Respiratory disease in HIV-infected children

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introduction

- in 1989 the first patient with HIV disease with admitted to the Red Cross War Memorial Children's Hospital in Cape Town

- during 1998 103 children with severe pneumonia were admitted to PICU in Cape Town of which 76 were entered into a study
  - median age 3 months
  - 21 (27.6%) were HIV infected
  - 15 of those had a diagnosis of HIV infection made at the time of PICU admission.

Zar et al, Pediatr, Crit Care Med, 2001

- since then anti-retroviral therapy has become available

aims

- to review patterns of respiratory disease seen in countries with a high prevalence of HIV disease
- to focus where possible on children with severe respiratory disease causing either PICU admission or death
- consider the impact of ARV therapy
- consider other preventative / treatment strategies

Table 2. Microbiological isolates (n) of children by HIV status

	HIV-positive	HIV-negative	OR (95% CI)	p
Blood culture (n)	19	53		
Streptococcus pneumoniae	2	3	1.96 (0.2–18.5)	.48
Staphylococcus aureus	1	2	1.42 (0–28.6)	.78
Gram-negative bacteria	0	4	0 (0–4.3)	.22
BAL/sputum (n)	21	52		
Pneumocystis carinii[a]	8	1	31.4 (3.5–1418.5)	<.001
Klebsiella pneumoniae	3	8	0.9 (0.1–4.5)	.93
Haemophilus influenzae	3	6	1.28 (0.2–6.8)	.75
Mycobacterium tuberculosis	3	3	2.7 (0.3–21.9)	.23
Acinetobacter baumanii	1	5	0.5 (0–4.6)	.5
Pseudomonas aeruginosa	3	2	4.17 (0.4–52.4)	.11
S. aureus	2	2	2.63 (0.2–38.1)	.34
Moraxella catarrhalis	2	2	2.63 (0.2–38.1)	.34
S. pneumoniae	0	2	0 (0–13.3)	.36
Cytomegalovirus	2	2	2.63 (0.2–38.1)	.34
Other viruses	1	3	0.82 (0–10.9)	.86

HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval.
[a]*P. carinii* was detected either by silver stain or immunofluorescence.

Zar et al, Pediatr Crit Care Med, 2001

Table 3. Intermittent positive pressure ventilation requirements and outcome of HIV-positive children by presence of PCP

Outcome	PCP (n = 8)	No PCP (n = 13)
IPPV, n (%)	7 (87.5)	1 (7.7)[a]
IPPV (days)	4 (2–6)	2 (2–2)
ICU (days)	7 (6–9)	6 (4–8)
Hospital (days)	10.5 (7–16.5)	18 (10–21)
Highest PIP (cm H_2O)	27 (25–28)	29 (29–29)
Highest PEEP (cm H_2O)	8 (7–12)	6 (6–6)
Highest FIO_2 (%)	0.7 (0.6–1.0)	0.9 (0.9–0.9)
Deaths, n (%)	3 (37.5)	3 (23.1)

Continuous variables are median (25^{th}–75^{th} percentile). HIV, human immunodeficiency virus; PCP, *Pneumocystis carinii* pneumonia; IPPV, intermittent positive pressure ventilation; ICU, intensive care unit; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure.

[a] $p < .005$ compared to children with PCP.

Zar et al, Pediatr Crit Care Med, 2001

Red Cross War Memorial Children's Hospital ICU -2001

- 136 (6.2%) admissions of 131 children with HIV infection or exposure
  - 88% ventilated on admission
  - median age 3.36m (mean 7.34)
  - median ICU stay 4d (mean 6.66)
  - median risk of mortality (PIM) 0.32
- bed days were 906 i.e 8% of total period

Red Cross War Memorial Children's Hospital ICU

136 HIV related admissions

37 (27%) deaths in ICU

99 ICU survivors

36 deaths,
20 never left hospital

63 survivors

57 (42%) deaths on that hospital admission

44 lost to hospital follow up

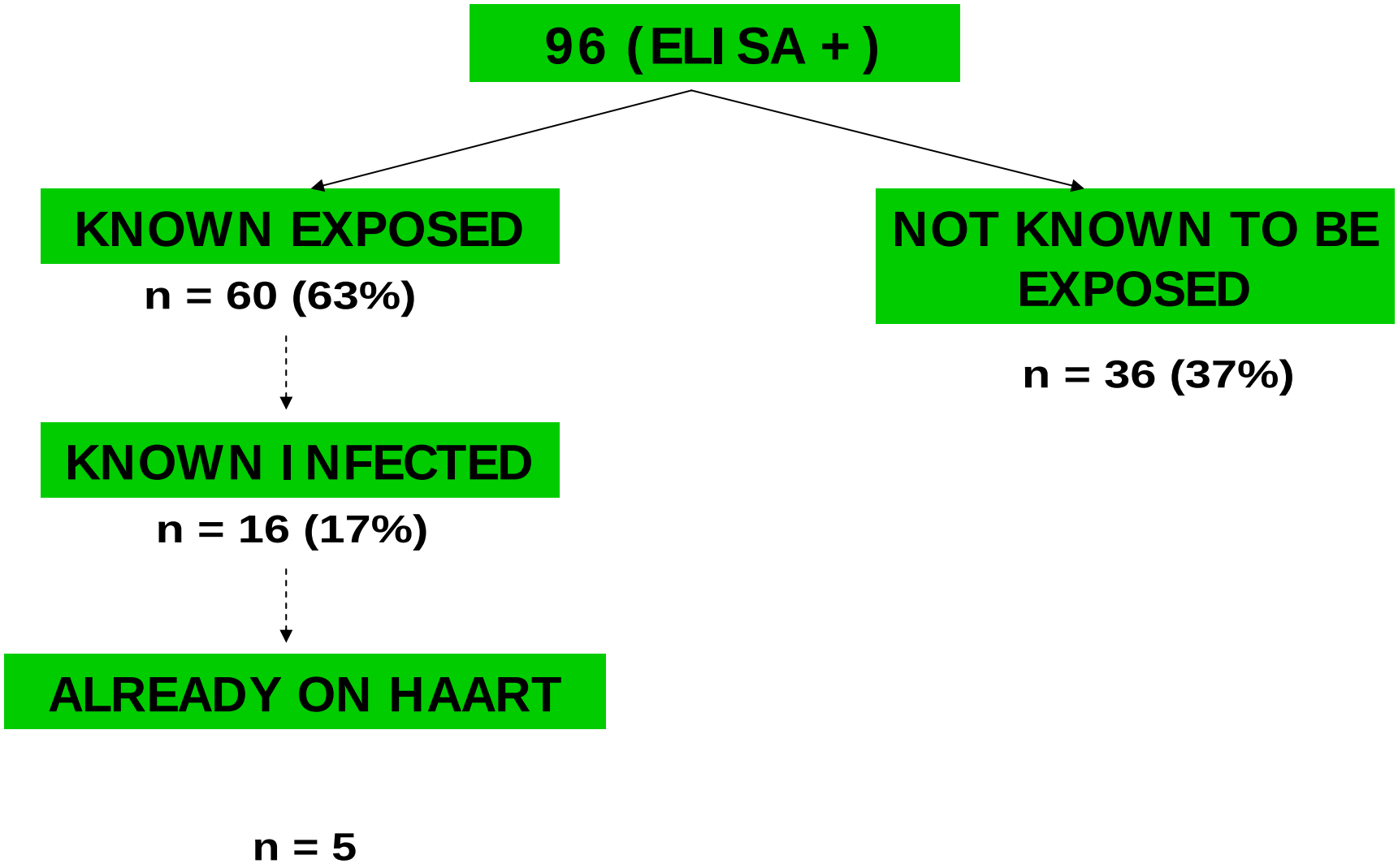
19 (14%) known to be OK

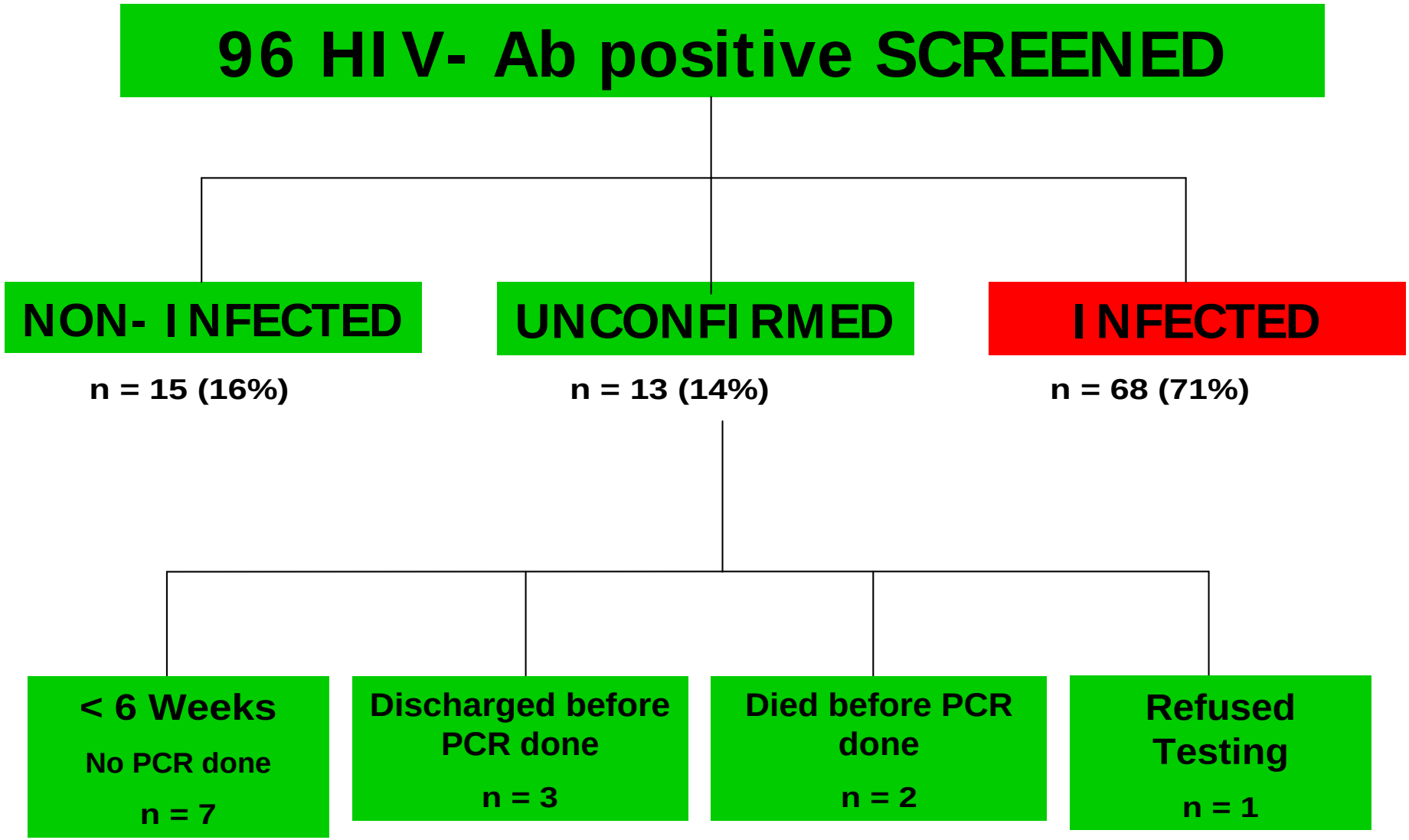
HIV Infected children, HAART and the PICU

