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Review Article

Systematic Review of Articles on Etiologies of Acute Respiratory Infections in Children Aged Less Than Five Years in Sub-Saharan Africa, 2000-2015

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Abstract

Background: Acute respiratory infections (ARIs) are the leading cause of mortality in children in low and middle income countries. Information about the etiologies of ARIs is crucial for prevention and case management strategies. This systematic review aims to describe the etiologies of ARIs in children < 5 years reported in studies conducted in Sub-Saharan African countries.

Methods: A systematic search was conducted using PubMed, Web of sciences and Google scholar to identify articles published in English or French containing data on the etiology of ARIs. In addition, databases of unpublished literature were screened. The review was limited to studies published from January 2000 to September 2015 and the selection of full-text articles for the final inclusion was done by two of the authors.

Results: Following the review of 78 full - text articles, we found that 29 met the inclusion criteria. The identified studies were conducted in 13 Sub - Saharan African countries from which South Africa with 8/29 (27.6%) studies and Kenya with 5/29 (17.2%) studies. Twenty-four (82.7%) were cross - sectional studies and 27 (93.1%) were hospital-based studies. RT - PCR for viruses and culture for bacteria and fungi were the main diagnostic methods used in the reviewed studies. Respiratory syncytial virus (RSV) (4.0% - 35.0%), parainfluenza viruses (PIV)1 - 4 (0.3% - 75.8%), influenza viruses (0.1% - 29.1%), adenovirus (AdV) (1.0% - 26.0%), rhinovirus (RV) (9.5% - 41.0%), human metapneumovirus (hMPV) (0.5% - 8.0%), *S. pneumoniae* (0.7% - 91.0%), S. aureus (0.9% - 42.9%) and *Klebsiella* spp (1.0% - 42.0%) were the most common pathogens detected in these studies.

Conclusion: To our knowledge, this is the first systematic review on the etiology of ARIs in Sub-Saharan Africa. Our results showed that many pathogens, and most commonly viruses, were associated with ARI cases in children less than five years. Unfortunately, the limited geographical distribution of these data from Sub-Saharan Africa do not allow the majority of countries to develop an efficient strategy of ARIs prevention and treatment.

Keywords: *Acute Respiratory Infections; Etiology; Children < 5 years; Systematic review; Sub-Saharan Africa; 2000-2015*

Abbreviations: LMIC: Low Middle Income Countries; ARI: Acute Respiratory Infection; ALRI: Acute Lower Respiratory Infection; CAP: Community Acquired Pneumonia; RSV: Respiratory Syncytial Virus; PIV: Parainfluenza Virus; hAdV: Human Adenovirus; hCoV: Human Coronavirus; hMPV: Human Metapneumovirus; hBoV: Human Bocavirus; WuPyV: WU Polyomavirus; KIpyV: KI Polyomavirus; RV: Rhinovirus; LRTI: Lower Respiratory Tract Infection; IFA: Immuno-Fluorescence Assay; PCR: Polymerase Chain Reaction; RT-PCR: Reverse Transcriptase – Polymerase Chain Reaction; EV: Enterovirus; CMV: Cytomegalovirus; hPeV: Human Parechovirus; S. aureus: Staphylo-

coccus aureus; H. influenza: Haemophilus influenza ; P. jirovecii: Pneumocystis jirovecii ; M. pneumoniae: Mycoplasma pneumoniae ; C. pneumoniae: Chlamydia pneumoniae ; P. aeruginosa: Pseudomonas aeruginosa; M. tuberculosis: Mycobacterium tuberculosis; DRC: Democratic Republic of Congo; PVC: Pneumococcal Vaccine Conjugate

Introduction

In low and middle income countries (LMICs), acute respiratory infections (ARIs) are a major cause of morbidity and mortality among children less than five years of age. Indeed, it is estimated that about 126 – 156 million cases of acute lower respiratory infections (ALRI) such as pneumonia and bronchiolitis occur worldwide each year in children leading to approximately 1.4 million deaths. More than 95% of these deaths occur in Africa and in South-East Asia [1-3].

Several pathogens cause ARIs. Especially in children < 5 years, respiratory viruses are more commonly identified than bacteria in ARI cases [4]. This may be explained by the fact that bacterial culture, which is the current standard diagnostic method for respiratory bacteria, has a low sensitivity in patients with community acquired pneumonia (CAP) [5,6]. Respiratory viruses such as respiratory syncytial virus (RSV), influenza viruses (A and B), parainfluenza viruses (PIV1-4), human adenovirus (hAdV) and human coronaviruses OC43 and 229E (hCoV-OC43, hCoV-229E) were initially identified as causes of ARIs [7].

