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REVIEW

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Epidemiology of community-acquired pneumonia and implications for vaccination of children living in developing and newly industrialized countries: A systematic literature review

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ABSTRACT

This systematic review evaluated the epidemiology of community-acquired pneumonia in children <6 y of age within 90 developing and newly industrialized countries. Literature searches (1990–2011), based on MEDLINE, EMBASE, Cochrane, CAB Global Health, WHO, UNICEF, country-specific websites, conferences, health-technology-assessment agencies, and the reference lists of included studies, yielded 8,734 records; 62 of 340 studies were included in this review. The highest incidence rate among included studies was 0.51 episodes/child-year, for children <5 y of age in Bangladesh. The highest prevalence was in Chinese children <6 months of age (37.88%). The main bacterial pathogens were *Streptococcus pneumoniae, Haemophilus influenzae* and *Mycoplasma pneumoniae* and the main viral pathogens were respiratory syncytial virus, adenovirus and rhinovirus. Community-acquired pneumonia remains associated with high rates of morbidity and mortality. Improved and efficient surveillance and documentation of the epidemiology and burden of community-acquired pneumonia across various geographical regions is warranted.

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Introduction

Annually, approximately 120–156 million cases of acute lower respiratory infections (ALRI) occur globally, with approximately 1.4 million resulting in death.[1-4] Of these, pneumonia kills an estimated 1 million children under the age of 5 every year and accounts for 15% of deaths in children <5 y of age,[5] with 90–95% of these deaths occurring in the developing world.[2-11] The majority (~2 thirds) of pneumonia episodes in children <5 y of age occurs in just 15 countries, with South Asia and Sub-Saharan Africa collectively enduring the largest burden of more than half the worldwide total cases of pneumonia in children.[1,12] Risk factors for community-acquired pneumonia (CAP) include age (<1 year), malnutrition, prematurity, immunosuppression, overcrowding, passive tobacco exposure, indoor fuel exposure, inadequate housing, overcrowding and the winter season.[10,13] The burden of disease has been worsened by the human immunodeficiency virus (HIV) epidemic.[14] Other co-existing illnesses, like malaria and diarrhea, are also important contributing factors to the increased CAP burden of disease in African and South Asian settings.[3,15,16]

The primary cause of CAP is usually bacterial, but isolating bacteria does not necessarily establish causation since the validity of the results might vary depending on the collected body fluid sample, and viral causes also exist.[17,18] *Streptococcus pneumoniae* is the main bacteriological causative pathogen of childhood pneumonia followed by *Haemophilus influenzae, Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. The most common pneumococcal serotypes include 1, 5, 6A, 6B, 14, 19F and 23F, which account for between 58% to 66% of invasive pneumococcal disease (IPD) in Africa and Asia, respectively.[19] Serotype 14 is the most common cause of IPD across the regions of Africa, Asia, Europe, Oceania, Latin America and the Caribbean, and North America.[19]

In general, there is a paucity of data on the epidemiology of CAP[1,2,11,20-22] in the developing and newly industrialised countries, as defined by the United Nations (UN);[23] one systematic review was published on the epidemiology of CAP in children across Latin America and the Caribbean.[24]

To further investigate the burden of CAP disease, we conducted a systematic literature review on the epidemiology of bacterial and viral pneumonia in children <6 y of age in 90 countries from the following regions: Africa, India and South Asia, Middle East, China, and Russia and CIS (Commonwealth of Independent States). More specifically,

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the review incorporates literature on the incidence and seasonality of CAP; the distribution of causative pathogens; antimicrobial resistance; country-specific CAP treatment guidelines; and country-specific vaccination recommendations. In addition, this review identifies gaps in the epidemiological data and research evidence and aims to consolidate all available data from these regions. To the best of our knowledge, no previous systematic review including these specific regions was previously published. The current review is relevant for decision makers when considering vaccine introduction in their countries, and also for the public health authorities interested to monitor childhood CAP over time.

Results

A total of 8,734 records were retrieved from the comprehensive search criteria, of which 62 studies reporting on the epidemiology of CAP were included for this review (Fig. 1). The included studies covered incidence, prevalence, mortality, distribution of pathogens and antimicrobial resistance. Publication dates ranged from 1990 to October 2011 and reported data for locations in Africa, India and South Asia, China, Middle East, and Russia and CIS.[25-86] Study designs included randomized controlled trials (RCTs; n = 7), cross-sectional (n = 51), case-series (n = 3) and case-control (n = 1) studies. The majority of studies (81%; 50/62) were of children <6 y of age with a diagnosis of CAP and covered geographical

