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Prevalence and Antimicrobial Resistance of Bacteria in Children With Acute Otitis Media and Ear Discharge

A Systematic Review

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Background: Of children with acute otitis media (AOM), 15%–20% present with acute onset ear discharge due to a spontaneous perforation of the tympanic membrane (AOMd). This review aims to quantify the prevalence and antimicrobial resistance (AMR) status of bacteria in children with AOMd in the pneumococcal conjugate vaccine (PCV) era.

Methods: Systematic searches were performed in PubMed, EMBASE and Cochrane Library from inception to June 7, 2019. Two reviewers extracted relevant data and assessed risk of bias independently. All English studies reporting any prevalence and/or AMR data of bacterial middle ear isolates from children with AOMd were included. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal checklist.

Results: Of 4088 unique records retrieved, 19 studies (10,560 children) were included. Overall quality was judged good. *Streptococcus pneumoniae* (median 26.1%, range 9.1%–47.9%), *Haemophilus influenzae* (median 18.8%, range 3.9%–55.3%), *Staphylococcus aureus* (median 12.3%, range 2.3%–34.9%) and *Streptococcus pyogenes* (median 11.8%, range 1.0%–30.9%) were the most prevalent bacteria. In 76.0% (median, range 48.7%–100.0%, 19 studies, 1,429 children) any bacterium was identified. AMR data were sparse and mainly limited to *S. pneumoniae*. We found no evidence of a clear shift in the prevalence of bacteria and AMR over time.

Conclusions: In children with AOMd, *S. pneumoniae* and *H. influenzae* are the 2 predominant bacteria, followed by *S. aureus* and *S. pyogenes* in the post-PCV era. AMR data are sparse and no clearly change over time was observed. Ongoing surveillance of the microbiology profile in children with AOMd is warranted to guide antibiotic selection and to assess the impact of children's PCV status.

Key Words: acute otitis media, ear discharge, otopathogens, antimicrobial resistance, review

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Acute otitis media (AOM) is one of the most common childhood infections and a leading cause of doctor consultations and antibiotic prescribing worldwide.[1,2] Around 15%–20% of children with AOM present with acute onset ear discharge due to a spontaneous perforation of the tympanic membrane (AOMd).[3,4] In contrast to widespread beliefs, children with AOMd have similar levels of ear pain and feel less well at presentation than those without ear discharge (AOMwd). Also, children with AOMd have a higher disease burden with higher rates of ear pain and/or fever at 3–7 days and more AOM recurrences and hearing problems at 3 months compared with children without ear discharge.[3,4] Antibiotics are more effective in children with AOMd than in those with AOMwd; number needed to treat to achieve resolution of ear pain and/or fever at days 3 to 7: 3 versus 8, respectively.[3] AOM guidelines therefore recommend clinicians to consider immediate antibiotic prescribing in children with AOMd,[5,6] in contrast to AOMwd, for which a watchful waiting approach is recommended for otherwise healthy children with nonsevere unilateral disease.[5,6]

It has been suggested that the differences in clinical picture and disease course between AOMwd and AOMd might be attributed to differences in causative pathogens. A 2016 systematic review including 38 published reports of microbiology of children with AOMwd found that *Streptococcus pneumoniae* (average detection rate of 27.8%), *Haemophilus influenzae* (23.1%) and *Moraxella catarrhalis* (7.0%) are the most common bacteria associated with AOMwd globally.[7] *Streptococcus pyogenes* is thought to be more prevalent in children with AOMd,[8–10] but data are conflicting.[9–11] The routine administration of pneumococcal conjugate vaccines (PCVs) during infancy has led to a change in childhood AOM epidemiology.[12–14] This review aims to provide an overview of the prevalence and antimicrobial resistance (AMR) of bacteria in children with AOMd in the post-PCV era.

MATERIAL AND METHODS

Our review protocol was published on PROSPERO (CRD42018100523).[15] The review was reported according to the most recent PRISMA statement.[16]

Primary Objective

To provide an up-to-date overview of the prevalence of bacteria and their AMR profile in children with AOMd in the post-PCV era.

Secondary Objectives

To explore, in children with AOMd, (1) whether the prevalence and AMR rates of bacteria varied over time; (2) PCV status of participating children impacted our results; and (3) how the definition of AMR as applied in the individual studies impacted our results.

