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Impact of vaccination on carriage of and infection by antibiotic-resistant bacteria: a systematic review and meta-analysis

Li Min Wang[1,2], Tiago Cravo Oliveira Hashiguchi[1], Michele Cecchini[1]

[1]Health Division, Organization for Economic Co-operation and Development, Paris; [2]Ecole des Hautes Études en Santé Publique (EHESP), Paris, France

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Corresponding author: Michele Cecchini, MD, MSc, DrPH, PhD
Health Division, Organization for Economic Co-operation and Development, 2, Rue André-Pascal, 75016 Paris, France
Tel: +33-1-4524-7857, Fax: +33-621375343
E-mail: Michele.cecchini@oecd.org

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This systematic review and meta-analysis aims to quantify the impact of vaccination on the incidence and prevalence of nonsusceptible infections and investigates the impact of vaccination programs on serotype replacement. We searched a comprehensive set of databases. Identified studies were assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and resulting evidence was analyzed using random-effect meta-analyses. Nineteen studies on pneumococcal conjugate vaccines (PCV) met our inclusion criteria. PCV decreases the incidence of nonsusceptible pneumococcal infections (PIs) by 56.91% (95% confidence interval [CI], -50.90% to -62.91%) and the probability of carriage of nonsusceptible pneumococcal bacteria by 28.10% (95% CI, -13.25% to -42.95%). The effect of PCV on PIs becomes higher when only serotypes specifically targeted by the vaccine are taken into account (-80.98%; 95% CI, -70.34% to -91.52%), while it becomes lower when all the PIs, including both susceptible and nonsusceptible PIs, are considered (-48.30%; 95% CI, -31.55% to -65.08%). The effect of PCV is found greater in populations with high prevalence of human immunodeficiency virus and for PCV covering a higher number of serotypes. Findings from this study suggest that vaccination programs may be an effective tool to prevent the spread of PIs and may play a significant role in tackling antimicrobial resistance.

Keywords: Streptococcus pneumoniae, Drug resistance, Vaccination, Systematic review, Meta-analysis

Introduction

Antimicrobial resistance (AMR) poses a serious threat to the health of humans, animals, and the environment. The World Health Organization listed it among the top ten threats to global health for 2019 [1], while, in Europe, the estimated health burden of AMR in 2015 was 170 disability adjusted life years per 100,000 population, equivalent to the combined burden of influenza, tuberculosis, and human immunodeficiency virus (HIV) [2]. AMR not only contributes to mortality and morbidity, but also exerts pressure on health systems in the form of more extensive and expensive treatments [3]. The Organization for Economic Co-operation and Development estimates that between the years 2015–2050, AMR will cost more than 134 billion USD (purchasing power parity) to the health systems of countries in Europe, the United States, Canada,

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and Australia [4].

While many factors contribute to the development of AMR, overuse and misuse of antibiotics is widely considered to be among the main drivers behind the selective pressure towards the spread and survival of resistant strains [5]. This is supported by data showing a significant association between the level of consumption of specific antibiotics and the resulting incidence of resistance in the bacteria they target [6]. While a number of policy actions to promote the prudent use of antimicrobials have already been implemented in many countries [4], forecasted growth in AMR indicates that stronger actions might need to be considered [7].

Vaccination programs present a promising additional avenue to promote the prudent use of antibiotics and to prevent the spread of AMR, along with their associated health and economic consequences [8]. Vaccinations can affect AMR by reducing the number of pathogens—including both pathogens susceptible and resistant to antibiotics—and by preventing their spread across humans. Vaccination programs may also reduce the need for antibiotic prescriptions and thus indirectly affect the development of new resistant strains by reducing selective pressure [9]. Finally, vaccination programs may confer indirect benefits to non-vaccine-recipients through herd immunity [10]. The potential benefits of vaccination programs may, however, be limited by vaccine coverage and vaccine efficacy. For example, it is estimated that more than half of the world's infant population does not currently receive the pneumococcal conjugate vaccines (PCV) [11], a vaccine for an infection with AMR potential. Additionally, any impact of the vaccine may be reduced or masked by serotype replacement of the pathogen, where disease in the population shifts to strains not included in the vaccine [12].

This study builds on previous literature looking at the effect of vaccination programs on AMR, essentially PCV, to provide an overview of existing evidence on a number of dimensions. Previous systematic reviews and meta-analyses on the topic were either limited in scope, focusing only on the effect of vaccination on the usage of antibiotic [13], or did not quantify aspects related to AMR prevalence and incidence [14]. This systematic review and meta-analysis aims to close these gaps by quantifying the impact of vaccination programs on the incidence and prevalence of nonsusceptible infections. In addition, this analysis provides new insights on whether, and to what extent, serotype replacement may take place following the implementation of a new vaccination program.

