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An assessment of the clinical effectiveness of World Health Organization guidelines for the management of pneumonia among hospitalised children in Kenya.

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Declaration

I, Ambrose Agweyu, declare that this thesis was submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

Acknowledgements

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GAPPD	Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
Hib	*Haemophilus influenzae* type B
HIV	Human immunodeficiency virus
PERCH	Pneumonia Etiology Research for Child Health
PMTCT	Prevention of Mother to Child Transmission of HIV
PRECIS	PRagmatic Explanatory Continuum Indicator Summary
RCT	Randomised Controlled Trial
RSV	Respiratory Syncitial Virus
SDG	Sustainable Development Goals
UNICEF	United Nations International Children's Fund
WAZ	Weight-for-age Z Score
WHO	World Health Organization

Abstract

Background: The effectiveness of World Health Organization (WHO) guidelines for pneumonia case management in sub-Saharan Africa has been contested. This thesis aims to determine the clinical effectiveness of these guidelines among children admitted to Kenyan hospitals in a period after the introduction of the pneumococcal and *Haemophilus influenzae* type B (Hib) conjugate vaccines. The studies focus on the treatment of children with chest indrawing pneumonia, who were previously regarded to be at high-risk requiring inpatient treatment but were reclassified as low-risk (non-severe) in the WHO guidelines updated in 2013.

Methods: This thesis consists of: (i) A systematic review linked to a national guideline-development exercise appraising the evidence for the WHO pneumonia guidelines, (ii) a prospective observational study evaluating adherence to, and effectiveness of the pneumonia guidelines in the national referral hospital in Kenya, (iii) a multi-centre pragmatic randomised controlled trial (RCT) comparing amoxicillin versus benzyl penicillin for chest indrawing pneumonia (iv) a cohort study comparing treatment effects among children enrolled in the antibiotic RCT with a similar group who received routine care, and (v) a multi-centre retrospective cohort study of children hospitalised with pneumonia describing factors associated with mortality, focusing on characteristics that increase risk of death among children who would, under current guidance, be assigned a non-severe classification.

Results: Although evidence from clinical trials supported the adoption of oral amoxicillin for severe pneumonia over benzyl penicillin (the standard treatment) for chest indrawing pneumonia, a Kenyan guideline development panel raised concerns of generalizability citing the limited data from sub-Saharan African populations in whom mortality was argued to be high. This concern was explored using prospectively-collected observational data from 385 children. Treatment failure and mortality were infrequent (<2%) for chest indrawing pneumonia where strict definitions requiring documented evidence of clinical deterioration were applied. In comparison, high rates of treatment failure (21.4%) and mortality (10.5%) were observed for severe pneumonia (formerly very severe pneumonia). Using propensity scores to model treatment effects comparing guideline recommended regimens with more costly, broad-spectrum alternatives, similar risks of treatment failure were observed in both groups. Amoxicillin was compared with benzyl penicillin in a pragmatic clinical trial of 527 children that also revealed low and comparable risks of treatment failure (8%) and mortality (<1%) for the two treatments. Consistent results were observed in an observational cohort of children hospitalised at the same health facilities over the period the trial was conducted. However, analyses of data from >16000 children suggested that the presence of commonly-occurring clinical signs may be associated with increased risk among children with non-severe pneumonia. Specifically, very low weight-for-age Z score (WAZ) or pallor in children with non-severe pneumonia were shown to be associated with absolute risks of mortality as high as those for severe pneumonia.

Conclusions: Findings from locally-conducted observational studies and a clinical trial indicate low risks of treatment failure and mortality among children with chest indrawing pneumonia following treatment with benzyl penicillin monotherapy or amoxicillin. In contrast, mortality for severe pneumonia was greater than 10 percent. These results are consistent with the updated WHO recommendations and have more recently informed the revision of the national policy for pneumonia case management in Kenya. However, these guidelines may apply to sub-populations of children with non-severe pneumonia and either very low WAZ or pallor. This evidence is expected to contribute to ongoing debates on the adoption of WHO guidance for pneumonia case management in similar settings across sub-Saharan Africa where coverage of the Hib and pneumococcal conjugate vaccines is high.

1   Introduction

Child mortality has declined substantially over recent decades; however, pneumonia continues to claim the lives of almost one million children annually. Over half of the global pneumonia-related deaths occur in sub-Saharan Africa (1, 2). Empirical treatment of children with clinically-suspected pneumonia using simple antibiotics is a major component in a package of evidence-based interventions promoted by the World Health Organization (WHO), UNICEF and other development partners to reduce mortality due to pneumonia (3). This strategy, widely referred to as case management, is founded on four basic assumptions: (i) a high proportion of fatal pneumonia is of bacterial origin (mostly *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae*), (ii) timely antibiotic therapy of these infections substantially reduces pneumonia case fatality, (iii) an algorithm based on simple clinical signs is sensitive and adequately specific in identifying children with pneumonia requiring antibiotic therapy, and (iv) health workers can use this algorithm and provide antibiotics to children (4). The effectiveness of this strategy has been studied widely with independent reports estimating that antibiotic treatment alone for severe forms of pneumonia may result in a 6 – 15 percent reduction in mortality (5, 6). Prior to the most recent revision of the WHO case management guidelines, a common clinical algorithm was adopted across all the major WHO regions and remained largely unchanged for almost 30 years. Under these guidelines, children with a history of a cough and difficulty in breathing were assigned to one of four levels of severity (including no pneumonia) based on presenting clinical signs. It is these signs that then informed the choice of empirical antibiotic treatment (Table 1).

Table 1: WHO (2005) guidelines for the management of children aged 2 - 59 months with a cough and/or difficulty breathing

Syndrome*	Clinical Signs	Recommended Antibiotic Treatment
Very severe pneumonia	Any one of: cyanosis, grunting, inability to drink, altered consciousness	Inpatient treatment Benzyl penicillin/ ampicillin and gentamicin (*plus* high dose co-trimoxazole for all HIV-exposed)
Severe pneumonia	Lower chest wall indrawing AND without signs of very severe pneumonia	Inpatient treatment Benzyl penicillin/ ampicillin monotherapy (if HIV-exposed, treat as very severe pneumonia)
Non-severe pneumonia	Fast breathing (RR≥50/min if age 2-11months; ≥40/min if age 12-59 months) AND without signs of severe or very severe pneumonia	Outpatient treatment Co-trimoxazole (or amoxicillin if child has HIV and is receiving co-trimoxazole prophylaxis)

*For a child without stridor, severe acute malnutrition or signs of meningitis

Inpatient treatment with injectable antibiotics was reserved for children with severe and very severe classifications of pneumonia while children with "non-severe pneumonia" were to be managed at home with oral antibiotics (7).