study over a
9 month period
until October 2003

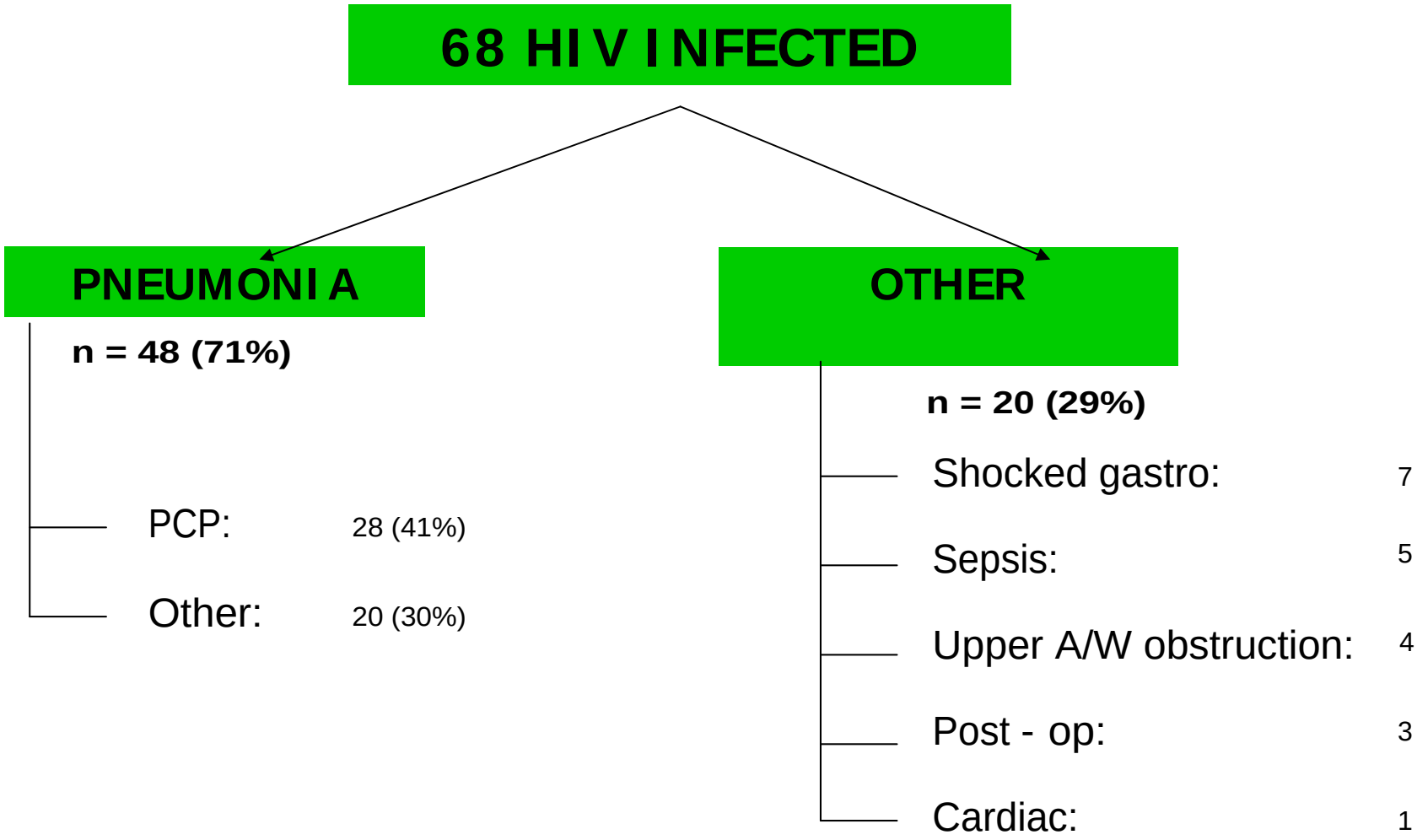
Cowburn C, Hatherill M, Eley B,
Nuttall J, Hussey G, Reynolds L,
Waggie Z, Vivian L, Argent A

On admission to PICU:

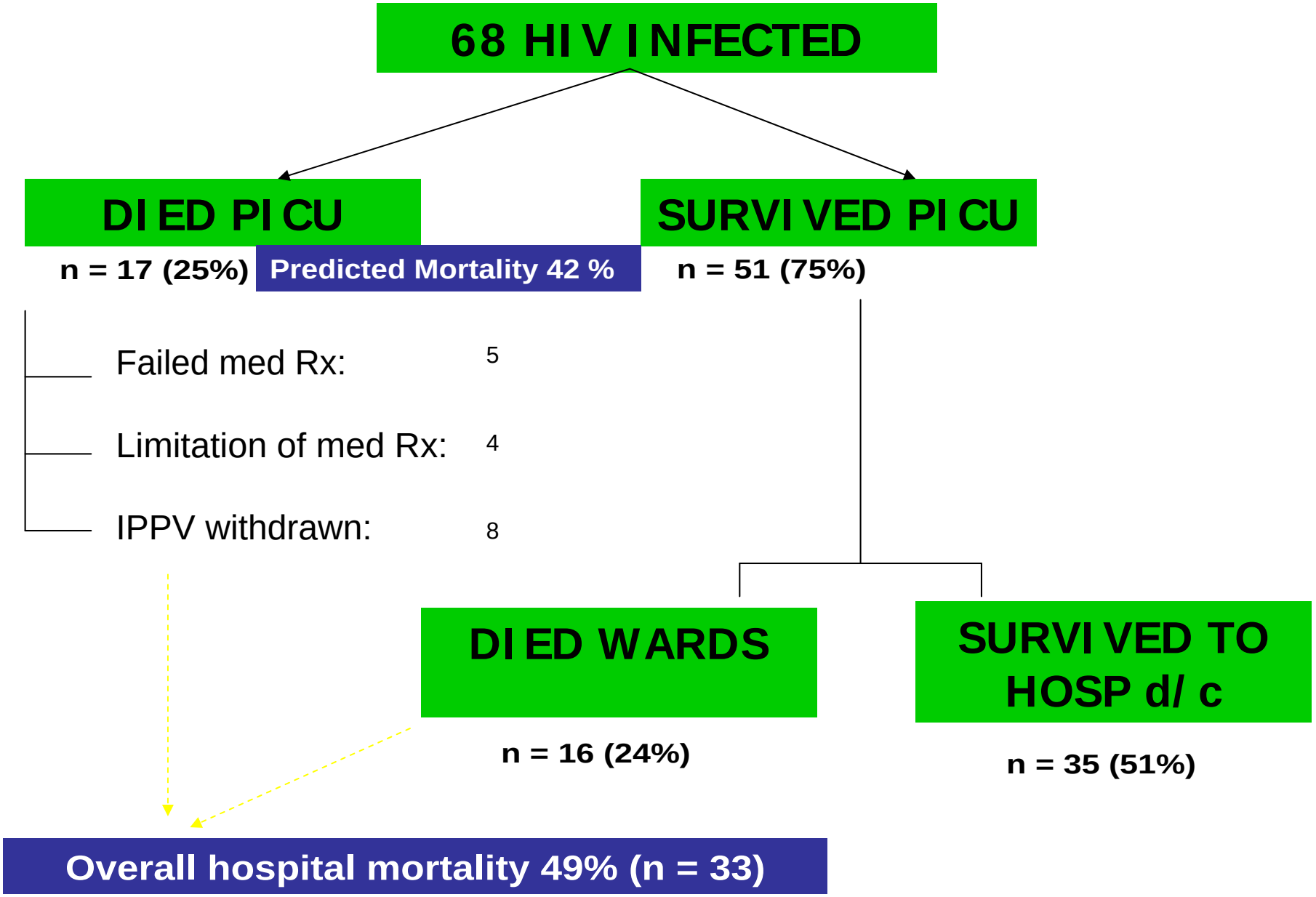


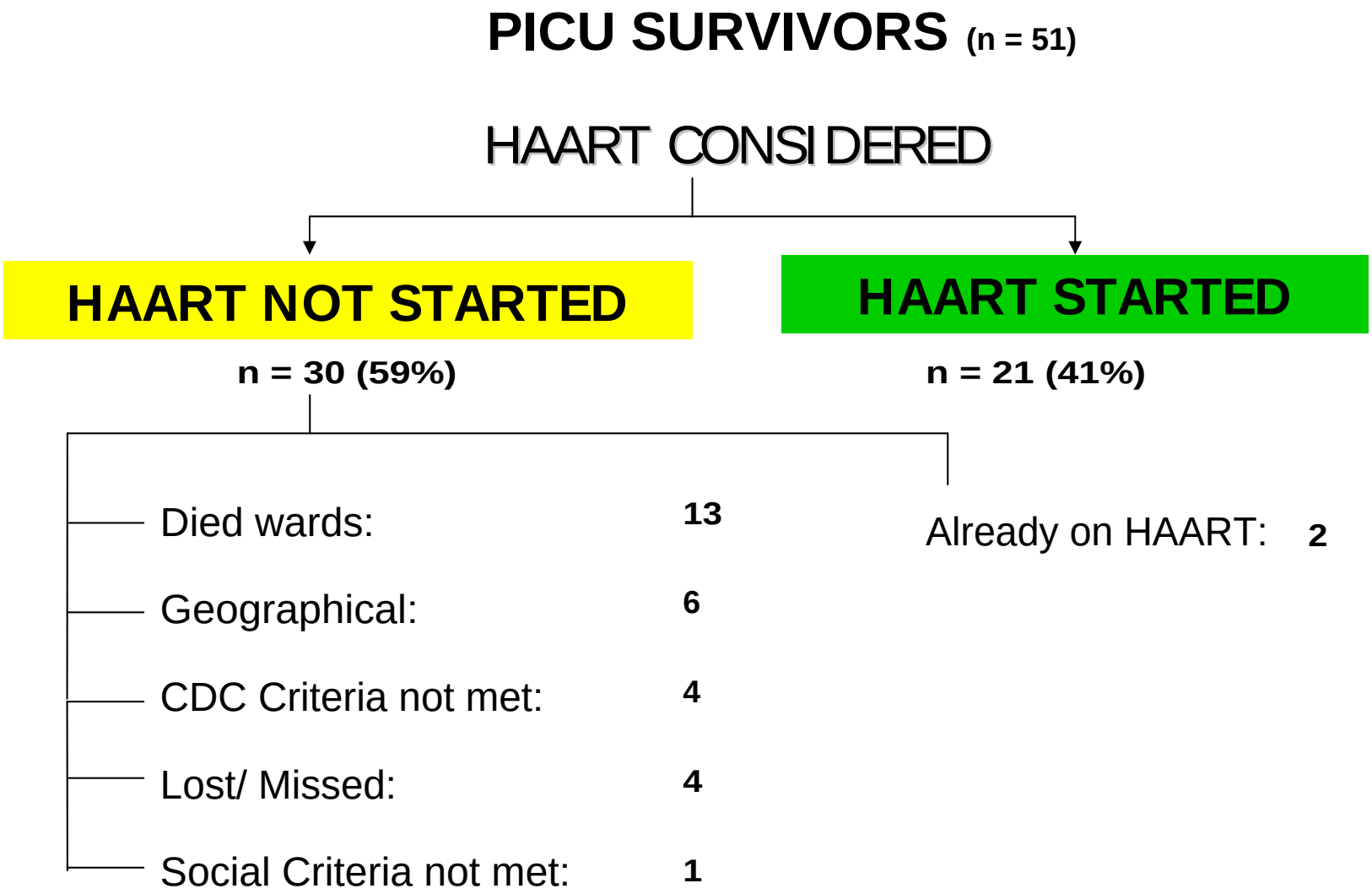

96 HIV- Ab positive SCREENED
NON- INFECTED
n = 15 (16%)
UNCONFIRMED
n = 13 (14%)
INFECTED
n = 68 (71%)
< 6 Weeks
No PCR done
n = 7
Discharged before PCR done
n = 3
Died before PCR done
n = 2
Refused Testing
n = 1

