

Table 1: PEDIATRIC INFECTIOUS EVENT TOOL FOR RESEARCH: case definitions and grading

(Case definitions are largely based on criteria from the World Health Organization Integrated Management of Childhood Illnesses and the Division of AIDS Grading of Adult and Pediatric Adverse Events)

Hospitalization events can be categorized into one or more of the case-definition categories and graded as either mild-moderate, severe or very severe:

- Mild-moderate generally corresponds with an event that may not warrant hospitalization
- Severe generally corresponds with an event that definitely warrants hospitalization
- Very severe is any event that meets criteria for a severe event and in which the severity criteria are present for ≥ 2 days OR in the case of tuberculosis, central nervous system infections, invasive bacterial infections and congenital infections any general danger sign is present for ≥ 2 days

General danger signs:

- O₂ saturation $\leq 92\%$ on pulse oximeter
- Any form of O₂ (NPO₂, NCO₂, HBO₂, NCPAP, ETT)
- Lower chest wall indrawing, recessions, nasal flare
- Unable to drink orally, requiring a NG, OG or IV fluid
- Vomiting everything
- Convulsions (witnessed) during admission
- Acutely unwell, lethargic, unconscious
- Apnea episodes witnessed during admission
- Stridor on inspiration & expiration
- Skin pinch > 2 seconds (CRT > 2 seconds)
- Tachypnea for age (0-1 months > 60bpm, 2-12 months > 50 bpm, 13-60 months > 40bpm)

1. RESPIRATORY TRACT INFECTIONS

Criteria for pneumonia, bronchiolitis or LTB cannot be fulfilled concurrently for the same event

Criteria for pneumonia and tuberculosis can be fulfilled concurrently for the same event

Criteria for bronchiolitis and tuberculosis can be fulfilled concurrently for the same event

Criteria for 1 of pneumonia, tuberculosis or LTB can be met concurrently with Measles

Criteria for 1 of pneumonia, tuberculosis or LTB can be met concurrently with Varicella Zoster

(a) Pneumonia

- History of cough or difficulty breathing

PLUS 1 or more of the following

- Tachypnea for age (on presentation/admission)
[0-2 months > 60bpm, 2-12 months > 50bpm, 13-60 months > 40bpm]
- Any form of O₂ required
- Chest X-ray consistent with pneumonia (consolidation/infiltrates)

Severe: At least 1 of the following

- ✓ Lower chest wall indrawing, recessions or nasal flaring
- ✓ Not able to drink or breastfeed
- ✓ Vomiting everything
- ✓ Convulsions during this illness
- ✓ Lethargic or unconscious

- ✓ O₂ saturation ≤ 92% measured by pulse oximeter
- ✓ Any form of O₂ (NPO₂, NCO₂, HBO₂, NCPAP, intubated)

Mild-moderate: No features of severe pneumonia

(b) Tuberculosis

- Started on TB treatment in hospital (none of below criteria necessary)

OR

- A close TB contact (an adult who has had PTB in last 12 months, who lives in the same household as child or someone with whom the child is in contact for long periods)

PLUS 2 or more of the following

- Persistent non-remitting cough or wheeze for > 2 weeks that has not responded to broad spectrum antibiotics for community acquired pneumonia
- Documented loss of weight, no weight gain, or unsatisfactory weight gain (i.e. not following own curve or crossing centiles downwards)
- Fatigue or reduced playfulness
- Persistent fever > 2 weeks
- Painless enlarged mass of matted cervical lymph nodes (> 2x2 cm), without visible local cause on scalp or response to oral antibiotics

AND/OR

- Abnormal chest X-ray suggestive of PTB (enlarged hilar lymph nodes; airway compression; lung parenchymal disease; miliary dissemination)

OR

- Bacteriological confirmation of TB on sputum, gastric aspirate or lymph node fine needle aspiration biopsy (Classify as “confirmed tuberculosis” if present; “probable tuberculosis” if absent)