In the following section (Section 2), I present a background to the issues tackled in this thesis, before providing the historical basis of the WHO case management guidelines in Section 3, and a brief description of the published aetiological studies on childhood pneumonia in Section 4. In Section 5, I outline some of the important risk factors that may account for variability in clinical outcomes of treatment over recent years and across populations under the existing case management guidelines, focusing on children in sub-Saharan Africa. I then summarise the individual publications that contribute to this thesis in Section 7 and finally present a discussion (Section 8), highlighting important areas for further research in the field in Section 9.

2 Background to the thesis

For the most recent revision of the guidelines for treatment of childhood illnesses, WHO adopted an evidence-driven approach to generate recommendations that were eventually incorporated in the updated Pocket Book for the Management of Sick Children (8). In this exercise, the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology was used to systematically appraise and rank existing evidence based on the quality of the primary studies, and ultimately develop recommendations after considering local contextual factors (9).

In what is widely regarded a major revision in the WHO guidelines for management of childhood pneumonia, the guideline development panel made a strong recommendation based on moderate quality evidence that children with indrawing pneumonia without danger signs should be treated as outpatients with oral amoxicillin – effectively downgrading their classification from severe to non-severe (Table 1). This decision was primarily based on evidence from three clinical trials comparing treatment effects of benzyl penicillin versus oral amoxicillin (10-12) and after considering additional factors including risks, benefits, acceptability and feasibility of adopting oral amoxicillin.

Researchers, policymakers and clinicians across sub-Saharan Africa have expressed reluctance to adopt these revised recommendations, citing concerns that the population of children presenting with indrawing pneumonia in Africa may experience poorer outcomes than those who were enrolled in the studies that eventually informed the WHO revised guidelines (13). Indeed, results from observational studies indicate that despite the guidelines being widely available, clinicians in Kenya frequently prescribe alternative, perceivably "stronger" antibiotics, presumably due to doubts regarding the effectiveness of the recommended treatment regimens (14, 15).

These concerns are supported by evidence from studies showing wide regional variation in the risk of death among children with pneumonia. In a systematic review of 37 published observational studies of children ranging from 0 – 59 months old hospitalised with pneumonia, reported case fatality was 0.4 percent in industrialized countries, 2.1 percent in southeast Asia and 3·9 percent in Africa (16) (Table 2). These data suggest that pneumonia-related mortality may be higher in sub-Saharan Africa than in other regions of the world including Asia, where the bulk of the data that informed the recent WHO pneumonia guideline updates were drawn from (8).

Table 2: Case fatality rates for severe acute lower respiratory infections in children younger than five years by region

Region	Aged 0 – 11 months		Aged 12 – 59 months		Aged 0 – 59 months	
	Studies	CFR (95% CI)	Studies	CFR (95% CI)	Studies	CFR (95% CI)
Africa	9	3·8% (2·4–5·9)	8	1·9% (1·2–3·2)	11	3·9% (2·7–5·5)
Americas	10	1·6% (1·1–2·4)	10	0·6% (0·2–1·3)	11	1·3% (0·8–1·9)
Europe	-	-	-	-	1	0·4% (0·3–0·5)
Southeast Asia	6	2·6% (1·4–4·7)	4	0.3% (0·1–0·9)	9	2·1% (1·1–4)
Western Pacific	1	2·4% (1·3–4·3)	-	-	3	2·3% (1·7–3·2)
Developing	25	2·4% (1·7–3·6)	21	0·8% (0·4–1·3)	32	2·3% (1·6–3·4)
Industrialized	1	0·8% (0·7–0·9)	1	0·3% (0·2–0·5)	3	0·6% (0·4–0·8)
Global	26	2·3% (1·5–3·4)	22	0·7% (0·4–1·2)	35	2·1% (1·4–3·1)

Adapted from Nair *et al.* 2013(16))   CFR – Case Fatality Rate   CI – Confidence interval

There is, therefore, uncertainty regarding the effectiveness of the global guidance for antibiotic therapy of pneumonia in Africa, fuelled by factors that are believed to have altered the epidemiology and clinical severity of pneumonia since the guidelines were introduced. Among these factors are: (i) Introduction of vaccines targeting *Haemophilus influenzae* type B and *Streptococcus pneumoniae* – previously the leading causes of bacterial pneumonia in children, (ii) changing prevalence of major risk factors for mortality in pneumonia, particularly HIV and possibly malnutrition, and (iii) increasing resistance to the antibiotics used for treating pneumonia. In addition, there are questions concerning the external validity of evidence derived from equivalence / non-inferiority clinical trials comparing antibiotics for pneumonia to routine clinical settings. Specifically, concerns have been raised regarding the very low case-fatality rate among clinical trial patients suggesting biased selection of children with lower severity of illness and the potential role of the so-called "Pollyanna Phenomenon" in antibiotic studies resulting from a "dilutional effect" of patients with self-limiting disease e.g. viral illness, who recover regardless of care, thus steering trial results towards equivalence (13, 17, 18).

To further expound on the bases of these controversies that may account for the hesitancy in adoption and implementation of the WHO guidelines in Kenya and other sub-Saharan African countries, a background to the original case management guidelines is provided in the following section.

3   Historical overview of WHO pneumonia case management

Recognizing the need to address the enormous burden of childhood pneumonia in developing countries a meeting was convened by WHO to develop a structured approach to the management of children with acute lower respiratory tract infections in low-level facilities (19) in 1980. At this meeting, initial draft of the algorithm for the management of childhood pneumonia that was subsequently adopted across developing countries approximately ten years later was shared. The primary evidence that informed the assignment of the severity classifications still currently in use in many countries today draws from work conducted in Papua New Guinea describing possible criteria for identifying children with acute respiratory infections requiring antibiotics and inpatient care (20). In this study, 350 children aged 0 – 59 months were enrolled prospectively using the presence of crepitations to define those

