Impact of vaccination on antibiotic usage: a systematic review and meta-analysis

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ABSTRACT

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Background: Vaccines may reduce antibiotic use and the development of resistance.

Objectives: To provide a comprehensive, up-to-date assessment of the evidence base relating to the effect of vaccines on antibiotic use.

Methods: Ovid MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov and WHO Trials Registry.

Study eligibility criteria: Randomised-controlled trials (RCTs) and observational studies published January 1998 to March 2018.

Participants: Any population.

Interventions: Vaccines versus placebo, no vaccine or another vaccine.

Methods: Titles, abstracts, and full-texts were screened independently by two reviewers.

Certainty of RCT evidence was assessed using GRADE.

Results: 4980 records identified; 895 full-text reports assessed; 96 studies included (24 RCTs, 72 observational). There was high certainty evidence that influenza vaccine reduces days of antibiotic use among healthy adults (1 RCT; n = 4253; rate reduction 28.1% [95% CI 16.0,

38.4]); moderate certainty evidence that influenza vaccines probably reduce antibiotic use in children aged 6 months to 14 years (3 RCTs; n = 610; ratio of means 0.62 [95% CI 0.54, 0.70] and probably reduces community antibiotic use in children aged 3-15 years (1 RCT; n = 10,985 person-seasons; risk ratio 0.68 [95% CI 0.58, 0.83]); moderate certainty evidence that pneumococcal vaccination probably reduces antibiotic use in children aged 6 weeks to 6 years (2 RCTs; n = 47,945; rate ratio 0.93 [95% CI 0.87, 0.99]) and reduces illness episodes requiring antibiotics in children aged 12-35 months (1 RCT; n = 264; rate ratio 0.85 [95% CI 0.75, 0.97]). Other RCT evidence was of low or very low certainty, and observational evidence was affected by confounding.

Conclusions: The evidence base is poor. Although some vaccines may reduce antibiotic use, collection of high-quality data in future vaccine trials is needed to improve the evidence base.

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Background

Antibiotic resistance is an increasing threat to human health globally(1, 2). It is estimated that during 2015 there were more than 600,000 antibiotic resistant infections and 33,000 related deaths in countries of the European Union and European Economic Area(3). In addition to mortality and morbidity, antibiotic-resistance leads to increased expenditure on more expensive and prolonged treatments(1). Projections suggest that antibiotic resistance will continue to grow across developed countries, with 10% of all spending on communicable diseases being used for resistance-related complications(4). In developing countries growth of antibiotic resistance may be much faster and with health systems under-resourced and already stretched, will result in enormous numbers of deaths, largely amongst newborns, young children and the elderly(4).

Overuse and inappropriate use of antibiotics have been identified as major contributing factors in the rise of antibiotic resistance(5, 6). Countries with high antibiotic consumption levels have higher incidence of antibiotic resistance(1, 6-9). Significant associations have been demonstrated between levels of consumption of specific antibiotics and the incidence of antibiotic resistance in the bacteria they target(7, 8). Yet despite growing global recognition of the urgency of the problem and efforts in many countries to improve antibiotic stewardship, the use of antibiotics in humans, animals and agriculture is still increasing globally year on year(6).

Immunisation has the potential to reduce antibiotic use. Vaccines against bacterial diseases may directly reduce antibiotic use through reduction of disease incidence. Vaccines against

viral or parasitic diseases whose primary manifestations are fever or diarrhoea may also reduce antibiotic use through reductions in symptom-based antibiotic prescribing(10-12). In addition, indirect benefits to non-recipients through the herd effect may reduce antibiotic use in the larger population. The potential of immunisation to reduce antibiotic use may, however, be affected by vaccine effectiveness and coverage. Further, any impact of bacterial vaccines on antibiotic use or resistance could be complicated or diminished by pathogen strain replacements, as the disease in the population shifts to serotypes not included in the vaccines(13-17).

This systematic review aims to provide a comprehensive and up-to-date assessment of the evidence relating to the effect of vaccines on antibiotic use, to evaluate the quality of the evidence, and to inform best practices for collection of antibiotic use data in future vaccine research.

Methods

Search strategy and selection criteria

This systematic review with meta-analysis was conducted in accordance with the SAGE Guidance for development of vaccine-related recommendations, the Cochrane Handbook, and the GRADE handbook(18-20). The review protocol was registered on PROSPERO and is publicly available ([CRD42018103881](https://doi.org/10.1111/CRD4.2018103881))(21).

RCTs and comparative observational studies were included that reported antibiotic use in any population following any vaccination on the current WHO list of available vaccines and pre-licence vaccines(22). Vaccines eligible for inclusion are listed in the Supplementary

Materials. Observational studies were eligible that compared antibiotic use between contemporaneous vaccinated and unvaccinated populations, or before and after vaccine introductions or immunisation campaigns. Case reports, narrative reviews and opinion pieces were excluded. No limitations were placed on language or place of publication.

Electronic searches for studies published from January 1998 to March 2018 were conducted in Ovid MEDLINE, Embase and the Cochrane Library. Search strategies are reported in the Supplementary Materials. Ongoing or recently completed studies that may report data were identified by searching ClinicalTrials.gov and the WHO Trials Registry. All records identified by the searches, and subsequently the full-text reports of records considered potentially eligible, were independently screened by two reviewers. In both stages, disagreements were resolved by a third reviewer. The reference lists of relevant systematic reviews and meta-analyses were screened, and experts in the field of vaccines and antibiotic resistance were contacted to check for further eligible studies.

This review compared people vaccinated with bacterial, viral, or parasitic vaccines with unvaccinated people (placebo or no vaccine) or people vaccinated with vaccines for non-febrile or rare conditions. We excluded comparisons of bacterial vaccines versus febrile viral or parasitic vaccines; different doses, schedules, or formulations of the same vaccine; and comparisons of vaccines for non-febrile or rare conditions with unvaccinated people.