Data Sources and Search Strategy

Systematic searches of PubMed, EMBASE and the Cochrane Library were performed from inception to June 7, 2019. A broad search strategy was designed using a combination of any key word relevant to "acute otitis media" and "antibiotic resistance or resistant bacteria or individual pathogens" as well as "acute otitis media" and "antibiotics," with database-specific syntaxes (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E354).

Patient and Public Involvement

Patients were not involved in the development or conduct of this review.

Study Selection

Two reviewers (S.H. and R.P.V.) independently screened titles and abstracts of unique records for eligibility using prespecified criteria. The same reviewers independently reviewed the full texts of potentially eligible papers. Any disagreements were resolved by discussion.

All studies reporting any prevalence or AMR data of bacterial middle ear isolates from children (0–16 years) with AOMd were included. Non-English studies, animal studies, studies conducted before the year 2000 (ie, before routine implementation of PCV in infancy), studies focusing on complicated AOM (>25% of sample consisting of otitis prone children, children with recurrent AOM, treatment failure or hospitalized children) and those from which the full text could not be retrieved were excluded. To extent the yield of relevant studies, the reference lists of included studies were reviewed to identify any additional articles.

Data Extraction and Quality Appraisal

Two review authors (S.H. and R.P.V.) independently extracted the following data from the included studies using a standardized data extraction form: year of conduction, study design, study population (country, age and the number of participants), prevalence and AMR data for the following bacterial isolates: *S. pneumoniae,* nontypeable *H. influenzae, M. catarrhalis, S. pyogenes*, *Staphylococcus aureus* and *Pseudomonas aeruginosa,* methods of sampling and antibiotic sensitivity testing and participants' PCV status.

AMR was primarily defined as nonsusceptibility to antibiotics (resistant and intermediate resistant strains combined).

Quality of included studies was assessed by 2 reviewers (S.H. and R.P.V.) independently using the Joanna Briggs Institute Critical Appraisal checklist.[17] Any disagreements were resolved by discussion.

Data Synthesis and Analysis

All statistical analysis were conducted with Rothman's Episheet.[18] In descriptive analysis, the prevalence (median and range) of bacterial middle ear isolates and their AMR rates to most commonly prescribed antibiotics for AOM (penicillin, amoxicillin, amoxicillin-clavulanic acid, trimethoprim/sulfamethoxazole, erythromycin, cephalosporin, quinolones and ampicillin). Forrest plots were used to summarize these findings. The total prevalence rates of individual bacteria were calculated by combining cultures where the bacterium was identified as a single isolate and those where the bacterium was identified together with other bacteria (mixed infection).

We assessed clinical and statistical heterogeneity across studies. When studies were sufficiently homogeneous, we aimed to calculate pooled prevalences as summary statistic.

In a sensitivity analysis, we excluded studies with <50 participants to assess the robustness of research findings. In a further sensitivity analysis, we restricted our AMR definition by analyzing resistance strains only (instead of combining resistant and intermediate resistant strains).

RESULTS

Search Results

The literature search yielded 7335 records. Removing duplicates left 4088 unique records. After title and abstract screening, 302 potentially relevant articles remained (Fig. 1). Of these, 285 were excluded for various reasons (Fig. 1), leaving 17 studies suitable for inclusion. A further 2 studies were retrieved from reviewing reference lists; these were not identified in our initial search strategy because the term "acute" was not mentioned in the titles and abstracts. This left 19 studies,[4,10,11,19–34] including 10,560 children (range 16–5580) suitable for inclusion in this review (Fig. 1).

Study Characteristics

Main study characteristics are presented in Table 1: 9 were conducted in Europe,[4,10,25,27–30,32,34] 7 in Asia,[19–21,23,24,26,33] 2 in South America[22,31] and 1 in North America.[11] The studies were conducted from 2000 to 2017 with 5 studies conducted after 2011. All studies were observational and most (74%) had a prospective cohort design. Three studies reported both culture and polymerase chain reaction (PCR) results,[19,32,34] while the remaining 16 studies reported culture results only. Seventeen studies used standard microbiologic techniques for isolation and identification, including the use of chocolate and blood agar, whereas methods were unclear in 2 studies.[4,31] The prevalence and AMR rates of bacteria could be extracted from 18 (95%) and 12 (63%) studies, respectively. Most studies (10/19) included only children who did not receive previous antibiotic treatment. In 7 studies, no information about antibiotic use was reported. In 1 study, 23% of the children received antibiotics in the previous month,[34] and in the remaining study, 12.4% of the children received antibiotics at the moment of swabbing.[28]

