age groups and for identification of factors influencing serotype distribution. This is crucial to allow vaccine design, implementation and continued effective control of pneumococcal disease [62].

Our findings indicate higher VE for all study outcomes in selected age groups (ie 12–23 months). This is likely a result of the fact that children in this age group had the opportunity to have completed the vaccination schedule recently. Nonetheless, as the overall disease burden is higher in younger children, impact as total burden of disease averted was most significant in younger age groups (ie <12 months), as reported in a global review of pneumococcal disease burden by age and region [63].

Issues related to study design were a major concern in this review. Most studies study analyzed secondary data, and all but two studies of pneumonia had a before-after or an interrupted time-series (ITS) approach. The assessment of vaccination through ecologic study design using aggregate data, such as ITS and before-after studies, provide impact measures that combined direct effects, related to individual protection from immune response, and indirect effects including non-vaccinated subjects who benefitted from reduced circulation of \( S. \) \textit{pneumoniae} \( S. \textit{pneumoniae} \) achieved with high vaccine coverage [64]. On the other hand, effectiveness measurements based on observational study designs, such as cohort and case-control studies, estimated the proportion of cases prevented in vaccinated subjects that were attributable to vaccination excluding indirect effects. A recent study describing methods and challenges for impact assessment of vaccination in LAC region reported a significant increase in the number of studies on pneumococcal vaccine impact [65]. As other authors have reported in developed countries [64], several are the methodological challenges faced when assessing vaccination impact, particularly considering PCV.

As reported in the literature [65], our results shows that most studies on impact of public health interventions used secondary data from health information systems, surveillance systems, and others sources, while few studies used primary data. As hospitalization and mortality outcomes are the most relevant outcomes of interest, it is expected that secondary data are the most used data sources. Data limitations inherent to health systems databases such as representativeness, completeness and reliability are thus present. As such, potential confounding and biases must be minimized in study design and analyses, or taken into account during result interpretation, following available recommendations [64].

This study has several limitations that are worth mentioning. While the strength of this analysis is to provide a wealth of information on the heterogeneity of the vaccine impact and effectiveness as well as on the methodological quality of the studies, there are some limitations. It was not possible to perform a meta-analysis which could allow us to estimate a common measure since we found an important heterogeneity on study designs, end points, and age group stratification within studies included in this analysis. Only studies from six countries were included in the final analysis. No studies from the Caribbean countries met the inclusion criteria for this study. The small number of countries investigated could affect the comprehensive understanding about the vaccine impact and effectiveness in Latin American countries.
Finally, potential publication bias, resulting in under publication of studies with negative results has to be considered when interpreting these results. We believe that the extensive literature search strategy and sources in our study contributed to reduce publication bias. Nonetheless, it is unclear to what extent and impact that selective publication of favorable results may have had in this review. Five of the 22 studies were funded by the industry, and 6 others had co-authors with some link to vaccine manufacturers. Nine studies were sponsored by governmental and/or international organizations and two did not disclose sponsorship. As shown in previous research [66], sponsors (including vaccine manufacturers and national immunization authorities) of studies included in this review may have contributed to give higher and earlier visibility to “positive” results. A time lag bias (favorable results published earlier) is also plausible, given that PCV introduction in national immunization programs in Latin American countries has started in 2008 and several studies have been identified in more recent years.

No studies in this review have compared the effectiveness of PCV-10 and PCV-13 directly, and thus, only indirect comparisons were possible. Considering the outcomes studied and the available evidence to date, we found no evidence of the superiority of one vaccine over the other with regards to impact and effectiveness on hospitalization reduction in children under 5 years old. Considering the inclusion criteria established in this study there is insufficient evidence so far to compare the impact and effectiveness of both vaccines with regards to mortality. Studies directly comparing the effect of PCV-10 and PCV-13 in developed countries have demonstrated similar effectiveness with different schedules on pneumonia and IPD hospitalizations [67, 68].