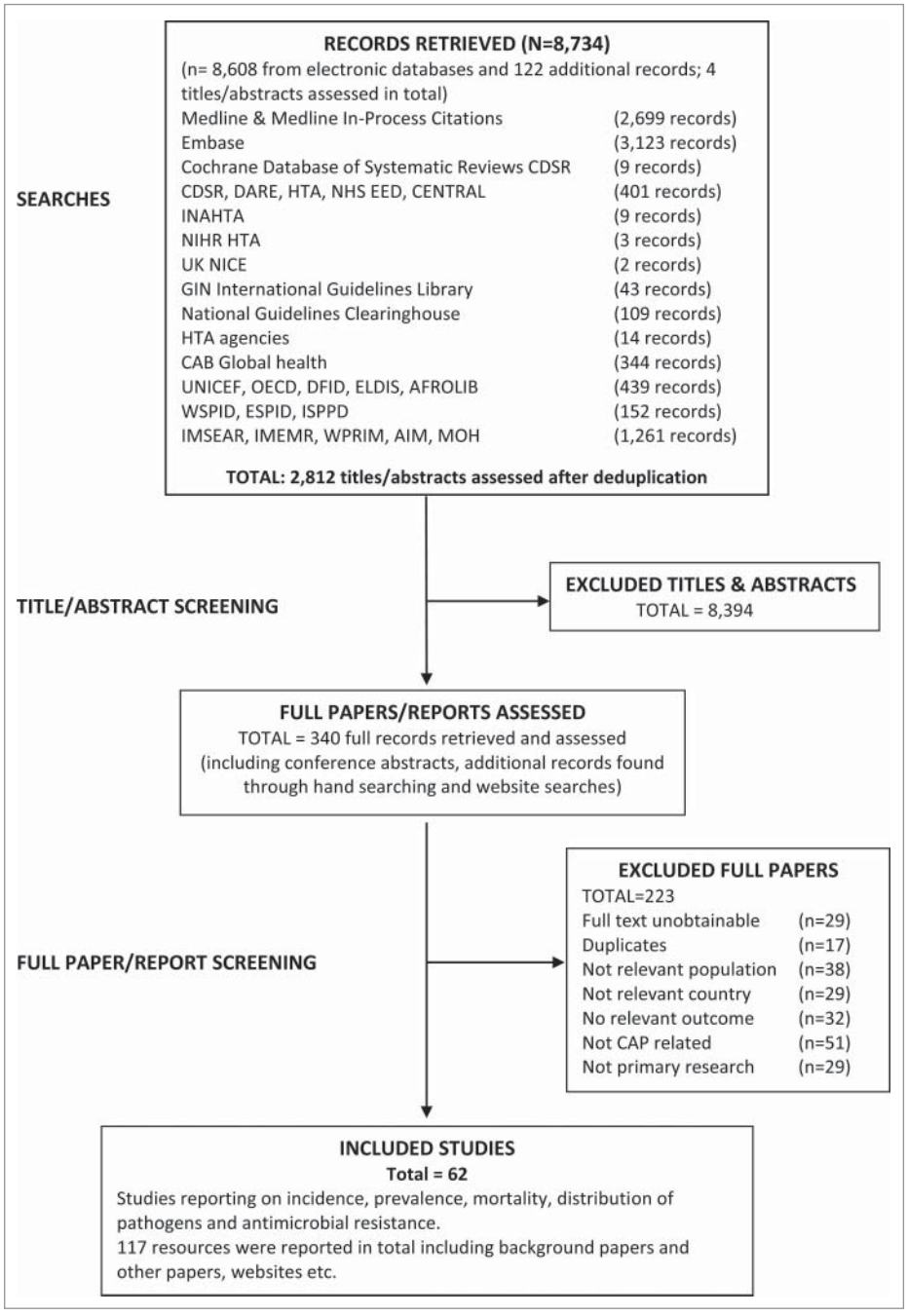

Figure 1. Flow of studies retrieved through electronic database searches

regions of Africa (n = 20); India and South Asia (n = 14); China (n = 13); and Middle East (n = 3). However, data for this age group were lacking for Russia and CIS. In order to identify further potentially relevant data, 12 studies of children <18 y of age (but including children <6 years) were also included; these studies covered Africa (n = 3), India and South Asia (n = 1), China (n = 3), Middle East (n = 3), and Russia and CIS (n = 2). The incidence, prevalence and mortality were reported by age, CAP severity, pathogen, presence of risk factors, and by season.

The majority of studies, including those of children >6 y of age, used the CAP definition as recommended by the WHO guidelines.[87]

Incidence

Data on the incidence of CAP were reported in 14 studies[25-38] (11 cross-sectional studies and 3 RCTs[30,31,36]), covering various

Table 1. Summary of included studies reporting on overall incidence and, by age, CAP severity, concomitant disease and seasonal variations.

Country (Study design)	N*	Age group	IR by age group / 1000 child-years	Overall IR / 1000 child-years	Season variation / 1000 child-years	Source
Mozambique (CS)	5,132	<3 m	61.0[a]	50.2[a]	NR	[25]
		3–12 m	59.4[a]			
		1–2 y	39.8[a]			
		<3 m	18.0[b]	19.1[b]		
		3–12 m	25.1[b]			
		1–2 y	14.7[b]			
Mali (CS)	44	0–11 m	0.33	NR	NR	[26]
		1–4 y	0.10			
Mali (CS)	289	0–11 m	9.98[c]	NR	NR	[27]
		1–4 y	1.61[c]			
		5–15 y	0.23[c]			
Kenya (CS)	1,078	<5 y	NR	6.98	Dec, 2.53 Jul, 11.75	[28]
Mozambique (CS)	2,951	<5 y	NR	133.5[d]	NR	[29]
Gambia (RCT)	42,848	2–5 m	0.97	1.29	NR	[30]
		6–11 m	1.62			
		12–17 m	1.46			
		18–23 m	1.20			
		24–29 m	0.78			
		30–35 m	0.94			
Gambia (RCT)	17,400	<6 m	3.15[e]	2.84[e]	Mar–Jun, 2.17	[31]
		6–11 m	2.93[e]		Jul–Nov, 4.21	
		12–17 m	3.48[e]		Dec–Feb, 1.71	
		18–23 m	2.66[e]			
		24–29 m	1.85[e]			
		<6 m	3.11[f]	2.95[f]	Mar–Jun, 2.40	
		6–11 m	3.09[f]		Jul–Nov, 4.24	
		12–17 m	3.61[f]		Dec–Feb, 1.70	
		18–23 m	2.77[f]			
		24–29 m	1.85[f]			
Bangladesh (CS)	6,167	<5 y	NR	1.07	NR	[32]
Bangladesh (CS)	12,062	<5 y	NR	511[d]	NR	[33]
India (CS)	2,118	<5 y	NR	NR	Annual, 96 Mar–Jun, 141 Jul–Sep, 117 Oct–Feb, 16	[34]
Bangladesh (CS)	977	1–11 m	650[d]	310[d]	NR	[35]
		12–23 m	482[d]			
		24–35 m	246[d]			
		36–47 m	140[d]			
		48–59 m	88[d]			
India (RCT)	17,951[g]	1–5 m	71.7 to 160.8	27.2 to 78.9	NR	[36]
		6–11 m	25.6 to 87.8			
		12–23 m	9.4 to 47.7			
China (CS)	554	<6 y	NR	NR	Mar–Jun; HRV-C detected, HRV-A ND. Jul–Nov; HRV-B detected. Jul–Sep; HRV-C ND.	[37]
Hong Kong (CS)	18,315	0–5 y	NR	19.4[d]	NR	[38]

*This is the number of CAP subjects within the study and NOT the total study sample size [a]severe clinical pneumonia; [b]radiologically confirmed pneumonia [c]rates are inclusive of children with ALRI and pneumonia [d]hospitalized children [e]vaccinated children (PCV-9) [f]unvaccinated children [g]data from 3 villages. CAP, community-acquired pneumonia; IR, incidence rate; CS, Cross-sectional study, RCT, Randomized controlled trial; NR, Not reported; HRV, Human rhinovirus; ND, not detected; m, month; y, year.

regions in Africa (n = 7),[25-31] India and South Asia (n = 5),[32-36] and China (n = 2)[37,38] (Table 1). Data from Middle East, Russia and CIS were non-existent. The 3 RCTs had a low risk of bias (based on Downs and Black's checklist),[88] with sample sizes ranging from 17,400 to 42,848. In contrast, most cross sectional studies had a high risk of bias with sample sizes ranging from 1,078 to 8,198. Therefore, the generalizability of results from cross-sectional studies is rather limited compared to that of RCTs.

Africa

Reported overall incidence rates ranged from 1.91 to 698 per 100,000 child-years in the 7 included studies.[25-31] Due to the high prevalence of reported cases in children <5 years, age is considered the most important risk factor for CAP. The highest incidence rate when assessed by age was reported in Kenyan infants <1 y of age (1,370/100,000 child-years).[30] The highest incidence rate of CAP assessed by season was reported at 1,175 per 100,000 child-years during the month of July in Kenya.[28]

India and South Asia

Overall incidence rates ranged from 31 to 50,526 per 100,000 child-years.[32-36] The highest incidence rate for this review was reported at 51 pneumonia episodes per 100 child-years in children <5 y of age from Bangladesh.[32] Children <11 months of age endured the highest burden of CAP at 65/100 child-years.[35] The highest incidence rate of CAP by season was reported during the months of March to June (summer season) at 14.1/100 child-years in Indian pre-schoolers.[34]

China

Only 2 studies from China reported on incidence rates of CAP.[37,38] The highest overall incidence rate was reported at 206.2/100,000 child-years in children <5 y of age from Hong Kong.[38]

Prevalence

Twenty-one studies in total reported data on the prevalence of CAP (Table 2 and Supplementary Table 1). Eighteen studies were of children <6 y of age covering geographical regions of Africa (n = 6),[26,29,39-42] China (n = 4),[37,43-45] India and South Asia (n = 5),[35,46-49] and Middle East (n = 3).[50-52] In addition, 3 studies from Africa (n = 1),[53] India and South Asia (n = 1)[54] and Russia and CIS (n = 1)[55] were of children <18 y of age (including children <6 years). The majority of these studies (86%; 18/21) were cross-sectional, except for 2 case-series[39,40] and one case-control.[44] The sample sizes were generally small, with the highest reported at 4,155. All of the studies had a high risk of bias (based on Downs and Black's checklist).[88] The majority of studies were hospital-based, making it difficult to generalize findings to the general population.