Eleven studies provided information about the PCV status of participants: 1 study reported prevaccination and postvaccination data[10] and in 2 studies children were not vaccinated,[23,27] whereas the PCV level of participants varied between 4.4% and 95% in 8 studies.[11,19,25,28–31,34]

Quality Appraisal

Overall quality of included studies was judged good (Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E355). However, data analysis was judged inadequate in 14 studies; in most of these studies, antimicrobial susceptibility was not reported for all isolates. Data reporting was unclear in 1 study.[26]

Prevalence of Bacteria

S. pneumoniae (median 26.1%, range 9.1%–47.9%; 18 studies, 2191 children), *H. influenzae* (median 18.8%, range 3.9%–55.3%; 17 studies, 2185 children) and *S. aureus* (median 12.3%, range 5.3%–34.9%; 13 studies, 592 children) were the 3 most prevalent bacteria, followed by *S. pyogenes* (median 11.8%, range 1.0%–30.9%; 16 studies, 1053 children) (Table 2). The prevalence of positive cultures (any bacterium identified) was 76% (median, range 48.7%–100%, 17 studies, 3643 children). Pooled prevalences were not calculated due to substantial heterogeneity across studies.

The prevalence of bacteria did not clearly change over time (Figure, Supplemental Digital Content 3, http://links.lww.com/INF/E356). Excluding the 3 studies with <50 participants revealed similar results as our main analysis. There was no clear evidence of a shift in pathogens when stratifying results according to PCV status (Figure, Supplemental Digital Content 4, http://links.lww.com/INF/E357).