who required antibiotics. Fast breathing was determined to have high specificity and sensitivity for identifying children requiring antibiotics. Lower chest wall indrawing was identified in all 50 children hospitalised with pneumonia with crepitations. This finding formed the basis of the current recommendation for inpatient treatment for children with indrawing. In a later study, the same team sought to validate the severity classification of pneumonia in a cohort of 748 children aged above 28 days admitted at three hospitals with WHO-defined severe forms of pneumonia. The overall mortality rate observed was 15 percent. Clinical signs that were found to be strongly associated with mortality in univariate analyses included the presence of malnutrition, cyanosis, duration of illness of five or more days, the absence of fever (among malnourished children), and inability to feed. Severe indrawing and grunting were weakly associated with mortality (P<0.06) while tachypnoea (respiratory rate >70 breaths per minute) showed no association with mortality (21). In a more recent review of six studies discussing the diagnostic utility of the WHO pneumonia case management clinical signs in predicting radiological pneumonia, sensitivity of tachypnoea ranged from 72 percent to 94 percent with specificities between 38 percent and 99 percent, while chest indrawing had reported sensitivities of between 46 percent and 78 percent (22). The authors of this review further report clinically-defined improvement 48 hours into treatment in at least 80 percent of children treated using recommended antibiotics, suggesting effectiveness of the guideline regimens. The lack of standardised definitions for clinical success or treatment failure in pneumonia is however acknowledged as a general limitation in this, and other studies (23, 24).

4   Aetiological studies on childhood pneumonia

Reliable data on the causes of pneumonia are scarce for several reasons: (i) The "gold standard tests" for microbiological diagnosis (lung aspirates and biopsy) are technically demanding, risky, invasive procedures. (ii) The yield from the traditional method of microbiological diagnosis using bacterial blood cultures is low, ranging from 1 – 7 percent (25, 26) (iii) Many patients present to hospital after having received antibiotics, further limiting the yield of available diagnostic tests. (iv) There is often difficulty distinguishing harmless commensal organisms from pathogens. Interpretation of results across studies is complicated further by the poor standardisation of case definitions and procedures (27).

The empirical antibiotic regimen for treatment of childhood pneumonia is based on a number of small studies summarised in a review of lung aspiration studies conducted in developing countries published in 1986 (28), several years prior the introduction of the pneumococcal and *Haemophilus influenzae* type B conjugate vaccines. A total of 13 studies conducted in 8 countries recruiting 1029 children were reviewed. Of these, 640 (62 percent) yielded positive bacterial cultures. The most frequently isolated organisms were *Streptococcus pneumoniae* (27 percent), *Haemophilus influenzae* (27 percent) and *Staphylococcus aureus* (17 percent). While this work provided valuable evidence on the causes of pneumonia in children, the primary studies had serious methodological limitations including the variability of case definitions used and the lack of appropriate control groups. These results were later supported in a large longitudinal study undertaken from 1985 – 1989 in ten low-income countries (29). In this project coordinated by the Board on Science and Technology for International Development (BOSTID), cohorts of children aged 0 – 59 months were recruited prospectively in both outpatient and inpatient departments. Data on sociodemographic and clinical characteristics, incidence, duration, prevalence and case fatality of respiratory tract infections were recorded for all patients. Specimens were also collected from a selected group of patients to study the aetiology of respiratory infections. Viruses were found to be more common than bacteria as causes of lower respiratory tract infections (14 – 64 percent versus 4.5 – 40 percent). However, the failure to obtain lung aspirate samples in this study may have reduced the ability to detect bacterial organisms. The most common bacterial organisms were *Streptococcus pneumoniae* followed by *Haemophilus influenzae* at all sites except in Pakistan where *H. influenzae* was more frequent.

Numerous smaller studies have been undertaken in a variety of settings since the BOSTID studies. In a survey of studies conducted between 2000 and 2010, 65 childhood pneumonia aetiology studies were identified, representing 41 countries (27). The wide variation in methods employed and lack of uniform case definitions across different studies was cited as a limitation to the potential collective utility of the individual studies to provide the lacking understanding of the causes of childhood pneumonia in the present era. Some of this information is anticipated to availed upon the announcement of the findings of the Pneumonia Etiology Research for Child Health (PERCH) project – a large rigorously conducted multicountry case control pneumonia aetiological study designed specifically to identify the expected etiologies of pneumonia in the period post-introduction of the pneumococcal and Hib vaccines (30). Available results from a pre-pneumococcal, post- *H. influenzae* type B vaccine

pilot study of 810 PERCH study participants in coastal Kenya showed a statistically significant association with hospitalisation (odds ratio, 12.5; 95 percent confidence interval, 3.1–51.5) for nasopharyngeal isolation of Respiratory Syncytial virus (RSV). However, the clinical significance of most viruses identified was not clear, given the high prevalence of viral detection in controls. Among 728 patients with both blood culture and HIV testing performed, a positive culture was more common among HIV-positive patients (14/69; 20 percent) than those who were HIV negative (36/659; 5 percent) (P<.001). Bacteria isolated in blood culture were: *Streptococcus pneumoniae* (n=30), nontyphi salmonellae (n=6), *H. influenzae* (n=4), *Escherichia coli* (n=4), *Klebsiella* species (n=3), group D streptococcus (n=1), *S. aureus* (n=1), *Burkholderia* species (n=1), *Moraxella catarrhalis* (n=1), and *Campylobacter jejuni* (n=1). The investigators were unable to determine the aetiology of pneumonia for the 32 fatal cases recruited.

5 Risk factors for clinical severity and mortality among children with pneumonia

Sonego *et al.* studied risk factors for mortality in a large systematic review of 77 studies conducted in low- and middle-income countries including almost 200,000 children (31). Very severe pneumonia, age below two months, *Pneumocystis carinii* infection, comorbidities including HIV infection and severe malnutrition, young maternal age, low maternal education, low socio-economic status, second-hand cigarette smoke exposure, and indoor air pollution were each independently associated with increased mortality. Childhood immunisation and attendance of antenatal care were associated with decreased odds of death. In this section, some of these factors that may have altered pneumonia-related mortality in Kenya and similar countries in the region are discussed in detail.