Africa

No data were found for the overall prevalence of CAP in Africa. However, data were found for prevalence related to age, malnutrition, CAP severity, and pathogen. A study from Uganda on the prevalence of CAP by severity suggested that children with severe pneumonia had a higher prevalence rate (83%; 117/140) compared to children with very severe pneumonia (16%; 23/140).[39] The most prevalent pathogen in studies with neonates was *Klebsiella pneumoniae* at 22%.[40] In children aged between 3 months and 5 y of age, *S. pneumoniae* was reported as the main causative agent for CAP.[41] The most prevalent viral pathogens were reported by several studies and included adenovirus (ADV), rhinovirus (RV) and respiratory syncytial virus (RSV).[29,41,42] The most prevalent viral pathogens during the rainy season were RV (56%), ADV (60%) and RSV (63%) and viral co-infections at 71%.[29] *S. pneumoniae* was the most prevalent pathogen in Gabon, reported at 35% (35/99) in children with a median age of 21 months (interquartile range 11–49 months).[53]

India and South Asia

A study by Naheed (2009) from Bangladesh reported on the prevalence of pathogens in CAP by age.[46] The results showed that 4% (161/4,155) of the specimens obtained from children aged 2–59 months were either *S. pneumoniae* (6%; 10/161) or *H. influenzae* type b (Hib) (3%; 5/161). The prevalence rate in children aged 2–11 months was reported at 4% (5/116) and 3% (4/116) for *S. pneumoniae* and Hib, respectively. Additionally, a prevalence rate of 11% (5/45) for *S. pneumoniae* and 2% (1/45) for Hib was reported among children with CAP aged 12–59 months.[46]

China

A study by Zhao et al.[43] reported on the prevalence of *S. pneumoniae* by age. The prevalence rate of *S. pneumoniae* was reported at 8.9% (90/1,011). By age, the prevalence rate of *S. pneumoniae* in CAP was between 5.7% (22/383) in children <6 months of age and 14.3% (5/35) in children aged 48–60 months.[43] Bacterial pathogens were more prevalent than viral pathogens, although mixed viral and bacterial pathogens were often reported.[45]

Middle East

Overall prevalence data were non-existent. The highest prevalence of CAP by age was reported at 66.3% (65/98) in children aged between 29 d and 12 months from Iran.[50] Somer et al.[52] reported that out of a sample of 140 children with CAP aged between 2 months to 15 years, 27% (38/140) were infected with *M. pneumoniae* and 5% (7/140) with *C. pneumoniae*.

Mortality

Data on mortality were reported by 12 studies from Africa (n = 7)[26-29,56-58] and India and South Asia (n = 5)[36,46,59-61] (Supplementary Table 2). Where available, data were reported according to age, CAP severity, concomitant disease and season and these data have been highlighted; however in many cases this level of detail was not available. All of the studies used a cross-sectional design with the exception of one RCT.[36] The studies consisted of very small sample sizes and had a high risk

Table 2. Summary of included studies reporting on prevalence by age, CAP severity, concomitant disease and seasonal variations.

Country (Study design)	N*	Age group	Prevalence by age group (%)	Prevalence by pathogen n (%)	Prevalence by concomitant disease, n (%)	Seasonal variation	Source
Uganda (CS)	140	2–59 m	NR	Unclear causative pathogen	HIV; 30 (21%)	NR	[39]
South Africa (CS)	23	2 w – 5 y	NR	*K. pneumoniae; 5 (22%)* RSV, 7 (30%)	HIV; 2 (9%)	NR	[40]
Gambia (CS)	278	3 m – 5 y	NR		Malnutrition	NR	[41]
				S. pneumoniae	11		
				Hib	3		
				Salmonella spp.	4		
				influenza A virus	8		
				influenza B virus	2		
				ADV	27		
				PIV	10		
				RSV	9		
Nigeria (CS)	323	2 w – 5 y	NR	RSV	28 (30%)	NR	[42]
				PIV	18 (19%)		
				influenza A virus	16 (17%)		
				S. pneumoniae	3 (1%)		
Mozambique (CS)	394	<5 y	NR		HIV	Rainy season	[29]
				RV	26 (30%)	76 (56%)	
				ADV	9 (24%)	34 (60%)	
				RSV	3 (10%)	24 (63%)	
				hMPv	7 (33%)	15 (52%)	
				Flu	4 (25%)	24 (86%)	
				PIV	3 (19%)	15 (75%)	
				EV	1 (14%)	9 (90%)	
				Co-infections		55 (71%)	
Mali (CS)	44	<4 y	NR	Pneumococcal pathogens	NR	Dry 34.1% Wet 43.1% Cool 22.7%	[26]
China (CS)	1,011	<6 m	37.88%	*S. pneumoniae*; 8.9%	NR	NR	[43]
		6–12 m	22.16%				
		12–24 m	17.90%				
		24–36 m	9.89%				
		36–48 m	8.70%				
		48–60 m	3.46%				
China (CC)	85	2–60 m	NR	*M. pneumoniae*; 6 (7.1%) *C. pneumoniae*; 3 (3.5%)	NR	NR	[44]
China (CS)	554	<6 y	NR	HRV-A; 51 (9%) HRV-B; 10 (2%) HRV-C; 38 (7%)	NR	NR	[37]
China (CS)	821	<1 y	NR	Viral; 353 (43%)	NR	NR	[45]
		1–3 y		Bacterial; 228 (27%)			
		3–5 y		Mixed viral and bacterial; 107 (13%)			
		>5 y		Mixed viral; 1% Mixed bacterial; 1%			
Bangladesh (CS)	4,155	2–11 m	NR	*S. pneumoniae*; 5 (4%) Hib; *4 (3%)*	NR	NR	[46]
		12–59 m		*S. pneumoniae*; 5 (11%) Hib; 1 (2%)			
Bangladesh (CS)	977	<5 y	NR	*S. pneumoniae*; 12	NR	NR	[35]
India (CS)	243	1–59 m	NR	*M. pneumoniae*; 24 (10%)	NR	NR	[47]
India, Nepal and Sri Lanka (CS)	1,468	2 m–5 y	NR	*S. pneumoniae*; 9 (0.6%) *H. influenzae*; 7 (0.5%)	NR	NR	[48]
India (CS)	93	<12 y	NR	Unclear	NR	NR	[49]
Iran (CS)	97	0–28 d	4 (4%)	NR	NR	NR	[50]
		29 d–12 m	65 (66.3%)				
		1–4 y	24 (24.5%)				
		4–9 y	4 (1%)				
United Arab Emirates (CS)	635	<5 y	NR	NR	NR	NR	[51]
Turkey (CS)	45	<8 y	NR	*M. pneumoniae*; 38 *C. pneumoniae*; 7	NR	NR	[52]

*This is the number of CAP subjects within the study and NOT the total study sample size.
[a]159 malnourished children.
CAP, community-acquired pneumonia; n (%), number (percentage); CC, Case-control study; CS, Cross-sectional study, RCT, Randomized controlled trial; NR, Not reported; RV, rhinovirus; ADV, adenovirus; RSV, respiratory syncytial virus; hMPV, human metapneumovirus; Flu, influenza virus; PIV, parainfluenza virus; EV, enterovirus; HIV, human immunodeficiency virus; Hib, *H. influenzae* type b; HRV, human rhinovirus; w, week; m, month; y, year.

of bias (ranging between 3 and 13 items on the Downs and Black's checklist). No data were found for China, Middle East, Russia and CIS.

