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Treatment Failure among Kenyan Children with Severe Pneumonia – a Cohort Study

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Abstract

Background—Pneumonia is the leading cause of childhood mortality worldwide. The WHO recommends presumptive treatment based on clinical syndromes. Recent studies raise concerns over the frequency of treatment failure in Africa.

Methods—We applied a definition of treatment failure to data prospectively collected from children who were 2-59 months with severe, or very severe pneumonia admitted to Kilifi District Hospital, Kenya form May 2007 through May 2008 and treated using WHO guidelines. The primary outcome was treatment failure at 48 hours.

Results—Of 568 children, median age 11 months, 165 (29%) had very severe pneumonia, 30 (5.3%) a positive HIV test and 62 (11%) severe malnutrition. 111 (20%, 95% CI 17-23%) children failed treatment at 48 hours and 34 (6.0%) died, 22 (65%) deaths occurred before 48 hours. Of 353 children with severe pneumonia, without HIV or severe malnutrition, 42 (12%) failed to respond at 48 hours, 15 (4.3%) failed at 5 days and one child (0.3%) died. Among 215 children with either severe pneumonia complicated by HIV or severe malnutrition, or very severe pneumonia, 69 (32%) failed to treatment at 48 hours, 47 (22%) failed at 5 days and 33 (16%) died. Treatment failure at 48 hours was associated with shock, bacteremia, very severe pneumonia, $Sa0_2$<95%, severe malnutrition, HIV, and age <1 year in multivariable models.

Conclusions—In this setting, few children with uncomplicated severe pneumonia fail treatment or die under current guidelines. Deaths mainly occurred early and may be reduced by improving prevention, pre-hospital care and treatment of sepsis.

Keywords

Pneumonia; Treatment Failure; Kenya

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INTRODUCTION

Acute lower respiratory tract infection is the leading cause of childhood mortality worldwide, mostly due to pneumonia, and mostly in developing countries.(1-3) The WHO recommends presumptive antibiotic treatment based on clinical syndromes involving history of cough or difficulty breathing with lower chest wall indrawing, or signs indicating very severe pneumonia.(4) These guidelines were developed before the HIV pandemic, before conjugate vaccines and in a context of different antimicrobial sensitivities. Recent reports from Southern Africa where there is a high prevalence of HIV infection, suggest that treatment failure is frequent. (5, 6) There are no recent data on the outcomes of pneumonia treatment from areas of Africa with a lower HIV prevalence.

WHO guidelines recommend reviewing treatment after 48 hours and changing antibiotics if there is no improvement, i.e. “slower breathing, less fever, eating better”.(7) The guidelines are unclear if one or all of the criteria must be met, and what quantity or quality of improvement is required to be “improved”. Labeling a child as failing when they are responding (albeit perhaps more slowly) may result in unnecessary changes of antibiotics or expensive investigations. However, not recognizing treatment failure may lead to a poor outcome when a change in antimicrobials or other procedures may have been beneficial.

In the face of these existing data and theoretical concerns, empiric data on the frequency of treatment failure in different regions of Africa are essential. We aimed to determine the frequency of treatment failure among children meeting clinical criteria for severe, and very severe pneumonia, admitted to a rural Kenyan district hospital and treated according to standard guidelines.

METHODS

Location

Kilifi District Hospital is located in a rural area in coastal Kenya. The hospital serves a predominantly rural farming population of ~240,000 of whom 18% are under 5 years old. *Haemophilus influenzae* type b conjugate vaccine, given at 6, 10, and 14 weeks, was introduced in late 2001, with high coverage and 90% reduction in disease due to Hib.(8) Pneumococcal conjugate vaccine was not introduced at the time of this study. The HIV prevalence at the hospital antenatal clinic was approximately 5% in 2007.