Clinical Diagnosis

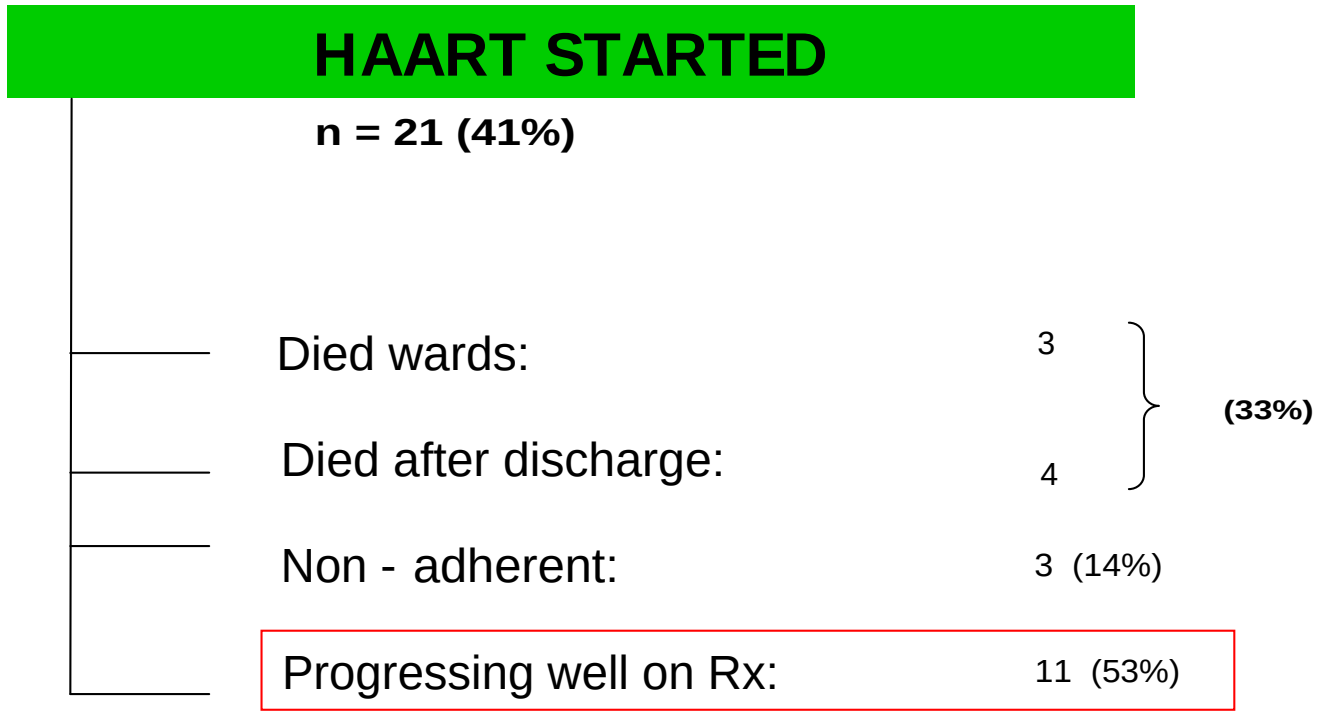


Survival

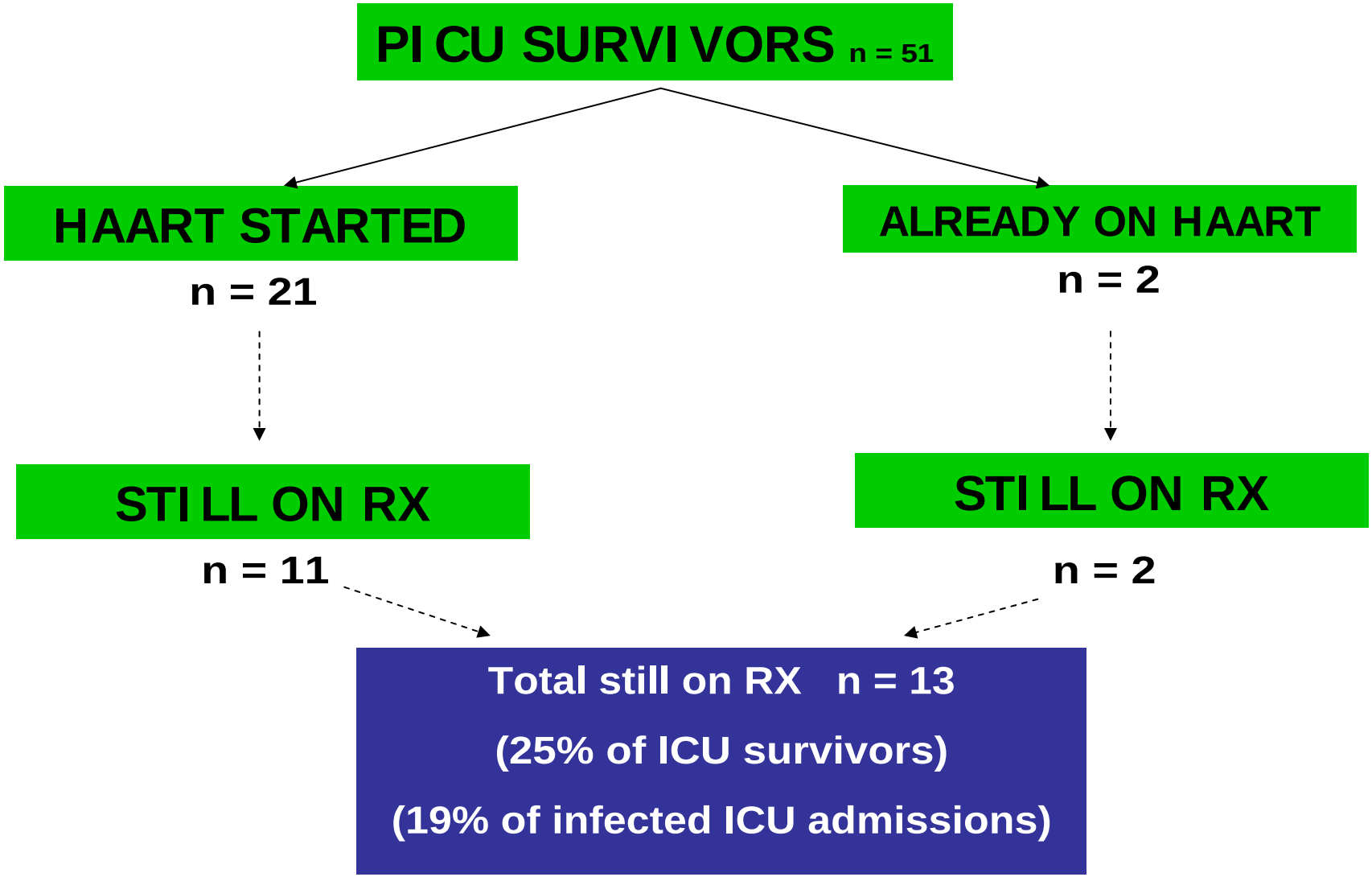

68 HIV INFECTED
DIED PICU
n = 17 (25%)
Predicted Mortality 42 %
SURVIVED PICU
n = 51 (75%)
Failed med Rx: 5
Limitation of med Rx: 4
IPPV withdrawn: 8
DIED WARDS
n = 16 (24%)
SURVIVED TO HOSP d/ c
n = 35 (51%)
Overall hospital mortality 49% (n = 33)


PICU SURVIVORS (n = 51)
HAART CONSIDERED
HAART NOT STARTED
n = 30 (59%)
HAART STARTED
n = 21 (41%)
Died wards: 13
Geographical: 6
CDC Criteria not met: 4
Lost/ Missed: 4
Social Criteria not met: 1
Already on HAART: 2

OUTCOME


HAART STARTED
n = 21 (41%)
Died wards:
3
Died after discharge:
4
(33%)
Non - adherent:
3 (14%)
Progressing well on Rx:
11 (53%)

OUTCOME


PICU SURVIVORS n = 51
HAART STARTED
n = 21
ALREADY ON HAART
n = 2
STILL ON RX
n = 11
STILL ON RX
n = 2
Total still on RX n = 13
(25% of ICU survivors)
(19% of infected ICU admissions)

other outcomes

- 12 month study in Kwa-Zulu-Natal
- 116 HIV-exposed infants were enrolled
  - 49 into the IPPV arm
  - 67 into the non-IPPV arm
  - median age of both groups 3.0 months (0.5-11 months)
- Survival to discharge for HIV-infected children in the IPPV and non-IPPV arms:
  - 41.9% and 24.6% respectively (p = 0.08).

Thirsk et al, S Afr Med J, 2003

Table 1 Survival rates from the literature of various combinations of HIV and other diseases

	Mortality rate (%)
HIV related acute LRTI in Africa[4 5]	15–28
HIV related ARF + ventilation[21 22]	19–50
HIV related ARF + ventilation + PCP[23 24]	40–100
HIV + ventilation[27]	53
HIV + PICU 1996, Durban[10]	100
HIV + PICU 1998, Johannesburg[29]	88
HIV + PICU 2001, Cape Town[30]	29
Developed world 3 month mortality[26 27]	10–32
Developed world 32 month mortality[23 24]	40–100

LRTI, lower respiratory tract infection; ARF, acute respiratory failure; PCP, *Pneumocystis carinii* pneumonia; PICU, paediatric intensive care unit.

Jeena et al, J Med Ethics, 2005

most recent ….

- retrospective review of admissions 2005– 2006

- 79 identified as HIV exposed or infected
  - 12 HIV infected on admission, of which 6 on HAART
  - 53 known to have positive HIV antibody tests on admission
  - 14 children with no pre-admission HIV testing,
  - median age 3 months (range 0 – 51 months).

- 31 (70%) admissions for respiratory failure

- 32 (74%) survived to PICU discharge,

- 22(51%) survived to hospital discharge,

- 2 currently in hospital 2 months post PICU discharge.

what is the pattern?

- fewer children with HIV are being admitted to the PICU (as a policy decision)
- the majority are
  - approx 3 m of age
  - previously apparently well
  - not known to have HIV
- the risk of mortality on admission has decreased
- despite the availability of ARVs mortality over time for children admitted to PICU has not changed

how is HIV related respiratory disease different?

- data from other sources in Africa
- organisms involved
- risk of respiratory disease
- clinical patterns

	Total	HIV positive (% of total)	Deaths (case fatality rate)
All cases	150	93 (62%)	33 (22%)
Age			
2–6 months	86	63 (73%)	26 (30%)
⩾6 months	64	30 (47%)	7 (11%)
Cause of death			
Not known	114	66 (58%)	18 (16%)
PCP*	16*	16 (100%)	10 (63%)*
Bacterial pneumonia*	21*	12 (57%)	6 (28·6%)*
Streptococcus pneumoniae	8	4	. .
Non-typhoidal salmonella†	7	3	. .
Haemophilus influenzae type b*	3*	2	. .
Group B streptococcus	1	1	. .
Aeromonas sp	1	1	. .
Campylobacter sp	1	1	. .

*One HIV-positive child who died was PCP positive on immunofluorescence and *Haemophilus influenzae* type b grew on blood culture, and has been included in both groups. †Include five *Salmonella typhimurium*; one *S enteritidis*; one non-typable *Salmonella* sp.

Table 1: **Outcome and HIV infection**

Graham et al, Lancet, 2000

Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study

*Chifumbe Chintu, Victor Mudenda, Sebastian Lucas, Andrew Nunn, Kennedy Lishimpi, Daniel Maswahu, Francis Kasolo, Peter Mwaba, Ganapati Bhat, Hiroshi Terunuma, Alimuddin Zumla, for the UNZA-UCLMS Project Paediatric Post-mortem Study Group**

- during a 3 year period there were 1603 children who were admitted and died of respiratory disease.

- parents of 25% of these agreed to PM

Chintu et al, Lancet, 2002

Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study

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- 137 (52%) were boys and 127 (48%) were girls
- 180 (68%) HIV1-positive and 84 (32%) negative.
- HIV-1 rates were
  - 77% for children aged 0–5m
  - 63% for 6–11m
  - 54% for 12–17 m, and
  - 68% for 18 m to younger than 16 years.