5.1 Impact of conjugate vaccines

Numerous studies have demonstrated the impact of both pneumococcal and Hib vaccines on the incidence of disease attributable to the two bacterial agents previously responsible for the greatest burden of childhood pneumonia. Evidence of effectiveness of these vaccines has been shown in both high and low-income settings (32-35). Epidemiological data from Kenya suggest that the introduction of the Hib

vaccine resulted in an 88 percent decline in invasive disease due to Hib within tree years of introduction (36) (Figure 2).
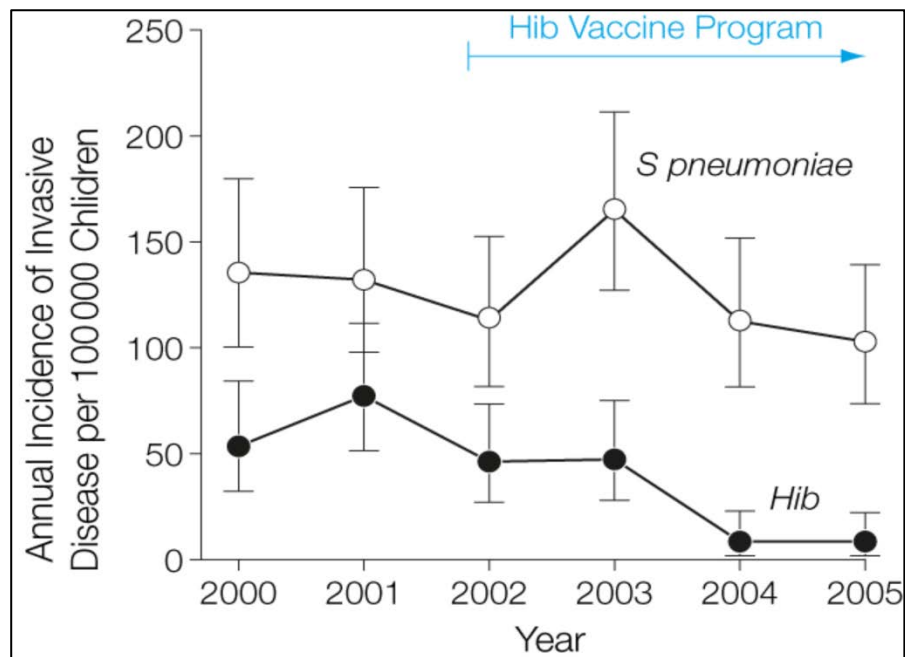
Figure 1: Incidence of invasive Haemophilus influenzae type B (Hib) Disease at Kilifi District Hospital pre- and post-Hib vaccine introduction (source: Cowgill *et al.*, 2006)

Early data from unpublished reports from the same site indicate a similar downward trend in the incidence of invasive pneumococcal disease following the introduction of the 10-valent pneumococcal conjugate vaccine to the national routine childhood immunisation schedule in 2011. These findings have an important bearing on the prevailing aetiological agents of pneumonia (37), particularly in settings with high coverage of the two vaccines, such as Kenya where the most recent national survey reports approximately 80 percent coverage for all basic vaccines among children aged 12 – 23 months (38).

5.2   Effect of undernutrition on pneumonia

Undernutrition is a well-established risk factor for childhood infections including pneumonia and is associated with high mortality in severe cases (39-42). The mechanisms underlying the increased incidence of pneumonia and poor clinical outcomes among undernourished children are still poorly understood but are widely thought to be partly linked to an acquired immune deficiency (43-45). In a systematic review of 16 studies, children with pneumonia classified with moderate and severe

malnutrition invariably experienced higher risks of death (41). In one study that enrolled almost 10,000 children in Chile, the risk of death among malnourished children was 121 times higher than that for children of normal nutritional status (46). In eleven of the studies in the review which reported on aetiology (total of 215 positive bacterial isolates studied), *Klebsiella pneumoniae* was the most frequently isolated pathogen (26 percent) followed by *Staphylococcus aureus* (25 percent), *Streptococcus pneumoniae* (18 percent) *Escherichia coli* (8 percent) and *Haemophilus influenzae* (8 percent). In their conclusion, the authors challenge the failure of the WHO guidelines to take account of the spectrum of pathogens responsible for pneumonia in malnourished children.

5.3   HIV infection and childhood pneumonia

HIV-infected children experience increased risks of acquiring pneumonia (47) and an increased frequency of pneumonia-related death (48-51). In addition, HIV-infected children are susceptible to a wider spectrum of organisms causing pneumonia than those who are HIV negative. *Mycobacterium tuberculosis* and *Pneumocystis jirovecii* are notably important causes of pneumonia in HIV-infected children (48, 52). With current efforts towards the elimination of mother to child transmission of HIV, mainly through increasing the coverage of the Prevention of Mother to Child Transmission (PMTCT) interventions (90 percent of HIV infected mothers in 2012) (53), the prevalence of HIV infection among children is expected to have declined globally. The most recent Kenya AIDS Indicator Survey reported a prevalence of HIV infection of 0.9 percent among children aged 18 months to 14 years (53). As paediatric HIV prevalence declines, the incidence of severe forms of pneumonia and mortality associated with the HIV are also expected to decrease. Of importance, however, is the increased burden and risk of poor outcomes (death and treatment failure) among children who are HIV-uninfected but born to HIV-infected mothers (HIV-exposed uninfected children) compared to HIV uninfected (48, 54-57). The mechanisms underlying this association are currently poorly understood but may be related to socioeconomic factors linked to living in an HIV-affected household or direct biological effects of increased exposure to maternally infections including cytomegalovirus, reduced transplacental transfer of antibodies from immunocompromised mothers, or impaired responses to vaccines (58).

6   Objective

The overarching objective of this PhD thesis is:

to assess the effectiveness of the World Health Organization guidelines for the management of childhood pneumonia among hospitalised children in Kenya.

7   Manuscripts for PhD submission

The works consist of: (i) A systematic review describing the process and results of evidence synthesis undertaken for clinical questions discussed during a national exercise for the local adaptation of the WHO pneumonia guidelines in Kenya. (ii) A prospective observational study of the adherence to and effectiveness of the national childhood pneumonia treatment guidelines in a large tertiary hospital. In this study, I also describe the use of propensity scores to model treatment effects of various antibiotic regimens adopted by hospital clinicians. (iii) A randomised controlled trial (RCT) conceptually borne out of the concerns raised by the national guideline panel of experts (described in the systematic review) comparing the effectiveness of oral amoxicillin versus benzyl penicillin for the treatment of children with severe pneumonia in Kenya. (iv) A cohort study examining the external validity of the findings of the RCT using data collected from a parallel observational cohort of children with pneumonia who received routine care at the RCT sites. (v) A retrospective cohort study of children hospitalised at 14 sites with pneumonia classified using the post-2013 WHO categories of severity (non-severe, and severe) that describes the factors associated with mortality, focusing on those that increase risk substantially among children who would be assigned a non-severe classification under current guidance. The five manuscripts, published in peer-reviewed journals, are summarised in the section below.