Patients and clinical methods

We applied an *a priori* definition of treatment failure to data prospectively collected at admission and daily thereafter among children aged 2 to 59 months meeting the WHO syndromic definition of “severe pneumonia” or “very severe pneumonia” (7) at admission between 26th May 2007 and 25th May 2008. Part of this cohort was previously described in relation to the viral etiology of severe pneumonia.(9) RSV was the most frequently detected respiratory virus, and the only virus significantly more frequently detected amongst children with severe pneumonia than amongst healthy controls or children with symptoms of mild upper respiratory tract infection. (9)

Severe pneumonia was defined as a history of cough or difficulty breathing and lower chest wall indrawing. The presence of inability to drink, central cyanosis or reduced level of consciousness defined very severe pneumonia.(7) As oxygen saturation monitoring was available, a modification of the WHO criteria, peripheral oxygen saturation <90% (Nelcor, USA) was used in addition to central cyanosis to define very severe pneumonia. Severe malnutrition was defined as weight for height <-3 z scores by WHO reference standards, or the presence of kwashiorkor. HIV testing was performed according to national policy for all

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pediatric hospital admissions using rapid antibody tests. Parents or guardians of those testing positive were given further counseling and referred for comprehensive care. Severe anemia was defined as hemoglobin <5 g/dl. Reduced conscious level was defined as prostration or coma (Blantyre coma score <3). Signs of shock were defined as weak pulse, capillary refill time >2 seconds or palpable core-limb temperature gradient.

A blood culture and malaria slide was taken at admission for all children. A nasal wash specimen for viral detection by multiplex PCR was taken in children without severe cardio-respiratory compromise. Microbiologic and virologic methods have been previously described.(9)

Clinical care was provided by research medical officers and clinical officers trained in the recognition of clinical signs and treatment of pneumonia according to WHO guidelines, including antibiotic treatment as follows: intravenous benzylpenicillin to children with severe pneumonia; either chloramphenicol alone or ampicillin plus gentamicin for children with very severe pneumonia; ; intravenous ampicillin for children with severe malnutrition; and intravenous ampicillin plus gentamicin plus cotrimoxazole at therapeutic doses for children with a positive HIV antibody test.(7, 10) Oxygen was administered if SaO_2<90%. The most severely ill children were managed on a high dependency unit, but mechanical ventilation was not available. Malaria parasitemia was treated according to national guidelines. Daily clinical observations were recorded by research clinicians and trained ward assistants. Treatment was changed by clinicians applying the WHO guidelines and reviewing laboratory results rather than by applying the study definition of failure. Because of processing time, results of admission blood cultures including antimicrobial sensitivities and viral diagnoses were not usually available within 48 hours.

The study was approved by the Kenya Medical Research Institute/National Ethical Review Committee. Written informed consent was obtained from the parent or guardian of each child.

Definition of treatment failure

The two elements in defining treatment failure are the length of time before re-assessment, and the criteria for failure.(5, 11-16) We searched PubMed (1955–2010) for studies defining treatment failure in severe pneumonia using the search term (pneumonia or “lower respiratory tract infection”) and (children) and (failure or guideline*). The search was limited to human studies, 1699 abstracts were reviewed and full-text articles were evaluated if the abstract suggested potential relevance. Further articles were identified through searching the reference lists of the selected articles. Findings are summarized in table 1. Our definition of treatment failure was established before data analysis was performed.

We defined treatment failure at 48 hours as i) worsening, compared to admission findings, of one or more of these clinical abnormalities: conscious level, SaO_2 <90%; respiratory rate (must have increased by at least 5 breaths/min), or temperature (if initially <37.5°C, must have increased to >37.5°C); or ii) or no improvement in any these clinical abnormalities; or iii) a new finding of: empyema, bacterial meningitis, signs of shock or renal impairment (creatinine >100 mmol/L); or iv) death.

We defined treatment failure at 5 days as i) meeting the 48 hour failure criteria at day 5; or ii) persistence of any two of the clinical abnormalities used to define failure at 48 hours; or iii) persistence of lower chest wall indrawing; or iv) death.

Clinical criteria for treatment failure were applied independently at 48 hours and day 5. Because of concerns that evaluation at 48 hours may over-classify failure among children

who are improving, and because the failure criteria for this analysis were not those used to adjust treatment at 48 hours, the definition was not cumulative. Thus, children failing at 48 hours did not fail at 5 days if they had improved by then. Death at any point before criteria were applied constituted treatment failure. Discharge was deemed non-failure.