Chintu et al, Lancet, 2002

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	Total*	Adjusted % (SE)†	HIV-positive (n=180)	HIV-negative (n=84)	Odds ratio (95%CI)	p
Diagnosis						
Acute pyogenic pneumonia	116 (44%)	39·1% (3·2)	74 (41%)	42 (50%)	0·70 (0·40–1·21)	0·22
PCP	58 (22%)	27·5 % (3·1)	52 (29%)	6 (7%)	5·28 (2·12–15·68)	0·0001
Tuberculosis	54 (20%)	18·8% (2·5)	32 (18%)	22 (26%)	0·61 (0·31–1·18)	0·16
CMV	43 (16%)	20·2% (2·8)	40 (22%)	3 (4%)	7·71 (2·33–40·0)	0·0002
Interstitial pneumonitis	30 (11%)	11·8% (2·1)	15 (8%)	15 (18%)	0·42 (0·18–0·96)	0·04
Shock lung	27 (10%)	11·5% (2·2)	24 (13%)	3 (4%)	4·15 (1·20–22·10)	0·03
Pulmonary oedema	19 (7%)	6·4% (1·6)	10 (6%)	9 (11%)	0·49 (0·18–1·38)	0·21
Lymphocytic interstitial pneumonitis	10 (4%)	3·8% (1·2)	9 (5%)	1 (1%)	4·37 (0·59–193·7)	0·21

PCP=*Pneumocystis carinii* pneumonia. *Fewer than ten cases were noted of: measles (five HIV-1-positive, two HIV-1-negative), pleurisy (five HIV-1-positive), pulmonary embolism (one HIV-1-negative), respiratory syncytial virus pneumonia (one HIV-1-positive, one HIV-1-negative), herpes simplex virus pneumonia (one HIV-1-positive), lipoidal pneumonia (one HIV-1-positive), malaria (two HIV-1-negative), normal lung (one HIV-1-positive, two HIV-1-negative), Kaposi's sarcoma (two HIV-1-positive), bronchiolitis (three HIV-1-positive). †Percentages and standard errors adjusted to show age/sex structure of all deaths from respiratory disease during the study period.

Table 1: **Lung diseases identified at necropsy, by HIV-1 status**

Chintu et al, Lancet, 2002

SO ….

- pneumocystis is an important cause of severe respiratory disease
- bacterial pneumonia is still a major problem
- tuberculosis is common (but not more than in HIV non-infected children
- what about other organisms?

Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1
Madhi et al, J Pediatr, 2000

estimated incidence

	HIV-infected/ 100 000	HIV-uninfected/ 100 000	Relative risk, 95% CI
RSV	1,444	309	1.92, 1.29-2.83
Influenza A/B	1,268	148	8.03, 5.05-12.76
Parainfluenza 1-3	893	106	8.46, 4.95-10.47
Adenovirus	481	32	15.07, 6.62-34.33

Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1
Madhi et al, Journal of Pediatrics, 2000

- HIV-infected children with viral associated SLRTI presented more commonly with pneumonia (63 of 68, 92.6%) vs125 of 177, 70.6%), *P* = .0002.
- RSV was the dominant viral pathogen isolated from HIV-uninfected children (90 of 181, 49.7% of all viruses isolated) but not in HIV-infected children
- The estimated risk for HIV-infected children 2 to 23 months of age with any viral associated LRTI was 3.85-fold greater (OR 3.85, 95% CI 3.05 to 4.86)

S.A. Madhi · N. Ramasamy · K. Petersen · A. Madhi
K.P. Klugman

Severe Lower Respiratory Tract Infections Associated with Human Parainfluenza Viruses 1–3 in Children Infected and Noninfected with HIV Type 1

Eur J Clin Microbiol Infect Dis (2002) 21:499–505

- Children hospitalised for LRTI who
  - fulfilled the (WHO) clinical criteria for severe pneumonia
    - i.e. tachypnea adjusted for age and lower chest wall indrawing and/or intercostal recession in malnourished children or who had an oxygen saturation of <90% as measured by pulse oximetry
  - whom HPIV 1–3 was isolated within 24 h of admission were included

Eur J Clin Microbiol Infect Dis (2002) 21:499–505
DOI 10.1007/s10096-002-0754-9

ARTICLE

S.A. Madhi · N. Ramasamy · K. Petersen · A. Madhi
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Severe Lower Respiratory Tract Infections Associated with Human Parainfluenza Viruses 1–3 in Children Infected and Noninfected with HIV Type 1

- overall mortality was higher among HIV-1-infected than –noninfected children
  - 5 of 24 [21%] vs. 0 of 56, respectively; *P*=0.001
- overall duration of hospitalisation was longer in HIV-1-infected children than in HIV-1-noninfected children
  - median 11.5 days [range, 1–15] vs. 7.5 days [range, 1–22], respectively; *P*=0.02].

Eur J Clin Microbiol Infect Dis (2002) 21:499–505
DOI 10.1007/s10096-002-0754-9

ARTICLE

S.A. Madhi · N. Ramasamy · K. Petersen · A. Madhi
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Severe Lower Respiratory Tract Infections Associated with Human Parainfluenza Viruses 1–3 in Children Infected and Noninfected with HIV Type 1

Table 2 Clinical signs and symptoms observed in HIV-1-infected and -noninfected children hospitalised with severe lower respiratory tract infection due to human parainfluenza virus types 1–3

Clinical sign	HIV-1-infected group (n=24)	HIV-1-noninfected group (n=56)	P value
Mean temperature in °C (±SD)[a]	37.2 (±0.8)	37.2 (±0.8)	0.68
Mean percent O_2 saturation (±SD)[b]	86.6 (±4.4)	88.4 (±4.3)	0.91
No. (%) with cyanosis	4 (16.7)	7 (12.5)	0.72
No. (%) with clubbing	4 (16.7)	3 (5.4)	0.18
No. (%) with crackles	18 (75.0)	42 (75.0)	0.99
No. (%) with wheezing	1 (4.2)	16 (28.6)	0.01
No. (%) with bronchial breathing	4 (17.4)	5 (8.9)	0.43
No. (%) with stridor	2 (8.3)	1 (1.8)	0.21

[a] Calculated on the basis of 16 and 40 observations in HIV-1-infected and -noninfected children, respectively
[b] Measured in room air by pulse oximetry. Calculated on the basis of 16 and 40 observations in HIV-1-infected and -noninfected children, respectively

Table 2. Relative importance of human metapneumovirus (hMPV), in relation to other common respiratory viruses, among infants hospitalized for lower respiratory tract infection.

	HIV-1–infected infants		HIV-1–uninfected infants	
Respiratory virus	No. (%) of infants (n = 401)	OR (95% CI)[a]	No. (%) of infants (n = 853)	OR (95% CI)[a]
Respiratory syncytial virus	45 (11.2)	0.31 (0.16–0.58)	271 (31.8)	0.22 (0.16–0.29)
hMPV[b]	15 (3.7)	Not applicable	78 (9.1)	Not applicable
Influenza A/B virus	14 (3.5)	1.07 (0.42–2.37)	26 (3.1)	3.20 (1.99–5.18)
Parainfluenza virus types 1–3	13 (3.2)	1.16 (0.51–2.63)	37 (4.3)	2.11 (1.44–3.08)
Adenovirus	3 (0.7)	5.21 (1.44–27.9)	33 (3.9)	2.42 (1.63–3.60)

[a] Relative difference in rate of isolation of hMPV in relation to other analyzed respiratory viruses.

[b] Figure was extrapolated from the studied population to entire cohort. That is, 3 cases of hMPV infection among 81 HIV-1–infected infants was extrapolated to equal 15 cases among the entire cohort of HIV-1–infected infants. Similarly, 10 cases of hMPV infection among the 110 HIV-1–uninfected infants who were tested were extrapolated to equal to 78 cases among the entire cohort of 853 HIV-1–uninfected infants.

Madhi et al, Clin Infect Dis, 2003

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Journal of Clinical Virology 35 (2006) 41–45

JOURNAL OF CLINICAL VIROLOGY

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Genetic characterization of respiratory syncytial viruses isolated from consecutive acute respiratory infections in a HIV infected child

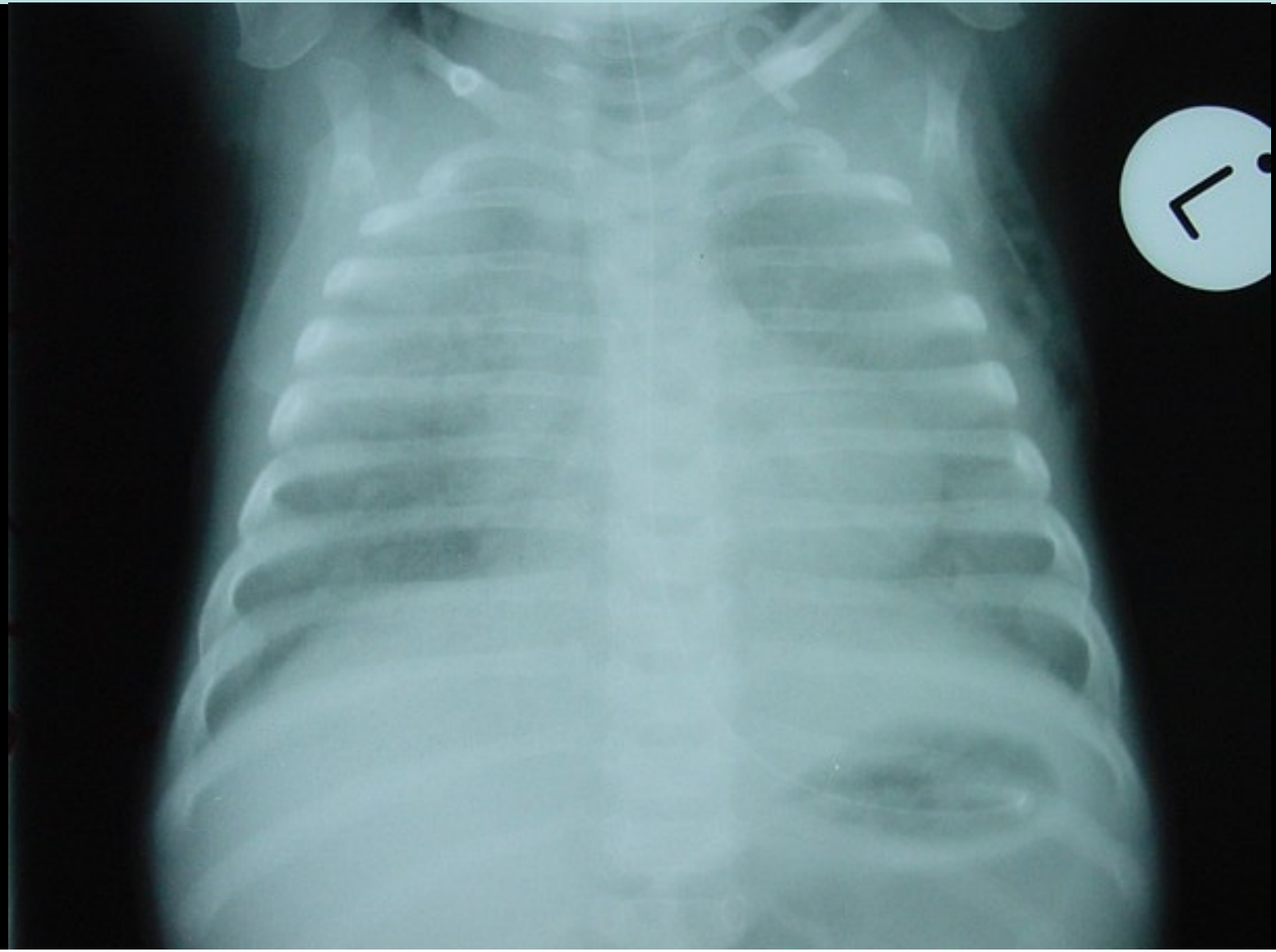
Juan Arbiza[a,*], Mabel Berois[a], Adriana Delfraro[a], Sandra Frabasile[a], Francisco Díaz Mitoma[c], Rose Milk[c], José C. Russi[b]

- 2 year old HIV infected child (on zidovudine)
- 3 separate isolates of RSV over period of 4 months
- all demonstrated to be the same strain (other isolates from the community during that period

SO …

- viral infections are more common in HIV-infected children
- the infections are more severe and less likely to be associated with wheezing
- the spectrum of viruses is different
- viruses may be shed for longer periods

