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World Health Organisation definition of "radiologically-confirmed pneumonia" may under-estimate the true public health value of conjugate pneumococcal vaccines

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Abstract

The public health benefit of conjugate pneumococcal vaccine (PCV) in preventing pneumonia would only be appreciated if the tool used for measuring "pneumococcal pneumonia" had good sensitivity. Exploratory studies in South Africa indicate that the sensitivity of "radiologically-confirmed pneumonia" (CXR-AC) underestimates the burden of pneumococcal pneumonia prevented by PCV by as much as 63%. The use of alternate markers such as C-reactive protein enhance the ability of measuring the burden of pneumonia preventable by PCV. A broadened definition of "pneumococcal pneumonia" which includes episodes of pneumonia associated with CXR-AC and those associated with an abnormal chest radiograph other than CXR-AC associated with a CRP of ≥40 mg/l should be considered an *a priori* outcome in future PCV efficacy trials.

Keywords: Pneumonia; Pneumococcal conjugate vaccine; Prevention; Pneumococcus; Chest radiographs; C-reactive protein

1. Burden of pneumonia and challenges in diagnosing bacterial etiology

Over 90% of the estimated 1.8 million annual deaths due to acute respiratory infections in children less than 5 years of age occur in developing countries and are mainly due to bacterial infections [1]. It is estimated that globally 11–20 million of the 146 million annual childhood episodes of pneumonia, 90% of which also occur in developing countries, require hospitalization [2]. A major obstacle to determining pathogen-specific causes of pneumonia is the lack of a sensitive test for diagnosing bacterial pneumonia [3]. Common bacteria colonizing the nasopharynx in children include *Streptococcus pneumoniae* (25–50%) [4], *Staphylococcus aureus* (20%) [5], *Haemophilus influenzae* mainly unencapsulated, but also 6–12% *H. influenzae* type b in children not vaccinated with *H. influenzae* type b conjugate vaccine, and *Moraxella catarrhalis* [6]. These very same bacteria are commonly implicated in the bacterial etiology of community-acquired pneumonia in children. Due to the high level of colonization it is however difficult to distinguish asymptomatic carriage pathogens from true etiological pathogens.

2. Challenges in evaluating the benefits of conjugate pneumococcal pneumonia against pneumonia

Recent advances in vaccinology have resulted in the development and introduction of conjugate bacterial vaccines that are able to prevent invasive disease as well as mucosal infections [7–9]. A major impediment to evaluating the efficacy and burden of pneumonia preventable by conjugate bacterial vaccines is the absence of a validated sensitive and specific method for confirming the pathogen-specific bacterial etiology of pneumonia [10]. Alternate indicators of the disease targeted by the vaccine are therefore required for measuring the effect of the vaccines against pneumonia. The sensitivity

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and specificity of any morphological feature on chest radiographs in diagnosing non-bacteremic bacterial pneumonia is uncertain. Some studies suggest that chest radiograph features are unhelpful in discriminating between bacterial and viral infections in children [11–13]. These studies may however be flawed as the tool for diagnosing "bacterial" pneumonia was not validated for sensitivity or specificity regarding non-bacteremic pneumonia. Many children with pneumonia in whom a virus but no bacteria were identified may have had unrecognized bacterial co-infections [14].

A study in The Gambia demonstrated the efficacy of *H. influenzae* type b conjugate vaccine in preventing non-bacteremic radiographically confirmed pneumonia as well as invasive disease [15]. This led to a working-group of the World Health Organisation proposing to using a chest radiographic outcome as a benchmark for evaluating the efficacy of PCV against pneumococcal pneumonia [16]. The definition of radiographically confirmed alveolar consolidation (CXR-AC) agreed upon was: "presence of a dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air bronchograms and sometimes associated with pleural effusion, or a pleural effusion in the lateral pleural space associated with a pulmonary infiltrate, or an effusion large enough to obscure such an opacity".

The uncertain sensitivity and specificity of CXR-AC for diagnosing vaccine-serotype specific pneumococcal pneumonia is further confounded by the potential of pneumococcal pneumonia to be caused by non-vaccine serotypes. The complexity of determining the effect of a vaccine in the absence of a gold-standard outcome-measure for diagnosing bacterial pathogen-specific pneumonia has been reviewed [17].