Statistical analysis

The primary endpoint was overall treatment failure at 48 hours, with 95% confidence intervals. Because treatment guidelines differ for severe pneumonia, and very severe pneumonia, severe malnutrition and HIV, these groups were initially analyzed separately. Ages were not normally distributed and were compared using the Kruskall-Wallis test. Clinical features at admission among children who failed and did not fail were analyzed as odds ratios. Observations at 48 hours were assessed for association with failure at day 5, but no other serial measurements were analyzed. Finally, independent associations with failure at 48 hours, 5 days, and death before 48 hours were modeled by forward stepwise multivariable logistic regression, starting with variables with a univariate association ($P<0.1$). Variables were retained in the final models if the likelihood ratio test P value was <0.05. Because of differing treatment recommendations, severity (severe pneumonia or very severe pneumonia), HIV status, severe malnutrition and a variable for their interaction were also retained. Analyses were performed using STATA version 9 (StataCorp, College Station, TX, USA).

RESULTS

During the study period, 710 children were eligible. In 66, parents did not consent and 76 were excluded because one or more of the data items at admission, 48 hours or at 5 days were missing. Compared with the included children, the 142 excluded children did not differ in age: median 13 months (IQR 5.0 to 23 months, P=0.48), very severe pneumonia (n=39 (27%, P=0.71)), HIV status (n=7 (4.9%, P=0.87)), severe malnutrition (n=6 (4.2%, P=0.42)) or case fatality (n=7, (4.9%, P=0.63)). There were no significant differences in these characteristics between those who had refused consent and those with missing data.

Analysis included 568 (80%) children (57% male), median age 11 months (IQR 5.7 to 23 months), 165 (29%) of whom had very severe pneumonia. The median duration of cough prior to admission was 3 days, 134 (24%) had cough for ≥5 days and 21 (4.1%) for ≥14 days. A positive HIV antibody test was found in 30 (5.3%) children and 62 (11%) were severely malnourished.

Thirty four (6.0%) children died during hospital admission: 22 (65%) died before 48 hours, including 6 (18%) children admitted *in extremis* who died before antibiotics could be administered. Three children (9%) died between 48 hours and 5 days, and 9 (26%) died after 5 days.

Thirty two (5.6%) children were bacteremic at admission: 18/403 (4.5%) with severe pneumonia and 14/165 (8.5%) with very severe pneumonia (P=0.01). In a multivariable model including very severe pneumonia, HIV, severe malnutrition and age, only HIV was significantly associated with bacteremia: OR 7.89 (95% CI 3.11 to 20.0). The pathogens isolated were Streptococcus pneumoniae (15), E. coli (5), Staphylococcus aureus (3) beta hemolytic *Streptococcus (3),* non-*Typhi Salmonella sp. (2), Haemophilus influenzae* type b (1), *Acinetobacter sp. (1)*, *Serratia sp. (1)*, *Burkholeria cepacia (1)* and an unidentified, non-fermenting Gram negative rod (1).

A nasal wash sample for respiratory virus detection was taken in 480 children. A respiratory virus was detected in 192/350 (55%) admissions with severe pneumonia and 58/130 (45%)

with very severe pneumonia. RSV was detected in 136 (28%) admissions: 105 (30%) in severe pneumonia and 31 (24%) in very severe pneumonia. Malaria parasitemia was present in 26 (4.7%) admissions.

At 48 hours, 111/568 (20%, 95% CI 17-23%) children had failed to respond. The risks of failure or death by 48 hours and 5 days are illustrated in table 2. We then compared the group of children with severe pneumonia that was uncomplicated by HIV or severe malnutrition to all other children (who had either severe pneumonia complicated by HIV or severe malnutrition, or very severe pneumonia). In these two groups, failure at 48 hours was observed in 42/353 (12%) and 69/215 (32%) respectively (P<0.001); failure at 5 days was observed in 15/353 (4.3%) and 47/215 (22%) respectively (P<0.001); and death occurred in 1/353 (0.3%) and 33/215 (16%) respectively (P<0.001).

Amongst children with very severe pneumonia categorized on the basis of an oxygen saturation <90% alone, treatment failure at 48 hours (24/94 (26%)) occurred less frequently than amongst those categorized as very severe because of inability to drink or breastfeed, impaired consciousness or central cyanosis (31/71 (44%, P=0.014)), but more frequently than amongst children with severe pneumonia (56/403 (14%, P=0.006)).