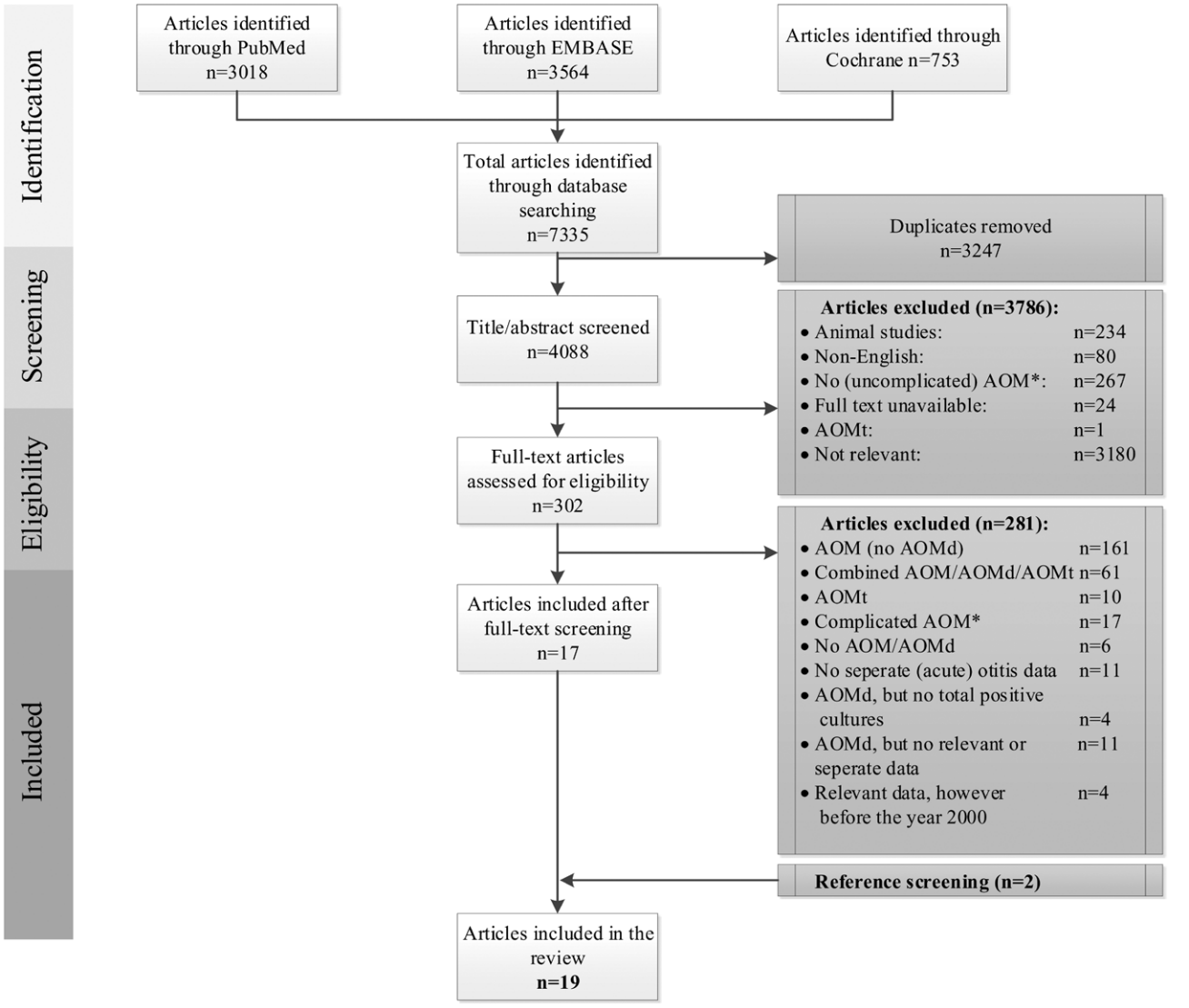

FIGURE 1. Flow chart included studies.

Antimicrobial Resistance

AMR data were mainly reported for *S. pneumoniae* with very limited data reported for the remaining bacteria (Table, Supplemental Digital Content 5, http://links.lww.com/INF/E358). Nonsusceptibility rates of *S. pneumoniae* to commonly used antibiotics varied widely between countries. Nonsusceptibility rates of pneumococcus to penicillin ranged from 0% to 65.8% (median 10.0%; 8 studies). Albeit being highly sensitive to quinolones (median nonsusceptibility rate 0.9%, range 0%–5.5%; median; 3 studies), nonsusceptibility rates to other antibiotics varied widely; amoxicillin: median 16.7% (range 0%–64.8%; 4 studies), trimethoprim/sulfamethoxazole: median 27.3% (range 0%–93.5%; 5 studies), erythromycin: median 36.5% (range 10.5%–99.1%; 6 studies) and cephalosporins: median 5.4% (range 0%–63.0%; 6 studies).

Nonsusceptibility rates of *S. pneumoniae* did not clearly change over time (Fig. 2). The limited data available did not permit us to assess the impact of children's PCV status on AMR.

When restricting the AMR definition to resistance strains only, antibiotic resistance rates of *S. pneumoniae* to the various antibiotics were considerably lower (Table, Supplemental Digital Content 6, http://links.lww.com/INF/E359).

DISCUSSION

This systematic review of studies conducted in the post-PCV era showed that, in children with AOMd, any bacterium is isolated in >3 quarter of middle ear fluid samples and that *S. pneumonia, H. influenzae, S. aureus* and *S. pyogenes* are the most prevalent bacteria.

A 2016 literature review found that *S. pneumoniae* (average detection rate: 27.8%) and *H. influenzae* (23.1%) are also the predominant bacteria in children with AOMwd globally[7]; *S. aureus* and *S. pyogenes* are, however, more common in AOMd than in AOMwd.[7,35,36] Also, a bacterium is more frequently isolated in children with AOMd than in those with AOMwd [any bacterium identified in 76% (range 48.7%–100%) versus 62% (range 25%–95%),[7]