Materials and Methods

The research methodology was designed according to the PICO (population, intervention, comparison, outcome) framework [15], presented in Table 1, and is broadly aligned with two previous systematic reviews on this topic [13,14]. The literature search was conducted using the following search terms: vaccine, immunization, antimicrobial, antibiotic, influenza, pneumococcal, haemophilus, and meningococcal. Randomized control trials (RCTs) and observational studies comparing antibiotic use between vaccinated and control populations (including people who were unvaccinated or vaccinated with another vaccine with no effect on the bacteria under study), or comparing antibiotic use between pre-vaccination and post-vaccination periods, were included in the review. Case reports, narrative reviews, opinion pieces, and studies including animals, were excluded. Studies were also limited to English only; no limitations were placed on place of publication or geographical scope of the analysis. Articles were not limited to specific population group categories (e.g., by age), but key categories were taken into account during data collection and analysis by, for example, carrying out subgroup analyses. Finally, while the research strategy did not place any limitation on the type of vaccination, we were able to identify only quantitative data on PCV to feed the meta-analysis.

Table 1. PICO (population, intervention, comparison, outcome) table defining the scope of the systematic review and meta-analysis

	The scope of the systematic review and meta-analysis
Population	Inclusion: individuals of all ages, both genders and of all health statuses, including healthy people and those with a disease Exclusion: individuals taking antibiotics prophylactically
Intervention	Vaccination by pneumococcal conjugate vaccine, influenza vaccine, haemophilus vaccine, or meningococcal vaccine Exclusion: administration of multiple vaccines among those included in the scope
Comparison group	Individuals not vaccinated, including pre- versus post-vaccination, placebo and control vaccine
Outcome	Primary outcomes: prevalence of infections nonsusceptible to antibiotics (treatment outcome); and antibiotic usage measured either individually or by population group (patient outcome) Exclusion: outcomes involving non-vaccine-serotypes

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Electronic searches were conducted for studies published from January 1998 to June 2019 in CENTRAL, Embase, PubMed Central, PubMed, and Google Scholar (limited to the first 100 results). Reference lists from relevant systematic reviews and meta-analyses were also screened and included if relevant [13,14].

For all included studies, data was independently extracted by two researchers, including data on study participants (age group, key population characteristics and potential confounders, vaccination status, location, and time of the study), type of intervention (type of vaccine), effectiveness of the intervention on the health outcomes, and characteristics of the study (statistical methods, length of the follow-up). Studies reporting evidence for multiple outcomes were considered as independent studies for each of the outcomes of interest, and contributed independently to the analyses.

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the strength of the study design and the certainty of the evidence [16]. The strength of each study was assessed according to possible limitations in study design, inconsistencies, and various risks of bias.

Data on carriage of and infection by bacteria was expressed in the form of attributable proportion among the exposed (APAE). APAE can be interpreted as the proportion of cases in the unvaccinated group that can be attributed to the absence of vaccination or, in other words, the proportion of cases that could be avoided by extending vaccination to the control group. Whenever APAE was not reported by the study, it was calculated as the risk difference between the unvaccinated and the vaccinated groups, divided by the incidence in the unvaccinated group.

Missing values for confidence intervals (CIs) were calculated from the p-values following standard approaches from the Cochrane handbook of systematic reviews [17]. Missing p-values were calculated with the chi-square test on the underlying data contained in the original papers.

The results of studies were pooled using random-effects models to calculate a summary effect size along with 95% CIs. The 'metan' package in Stata version 15.0 (Stata Corp., College Station, TX, USA) was used to create a model which placed more weight on studies with larger sample sizes [18]. Visual inspection of forest plots and the I2 statistic were used to assess heterogeneity, in accordance with Cochrane guidelines [19]. Analyses were stratified by category of antibiotics, and a rich set of sensitivity analyses was carried out to test the potential impact of key confounders.

Results

Eligible literature

Following removal of duplicates, 2,659 records were identified through searches of electronic databases and other sources. After excluding 2,515 abstracts, 144 full-text reports were assessed, of which 125 were excluded for reasons summarized in Fig. 1.

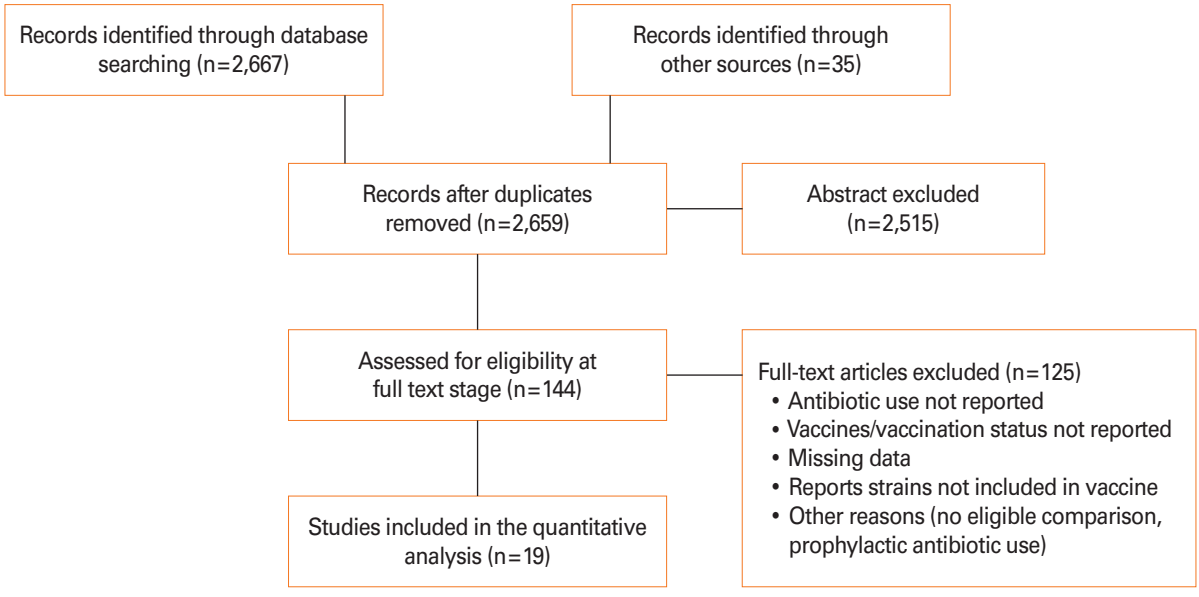

Fig. 1. Flow diagram of the literature search.