Pneumocystis pneumonia



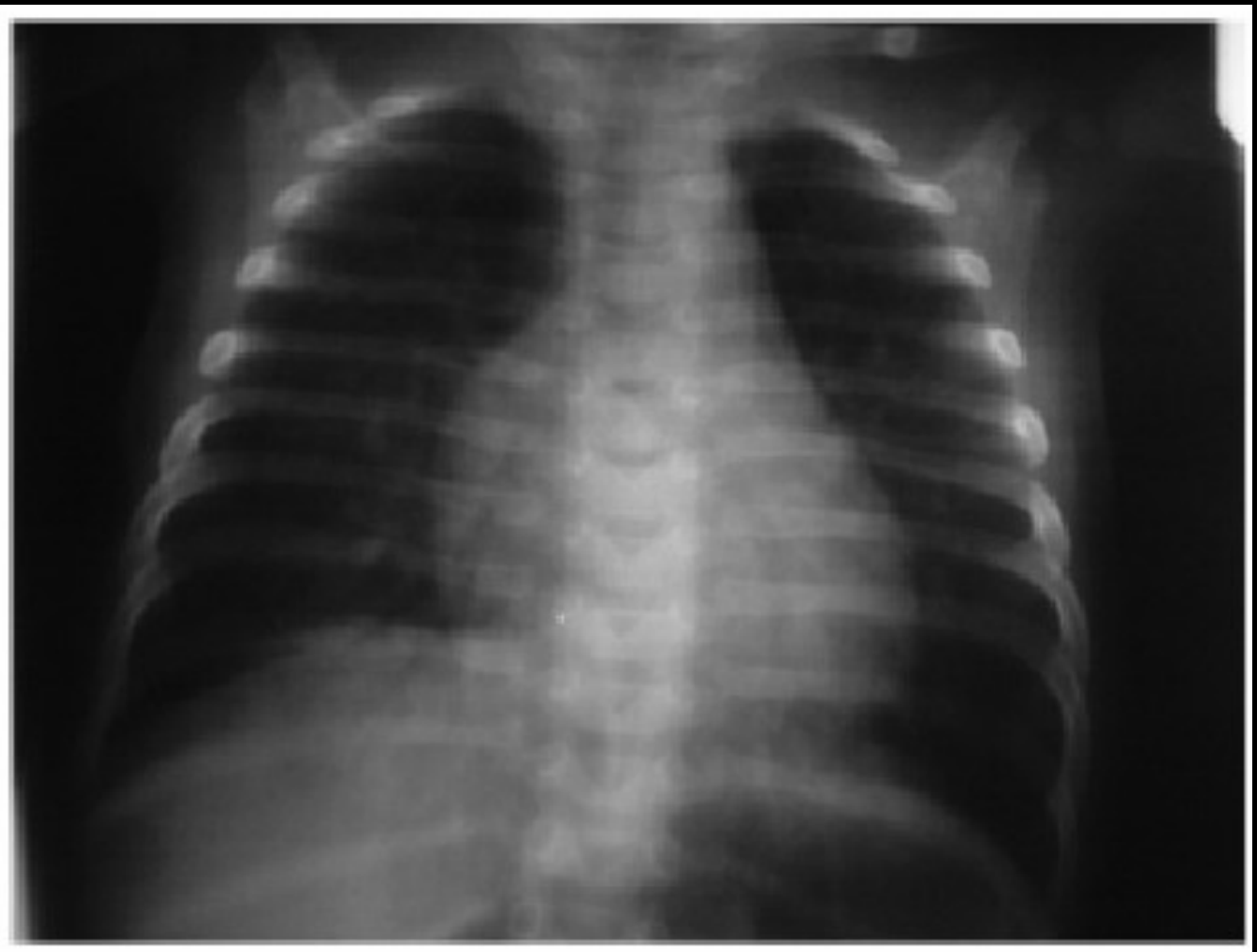


Figure 2 CXR of an HIV-infected Malawian infant with confirmed PJP showing hyperinflation. CXR = chest X-ray; HIV = human immunodeficiency virus; PJP = *Pneumocystis jirovecii* pneumonia.

Graham, Int J Tuber Lung Dis, 2005

	PCP (n=16)	Bacteria pneumonia (n=21)	Others (n=114)	p*
Characteristics				
Age (months)	3 (2–5)	5 (2–27)	5 (2–59)	0·0003
Male/female	4/12	11/10	65/49	0·09
Duration of cough (days)	5 (2–30)	3 (1–21)	3 (1–30)	0·27
HIV positive	16 (100%)	12 (57%)	66 (58%)	0·005
On admission				
Temperature (°C)	37·8 (36·2–39·0)	39·0 (36·0–40·0)	38·2 (35·5–40·5)	0·0006
Respiratory rate (per min)	80 (60–110)	80 (54–120)	72 (42–120)	0·23
Oxygen saturation in air (%)	60 (30–92)	86 (38–94)	89 (28–99)	0·003
Oxygen therapy	15 (94%)	9 (43%)	35 (31%)	0·002
Ausculation				
Focal abnormalities	3	15	45	0·003
Diffuse abnormalities	5	0	19	0·01
Clear chest	8	6	49	0·09
Chest radiograph				
Interstitial infiltrates	11	2	..	0·0006
Hyperinflation	11	4	..	0·006
Segmental consolidation	6	3	..	0·14
Lobar consolidation	1	11	..	0·004
Pleural fluid	0	5	..	0·06

Data are median (range) or number of children. *Comparisons are between PCP and bacterial pneumonia.

Table 2: **Comparison of clinical presentation between PCP and bacterial pneumonia**

Graham et al, Lancet, 2000

International Journal of Infectious Diseases (2006) 10, 282–285

http://intl.elsevierhealth.com/journals/ijid

Clinical indicators of *Pneumocystis jiroveci* pneumonia (PCP) in South African children infected with the human immunodeficiency virus

Geoffrey L. Fatti [a], Heather J. Zar [b,*], George H. Swingler [b]

- 151 HIV-infected children
  - with a median age of 9 m (IQR 3—23 m) enrolled
  - 80 (53%) males and 71 females.
  - 15 had PCP 9.9% (95% CI 5.9—15.5%) of pneumonia cases in the sample.
  - 59 (39.1%) children were taking trimethoprim—sulfamethoxazole prophylaxis

- Other organisms cultured from respiratory secretions included
  - Staphylococcus aureus (15.0%)
  - Klebsiella pneumoniae (10.9%)
  - Haemophilus influenzae (8.8%)
  - Mycobacterium tuberculosis (7.4%)
  - CMV (14.3%)..

Fatti et al, contd

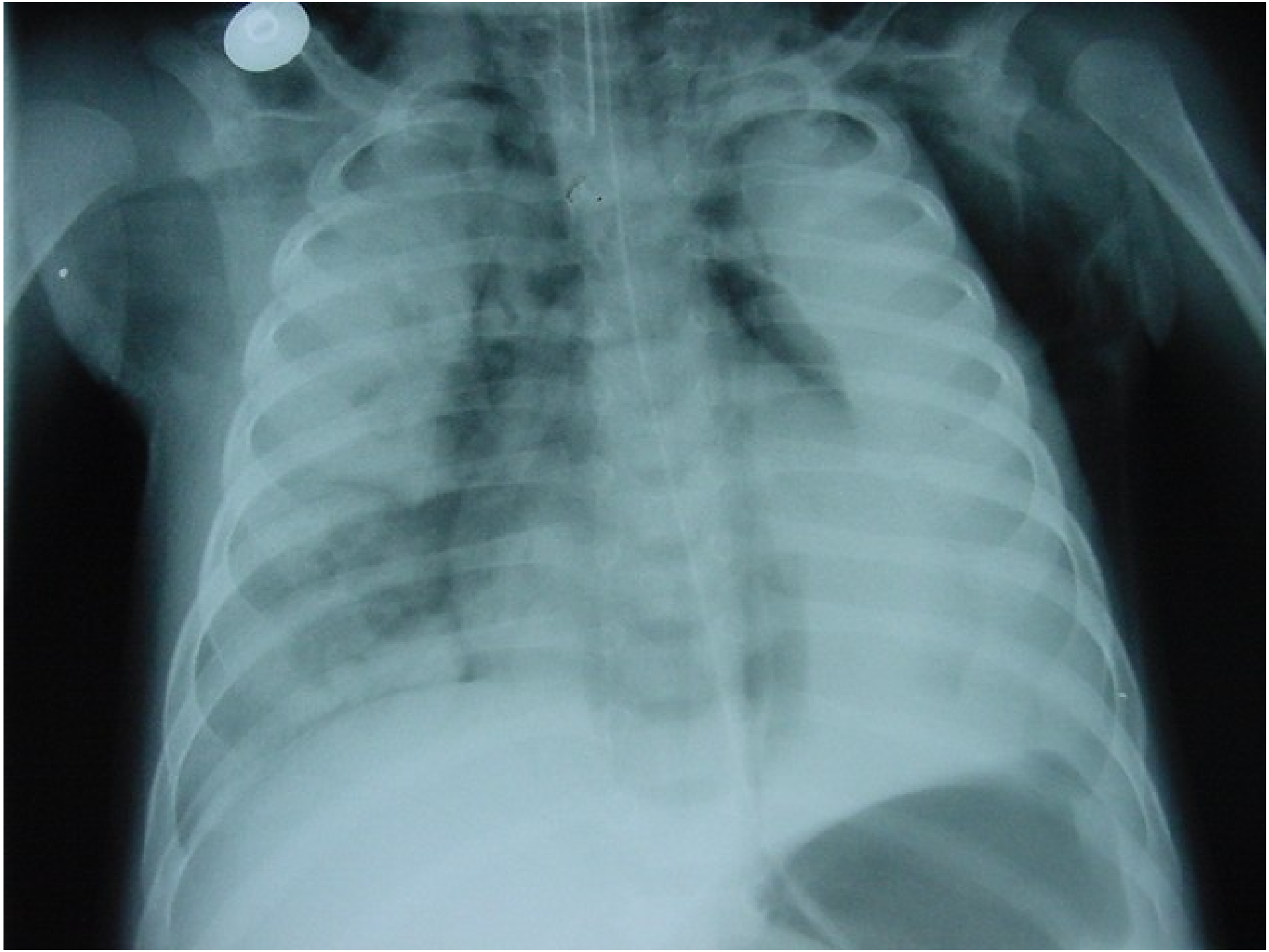
- Four variables were found to be independent risk factors for a diagnosis of PCP:
  - age <6 months (OR 15.6; 95% CI 2.4— 99.8; p = 0.004),
  - respiratory rate >59 breaths/min (OR 8.1; 95% CI 1.5—53.2; p = 0.018)
  - arterial hemoglobin oxygen saturation 92% (OR 5.1; 95% CI 1.0—26.1; p = 0.052)
  - absence of history of vomiting at presentation (OR 11.2; 95% CI 1.9—68.0; p = 0.008).