The most common criteria for failure at 48 hours were: worsening respiratory rate, worsening temperature, worsening oxygen saturation or death (table 3). The most common criteria for failure at 5 days were persistent lower chest wall indrawing, persistent or worsening oxygen saturation or temperature, or death.

The clinical features independently associated with failure at 48 hours and 5 days and death before 48 hours are shown in table 4. Variables that were examined, but not independently associated with treatment failure or death before 48 hours in the multivariable models were: gender, respiratory rate, temperature, severe anemia, malaria parasitemia and detection of a respiratory virus. For severe pneumonia, failure at 48 hours occurred in 19/105 (18%) of those with RSV detected, 31/192 (16%) with any other respiratory virus detected, 21/158 (13%) with no virus detected and 4/53 (8%) among untested children (P=0.34). For very severe pneumonia, failure at 48 hours occurred in 11/31 (35%) of those with RSV detected, 6/27 (22%) with any other respiratory virus detected, 17/72 (24%) with no virus detected and 21/35 (60%) among untested children (mostly untested because of respiratory or cardiovascular compromise) (P=0.25).

Among children who survived to 48 hours (n=546), their subsequent clinical progress was influenced very strongly by their existing response to treatment; by 5 days of admission, treatment failure was observed in 31% (28/89) of those who had already failed at 48 hours and in 2.6% (12/457) of those who had responded at 48 hours: OR 17.0 (95% CI 7.83 to 38.4). Restricting the analysis of clinical features at admission associated with failure at day 5 to those who had not failed at 48 hours, only one variable remained significantly associated: cough for >14 days: OR 10.9 (95% CI 2.87 to 41.5).

DISCUSSION

At 48 hours after admission, 20% of children at a rural Kenyan district hospital with severe or very severe pneumonia were failing to respond to treatment. Among children with severe pneumonia, uncomplicated by HIV or severe malnutrition, few children ultimately failed treatment or died (table 2). However, amongst children with very severe pneumonia, or the complications of HIV or severe malnutrition, one third failed to respond at 48 hours and one in six died. The majority of deaths occurred before 48 hours, principally amongst those who were profoundly ill at admission. Failure to respond by 48 hours was strongly associated with failure at 5 days.

Compared with the cohort studied by McNally et al in South Africa,(5) our participants were older, had a much lower prevalence of HIV infection or exposure (5.6% vs. 68%) and less very severe pneumonia (29% vs. 71%). Whilst we found that the overall risk of failure at 48 hours was lower than reported by McNally et al, amongst children with very severe pneumonia, HIV or severe malnutrition our finding that 32% had failed at 48 hours was comparable to the 35% reported in that study. Another cohort in South Africa and Zambia comparing children without HIV to those with mild or asymptomatic HIV infection was reported by Jeena et al.(6) In that study, which excluded severe malnutrition, the prevalence of HIV infection (23% confirmed) was much higher than in our cohort, and the overall proportion failing treatment at 2 days (12%) was similar to that which we found for uncomplicated severe pneumonia.

Our findings suggest that guidelines for treating very severe pneumonia and severe pneumonia complicated by HIV or severe malnutrition need to be re-examined. We did not aim to determine the full spectrum of etiology and there were too few bacterial isolates to analyze treatment failure in relation to *in vitro* antimicrobial susceptibilities. We did find that clinically identified sepsis or bacteremia at admission was strongly associated with death and treatment failure. Studies in Mozambique and Uganda, (17), (18) report a similar set of clinical parameters to be associated with fatal pneumonia: very severe pneumonia, HIV, severe malnutrition, hypoxemia and bacteremia.

The fact that deaths mainly occurred early suggests several potential strategies for reducing mortality: prevention through vaccination; early effective treatment in the community; earlier referral of hospitalized cases and improved supportive management of sepsis. The introduction of pneumococcal conjugate vaccination (PCV) is likely to significantly alter the etiology of childhood pneumonia. (19) Changes in outcomes following its introduction in Kenya in early 2011 will be analyzed using the same definitions of treatment failure. Strategies to improve care-seeking, access to care and referral are needed, (20, 21) and there is evidence that these can be successful.(22, 23) Treatment of lower risk ‘ambulatory’ cases of severe pneumonia as an outpatient with oral antibiotics may allow attention to be focused on more severely ill children.(14) The initial case management of suspected sepsis should include prompt administration of antibiotics since delays have been shown to be associated with poorer outcomes.(24, 25) However, the optimal fluid management of shock is controversial, with results of a large African trial that included children with pneumonia conflicting with existing guidelines such as the WHO Emergency Triage and Treatment (ETAT) recommendations. (26)