All of the 19 studies included related to pneumococcal vaccines with no additional studies identified for other eligible vaccines [20-38]. Most of the studies (15 studies) were carried out in high-income countries, mainly in the United States (10 studies) and South Korea (two studies), with only four studies carried out in low- or middle-income countries: South Africa (three studies) and Morocco (one study). The majority of studies employed an observational approach, with only two studies carried out as RCTs [30,33]. With the exception of four studies [22,24,29,36], all the included studies reported estimates on multiple dimensions, with one study reporting a total of seven estimates [27]. In total, it was possible to retrieve 67 estimates regarding the impact of PCV on: all nonsusceptible pneumococcal infections (PIs) (50 estimates), PCV-specific serotypes PI (seven estimates), and all PI (10 estimates) (Table 2).

In 68% of cases (34 estimates), the related medical outcome was incidence of an infection. The remaining 16 estimates (22%) referred to the probability of carriage of nonsusceptible bacteria, usually defined by underlying studies as a positive test with no sign of infection. Nonsusceptibility to penicillin was the most studied outcome, accounting for 43% of all estimates (29 estimates). Macrolides were the second most represented class of antibiotics with 11 estimates, followed by trimethoprim/sulfamethoxazole (TMP/SMX) and cephalosporins with, respectively, seven and four estimates. Finally, it was possible to identify seven estimates for other antibiotics as well as seven estimates for nonsusceptibility to multiple antibiotics.

Three potential confounders were identified while reviewing included studies: population age, type of PCV vaccination, and populations with high prevalence of HIV. Two thirds of the estimates (44 estimates) concerned a child population with other estimates including people from all the age groups. PCV7—the PCV targeting seven different serotypes—was the most studied vaccine, with 39 estimates, followed by PCV13 (15 estimates) and PCV9 and PCV10 with, respectively, eight and five estimates each. Eleven estimates, from three studies [30,33,37], focused on population with high prevalence of HIV-positive patients, reaching up to 23% of the sample in the study by Mbelle et al. [33].

Quality of the studies

Following the GRADE approach, studies were generally categorized as being of low (36.8%) or very low (52.6%) quality, mainly because many studies were carried out as observational studies (rather than RCTs) or because they were at serious or high risk of bias, including due to non-blinding. Two studies, however, were categorized as of being high quality [30,33]. Studies with high-quality evidence were more likely to assess the impact of vaccination programs (PCV9) on child populations in middle-income settings or to be RCTs. Further information on each study, including the GRADE rating and reasons for downgrading the certainty of the evidence, are reported in Supplement 1.

Efficacy of pneumococcal conjugate vaccines on all nonsusceptible infections

The meta-analysis of studies reporting changes in rates of all nonsusceptible PI following vaccination indicates that, overall, PCV decreases the incidence of these infections by 56.91% (95% CI, -50.90% to -62.91%) (Fig. 2). In the subgroup analysis by type of antibiotic, reduction of nonsusceptible infections is lowest for macrolides (-51.05%; 95% CI, -49.56% to -52.54%) and highest for cephalosporins (-84.11%; 95% CI, -77.25% to -90.97%). The result for cephalosporins is also the only value that is statistically significantly different from the pooled result. The analysis of the i^2 value suggests a high grade of heterogeneity for the sub-group analyses on nonsusceptibility to penicillin, TMP/SMX and multiple antibiotics. Heterogeneity does not seem to be significant for all the other subgroup analyses.

Efficacy of pneumococcal conjugate vaccines on carriage of nonsusceptible bacteria

The impact of PCV vaccination on the probability of carriage of nonsusceptible pneumococcal bacteria is significantly smaller than the impact of PCV on the incidence of nonsusceptible PIs (Fig. 3). Overall, the implementation of a PCV program is estimated to reduce the probability of carriage of nonsusceptible pneumococcal bacteria by 28.10% on average (95% CI, -13.25% to -42.95%). The impact is estimated to be lowest, and non-statistically significant, for PIs nonsusceptible to penicillin (-14.46%; 95% CI, 14.12% to -43.03%) and highest for infections nonsusceptible to multiple antibiotics (-53.19%; 95% CI, -18.12% to -88.25%), although this value is based on a single study [34]. The subgroup analysis by type of antibiotic suggests that there are no statistically significant differences in the effects of PCV across different types of antibiotics. In addition, CIs for estimated changes in the probability of carriage of nonsusceptible pneumococcal bacteria by type of antibiotic systematically overlap with estimated

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Table 2. Characteristics of the include studies