1. Agweyu A, Opiyo N, and English M. *Experience developing national evidence-based clinical guidelines for childhood pneumonia in a low-income setting - making the GRADE? BMC Pediatr. 2012;12:1.*

In 2009, the Kenyan Ministry of Health requested for technical support to revise the national paediatric guidelines. I was responsible for conducting evidence synthesis for clinical questions specific to antibiotic treatment of childhood pneumonia. With relatively limited resources, we applied a modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

to appraise and summarise the available evidence ahead of the guideline review meeting. Evidence from clinical trials, although initially ranked as high quality, frequently raised concerns of generalizability among the panellists based on the absence of studies conducted in sub-Saharan African populations in whom mortality was argued to be high. A notable example was the panel's decision to vote strongly against adoption of oral amoxicillin for severe pneumonia over benzyl penicillin despite moderate quality evidence suggesting clinical equivalence between the two and additional factors favouring amoxicillin. In this paper, we argue that, while this exercise may have fallen short of the rigorous requirements recommended by the developers of GRADE, it represented a major improvement on previous attempts at guideline development in low-income countries and offers valuable lessons for future similar exercises where resources and locally-generated evidence are scarce.

2. Agweyu A, Kibore M, Digolo L, Kosgei C, Maina V, Mugane S, Muma S, Wachira J, Waiyego M, and Obimbo E. *Prevalence and correlates of treatment failure among Kenyan children hospitalised with severe community-acquired pneumonia: a prospective study of the clinical effectiveness of WHO pneumonia case management guidelines. Trop Med Int Health. 2014;19(11):1310-20.*

Against a background of limited local evidence on the effectiveness of the WHO pneumonia case management guidelines, I led a team of investigators in conducting a prospective observational study on the clinical outcomes of pneumonia in a large teaching hospital in Nairobi, Kenya. In this study of 385 children, treatment failure was heavily influenced by early changes in therapy by clinicians in the absence of an obvious clinical rationale. Where a strict definition of treatment failure requiring documented evidence of clinical deterioration was applied, low rates of failure were observed. Non-adherence to treatment guidelines was common (41 percent of children with severe pneumonia and 33 percent those with very severe pneumonia). Taking advantage of the large number of children who were treated with non-standard regimens, I used propensity scores to model treatment effects comparing guideline recommended regimens with more costly, broad-spectrum alternatives used while accounting for imbalances in the distribution of baseline characteristics that may have influenced clinician treatment choices. In these exploratory analyses, similar risks of treatment failure were observed in both groups. In my conclusions, I am careful to state the limitations of the findings and recommend appropriately designed pragmatic trials to address clinical questions of this nature.

3. Agweyu A, Gathara D, Oliwa J, Muinga N, Edwards T, Allen E, Obimbo E, and English M, on behalf of the Severe Pneumonia Study Group. *Oral amoxicillin versus benzyl penicillin for severe pneumonia among Kenyan children: a pragmatic randomized controlled noninferiority trial. Clin Infect Dis. 2015;60(8):1216-24.*

While clinical trials conducted in predominantly Asian populations demonstrating clinical equivalence between amoxicillin and benzyl penicillin led to a revision of the WHO pneumonia guidelines in 2013, Kenyan policymakers declined to support a change in the guidelines in the absence of supporting evidence from African populations citing concerns of high mortality in Africa. Details of the national guideline development exercise which involved over 70 experts form clinical, policy and academic backgrounds are provided in the first paper summarized above (Agweyu *et al.* 2012). In response to this gap in evidence, I led a team in designing and conducting a multi-centre pragmatic clinical trial to compare the effectiveness of the two antibiotics. A total of 527 children aged 2–59 months with severe pneumonia as defined in the 2005 WHO guidelines were recruited from 6 public hospitals across Kenya. The risk of treatment failure was 7.7 percent in the amoxicillin arm and 8.0 percent in the benzyl penicillin arm at 48 hours in per-protocol analyses (risk difference, −0.3 percent [95 percent confidence interval, −5.0 percent to 4.3 percent]), indicating non-inferiority within the pre-specified margin of 7 percent at 48 hours. Similar results were obtained in intention-to-treat analyses. Mortality was low (0.8 percent) and comparable to reported findings of the previous trials conducted in Asia that informed the WHO technical updates in 2013. The findings of this study offer important evidence for policymakers in sub-Saharan African considering the local adaptation of the recent global recommendations for the management of childhood pneumonia.

4. Agweyu A, Oliwa J, Gathara D, Muinga N, Allen E, Lilford RJ, and English M. *Comparable outcomes among trial and nontrial participants in a clinical trial of antibiotics for childhood pneumonia: a retrospective cohort study. J Clin Epidemiol. 2018;94.*

Evidence derived from well-conducted randomised controlled trials (RCTs) is generally regarded to be of high quality. However, critics often argue that the strict enrolment criteria and intensive follow up of patients enrolled in clinical trials compromise the generalizability of the findings to routine care settings. In public

hospitals in many low- and middle-income countries, the quality of care delivered to patients in routine settings is substantially poorer than that provided for patients enrolled in clinical trials (regardless of treatment allocation). In this paper, I seek to compare mortality among children enrolled in the RCT comparing the effectiveness of two antibiotics for severe childhood pneumonia described above (Agweyu *et al*, 2015), with a similar observational cohort of children hospitalised at the same health facilities over the period the trial was conducted. Out of 1709 eligible children, 30.8 percent were enrolled in the RCT. No difference was observed in mortality between the two groups in unadjusted analyses comparing RCT versus non-RCT participants (OR 0.6; 95 percent CI 0.2 to 1.9). Similar results were found in adjusted models using multiple imputation to account for missing data. In the discussion, I highlight the utility of the findings of this study for policymakers considering the generalizability of evidence from clinical trials suggesting low mortality among children with severe pneumonia. I also describe the methodological limitations of using routine data for policy making, particularly in settings where health information systems are weak.

5. **Agweyu A,** Lilford RJ, and English M. *Appropriateness of clinical severity classification of new WHO childhood pneumonia guidance: a multi-hospital, retrospective, cohort study. Lancet Glob Heal. 2018;6(1):e74–83.*

In this analysis of more than 16,000 inpatient pneumonia episodes, I explore the factors that may account for high mortality in a setting where comorbidities are common, and coverage of pneumococcal and *Haemophilus influenzae* type B conjugate vaccines is high.