More recently, use of advanced molecular diagnostic techniques, has helped to identify other respiratory viruses associated with ARIs including human metapneumovirus (hMPV) [8], human Boca virus (hBoV) [9], human coronavirus NL63 (hCoV-NL63) [10], human coronavirus HKU1 (hCoV-HKU1) [11], WU and KI polyomaviruses (WUPyV, KIPyV) [12,13]. Moreover, human rhinovirus (RV) is involved in the majority of common colds and often induces lower respiratory tract infections (LRTI) [14]. A better understanding of the range of ARI pathogens is essential for the clinical management of cases and the design of preventive strategies to reduce child morbidity and mortality.

To our knowledge, no recent systematic review was conducted on the etiologies of ARIs in children less than five years of age in sub-Saharan Africa. The present study aimed to summarize published and unpublished literature on the etiology of ARIs in children in sub-Saharan African countries and identify gaps of information in order to improve knowledge on this essential topic. We focused our review on sub-Saharan Africa as epidemiological, socioeconomic, and vaccine policy factors in northern Africa would likely be substantially different [15].

Materials and Methods

Search strategy and selection criteria

We undertook a systematic literature review to identify studies with data on etiology of acute respiratory infections in children less than five years. We conducted searches in PubMed, Web of sciences and Google scholar using combinations of key search terms: “etiology”, “acute respiratory infections”, “upper respiratory infections”, and “lower respiratory infections”, “pneumonia”, “influenza-like illnesses”, “children and Africa”. Search was also done in unpublished literature of Burkina Faso. An online search of journals was also performed by examining the reference lists of relevant articles. The search was limited to studies published in English or French, focused on children < 5 years old in sub - Saharan Africa, published between January 1, 2000 to September 30, 2015 and in which the pathogens were identified using Immuno-Fluorescence Assays (IFA), PCR (Polymerase Chain Reactions), viral culture, bacteria culture or a combination of these methods [Table 1]. We excluded studies that reported results from the general population, studies targeting children with chronic respiratory infections and review studies. The initial search was conducted in November 2014 and a second search was performed in early October 2015 looking at studies published from November 2014 to September 2015 to ensure that no recent articles were missed in this review.

Inclusion criteria	Exclusion criteria
Studies published between Jan 1, 2000 and September 30, 2015	Studies that reported results from children with chronic respiratory infection
Studies focused on children younger than 5 years, or data reported separately for this age group	Studies conducted in the general population
Studies published in English or in French	Reviews (studies)
Studies that reported results from sub-Saharan Africa	
Studies with data for laboratory-confirmed cases	
Studies which have been carried out in community or at health facilities	

Table 1: *Inclusion and exclusion criteria of the reviewed acute respiratory infection (ARI) studies.*

One author screened titles and abstracts using the inclusion and exclusion criteria to identify potential studies with ARI etiology data in children < 5 years old. Two authors reviewed the full text of all potentially relevant studies to determine final inclusion. Any discrepancy was discussed and if necessary, we referred to a 3rd author to reach consensus.

Data extraction

Data were extracted by one author and checked by a second author. Any disagreements were resolved by consensus with a 3rd author. We extracted data using a structured Excel database. We extracted the following information: author's name, country and setting of study, period of the study, study design, target populations, sample size, year of publication, description of symptoms and/or diagnostic criteria, length of follow-up, tested specimens, diagnostic method and pathogens testing.

Data Synthesis

We did not assess the quality of the articles but aimed instead to summarize all those identified. We synthetized data by summarizing the key results of each study. Given the variety of types of studies included in the review, including simple descriptive to analytic studies, we found a synthesis more appropriate than a formal meta - analysis. A table was created that list all the pathogens identified in individual studies along with relevant information on the study: design, population, sample size, location, diagnostic methods and year of publication.

Results

Literature review

The initial database search identified 1690 articles. Seventeen [16] additional articles were identified through manual search of grey literature. After the preliminary screening of titles and abstracts, 75 full -text articles were assessed for eligibility. Of these, 49 were excluded because they did not meet inclusion criteria leaving 26 studies [17-41] with ARI that were included [Figure 1]. A second search was performed to ensure that no recent articles were missed in this review. This search retrieved 74 new articles and 3 of which [42-44] met the inclusion criteria for this study.