Author	Country/population	Study design	Intervention/ comparison group	Outcome	Effect: vaccine vs. control (or effect)	Quality (GRADE)
Black et al. [20] (2004)	USA; children	Observational	PCV7; non-vaccinated children	Incidence of all resistant serotypes	Penicillin: 19.5% vs. 28.9% (p<0.001) Macrolides: 15.0% vs. 29.5% (p<0.001) Others: 13.9% vs. 39.3% (p<0.001)	Low
				Incidence of all infections	Penicillin: -84.0% (-90.5%, -74.7%)	
Cho et al. [21] (2012)	South Korea; children aged <5 years	Observational	PCV7; pre-vaccination period	Carriage of targeted serotypes	Penicillin: 100% vs. 83.7% (p<0.01)	Low
				Carriage of all serotypes	Penicillin: 95.4% vs. 83.5% (p<0.001)	
Cho et al. [22] (2014)	South Korea; individuals aged <18 years	Observational	PCV7; pre-vaccination period	Incidence of targeted serotypes	Multiple atbs: -43.5% (p<0.001)	Very low
Cohen et al. [23] (2006)	France; children aged 6–24 months with acute otitis media	Observational	PCV7; pre-vaccination period	Carriage of all serotypes	Penicillin: 30.2% vs. 47.6% (p<0.001)	Very low
				Carriage of targeted serotypes	Penicillin: 18% vs. 34% (p<0.001)	
				Carriage of all infections	Penicillin: 59.2% vs. 71.1% (p< 0.001)	
Diawara et al. [24] (2015)	Morocco; children aged <5 years	Observational	PCV13; pre-vaccination period	Incidence of all serotypes	Penicillin: 24.4% vs. 49.5% (p<0.005) TMP/SMX: 8.9% vs. 38.5% (p<0.001) Macrolides: 22.2% vs. 28.6% (p=0.43) Others: 26.7% vs. 44.0% (p<0.05)	Very low
				Incidence of all infections	Penicillin: 34.6 vs. 13.5 cases 100,000 (p<0.001)	
Hammitt et al. [25] (2006)	USA; individuals aged <5 or >18 years	Carriage survey	PCV7; pre-vaccination period	Carriage of all serotypes	Penicillin: 25.5% vs. 24.7% (p=0.83) Others: 5.6% vs. 11.6% (p<0.005) Macrolides: 8.0% vs. 13.1% (p=0.032) TMP/SMX: 20.2% vs. 21.2% (p=0.61) Cephalosporins: 5.8% vs. 11.3% (p=0.012)	Low
Hampton et al. [26] (2012)	USA; individuals aged <5 years	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: -78.0% (-79.0%, -77.0%)	Very low
				Incidence of targeted serotypes	Penicillin: -99.6% (-99.8%, -99.4%)	
Hennessy et al. [27] (2005)	USA; children aged <5 years	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: 14.8% vs. 18.6% (p=0.26) TMP/SMX: 17.2% vs. 22.4% (p=0.13) Macrolides: 9.4% vs. 18.7% (p=0.003) Cephalosporins: 0.0% vs. 0.5% (p=0.51) Others: 4.3% vs. 3.8% (p=0.9) Multiple atbs: 16% vs. 22.1% (p=0.06)	Very low
				Incidence of all infections	Penicillin: 15.1 vs. 22.7 cases 100,000 (p<0.001)	
Hsu et al. [28] (2009)	USA; individuals with pneumococcal meningitis	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: -41.1% (p<0.001) Others: -64.0% (p<0.001) Cephalosporins: -60.0% (p<0.001)	Very low
				Incidence of all infections	Penicillin: -30.1% (p<0.001)	

