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Change in WHO severe pneumonia case definition; implications

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Impact of the change in the WHO severe pneumonia case definition on hospitalized pneumonia epidemiology: case studies from six countries

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Abstract

Objective To quantify the impact of the change in definition of severe pneumonia on documented pneumonia burden.

Methods We reviewed existing data acquired during observational hospitalized pneumonia studies, before the introduction of the pneumococcal conjugate vaccine, in infants aged 2–23 months from Fiji, Gambia, Lao People's Democratic Republic, Malawi, Mongolia and Viet Nam. We used clinical data to calculate the percentage of all-cause pneumonia hospitalizations with severe pneumonia, and with primary end-point consolidation, according to both the 2005 or 2013 World Health Organization (WHO) definitions. Where population data were available, we also calculated the incidence of severe pneumonia hospitalizations according to the different definitions.

Findings At six of the seven sites, the percentages of all-cause pneumonia hospitalizations due to severe pneumonia were significantly less ($P < 0.001$) according to the 2013 WHO definition compared with the 2005 definition. However, the percentage of severe pneumonia hospitalizations, according to the two definitions of severe pneumonia, with primary end-point consolidation varied little within each site. The annual incidences of severe pneumonia hospitalizations per 100 000 infants were

significantly less (all $P < 0.001$) according to the 2013 definition compared with the 2005 definition, ranging from a difference of -301.0 (95% confidence interval, CI: -405.2 to -196.8) in Fiji to -3242.6 (95% CI: -3695.2 to -2789.9) in the Gambia.

Conclusion The revision of the WHO definition of severe pneumonia affects pneumonia epidemiology, and hence the interpretation of any pneumonia intervention impact evaluation.

Introduction

Pneumonia is the leading cause of post-neonatal deaths in children younger than 5 years, with much of deaths occurring in low- and middle-income countries.^{1,2} Several interventions exist that prevent pneumonia,³ including the pneumococcal conjugate vaccine; however, this vaccine is relatively expensive, meaning that governments require evidence of its health benefits in routine use. Such evidence is often provided by hospital admission data, but this requires a standardized pneumonia case definition as well as uniform admission criteria for pneumonia. To improve the case management of pneumonia in low- and middle-income countries, the World Health Organization (WHO) developed the Integrated Management of Childhood Illness guidelines in 1995.

In 2005, these guidelines⁴ defined severe pneumonia as the presence of cough or difficulty in breathing and tachypnoea (>50 breaths per minute for children aged 2–11 months and >40 breaths per minute for children aged 12–59 months) plus lower chest indrawing, and one or more of the general danger signs, which include: an inability to drink; persistent vomiting; convulsions; lethargy; unconsciousness; stridor in calm child; severe malnutrition (as documented in the medical records); central cyanosis; or a saturation of oxygen of $<90\%$ in room air. Many low- and middle-income countries adopted these criteria. However, equivalence and non-inferiority studies found no difference in treatment failure rates between patients with pneumonia with lower chest indrawing who were treated with parenteral antibiotics in hospital, and outpatient treatment with oral antibiotics.^{5,6} As a result, WHO modified the classification of pneumonia severity;⁷ the 2013 definition of severe pneumonia requiring hospital admission is the presence of cough or difficulty in breathing and tachypnoea plus one or more of the general danger signs, but not lower chest indrawing.

Between 2010 and 2013, before the WHO case definition for severe pneumonia was revised, more than 54 countries, supported by Gavi, the Vaccine Alliance, implemented the pneumococcal conjugate vaccine.⁸ The impact of this change in case definition on the documented burden of severe pneumonia is unclear.

We therefore assess clinical data describing pneumonia hospitalizations in six countries and determine the effect of the revised WHO 2013 definition of severe pneumonia on the proportion of all-cause hospitalized pneumonia cases that are classified as severe, and on the incidence of severe hospitalized pneumonia. We also explore the impact of this change in the case definition on radiological pneumonia, that is, patients with primary end-point consolidation evident from chest X-ray. Using observational data from seven sites, two from the African Region and five from the Western Pacific Region, we describe the epidemiology of severe pneumonia using both the 2005 and 2013 WHO definitions. We quantify the apparent reduction of hospitalized pneumonia cases with severe pneumonia, as well as the apparent fall in annual incidence of severe pneumonia hospitalizations with primary end-point consolidation, resulting directly from the change in definition of severe pneumonia.