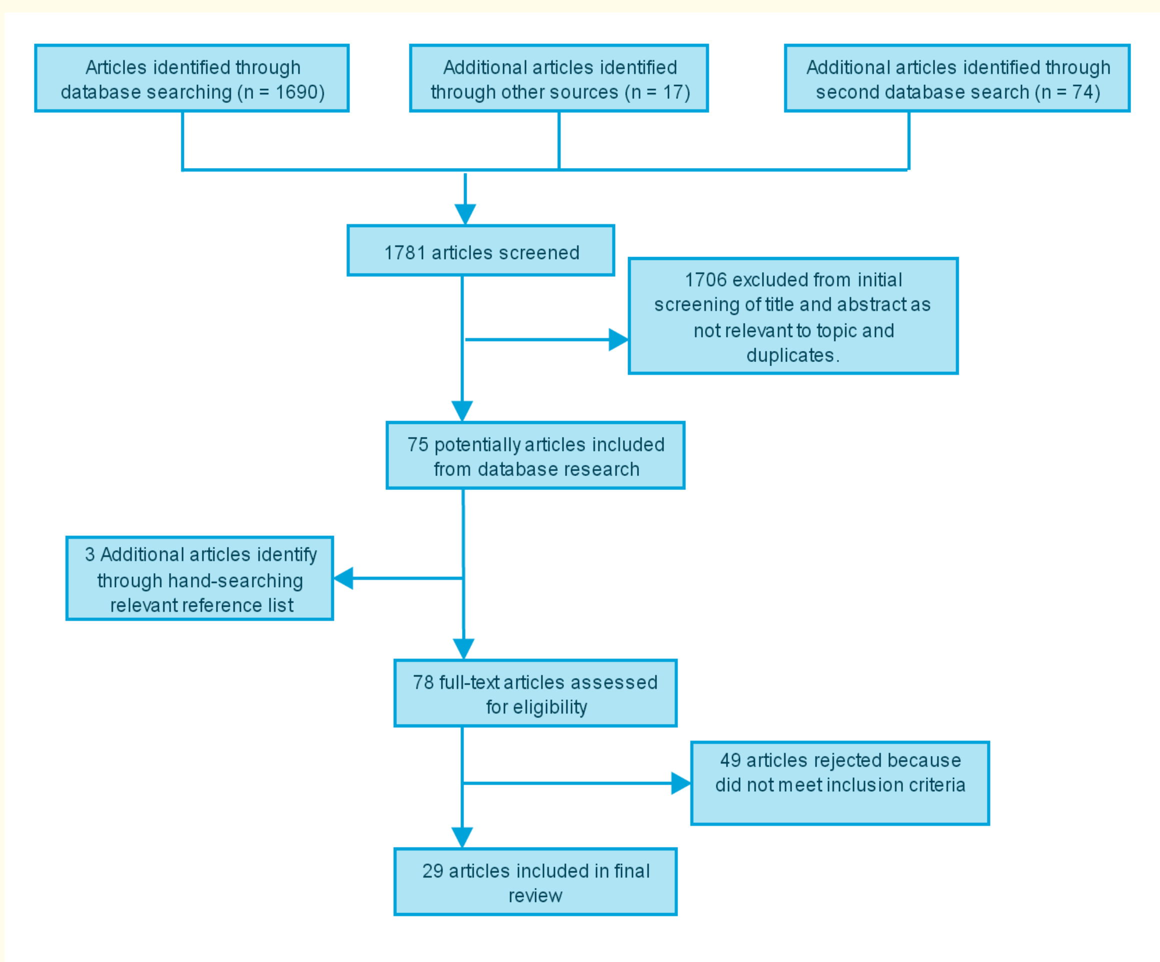

Figure 1: *Flow diagram for selection of studies.*

Characteristics of articles

The 29 articles reported on a total of 23,539 patients. The sample size ranged from 23 to 8723 ARI patients per study. The included studies were carried out in 13 countries. Eight (8) studies were conducted in South Africa, 5 in Kenya, 3 in Mozambique, 2 in Gambia, Ghana, and Uganda respectively, and 1 each in Burkina Faso, Botswana, Cameroon, Gabon, Nigeria, Senegal and Tanzania.

Twenty-four (82.7%) studies were cross-sectional studies and 5 (17.3%) were case-control studies. There were 27 (93.1%) hospital-based studies and 2 (6.9%) community - based studies. The study setting was urban in 18 (62.1%) studies, rural in 7 (24.1%) and mixed (rural, semi-rural and urban) in 4 (13.8%) studies.