TABLE 1. Study Characteristics of Included Studies

Study	Country	Design*	Year	Children (n)	Age (mo)	Pathogens†	Cultures (n)	Cultures Pos [n (%)]	Susceptibility†	Sample Method‡	Pathogen
Ubukata 2018	Japan	Prospective	2016–2017	318	0–180	1;2;3;4;6	318	258 (81%)	No data	Culture/PCR	Bacterium
Naziat 2018	Bangladesh	Prospective	2014–2015	981	0–168	1;2;3;4;5;6	891	452 (51%)	1;2	Culture	Bacterium
Ling Ding 2018	China	Retrospective	2013–2015	228	0–156	1;2;3;4;5;6	228	181 (79%)	4	Culture	Bacterium
Rosenblut 2017	Chile	Prospective	2009–2010	17	4–59	1;2;3;6	17	15 (88%)	No data	Culture	Bacterium
Cilveti 2017	Spain	Prospective	2011–2014	487	2–96	1;2;3;6	521	481 (92%)	1;2	Culture/PCR	Bacterium
Sonsuwan 2016	Thailand	Prospective	2007–2008	40	3–60	1;2;3;4;5;6	53	53 (100%)	1;4	Culture	Bacterium
Ding 2015	China	Prospective	2011–2013	229	0–216	1;2;3;4;6	229	159 (69%)	1	Culture	Bacterium
Linden 2015	Germany	Prospective	2008–2011	944	2–60	1;2;3;4;6	963	341 (35%)	No data	Culture	Bacterium
Lee 2014	Korea	Retrospective	2001–2010	215	0–192	1;4;5	215	156 (73%)	5	Culture	Bacterium
Setchanova 2013	Bulgaria	Retrospective	1994–2011§	168	0–168	1;2	n.a.¶	168	1;2	Culture	Bacterium
Rodrigues 2013	Portugal	Prospective	2010–2011	113	3–158	1;2;3;6	113	55 (49%)	No data	Culture	Bacterium
Marchisio 2013	Italy	Retrospective	2001–2011	458	0–72	1;2;3;4;6	705	487 (69%)	1;2;3;4;6	Culture	Bacterium
Grevers 2012	Germany	Prospective	2008–2010	76	3–60	1;2;6	76	36 (47%)	1;2	Culture	Bacterium
Stamboulidis 2011	Greece	Prospective	2000–2008	5580	0–168	1;2;3;6	5580	2409 (43%)	1	Culture	Bacterium
Sierra 2011	Colombia	Prospective	2008–2009	16	3–60	1;2;3	16	13 (81%)	No data	Culture	Bacterium
Neumark 2011	Sweden	Prospective	2007–2009	68	24–192	1;2;3;6	68	41 (60%)	No data	Culture/PCR	Bacterium
Junejo 2011	Pakistan	Prospective	2007–2009	484	0–180	1;2;4;5;6	484	307 (63%)	1;2;4;5;6	Culture	Bacterium
Smith 2010	UK	Prospective	2003–2006	38	6–120	1;2;4;5;6	38	22 (58%)	No data	Culture	Bacterium
Brook 2009	USA	Retrospective	1993–2006§	100	5–144	1;2;3;6	125	109 (87%)	1	Culture	Bacterium

*All studies were either cohort, cross-sectional or database studies.
†1, *Streptococcus pneumoniae*; 2, nontypeable *Haemophilus influenzae*; 3, *Moraxella catarrhalis*; 4, *Staphylococcus aureus*; 5, *Pseudomonas aeruginosa*; 6, *Streptococcus pyogenes*.
‡Culture results extracted.
§Setchanova reported separate data from 1994 to 2004 (n = 49) and 2006 to 2011 (n = 79). Brook reported separate data from 1993 to 1998 (n = 60) and 2001 to 2006 (n = 50). Only the data after 2000 are used in this review.
¶Only *S. pneumoniae* or *H. influenzae* positive strains were studied; prevalence data not available.