3. Importance of measuring vaccine preventable disease and not only vaccine efficacy

Whereas the specificity of the outcome would influence the vaccine efficacy calculation in a clinical trial, an outcome with a high specificity but low sensitivity may yield a high "vaccine efficacy" but underestimate the burden of disease that is prevented by the vaccine. As an example (Fig. 1), consider the scenario where pneumococci were identified in 80% of episodes of children with CXR-AC, whereas pneumococci were identified in only 20% of pneumonia episodes in which the chest radiograph was categorized as not having CXR-AC. In this example CXR-AC would have a higher specificity for diagnosing "pneumococcal pneumonia" than pneumonia not associated with CXR-AC.

The accurate measurement of the burden of preventable pneumococcal pneumonia would however also depend on the sensitivity of the outcome used. This is pertinent as only 16.5–19% of lower respiratory tract episodes among placebo recipients participating in the PCV efficacy trials in The Gambia and among HIV uninfected children in South Africa had evidence of CXR-AC [18,19]. A more recent hospital-based study on community-acquired pneumonia, the first to use the WHO recommendations for interpreting chest radiographs, showed that 34% of children hospitalized for severe lower respiratory tract infections had CXR-AC [20].

Continuing with the example, consider that for every 20 episodes of radiologically-confirmed pneumonia there were 80 episodes of pneumonia in which the chest radiographs did not show evidence of CXR-AC. The absolute burden of pneumococcal pneumonia prevented would equal the sum of the product of [(number of episodes of specific radiograph pattern of pneumonia) × (specificity of outcome) × (efficacy

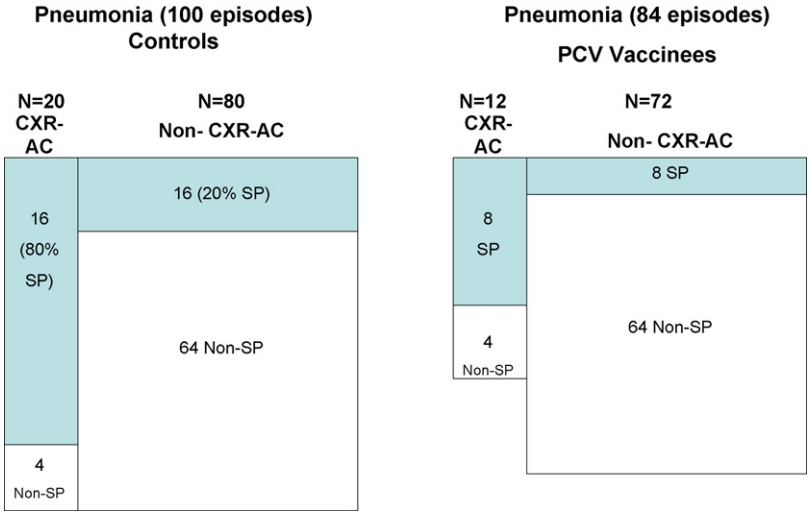

Fig. 1. Illustration of effect of specificity and sensitivity of chest radiographs in detecting the burden of pneumococcal pneumonia prevented by conjugate pneumococcal vaccination (PCV).
Legend: CXR-AC = World Health Organisation defined radiologically-confirmed pneumonia. Non-CXR-AC = any CXR feature other than presence of CXR-AC. SP = *Streptococcus pneumoniae.* Non-SP = non-pneumococcal pneumonia episodes.

of vaccine against specific radiographic pattern of pneumonia)]. Therefore, as illustrated in Fig. 1 assuming that PCV prevents 50% of pneumococcal pneumonia irrespective of the chest radiograph features, the burden of CXR-AC prevented would be (20 episodes × 80% [specificity] × 50% [percentage reduction]) 8 episodes compared with the same number of pneumococcal pneumonia episodes prevented (i.e. 80 episodes × 20% [specificity] × 50% [percentage reduction] in which the chest radiograph did not have evidence of CXR-AC. Hence, the use of CXR-AC alone in such a setting would have under-estimated the burden of pneumonia prevented by PCV by 50%.

Measuring the burden of vaccine preventable disease has become all the more important during the course of the evaluation of conjugate bacterial vaccines since one of the key limitations to the introduction of these vaccines into developed and more so into developing countries would be the relatively high costs of these vaccines. Therefore, an accurate assessment of the vaccine efficacy as well as preventable burden of pneumonia, the most common manifestation of severe pneumococcal disease in children, would be instrumental in determining the cost-benefit ratio of introducing these vaccines into many countries.