In 20 (68.9%) studies, the pathogens were identified in respiratory specimens including nasal swab, oropharyngeal swab, nasopharyngeal swab, nasopharyngeal aspirate, induced sputum, tracheal aspirate, Broncho alveolar lavage and lung aspiration. Two studies (6.9%) reported collecting blood and 8 studies (27.6%) reported collecting blood and respiratory specimens.

Respiratory viruses were detected using conventional PCR, real time RT - PCR or multiplex RT - PCR solely or combined with conventional methods such as viral culture and immunofluorescence. Bacteria and fungi were detected by PCR, culture and immunoassay. Study characteristics are summarized in [Table 2].

	Location, Year	Design	Age range	Sample size	Clinical presentation of tested patients	Tested specimens	Diagnostic methods
Africa, Central							
Lekana-Douki SE., 2014 (38)	Gabon; urban, semi rural and rural; 2010 – 2011	Hospital based cross-sectional study	0 – 4 years	810	ILI	Nasal swabs	Multiplex real time RT-PCR
Njouom R., 2012 (35)	Cameroon; urban, semi-urban and rural; 2009	Hospital based cross-sectional study	0 – 4 years	250	ILI	Throat and/or naso-pharyngeal swab	Multiplex RT - PCR
Africa, Eastern							
Uriyo J., 2006 (23)	Kilimanjoaro CMC, Tanzania; urban; 2003	Hospital based cross-sectional study	2 – 60 Months	72	Severe pneumonia	Induced sputum	PCR – Culture
Bii CC ., 2006 (25)	Nairobi, Kenya; urban; 2002 – 2003	Hospital based cross-sectional study	≤ 23 months	60	Severe pneumonia	Induced sputum	Immunofluorescence – Culture
Bakeera-Kitaka S., 2004 (22)	Mulago Hospital, Kampala, Uganda; urban; 2001	Hospital based cross-sectional study	2 – 60 months	121	Severe pneumonia	Induced sputum	Immunofluorescence
Were FN., 2002 (20)	Kenyatta National Hospital, Nairobi, Kenya; urban; 2000	Hospital based cross-sectional study	7 – 30 days	50	Pneumonia	Nasopharyngeal aspirate	Enzyme Immunoassay (EIA)
Bii CC., 2002 (18)	Mbagathi District Hospital, Nairobi, Kenya; urban; 2002	Hospital based cross-sectional study	≤ 59 months	157	Pneumonia	Nasopharyngeal aspirate	RT – PCR, Culture
Nantanda R., 2008 (28)	Mulago Hospital, Kampala, Uganda; urban; 2005 – 2006	Hospital based cross-sectional study	2 – 59 months	2973	Severe pneumonia	Blood – Induced sputum	Culture
Feikin DR., 2013 (37)	Lwak Hospital, Nyanza, Kenya; rural; 2007 – 2010	Case-control study	≤ 59 months	810	SARI	Blood, Nasopharyngeal and Oropharyngeal swabs	Real time RT-PCR, Culture
Hammitt LL *et al*., 2012 (34)	Kilifi District, Kenya; rural; 2010	Case – control study	1 – 59 months		Severe pneumonia – Very severe pneumonia	Blood, induced sputum, serum, oro-pharyngeal swab, nasopharyngeal swab	Culture; multiplex real time RT-PCR; serology