The findings of this study attempt to refine the WHO pneumonia case management algorithm by identifying sub-populations of children at high risk of death who would, under current guidance, be classified as low risk and managed as outpatients.

I apply logistic regression to model risks for mortality, using multiple imputation with appropriate sensitivity analyses to account for missing data. I also calculate absolute risks of death for sub-groups of children categorized as 'non-severe pneumonia' presenting with pre-specified clinical features that would not result in a 'severe' classification according to WHO criteria. Data from all children hospitalised with pneumonia at 14 public hospitals in Kenya between 1 March 2014 and 29 February 2016 were included. Among all children with pneumonia 832/16031 (5·2 percent) died. Mortality was considerably higher in those with severe pneumonia (14.2 percent) compared with non-severe pneumonia (2.7 percent). Among children with non-severe pneumonia, severe pallor (adjusted risk ratio (aRR) 5.8; 95% CI 5.1–6.7),

mild/moderate pallor (aRR 3.6; 95% CI 3.2–4.0), and weight-for-age Z (WAZ) score <-3SD (aRR 3.9; 95% CI 3.5–4.4) were strongly and independently associated with increased mortality. Children classified as non-severe pneumonia with any of these three signs were also observed to have absolute risks of death that were comparable to those fulfilling the WHO criteria for severe pneumonia.

This study has important implications in the context of the current WHO policy environment advocating for outpatient treatment for all but those children with a limited set of clinical signs that currently define severe pneumonia. While severe pallor would warrant hospitalisation, the current recommendations for case management do not consider very low WAZ or mild/moderate pallor as important risk factors. I note that 1272/12025 (10.6 percent) children defined as having non-severe pneumonia in this study with either of these two risk factors would be expected to be managed at home under current recommendations.

In conclusion, I affirm that WHO recommendations misclassify some children as having mild disease suitable for home-based care. I also call for clinicians to exercise caution in decision making when considering the appropriate management for children with non-severe pneumonia in the presence of the risk factors identified.

8   Discussion

This thesis describes the journey taken to generate revised evidence-based guidelines for the care of children with pneumonia in Kenya, even as the WHO issued its global guidance that remains contested in many sub-Saharan African countries. The five studies collectively illustrate some of the key issues facing practising clinicians, researchers and policymakers in the region, regarding the pneumonia case management guidelines. I further attempt to address some of the questions raised and highlight the major gaps in evidence for future research.

Until recently, guideline development was an opaque process that varied widely across institutions (59, 60). The growing demand for transparent, systematic approaches for guideline development has resulted in new challenges for institutions responsible for generating and updating clinical guidelines. These challenges are particularly apparent in settings where resources and technical expertise are limited. In Kenya, an adapted form of the GRADE system has been applied to update the national paediatric guidelines on several occasions since it was first attempted more than five years ago (61).

Pragmatic trials are purposefully designed to generate evidence that can be generalized to real-world settings. This quality is an important consideration when determining the usefulness of study findings for decision making (62) and has been a key concern among policymakers debating the appropriateness of adopting the revised WHO pneumonia recommendations (13). PRECIS-2 (an improvement on the 2009 PRECIS tool (63)) is a simple tool comprising nine domains developed to aid trialists in designing studies aligned to the purpose for which they are designed (64). Historically, clinical trials have been categorised into two distinct descriptions: explanatory or pragmatic (65). This approach has been criticised for being over-simplistic (66). Consequently, there has been a shift towards describing studies in terms of where they lie along the efficacy-effectiveness spectrum. The PRECIS-2 tool assigns a score out of 5 points to each of the nine domains, with a score of 1 representing very explanatory and 5, very pragmatic. In Figure 2, this tool is used to evaluate our trial comparing amoxicillin versus benzyl penicillin for severe childhood pneumonia with an overall conclusion that the trial was moderately pragmatic.
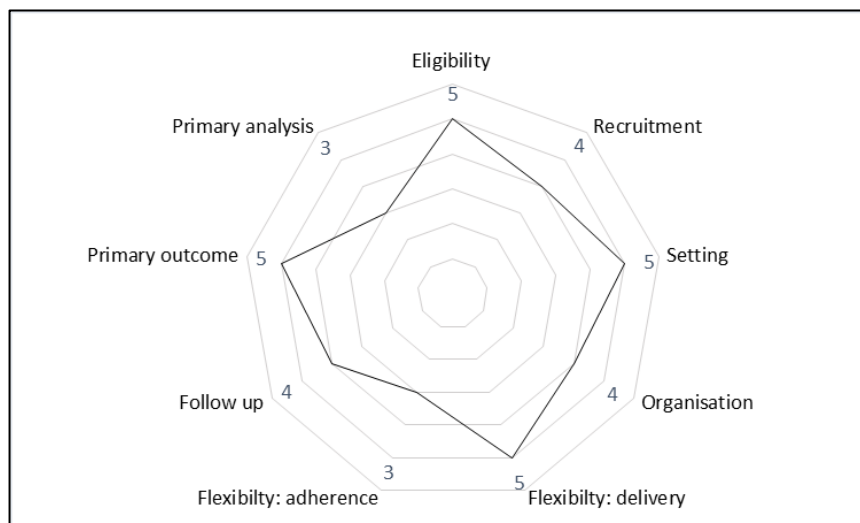
Figure 2: PRECIS-2 wheel for amoxicillin versus benzyl penicillin clinical trial

To mitigate the potential for subjective assignment of scores, a table displaying the rationale for the allocated scores is provided in Table 3.

Table 3: Rationale supporting PRECIS-2 scores for amoxicillin versus benzyl penicillin clinical trial

PRECIS-2 Domain	Score*	Rationale
1. **Eligibility**	5	Eligibility criteria were flexible. A majority of the participants had one or more comorbidity. Additional analyses (reported separately) confirmed representativeness of the study participants to other patients receiving routine care at the study sites
2. **Recruitment**	4	Participants were recruited by an individual clinician on site at the point of admission for general hospital patients
3. **Setting**	5	The study was conducted in the inpatient departments of public hospitals alongside routine care for non-study patients
4. **Organization**	4	The core team conducting the trial (including the principal investigator), had very limited experience conducting clinical trials. Some support was provided remotely by an established clinical trial unit
5. **Flexibility: delivery**	5	The intervention was delivered by caregivers of study patients with no formal supervision provided. This was identical to what would be done under routine care
6. **Flexibility: adherence**	3	Logs were maintained to determine quantities of study drug administered to the study patients. Inappropriate administration of study drugs was captured as protocol violations
7. **Follow up**	3	One study clinician was responsible for overall follow up of study patients. However, clinicians delivering care to non-study patients were not explicitly restricted from making decisions on changes in management for study patients. Outpatient follow up for the secondary outcome following hospital discharge was limited to a telephone call or a single return visit 14 days after recruitment
8. **Primary outcome**	5	The primary outcome, treatment failure, was highly relevant to participants as it included the development of signs of clinical deterioration including death.
9. **Primary analysis**	3	Data were collected on an online database which was monitored actively by the study team. Reasonable effort was made to ensure completeness of data. Both intention to treat and per protocol analyses were undertaken