Currently PCV is one of the most expensive vaccines recommended by PAHO and WHO, accounting 75% of the total vaccine cost of immunizing a child in the majority of LAC countries [69]. It is crucial for policy makers to consider the affordable vaccine price whether they decide to keep the vaccines or introduce them into the national immunization programs. The available body of evidence included in this review ratifies the value of pneumococcal conjugate vaccines in the national EPI as a public health intervention, given the fact that these vaccines lead to a substantial reduction on hospitalization and mortality due to IPD, pneumonias, and meningitis in children.

Supporting Information

S1 Appendix. Protocol registered in PROSPERO (PDF)

S2 Appendix. PRISMA checklist (DOC)

S3 Appendix. Search strategies (PDF)

S4 Appendix. Supplementary search strategies (PDF)

S5 Appendix. Excluded articles and reasons for exclusion (PDF)

S1 Table. Risk of bias assessment of pneumonias end point. (DOCX)

S2 Table. Risk of bias assessment of pneumococcal meningitis endpoint. (DOCX)
Acknowledgments

The author is a staff member of the Pan American Health Organization. The author alone is responsible for the views expressed in this publication, and they do not necessarily represent the decisions or policies of the Pan American Health Organization. LABC is a professor/researcher at ENSP and has collaborated with Bio-Manguinhos vaccine manufacturer in projects related to yellow fever. ESFC and MSMS are researchers from ENSP and Gonçalo Moniz Institute respectively and have no links or collaboration with Bio-Manguinhos. ENSP, Gonçalo Moniz Institute and Bio-Manguinhos are independent units/departments within Fiocruz.

Author Contributions

Conceptualization: LHO LABC ESFC MSMS AFC CRM CMT.
Data curation: LHO LABC ESFC MSMS AFC CRM CMT.
Formal analysis: LHO LABC ESFC CMT.
Funding acquisition: LHO CRM.
Investigation: LHO LABC ESFC MSMS AFC CRM CMT.
Methodology: LHO LABC ESFC MSMS AFC CRM CMT.
Project administration: LHO.
Resources: LHO LABC ESFC MSMS AFC CRM CMT.
Supervision: LHO.
Visualization: LHO LABC ESFC MSMS AFC CRM CMT.
Writing – original draft: LHO LABC AFC CMT.
Writing – review & editing: LHO LABC ESFC MSMS AFC CRM CMT.

References

1. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. Lancet. 2013; 381(9875):1405–16. doi: 10.1016/S0140-6736(13)60222-6 PMID: 23582727
2. O’Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet. 2009; 374(9693):893–902. doi: 10.1016/S0140-6736(09)61204-6 PMID: 19748398
3. Sinha A, Constenla D, Valencia JE, O’Loughlin R, Gomez E, de la Hoz F, et al. Cost-effectiveness of pneumococcal conjugate vaccination in Latin America and the Caribbean: a regional analysis. Rev Panam Salud Publica. 2008; 24(5):304–13. PMID: 19141172
4. Valenzuela MT, O’Loughlin R, De La Hoz F, Gomez E, Constenla D, Sinha A, et al. The burden of pneumococcal disease among Latin American and Caribbean children: review of the evidence. Rev Panam Salud Publica. 2009; 25(3):270–9. PMID: 19454155
5. World Health Organization. Pneumococcal vaccines WHO position paper-2012. Wkly Epidemiol Rec. 2012; 87(14):129–44. PMID: 24340399
6. Pan American Health Organization. Technical Advisory Group on Vaccine-Preventable Diseases, editor. Final report of the 19th TAG Meeting; 2011 July 6–8; Buenos Aires, Argentina. Washington: PAHO; 2011 [cited 2016 Jul 5]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=14164&Itemid=&lang=fr
7. de Oliveira LH, Toscano CM, Sanwogou NJ, Ruiz-Matus C, Tambini G, Roses-Periago M, et al. Systematic documentation of new vaccine introduction in selected countries of the Latin American Region. Vaccine. 2013; 31 Suppl 3:C114–22.
Impact and Effectiveness of PCV on Hospitalization and Mortality in Children: A Systematic Review

8. de Oliveira LH, Trumbo SP, Matus CR, Sanwogou NJ, Toscano CM. Pneumococcal conjugate vaccine introduction in Latin America and the Caribbean: progress and lessons learned. Expert Rev Vaccines. 2016;1–10. Epub 2016/03/17.