4. Translating "vaccine-efficacy" against pneumonia into vaccine preventable burden of disease

When "vaccine efficacy" is measured against the outcome of "culture-confirmed IPD due to vaccine serotypes", the proportion of the outcome which is related to *S. pneumoniae* and the proportion of *S. pneumoniae* implicated in the outcome which are vaccine-serotypes are 100% each. Therefore, the vaccine efficacy calculation would provide a direct evaluation of the vaccine effect in preventing vaccine serotype specific IPD and is the sum of the product of: (i) the proportional contribution of the individual serotype in causing "vaccine-serotype" IPD; and (ii) the efficacy of the vaccine in reducing the incidence of IPD due to that individual serotype.

The interpretation of vaccine-efficacy using CXR-AC as an outcome in measuring the effect of the PCV against pneumococcal pneumonia is however more complex, in part because of the above mentioned reasons. Since we are unable to identify the actual pathogen causing CXR-AC, neither the proportion of CXR-AC due to *S. pneumoniae,* nor the proportion of *S. pneumoniae* serotypes which are vaccine-serotypes are known. Additionally, as has been observed albeit at a low magnitude with IPD and a much greater extent for the mucosal infection of acute otitis media, vaccination with PCV predisposes to an excess of disease due to non-vaccine serotypes [8,21]. In the absence of being able to identify the pathogens causing CXR-AC, the extent of non-vaccine serotypes causing an excess of CXR-AC among PCV recipients would be unknown and may obscure the true effect of the vaccine against vaccine-serotypes negatively.

5. Natural histopathological and radiologic progression in individuals with pneumococcal pneumonia

Although most reviews indicate that a homogenous infiltrate of a segment or more of a lobe is suggestive of pneumococcus and possibly other bacteria, in all likelihood there is a continuum in the spectrum of the radiographic features of pneumococcal pneumonia [11,22]. In one study, an equal number of adult subjects in whom pneumococcal pneumonia were diagnosed presented with lobar consolidation or bronchopneumonia chest radiographic infiltrates [23].

That there is a spectrum in the radiographic presentation of pneumococcal pneumonia is expected when considering the histopathological changes observed following establishment of pneumococcal infection in the lung. In a susceptible host in whom there is an imbalance between the host immunity and virulence of the bacterium infecting the lung, pneumococcal infection of the lung may occur. This may result from micro-aspiration or contiguous spread of pneumococci from the nasopharynx into the alveoli space, usually within 1–2 months of acquisition of a new serotype of pneumococcus [24]. The histopathological changes during the initial 2 days of infection of the alveoli are primarily associated with local capillary congestion with leukocytes and minimal fibrin deposition in the alveoli [25,26]. The corresponding chest radiograph features at this stage are unlikely to show much confluent consolidation of air-space in the lung. In the absence of effective antimicrobial treatment or immune response, there is progression in the histopathological features which are in keeping with fluid and a cellular infiltrate into the alveoli as well as further fibrin deposition. The exudate is further disseminated into adjacent alveoli through the canals of Kohn and pores of Lambart [25]. It is at this stage that the fully-fledged radiographic changes of "pneumococcal pneumonia" probably become radiologically evident. The early radiographic presentation may also be associated with patchy non-segmental infiltrates along the larger bronchioles (i.e. bronchopneumonic changes) resulting from contiguous spread of the bacterium down the airways, which subsequently may also progress to the development of confluent areas of segmental consolidation. Less commonly, pneumococci may infect the lung through hematogeneous dissemination in the body, which classically may present as a "round-pneumonia" on chest radiographs with subsequent progression to involve an entire lobe of the lung [22].

Therefore, in addition to the timing of the chest radiograph in relation to the establishment of infection in the alveolar airspace, the histopathological and radiological features associated with pneumococcal pneumonia may also be influenced by the pathogenesis of infection of the lung and antibiotic therapy during the course of the illness [22]. It is not possible to consider all these factors when performing clinical trials evaluating the effect of vaccine against pneumonia. One way of overcoming the potentially confounding effect of the timing of the chest radiographs and possibly attenuating effect

of preceding antibiotics would be the adjunctive or alternate use of other markers of bacterial infections such as C-reactive protein (CRP), procalcitonin or other measures of pneumococcal infection including antigen or antigen-antibody assays if such markers were less affected by the precise timing of the infection [27–29]. The sensitivity and specificity of these assays however also lack validation, more-so in diagnosing serotype-specific non-bacteremic pneumococcal pneumonia. The usefulness of CRP and procalcitonin in discriminating between bacterial and non-bacterial infections is controversial and has been reviewed [30]. Much of this controversy regarding the usefulness of CRP and procalcitonin relate to the absence of an accurate gold-standard of "bacterial pneumonia" against which the predictive value of these assays can be measured.