* Score of 5 = very pragmatic; 1 = very explanatory

In the most recent review of the national paediatric guidelines, primary evidence from the clinical trial presented in this thesis (67) was presented to the guideline panel considering the revision of the pneumonia treatment protocol. In contrast with a very similar exercise conducted in 2010, described in the first paper of this thesis (68), the panellists issued a strong recommendation based on what was concluded to be high-quality evidence in support for the use of amoxicillin in place of benzyl penicillin for children with indrawing pneumonia without danger signs. This recommendation ultimately resulted in the recent revision of the Kenya national policy for pneumonia treatment (69) (Table 4).

Table 4: Kenyan Ministry of Health (2016) and WHO (post-2013) guidelines for the management of children aged 2 - 59 months with a cough and/or difficulty breathing

Syndrome*	Clinical Signs	Recommended Antibiotic Treatment
Severe pneumonia	*Any one of: cyanosis, grunting, oxygen saturation<90 percent, inability to drink/breastfeed, altered consciousness*	Inpatient treatment Benzyl penicillin/ ampicillin and gentamicin (*plus* high dose co-trimoxazole for all HIV-exposed infants)
Pneumonia	*No signs of severe pneumonia* *AND* *Indrawing OR* *Fast breathing (RR≥50/min if age 2-11months; ≥40/min if age 12-59 months)*	Outpatient treatment Oral amoxicillin (if HIV-exposed with indrawing, treat as severe pneumonia)

*For a child without stridor, severe acute malnutrition or signs of meningitis

Availing guidelines alone, however, has been shown to be insufficient for changing clinical practice in a range of settings, particularly where health systems are weak (70-74). A recently concluded clinical trial seeks to evaluate alternative approaches to providing feedback to health care workers to promote the uptake of the new guidelines for the management of indrawing pneumonia using oral amoxicillin (ClinicalTrials.gov registration Identifier NCT02817971).

In September 2015, world leaders adopted the Sustainable Development Goals (SDG) – a comprehensive framework that defines the global development agenda from 2016 to 2030 (75). Among the 17 goals, SDG 3 aims to end preventable deaths of newborns and children, and to reduce the under-5 mortality, to at least as low as 25 per 1,000 live births by 2030 (against an estimated rate of 46 per 1,000 live births in 2013 (1)). To achieve this ambitious target, governments and development partners must align their efforts towards addressing the leading causes of mortality and in regions where most deaths occur. Pneumonia has traditionally been referred to as the neglected childhood killer (76-78), receiving disproportionately less public attention and resources than other global public health priorities such as HIV and malaria (79). Recent initiatives such as the WHO/UNICEF-led integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) (80) and the HIFA2015/CHILD2015 Childhood Pneumonia Project, sponsored by the British Medical Association (81), have been specifically borne out of the urgent need to increase awareness and action on childhood pneumonia. Ultimately, more resources are needed to support research to generate relevant evidence to inform the development of effective policies to decisively address the burden of pneumonia. The apparent responsiveness of Kenyan policymakers to new evidence during the development of pneumonia guideline recommendations is a promising sign for researchers considering the various clinical questions whose existing recommendations are based on evidence that is either weak or outdated.

8.1   Limitations

A major weakness of studies undertaken in this thesis was the use of routine clinical data (studies (iv) and (v)). The accuracy of the recorded data could not be ascertained, and missing data were commonly encountered in the observational studies. To mitigate this effect, multiple imputation by chained equations was performed for variables included in the analyses that relied on routinely-collected clinical data. The efficiency of this approach was enhanced by the large sample sizes of the populations studied.

Reliable data on microbiological aetiology linked to clinical diagnosis and ultimately outcomes may have addressed the objective to examine the effectiveness of the pneumonia treatment guidelines more comprehensively. This was however not feasible with the limited resources available and the challenges of accurately determining the aetiology for cases of childhood pneumonia, even where resources are unrestricted.

The results showing overall low risks of treatment failure and mortality for children with indrawing pneumonia, comparable to other settings are however reassuring and offer indirect information on the effectiveness of the existing guidelines in both routine care and clinical trial settings.

The hospital where study (ii) was conducted is a large tertiary teaching hospital in the Kenyan capital city, while the other studies (iii), (iv) and (v), were conducted in district-level hospitals that were part of a clinical network in which a feedback-driven intervention to improve care for hospitalised children has been taking place since 2013 (15). It may, therefore, be argued that the study sites were not strictly representative of routine care settings, particularly for study (v), which included patients hospitalised between 2014 and 2016 (during the period of the network intervention). I, however, argue that the availability of data of reasonable quality to reliably address the study questions, that would otherwise be unavailable through the routine health information system in other hospitals outside the network (82), far outweighs the potential intervention effect at the study sites.

9   Areas for further research

Among the research questions that are likely to be of interest to policymakers in the immediate future are:

(i)   What is the most effective management for children with pneumonia presenting with danger signs in low-resource settings?

Case fatality among children with pneumonia presenting with one or more danger signs was greater than 10 percent in two studies of Kenyan children reported in this thesis, even among those who received guideline-recommended antibiotics. High mortality may be attributable to late presentation attributable to delays in care seeking and/or inefficiencies in the referral system, diminished efficacy of recommended treatments (factors related to the interactions between patient, pathogen and drug), misdiagnosis (referred to in (ii) below) or inadequate aspects of supportive care (such as feeding, fluids, oxygen or capacity to provide intensive care and monitoring). The latter possibility is of particular interest as the burden of "pneumonia" cases attributable to bacterial causes declines, and a larger fraction of severe presentations are increasingly likely to be due to diagnoses presenting with respiratory distress indistinguishable from true pneumonia such as metabolic acidosis in sepsis, dehydration or severe malaria or

decompensated anaemia. The much-needed evidence to address these questions highlights the need for locally conducted high quality pragmatic clinical trials of alternative interventions for the care of critically ill children in resource-limited settings.