Africa

Tornheim et al.[28] reported the overall mortality rate of CAP at 65/100,000 person-years for children <5 y of age, and 24/100,000 person-years for children >5 y of age in Kenya. The overall mortality rates ranged from 8% to 15.3%, respectively.[29,56] The highest overall mortality rates were from studies of children with either HIV, severe malnutrition, unvaccinated and very severe pneumonia.[26,29,56] The differences in CAP mortality according to season were reported by only 1 study, which included Kenyan children living in various slums across Nairobi.[58] The reported mortality rates varied across the year. The highest mortality rate was reported during the month of June at 60.1/100,000 person years and the lowest was reported in the month of November at 16.4/100,000 person years. Thereafter, a steady rise in mortality was reported from December to March.[58]

India and South Asia

Naheed et al.[46] reported on the mortality rates in Indian children aged <5 y of age. The mortality rates were reported by age, CAP severity and malnutrition. The results showed that children <12 months of age had a mortality rate of 4% (123/2,897), while the rate for those aged 12–59 months was 2% (27/1,258).[46] One study reported on mortality rates across 3 villages in India.[36] The overall mortality rates ranged from 0.89% to 3.32% for children with severe pneumonia and from 0.77% to 2.35% for children with pneumonia.[36]

Distribution of viral and bacterial pathogens

Twenty-two studies in total reported on the distribution of pathogens (Table 3 and Supplementary Table 3). The studies covered geographical regions of Africa (n = 3),[29,41,62] India and South Asia (n = 2),[48,59] and China (n = 8).[37,43,45,63-67] Nine studies from Middle East (n = 3),[68-70] Russia and CIS (n = 1),[71] Africa (n = 2),[72,73] and China (n = 3)[74-76] included children of various age groups.

Africa

Adegbola et al.[41] reported data on 159 malnourished children with pneumonia. The most common pathogens were *S. pneumoniae* (6.9%; 11/159), followed by *H. influenzae* (3.7%; 6/159) and *Salmonella* spp (2.5%; 4/159); however the total number of isolates were not clearly reported. The results were consistent with the data on 119 well-nourished children with pneumonia, where *S. pneumoniae* was identified in 26.1% (31/119) of children; *H. influenzae* in 6.7% (8/119); *Staphylococcus aureus* in 2.5% (3/119) and *Salmonella* spp in only one child. The distribution of viral pathogens was reported by only one study of children ≤60 months of age from Mozambique.[29] The study reported that the highest number of patients infected with the viral pathogens were children aged 3–12 months and 12–60 months. Around 50% (67/135) of the RV isolates were obtained from children aged 3–12 months, and 40% (54/135) from children aged 12–60 months; 30% (26/135) were from children with HIV. Additionally, 57 ADV isolates were obtained, of which 77% (44/57) were detected in children between the ages of 12–60 months and 21% (12/57) in children aged between 3–12 months; 24% (9/57) of the ADV isolates were found in children with HIV.

India and South Asia

A study by Rahman et al.[59] of children <5 y from Bangladesh identified *H. influenzae* as the dominant pathogen accounting for 60% (15/25) of the total isolates from invasive diseases. The non typeable *Haemophilus influenzae* (NTHi) isolates accounted for 24% (6/25). A sentinel study from Sri Lanka in children aged 2 months to 5 y identified *S. pneumoniae* as the dominant pathogen (0.6%; 9/1,468 children) followed by *H. influenzae* (0.5%; 7/1,468 children). However, other species (not reported by study) were reported in 11% (161/1468 children) of the children with pneumonia.[48]

China

A study by Yao et al.[64] reported on the most common serotypes of *S. pneumoniae*. The data showed that serotypes 19F accounted for 56% (188/338), followed by 19A at 14% (47/338), 23F at 10% (34/338), 6B at 5%(16/338), and 14 at 4% (12/338) of the causative serotype for CAP. In children aged between 1–60 months, *K. pneumoniae* was the most dominant pathogen accounting for 22.3% (170/761), followed by *Escherichia coli* at 17.1% (130/761), *S. pneumoniae* at 11.7% (89/761), *S. aureus* at 8.3% (63/761), and *H. influenzae* and *Haemophilus parainfluenzae* at 7.9% (60/761) collectively.[66] Additionally, human RV species C (HRV-C) was detected in children <6 months of age at 7.32 % (18/246) and at 9.9% (8/81) of the 6–12 months old. Human RV species B (HRV-B) was only detected in children <6 y of age and those aged 12–24 months, at 2.03% (5/246), and 5.9% (2/34), respectively.[37] A similar study of children with CAP from China reported *S. pneumoniae* serotypes of 19F, 23F, 6B and 4 to be the most dominant in children aged <5 y.[43] The results indicated that 19F accounted for 62% (56/90), 23F for 16% (14/90), 6B for 10% (9/90) and 4 for 7% (6/90). In neonates (<28 days of age), the most frequently detected pathogen out of 425 isolates was *E. coli* (27%; 115/425 isolates), followed by *K. pneumoniae* (18%; 77/425 isolates) and *H. influenzae* (7%; 31/425 isolates).[63] No data on the seasonal distribution of pathogens across all geographical regions were reported.

Antimicrobial resistance

In total, 9 studies reported data on antimicrobial resistance among bacterial pathogens causing CAP (Supplementary Table 4). The studies covered regions from China (n = 4),[63,64,67,77] Bangladesh (n = 2)[32,35] and Sri Lanka (n = 1).[48] Additionally, 2 studies from China were included (children <18 y of age)[75,76] (Supplementary Table 5). No data were reported for Africa. Given this lack of data, supplementary information

Table 3. Summary of included studies reporting on the distribution of pathogens and serotypes.

Country Origin of samples	N*	Age group	Population	Bacterial pathogen	Viral pathogen	Serotype	Total number of isolates/ strains obtained	n (%) (no of patients with pathogen/ serotype)	N (%) (total number of patients from whom isolates were obtained)	Source
Origin of samples				n						
Gambia	278	3 m - 5 y	Malnourished with pneumonia	*S. pneumoniae*	NR	NR	Unclear	11 (7%)	159	[41]
Nasopharyngeal, blood samples, lung aspiration, sputum and pleural aspirate				Hib				3 (1.9%)		
				Other *H. influenzae*				3 (1.9%)		
				Salmonella spp				4 (2.5%)		
				E. coli				1 (0.6%)		
				K. pneumoniae				1 (0.6%)		
				S. aureus				1 (0.6%)		
				S. epidermis				1 (0.6%)		
				Other Streptococci				2 (1.25%)		
				M. tuberculosis				4 (2.5%)		
			Well-nourished with pneumonia	*S. pneumoniae*			Unclear	31 (26%)	119	
				Hib				8 (6.7%)		
				Salmonella spp				1(0.8%)		
				Acinetobacter spp				1 (0.8%)		
				S. aureus				3 (2.5%)		
				Other Streptococci				2 (1.7%)		
Nigeria	399	2–59 m	Children with pneumonia and meningitis*	*S. pneumoniae*	NR	NR	399	9 (10%)	90	[62]
Blood samples				Hib				2 (2.2%)		
				Other spp (NR)				72 (80%)		
Mozambique	835	<5 y	Children with CAP	NR	RV	NR	135		135	[29]
Nasopharyngeal aspirate and blood samples		<3 m						14 (10%)		
		3–12 m						67 (50%)		
		12–60 m						54 (40%)		
		HIV-infected						26 (30%)		
		<3 m			ADV		57	1 (2%)	57	
		3–12 m						12 (21%)		
		12–60 m						44 (77%)		
		HIV-infected						9 (24%)		
		<3 m			RSV		38	11 (29%)	38	
		3–12 m						16 (42%)		
		12–60 m						11 (29%)		
		HIV-infected						3 (10%)		
		<3 m			hMPV		29	6 (21%)	29	
		3–12 mo						16 (55%)		
		12–60 m						7 (24%)		