Methods

Data sources

We requested data from investigators undertaking retrospective or prospective hospitalized pneumonia studies in children aged 2–23 months from seven sites in six countries before the introduction of the pneumococcal conjugate vaccine: Fiji, Gambia,⁹ Lao People's Democratic Republic, Malawi,^{10–12} Mongolia and Viet Nam (with separate data sets for Hanoi and Ho Chi Minh City; Table 1). We reviewed the individual medical records of patients from all sites and extracted clinical information, including: age, respiratory rate and the presence of lower chest wall indrawing, stridor when calm or any general danger signs (inability to drink or vomiting everything, convulsions, lethargy or unconsciousness). Further details on the data collection methods at each study site are available from the corresponding author.

Data processing

We used the extracted clinical information to classify pneumonia cases as severe according to the 2005 and 2013 WHO definitions of severe pneumonia and calculated the median age (in months) and interquartile range of patients for each site. We compared the different median ages of the children with severe pneumonia according to the different definitions using the non-parametric *K*-sample test on the equality of medians. We also calculated the percentage of all-cause pneumonia hospitalizations with lower chest wall indrawing.

For those sites at which radiography data were collected (Fiji, Gambia, Mongolia and Viet Nam), an experienced radiologist, blind to the clinical findings, reinterpreted all chest

radiographs to determine the presence of primary end-point pneumonia according to WHO criteria.^{14,15}

Where population data and a defined catchment population were available (Fiji, Gambia, Mongolia and Ho Chi Minh City in Viet Nam), annual incidence rates with 95% confidence intervals (CI) of hospitalizations from severe pneumonia according to both definitions, as well as the incidence of patients with primary end-point consolidation, were calculated per 100 000 infants aged 2–23 months. The differences in these incidence rates, with 95% CIs, were calculated using standard errors where appropriate.

We conducted all statistical analyses using the software Stata, version 14.0 (StataCorp. LLC, College Station, United States of America).

Results

Our analysis of the impact of the change in definition of severe pneumonia included 24 287 pneumonia hospitalizations of children aged 2–23 months (Table 1). The median ages of hospitalized pneumonia patients with severe pneumonia according to either the 2005 or 2013 definition ranged from 5 months in Hanoi to 12 months in Mongolia, and did not differ significantly by pneumonia case definition at each site (all $P > 0.05$; Table 2).

The percentage of all-cause pneumonia hospitalizations with lower chest wall indrawing ranged from 64.5% (169/262) in Hanoi to 97.4% (15 300/15 709) in Malawi (Table 3). At six of the seven sites, the percentages of all-cause pneumonia hospitalizations due to severe pneumonia were significantly less (all $P < 0.001$) according to the 2013 WHO definition compared with the 2005 definition (Table 3). The percentage differences ranged from –7.0% (95% CI: –17.0 to 2.6) in Ho Chi Minh City to –49.9% (95% CI: –51.4 to –48.4%) in Malawi. When classifying severe pneumonia by the 2013 definition compared with the 2005 definition, the largest reductions were observed in data from the Gambia (–47.0; (733–285)/953) and Malawi (–49.9; (11 163–3327)/15 709). Between sites, the percentage of all-cause pneumonia hospitalizations due to severe pneumonia, according to the 2005 definition, varied from 50.0% (190/380) in Ho Chi Minh City to 81.9% (555/678) in Lao People's Democratic Republic; when adopting the 2013 definition, this ranged from 21.2% (3327/15 709) in Malawi to 56.6% (384/678) in Lao People's Democratic Republic. The percentage of severe pneumonia hospitalizations with primary end-point consolidation varied little within each site between the two definitions of severe pneumonia, from a reduction of 5.0% (1/71 to 10/155) at Hanoi to an increase of 1.2% in both the Gambia

(60/285 to 146/733) and in Ho Chi Minh City (20/163 to 21/190). Between sites, however, the percentage of severe pneumonia hospitalizations with primary end-point consolidation varied from 6.5% (10/155) in Hanoi to 19.9% (146/733) in the Gambia according to the 2005 WHO definition, and varied from 1.4% (1/71) in Hanoi to 21.1% (60/285) in the Gambia using the 2013 definition.