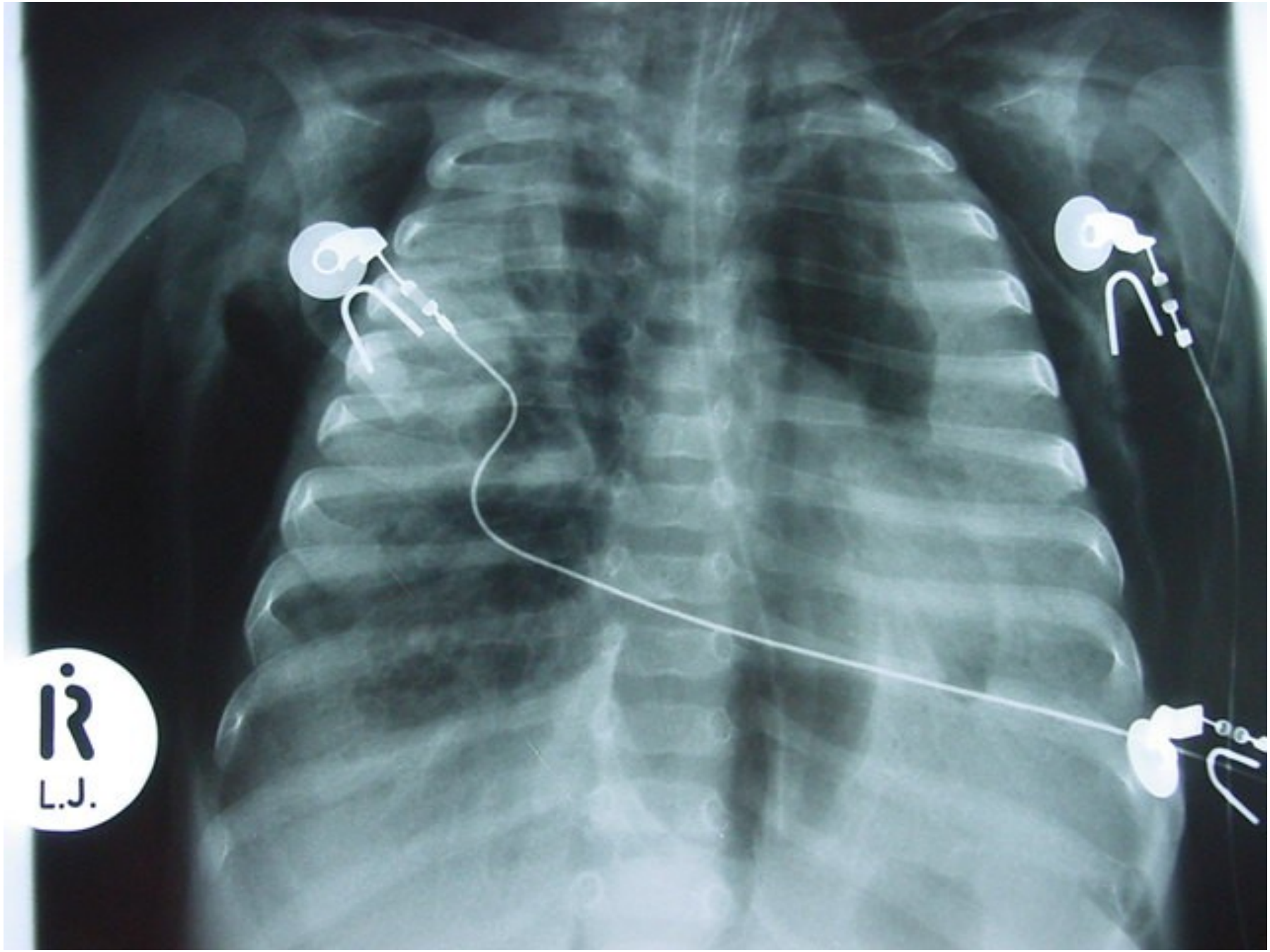
Table 1 Interval likelihood ratios and post-test probabilities of PCP with varying pre-test probabilities of PCP, according to the number of clinical indicators present in a child

Number of indicators	Interval likelihood ratio (95% CI)	Post-test probabilities, % (95% CI) of PCP with differing pre-test probabilities of PCP		
		If pre-test probability = 10%	If pre-test probability = 20%	If pre-test probability = 49% (severe pneumonia)
0	0	0	0	0
Any 1	0	0	0	0
Any 2	0.6 (0.2–1.7)	7 (2–16)	13 (5–30)	38 (18–62)
Any 3	5.0 (2.0– 12.5)	36 (18–58)	56 (33–76)	83 (66–92)
All 4	36.0 (4.4–96.5)	80 (33–97)	90 (52–96)	97 (81–99)

Three pre-test probabilities of PCP have been used: the samples' proportion of PCP (10%), the maximum reported proportion of PCP amongst HIV-infected children hospitalized with pneumonia (49%), and an intermediate value of 20%.

Fatti et al, Int J Infect Dis, 2006




R
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airleaks

- clinical impression of relatively frequent air leaks with pneumocystis and HIV

- adult association with pneumothorax and
  - previous acute pneumonia
  - presence of pneumatocoels

Metersky et al, Chest, 1995

- 38 cases of PCP in 32 children
  - 8 pneumothoraces
  - 5 pulmonary air cyst
  - 1 pneumomediastinum

Sivit et al, Pediatr Radiol, 1995

Tuberculosis

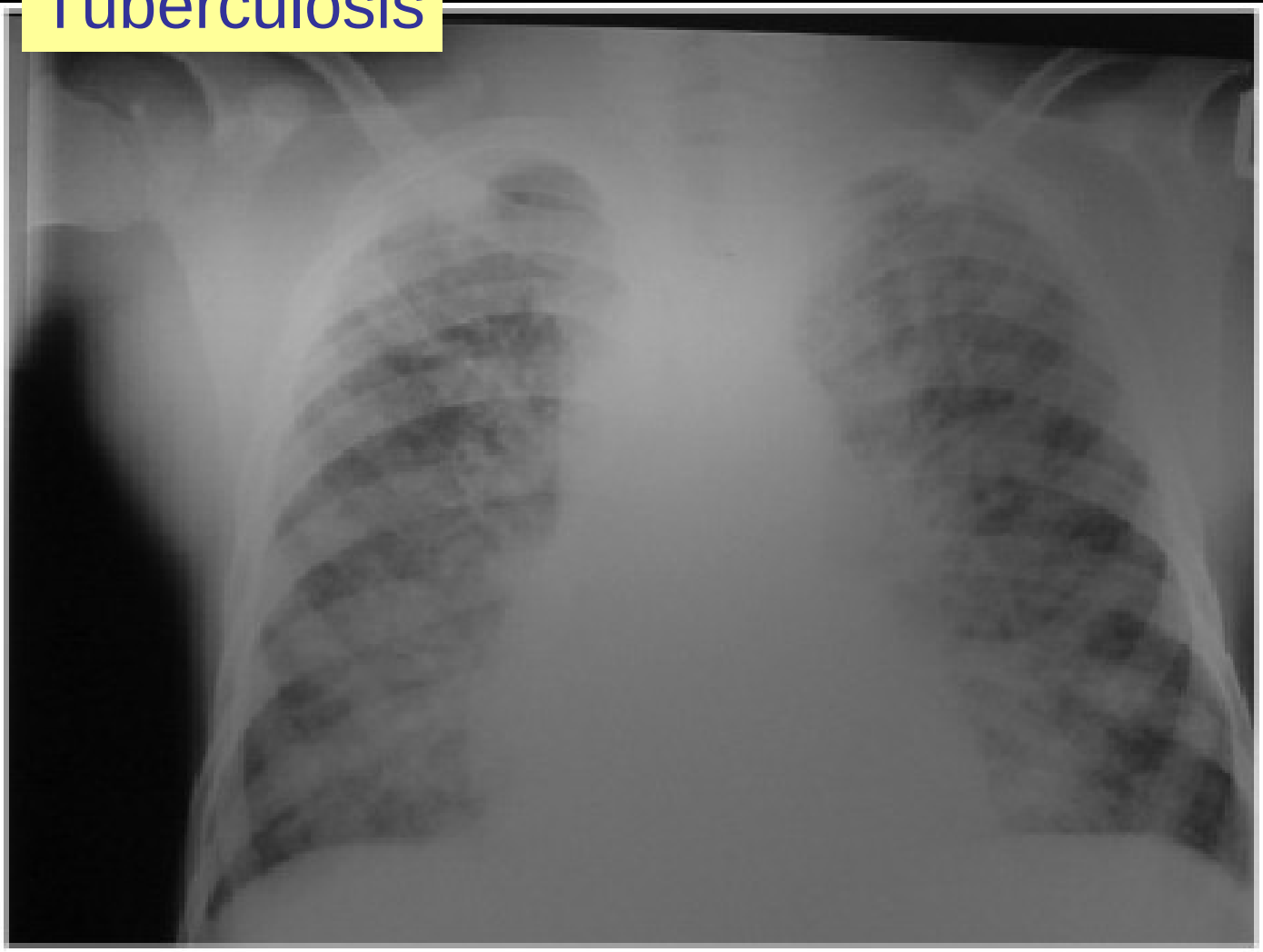


Figure 3 CXR of a 4-year-old HIV-infected Malawian child with a clinical diagnosis of LIP showing bilateral reticulonodular infiltration and adenopathy. CXR = chest X-ray; HIV = human immunodeficiency virus; LIP = lymphoid interstitial pneumonitis.

Graham,
Int J Tuber Lung Dis,
2005

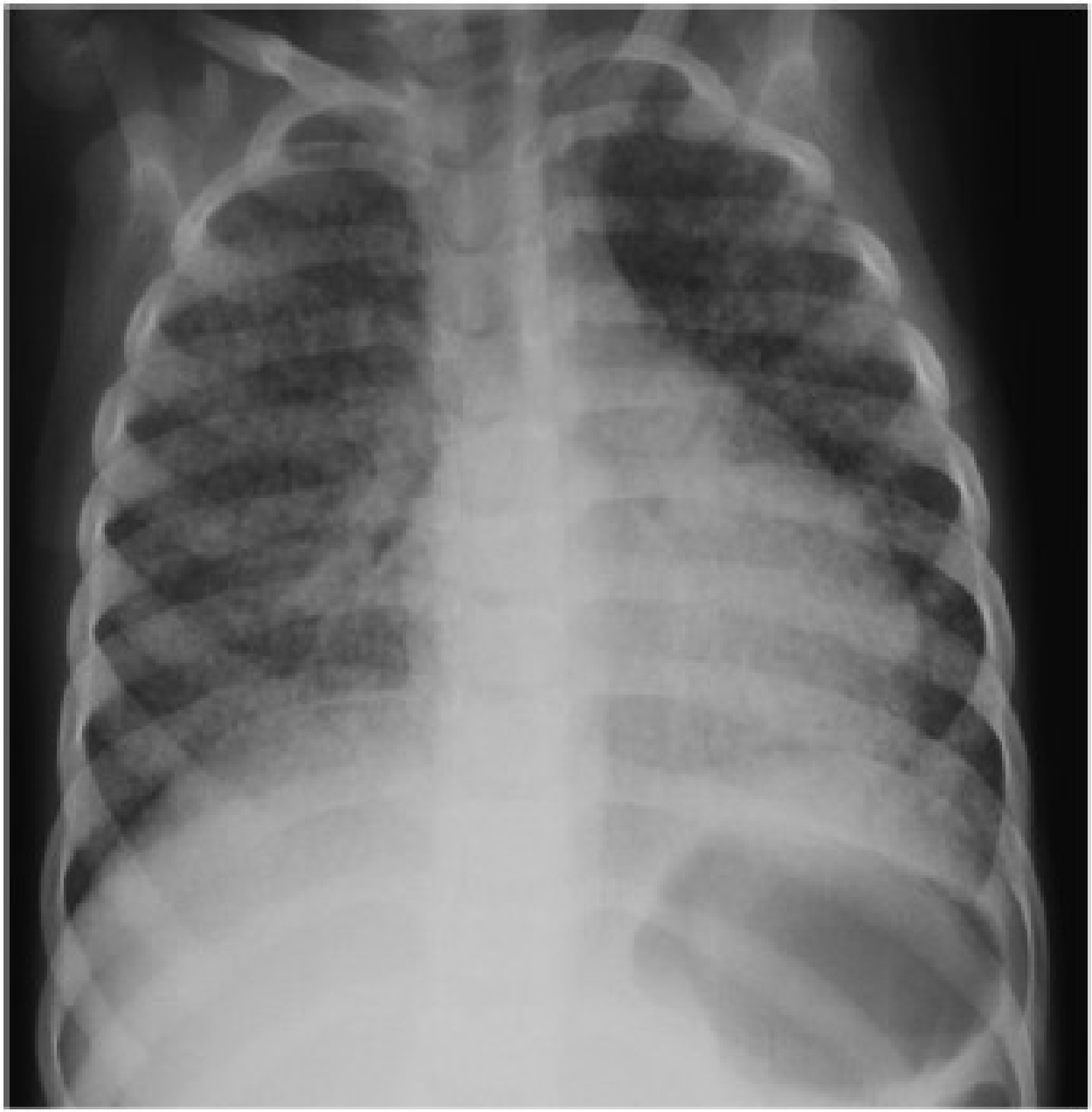


Figure 5 CXR showing typical micronodular pattern of miliary tuberculosis in contrast to the reticular pattern of LIP in Figure 3.