		HIV-infected						7 (33%)		
		<3 m			Influenza		28	4 (14%)	28	
		3–12 m						7 (25%)		
		12–60 m						17 (61%)		
		HIV-infected						4 (25%)		
		<3 m			PIV		20	4 (20%)	20	
		3–12 m						7 (35%)		
		12–60 m						9 (45%)		
		HIV-infected						3 (19%)		
		<3 m			EV		10	3 (30%)	10	
		3–12 m						3 (30%)		
		12–60 m						4 (40%)		
		HIV-infected						1 (14%)		
		<3 m			Co-infections		77	7 (9%)	77	
		3–12 m						21 (27%)		
		12–60 m						49 (64%)		
		HIV-infected						14 (25%)		
India, Nepal and Sri Lanka	1,468	2–59 m	Children with either pneumonia or meningitis*	*S. pneumoniae*	NR	NR	1,468	9 (0.6%)	1,468	[48]
				H. influenzae				7 (0.5%)		
Blood samples				Other spp (NR)				161 (11%)		
Bangladesh	Unclear	<5 y	Children with *H. influenzae* related diseases	Hib	NR	NR	25	15 (60%)	25	[59]
Blood samples				Other serotypes				4 (16%)		
				NTHi				6 (24%)		
China	760	<28 d	Neonates with CAP	*E. coli*	NR	NR	425	115	425	[63]
Respiratory tract aspirates and blood samples				*K. pneumoniae*				(27%)		
				H. influenzae				77 (18%)		
				B. cepacia				31 (7%)		
				C. freundii				14		
				B. cloacae				(3.3%)		
				A. baumannii				11		
				H. parainfluenzae				(2.6%)		
				Other enterobacter				11		
				P. aeruginosa				(2.6%)		
				Stenotrophomonas				5 (1.2%)		
								5 (1.2%)		
								5 (1.2%)		
								2 (0.5%)		
								2 (0.5%)		
				S. aureus			142	83		
				S. epidermidis				(19.5%)		
				S. haemolyticus				27 (6.3%)		
				Other Staphylococci				11 (2.6%)		
				Streptococcus				11 (2.6%)		
				C. albicans				5 (1.2%)		

(*Continued*)

Table 3. (*Continued*)

Country Origin of samples	N*	Age group	Population	Bacterial pathogen	Viral pathogen	Serotype	Total number of isolates/ strains obtained	n (%) (no of patients with pathogen/ serotype)	N (%) (total number of patients from whom isolates were obtained)	Source
China	3,865	<5 y	Children hospitalised with CAP	*S. pneumoniae*	NR	19F	338	188	338	[64]
Hypopharyngeal aspirate; respiratory tract aspirate; blood samples and pleural fluid						19A				
						23F		(55.6%) 47		
						6B		(13.9%)		
						14		34 (10.1%)		
						4		16 (4.7%)		
						6A		12 (3.6%)		
						15B		8 (2.4%)		
						3		4 (1.2%)		
						2		4 (1.2%)		
						5		2 (0.6%)		
						10A		1 (0.3%)		
						11A		1 (0.3%)		
						33F		1 (0.3%)		
						NI		1 (0.3%)		
								1 (0.3%)		
								18 (5.3%)		
China	280	<6 y	Cross sectional	NR	RSV		27	27	280	[65]
Blood samples					PIV		16	(9.6%)		
					ADV		24	16		
					Flu		6	(5.7%)		
								24 (8.6%)		
								6 (2.1%)		
China	554	1 m - 13 y	Children hospitalised with CAP	NR	HRV-A		554	NR	554	[37]
Nasopharyngeal aspirate		≤6 m					246	31	246	
		6.1–12 m					81	(12.6%)	81	
		12–24 m					34	9 (11.1%)	34	
		24.1–36 m					23	3 (8.8%)	23	
		36.1–72 m					46	3 (13.0%)	46	
		≥72 .1 m					124	2 (4.3%)	124	
		≤6 m						3 (2.4%)		
		6.1–12m								
		12–24 m			HRV-B			5 (2.0%)	Unclear	
		24.1–36 m						0		
		36.1–72 m						2 (5.9%)		
		≥72 .1 m						0		
								0		
								3 (2.4%)		
		≤6 m			HRV-C			18	Unclear	
		6.1–12 m						(7.3%)		
		12–24 m						8 (9.9%)		
		24.1–36 m						4		
		36.1–72 m						(11.8%)		
		≥72 .1 m						2 (8.7%)		
								3 (6.5%)		
								3 (2.4%)		

China Respiratory tract aspirates	1,441	1–6 m	Children with CAP	*K. pneumoniae* *E. coli* *S. aureus* *S. pneumoniae*	NR	NR	761	120 77 39 22	Unclear	[66]
		7–12 m		*K. pneumoniae* *E. coli* *S. aureus* *S. pneumoniae*				28 27 5 23	Unclear	
		13–24 m		*K. pneumoniae* *E. coli* *S. aureus* *S. pneumoniae*				13 22 8 22	Unclear	
		25–60 m		*K. pneumoniae* *E. coli* *S. aureus* *S. pneumoniae*				9 4 11 22	Unclear	
China Sputum samples	1,011	<5 y	Children with CAP	*S. pneumoniae*		19F 23F 6B 4	90	56 (62.2%) 14 (15.6%) 9 (10.0%) 6 (6.7%)	90	[43]
China Blood samples	NR	<5 y	Children with S. *pneumoniae* invasive and non-invasive isolates (no separate data for pneumonia reported)	*S. pneumoniae*	NR	Invasive isolates 19F 19A 14 6B 23F 15 5 11	31	7 (22.5%) 9 (29.0%) 4 (12.9%) 0 1 (3.2%) 0 3 (9.7%) 2 (6.5%)	Unclear	[67]
						Non-Invasive 19F 19A 14 6B 23F 15 5 11	420	183 (43.5%) 44 (10.4%) 31 (7.4%) 33 (7.9%) 25 (6.0%) 20 (4.8%) 0		

(*Continued*)

Table 3. (*Continued*)