The primary outcome was use of any antibiotic, measured individually or by class.

Data extraction

For all included studies, data were extracted on study participants (age, sex, vaccination status, health status), measures of antibiotic use (individual patient-level data or estimates of relative effect; data collection methods), setting (location, context, pertinent potential confounders) and statistical methods, including information about any reported adjustment for clustering or confounders. Data were extracted by one reviewer using pre-tested data extraction forms and cross-checked by a second reviewer. Disagreements were resolved by referring to study reports and through discussion.

Risk of bias and certainty of the evidence

The risk of bias of all included studies was assessed by one reviewer and cross-checked independently by a second reviewer. Disagreements were resolved through discussion. For RCTs, the Cochrane Risk of Bias tool for RCTs was used(24). For observational studies with contemporaneous comparisons, the Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used (25). For observational studies with time-based comparisons, the Cochrane Effective Practice and Organisation of Care (EPOC) suggested risk of bias criteria were used(26). Studies with both contemporaneous and time-based comparisons were assessed with both tools. For the observational studies, the main confounders likely to be reported by studies were considered to be age, sex, and co-existing health conditions; information on health care utilisation and access, also an important confounder, was taken into account where available.

We used the GRADE approach to assess the certainty of evidence from RCTs. Evidence started at high certainty, but could be downgraded to moderate, low or very low if there were limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, or publication bias(19).

Data analysis

RCT data were combined as available using a random-effects model. Where antibiotic use was reported as a proportion, risk ratios were calculated with 95% confidence intervals (CIs) to estimate effects. When reported as a rate over time, rate ratios and their 95% CI were calculated. When studies reported a mean number of antibiotic courses, we calculated the ratio of means after log-transforming the data to account for skewness. Visual inspection of forest plots and the I^2 statistic were used to assess statistical heterogeneity in accordance with Cochrane guidance(23). For observational studies, study and population characteristics, overall risk of bias assessment and summary results were tabulated (Supplementary Materials).

Role of the funding source

The Wellcome Trust was involved in the conception of the research, but had no role in data collection, analysis, or interpretation.

Results

Following removal of duplicates, 4980 records were identified by the searches of electronic databases and other sources. After excluding 4085 abstracts, 895 full-text reports were assessed, of which 787 were excluded for reasons summarised in Figure 1. Overall, 108 articles reporting 96 studies were included: 24 RCTs, 33 observational studies with

contemporaneous comparisons, 37 with time-based comparisons, and two studies with both(27, 28).

Most identified studies related to pneumococcal vaccines (8 RCTs, 50 observational studies) or influenza vaccines (16 RCTs, 14 observational). Fewer studies assessed pneumococcal and influenza vaccines combined (2 observational), measles vaccines (1 RCT, 1 observational), Haemophilus influenzae type b (Hib) vaccine (3 observational), pertussis vaccine (2 observational), meningococcal vaccine (1 observational) and rotavirus vaccine (1 observational). No studies were identified for other eligible vaccines.

The characteristics of included RCTs, summary results, risk of bias assessment and GRADE rating are presented in Tables 1 and 2 and Figure 2. Reasons for downgrading the certainty of evidence are reported as footnotes in Table 2. Of the 24 RCTs, twelve were wholly or primarily conducted in Europe, five were in North America, four in Australia, and one each in the Middle East, Africa and East Asia. Twenty (83.3%) used self-reported data for antibiotic use outcomes, one used medical records, and two used administrative databases (Table 1). The data source for one study was unclear.

Eight RCTs reported antibiotic use following pneumococcal vaccinations (Tables 1 & 2; Figure 3), with five different outcome measures: the rate of antibiotic courses/person-time(29-31); the number of antibiotics courses/person(32); the number of illness episodes resulting in antibiotic use/person-time(33); the proportion of participants receiving antibiotics (34, 35); and days of antibiotic use(36).

There was moderate certainty evidence that pneumococcal vaccination probably results in a modest reduction in rates of antibiotic purchases or prescriptions in children aged six weeks

to six years compared to control or placebo (2 RCTs; n = 47,945; rate ratio 0.93 [95% CI 0.87, 0.99]) over 6-21 months (Figure 3)(30, 31). In one of these RCTs, children in both the vaccine and control arms also received influenza vaccine(30). A third RCT (n = 37,868; very low certainty evidence) provided no usable data, but reported that a completed vaccination series in infants aged <2 months was associated with a reduction in antibiotic prescriptions of 5.7% (95% CI 4.2, 7.2%) over 8-42 months (29).

There was moderate certainty evidence that pneumococcal conjugate vaccine probably results in fewer illness episodes requiring antibiotic use than meningococcal C control vaccine in children aged 12 to 35 months (1 RCT; n = 261; rate ratio 0.85 [95% CI 0.75, 0.97]) over two years(33).

For all other antibiotic use outcomes, there was only very low certainty evidence for pneumococcal vaccines. In one RCT pneumococcal polysaccharide vaccine (PPV23) was associated with a reduction in the number of antibiotic courses received over two years by adults with COPD compared to placebo (1 RCT; n = 144; risk ratio 0.24, 95% CI 0.12 to 0.50) (32). Two RCTs reported no significant difference in the proportions of vaccinated and unvaccinated participants who received antibiotics following pneumococcal vaccine, one in infants aged <12 weeks and one in adults with COPD and a third RCT reported no difference in days of ear-related antibiotic use between children aged one to seven years(34-36).