6. Sub-studies aimed at a more sensitive indicator of pneumococcal pneumonia

It is in the above context that although the vaccine efficacy trial performed in South Africa was powered to study the efficacy of a 9-valent PCV against culture-confirmed invasive pneumococcal disease and CXR-AC, a number of "hypothesis-generating" sub-analyses and sub-studies were performed [18,31,32]. Some of these studies evolved through discussions in the WHO working-group [16] and were only undertaken after the finalization of the analysis plan for the vaccine-efficacy trial. The sub-studies primarily associated with determining whether different clinical definitions or the use of pro-inflammatory markers such as procalcitonin and CRP were able to enhance the specificity and/or sensitivity of CXR-AC as an outcome measure in evaluating PCV [18,31,32]. Additional previously unpublished data are included in the last column of Table 1. In this analysis, vaccine efficacy and vaccine preventable burden of disease was measured using an outcome of the presence of either CXR-AC or an episode of LRTI associated with an abnormal infiltrate on chest radiograph that was determined not to fulfill the criteria of CXR-AC and which was associated with a CRP level above a defined threshold of $\geq$40 mg/l. Chest radiographs were considered to have an abnormal non-CXR-AC infiltrate if either the pediatrician or radiologist considered the chest radiograph to have such an infiltrate.

The remainder of this review focuses on summarizing the findings of the sub-studies/analyses among HIV uninfected children in the South African trial [18,31,32]. The relative specificity of different outcome-measures as proxy markers of "pneumococcal pneumonia" was determined as the "vaccine-efficacy" of the individual outcome-measures relative to that observed for the benchmark outcome of CXR-AC. This was based on the assumption that the only factor that would influence the vaccine efficacy calculation would be a change in the specificity of the outcome, since the effect of the vaccine against vaccine serotype specific pneumonia and the proportion of pneumonia due to those serotypes would

Table 1
Conjugate pneumococcal vaccine efficacy (VE) and burden of pneumonia prevented in human immunodeficient virus type-1 uninfected children in the South African phase 3 efficacy trial

Outcome	All episodes clinically diagnosed LRTI[a]		CXR-AC and serological test done[b]		CXR without CXR-AC and serological test done[c]		CXR-AC or other Infiltrate observed on CXR[c]	
	VE (95% C.I.)	VAR (95% C.I.)[d]	VE (95% C.I.)	VAR (95% C.I.)[d]	VE (95% C.I.)	VAR (95% C.I.)[e]	VE (95% C.I.)	VAR (95% C.I.)[e]
Clinical LRTI	7 (−1; 14)	172 (−25; 344)	Not calculated		2(−10; 12)	50 (−322; 381)	9 (−7; 22)	150 (−117; 367)
WHO severe LRTI	11 (1; 20)	164 (15; 298)	Not calculated		10 (−5; 23)	180 (−90; 414)	9 (−11; 25)	90 (−110; 250)
CXR-AC	20 (3; 35)	100 (15; 175)	21 (1; 37)	100 (5;176)	Not applicable	Not applicable	15 (−6; 32)[f]	134 (−54; 286)[f]
CRP $\geq$40 mg/l	Not calculated		25 (−4; 46)	49 (−8; 90)	32 (10; 48)	205 (64; 308)	22 (7; 35)[g]	350 (111; 557)[g]
CRP $\geq$120 mg/l	Not calculated		38 (0–61)	40 (0–64)	41 (−5; 66)	70 (−9; 113)	19 (1; 34)[g]	204 (11; 365)[g]

[a] Analysis of all children hospitalized until 15th November 2001 for lower respiratory tract infection (LRTI) looking at different clinical definitions in relation to radiographically confirmed pneumonia (CXR-AC) [18].
[b] Study involved all episodes in children with CXR-AC until 15th November 2001 in whom samples were available for serological tests.
[c] Analysis restricted to episodes of LRTI that occurred in children less than 24 months of age in whom CXR was performed and did not show evidence of CXR-AC and in whom samples were available for serological testing.
[d] Vaccine attributable reduction (VAR) calculated per 100,000 child years of observation.
[e] VAR expressed as per 100,000 study participants.
[f] This is the calculation for CXR-AC for ALL children included in this sub-analysis in whom samples were available for testing.
[g] Calculations include all LRTI episodes with CXR-AC plus those LRTI episodes with a CXR that has an infiltrate other than CXR-AC and which is associated with the defined CRP level.

remain constant in the study-population. A caveat of this however may be that the vaccine may be more efficacious in preventing a certain spectrum of pneumococcal pneumonia identified by an alternate outcome-marker rather than the difference in vaccine efficacy for that outcome being solely due to a difference in the specificity of the outcome for diagnosing pneumococcal pneumonia.