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Table 2. Continued

Author	Country/population	Study design	Intervention/ comparison group	Outcome	Effect: vaccine vs. control (or effect)	Quality (GRADE)
Kaplan et al. [29] (2004)	USA; hospitalized infants and children	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: -12% (p=0.018)	Low
Klugman et al. [30] (2003)	South Africa; children aged 28–84 days	RCT	PCV9; placebo	Incidence of all serotypes	Penicillin: -67% (-88%, -19%) TMP/SMX: -56% (-78%, -16%) Multiple atbs: -56% (-77%, -21%)	High
				Incidence of all infections	Multiple atbs: 16.6 vs. 33.1 cases 10,000 (p<0.001)	
Kyaw et al. [31] (2006)	USA; individuals of any age	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: -57.0% (-58.0%, -55.0%) Macrolides: -51.0% (-53.0%, -50.0) Multiple atbs: -59.0% (-60.0%, -58.0%)	Very low
				Incidence of targeted serotypes	Penicillin: -87.0% (-88.0%, -86.0%)	
				Incidence of all infections	Penicillin: 12.6 vs. 25.1 cases 100,000 (p<0.001)	
Marom et al. [32] (2017)	Israel; children aged <6 years with acute otitis media	Observational	PCV7 or PCV13; pre-vaccination period	Incidence of all serotypes	Penicillin: 35.3% vs. 67.7% (p=0.009) Macrolides: 9.0% vs. 40.0% (p=0.003) TMP/SMX: 0.0% vs. 57.0% (p<0.001) Multiple atbs: 0.0% vs. 23.0% (p=0.004)	Very low
Mbelle et al. [33] (1999)	South Africa; infants	RCT	PCV9; placebo	Carriage of all serotypes	Penicillin: 21.0% vs. 41.0% (p=0.002) Macrolides: 4.0% vs. 6.0% (p=0.45) TMP/SMX: 23.0% vs. 35.0% (p=0.003) Others: 15.9% vs. 19.2% (p=0.46)	High
Sigurdsson et al. [34] (2017)	Iceland; children aged <4 years	Repeated cross-sectional	PCV10; unvaccinated	Carriage of all serotypes	Penicillin: 10.4% vs. 11.2 (p=0.76) Macrolides: 9.0% vs. 13.1% (p=0.05) TMP/SMX: 12.1% vs. 22.1% (p<0.001) Others: 27.7% vs. 39.2% (p<0.001) Multiple atbs: 4.4% vs. 9.4% (p=0.003)	Very low
Stephens et al. [35] (2005)	USA; individuals aged >0 year	Observational	PCV7; unvaccinated	Incidence of all serotypes	Macrolide: -68.8% (p<0.0001)	Very low
				Incidence of targeted serotypes	Macrolide: -82.9% (p<0.001)	
				Incidence of all infections	Macrolide: -55.4% (p<0.0001)	
Tomczyk et al. [36] (2016)	USA; individuals aged >0 year	Observational	PCV13; pre-vaccination period	Incidence of all serotypes	Multiple atbs: 31.1% vs. 42.6% (p<0.001)	Low
von Gottberg et al. [37] (2014)	South Africa; children aged <2 years	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: -82.0% (-85.0%, -78.0%) Cephalosporins: -85.0% (-91.0%, -77.0%) Multiple atbs: -66.0% (-70.0%, -62.0%)	Low
				Incidence of targeted serotypes	Penicillin: 47.0% vs. 70.0% (p<0.001)	
				Incidence of all infections	Penicillin: -40.0% (-42.0%, -37.0%)	
Whitney et al. [38] (2003)	USA; children aged <2 years	Observational	PCV7; pre-vaccination period	Incidence of all serotypes	Penicillin: -34.9% (p<0.001)	Low
				Incidence of all infections	Penicillin: -29.1% (p<0.05)	

GRADE, Grading of Recommendations Assessment, Development and Evaluation; PCV, pneumococcal conjugate vaccines; atbs, antibiotics; TMP/SMX, trimethoprim/sulfamethoxazole; RCT, randomized clinical trial.

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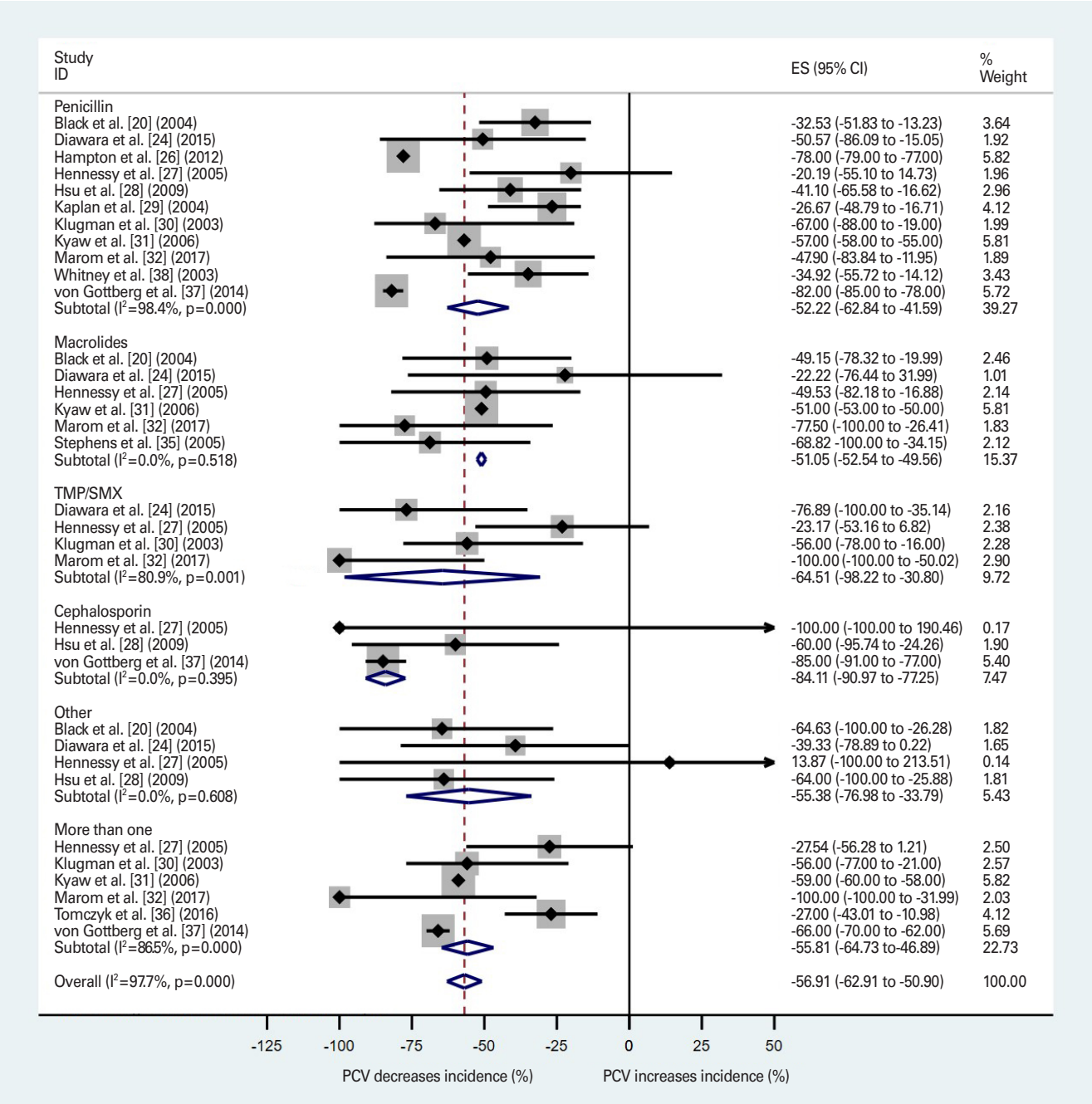