Sixteen RCTs reported antibiotic use following influenza vaccinations (Tables 1 & 2; Figure 4) with four different outcome measures: the mean number of antibiotic courses/person(37-44); the proportion of participants receiving any antibiotics(45-50); days of antibiotic use(51); and the rate of antibiotic prescriptions/person-days(30).

In pooled analysis of three RCTs, there was moderate certainty evidence that influenza vaccines probably reduced the number of courses of antibiotics prescribed to infants and children aged 6 months to 14 years compared to no vaccine or placebo (3 RCTs; n = 610; ratio of means 0.62 [95% CI 0.54, 0.70])(38, 41, 43).

There was high certainty evidence from one large RCT that intranasal influenza virus vaccine resulted in a reduction of 28.1% in the number of days taking antibiotics for febrile illness compared to placebo among healthy adults aged 18 to 64 years during a 14-week influenza outbreak period (1 RCT; n = 4253; rate reduction 28.1% [95% CI 16.0, 38.4])(51).

There was moderate certainty evidence from one large trial that influenza vaccination in children aged 3-15 years probably reduces the proportions of participants receiving antibiotics in the vaccinated children, families and community contacts over three years compared with control (1 RCT; n = 10,985 person-seasons; risk ratio 0.68 [95% CI 0.58, 0.83])(48, 52).

For other outcome measurements and populations evidence was considered to be of low or very low certainty. There was low certainty evidence of a reduction in the number of courses of antibiotics after vaccination in older adults with chronic bronchitis (1 RCT; n = 138; ratio of means 0.68 [95% CI 0.64, 0.73])(39). There was low or very low certainty evidence from nine RCTs that influenza vaccination was associated with no significant effect on the number of antibiotic courses or prescriptions per person or household, the proportions of participants receiving antibiotics, or the rate of prescribing over time in infants, children, adults aged 18-74 years, adults with COPD and all age groups(30, 37, 40, 42, 44-47, 49, 50).

Measles vaccine was considered by one RCT that reported very low certainty evidence that early vaccination (at 18 weeks) had no effect on antibiotic use compared with standard vaccination at nine months(53).

The characteristics, main results and overall risk of bias assessments of all included observational studies are presented in Supplementary Materials. Of the 72 observational studies, 37 were conducted in Europe, 18 in North America, eight in the Middle East/Central Asia, five in East Asia, and two each in South America and Australia. Thirty-seven used medical records or physician-reported data, 15 used self-reported data and 14 used regional or national database data. The source of data for six studies was unclear. The majority of the observational studies did not appropriately adjust estimates of antibiotic use for confounding and were considered to be at critical risk of bias by the Cochrane ROBINS-I tool, or high risk of bias in time-based studies.

Discussion

This systematic review aimed to provide an up-to-date and comprehensive assessment of evidence relating to the effect of vaccines on antibiotic use. Evidence from RCTs related largely to pneumococcal and influenza vaccines, with only one trial of measles vaccine. There was little opportunity for meta-analysis due to heterogeneity in populations and outcome measurements. Evidence from observational studies also related largely to pneumococcal and influenza vaccines. RCTs reported only reductions or no significant difference in antibiotic use following vaccinations, while observational findings ranged from reduced to increased use. Notably, the identified data emanate overwhelmingly from high-

income Western countries. Of the 96 included studies only six were from eastern Asia, two from South America and one from Africa.

For comparisons and outcomes in which high or moderate certainty evidence from RCTs existed, significant reductions in a number of measures of antibiotic use were reported in healthy children, healthy adults and whole communities. In healthy children, most trials reported significant reductions in antibiotic use after pneumococcal vaccination, although the effects were modest. For rates of prescribing, there was moderate certainty evidence from two pooled trials with a rate ratio of 0.93 (95% CI 0.87, 0.99) in children aged six weeks to six years (30, 31). A third trial reported a reduction in the number of illness episodes requiring antibiotic use in children aged 12 to 35 months with a rate ratio of 0.85 (95% CI 0.75, 0.97) over two years(33). For influenza vaccines, there was moderate certainty evidence from three pooled trials of a slightly more marked reduction in the number of courses of antibiotics prescribed to infants and children aged 6 months to 14 years, with a ratio of means of 0.62 (95% CI 0.54, 0.70)(38, 41, 43). In healthy adults, there was high certainty evidence from one large trial that intranasal influenza virus vaccine resulted in a 28.1% reduction in the number of days taking antibiotics for febrile illness during an influenza outbreak period(51).

Vaccination can offer both direct protection against the target disease to the individual recipient and indirect benefits to non-recipients by reducing disease prevalence and thus risk of infection. Few trials measured antibiotic use other than by those receiving immunisation and controls, which means that any herd effect on antibiotic use was not recorded. However, the largest effect identified by this review was from a large cluster-randomised trial that reported moderate certainty evidence that influenza vaccination of children aged 3-15 years was associated with smaller proportions of vaccinated children,

families and community contacts receiving antibiotics over three years compared with control, with a risk ratio of 0.68 (95% CI 0.58, 0.83)(48, 52).

For other populations, comparisons and outcome measures RCT evidence was considered to be of low or very low certainty, most commonly downgraded for risks of bias and for imprecision, either because of small sample size or estimates that included both benefit and detriment.

Most included observational studies' reported estimates of antibiotic use without adjusting for important confounding factors that can affect antibiotic use, and thus their findings must be interpreted with caution. While antibiotic use measured over extended periods of time may indeed be affected by the introduction of a vaccine or by immunisation campaigns, it may also be affected by other factors: clinical guidelines or practice may change; campaigns on prudent antibiotic use may have targeted clinicians, the public, or both; and factors such as climate, economy, health service provision can all affect needs for and access to antibiotics. Many studies also featured populations defined by diagnoses that may not be representative of general populations. In addition, health service utilisation habits vary between people so that individuals who are more likely to seek immunisation may also be more likely to seek health care generally and consequently to receive antibiotics.