The sensitivity of different outcome-markers in detecting the burden of pneumococcal pneumonia prevented by PCV was estimated by comparing the vaccine attributable reduction (VAR) observed for the outcome relative to the VAR measured using CXR-AC as an outcome. As an example, the VAR for CXR-AC associated with the presence of either a CRP level of ≥40 mg/l or procalcitonin of ≥5.0 ng/ml was 40, whereas that of CXR-AC alone was 100. Therefore, the sensitivity of the former outcome in detecting the burden of pneumonia prevented by vaccination was 40% (40 versus 100) relative to the CXR-AC outcome.

7. Summary results of sub-studies aimed at improving on the sensitivity of CXR-AC in detecting the burden of pneumococcal pneumonia prevented by vaccination

An initial study in children with CXR-AC indicated a synergistic advantage in using CRP and PCT as adjunctive markers for improving the specificity of CXR-AC. A subsequent study in children hospitalized for LRTI in the absence of CXR-AC as well as irrespective of chest radiograph features suggested that CRP offered greater potential than procalcitonin for measuring the effect of PCV against pneumococcal pneumonia [32]. The key findings from these studies, with a special focus on the usefulness of CRP in measuring the efficacy and burden of pneumonia preventable by PCV are summarized in Table 1.

Although an outcome of CXR-AC and a CRP of ≥120 mg/l provided a higher vaccine efficacy estimate (38%) than CXR-AC alone (21%; $P < 0.001$), the burden of prevented disease using the former outcome was only 40% compared when using an outcome of CXR-AC alone. Conversely, an outcome of clinical LRTI provided a lower vaccine efficacy than CXR-AC (7% versus 20%; $P < 0.001$), however detected 41.9% (VAR: 172 versus 100; $P < 0.001$) more episodes of pneumonia prevented compared to that detected using CXR-AC alone.

Among children with LRTI in whom a chest radiograph was performed and who did not have evidence of CXR-AC (Table 1; column 3), the use of CRP ≥40 mg/l as an adjunct marker of possible "pneumococcal pneumonia" resulted in a higher vaccine efficacy estimate (32% versus 2%; $P < 0.001$) and a higher estimate of the burden of pneumonia prevented (VAR: 205 versus 50; $P < 0.001$) compared to the clinical outcome of LRTI alone. The lower VAR estimate for clinical LRTI compared to LRTI episodes associated with CRP ≥40 mg/l may be due to an increased risk of LRTI episodes associated with CRP <40 mg/l in PCV vaccinees than placebo recipients. Although the vaccine efficacy estimate when using a CRP threshold of ≥120 mg/l was greater than when using a threshold of ≥40 mg/l (41% versus 32%; $P < 0.001$), this was associated with only one-third of burden of pneumonia that was prevented being detected (VAR 70 versus 205, respectively; $P < 0.001$) compared to when using a CRP of ≥40 mg/l. The estimate of the burden of pneumococcal pneumonia prevented using an outcome of a CXR performed and no CXR-AC but a CRP ≥40 mg/l was 1.5-fold ($P = 0.0001$) greater compared to the outcome of CXR-AC alone (VAR: 205 versus 134, respectively).

Because PCV has been found to reduce upper respiratory tract infections by 15% [35], and as a clinical diagnosis of LRTI may have a high sensitivity but only low-to-moderate specificity for diagnosing bacterial pneumonia, further analysis was performed to exclude children in whom there was consensus by the radiologist and pediatrician that the chest radiograph was normal. The effect of the study vaccine against a broadened definition of presence of CXR-AC or presence of an abnormal infiltrate on chest radiograph in the presence of a CRP of ≥40 mg/l was evaluated (Table 1; last column). This broadened definition provided a similar vaccine efficacy as CXR-AC alone (22% versus 15%) however detected 2.6-fold (VAR: 350 versus 134; $P = 0.0001$) more episodes of pneumococcal pneumonia that were prevented by vaccination than CXR-AC alone.