TABLE 2. Prevalence Rates of Otopathogens

	Samples *Streptococcus pneumoniae*				*Haemophilus influenzae*			*Moraxella catarrhalis*			*Staphylococcus aureus*			*Pseudomonas aeruginosa*			*Streptococcus pyogenes*			Any Bacterium		
Study	n	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Ubukata 2018*	318	71	22.3	18.0–27.2	176	55.3	49.8–60.7	4	1.3	0.4–3.0	17	5.3	3.2–8.3				13	4.1	2.3–6.7	258	81.1	76.5–85.2
Naziat 2018	891	164	18.4	16.0–21.1	187	21.0	18.4–23.8	4	0.4	0.1–1.1	83	9.3	7.5–11.4	38	4.3	3.1–5.7	9	1.0	0.5–1.8	452	50.7	47.4–54.0
Ling Ding 2018	228	83	36.4	30.3–42.8	9	3.9	1.9–7.1	1	0.4	0.0–2.1	37	16.2	11.9–21.4	10	4.4	2.2–7.7	4	1.8	0.6–4.2	181	79.4	73.8–84.3
Rosenblut 2017	17	5	29.4	11.7–53.7	8	47.1	24.8–70.3	1	5.9	0.3– 25.8							2	11.8	2.0– 33.7	15	88.2	66.3–98,0
Cilveti 2017	521	208	39.9	35.8–44.2	251	48.2	43.9–52.5				35	6.7	4.8–9.1				71	13.6	10.9–16.8	480	92.1	89.6–94.2
Sonsuwan 2016	53	5	9.4	4.7–25.6	19	35.8	23.8– 49.4	1	1.9	0.1– 9.0	14	26.4	15.9– 39.5	6	11.3	4.7– 22.1	3	5.7	1.5–14.6	53	100.0	94.5–100.0
Ding 2015	229	108	47.2	40.8–53.6	17	7.4	4.5– 11.4	1	0.4	0.0– 2.1	43	18.8	14.1–24.2				4	1.7	0.6– 4.2	159	69.4	63.2– 75.1
Linden 2015	963	88	9.1	7.4–11.1	63	6.5	5.1–8.2	8	0.8	0.3–1.6	97	10.1	8.3–12.1				113	11.7	9.8–13.9	819	85.0	82.7–87.2
Lee 2014	215	59	27.4	21.8–33.7							75†	34.9	28.8–41.4	9	4.2	2.1–7.5				156	72.6	66.3–78.2
Rodrigues 2013	113	28	24.8	17.5–33.3	11	9.7	5.2–16.3	15	13.3	7.9–20.5							17	15.0	9.3–22.5	55	48.7	39.5–57.9
Marchisio 2013	705	112	15.9	13.3–18.7	265	37.6	34.1–41.2	8	1.1	0.5–2.1	49	7.0	5.2–9.0				90	12.8	10.5–15.4	487	69.1	65.6–72.4
Grevers 2012	76	10	13.2	6.9–22.2	14	18.4	10.9–28.3	0	0.0	0.0–3.9	8	10.5	5.0–19.0	2	2.6	0.4–8.4	13	17.1	9.9–26.8	36	47.4	36.3–58.6
Stamboulidis 2011-2‡	1061	373	35.2	32.3–38.1	459	43.3	40.3–46.3	35	3.3	2.3–4.5							328	30.9	28.2–33.7			
Stamboulidis 2011-1‡	1548	741	47.9	45.4–50.4	650	42.0	39.5–44.5	67	4.3	3.4–5.4							342	22.1	20.1–24.2			
Sierra 2011	16	7	43.8	21.5–68.0	5	31.30	12.4–56.3													13	81.3	57.0–95.0
Neumark 2011§	68	12	17.6	9.9–28.1	5	7.4	2.7–15.5	6	8.8	3.7–17.4							6	8.8	3.7–17.4	41	60.3	48.3–71.4
Junejo 2011	484	63	13.0	10.2–16.2	22	4.50	2.9–6.7				114	23.6	19.9–27.5	7	1.40	0.6–2.8	19	3.9	2.5–6.0	307	63.4	59.1–67.6
Smith 2010	38	5	13.2	5.0–26.8	3	7.9	2.0–20.0				7	18.4	8.4–33.1	2	5.3	0.9–16.3	7	18.4	8.4–33.1	22	57.9	41.9–72.7
Brook 2009‡	64	22	34.4	23.5–46.6	12	18.8	10.6–29.7	6	9.4	3.9–18.5	9‡	14.1	7.1–24.2				5	7.8	2.9–16.5	58	90.6	81.5–96.1

*Rates consist of samples positive for both PCR and culture.
†The separate MRSA and MSSA data are combined.
‡Data conduction: Stamboulidis 2011-1: 2000–2003; Stamboulidis 2011-2: 2005–2008; Brook 2009: 2001–2006.
§Combined PCR and culture data.