A 2012 systematic review that considered the effect of vaccines on antibiotic use included three randomised controlled trials (RCTs) and four epidemiological studies, all reporting decreased antibiotic use following influenza and pneumococcal vaccines(54). However, the review acknowledged important limitations in the evidence. As antibiotic use is commonly a secondary outcome, it is possible that non-significant or negative effects remain unreported. Reductions in antibiotic use reported by two of the included epidemiological studies

followed introduction or increased uptake of vaccines, but this coincided with campaigns to promote rationale use of antibiotics, so that the impact of the vaccines was unclear(55, 56). Although the current review identified considerably more studies reporting antibiotic use following vaccinations, in general, the review found the evidence base to be limited and affected by methodological weaknesses.

This review and the evidence base are affected by some limitations. Although title and abstract screening sought to include all studies whose title, abstract, focus or design suggested they may report on antibiotic use after vaccinations, it is possible that some studies with relevant data may have been excluded. Although searches were conducted for ongoing trials in ClinicalTrials.gov and the WHO Trials Registry, it is possible that additional unpublished trials exist, leading to publication bias. The limited number of studies included in the meta-analyses did not allow for formal publication bias assessment. In all study types, the quality of antibiotic use data varied widely. In most studies, antibiotic use measurements were secondary outcomes and often not well-defined or reported. The potential to synthesise results was reduced by the multiplicity of outcome measures reported. It is possible that outcomes were selected for reporting based on the data available rather than a priori. As most of the included RCTs were not accompanied by a published protocol or a trial registration, we were unable to properly assess the risk of selective outcome reporting. In addition, the reliability of data may be uncertain in some studies as they were derived from sources external to the studies or were self-reported and subject to recall bias.

Uncertainty about the quality of data relating to antibiotic use reported by the trials may be further compounded by lack of information about the indications for which they were prescribed or whether prescribing was truly justified. For some indications of a bacterial aetiology antibiotics are not always necessary, while for viral diseases unnecessary

prescribing may be based solely on histories of fever or diarrhoea. It might be argued that the relatively modest reported effects of vaccines on antibiotic use may be even less if only truly justified prescribing was considered. However, trials often recruit relatively healthy populations due to exclusion criteria, during follow up participants are often monitored more closely by clinicians, and treatments may be standardised by protocols. Thus, antibiotic use may be less in trial populations than would be the case in uncontrolled circumstances, so that trials-based evidence may underestimate the effect of vaccines on both justified and symptom-based prescribing.

A standard measure of antibiotic use, consistently reported by researchers, would facilitate more robust assessment of the impact of vaccines on antibiotic use. Antibiotic use is an important potential effect of vaccination and will always reflect an adverse outcome, whether prescribed with a good reason or superfluously. Previous studies have shown that colonisation by resistant bacteria follows antibiotic treatment in treated individuals, and correlations have been observed between levels of antibiotic use and antibiotic resistance at the level of hospital wards, communities, populations and countries (7, 8, 57, 58). Therefore, we propose that future RCTs assessing vaccines against conditions that cause fever or other symptoms that might be interpreted as a bacterial infection, should as a minimum report on the proportions of randomised patients receiving antibiotics and some measure of total antibiotic use. Where there exists a rationale for differences between classes of antibiotics, studies should collect data on antibiotic use by class or by specific agent.

Conclusions

Evidence relating to the effect of immunisation on antibiotic use identified by the review related overwhelmingly to pneumococcal and influenza vaccines. Limited evidence from RCTs suggested either significant reductions in antibiotic use following vaccination or no significant difference, with no trial reporting an increased use. More good quality evidence is needed regarding the effect of vaccines on antibiotic use in all regions of the world. Data on antibiotic use should be collected prospectively from reliable sources and standardisation of outcome measurements would facilitate future synthesis. Future RCTs assessing the effect of vaccinations should collect and report data on antibiotic use. Prospective observational studies should collect data on antibiotic use and on potential confounding factors.

Contributors

BB was involved in screening, data extraction, analysis and interpretation and drafted the final report; NH, HB and GV were involved in study conception, design, screening, data extraction, analysis and interpretation and contributed to the final report; BS conducted the searches and contributed to the final report; EK was involved in study conception and provided comments on the final report; CG and MP were involved in study conception and design, interpretation and contributed to the final report. All authors approved the submitted version.

Declaration of interests

BB, NH, HB, BS, GV and CG were employed by Cochrane Response, which received funding from the Wellcome Trust to conduct the research; all have no other disclosures. EK is

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429 conduct, results or conclusions. MP has nothing to disclose.