9. Johns Hopkins Bloomberg School of Public Health. International Vaccine Access Center. State of PCV use and impact evaluations: a strategic gap analysis of the global evidence from published and ongoing impact studies evaluating routine PCV use. Baltimore, MD: IVAC; 2016 [cited 2016 Jul 7]. Available from: http://www.jhsph.edu/research/centers-and-institutes/ivac/resources/PCVImpactGapAnalysis_MAR2016_FINAL_public.pdf

10. Wells GS, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses: Ottawa Hospital Research Institute, 2008 [cited 2016 Jun 20]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

11. National Institutes of Health. National Heart, Lung and Blood Institute (US). Quality assessment tool for before-after (pre-post) studies with no control group [Internet]. Bethesda, MD: NIH; 2014 [cited 2016 Jul 5]. Available from: http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after

12. Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. Int J Technol Assess Health Care. 2003; 19(4):613–23. PMID: 15095767

13. Lawley CM, Lain SJ, Algert CS, Ford JB, Figtree GA, Roberts CL. Prosthetic heart valves in pregnancy: a systematic review and meta-analysis protocol. Syst Rev. 2014; 3:8. doi: 10.1186/2046-4053-3-8 PMID: 24444192

14. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 2007; 36(3):666–76. doi: 10.1093/ije/dym018 PMID: 17470488

15. Domingues CM, Verani JR, Montenegro Renoiner EI, de Cunto Brandileo MC, Flannery B, de Oliveira LH, et al. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study. Lancet Respir Med. 2014; 2(6):464–71. doi: 10.1016/S2213-2600(14)70060-8 PMID: 24726406

16. Verani JR, Domingues CM, Moraes JC. Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease. Vaccine. 2015.

17. Hortal M, Estevan M, Meny M, Iraola I, Laurani H. Impact of pneumococcal conjugate vaccines on the incidence of pneumonia in hospitalized children after five years of its introduction in Uruguay. PLoS One. 2014; 9(6):e98567. doi: 10.1371/journal.pone.0098567 PMID: 24905093

18. Hortal M, Meny M, Estevan M, Arieta Fernando, Laurani H. Effect of 7 and 13-valent pneumococcal conjugate vaccines different number of doses for pneumonia control in 2008 and 2010 Birth Cohort Children Uruguay. World J Vaccines. 2015.

19. Hirose TE, Maluf EM, Rodrigues CO. Pneumococcal meningitis: epidemiological profile pre- and post-introduction of the pneumococcal 10-valent conjugate vaccine. J Pediatr (Rio J). 2015; 91(2):130–5.

20. Grando IM, Moraes C, Flannery B, Ramalho WM, Horta MA, Pinho DL, et al. Impact of 10-valent pneumococcal conjugate vaccine on pneumococcal meningitis in children up to two years of age in Brazil. Cad Saude Publica. 2015; 31(2):276–84. PMID: 25760162

21. Becker-Dreps S, Amaya E, Liu L, Moreno G, Rocha J, Briceno R, et al. Changes in childhood pneumonia and infant mortality rates following introduction of the 13-valent pneumococcal conjugate vaccine in Nicaragua. Pediatr Infect Dis J. 2014; 33(6):637–42. doi: 10.1097/INF.0000000000000269 PMID: 24445827