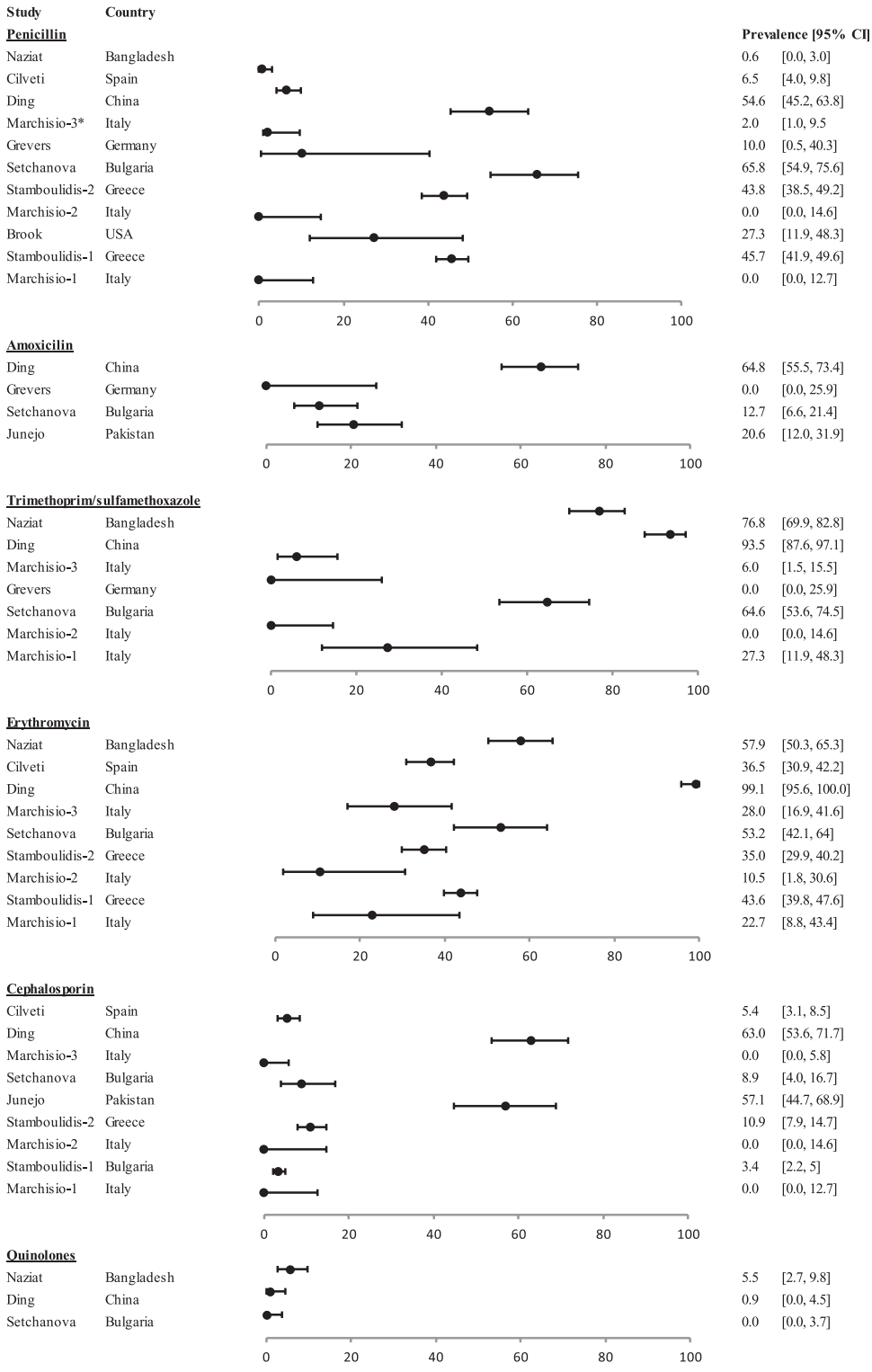

FIGURE 2. Prevalence rates of *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus* and no bacterium according to year.

respectively]. These findings add to the growing body of evidence that AOMwd and AOMd might be regarded as different parts of the spectrum of the AOM disease entity.