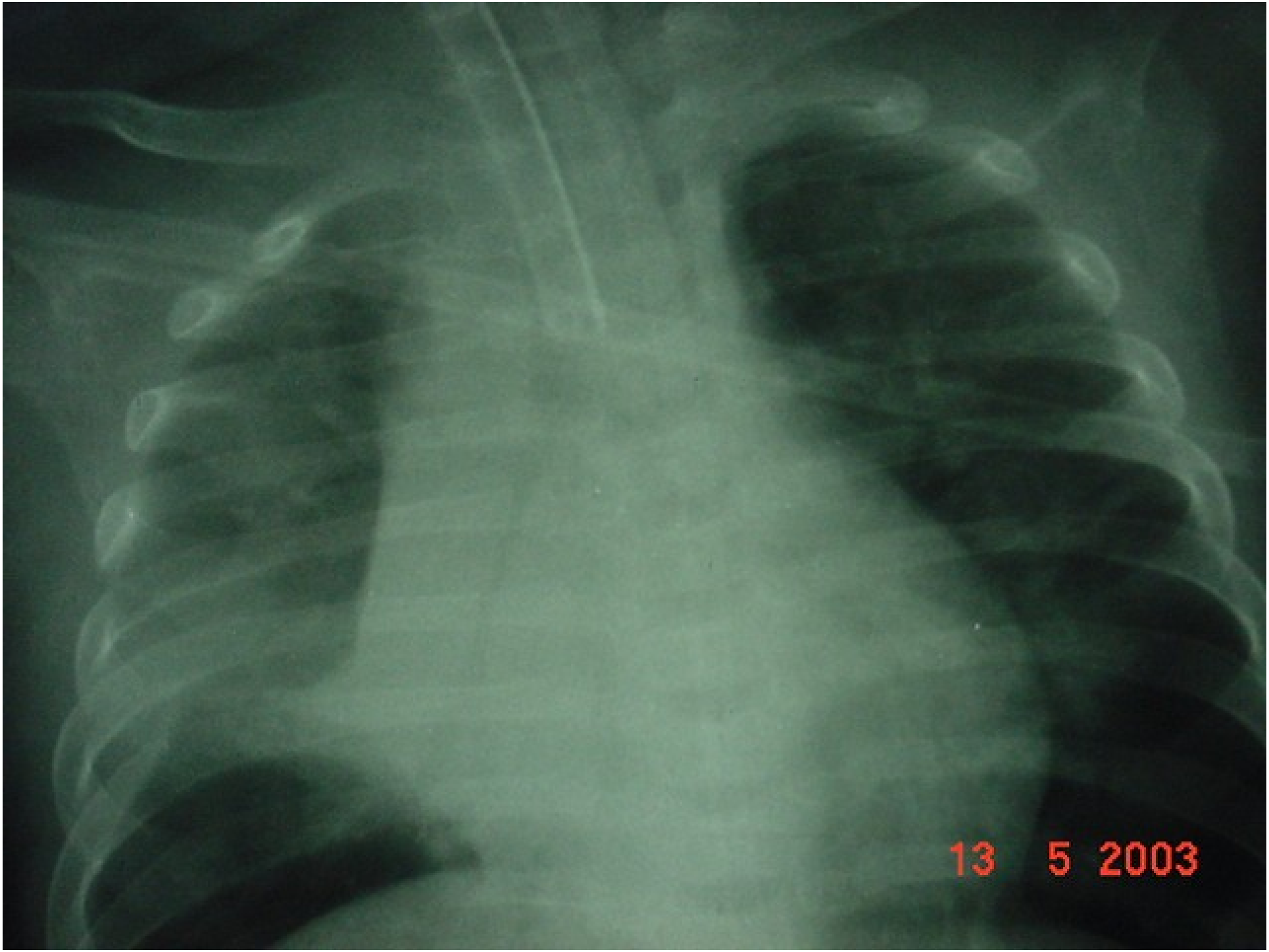
Graham,
Int J Tuber Lung Dis,
2005

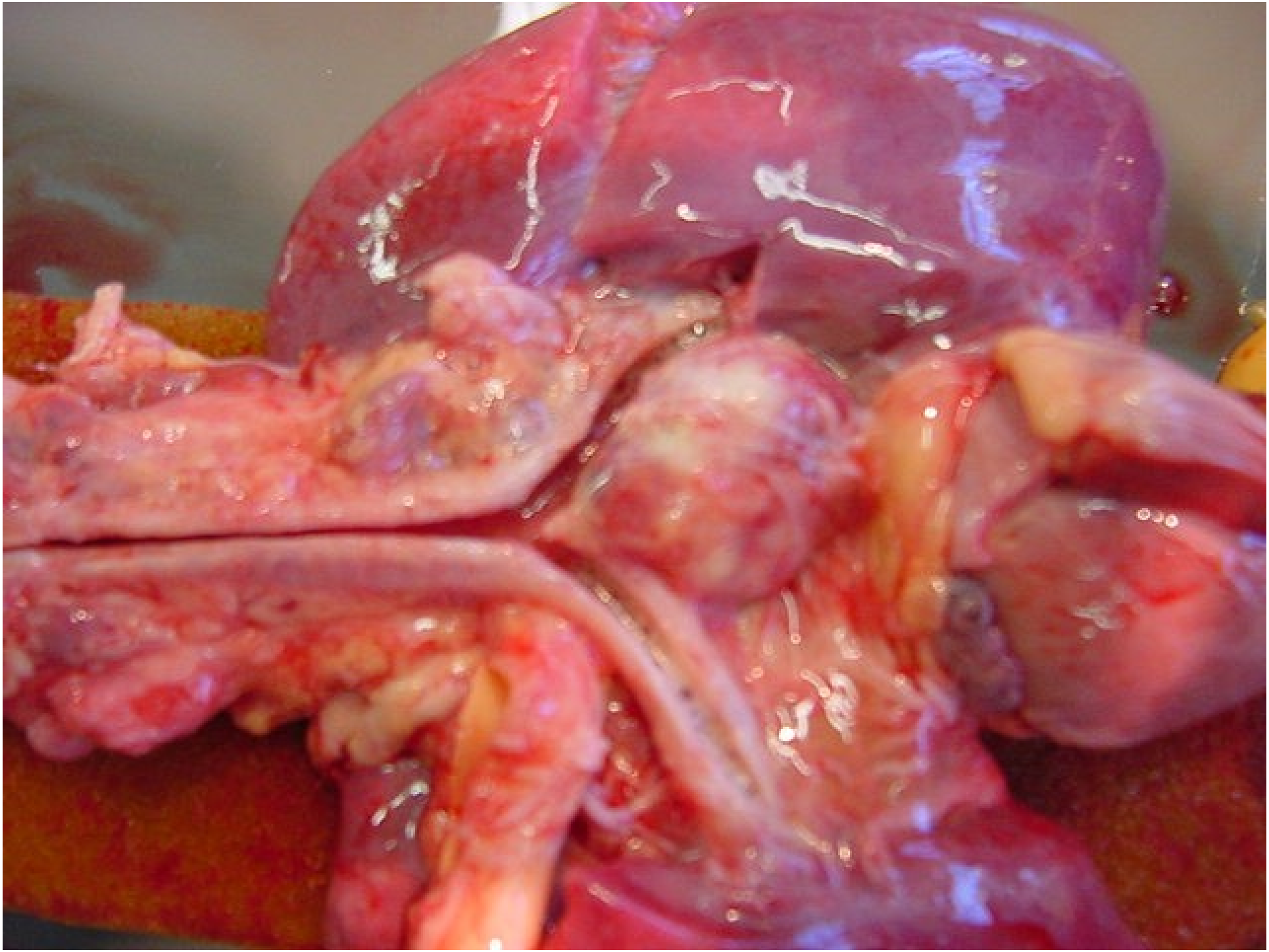
Table 3 Clinical and radiographic features that help to differentiate pulmonary and miliary TB from LIP in children

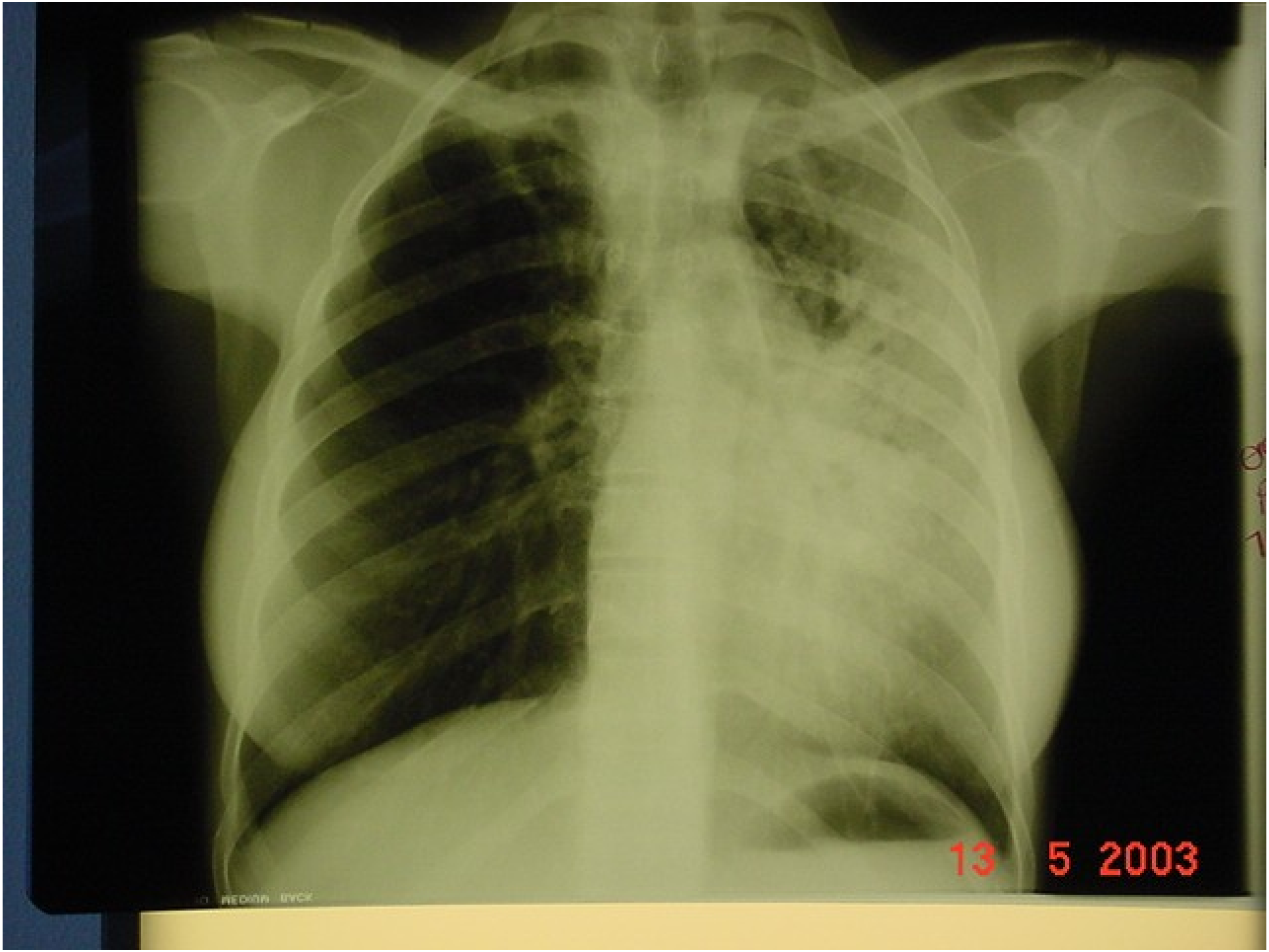
Feature	PTB	Miliary TB	LIP
Clinical			
Respiratory symptoms	Common	Uncommon	Common
Persistent fever	Common	Common	Common
Wasting	Common	Often marked	Variable
Generalised lymphadenopathy	Uncommon	Uncommon	Common
Parotid enlargement	Rare	Rare	Common
Clubbing	Uncommon	Rare	Common
Marked hepatomegaly	Uncommon	Uncommon	Common
Chest X-ray			
Focal parenchymal	Common	Uncommon	Uncommon
Diffuse micronodular	Negative	Common	Uncommon
Diffuse reticular	Negative	Negative	Common
Lymphadenopathy	Common	Uncommon	Common

PTB = pulmonary tuberculosis; LIP = lymphoid interstitial pneumonitis.