22. Diaz J, Terrazas S, Birrenbach AL, Toscano CM, Alencar GP, Alvarez A, et al. Effectiveness of the 10-valent pneumococcal conjugate vaccine (pcv-10) in children in Chile: a nested case-control study using Nationwide Pneumonia Morbidity and Mortality Surveillance Data. PLoS One. 2016; 11(4):e0153141. doi: 10.1371/journal.pone.0153141 PMID: 27058873

23. Minamisawa R, Sgambatti S, Moraes-Neto OL, Cristo EB, Escalante JJC, Birrenbach AL, et al. Impact of PCV10 introduction on pneumonia mortality rates in Brazil: a time series analysis. Poster Session Pneumococcal Pneumonia—Risk Business at: 9th International Symposium on Pneumococci and Pneumococcal Diseases; 2014 Mar 9–13; Hyderabad, India. Poster Paper 0556. (Pneumonia 2014, vol. 3, Special issue, p. 248)

24. Suarez V, Michel F, Toscano CM, Birrenbach AL, Gonzales M, Vargas V, et al. Impact of pneumococcal conjugate vaccine in children morbidity and mortality in Peru: time series analyses. Vaccine. 2016; 34(39):4738–43. doi: 10.1016/j.vaccine.2016.07.027 PMID: 27521230
Afonso ET, Minamisawa R, Bierenbach AL, Escalante JJ, Alencar AP, Domingues CM, et al. Effect of 10-valent pneumococcal vaccine on pneumonia among children, Brazil. Emerg Infect Dis. 2013; 19(4):589–97. doi: 10.3201/eid1904.121198 PMID: 23628462

Andrade AL, Afonso ET, Cristo EB, Morais-Neto OL, Policena CM, Bierenbach AL, et al. Overall and indirect effect of PCV10 on pneumonia hospitalizations in children in Brazil after 3 years of vaccination. Poster Session at: 33rd Annual European Society for Paediatric Infections Diseases Meeting; 2015 May 12–16. Leipzig, Germany; 2015 [cited 2016 Jul 7]. Poster 0808, p. 1101. Available from: http://espid2015.kenes.com/Documents/ESPID%202015%20Abstracts.pdf

Scotta MC, Veras TN, Klein PC, Tronco V, Polack FP, Mattielo R, et al. Impact of 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) on childhood pneumonia hospitalizations in Brazil two years after introduction. Vaccine. 2014; 32(35):4495–9. doi: 10.1016/j.vaccine.2014.06.042 PMID: 24958703

Sgambatti S, Minamisawa R, Bierenbach AL, Toscano CM, Vieira MA, Policena G, et al. Early impact of 10-valent pneumococcal conjugate vaccine in childhood pneumonia hospitalizations using primary data from an active population-based surveillance. Vaccine. 2016; 34(5):663–70. doi: 10.1016/j.vaccine.2015.12.007 PMID: 26706272

Gaiano A, Rancajo C, Sagradino S, de Valles Juárez M, Biscayart C, Rearte A, et al. Notificación de neumonías y meningitis en niños después de la introducción de la vacuna antineumocócica conjugada al calendario nacional de vacunación. Rev Argent Salud Publica. 2013; 4(17):45–8.

Gentile A, Bakir J, Bialorus L, Caruso L, Mirra D, Santander C, et al. Impact of the 13-valent pneumococcal conjugate vaccine on the incidence of consolidated pneumonia in children younger than 5 years old in Pilar, Buenos Aires: A population-based study. Arch Argent Pediatr. 2015; 113(6):502–9. doi: 10.5546/aap.2015.502 PMID: 26593795

Sgambatti S, Minamisawa R, Bierenbach AL, Toscano CM, Vieira MA, Policena G, et al. Impact of a pediatric PCV-13 pneumococcal conjugate vaccine on childhood pneumonia hospitalization rates 3 years before and after PCV10 introduction in Brazil. Poster Session at: 32nd Annual European Society for Paediatric Infections Diseases Meeting; 2014 May 6–10; Dublin, Ireland; 2014 [cited 2016 Jul 7]. Abst. 491. Available from: http://cmoffice.kenes.com/cddemo/data/HtmlApp/main.html