Theoretically, prevalences of bacteria isolated in AOMd and AOMwd may differ due to the sampling technique; the middle ear fluid from children with AOMd is obtained from visible

ear discharge in the external ear canal and may be contaminated with commensal bacteria. In AOMwd, tympanocentesis is required to obtain a middle ear fluid sample from children, with this procedure contamination with commensal bacteria is less likely. With *S. aureus* being a common component of the microbiota in the ear canal, one may argue that this leads to an overestimation of this bacterium in AOMd. There is, however, increasing evidence that *S. aureus* should be regarded as an important upper respiratory tract pathogen originating from the nasopharyngeal niche.[37,38] This is further substantiated by a recent study in children with ventilation tubes who developed acute ear discharge; it found a high correlation between the abundances of *S. aureus* in nasopharynx and otorrhea samples.[39,40]

In our study, nonsusceptibility rates of *S. pneumoniae* to penicillin in AOMd varied between 0% and 65.8% (median 10.0%). A pooled analysis including 10 studies of children with AOMwd showed an average nonsusceptibility rate of 18.5%.[36] We found no clear evidence of a shift in AMR over time in AOMd which is in agreement with a recent review of studies involving children with AOMwd,[35] but the small sample means inferences must be cautious. Besides that, AMR data should be interpreted in the context of PCV status, availability and adherence to local AOM guidelines and general antibiotic since this may substantially impact AMR.

To our knowledge, we are the first to systematically synthesize prevalences of bacteria and their AMR profile in children with AOMd. To capture only data relevant to our study population of interest, that is, children with AOMd, and to avoid contamination with chronic suppurative otitis media cases, we excluded all studies that did not provide data for children with AOMd only or in which the diagnosis was not explicitly described. We prospectively registered our study protocol.[15] While conducting this review, we broadened the scope of our review by also including data on the prevalence of bacteria in children with AOMd. Because we designed very broad literature search syntaxes—including the names of the individual bacteria of interest—and reviewed all reference lists of relevant studies, we consider it unlikely that we missed any relevant data.

Some important limitations deserve further attention. First, while large numbers of studies have been published on the prevalence of bacteria in children with AOMwd,[7,41] relatively few studies have focused on children with AOMd. Large differences between studies (eg, number of participants, design, country and setting of conduct) resulted in substantial clinical and statistical heterogeneity across studies which did not allow us to calculate summary statistics. Second, most studies relied on conventional culture to identify bacteria. This has likely resulted in an underestimation of the prevalence rate of bacteria because PCR techniques are more accurate than culture in detection of bacteria in middle ear fluid.[7,36,42] Third, the absence of evidence of a shift in microbiology profiles over time in our review should be interpreted in the context of the limited available information on children's PCV status and the few data of recent years. Previous studies of childhood AOMwd showed that the introduction of more-valent PCVs has led to a shift in otopathogens from vaccine-type pneumococci to nonvaccine-type pneumococci and other otopathogens including nontypeable *H. Influenza* and *S. aureus* and impacted AMR patterns.[12–14,43] However, the data from included studies in this review are too limited to draw any meaningful conclusion regarding the shift of bacteria from the early post-PCV to the late post-PCV years. Fourth, this review did not focus on viruses. Virus alone can cause AOM (around 5% of middle ear fluid samples of children with AOMwd contain only viruses)[44] and evidence is accumulating that the interplay between viruses and bacteria in the upper respiratory tract may play an important role.[45] In our sample of studies, no one did report data on viruses. Future studies should focus on the interplay between viruses and bacteria during upper respiratory tract infections and the progression to AOM to initiate new (preventive) interventions.

Finally, we excluded children with complicated AOM, including those with treatment failure, from our analysis to maximize generalizability of our review findings to children with AOMd presenting to primary care and limit the potential impact of previous antibiotic exposure to the microbiology profile as much as possible. As a consequence, we were unable to link the microbiology data to the risk of severe intracranial or extracranial suppurative complications and/or hospitalizations. Future research is needed to bridge this knowledge gap.

CONCLUSION

In children with AOMd *S. pneumoniae* and *H. influenzae* are the 2 predominant bacteria, followed by *S. aureus* and *S. pyogenes*, in the post-PCV era. Antimicrobial resistance data were sparse and mainly limited to *S. pneumoniae*. No clear change over time was observed. The limited data available did not permit us to assess the impact of children's PCV status, and therefore ongoing surveillance of the microbiology profile is warranted.

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