Africa, Southern							
Hussey GD., 2000 (16)	Cape Town, South Africa; urban; 1995 – 1996	Hospital based cross-sectional study	≤ 2 years	1288	ALRTI	Nasopharyngeal aspirate	Enzyme-Immunoassay, Viral culture
Madhi S., 2002 (19)	Soweto, South Africa; urban; 1997 – 1999	Hospital based cross-sectional study	≤ 59 months	142	Severe LRTI	Nasopharyngeal aspirate	Immunofluorescence
Delport SD., 2002 (21)	Pretoria, South Africa; urban; 1994 – 1995	Hospital based cross-sectional study	≤ 59 months	23	Severe pneumonia	Blood sample; Tracheal aspirate; nasopharyngeal aspirate.	Culture, Immu-nofluorescence
Smuts H., 2008 (27)	CWM Children's Hospi-tal, Cape Town, South Africa; urban; 2003 – 2004	Retrospective cross-sectional study	13 days - 5 years	1055	ARTI	Tracheal aspirate, bronchoalvealoar lavage	Viral Culture, Immu-nofluorescence, RT-PCR
Zar HJ., 2001 (17)	CWM Children's Hospi-tal, Cape Town, South Africa; urban; 1998	Hospital based cross-sectional study	2 – 23 months	151	Pneumonia	Blood, Induced sputum or Bron-choalveloar lavage, nasopharyngeal aspirate, gastric lavage.	Culture, Immu-nofluorescence
O'Callaghan-Gordo C., 2011 (32)	Manhiça District Hospi-tal, Mozambique; rural; 1999 – 2000	Hospital based cross-sectional study	≤ 12 months	333	ARI	Nasopharyngeal aspirate	Multiplex RT – PCR
O'Callaghan-Gor-do., 2011* (33)	Manhiça District Hospi-tal, Mozambique; rural; 2006 – 2007	Hospital based cross-sectional study	≤ 59 months	807	Pneumonia	Nasopharyngeal aspirate, blood	Multiplex RT-PCR, Culture
Venter M., 2011 (31)	Pretoria, South Africa; urban; 2006 – 2007	Case-control study	≤ 59 months	610	ARI	Nasopharyngeal aspirate	Multiplex real time RT-PCR, Conventional nested RT-PCR, Immu-nofluorescence
Cohen C., 2015 (39)	South Africa; urban, semi-urban and rural; 2009 – 2010	Hospital based cross-sectional study	≤ 59 months	8723	ALRTI	Nasopharyngeal aspirate; Blood samples	RT-PCR

Nunes MC., 2014 (42)	South Africa; urban; 2000 – 2002	Hospital based surveillance	< 2 years	1460	ALRTI	Nasopharyngeal aspirate	Immunofluorescence assay; Nested PCR; Multiplex PCR
Kelly MS., 2015 (44)	Gaborone, Bostwana; urban; 2012 – 2014;	Case-control study	1 – 23 months	310	Pneumonia	Nasopharyngeal swabs	Real time Multiplex PCR; Uniplex PCR
Lanaspa M., 2015 (43)	Manhiça District Hospital, Mozambique; rural; 2006 – 2007;	Hospital based cross-sectional study	≤ 59 months	834	Severe pneumonia	Nasopharyngeal aspirate; Blood samples	Multiplex RT-PCR, Blood Culture
Africa, Western							
Ouédraogo S., 2014 (41)	Ouagadougou, Burkina Faso; urban; 2010 – 2011	Hospital based cross-sectional study	0 – 3 years	209	ARTI	Nasopharyngeal aspirate	Immunofluorescence, Culture, Multiplex RT-PCR
Schwarz NG., 2010 (30)	Agogo, Ghana; rural; 2007 – 2009	Hospital based cross-sectional study	2 – 60 months	948	Pneumonia	Blood	Culture
Howie SRC., 2014 (40)	Gambia; rural and urban; 2007 – 2009	Hospital based cross-sectional study	2 – 59 months	55	Severe pneumonia	Lung aspiration or Pleural fluid aspiration	RT-PCR, Culture
Kwofie TB., 2012 (36)	Komfo Anokye Hospital, Ghana; urban; 2008	Hospital based cross-sectional study	≤ 59 months	128	ALRTI	Nasopharyngeal swab; Blood	Real time RT-PCR, Culture
Niang MN., 2010 (29)	Dielmo-Ndiop, Senegal; rural; 2007	Population based cross-sectional study	≤ 59 months	82	ARI	Nasopharyngeal swabs	Multiplex RT-PCR, Viral culture
Weber MW., 2006 (24)	MRC Hospital, Faraja, Gambia; urban; 2005	Case-control study	≤ 59 months	649	ARTI	Nasopharyngeal aspirate, Lung aspiration	RT-PCR, Immunofluorescence, viral culture
Johnson AW., 2008 (26)	University College Hospital, Ibadan, Nigeria; urban;	Population based cross-sectional study	≤ 59 months	419	CAP	Blood,	Immunofluorescence, Culture

Table 2: *Bacteria and fungi were detected by PCR, culture and immunoassay.*

Pathogens detected

Prevalence of viral pathogens

Articles reporting the prevalence of viral pathogens are summarized in [Table 3]. Respiratory viruses were tested for 23 (79.31%) studies. Among 20 providing information on RSV, the prevalence ranged from 4.0% to 35.0%. The majority of studies screened for the presence of RSV infection by using molecular method (RT - PCR). A high RSV prevalence (35.0%) was identified in Botswana among children 1 – 23 months of age with severe pneumonia [44] tested by RT-PCR. In contrast, a low RSV prevalence (4.0%) was identified in South African children hospitalized with acute respiratory tract infections [27] using an indirect immunofluorescence assay.