Severe: At least 1 of the following

- ✓ Severe respiratory distress – tachypnea for age PLUS at least 1 of lower chest wall indrawing or O₂ required
- ✓ Wheezing (low pitched monophonic) not responding to bronchodilator
- ✓ Neck stiffness, lethargy, persistent irritability, reduced level of consciousness or convulsions
- ✓ Hepatosplenomegaly (age defined)
- ✓ Peripheral edema
- ✓ Distended abdomen with or without ascites
- ✓ Angulation of the spine/gibbus

OR

- ✓ Hospital diagnosed extrapulmonary or miliary TB

Mild-moderate: No features of severe tuberculosis

(c) Bronchiolitis

- History of cough or difficulty breathing

PLUS 1 or more of the following

- Wheeze on history or physical exam
- Evidence of hyperinflation on physical exam (liver ptosis or reduced cardiac dullness or hyperresonance)
- Evidence of hyperinflation on chest X-ray (> 8 posterior ribs above the diaphragm) but no consolidation/infiltrates on chest X-ray suggestive of pneumonia

Severe: At least 1 of the following

- ✓ Tachypnea for age [0-2 months > 60bpm, 2-12 months > 50bpm, 13-60 months > 40bpm]
- ✓ Lower chest wall indrawing, nasal flaring or prolonged expiration
- ✓ Not able to drink or breastfeed
- ✓ Vomiting everything
- ✓ Convulsions during this illness
- ✓ Lethargic or unconscious
- ✓ Apnea on history or witnessed
- ✓ O₂ saturation ≤ 92% measured by pulse oximeter
- ✓ Any form of O₂ (NPO₂, NCO₂, HBO₂, NCPAP, intubated)

Mild-moderate: No features of severe bronchiolitis

(d) Laryngotracheobronchitis

- History of cough or difficulty breathing

PLUS

- Stridor

Severe: Any 1 of the following on admission

- ✓ O₂ saturation ≤ 92% measured by pulse oximeter
- ✓ Not able to drink or breastfeed
- ✓ Lethargic or unconscious
- ✓ Stridor on inspiration and expiration

Mild-moderate: No features of severe LTB

(e) Otitis Media

At least 2 of the following:

- History of ear pain, child pulling at ear
- History of ear discharge
- Visible ear discharge on examination
- Inflamed tympanic membrane

Severe: Any 1 of the following

- ✓ Any general danger sign
- ✓ Tender swelling behind the ear or clinical diagnosis of mastoiditis

Mild-moderate: No features of severe Otitis Media

2. DIARRHOEA

Criteria for acute and persistent diarrhoea cannot be met concurrently

Criteria for dysentery can be met concurrently with acute OR persistent diarrhoea

Criteria for 1 of acute or persistent diarrhoea can be met concurrently with any other category

(a) Acute Diarrhoea

- Liquid stools (more unformed than usual) with increased number of stools < 14 days

Severe: At least 2 of the following

- ✓ Not able to drink or drinking poorly
- ✓ Lethargic or unconscious
- ✓ Skin pinch takes > 2 seconds to return to normal
- ✓ Sunken eyes

OR

- ✓ $\geq 10\%$ dehydration

Mild-moderate: No signs of severe

(b) Persistent Diarrhoea

- Liquid stools (more unformed than usual) with increased number of stools ≥ 14 days

Severe: At least 2 of the following (any dehydration)

- ✓ Not able to drink or drinking poorly
- ✓ Lethargic or unconscious
- ✓ Restless or irritable
- ✓ Sunken eyes
- ✓ Skin pinch takes > 1 second to return to normal or “reduced skin turgor”

OR:

- ✓ Any loss of weight
- ✓ $\geq 5\%$ dehydration

Mild-moderate: No visible dehydration or weight loss

(c) Dysentery

- Any blood in the stool

Severe: At least 1 of the following

- ✓ Age < 12 months
- ✓ Any dehydration present

Mild-moderate: No features of severe dysentery

3. SKIN AND MUCOCUTANEOUS INFECTIONS

Criteria for measles, varicella and non-specific viral exanthem cannot be met concurrently