Children who were classified as having very severe pneumonia on the basis of pulse oximetry without impaired consciousness, inability to drink or central cyanosis failed treatment more frequently than those classified as having severe pneumonia. Furthermore, children admitted with mild hypoxemia (90 to 95%) did worse than those with higher oxygen saturations. Taken together, these findings strongly support the value of pulse oximetry in categorizing pneumonia severity. Previous studies of hypoxemia in childhood pneumonia have taken 90% oxygen saturation as the lower limit of normal at sea level. (27, 28) Randomized trials are needed on whether the threshold for providing oxygen should be raised.

Our study had several limitations. Data from a significant proportion of eligible admissions were not analyzed because one or more of the admission or daily observation variables were missing (11%), or consent was declined (9%). However, we identified no differences in clinical characteristics or case fatality between those excluded and those analyzed. Our data are also limited by being from only one site.

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TABLE 1

Studies defining treatment failure in severe or very severe pneumonia.

Reference	Study population	N	Clinical Definition of Treatment Failure	Failure
Shann *et al.* 1985(29)	Ages not stated; Papua New Guinea; Inpatients; Severe pneumonia	748	At any point: Change of antibiotic treatment; Death	15.9%
Strauss *et al.* 1998(30)	2–59 months; Pakistan; Outpatient and inpatient; Non-severe and severe pneumonia	595	At 48 hours, any of: Resting $SaO_2 \leq 87\%$; tachypnoea; any danger sign; No improvement or deterioration in the opinion of a senior clinician	20.5%
Duke *et al.* 2002(31)	1-59 months; Papua New Guinea; Inpatient; Very severe pneumonia	1116	At 5 days, any 4 of: Fever, Tachypnoea/apnoeas, chest wall indrawing, crepitations, bronchial breathing, low oxygen sats; Death ; Readmission within 1 month	18.6%
Addo-Yobo *et al.* 2004(14)	3–59 month; International; Inpatient; Severe pneumonia	1702	At 48 hours, any 1 of: Danger signs, low SaO_2, persistent indrawing, serious adverse drug reaction, new antibiotic, new comorbidity, abscondment, death	19%
McNally *et al.* 2007(5)	1-59 months; South Africa; Inpatient; Severe and very severe pneumonia	358	At 48 hours, persistence or worsening of any 1 of: heart rate, respiratory rate, temperature, inability to drink, increased oxygen requirements; New danger signs; Absconded; Change of antibiotic for new disease or blood culture result; Death	35%
Asghar *et al.* 2008 (12) (SPEAR study)	2-59 months; International; Inpatient; Very severe pneumonia	958	At day 5, persistent or new: Inability to drink, tachypnoea, reduced conscious level, meningitis, empyema, renal failure, septic shock; Serious adverse drug reaction; Change of antibiotic treatment; Abscondment; Death	13.5%
Hazir *et al* 2008(15)	3-59 months; Inpatient versus outpatient; Severe pneumonia	2037	At day 3: Clinical deterioration; Persistence of fever with lower chest indrawing; Hospitalisation of outpatient; Development of comorbid condition requiring antibiotic; Abscondment; Death	8%
Addo Yobo *et al.* 2011(32)	2-59 months, multi-national; Severe pneumonia	823	At 72 hours, persistence of fever and lower chest indrawing. Or, at day 6, clinical deterioration; Inability to take oral medication because of persisting vomiting; serious adverse event related to amoxicillin; developing a co-morbid condition; either fever or lower chest indrawing; new chest indrawing or fast breathing	9.2%