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NOT PEER REVIEWED

Table 1: Characteristics of included randomised controlled trials

Study ID	Country, dates	Population description, number randomised & data source	Intervention/comparison groups	Antibiotic use outcomes reported
Pneumococcal vaccine				
Dagan 2001(33)	RCT (individual) Israel Study dates not reported	Healthy boys and girls aged 12 to 35 months attending day care centres. N = 261 Antibiotic use data: parental self-report	Intervention: 9-valent pneumococcal conjugate vaccine (Wyeth-Lederle Vaccines). Children aged 12-17 months received two intramuscular injections 2 to 3 months apart, and those aged 18-35 months received a single intramuscular injection. Comparison: Meningococcus C conjugate vaccine (Wyeth-Lederle).	Number of illness episodes resulting in antibiotic use
Fireman 2003(29)	RCT (individual) USA 1995 to 1999	Infants aged <2 months old attending Kaiser Permanente clinics. N = 37,868 Antibiotic use data: health insurance database	Intervention: PCV7 heptavalent pneumococcal conjugate vaccine (Wyeth) given at 2, 4 and 6 months of age and a booster at 12 to 15 months. Comparison: Meningococcal C conjugate vaccine (Wyeth).	Number of antibiotic prescriptions
Jansen 2008(30)	RCT (individual) Netherlands 2003 to 2005	Children aged 18 to 72 months with a previously diagnosed respiratory tract infection. General practitioners' clinics N = 579 Antibiotic use data: parental self-report & clinician data collection form	Intervention: PCV7 (Prevenar) with Influvac (trivalent influenza vaccine). Two vaccinations 4 to 8 weeks apart in the year of inclusion. Comparison: Placebo with Influvac (trivalent influenza vaccine). Two vaccinations 4 to 8 weeks apart in the year of inclusion. Children included in both first and second years of study received second Influvac vaccination in the subsequent year.	Number of antibiotic prescriptions
Palmu 2014(31)	RCT (individual) Finland	Children aged 6 weeks to 18 months recruited through health-	Intervention: pneumococcal PCV10 (Haemophilus influenzae protein D conjugate vaccine, PHiD-CV10)	Number of antibiotic

	Feb 2009 - Dec 2011	care centres, local well-baby clinics and dedicated study clinics throughout Finland. N = 47,366 Antibiotic use data: from national administrative register, linked by personal identity code	(GlaxoSmithKline). Either 2+1 or 3+1 (primary vaccination) or 2 doses (catch up vaccination). Comparison: Hep A or B vaccine (age dependent).	prescriptions; vaccine effectiveness
Steentoft 2006(34)	RCT (individual) Denmark Study dates not reported	Patients with chronic obstructive lung disease. N = 49 Antibiotic use data: patient self-report	Intervention: Pneumovax® 23-polyvalent pneumococcal vaccine, 0.5 ml given subcutaneously, with steroids given before, after, or before and after vaccination. Comparison: Unvaccinated and 4 weeks of steroid treatment.	Proportion of people receiving antibiotics
van Gils 2009(35)	RCT (individual) Netherlands July 2005 to February 2008	Infants aged <12 weeks. 50% male, mean age at first vaccination 8.8 months. N = 1003 Antibiotic use data: parental self-report	Intervention: 7-valent pneumococcal polysaccharide protein conjugate vaccine (CRM197-PCV-7; Wyeth Pharmaceuticals). Either 2 doses (at 2 and 4 months) or 3 doses (at 2, 4 and 11 months). Comparison: Unvaccinated	Proportion of people receiving antibiotics
Veenhoven 2003(36)	RCT (individual) Netherlands Apr 1998 - Jan 2002	Children aged 1-7 years with 2 episodes of acute otitis media in the previous year. Median age 2 (1-6); 62% male. N = 383 Antibiotic use data: parental self-report	Intervention: Children aged 12–24 months were immunised with PCV7 (Prevnam, Wyeth) twice (with a 1-month interval between immunisations) followed 6 months later by PPSV23. Children aged 25–84 months received one dose of PCV7, followed 7 months later by PPSV23. Comparison: Hepatitis A (aged 25–84 months) or B (aged 12–24 months) vaccines	Days of ear-related antibiotic use
Yilmaz 2013(32)	RCT (individual) Country not clear: UK or Turkey	Chronic obstructive pulmonary disease patients N = 144 Antibiotic use data: source not reported	Intervention: 23-valent polysaccharide pneumococcal vaccine (PCV23). Comparison: Placebo	Number of antibiotic courses

	Study dates not reported			
Influenza vaccine				
Allsup 2003(45)	RCT (individual) UK Sept 1999 - May 2000	Healthy individuals aged 65 to 74 years without risk factors for influenza identified from 20 general practices. N = 729 Antibiotic use data: medical records	Intervention: Trivalent, split virion influenza vaccine (Wyeth Laboratories). Single injection (0.5 ml) administered into the right deltoid muscle. Comparison: Placebo	Proportion of people receiving antibiotics
Belshe 1998(46)	RCT (individual) USA Aug 1996 - Mar 1998	Healthy children aged 15 to 71 months. 52% male, mean age 43 months. N = 1602 Antibiotic use data: parental self-report	Intervention: Aviron intranasal live attenuated, cold-adapted, trivalent influenza vaccine. Either 1 or 2 doses. 2 x 0.25-ml aliquots (one per nostril) as a large-particle aerosol, for a total delivered volume of 0.5 ml. Comparison: Placebo	Proportion of people receiving antibiotics
Bridges 2000(47)	RCT (individual) USA Oct 1997 – March 1999	Healthy working adults. Median age 43-44 years. Recruited through emails and work site presentations. N = 2375 Antibiotic use data: patient self-report	Intervention: Trivalent inactivated influenza vaccine (FluShield, Wyeth-Lederle). 1 dose Comparison: Placebo. Sterile saline.	Proportion of people receiving antibiotics
Clancy 2016(37)	RCT (individual) Australia 2011	Adults aged 40 to 85 years with diagnosis of moderate-severe chronic obstructive pulmonary disease. 62% male. N = 320 Antibiotic use data: patient self-report	Intervention: Oral nontypeable Haemophilus influenzae (NTHi) vaccine (HI-164OV). 3 courses of HI-164OV enteric-coated tablets, two tablets daily for 3 consecutive days, with courses repeated at days 28 and 56. Comparison: Placebo	Number of antibiotic courses or prescriptions