Table 4 summarizes the annual incidences of all-cause pneumonia hospitalizations due to severe pneumonia according to both 2005 and 2013 definitions of severe pneumonia, as well as the differences in these incidences. At all sites for which relevant data were available, the annual incidences were significantly less (all $P < 0.001$) according to the 2013 definition compared with the 2005 definition, ranging from a difference of -301.0 (95% CI: -405.2 to -196.8) in Fiji to -3242.6 (95% CI: -3695.2 to -2789.9) in the Gambia. Between sites, the annual incidence of pneumonia hospitalizations with primary end-point consolidation ranged from 160.7 (95% CI: 137.7 to 186.5) in Fiji to 1056.8 (95% CI: 892.3 to 1242.7) in the Gambia when severe pneumonia was classified according to the 2005 definition, and ranged from 138.4 (95% CI: 117.1 to 162.5) in Fiji to 529.9 (95% CI: 324.0 to 817.3) in Ho Chi Minh City when using the 2013 definition. The annual incidences of pneumonia hospitalizations with the presence of primary end-point consolidation were significantly different according to the definition of severe pneumonia used in data from Gambia, Mongolia and Ho Chi Minh City in Viet Nam ($P < 0.001$), but the difference was not significant in the data from Fiji ($P = 0.09$).

Discussion

We have shown that, in six out of seven sites from the African and Western Pacific Regions, the percentage of pneumonia hospitalizations in children aged 2–23 months with severe pneumonia was significantly less using the 2013 definition of severe pneumonia compared with the 2005 definition. Similarly, at sites where incidence could be calculated, we have demonstrated that the annual incidence of pneumonia hospitalizations with severe pneumonia was significantly less using the 2013 definition of severe pneumonia compared with the 2005 definition. These findings are not unexpected given that the presence of lower chest wall indrawing (without danger signs) is no longer included in the 2013 WHO case definition for severe pneumonia;⁸ we calculated that 64.5 to 97.4% of hospitalized pneumonia cases had lower chest wall indrawing.

An unpublished review (Nordgren M, XXXXX, personal communication, 2016) of the impact of the pneumococcal conjugate vaccine on pneumonia burden in infants younger than 2 years from observational studies and double-blinded randomized controlled trials, using the case definitions all-cause pneumonia, WHO-defined pneumonia (year not specified) and pneumococcal pneumonia, found much variability. The varying sensitivity and specificity of the different case definitions^{9,16,17} mean that the magnitude of the impact of the vaccine on pneumonia calculated from studies of different design and using different case definitions cannot be directly compared.

Primary end-point consolidation has moderate sensitivity and specificity, and is the end-point which has shown reasonable consistency within clinical trials.^{18,19} However, in low- and middle-income countries, whether an infant receives a chest radiograph is often determined by clinical severity; those with danger signs (and not lower chest wall indrawing) are more likely to receive a radiograph compared with those without, irrespective of which WHO severe pneumonia definition is used. Unfortunately, we were unable to compare the percentage of pneumonia hospitalizations with danger signs, as each site used slightly different definitions of danger signs; this may explain why our findings show that, within each site, the changes to the definition of severe pneumonia had no significant effect on the percentage of severe pneumonia hospitalizations with radiological pneumonia. However, the incidence of pneumonia hospitalizations with primary end-point consolidation was significantly different, depending on the definition of severe pneumonia, within three of the four sites for which data were available.

Unsurprisingly, we observed variability in the incidence of pneumonia hospitalizations with severe pneumonia between sites, regardless of the case definition used. The incidence of hospitalized pneumonia is affected by many factors, including income, comorbidities and exposure to air pollution;^{20,21} variability between countries in hospitalized pneumonia burden is therefore to be expected. In addition, the incidence of pneumonia hospitalizations with severe pneumonia is also influenced by access to care and admission criteria.²² For example, despite being tertiary facilities, both Vietnamese sites had a lower percentage of pneumonia admissions that were severe according to the 2005 definition than compared with other sites, indicating a lower threshold for admission and/or better health-seeking behaviour. A recent study has reported that many children with non-severe respiratory disease are admitted to primary, secondary and tertiary care facilities in Viet Nam.²³ We found that the presence of lower chest wall indrawing varied between the two