Country Origin of samples	N*	Age group	Population	Bacterial pathogen	Viral pathogen	Serotype	Total number of isolates/ strains obtained	n (%) (no of patients with pathogen/ serotype)	N (%) (total number of patients from whom isolates were obtained)	Source
								2 (0.5%)		
China Blood and nasopharyngeal samples	821	<1 y	Children admitted with CAP		RSV	NR	Unclear	75 (23%)	320	[45]
					Flu			27 (8%)		
					ADV			35 (11%)		
					PIV			28 (9%)		
		1–3 y			RSV			35 (16%)	221	
					influenza			17 (8%)		
					ADV			17 (8%)		
					PIV			15 (7%)		
		3–5 y			RSV			22 (15%)	147	
					Flu			14 (10%)		
					ADV			9 (6%)		
					PIV			10 (7%)		
		>5 y			RSV			17 (13%)	133	
					Influenza			17 (13%)		
					ADV			6 (5%)		
					PIV			9 (7%)		
		<1 y		*S. pneumoniae*				26 (8%)		
				Hib				35 (11%)		
				M. catarrhalis				10 (3%)		
				M. pneumoniae				10 (3%)		
		1–3 y		*S. pneumoniae*				56 (25%)		
				Hib				40 (18%)		
				M. catarrhalis				2 (0.9%)		
				M. pneumoniae				17 (8%)		
		3–5 y		*S. pneumoniae*				16 (11%)		
				Hib				10 (7%)		
				M. catarrhalis				1 (0.7%)		
				M. pneumoniae				24 (16%)		
		>5 y		*S. pneumoniae*				21 (16%)		
				Hib				10 (8%)		
				M. catarrhalis				1 (0.8%)		
				M. pneumoniae				42 (32%)		

*This is the number of CAP subjects within the study and NOT the total study sample size; CAP, community acquired pneumonia; RSV, respiratory syncytial virus; RV, rhinovirus; ADV, adenovirus; hMPV, human metapneumovirus; Flu, influenza virus; PIV, parainfluenza virus; EV, enterovirus; HIV, human immunodeficiency virus; Hib, *H. influenzae* type b; HRV, Human rhinovirus; NI, Not identified; d, day; m, month; y, year.

was also reported from an additional 8 studies which included data for children <18 y of age with IPD (including children <6 years).[89-96] These studies covered China (n = 3),[89-91] Middle East (n = 4),[92-95] and Russia and CIS (n = 1).[96]

India and South Asia

Studies by Brooks et al.[29] and Arifeen et al.[32] established that *S. pneumoniae* isolates from children with CAP were susceptible to penicillin (97% and 85%, respectively), which is the most widely used antibiotic in developing countries. Contrarily, a sentinel study by Batuwanthudawe et al.[48] reported data for Sri Lanka which suggested that isolates of *S. pneumoniae* (predominant serotypes 19F and 23F) were highly resistant to penicillin (91.30%), and also showed considerable resistance to other antimicrobial agents including co-trimoxazole (73.91%), chloramphenicol (26.09%), erythromycin (60.87%) and cefotaxime (47.83%).

China

Wang et al.[63] reported on the degree of antimicrobial resistance of various pathogens like *S. aureus, Staphylococcus epidermidis, E. coli, H. influenzae* and *K. pneumoniae* to the different antibiotics used in China. The data showed that *H. influenzae* and *K. pneumoniae* were highly sensitive to meropenem (100% each) whereas S. *aureus* was highly sensitive to quinupristin/dalfopristin (98.6%) and resistant to penicillin (3.3% sensitivity). In addition, *S. epidermidis* was highly sensitive to quinupristin/dalfopristin (96.7%) but not to penicillin (2.3%). *E. coli* was fully sensitive to meropenem and imipenem (100% each) but less sensitive to ampicillin (48.9%) and amoxicillin (4.3%).[63] A similar study by Zhao et al.[43] presented data on the resistance of antibiotics to Hib. The highest resistance of 22.2% to ampicillin was reported compared to ampicillin/sulbactam and cefaclor which were 100% effective against the pathogen.

Another study by Yao et al.[64] tested the resistance of antibiotics to *S. pneumoniae* and the data showed the bacteria were susceptible to the majority of the antibiotics. On the other hand, erythromycin showed the highest level of resistance at 99.7% compared to penicillin (1.8%), ofloxacin (0.3%) and imipenem (1.5%). Additionally, Liu et al.[67] reported *S. pneumoniae* to be fully resistant to penicillin and erythromycin (at 100% each) followed by clindamycin at 96.8%, tetracycline at 93.5% and trimethoprim-sulfamethoxazole (TMP-SMX) at 83.9%.

Liu et al.[67] reported that, in China, 96.6% of S. *pneumoniae* isolates were resistant to erythromycin, tetracycline and clindamycin. In addition, there was also some evidence of resistance to TMP-SMX (82.8%), cefaclor (65.5%), and penicillin (55.2%). However, a previous study by Yao et al.[89] reported that *S. pneumoniae* isolates showed no evidence of full resistance to any of the studied antibiotics, although penicillin had the highest intermediate resistance (54.5%). Li et al.[90] reported the highest full resistance of *S. pneumoniae* to tetracycline at 79% followed by erythromycin at 72% and TMP-SMX at 70%. In addition, another study from Hong Kong reported that 85.2% of *S. pneumoniae* isolates were resistant to erythromycin followed by cefotaxime (33.0%).[91]

Two additional studies from China (of subjects with a wide age range) of children with CAP, reported on antimicrobial resistance of various pathogens against the most commonly used antibiotics.[75,76] A study by Zeng et al.[76] reported that of the 48 strains of *S. pneumoniae* isolated, 50% were fully resistant to penicillin followed by 45.8% to erythromycin and 45.8% to cephazolin. Also, 52.5% and 56.5% of *S. haemolyticus* isolates were resistant to penicillin and cephazolin. Of the 16 strains of *S. aureus* isolated, 100% showed full resistance to penicillin and 87.5% to erythromycin and cephazolin each. A similar study by Wang et al.[75] reported 100% full resistance of the S. *pneumoniae* isolates to erythromycin followed by 90.6% to penicillin, and 94.3% to clindamycin. Hib was reported to have full resistance to meropenem and ciprofloxacin.

Middle East

A study by Percin et al.[92] from Turkey reported full resistance of *S. pneumoniae* isolates to TMP-SMX at 36% followed by penicillin at just 6%. Similarly, a study by Ercan et al.[93] from Turkey, reported on the resistance of S. *pneumoniae* to TMP-SMX at 63.3% followed by erythromycin at 40% and tetracycline at 33.3%. A study by Shibl et al.[94] from Saudi Arabia reported *S. pneumoniae* resistance of 26% to erythromycin and 12% to penicillin. Finally, a study from Kuwait reported that serotypes 19F and 23F from *S. pneumoniae* showed intermediate resistance to penicillin in comparison to serotypes 6B, 6A, 19A and 14, for which no significant resistance was reported.[95]

Russia and CIS

Due to the lack of data in children <6 y of age with CAP in Russia, a study by Katz et al.[96] was included. The study included children with IPD aged 16–70 months. The results showed the highest resistance of 61.4% to TMP-SMX, followed by tetracycline at 32.5%, clindamycin at 19.3%, erythromycin at 16.7% and the lowest resistance to chloramphenicol at 6%.[96] On average, data suggested that the high resistance levels are seen where TMP-SMX, erythromycin and tetracycline antibiotics are used, suggesting that the use of penicillin (as a major antibiotic) for treatment of IPDs is very low in comparison to TMP-SMX, erythromycin and tetracycline. However, this could be due to the natural resistance of the pathogens to penicillin after its extensive use in recent years.

Discussion

This is the first comprehensive review of the epidemiology and burden of CAP in children <6 y of age within developing and newly industrialized countries using a rigorous search strategy. Several CAP-related outcomes were covered, including incidence, prevalence, mortality, seasonal variation, distribution of pathogens and antimicrobial resistance.