Esposito 2003(38)	RCT (individual) Italy Dec 2000 - Apr 2001	Children aged 6 months to 9 years with history of recurrent respiratory tract infections attending an infectious diseases outpatient clinic. N = 127 Antibiotic use data: parental self- report	Intervention: Nasalflu intranasal influenza vaccine (Berna Biotech). Inactivated, trivalent, virosome-formulated subunit influenza vaccine. Two single doses of 0.2 ml on days 1 and 8 ± 1. Comparison: Placebo (saline solution).	Number of antibiotic courses or prescriptions
Gao 2011(39)	RCT (individual) China Sept 2008 - Nov 2009	Patients ≥ 60 years of age with chronic bronchitis N = 138 Antibiotic use data: patient self- report	Intervention: Influenza vaccine (Shanghai Institute of Biological Products). 0.5 ml of influenza vaccine to the upper arm deltoid muscle. Comparison: Unvaccinated	Number of antibiotic courses or prescriptions
Hoberman 2003(40)	RCT (individual) USA Oct 1999 - Mar 2001	Children aged 6 to 24 months recruited from primary care centre and from the community via radio and newspaper advertisements. 52.4% male. N = 793 Antibiotic use data: parental self- report	Intervention: Fluzone inactivated trivalent subvirion influenza vaccine. 2 doses 4 weeks apart (0.25 mL each) given intramuscularly. Comparison: Placebo	Number of antibiotic courses or prescriptions
Jansen 2008(30)	RCT (individual) Netherlands 2003 to 2005	Children aged 18 to 72 months with a previously diagnosed respiratory tract infection. General practitioners' clinics N = 579 Antibiotic use data: parental self- report & clinician data collection form	Intervention: Influvac (trivalent influenza vaccine) with placebo. Two vaccinations 4 to 8 weeks apart in the year of inclusion. Children included in both first and second years of study received second Influvac vaccination in the subsequent year. Comparison: Recombinant HBV vaccine (Engerix-B Junior; GlaxoSmithKline) + placebo vaccination. Two vaccinations 4 to 8 weeks apart in the year of inclusion.	Number of antibiotic prescriptions

Loeb 2010(48, 52)	RCT (cluster) Canada Sept 2008 – June 2009	Children and adolescents aged 36 months to 15 years randomized. All community members observed. N = 10,985 person-seasons Antibiotic use data: parental self-report	Intervention: Inactivated seasonal influenza vaccine recommended for the 2008-2009 influenza season (Vaxigrip, Sanofi Pasteur). One 0.5-mL dose of the study vaccine intramuscularly. Children < 9 years previously unvaccinated at the time of immunization received a second 0.5-mL dose 4 weeks after the first. Comparison: Hepatitis A vaccine (Avaxim-Pediatric, Sanofi Pasteur)	Proportion of people receiving antibiotics
Marchisio 2002(49)	RCT (individual) Italy Nov 1999 - July 2000	Children aged 1 to 5 years with a history of acute otitis media. Mean age 32.6 months +/- 14.6 (vaccine) and 36.2 +/- 15.9 (control), 56.7% (vaccine) and 63.6% (control) male. N = 133 Antibiotic use data: parental self-report	Intervention: Nasalflu intranasal, inactivated, virosomal subunit influenza vaccine (Berna Biotech). Two doses on days 1 and 8. The spray consisted of a 2-shot large-particle aerosol designed to deliver one 0.1-mL aliquot per nostril, for a total volume of 0.2mL. Comparison: Unvaccinated	Proportion of people receiving antibiotics
Marchisio 2009(41)	RCT (individual) Italy Oct 2006 - Apr 2007	Children aged 1 to 5 years with a history of recurrent acute otitis media N = 180 Antibiotic use data: parental self-report	Intervention: Inactivated virosomal-adjuvanted subunit influenza vaccine (Inflexal V, Berna Biotech). Dose 1 followed by dose 2 29 +/- 3 days later. Children aged <36 months received 0.25 mL of the vaccine, and older children 0.5 mL. Comparison: Unvaccinated	Number of antibiotic courses or prescriptions
Nichol 1999(51)	RCT (individual) USA Sept 1997 - Mar 1998	Adults aged 18 to 64 years working at least 30 hours per week outside the home were recruited from health insurance carriers, work sites and through advertising N = 4561 Antibiotic use data: patient self-report	Intervention: Live attenuated influenza vaccine (FluMist, Aviron). Single dose intranasal spray containing three virus strains. Comparison: Placebo	Days taking antibiotics for febrile illness

Pisu 2005(42)	RCT (individual) USA Nov 1996 - Apr 1999	Families of children aged 2 to 5 years attending day care centres recruited from 10 US Navy-affiliated day care centers. N = 260 Antibiotic use data: parental self-report	Intervention: Inactivated influenza vaccine (Wyeth-Lederle). Comparison: Hepatitis A vaccine	Number of antibiotic courses or prescriptions per household
Principi 2003(43)	RCT (individual) Italy 2001 to 2002	Healthy children aged 6 months to 5 years. 53.8% boys, median age 3.2 years. N = 303 Antibiotic use data: parental self-report	Intervention: Inflexal V intramuscular virosomal influenza vaccine (Berna Biotech). Comparison: Unvaccinated	Number of antibiotic courses or prescriptions
Tandon 2010(44)	RCT (individual) Australia Apr 2006 - Oct 2006	Adults aged 47 to 88 years with severe recurrent chronic obstructive pulmonary disease. 76% male. N = 38 Antibiotic use data: patient self-report	Intervention: HI-164OV non-typeable Haemophilus influenzae enteric-coated tablets. Three courses of tablets, two tablets daily for three consecutive days (before breakfast), with courses repeated at day 28 and day 56. Comparison: Placebo	Number of antibiotic courses or prescriptions
Vesikari 2006(50)	RCT (individual) Belgium, Finland, Israel, Spain, United Kingdom Oct 2000 - May 2002	Healthy children aged 6 to <36 months attending day care $\geq$ 12 hours/week. Mean age 24 months, 51% male. N = 1784 Antibiotic use data: parental self-report	Intervention: CAIV-T Cold-Adapted Influenza Vaccine-Trivalent- (Wyeth Vaccines Research). Comparison: Placebo	Proportion of people receiving antibiotics
Measles vaccine				