	RSV	hMPV	PIV	Influenza	hRV	AdV	hCoV	EV	Other viruses
Lanaspa M., 2015 (43)	6.1%	4.8%	3.8%	Influenza A 2.6% Influenza B 2.2%	24.1%	12.6%		2.2%	
Kelly MS., 2015 (44)	35%	6%	PIV1 1% PIV2 1% PIV3 4%	Influenza A 2% Influenza B 1%	hRV A 11% hRV B 2% hRV C 13%	1%			
Nunes MC., 2014 (42)	16.3%	7.4%	4%	Influenza A 4.2%	31.9%	2%	hCoV229E 0.27% hCoV-HKU1 1.5% hCoV-NL63 2.3% hCoV-OC43 6.6%		hBoV 11.9% WUPyV 10.7% KIPyV 6.2%
Lekana-Douki SE, 2014 (38)	13.5%	1.8%	PIV1 3.6% PIV2 2.8% PIV3 7.2%	Influenza A 6.8% Influenza B 5.1%	9.5%	17.5%	hCoV-229E 0.7% hCoV-HKU1 1.2% hCoV-NL63 1.5% hCoV-OC43 4.1%	14.7%	hPeV 0.6%
Feikin DR, 2013 (37)	22%	5.1%	PIV1 1.0% PIV2 3.2% PIV3 6.1%	Influenza A 6.6% Influenza B 1.2%	RV/EnV 50%	16%		RV/EnV 50%	hPeV 1.5%
Niang MN., 2010 (29)	23.6%		3.5%	Influenza A 29.1% Influenza B 12.7% Influenza C 3.7%	14.6%		hCoV-229E 3.7% hCoV-NL63 7.2%		hBoV 1.8%
Cohen C, 2014 (39)	26%	6%	PIV1 2.0% PIV2 1.3% PIV3 6.0%	Influenza 7%	37%	26%		10%	
Hammitt LL, 2012 (34)	26.5%	3.1%	PIV1 1.1% PIV2 0.6% PIV3 5.8% PIV4 1.4%	Influenza A 0.9% Influenza B 0.3% Influenza C 0.4%	22.9%	4.8%	hCoV-229E 2.1% hCoV-NL63 0.5% hCoV-OC43 2.7%		
Venter M, 2011 (31)	30.1%	4.8%	PIV1 1.0% PIV2 1.2% PIV3 7.8%	Influenza A 3.4% Influenza B 1.6%	33%	5.7%	hCoV-229E 0.3% hCoV-HKU1 0.2% hCoV-NL63 2.1% hCoV-OC43 1.8%		
O'Callaghan-Gordo, 2011(32)		7%	PIV1 0.6% PIV2 1.2% PIV3 2.7% PIV4 0.3%	Influenza A 12.3% Influenza B 3.0%	26%			3%	
O'Callaghan-Gordo, 2011* (33)	11%	8%	PIV1 0.6% PIV2 2.1% PIV3 1.5% PIV4 2.3%	Influenza A 4.4% Influenza B 3.8%	41%	21%		4%	

Smuts H, 2008 (27)	4%		PIV1 0.57% PIV2 0.38% PIV3 3.0%	Influenza A 0.76% Influenza B 0.09%		6.2%	hCoV-NL63 0.85%		CMV 15.0%
Howie SRC, 2014 (40)	4%.			Influenza C 2%		4%	hCoV-HKU1 2%	2%	hBoV 4%
Ouédraogo S, 2014 (41)	9.1%	0.5%	0.5%	Influenza A 3.8%	35.4%	1%		12.4%	
Weber WM, 2006 (24)	8.47%		6.5%	Influenza A 8% Influenza B 3.7%		9.9%			
Njouom R, 2012 (35)	10.4%		12%	Influenza A 18.4%	25.6%				
Hussey GD, 2000 (16)	16.4%		2.5%	Influenza B 0.6%		3.7%			
Kwofie TB, 2012 (36)	14.1%		7.8%	Influenza B 0.8%		10%			
Johnson AW, 2008 (26)	30.4%		PIV3 19.5%	Influenza A 17.3%					
Bii CC, 2002 (18)	22%		5%			4%			
Madhi SA *et al*, 2002 (19)			PIV1 22.6% PIV3 75.8%						
Delport SD, 2002 (21)	20.4%								
Zar HJ, 2001 (17)									CMV 14.3%

Table 3: *Results of studies reporting prevalence of viral pathogens.*

Among 20 studies, the prevalence of PIV was found to be between 0.6% and 22.6% for PIV1, 0.4% and 3.2% for PIV2, 1.5% and 75.8% for PIV3, and 0.3% and 3.2% for PIV4. Three studies reported the prevalence of PIV4 infection and RT-PCR was the most frequent diagnosis method used.