The incidence rates among children <6 y of age varied greatly between the included studies according to age, severity of CAP and season. In general, incidence rates were higher for infants, for more severe CAP episodes and during wet/rainy seasons. The highest incidence rate from this review was reported in Bangladesh,[33] with 0.51 episodes per child-year, for

children <5 y of age hospitalized with pneumonia. A previous systematic review reported an incidence rate of pneumonia in children <5 y at 0.29 episodes per child-year in developing countries in comparison with 0.05 episodes per child-year in developed countries.[12] Other systematic reviews assessed the incidence rate of pneumonia in Chinese children <5 y of age at ~0.13 episodes per child-year between 1980 and 2008[97] while the incidence rate of CAP or hospitalized pneumonia ranged from 0.06 to 0.27 episodes per person-year between 1985 and 2008.[98] A more recent estimate by Rudan et al.[2] has shown a decreasing trend in the burden of pneumonia from 2000 to 2010. Although there is a paucity of data on CAP burden in the Russian Federation, previous expert evaluations estimated an incidence of pneumococcal CAP of 490–1,300 cases per 100,000 child-years in children <6 years, according to a recent publication.[99]

Prevalence data from developing countries were very scarce. There was variation in the prevalence rate by age, pathogen, co-infections (HIV, malaria) and season. Infants had a higher CAP prevalence rate compared to those >12 months of age.[50] HIV positive children had a higher prevalence rate of pneumonia.[39] Children with malaria are at risk of bacterial infection, which results in an increased risk of mortality.[16] Moreover, in highly affected malaria endemic regions, the diagnosis of pneumonia may be uncertain because malaria and severe pneumonia in hospitalized young children show remarkable clinical similarities.[100,101] Wrong diagnosis often leads to under-treatment of pneumonia[102] or to inappropriate prescription of antibiotics to children with malaria,[103] increasing antimicrobial resistance levels in the community.

There were very limited data on the overall mortality of CAP from the included studies. Pneumonia was accountable for at least 19% of worldwide deaths of children <5 y of age, 70% of these deaths occurring in Sub-Saharan Africa, India and South Asia.[12] Nigeria had the greatest burden of mortality of children <5 y with pneumonia at 177,000 children, considered the highest in Africa and the second largest worldwide, after India.[104] Also, the highest mortality rates were recorded in Kenya during the wet and rainy season.[58] A systematic literature review from China covering the period between 1980 and 2008 reported the mortality rate of all-cause pneumonia at 526 per 100,000 child-years in children aged between 1 and 59 months.[97]

Higher mortality rates were generally reported for: un-vaccinated, malnourished and HIV-positive children;[56] children with severe (45%) and very severe pneumonia (51%);[46] infants compared to those >12 months of age.[27]

In the studies included, bacteria were more frequent than viral pathogens, although a trend of co-infections was noted. A recent review has shown that the true incidence of pulmonary bacterial co-infection with a viral respiratory infection in hospitalized infants and children is difficult to assess, but can vary widely from under 1 to 44%.[105] However, viral pathogens were not explored as causal agents at laboratory level. Furthermore, even the bacterial pathogens were probably underreported due to a lack of established protocols for specific pathogens. *S. pneumoniae* was the most common bacterial cause of CAP, followed by *H. influenzae* and *M. pneumoniae*. Hib was not highly reported. The most prevalent pneumococcal serotypes were 19F, 19A, 23F, 6B, and 14; however, they were reported only from China. Serotypes 1, 6A/6B, 14 and 23F were reported as the most dominant in children in Malawi.[72] A similar research carried out in children with CAP from Latin America and the Caribbean,[24] showed that *S. pneumoniae* was the dominant pathogen followed by *H. influenzae*, while the dominant pneumococcal serotypes were 14, 1 and 5.[24] The burden of viral pathogens in children from the included studies is consistent with the results from other regions of the world.[2,24]

Data from the Russian Federation and CIS covering the screened period were very limited. However, a recent publication reported on serotyping and antibiotic susceptibility testing performed on 863 non-invasive pneumococcal isolates from children <6 y of age who sought medical care at 5 pediatric hospitals in Moscow between 2009 and 2013.[99] The most common pneumococcal serotypes were 19F, 6B, 23F, 14, 6A, 3 and 19A.

There was even a greater variation in the type of antibiotic used to treat CAP, depending on geographical region. This is potentially due to the variation in the resistance patterns of some antibiotics across the various countries, suggesting that some antibiotics would be less effective for the treatment of pneumonia. Some adaptations may be required especially where high-risk patients are concerned (e.g. patients with HIV, malnutrition, sickle-cell anaemia, or in combination), who may need various drug combinations to effectively treat pneumonia.

HIV-infected children are treated with various antibiotics, in combination with antiretroviral drugs.[106] Due to the increased penicillin resistance in recent years, modifications in the use of penicillin as the preferred drug has ceased with the recommendation for the use of co-trimoxazole and amoxicillin as recommended by the WHO/UNICEF.[13] In our review we observed a trend for a higher resistance of *S. pneumoniae* and *H. influenzae* compared to (in descending order) erythromycin, TMP-SMX, tetracycline and penicillin across China, Africa, India and South Asia. In China, *S. pneumoniae* and *H. influenzae* showed very high resistance to other antibiotics, including meropenem and imipenem[63] and very low resistance to amoxicillin and ampicillin compared to India and South Asian countries.

Antimicrobial resistance is a major problem in countries where antibiotic use is unregulated and are available without prescription in combination with the higher density populations.[107] Therefore, concerns still remain about combating the spread of antimicrobial resistance especially in children with pneumonia. In Russia, for example, the rate of multidrug-resistant pneumococci was reported at 22%, while the resistance rate to penicillin and erythromycin was 28% and 26%, respectively.[99]

Recent developments in reducing antimicrobial resistance have been supported by the WHO; the 2011 WHO Health Day campaign demonstrated the need for further research into antimicrobial resistance worldwide. Additionally, in 2013, WHO and UNICEF launched the integrated Global action plan for pneumonia and diarrhea (GAPPD).[108] The aim of GAPPD is to end preventable childhood deaths due to pneumonia and diarrhea by 2025.[108]

Immunization of children with conjugate vaccines has proven to be a successful strategy to prevent infections caused by various encapsulated bacteria. For the prevention of childhood pneumonia, several effective vaccines are currently

available. These include the relatively new Hib conjugate vaccine and pneumococcal conjugate vaccines (PCVs). PCVs against *S. pneumoniae* have been proven to reduce morbidity and mortality of CAP.[109,110] Since its introduction in 2000, the heptavalent PCV (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F), PCV7-CRM (Pfizer, New York, NY, USA), currently licensed for use worldwide, was shown to be effective in providing protection against pneumonia.[111] Recently, 2 extended valency PCVs (the 10-valent NTHi protein D conjugate vaccine [PHiD-CV; GSK Vaccines, Rixensart, Belgium] and the 13-valent CRM_{197} conjugate vaccine [PCV13-CRM; Pfizer, New York, NY, USA]) that also contain the important serotypes 1, 5 and 7F, gradually replace PCV7-CRM.[112]

A comprehensive comparison of CAP epidemiology pre- and post-vaccination would be very useful since it was shown that national PCV-7 vaccination has reduced the incidence of vaccine-type IPD.[113,114] However, as of December 2012, only 44%(86/194) of the WHO member states had introduced PCV into national immunization programs.[115] PCV was introduced in national immunization programs in 41% (19/46) of member states in the African Region, 33% (9/27) of member states in the Western Pacific Region, and none of 11 member states in the South East Asia Region.[115] In 2014, PCV was introduced in 117 countries, up from 103 countries in 2013. Global coverage was estimated at 31% in 2014, up from 25% in 2013. Coverage levels were estimated at 83% in the Americas, 50% in the African Region and at only 2% in the Western Pacific Region.[116]

The results of our study support the WHO recommendation of vaccination against *S. pneumoniae* and Hib, since pneumonia is still a high risk in children (<5 years). Along with vaccination, proper management of emerging cases is needed in the community, health centers and hospitals. Further effective strategies recommended by WHO include exclusive breastfeeding for the first 6 months of life, improvement of nutrition and prevention of low birth weight, pollution control and prevention of HIV infections.[117]

The strength of this review lies in its general adherence to the established methods for conducting systematic reviews, including extensive literature searching methods, an inclusive publication date range, and the screening and inclusion of non-English language papers.