TABLE 2

Frequency of treatment failure and death at 48 hours and 5 days

Failure status at 48 hours			**Failure status at day 5**		
Pneumonia type	Uncomplicated	Complicated by HIV or malnutrition	Pneumonia type	Uncomplicated	Complicated by HIV or malnutrition
Severe	42/353 (12%)	14/50 (28%) P=0.002[a]	Severe	15/353 (4.2%)	5/50 (10%) P=0.09[a]
V. Severe	39/131 (30%) P<0.001[b]	16/34 (47%) P=0.06[a] P=0.07[b]	V. Severe	27/131 (21%) P<0.001[b]	15/34 (44%) P<0.001[a] P=0.006[b]
Cumulative deaths by 48 hours			**Cumulative deaths by day 5**		
Pneumonia type	Uncomplicated	Complicated by HIV or malnutrition	Pneumonia type	Uncomplicated	Complicated by HIV or malnutrition
Severe	0/353 (0%)	1/50 (2%) P=0.12[a]	Severe	1/353 (0.3%)	1/50 (2%) P=0.23[a]
V. Severe	15/131 (11%) P<0.001[b]	6/34 (18%) P=0.39[a] P=1.0[b]	V. Severe	15/131 (11%) P<0.001[b]	8/34 (24%) P=0.07[a] P=0.003[b]

[a] Complicated by HIV or severe malnutrition compared to uncomplicated

[b] Very severe pneumonia compared to severe pneumonia

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TABLE 3

Criteria for treatment failure at 48 hours and 5 days

Criterion for treatment failure at 48 hours	**Frequency at 48 hours N=111**	**Frequency at 5 days N=62**
Worsening conscious level	4 (3.6%)	3 (5%)
Persistent reduced conscious level	-	0 (0%)
Worsening SaO_2	19 (17%)	2 (3%)
Persistent SaO_2 <90%	-	19 (31%)
Worsening respiratory rate	61 (55%)	12 (19%)
Persistent respiratory rate	-	5 (8%)
Worsening temperature	22 (20%)	1 (2%)
Persistent temperature	-	4 (6%)
Persistent lower chest wall indrawing	-	31 (50%)
New empyema	0 (0%)	0 (0%)
New bacterial meningitis	2 (1.8%)	2 (3%)
New renal impairment	0 (0%)	1 (2%)
New signs of shock	3 (2.7%)	4 (6%)
Death	22 (20%)	25 (40%)

Note: proportions exceed 100% as children may have had more than one reason for failure, there is no overlap with 'death'.

TABLE 4

Odds ratios from multivariable models of the clinical features at admission associated with treatment failure and early death

Exposure variable ascertained on admission	Number exposed (%) N=568	Treatment failure at 48 hours	Death before 48 hours	Treatment failure at day 5
Age < 1 year	293 (52%)	1.66 (1.05 – 2.61)	-	-
Very severe pneumonia	165 (29%)	1.93 (1.15 – 3.23)	26.5 (3.36 – 208)	2.93 (1.48 – 5.81)
Oxygen saturation <95% at admission	134 (24%)	1.78 (1.06 - 3.00)	-	2.88 (1.48 – 5.59)
Signs of shock on admission	43 (8%)	2.52 (1.24 – 5.12)	9.99 (3.36 – 29.7)	2.66 (1.15 – 6.14)
Bacteremia on admission	32 (6%)	3.06 (1.35 – 6.92)	-	4.91 (1.90 – 12.7)
History of convulsions	32 (6%)	-	6.83 (2.01 – 23.2)	-
Cough for >14 days	56 (10%)	-	-	3.87 (1.83 – 8.19)
Wheeze on admission	89 (16%)	-	N/A *	-
Positive HIV antibody test, not severely malnourished **Severe Malnutrition, negative HIV test** **Positive HIV test and severe malnutrition**	22 (4%) 54 (10%) 8 (2%)	3.45 (1.31 – 9.06) 1.94 (1.01 – 3.74) 0.17 (0.02 – 1.48)	4.62 (0.75 – 28.5) 1.37 (0.35 – 5.31) N/A **	2.21 (0.61 – 8.03) 1.80 (0.91 – 4.69) 0.46 (0.04 – 5.79)

'-' *indicates that the factor did not contribute to that model.*

* *No child with wheeze died within 48 hours.*

** *No child with both HIV and malnutrition died within 48 hours.*

For each exposure variable, the reference value is the absence of that exposure. For very severe pneumonia, the reference category is severe pneumonia. For HIV and severe malnutrition the reference category is having neither severe malnutrition nor a positive HIV test.