The prevalence of influenza virus infection in 19 studies ranged from 0.8% to 29.1% for influenza A, 0.1% to 12.7% for influenza B and 0.4% to 3.7% for influenza C. Influenza C was detected only in 3 studies and RT-PCR was the main diagnosis technique.

Among 16 studies providing information of the prevalence of AdV infections, the prevalence ranged from 1.0% to 26.0%. Adenoviruses were detected mainly by PCR. Using nasopharyngeal aspirate, a high prevalence (26.0%) was found among children less than five years old hospitalized for LRTI in South Africa [39]. Using nasopharyngeal swab specimens, a low prevalence (1%) was reported in Botswana among children aged from 1 – 23 months who were hospitalized with severe pneumonia [44].

Among 13 studies, the prevalence of rhinovirus infections ranged from 9.5% to 41.0%. One study [44] reported type-specific prevalence of 11% for rhinovirus A, 2% for rhinovirus B (2%) and 13% for rhinovirus C.

	S.pneumoniae	*H.influenzae*	*S.aureus*	*M. pneumoniae*	*C.pneumoniae*	*Klebsiella* spp	*Salmonella* spp	Candida spp	*Pneumocystis* spp	Other pathogens
Lanaspa M, 2015 (43)	6.3%	3.4%	0.9%				0.8%		P. jirovecii 6.8%	Enteric bacilli 1.5%
Cohen C, 2014 (39)	4%									
Bii CC, 2006 (25)	5%	3%	13%			K. pneumoniae 43%		C. albicans 45% C.tropicalis 7% C. glabrata 5%	P. jirovecii 13%	*E. coli* 18% P. aeruginosa 3%
Uriyo J, 2006 (23)	63.9%								P. jirovecii 2.8%	*M. tuberculosis* 1.4%
Zar HJ *et al.*, 2001 (17)	1.4%	8.8%	15%			K. pneumoniae 10.9%			P. carinii 9.9%	*P. aeruginosa* 8.2% *M. tuberculosis* 7.4% *M. catarrhalis* 2.7%
Weber WM, 2006 (24)					9.4%					
Nantanda R, 2008 (28)	33.3%	9.5%	42.9%			9.5%	*S. enteritidis* 4.8%			
Bakeera-Kitaka S, 2004 (22)									P. carinii 16.5%	
Were FN, 2002 (20)					51%					

Delport SD, 2002 (21)						*K. pneumoniae* 27.73%				
Schwarz NG, 2010 (30)	4.6%		2.9%			Klebsiella spp 1.2%	S. non typhi 9.3% S. typhi 2.3%			
Johnson AW, 2008 (26)	5.1%		37.3%			Klebsiella spp 15.3%				
Hammitt LL, 2012 (34)				0.4%						
Kwofie TB, 2012 (36)			7.8%			Klebsiella spp 1.5%				
O'Callaghan-Gordo C, 2011 (32)	29%	29%	11%							
Feikin DR, 2013 (37)	0.7%	0.1%		1.5%			S. non typhi 1.9%			
Ouédraogo S, 2014 (41)	27.7%		42.4%			K. pneumoniae 30.3%				
Howie SRC, 2014 (40)	91%	23%	6%			Klebsiella spp 4%				
Bii CC, 2002 (18)	26%		3%	33.7%		K. pneumoniae 1%	1%	13%		*E. coli* 2%

Table 4: *Results of studies reporting the prevalence of bacterial and fungal pathogens.*

The prevalence of hMPV infection ranged from 0.5% to 8.0% (11 studies) and enterovirus (EV) from 2.2% to 14.7% (8 studies). Among 7 studies, the prevalence of human coronavirus (hCoV) infection ranged from 0.3% to 3.7% for hCoV - 229E, 0.2% to 2.0% for hCoV - HKU1, 0.5% to 7.2% for hCoV - NL63 and 1.8% to 6.6% for hCoV - OC43.

Among less common pathogens, the prevalence was 10.7% for WUPyV (1 study), 6.2% for KIPyV (1 study), 14.3% and 15.0% for cytomegalovirus (CMV) (2 studies), 0.6% and 1.5% for human par echovirus (hPeV) (2 studies) and 1.8% to 11.2% for human Boca virus hBoV (3 studies).