Vietnamese sites, suggesting that the admission criteria also vary between these hospitals. Furthermore, the diagnosis of lower chest wall indrawing is observer dependent, also affecting within-site observations.²⁴ Although the presence of danger signs was not recorded consistently between the sites, the key clinical criteria of severe pneumonia using either the 2005 or 2013 severe pneumonia definition (age-specific respiratory rate, cough and presence of lower chest wall indrawing) were recorded consistently at each site, making within-site comparisons possible.

The change from the 2005 to 2013 severe pneumonia case definition aimed to simplify the pneumonia treatment algorithm for community health workers and reduce unnecessary burden on families and health-care services.²⁵ However, our findings need to be considered when discussing changes in the epidemiological impact on pneumonia burden and pneumonia impact evaluation. If clinicians have changed their admission criteria for pneumonia in accordance with changes in WHO guidelines, then the incidence of pneumonia hospitalizations will appear to decline regardless of any intervention, because of children with pneumonia and lower chest indrawing (no danger signs) now being managed as outpatients. For pneumonia epidemiology and pneumonia intervention evaluations, our findings highlight the importance of stating which WHO definition is used and whether admission criteria changed during the observation period. Further studies are also required to understand the impact of this definitional change in high-mortality settings, where rates of bacterial pneumonia are increased and lower chest wall indrawing has been identified as an independent risk factor for mortality.²⁶

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Competing interests:

None declared.

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Table 1. Impact study of WHO severe pneumonia case definition change: data sources in six countries

Country, city or region	Hospital (level of care)	Study design	Period	No. all-cause pneumonia hospitalizations of children aged 2–23 months	WHO guidelines used
Fiji, Suva	Colonial War Memorial Hospital (tertiary)	Retrospective	2007 to 2011	3254	2005
Gambia, Upper River Region	Basse health centre (primary and secondary)	Prospective ⁹	May 2008 to Aug 2009	953	None; study-specific criteria ¹³
Lao People's Democratic Republic, Vientiane	Mahosot, Settathirath, Hospital 103, National Child, Mother and Child Hospitals (tertiary); nine district hospitals (secondary)	Retrospective	2011 to 2013	678	2005
Malawi	16 out of 24 district hospitals (secondary)	Prospective ^{10–12}	Oct 2000 to Jun 2003	15 709	2005 ^a
Mongolia, Ulaanbaatar	Four district hospitals (secondary), National Mother and Child Hospital (tertiary)	Prospective	April 2015 to May 2016	3051 ^b	2005
Viet Nam, Hanoi	National Children's Hospital (tertiary)	Retrospective	2010	262 ^c	None
Viet Nam, Ho Chi Minh City	Children's Hospital No. 2 (tertiary)	Retrospective	2010	380	2005

WHO: World Health Organization.

^a Guidelines used were the same as the 2005 definition, although the study was performed before these guidelines were available.

^b Only children with clinical information included.

^c Every 10th pneumonia discharge in 2010 was included.

Table 2. Median age of pneumonia hospitalizations due to severe pneumonia in infants aged 2–23 months in six countries

WHO definition	Median age in months (interquartile range) ^a						
	Fiji	Gambia	Lao People's Democratic Republic	Malawi	Mongolia	Viet Nam	
						Hanoi	Ho Chi Minh City
2005 ⁴	9 (5 to 14)	10 (6 to 17)	11 (6 to 16)	8 (5 to 13)	12 (7 to 17)	5 (3 to 11)	9 (5 to 15)
2013 ⁷	8 (5 to 13)	11 (6 to 18)	11 (6 to 15)	8 (5 to 13)	12 (7 to 17)	5 (3 to 9)	9 (5 to 16)
<i>P</i> -value	0.346	0.789	0.275	0.924	0.640	0.156	0.126

WHO: World Health Organization.

^a Median ages of children hospitalized with severe pneumonia compared using the non-parametric *K*-sample test on the equality of medians.