Fig. 2. Forest plot for effect of pneumococcal conjugate vaccine (PCV) on the incidence of nonsusceptible pneumococcal infections. Weights are from random effects analysis. ES, estimates; CI, confidence interval.

changes in the incidence of nonsusceptible PIs.

Additional analyses and sensitivity analyses

Fig. 4 reports the summary results of the additional analyses and sensitivity analyses related to the changes in rates of all nonsusceptible PIs, with the underlying calculations presented in Supplement 1. The impact of PCV becomes statistically significantly higher when only serotypes specifically targeted by the vaccine are taken into account (-80.98%; 95% CI, -70.34% to -91.52%), as opposed to all the serotypes (-56.91%; 95% CI, -50.90% to -62.91%). At the same time, the implementation of the vaccination program decreases the incidence of all the PIs, including both susceptible and nonsusceptible PIs, by 48.30% (95% CI, -31.55% to -65.08%).

The sensitivity analysis concludes that there is no statistically different effect by population age, with effects on chil-

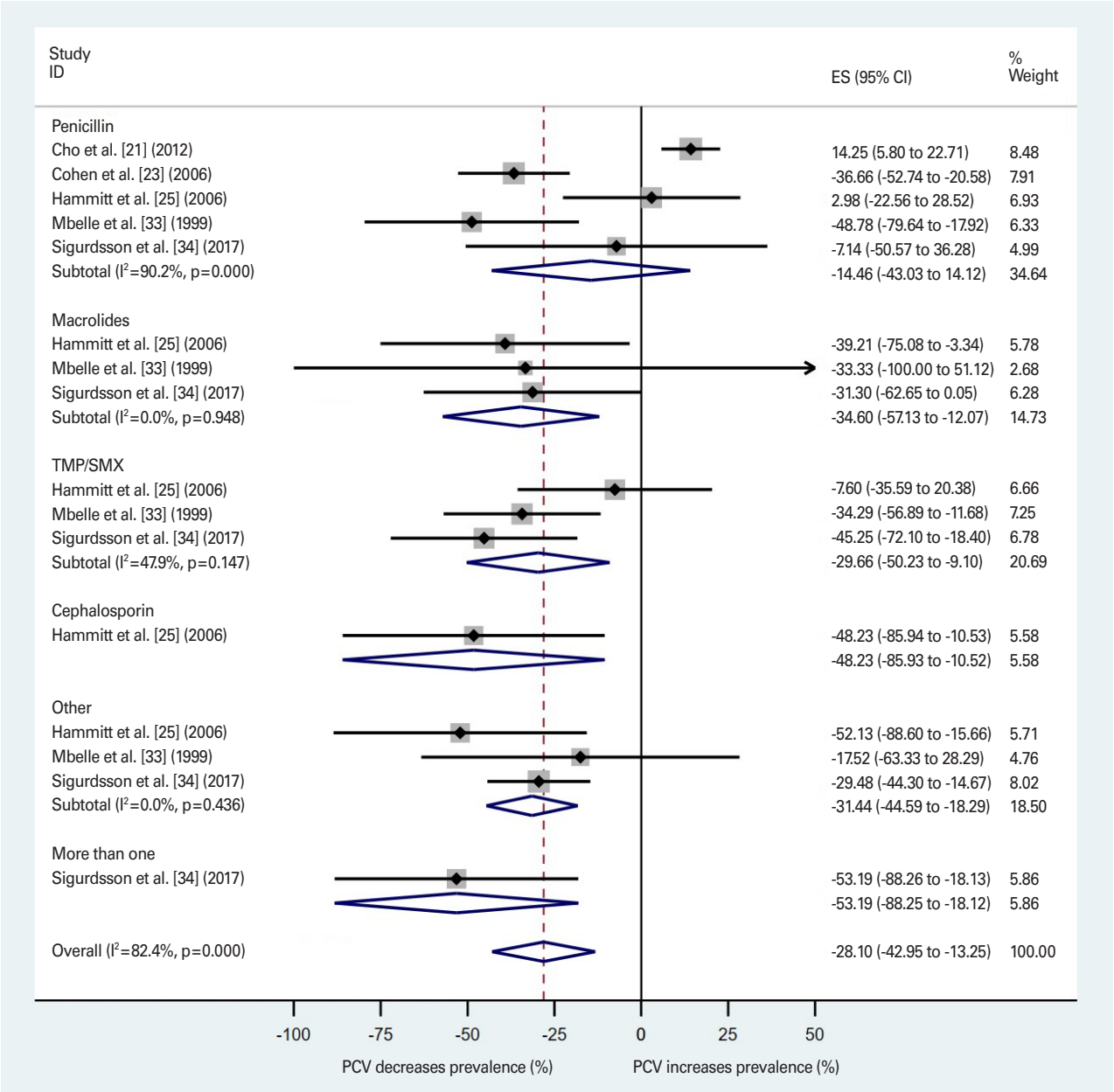

Fig. 3. Forest plot for effect of pneumococcal conjugate vaccine (PCV) on the carriage of nonsusceptible pneumococcal bacteria. Weights are from random effects analysis. ES, estimates; CI, confidence interval.