Criteria for stomatitis or bacterial skin infection can be met concurrently with any other category including skin and mucocutaneous infections

(a) Measles

- Fever (on history or exam) AND diffuse maculopapular rash

PLUS 1 of

- Cough, coryza or conjunctivitis

Severe: At least 1 of the following

- ✓ Pneumonia (as previously defined)
- ✓ LTB (as previously defined)
- ✓ Diarrhoea (as previously defined)
- ✓ Any general danger signs*

Mild-moderate: No features of severe measles

(b) Varicella Zoster

- Fever AND diffuse vesicular rash

Severe: At least 1 of the following

- ✓ Pneumonia (as previously defined)
- ✓ LTB (as previously defined)
- ✓ Any general danger sign*

Mild-moderate: No features of severe varicella zoster

(c) Non-specific viral exanthema

- Fever AND rash

AND

- Doesn't meet criteria for measles or varicella zoster

Severe: Presence of any general danger sign

Mild-moderate: No features of severe viral exanthem

(d) Stomatitis

- Erythema AND ulceration of oral mucosa (lips, gingiva or tongue)

Severe: At least 1 of the following

- ✓ Stridor
- ✓ Unable to eat orally, requiring nasogastric, orogastric or intravenous fluids

Mild-moderate: No features of severe stomatitis

(e) Bacterial Skin Infection

At least 1 of the following:

- Impetigo (diffuse pustular eruption)
- Abscess
- Cellulitis

Severe: Presence of any general danger sign

Mild-moderate: No features of severe bacterial skin infection

4. INVASIVE BACTERIAL INFECTIONS

Hospital diagnosis of any of the following:

- Meningitis - diagnosis based on clinical features and abnormal cerebrospinal fluid
- Necrotising enterocolitis
- Septic arthritis
- Osteomyelitis
- Pyomyositis
- Bacterial septicemia – blood culture positive
- Urinary tract sepsis – sterile urine culture positive

Severe – Always

5. CONGENITAL INFECTIONS

Hospital diagnosis of any of the following:

- Congenital tuberculosis
- Congenital syphilis
- Congenital CMV
- Neonatal Herpes Simplex Virus infection
- Other pediatrician/specialist diagnosed congenital infection

Severe – Always

Table 2: Poisson regression models assessing associations with infectious-cause hospitalization in HIV uninfected infants between 29 days and 12 months of age (vaccination status sensitivity analyses)

		Model E: Adjusted IRR (n=888)	Model F: Adjusted IRR (n=807)	Model G: Adjusted IRR (n=888)	Model H: Adjusted IRR (n=807)
HIV exposure		2.15 (1.27-3.65)	1.75 (1.01-3.02)	2.04 (1.20-3.48)	1.71 (0.99-2.95)
Maternal education (secondary schooling completed)		0.84 (0.49-1.44)	0.80 (0.46-1.37)	0.81 (0.47-1.40)	0.78 (0.45-1.34)
Maternal age at delivery (years)		0.94 (0.90-0.99)	0.93 (0.89-0.98)	0.94 (0.90-0.99)	0.93 (0.89-0.98)
Reside in formal housing (vs informal dwelling)		0.65 (0.39-1.08)	0.72 (0.43-1.20)	0.69 (0.41-1.15)	0.77 (0.46-1.28)
Male sex of infant		1.28 (0.78-2.10)	1.35 (0.83-2.21)	1.32 (0.80-2.17)	1.39 (0.85-2.27)
All vaccinations up-to-date	No	1	1		
	Yes	0.52 (0.29-0.94)	0.60 (0.34-1.07)		
	Unknown	0.53 (0.29-0.99)	0.56 (0.30-1.05)		
Preterm birth (<37 weeks gestation)			2.34 (1.26-4.33)		2.41 (1.29-4.49)
Breastfeeding duration (months)			0.92 (0.86-0.98)		0.92 (0.86-0.98)
Variance of random effect (95% CI)		1.44 (0.74-2.82)	1.07 (0.47-2.43)	1.59 (0.85-2.99)	1.19 (0.56-2.55)

Abbreviations: IRR - incidence rate ratio; CI - confidence interval

Note: Models E and F include vaccination status with an 'unknown' category. Models G and H exclude vaccination status.