The findings of our study may however differ from other situations. Table 2 summarizes the key findings involving the three published studies that have measured the efficacy of PCV against pneumonia [7,9,18,19]. Common to all the studies was that PCV prevented 6–7% of all clinical diagnosed LRTI across the studies and that in the control arm of each study the incidence of CXR-AC was approximately one-fifth to that of clinically diagnosed LRTI. On the contrary, there was a wide variation in the sensitivity of CXR-AC in detecting the burden of pneumococcal pneumonia which was prevented by PCV. Whilst CXR-AC as an outcome detected the vast majority (88%) of pneumonia prevented in The Gambia, it only detected 59% of the pneumonia prevented in South Africa relative to using the VAR of "clinically diagnosed LRTI" as a benchmark. This difference in the sensitivity of CXR-AC in detecting the burden of pneumococcal pneumonia that was prevented in The Gambia compared to South Africa may be due to factors such as delayed presentation to health-care facilities until more ill and less access to antibiotics at the community level in The Gambia. The sensitivity of radiographically confirmed pneumonia in detecting the burden of pneumococcal pneumonia prevented in the US study, which did not use the WHO recommended guidelines for interpretation and reporting, was found to be 78% relative to that of clinically diagnosed LRTI. Direct comparisons of the effect of PCV against pneumococcal pneumonia in the different studies are limited due to differences in study-design, study-population, possible antibiotic treatment preceding chest radiography, indications and threshold for

Table 2
Summary of conjugate pneumococcal vaccine efficacy (VE) burden of pneumonia prevented in efficacy trails in the USA, South Africa and The Gambia

Country where study done	All clinically diagnosed LRTI			Radiologically-confirmed pneumonia (CXR-AC)		
	V.E (95% C.I.)	Incidence in controls[a]	VAR[b]	V.E. (95% C.I.)	Incidence in controls[a] (proportion)[c]	VAR[b]
USA [7]	6.0 (−1.5; 11)	4580	230	18 (5; 29)	1010 (22%)[c]	180 (78%)[d]
RSA HIV uninfected children [18]	7.0 (−1; 14)	2566	172	20 (3; 35)	491 (19%)[c]	100 (59%)[d]
The Gambia–per protocol [19]	7.0 (1; 12)	24850	1700	37 (27; 45)	4090 (17%)[c]	1490 (88%)[d]

Note: Intent-to-treat data included from the USA and South African studies.
[a] Incidence rate per 100,000 child years in the control group of the trial.
[b] Vaccine attributable reduction (VAR) per 100,000 child years.
[c] Percentage in parenthesis is the proportion of clinically diagnosed lower respiratory tract infection (LRTI) that had evidence of "radiologically-confirmed pneumonia" among placebo recipients.
[d] Percentage of CXR-AC VAR compared to VAR observed for clinically diagnosed LRTI.

performing chest radiographs and case-ascertainment strategies.

8. Conclusions

The analyses presented here indicated that exclusive use of the WHO defined CXR-AC markedly underestimated the burden of pneumococcal disease preventable by PCV in the South African efficacy trial. Additionally, other factors need to be considered when determining the public health value of PCV which is independent of the sensitivity and specificity of the endpoint used for detecting pneumococcal pneumonia. This includes issues such as the impact of the vaccine against mortality and differences in cost-of-care of managing pneumonia. These issues are beyond the scope of this review.

We have described that the use of CRP may provide an alternate independent proxy for measuring vaccine efficacy and preventable burden of pneumonia compared to the use of chest radiographs [32]. CXR-AC however remains a benchmark that has been agreed upon for evaluating vaccine efficacy [16]. The data from the sub-studies suggest that at the least the use of CRP be considered together with chest radiographs in broadening the outcome used to measure the effect of PCV against pneumococcal pneumonia. In particular, to reduce the chance of under-estimating the burden of pneumococcal pneumonia that is preventable by PCV, an outcome including all cases of CXR-AC together with episodes of LRTI that are associated with an abnormal infiltrate without evidence of CXR-AC and in which the CRP is $\geq$40 mg/l needs to be considered in future vaccine trials.

The data from the South African sub-studies and ad-hoc analysis however need to be tested *a priori* in future studies. Furthermore, differences between different clinical trials and studies include (i) the design of studies (e.g. purely hospital based surveillance for outcomes versus in-patient and out-patient surveillance; active versus passive surveillance for outcome cases); (ii) health-care resources and health-care access in the community (e.g. access to antibiotics outside of clinical trail setting); (iii) the threshold for investigating subjects even in a clinical trial situation; (iv) presence of other endemic illness (e.g. malaria), may all possibly influence the findings in other populations.

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