Prevalence of bacteria and fungi pathogens

Articles reporting the prevalence of bacterial and fungal pathogens are summarized in Table 4. Nineteen studies (65.5%) with information about prevalence of bacterial and fungal infections were identified. Thirteen studies reported information on Streptococcus pneumoniae infection prevalence, 11 on Staphylococcus aureus (S. aureus), 10 on Klebsiella spp, 7 on Haemophilus influenza (H. influenza), 5 on Pneumocystis jiroveci (P. jiroveci) and Salmonella spp respectively, 3 on Mycoplasma pneumoniae (M. pneumpniae), and 2 on Chlamydia pneumoniae (C. pneumoniae), Candida spp, Pseudomonas aeruginosa (P. aeruginosa), Mycobacterium tuberculosis (M. tuberculosis), and Escherichia coli (*E. colis*) respectively. The prevalence range of these different pathogens was: S. pneumoniae (0.7% - 91.0%), S. aureus (0.9% - 42.9%), Klebsiella spp (1.0% - 42.9%), H. influenza (0.1% - 29.0%), P. jiroveci (9.9% - 16.5%), Salmonella spp (0.8% - 9.2%), C. pneumoniae (9.4% and 51.0%), Candida spp (13.0% ad 45.0%), P. aeruginosa (3.0% and 8.2%), M. tuberculosis (1.4% and 7.4%) and *E. coli* (2% and 18%). The majority of studies on these pathogens were conducted between 2000 - 2009.

Discussion

To our knowledge, this is the first systematic review of the etiology of ARIs in sub-Saharan Africa. Our study reported that many pathogens were detected in different clinical specimens among children less than five years old with ARIs. RSV, PIV, influenza virus, AdV, hRV, S. pneumoniae, S. aureus and Klebsiella spp were the most frequently detected pathogens. PCR was the diagnostic tool most used in these studies; it improves the diagnostic sensitivity over conventional methods for the detection of pathogens in clinical samples [45] and the use of PCR could explain the increase in the detection of pathogens associated to ARIs as compared to conventional methods. Therefore, the findings of PCR testing in respiratory specimens from non-sterile sites must be interpreted judiciously. The presence of viral and bacterial nucleic acids in these specimens does not necessarily mean that these pathogens caused the ARI symptoms [46,47]. In this case, sampling of healthy controls is needed to assess contribution of various pathogens to clinical symptoms. In our study, only 5 (17.3%) studies used this approach. The results of these studies [24,31,34,37] reveal that RSV, influenza virus and PIV 3 are more frequently identified in ARI cases than in healthy controls. More high quality studies on etiologies of ARIs in children are needed in sub-Saharan African countries.

We found little or no data on the etiology of ARIs in many sub-Saharan Africa countries. Indeed, of the 43 sub-Saharan Africa countries, the 29 studies included in this review were done only in 13 countries and about half of these studies were carried out in only two countries: 8 in South Africa and 5 in Kenya. In addition, our literature review identified only one study in Nigeria and none in Democratic Republic of Congo (DRC), both of which are among the 5 countries with the highest burden of child pneumonia deaths in the world [2]. This lack of data could be due in part to a low implementation of research in sub - Saharan African countries.

Also, the majority of these studies were performed before 2010. With the introduction of pneumococcal (PVC) and Haemophilus influenza type b (Hib) conjugate vaccines in many sub-Saharan Africa countries over the last decade [48,49], studies to define the changing epidemiological pattern of pathogens associated with ARIs in children are essential.

Our study has several limitations. First, only publications in the English or French literature were included, excluding for example, data published in Portuguese, which is the official language of five countries (Angola, Cape Verde, Guinea Bissau, Mozambique and Sao Tome and Principe) and Spanish, which is the official language of Equatorial Guinea. Second, the unpublished literature of sub-Saharan coun-

tries other than Burkina Faso was not included in this systematic review. Third, we did not assess study quality but included all articles that met our inclusion criteria.

Figure 2: *Location of the 29 included studies.*

Conclusion

In conclusion, our study revealed that many pathogens mainly viruses are associated with ARIs in children less than five years old. The WHO global strategy to control ARIs in children under five need to account for the importance of non-bacterial cases. The results also highlighted the lack of data in several sub - Saharan Africa countries. Further high quality studies are required to determine the role of viruses and bacteria in childhood ARIs and to define the epidemiology of bacterial ARIs after the introduction of two bacterial conjugate vaccines. Additionally, future systematic reviews should appropriately address the quality of the studies.

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