Models E and G include possible confounders; Models F and H also include mediators (preterm birth and breastfeeding).

Adjusted IRRs (and 95% confidence intervals) were obtained from mixed-effects Poisson regression models (log link function; normally distributed random effect by infant; observation time as an offset). Second-born twins and infants with high-risk congenital anomalies were excluded from analyses.

Table 3: Poisson regression models assessing associations with infectious-cause hospitalization in HIV uninfected infants between 29 days and 12 months of age (sensitivity analyses with observation time adjusted for time infants were potentially out-of-province)

	Model I: Adjusted IRR (n=623)	Model J: Adjusted IRR (n=611)
HIV exposure	2.79 (1.46-5.30)	1.90 (0.98-3.69)
Maternal education (secondary schooling completed)	0.72 (0.37-1.38)	0.68 (0.36-1.30)
Maternal age at delivery (years)	0.94 (0.89-0.99)	0.94 (0.89-0.99)
Reside in formal housing (vs informal dwelling)	0.78 (0.43-1.41)	0.85 (0.48-1.52)
Male sex of infant	1.46 (0.81-2.64)	1.47 (0.83-2.61)
All vaccinations up-to-date	0.52 (0.28-0.94)	0.61 (0.34-1.0)
Preterm birth (<37 weeks gestation)		2.16 (0.04-4.51)
Breastfeeding duration (months)		0.90 (0.83-0.97)
Variance of random effect (95% CI)	1.48 (0.68-3.22)	1.12 (0.45-2.83)

Abbreviations: IRR - incidence rate ratio; CI – confidence interval

Note: Model I includes possible confounders; Model J also includes mediators (preterm birth and breastfeeding).

Adjusted IRRs (and 95% confidence intervals) were obtained from mixed-effects Poisson regression models (log link function; normally distributed random effect by infant; observation time as an offset). Second-born twins and infants with high-risk congenital anomalies were excluded from analyses.

Table 4: Poisson regression models assessing associations with infectious-cause hospitalization in HIV uninfected infants between 29 days and 12 months of age (sensitivity analyses excluding infants who had low level of certainty of HIV infection status, i.e. who were not tested for HIV at ≥ 6 weeks of age)

	Model K: Adjusted IRR (n=586)	Model L: Adjusted IRR (n=575)
HIV exposure	3.07 (1.59-5.90)	2.03 (1.04-3.94)
Maternal education (secondary schooling completed)	0.71 (0.36-1.39)	0.66 (0.34-1.28)
Maternal age at delivery (years)	0.95 (0.90-1.00)	0.95 (0.90-1.00)
Reside in formal housing (vs informal dwelling)	0.86 (0.47-1.57)	0.98 (0.54-1.76)
Male sex of infant	1.39 (0.76-2.53)	1.40 (0.78-2.51)
All vaccinations up-to-date	0.50 (0.27-0.91)	0.57 (0.32-1.04)
Preterm birth (<37 weeks gestation)		2.42 (1.16-5.04)
Breastfeeding duration (months)		0.89 (0.82-0.96)
Variance of random effect (95% CI)	1.45 (0.66-3.20)	1.03 (0.39-2.72)

Abbreviations: IRR - incidence rate ratio; CI – confidence interval

Note: Model K includes possible confounders; Model L also includes mediators (preterm birth and breastfeeding). Adjusted IRRs (and 95% confidence intervals) were obtained from mixed-effects Poisson regression models (log link function; normally distributed random effect by infant; observation time as an offset). Second-born twins and infants with high-risk congenital anomalies were excluded from analyses.