Pinto L, Veras T, Scotta M, Tronco V, Klein P, Daudt A, et al. Impact of introducing the 10-valent pneumococcal conjugate vaccine on childhood hospitalizations for bacterial pneumonia in Brazil. Poster session: Pediatric Respiratory Epidemiology at: 23rd Annual Congress European Respiratory Society; 2013 Set 7–11; Barcelona, Spain; 2013 [cited 2016 Jul 7]. Poster P4324. (European Respiratory Journal 2013, vol 42, Suppl 57, p. 924). Available from: http://erjournal.ersnet.org/abstract_print_13/files/Abstract_book_2013.pdf

Gentile A, Bakir J, Bialorus L, Caruso L, Fernández MI, Mirra D, et al. Effectiveness of PCV13 vaccine to prevent consolidated pneumonia: population-based study in children under 5 years. Poster session: Pediatric Bacterial Infections at: IDWeek 2015; 2015 Oct 7–11; San Diego, California; 2015 [cited 2016 Jul 7]. Poster 1765, p. 1234. Available from: https://idsa.confex.com/idsa/2015/webprogram/Paper40289.html

Hortal M, Laurani H, Meny M, Estevan M, Arrieta F. Effectiveness of 7 and 13-valent pneumococcal conjugate vaccines for consolidated pneumonia in hospitalized children. Paper presented at: 9th International Symposium on Pneumococci and Pneumococcal Diseases; 2014 Mar 9–13; Hyderabad, India. Poster 0059. (Pneumonia 2014, vol 3, Special issue, p. 142).

Gentile A, Bakir J, Bialorus L, Caruso L, Mirra D, Santander C, et al. Population-based surveillance: incidence of consolidated pneumonia and pneumococcal disease in children of Concordia, Argentina. Comparison with the pre-13-valent pneumococcal vaccine (PCV-13) routine immunization period. Paper presented at: 9th World Conference of the World Society for Pediatric Infectious Diseases; 2015 Nov 18–21; Rio de Janeiro, Brazil, 2015 [cited 2016 Jul 7]. Abst. 0420, p. 73. Available from: http://wspid.kenes.com/Documents/WSPID%20All%20Abstracts.pdf

Andrade AL, Minamisawa R, Policena G, Cristo EB, Domíngues CMS, Brandilleone MCD, et al. Evaluating the impact of PCV-10 on invasive pneumococcal disease in Brazil: a time-series analysis. Hum Vaccin Immunother. 2016; 12(2):85–92. doi: 10.1080/21645515.2015.1117713 PMID: 26905679

Becker-Dreps S, Amaya E, Liu L, Moreno G, Rocha J, Briceño R, et al. Impact of a pediatric PCV-13 immunization program on hospitalizations and outpatient visits for pneumonia in Nicaragua. Poster Session: Pneumococcal Vaccine in Children and Adults at: IDWeek 2013; 2013 Oct 2–6; San Francisco, California; 2013 [cited 2016 Jul 7]. Poster 448, p. 319. Available from: https://idsa.confex.com/idsa/2013/webprogram/Paper40289.html
39. Vizzotti C, Rancaño C, Juarez M, Sagradini S, Gaiano A, Neyro S, et al. Argentinians experience 2 years after universal PCV13 introduction: the importance of a national epidemiological surveillance system to monitoring a vaccination strategy. Poster session: Global Pneumococcal Disease and Policies for Control at: 9th International Symposium on Pneumococci and Pneumococcal Diseases; 2014 Mar 9–13; Hyderabad, India. Poster 0518. (Pneumonia 2014, vol. 3, Special issue, p. 243).