dren and adult population overlapping to a substantial degree. Conversely, the effect of PCV vaccination is statistically significantly greater in populations with high prevalence of HIV infections. Finally, studies assessing the effect of PCV13 show a greater impact for this vaccination compared to studies assessing PCV7 vaccinations; with reductions of infection rates by, respectively, 68.31% (95% CI, -57.73% to -78.89%) and 49.20% (95% CI, -41.28% to -57.12%).

A set of additional analyses and sensitivity analyses focusing on the probability of bacterial carriage, whose results can be found in Supplement 1, does not identify any particular pattern of how the effectiveness of a PCV program may be affected by age group, type of vaccine or HIV prevalence. However, the number of estimates contributing to the analysis is much smaller.

Discussion

The aim of this systematic review and meta-analysis was to provide a comprehensive assessment of evidence for the ef-

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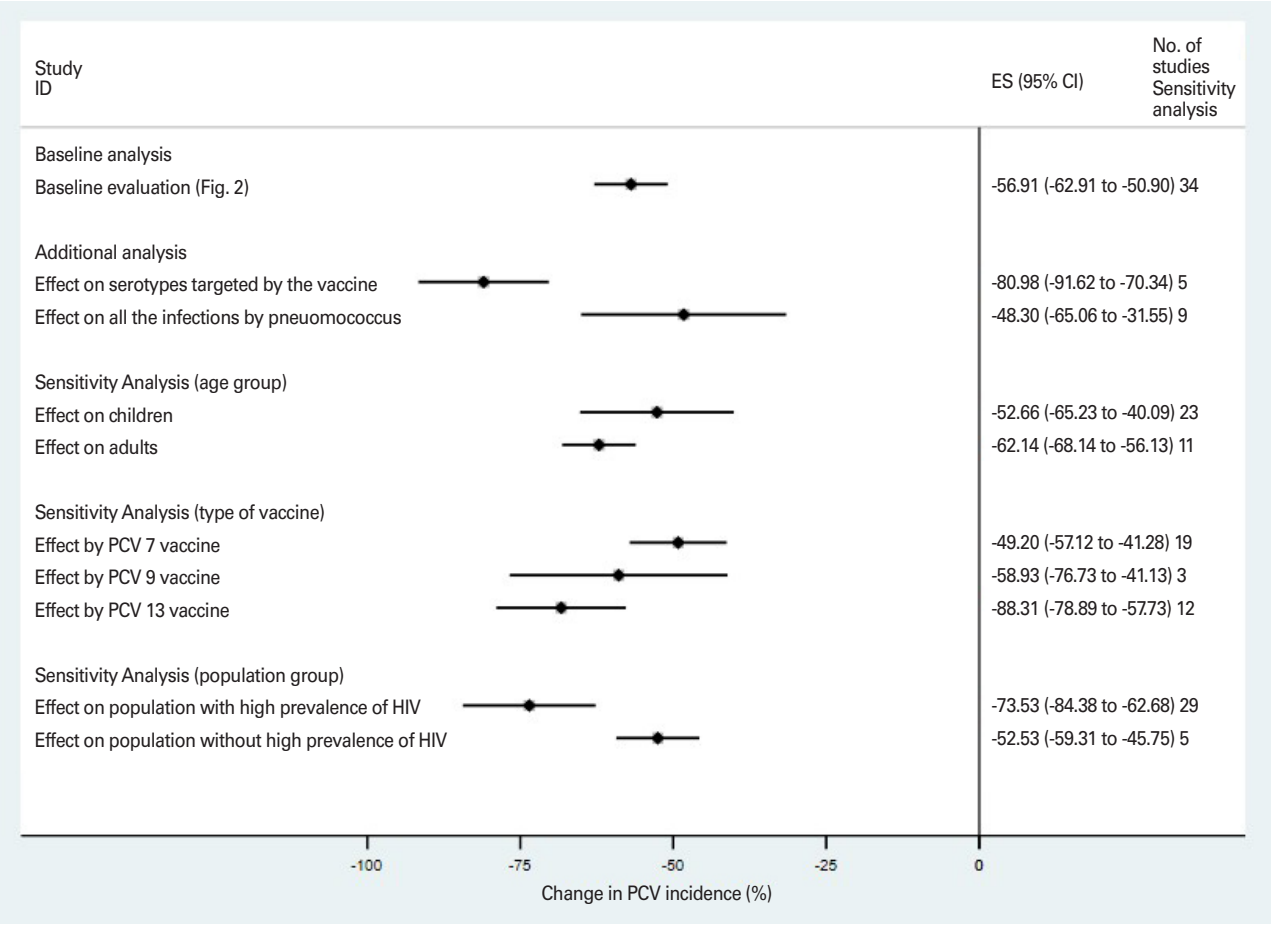

Fig. 4. Forest plot for effect of pneumococcal conjugate vaccine (PCV) on the incidence of nonsusceptible pneumococcal infections: additional analyses and sensitivity analysis. Weights are from random effects analysis. ES, estimates; CI, confidence interval; HIV, human immunodeficiency virus.

fect of vaccination on AMR. Findings from this study have three important implications.