Hansen 2017(53)	RCT (individual) Guinea-Bissau Aug 2013 - Jan 2014	Children aged < 5 months invited to take part in the trial during home visits/clinic attendance. N = 651 Antibiotic use data: parental self- report	Intervention: measles vaccine (Edmonston Zagreb strain, Serum Institute of India, Pune, India). Single dose of 0.5 ml. Comparison: Unvaccinated	Recent antibiotic use
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RCT: randomised controlled trial; PCV7: heptavalent pneumococcal conjugate vaccine; HBV: Hepatitis B vaccine; PCV10: ten-valent pneumococcal conjugate vaccine; PHiD-CV10: ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine; PPSV23: pneumococcal polysaccharide vaccine

Table 2: Estimates of effect from individual RCTs on pneumococcal, influenza, or measles vaccines

Study ID	Population	Outcome	Outcome data		Estimate of effect (95% CI)	Certainty of the evidence (GRADE)
			Vaccine	Control		
Pneumococcal vaccines						
Jansen 2008(30)	Children aged 18 to 72 months	Number of antibiotic prescriptions during influenza season (events/person-days) [follow up: 18 or 6 months depending on year of inclusion]	68/67867 (197 children)	72/60515 (187 children)	Rate ratio 0.84 (0.60, 1.17)	⊕⊕⊕O MODERATE ¹ Pooled estimate Rate ratio 0.93 (0.87, 0.99)
Palmu 2014(31)	Children aged 6 weeks to 18 months	Number of antibiotic purchases (events/person-years) [follow up 14-21 months depending on time of inclusion]	63585/40423	34852/20427	Rate ratio 0.93 (0.87, 0.99)	
Fireman 2003(29)	Children aged 6.5 to 24 months	Number of antibiotic prescriptions [follow up 8-42 months depending on time of inclusion]	NR	NR	Vaccine reduced prescriptions by 5.7% (4.2, 7.2%)	⊕OOO VERY LOW ^{1,2}
Yilmaz 2013(32)	Adults with COPD	Number of antibiotic courses (events/person) [follow-up: 2 years]	11/116	11/28	Risk ratio 0.24 (0.12, 0.50)	⊕OOO VERY LOW ^{3,4}
Dagan 2001(33)	Children aged 12 to 35 months	Number of illness episodes resulting in antibiotic use (events/person-months) [follow-up: 2 years]	350/2797 (131 children)	405/2759 (130 children)	Rate ratio 0.85 (0.75, 0.96)	⊕⊕⊕O MODERATE ¹
Steentoft 2006(34)	Adults with COPD	Proportions of people receiving antibiotics (events/persons) [follow-up: 6 months]	29/37	9/12	Risk ratio 1.05 (0.72, 1.51)	⊕OOO VERY LOW ^{5,6}

van Gils 2009(35)	Infants aged <12 weeks	Proportions of people receiving antibiotics (events/persons) [follow-up: 24 months]	29/656	10/321	Risk ratio 1.42 (0.70, 2.88)	⊕○○○ VERY LOW ^{7,8}
Veenhoven 2003(36)	Children aged 1-7 years with previous acute otitis media	Days of ear-related antibiotic use [follow-up: 26 months]	(190 children)	(193 children)	Reported no significant difference	⊕○○○ VERY LOW ^{1,2}
Influenza vaccines						
Hoberman 2003(40)	Infants & children up to 24 months	Number of antibiotic courses or prescriptions (mean) [at 4 months]	1.91 ± 2.46 (513 children)	1.80 ± 2.11 (252 children)	Ratio of means 1.06 (0.88, 1.27)	⊕⊕○○ LOW ^{1,6}
Esposito 2003(38)	Children aged 6 months to 9 years	Number of antibiotic courses or prescriptions (mean) [at 4 months]	1.31 ± 1.33 (64 children)	2.35 ± 1.59 (63 children)	Ratio of means 0.56 (0.41, 0.75)	⊕⊕⊕○ MODERATE ¹ Pooled estimate Ratio of means 0.93 (0.87, 0.99)
Marchisio 2009(41)	Children aged 1 to 5 years	Number of antibiotic courses or prescriptions (mean) [at 6 months]	1.47 ± 1.26 (90 children)	2.59 ± 1.72 (90 children)	Ratio of means 0.57 (0.45, 0.71)	
Principi 2003(43)	Children aged 6 months to 5 years	Number of antibiotic courses or prescriptions (mean) [at 5 months]	1.36 ± 1.28 (202 children)	1.98 ± 1.59 (101 children)	Ratio of means 0.69 (0.56, 0.84)	
Clancy 2016(37)	Adults with COPD aged 40 to 85 years	Number of antibiotic courses or prescriptions (mean) [at 9 months]	2.3 ± 3.5 (160 persons)	2.1 ± 2.9 (160 persons)	Ratio of means 1.10 (0.80, 1.51)	⊕⊕○○ LOW ^{1,6} Pooled estimate Ratio of means 1.10 (0.80, 1.15)
Tandon 2010(44)	Adults with COPD aged 47 to 88 years	Number of antibiotic courses or prescriptions (mean) [at 2 years]	1.06 (18 persons)	2.4 (20 persons)	Not estimable	
Gao 2011(39)	Adults >60 years with chronic bronchitis	Courses of treatment of acute infection with antibiotics (mean) [at 1 year]	6.812 ± 1.364 (73 persons)	10.011 ± 2.111 (65 persons)	Ratio of means 0.68 (0.64, 0.73)	⊕⊕○○ LOW ^{1,4}