However, our systematic review has several limitations. Firstly, due to the heterogeneity in reporting the outcomes, statistical pooling or a meta-analysis could not be performed. Some of the studies presented unreliable data on incidence, mortality and prevalence rates, making it very difficult to draw comparisons. The variations in methodological quality of the studies, with majority of studies having a high risk of bias, implied that data may be over/underestimated, therefore, unreliable. Additionally, although the WHO definition of childhood pneumonia is the most frequently used in field studies, a broader definition of CAP was adopted for this review to ensure that all studies describing CAP as an infection acquired outside the hospital environment. Depending on the case definition, the burden of CAP in children may be over– or underestimated.[118] Finally, as the focus of this review was to provide a literature overview as sensitive as possible, sample size was not considered as an exclusion criterion.

Conclusions

In conclusion, CAP within the 90 developing and newly industrialised countries included in the current review remains a disease associated with very high rates of incidence and mortality. This overview is useful to policy and decision making within these countries when considering the implementation and monitoring of CAP preventive measures. The data presented provides an overview of the best available evidence on the burden of CAP data up to 2012, prior to pneumococcal vaccines being widely used in the countries considered, and show critical gaps in the pathophysiology, etiology and epidemiology of pneumonia in the included countries. Therefore, several preventative and management measures aimed at reducing the burden of CAP in developing and newly industrialised countries are essential. Additionally, new research should also aim to use strict diagnostic criteria in assembling a sample and adequately report this in publications. Studies of bacterial etiology should include much larger samples to add further reliability to the evidence-base.

Materials and methods

Search strategy

The methods for this systematic literature review adhered, wherever possible, to recommendations and guidance published by the Center for Reviews & Dissemination (CRD), York, UK and the Cochrane Collaboration Handbook.[119,120] Searches were undertaken in several stages to identify relevant information, such as epidemiological data and statistics, systematic reviews, burden of disease studies, guidelines, national guidance and vaccination status. Searches were not limited by language or publication status. Electronic databases included MEDLINE, EMBASE, Cochrane Library, CAB Global Health, country-specific health ministries, UNICEF, WHO and health-technology-assessment (HTA) agencies (Supplementary Material, Appendix 1). The review included all study designs, including RCTs, cross-sectional, cohort, case-control studies as well as case-series. The outcomes of interest included incidence, prevalence, mortality, distribution of pathogens and antimicrobial resistance in children with CAP.

Study Selection and Eligibility Criteria

Eligible studies had to report data for children <6 y of age (where data were scarce, studies of children with a wide age range were also included) within 90 developing and newly industrialised countries (the newly industrialised countries are an intermediate category between fully developed and developing countries) across 5 regions of interest: Africa, India and South Asia, China, Middle East, and Russia and CIS (please see Supplementary Material, Appendix 2 for a list of the countries included). As described previously, we used the United Nations classification, but also geographic criteria to include the regions were knowledge gaps about CAP were identified. Latin America and the Caribbean were not included in our search, since these regions were covered by another systematic review, published in 2012.[24] Children had to have been diagnosed with CAP (using any reported definition) or be at-risk of pneumonia due

to the following bacteria or viruses: *S. pneumoniae, H. influenzae* (encapsulated [a, b, c, d, e and f] and unencapsulated/NTHi), *M. pneumoniae, S. aureus* and *Legionella pneumophila*, influenza A and B viruses, parainfluenza virus (PIV), RSV, ADV or RV. Risk factors of interest were HIV, malnutrition, sickle cell disease and vaccination status.

For this review, we adopted a broad definition of CAP which ensured that all studies describing CAP as an infection acquired outside the hospital environment with some relation to the definition as recommended by the WHO guidelines.[87] The WHO definition states that "mild pneumonia is reported as tachypnea (fast breathing) in a child (defined as ≥50 breaths/min in children under 12 months of age and ≥40 breaths/min in children over 12 months of age) in the absence of lower chest wall indrawing or other signs and symptoms of WHO-defined severe pneumonia." A summary of findings on the guidelines used across the included studies is presented in Supplementary data, Appendix 3.

Screening and data collection

Two reviewers working independently screened the titles and abstracts of the retrieved literature for relevance. Full papers were then ordered and screened in detail for inclusion in the review. Any disagreements between the 2 reviewers at any stage were resolved through a consensus or by the involvement of a third reviewer. Data were extracted using a pre-piloted excel extraction sheet in Microsoft Excel (version 2010).

Assessment of risk of bias

The risk of bias of observational studies was assessed using Downs and Black's 27 item checklist for the methodological quality assessment of non-RCTs.[88] The checklist items for observational studies focused on the use of an appropriate recruitment strategy, response rates, sample representativeness of the general population, objective and reliable outcome measures, use of a power calculation, appropriate use of statistical methods and evidence of bias within the studies (see Supplementary Material, Appendix 4). Due to the heterogeneity in the reporting of outcomes, it was not possible to carry out a planned meta-analysis. The number of items met for the studies ranged from 3 to 23 of the 27 checked items on the list. The majority of the studies had a cross-sectional design with a number of items met ranging from 6 to 11. The average number of items met for the included RCTs was 20. The data were grouped by geographical region.

Data synthesis and analysis

The heterogeneity of the included studies precluded statistical pooling of data. Instead, results have been narratively summarized, taking into account the reliability of the data and generalizability of the findings. Gaps in the research base were also highlighted.

Abbreviations

ADV	adenovirus
ALRI	acute lower respiratory infections
CAP	community-acquired pneumonia
CIS	Commonwealth of Independent States
CRD	Center for Reviews & Dissemination
GAPPD	Global action plan for pneumonia and diarrhea
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HTA	health-technology-assessment
IPD	invasive pneumococcal disease
NTHi	non typeable *Haemophilus influenza*
PIV	parainfluenza virus
PCV	pneumococcal conjugate vaccines
RCT	randomized controlled trial
RV	rhinovirus
RSV	respiratory syncytial virus
TMP-SMX	trimethoprim-sulfamethoxazole

Disclosure of potential conflicts of interest

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Author contributions

JK contributed to developing the protocol, writing and critical revision of the report and provided project supervision. RDA, JPY, JPC, and JES participated to the concept of the literature review and were involved in the analysis and interpretation of the data. All authors have contributed to the manuscript development and have reviewed all drafts and provided approval prior submission. All authors are accountable for all aspects of the work.

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