First, vaccinations can offer both direct personal protection against target diseases as well as indirect benefits to non-recipients by reducing bacterial carriage and thus the risk of resistant infection. While by providing immunity, PCV has a greater effect on the incidence of PIs, our analyses also find a statistically significant effect on the probability of carrying a resistant bacterium, suggesting that PCV may effectively decrease bacteria proliferation.

Second, serotype replacement is likely to take place following the introduction of a vaccination program but the replacement does not seem to be complete and PCV remain effective. As the analysis enlarges the scope of the PI taken into account, by moving from assessing the effect of the PCV on PI by nonsusceptible serotypes targeted by the vaccine, to all nonsusceptible serotypes, to all PIs, the effectiveness of PCV decreases. Similarly, PCV13, which covers a higher number of serotypes, shows a higher impact on PIs compared to PCV7, which targets a lower number of serotypes. However, findings also show that PCV is consistently associated with a statistically significant decrease in PIs. Even when the most comprehensive outcome is considered—i.e., total incidence of PIs—PCV almost halves the probability of infection. However, the possibility that, in the very long-term, non-targeted serotypes may completely replace targeted serotypes cannot be excluded.

Third, PCV programs are particularly effective in groups of individuals at higher risks for developing communicable diseases. The analyses on the effectiveness of PCV programs in population with high prevalence of HIV show statistically significantly higher results compared to the analyses focusing on population with low prevalence of HIV.

This study addresses some of the gaps identified by the previous systematic reviews and meta-analysis by extending its focus to changes in incidence of PIs and by including an

extensive set of sensitivity analyses. Nonetheless, results from this study should be interpreted with caution due to a number of limitations. Populations targeted by the studies differed quite significantly in terms of a number of factors such as age group, diagnosis and setting. Therefore, these populations may not be fully representative of general populations. In addition, studies were carried out over almost 20 years and, during this period, a number of other influencing factors may have modified the likelihood of using antibiotics or the prevalence of nonsusceptible infections. For example, changes in clinical practices, upscaling of interventions to tackle AMR, and differences in the provision of healthcare services may have all played a significant role that cannot be adjusted for in our analyses. From a methodological point of view, in order to maximize the number of studies contributing to the pooled estimates, this study has used standard approaches to estimate missing values. While this is a standard procedure, which is well codified in the literature [17], deriving missing information ex-post increases the uncertainty in the findings, particularly because the methodologies used are based on conservative approaches likely to produce wider CIs compared to those usually evaluated on the original data. However, if anything, this means that results from this study are conservative with results showing a larger uncertainty range.

In a policy-making perspective, it is also important to emphasize two issues. First, PIs are still considered a major public health problem worldwide, with approximately 72 million of the global infant population not being vaccinated, either because they live in one of the 50 countries that have not yet introduced the PCV, or because they are not reached by the immunization services [11]. Many of these persons live in areas of the world with very high levels of AMR [7]. Findings from this study suggest that upscaling vaccination practices in these countries may have a significant impact on AMR.

However, at the same time, findings from this study do not support vaccinations as the only solution to tackle AMR. First of all, vaccinations only exist for a limited number of infections and for a limited number of serotypes within a single species of bacteria. For example, while more than 90 types of serotypes for *Streptococcus pneumoniae* are known [39], the most comprehensive vaccine included in this analysis only covers 13 different serotypes, although these are arguably the most prevalent. Second, despite the very wide research strategy aiming to carry out a meta-analysis for as many vaccines as possible, data could be found only for PCV with no useful quantitative evidence on, for instance, influenza vaccination or for *Haemophilus influenza*, two infections for which vaccination is available. Finally, while findings from this analysis suggest that serotype replacement should not be a major concern in the medium-term (up to a decade), lack of evidence limits our results only to PIs, leaving the possibility that vaccinations may lead to replacement by other bacteria or by other serotypes in the very long term. Consequently, while AMR is likely to be reduced for several years after the implementation of a vaccination program and for the bacteria and serotypes specifically targeted by the vaccination, the very long-term effects are more difficult to assess. However, at the same time, findings from this study support the use of vaccination programs as one of the tools that countries can implement to limit the spread of PIs.

ORCID

Li Min Wang *https://orcid.org/0000-0002-2759-4131*
Tiago Cravo Oliveira Hashiguchi
https://orcid.org/0000-0001-7352-5287
Michele Cecchini *https://orcid.org/0000-0001-7634-6436*

Supplementary Materials

Supplementary materials are available at Clinical and Experimental Vaccine Research website (http://www.ecevr.org).

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