(ii)   How useful are the WHO clinical signs for determining the need for, and choice of antibiotics for children with severe pneumonia?

As a result of the introduction of conjugate vaccines, there are theoretical concerns regarding the diminishing utility of clinical algorithms that were already known to have modest specificity to detect bacterial pneumonia. As a consequence, there need to test new approaches to classify pneumonia for the purpose of informing appropriate treatment. Related to this focus is a growing interest in the development and testing of low-cost point-of-care diagnostics, with the ability to discriminate between bacterial pneumonia and other common causes of acute respiratory distress with reasonable accuracy and reliability. As the campaign for rational antibiotic use continues to grow, linked to fears of rising levels of antibiotic resistance, this gap in evidence is likely to continue to gain attention.

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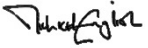
11   Appendices

11.1   Statements of contribution

Paper I: Experience developing national evidence-based clinical guidelines for childhood pneumonia in a low-income setting - making the GRADE?
Ambrose Agweyu, Newton Opiyo and Mike English

Ambrose Agweyu, supported by Mike English and Newton Opiyo, was primarily responsible for the systematic review of pneumonia case management. Ambrose Agweyu produced the first draft of the report on use of GRADE that was further developed with input from Mike English and Newton Opiyo. All authors reviewed and approved the final version of the manuscript.

I agree that Ambrose Agweyu made the aforementioned contribution to the paper.

Newton Opiyo   ………………………………   Date: 19 May 2017

Mike English   ………………………………   Date: 19 May 2017

Paper II: Prevalence and correlates of treatment failure among Kenyan children hospitalised with severe community-acquired pneumonia: a prospective study of the clinical effectiveness of WHO pneumonia case management guidelines.

Ambrose Agweyu, Minnie Kibore, Lina Digolo, Caroline Kosgei, Virginia Maina, Samson Mugane, Sarah Muma, John Wachira, Mary Waiyego, and Elizabeth Obimbo.

Ambrose Agweyu led the development of the study protocol. All of the authors participated in the design of the study and collection of data. Ambrose Agweyu produced the initial draft of the manuscript. All the co-authors reviewed and approved the final report prior to submission.

I agree that Ambrose Agweyu made the aforementioned contribution to the paper.

Minnie Kibore   ……………………………………   Date: 19 May 2017

Lina Digolo   ……………………………………   Date: 19 May 2017

Caroline Kosgei   ……………………………………   Date: 19 May 2017

Virginia Maina   ……………………………………   Date: 19 May 2017

Samson Mugane   ……………………………………   Date: 19 May 2017

John Wachira   ……………………………………   Date: 19 May 2017

Mary Waiyego   ……………………………………   Date: 19 May 2017

Elizabeth Obimbo   ……………………………………   Date: 19 May 2017

Paper III: Oral amoxicillin versus benzyl penicillin for severe pneumonia among Kenyan children: a pragmatic randomized controlled noninferiority trial.

Ambrose Agweyu, David Gathara, Jacquie Oliwa, Naomi Muinga, Tansy Edwards, Elizabeth Allen, Elizabeth Obimbo, and Mike English on behalf of the Severe Pneumonia Study Group.

Ambrose Agweyu led the design of the study with input from, David Gathara, Jacquie Oliwa, Naomi Muinga, Elizabeth Allen, Elizabeth Obimbo, and Mike English participated in the design of the study and collection of data. Ambrose Agweyu produced the initial draft of the manuscript that was further developed by Mike English, Elizabeth Obimbo, and Elizabeth Allen, the trial statistician, who oversaw the analyses. Members of the wider Severe Pneumonia Study Group contributed to the planning and conduct of the study as co-investigators within the Ministry of Health, as site principal investigators, or as study clinicians. All authors reviewed and approved the final manuscript.

I agree that Ambrose Agweyu made the aforementioned contribution to the paper.

David Gathara .... Date: 19 May 2017

Jacquie Oliwa .... Date: 19 May 2017

Naomi Muinga .... Date: 19 May 2017

Tansy Edwards .... Date: 19 May 2017

Elizabeth Allen .... Date: 19 May 2017

Elizabeth Obimbo   ……………………………………   Date: 19 May 2017

Mike English   ……………………………………   Date: 19 May 2017

Paper IV: Comparable outcomes among trial and nontrial participants in a clinical trial of antibiotics for childhood pneumonia: a retrospective cohort study

Ambrose Agweyu, Jacquie Oliwa, David Gathara, Naomi Muinga, Elizabeth Allen, Richard J. Lilford, and Mike English

Ambrose Agweyu conceived the study supported by Jacquie Oliwa, David Gathara, Naomi Muinga, Elizabeth Allen, Richard Lilford, and Mike English. Ambrose Agweyu, Jacquie Oliwa, David Gathara, Naomi Muinga, and Mike English were involved in collection of data. Ambrose Agweyu conducted analyses and produced the initial draft of the manuscript that was further developed by Richard J. Lilford, Mike English, and Elizabeth Allen. All authors reviewed and approved the final version of the manuscript.

I agree that Ambrose Agweyu made the aforementioned contribution to the paper.

Jacquie Oliwa   ………………………………   Date: 19 May 2017.

David Gathara   ………………………………   Date: 19 May 2017

Naomi Muinga   ………………………………   Date: 19 May 2017

Elizabeth Allen   ………………………………   Date: 19 May 2017

Richard J. Lilford   ………………………………   Date: 19 May 2017

Mike English   ………………………………   Date: 19 May 2017

Paper V: Appropriateness of clinical severity classification of new World Health Organization (WHO) childhood pneumonia guidance: a multi-hospital retrospective cohort study

Ambrose Agweyu, Richard J. Lilford, and Mike English on behalf of the Clinical Information Network Author Group

Ambrose Agweyu, Richard J. Lilford, and Mike English jointly conceived the study. Ambrose Agweyu undertook the analyses with support from Richard Lilford, and Mike English. Ambrose Agweyu drafted the manuscript with input from Richard Lilford, and Mike English. The wider Clinical Information Network Group contributed to the design of the data collection tools, conduct of the work, collection of data and data quality assurance that form the basis of this report. All authors review and approved the final manuscript.

I agree that Ambrose Agweyu made the aforementioned contribution to the paper.

Richard J. Lilford   …………………………………   Date: 19 May 2017

Mike English   …………………………………   Date: 19 May 2017