40. Vizzotti C, Rearte A, Juarez M, Rancaño C, Sagradini S, Gaiano A, et al. Universal vaccination with PCV13 in Argentina: time series analysis 2008–2013 of bacterial pneumonia admissions in children under 5 years old. Poster session: Global Pneumococcal Disease and Policies for Control at: 9th International Symposium on Pneumococci and Pneumococcal Diseases; 2014 Mar 9–13; Hyderabad, India. Poster 0517. (Pneumonia 2014, vol. 3, Special issue, p. 244).

41. Azevedo J, Santos M, Silva M, Leite C, Pedroso M, Cordeiro S, et al. Progressive changes in pneumococcal meningitis in a large urban center in Brazil after 4 years of 10-valent pneumococcal conjugate vaccine (PCV10) introduction. Paper presented at: 115th Annual Meeting of the American Society for Microbiology; 2015 May 30–Jun 2; New Orleans, Louisiana, USA. Poster 2284.

42. Liphaus B, Okay MIG, Yu ALF, Ribeiro AF, Carvalhanas TRMP, Safadi MAP. Decline in pneumococcal meningitis after introduction of 10-valent pneumococcal conjugate vaccine in São Paulo, Brazil. Paper presented at: 8th International Symposium on Pneumococci and Pneumococcal Disease; 2012 March 11–15; Iguacu Falls, Brazil; 2012 [cited 2016 Jul 7]. Poster 322. p. 619. Available from: http://www2.kenes.com/ISPPD/Scientific/Documents/FinalAbstractbook.pdf

43. Domingues C, Verani JR, Montenegro ER, Brandileone MCC, Flannery B, Oliveira LH, et al. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study. Poster session: Controlling Pneumococcal Disease Around the Globe at: 9th International Symposium on Pneumococci and Pneumococcal Diseases; 2014 Mar 9–13; Hyderabad, India. Poster 0288. (Pneumonia 2014, vol. 3, Special issue, p. 145).

44. Garcia Gabarrot G, Lopez Vega M, Perez Giffoni G, Hernandez S, Cardinal P, Felix V, et al. Effect of pneumococcal conjugate vaccination in Uruguay, a middle-income country. PLoS One. 2014; 9(11): e112337. doi: 10.1371/journal.pone.0112337 PMID: 25375647

45. Valenzuela MT, Seoane M, Canais A, Pidal P, Hormazabal JC, Araya P, et al. Vigilancia de laboratorio de Streptococcus pneumoniae procedente de enfermedad invasora, Chile 2007–2012. Rev Chilena Infectol. 2014; 31(6):651–8.

46. Instituto de Salud Pública de Chile. Vigilancia de laboratorio de streptococcus pneumoniae procedente de enfermedad invasora. Chile, 2007–2015. Bol Inst Salud Publica Chile. 2015; 5(7):1–17.

47. Andrade AL, Minamisava EB, Policena G, Cristo EB, Morais-Neto OL, Domingues CMAS, et al. Effect of 10-valent pneumococcal conjugate vaccine on meningitis and invasive disease after 3 years of routine immunization in Brazil. Paper presented at: 33rd Annual European Society for Paediatric Infections Diseases Meeting; 2015 May 12–16. Leipzig, Germany; 2015 [cited 2016 Jul 7]. Abst. 0915, p. 250. Available from: http://espid2015.kenes.com/Documents/ESPID%202015%20Abstracts.pdf.

48. Rodrigues LC, Smith PG. Use of the case-control approach in vaccine evaluation: efficacy and adverse effects. Epidemiol Rev. 1999; 21(1):56–72. PMID: 10520473

49. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. III. Design options. Am J Epidemiol. 1992; 135(9):1042–50. PMID: 1595690

50. Andrade AL, Ternes YM, Vieira MA, Moreira WG, Lamaro-Cardoso J, Kipnis A, et al. Direct effect of 10-valent pneumococcal vaccination on pneumococcal carriage in children Brazil. PLoS One. 2014; 9(6):e98128. doi: 10.1371/journal.pone.0098128 PMID: 24892409

51. Moreira M, Cintra O, Harriague J, Hausdorff WP, Hoet B. Impact of the introduction of the pneumococcal conjugate vaccine in the Brazilian routine childhood national immunization program. Vaccine. 2016; 34(25):2766–78. doi: 10.1016/j.vaccine.2016.04.006 PMID: 27113162

52. Loo JD, Conklin L, Fleming-Dutra KE, Knoll MD, Park DE, Kirk J, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on prevention of pneumonia. Pediatr Infect Dis J. 2014; 33(Suppl. 2):S140–S51.

53. Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreno RA, Nohynek H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev. 2009;(4):Cd004977. doi: 10.1002/14651858.CD004977.pub2 PMID: 19821336

54. Rudan I, O’Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health. 2013; 3(1):010401. doi: 10.7189/jogh.03.010401 PMID: 23826505
55. Zhou F, Kyaw MH, Shefer A, Winston CA, Nuorti JP. Health care utilization for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States. Arch Pediatr Adolesc Med. 2007; 161(12):1162–8. doi: 10.1001/archpedi.161.12.1162 PMID: 18056561

56. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005; 365(9465):1139–46. doi: 10.1016/S0140-6736(05)17187-6 PMID: 15794968

57. Greenberg D, Givon-Lavi N, Ben-Shimol S, Ziv JB, Dagan R. Impact of PCV7/PCV13 introduction on community-acquired alveolar pneumonia in children <5 years. Vaccine. 2015; 33(36):4623–9. doi: 10.1016/j.vaccine.2015.06.062 PMID: 26116251

58. Bonner K, Welch E, Elder K, Cohn J. Impact of Pneumococcal Conjugate Vaccine Administration in Pediatric Older Age Groups in Low and Middle Income Countries: A Systematic Review. PLoS One. 2015; 10(8):e0135270. doi: 10.1371/journal.pone.0135270 PMID: 26332848

59. Palmo AA, Klipi TM, Rinta-Kokko H, Nohynek H, Toropainen M, Nuorti JP, et al. Pneumococcal conjugate vaccine and clinically suspected invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case-control study. Euro Surveill. 2016; 21(14).

60. Principi N, Esposito S. The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on serotype 19A invasive pneumococcal disease. Expert Rev Vaccines. 2015; 14(10):1359–66. doi: 10.1586/14760584.2015.1075884 PMID: 26289973

61. Russell F, Sanderson C, Temple B, Henao-Restrepo AM, Mulholland K. Global review of the distribution of pneumococcal disease by age and region: implications for vaccination schedules. Paper presented at: 8th International Symposium on Pneumococci and Pneumococcal Disease; 2012 March 11–15; Iguacu Falls, Brazil; 2012 [cited 2016 Jul 7]. Poster 41, p. 352. Available from: http://www2.kenes.com/ISPPD/Scientific/Documents/FinalAbstractbook.pdf

62. Sartori AM, Nascimento AF, Yuba TY, Soarez PC, Novaes HM. Methods and challenges for the health impact assessment of vaccination programs in Latin America. Rev Saude Publica. 2015; 49. Epub 2016/01/14. PubMed Central PMCID: PMCPMC4687821.

63. Sterne JAC, Egger M, Moher D. Addressing reporting bias. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester (UK): Johns Wiley & Sons; 2008. Chapter 10.

64. Berglund A, Ekelund M, Fletcher MA, Nyman L. All-cause pneumonia hospitalizations in children <2 years old in Sweden, 1998 to 2012: impact of pneumococcal conjugate vaccine introduction. PLoS One. 2014; 9(11):e122111. doi: 10.1371/journal.pone.0112211 PMID: 25379659

65. Pan American Health Organization. Technical Advisory Group on Vaccine-preventable Diseases, editor. Final report of the 23rd TAG Meeting; 2015 1–3 July; Varadero, Cuba. Washington, DC: PAHO, 2015 [cited 2016 Jul 5]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=31233&Itemid=270&lang=fr