Pisu 2005(42)	Children aged 2 to 5 years randomised. Families observed.	Number of antibiotic courses or prescriptions (mean per household) [at 5 months]	0.9 ± 1.33 (75 households)	1.1 ± 3.181 (48 households)	Ratio of means 0.82 (0.34, 1.98)	⊕⊕○○ LOW ^{1,6}
Belshe 1998(46)	Children aged 15 to 71 months	Proportions of people receiving antibiotics (events/persons) [follow-up: 12 months]	310/1070	218/532	Risk ratio 0.71 (0.62, 0.81)	⊕○○○ VERY LOW ^{6,9,10} Pooled estimate Risk ratio 0.78 (0.58, 1.05)
Marchisio 2002(49)	Children aged 1 to 5 years	Proportions of people receiving antibiotics (events/persons) [follow-up: 6 months]	26/67	42/66	Risk ratio 0.61 (0.43, 0.87)	
Vesikari 2006(50)	Children aged 6 to <36 months	Proportions of people receiving antibiotics (events/persons) [follow-up: 12 months]	376/951	261/664	Risk ratio 1.01 (0.89, 1.14)	
Bridges 2000(47)	Adults aged 18-64 years	Proportions of people receiving antibiotics (events/persons) [follow-up: 12 months]	33/576	39/554	Risk ratio 0.81 (0.52, 1.27)	⊕⊕○○ LOW ^{1,6}
Loeb 2010(48, 52)	Children aged 3-15 years randomised. All ages observed.	Proportions of people receiving antibiotics (events/persons) [follow-up: 3 years]	213/5922	263/5063	Risk ratio 0.69 (0.58, 0.83)	⊕⊕⊕○ MODERATE ¹¹
Allsup 2003(45)	Adults aged 65 to 74 years	Proportions of people receiving antibiotics (events/persons) [follow-up: 6 months]	38/522	9/177	Risk ratio 1.43 (0.71, 2.90)	⊕○○○ VERY LOW ^{5,6}
Jansen 2008(30)	Children aged 18 to 72 months	Antibiotic prescriptions (rate per 1000 child days) during influenza seasons [follow up: 18 or 6 months depending on year of inclusion]	1.2 (0.8 to 1.9) (187 children)	1.4 (0.9 to 2.1) (195 children)	Incidence rate ratio 0.89 (0.50, 1.61)	⊕⊕○○ LOW ^{6,9}
Nichol 1999(51)	Adults aged 18 to 64 years	Number of days antibiotics for febrile illness/person-days [follow-up: 4 months]	525/2833	459/1420	Rate reduction 28.1% (16.6, 38.0)	⊕⊕⊕⊕ HIGH

Measles vaccine						
Hansen 2017(53)	Children aged < 5 months	Proportions reporting recent antibiotic use (events/persons) [at 9 months of age]	31/346	17/166	Risk ratio 0.87 (0.50, 1.53)	⊕○○○ VERY LOW ^{5,6}

RCT: randomised controlled trial; COPD: chronic obstructive pulmonary disease; CI: confidence interval; NR: not reported

¹ Downgraded one level for unclear risk of bias in several domains

² Downgraded two levels for reporting bias: no usable data reported

³ Downgraded two levels for unclear risk of bias in all domains

⁴ Downgraded one level for imprecision: low sample size

⁵ Downgraded two levels for unclear or high risk of bias in multiple domains

⁶ Downgraded one level for imprecision: crosses line of no effect

⁷ Downgraded one level for unclear or high risk of bias relating to blinding

⁸ Downgraded two levels for serious imprecision: wide confidence intervals, crosses line of no effect

⁹ Downgraded one level for unclear or high risk of bias in several domains

¹⁰ Downgraded two levels for serious statistical inconsistency

¹¹ Downgraded one level for potential reporting bias: retrospectively registered with no protocol; antibiotic data not reported in original study report

Figure 1: PRISMA study flow diagram

Figure 2: Risk of bias in included randomised controlled trials

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Allsup 2003	?	+	+	?	+	+	+
Belshe 1998	?	?	+	+	?	?	+
Bridges 2000	+	?	+	+	+	?	+
Clancy 2016	+	?	+	+	?	?	?
Dagan 2001	?	?	+	+	?	?	+
Esposito 2003	?	+	+	+	+	?	+
Fireman 2003	?	?	+	+	+	?	+
Gao 2011	?	?	?	?	?	?	+
Hansen 2017	?	?	+	+	+	?	?
Hoberman 2003	+	?	+	+	+	?	+
Jansen 2008	?	?	+	+	+	?	+
Loeb 2010	+	+	+	+	+	?	+
Marchisio 2002	?	?	+	+	+	?	?
Marchisio 2009	?	?	+	?	+	?	+
Nichol 1999	+	+	+	+	+	?	+
Palmu 2014	?	?	?	?	+	?	+
Pisu 2005	?	?	?	?	?	?	+
Principi 2003	?	?	?	?	?	?	?
Steentoft 2006	?	?	+	+	+	?	?
Tandon 2010	?	?	+	?	+	?	+
van Gils 2009	+	+	+	?	+	+	+
Veenhoven 2003	+	?	+	?	+	?	+
Vesikari 2006	?	+	+	+	+	?	+
Yilmaz 2013	?	?	?	?	?	?	?

Figure 3. Forest plot for effect of pneumococcal conjugate vaccine on number of antimicrobial purchases or prescriptions

Figure 4. Forest plots for influenza vaccines

4.1: Number of antibiotic courses or prescriptions [follow-up: 4 months to 2 years]

4.2: Proportions of people receiving antibiotics [follow up: 6 months to 3 years]