Table 3. Properties of all-cause pneumonia hospitalizations in infants aged 2–23 months in six countries

Property of all-cause pneumonia	Fiji (<i>n</i> =3254)	Gambia (<i>n</i> =953)	Lao People's Democratic Republic (<i>n</i> =678)	Malawi (<i>n</i> =15709)	Mongolia (<i>n</i> =3051)	Viet Nam	
						Hanoi (<i>n</i> =262)	Ho Chi Minh City (<i>n</i> =380)
With lower chest wall indrawing							
No. (%)	2665 (81.9)	711 (74.5)	443 (65.3)	15300 (97.4)	2416 (79.2)	169 (64.5)	338 (88.9)
With severe pneumonia							
No. (%)	2193 (67.4)	733 (76.9)	555 (81.9)	11163 (71.1)	2337 (76.6)	155 (59.2)	190 (50.0)
according to 2005 WHO definition ⁴							
No. (%)	1838 (56.5)	285 (29.9)	384 (56.6)	3327 (21.2)	1422 (46.6)	71 (27.1)	163 (42.9)
according to 2013 WHO definition ⁷							
Percent difference (95% CI)	-10.9 (-14.7 to -7.1)	-47.0 (-51.0 to -43.1)	-25.2 (-34.3 to -16.4)	-49.9 (-51.4 to -48.4)	-30.0 (-33.9 to -26.1)	-32.1 (-43.3 to -20.8)	-7.1 (-17.0 to 2.6)
Of those with severe pneumonia, with primary end-point consolidation^a							
No. (%)	238 (10.9)	146 (19.9)	NA	NA	268 (11.5)	10 (6.5)	21 (11.1)
according to 2005 WHO definition ⁴							
No. (%)	211 (11.5)	60 (21.1)	NA	NA	167 (11.7)	1 (1.4)	20 (12.3)
according to 2013 WHO definition ⁷							
Percent difference (95% CI)	0.6 (-1.4 to 2.7)	1.2 (-2.7 to 5.8)	–	–	0.3 (-2.0 to 2.5)	-5.0 (-9.9 to -0.1)	1.2 (-5.9 to 8.4)

CI: confidence interval; NA: not available; WHO: World Health Organization.

^a Chest radiographs interpreted by independent radiologists, classifying primary end-point consolidation as per WHO definition.¹⁴

Table 4. Annual incidence of pneumonia hospitalizations with severe pneumonia in children aged 2–23 months in four countries

Incidence	Incidence per 100 000 infants ^a (95% CI)			
	Fiji	Gambia	Mongolia	Viet Nam, Ho Chi Minh City
All-cause pneumonia				
Annual incidence according to 2005 WHO definition ⁴	1671.4 (1595.1 to 1750.5)	530.4 (4928.3 to 5703.8)	4661.2 (4649.7 to 672.3)	5034.4 (4358.7 to 5780.9)
Annual incidence according to 2013 WHO definition ⁷	1370.4 (1301.3 to 1442.2)	2062.8 (1830.3 to 2316.8)	2836.2 (2824.7 to 2847.3)	4319.0 (3692.8 to 5017.1)
Difference	-301.0 (-405.2 to -196.8)	-3242.6 (-3695.2 to -2789.9)	-1825.0 (-2064.7 to -1585.3)	-715.4 (-718.5 to -712.3)
With primary end-point consolidation^b				
Annual incidence according to 2005 WHO definition ⁴	160.7 (137.7 to 186.5)	1056.8 (892.3 to 1242.7)	534.5 (515.1 to 552.9)	556.4 (344.8 to 849.3)
Annual incidence according to 2013 WHO definition ⁷	138.4 (117.1 to 162.5)	434.3 (331.4 to 559.0)	333.1 (314.1 to 351.9)	529.9 (324.0 to 817.3)
Difference	-22.3 (-55.0 to 10.4)	-622.5 (-826.1 to -418.8)	-201.4 (-283.0 to -119.9)	26.5 (25.4 to 27.5)

CI: confidence interval; NA: not available; WHO: World Health Organization.

^a Aged 2–23 months.

^b Chest radiographs interpreted by independent radiologists, classifying primary end-point consolidation as per WHO definition.¹⁴

Note: The table only presents data for sites with available population data and a defined catchment.