Graham, Int J Tuber Lung Dis, 2005


13 5 2003




13 5 2003

HIV and TB in neonates

- subgroup of 42 HIV-1-infected women with tuberculosis during pregnancy
  - eight (19%) exposed babies acquired in-utero HIV-1 infection
  - highest rate of in-utero transmission of HIV-1 documented
  - intrauterine transmission generally in the range of 5–10%.

De Cock et al, JAMA, 2000

- 37–77% of 15–49 year olds with tuberculosis in Africa may have associated HIV infection.

Corbett et al, Arch Intern Med, 2003

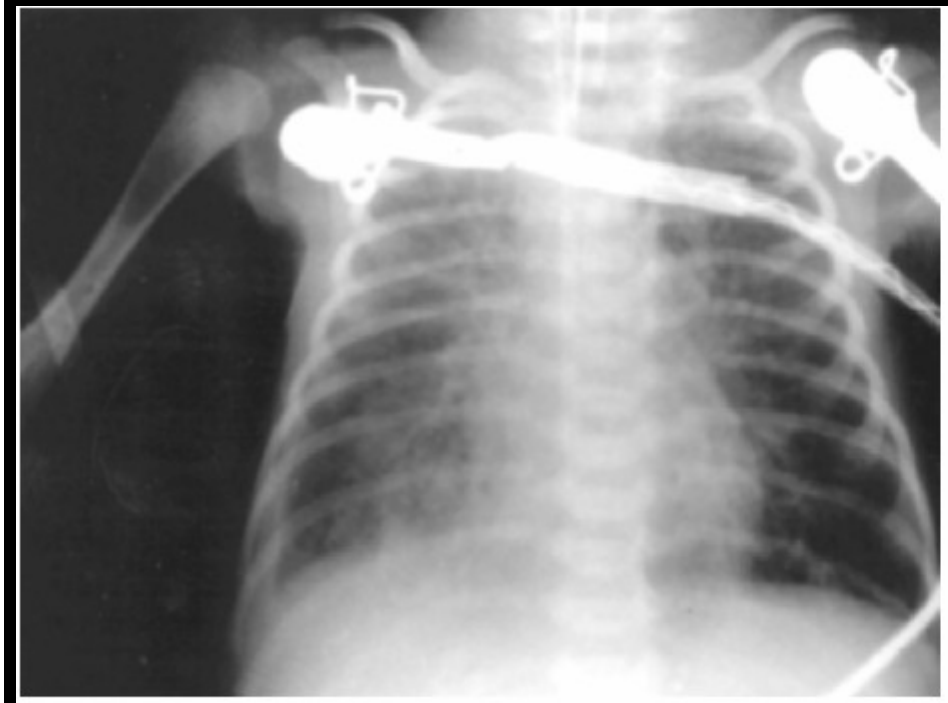


Figure 1. Chest radiograph of neonate with severe bilateral bronchopneumonia requiring mechanical ventilatory support. Endotracheal aspirate grew M tuberculosis.

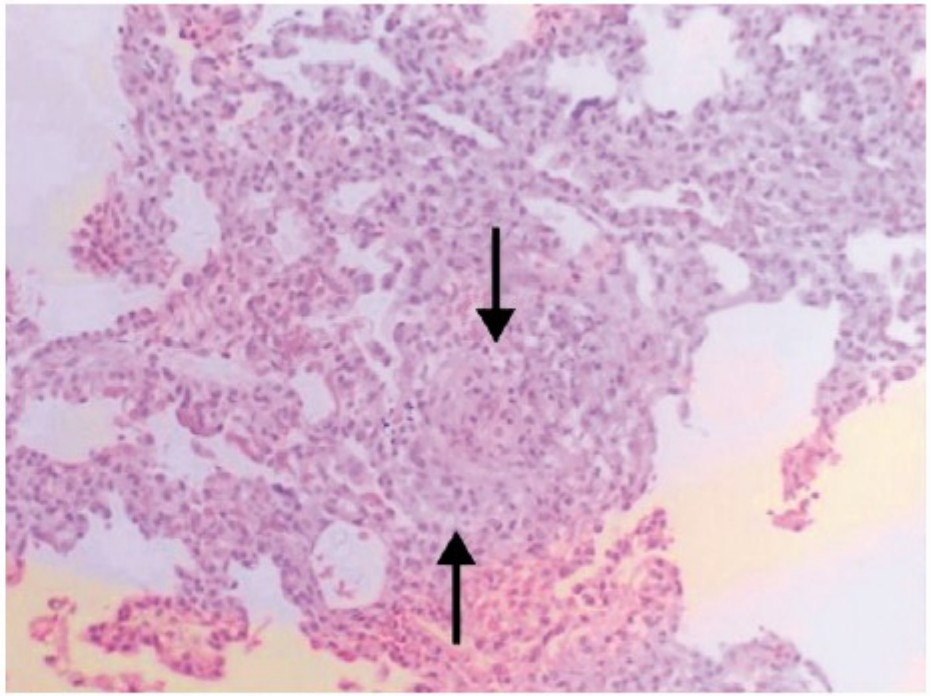


Figure 2. Tuberculosis granuloma in lung biopsy sample of neonate with culture-proven tuberculosis.

Pillay et al, Lancet Infect Dis, 2004

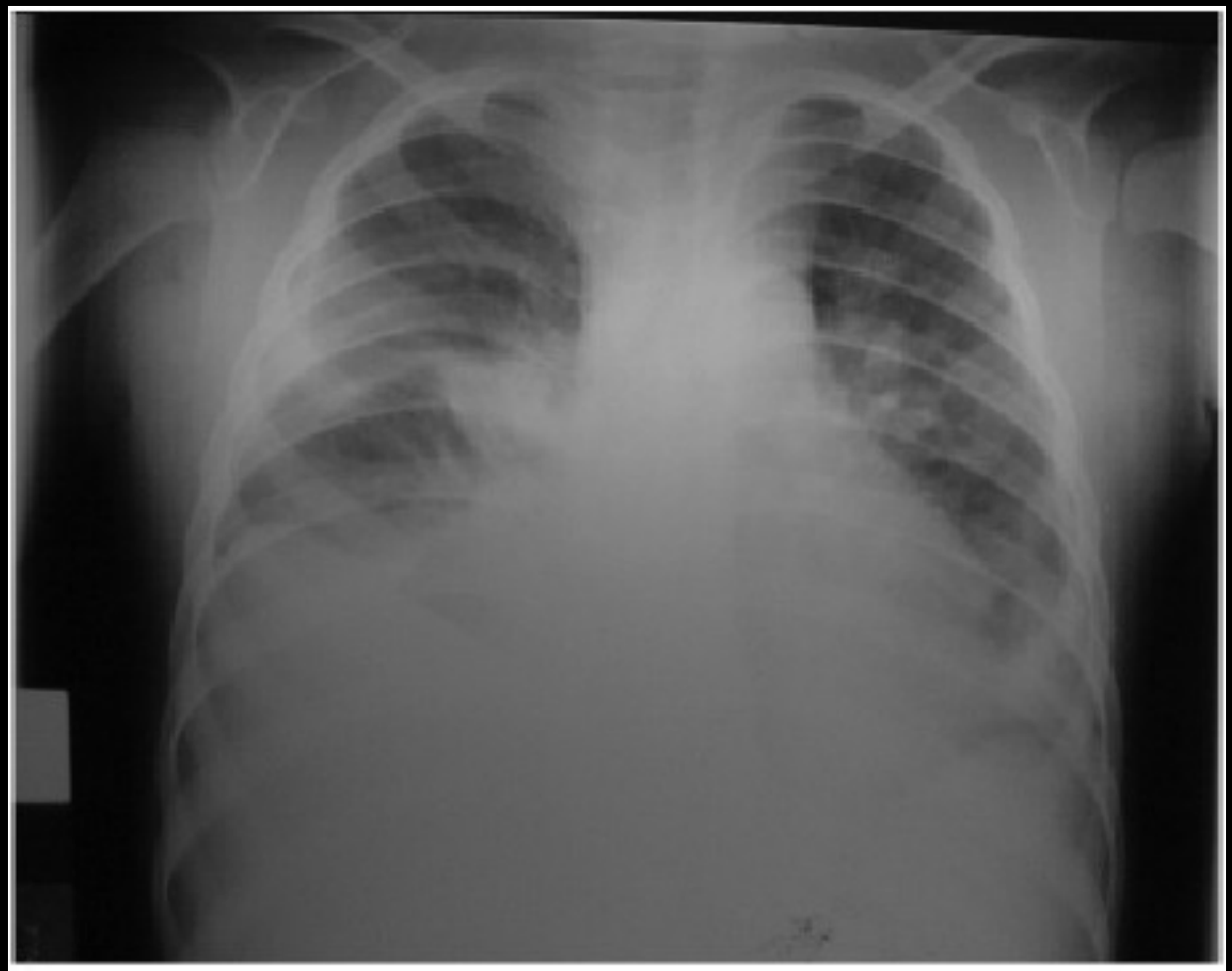


Figure 7 CXR of an HIV-infected Malawian child aged 8 years showing bilateral adenopathy and infiltration with right pleural effusion who also had typical Kaposi's sarcoma lesions on the palate. CXR = chest X-ray; HIV = human immunodeficiency virus.

Graham, Int J Tuber Lung Dis, 2005

how does one prevent admission?

- provision of anti-retroviral therapy
- cotrimoxazole prophylaxis
- immunization
- early and appropriate therapy for episodes of respiratory infection

Respiratory manifestations in HIV-infected children pre- and post-HAART in Abidjan, the Ivory Coast

A. Kouakoussui[1], P. Fassinou[2], M.F. Anaky[1], N. Elenga[1], R. Laguide[1], M.L. Wemin[3], R. Toure[4], H. Menan[4], F. Rouet[4] and P. Msellati[5,*]

Table 1 Incidence of respiratory manifestations in HIV-infected children pre-HAART, by age group.

Age group	URTI		Bronchitis		LRTI		TB		PCP			
	N	Inc/100 c/months	N	Inc/100 c/months	N	Inc/100 c/months	N	Inc/100 c/months	N	Inc/100 c/months	N events total	Follow-up in c/months
<2	15	16.45	20	21.93	5	5.48	1	1.1	0		111	91.2
2–5	18	7.68	37	15.78	12	5.12	2	0.85	1	0.43	195	234.4
>5	19	8.1	28	11.94	17	7.25	1	0.43	1	0.43	240	234.5
Total	52	9.29	85	15.18	34	6.07	4	0.71	2	0.36	546	560

C/months: children/months.

Table 3 Incidence of respiratory manifestations in HIV-infected children treated with HAART, by age group.

Age group	URTI		Bronchitis		LRTI		TB		PCP			
	N	Inc/100 c/months	N	Inc/100 c/months	N	Inc/100 c/months	N	Inc/100 c/months	N	Inc/100 c/months	N events total	Follow-up in c/months
<2	7	7.63	21	22.89	4	4.36	0		0		71	91.73
2–5	28	5.49	72	14.11	15	2.94	0		0		241	510.2
>5	66	5.13	86	6.69	22	1.71	3	0.23	0		479	1286.4
Total	101	5.35	179	9.48	41	2.17	3	0.16	0		791	1888

C/months: children/months.

Table Summary of recommended interventions for prevention of respiratory illness in HIV-infected children in developing countries and major research questions

Intervention	Efficacy for	Research questions
CTX prophylaxis	PCP	Efficacy for prophylaxis of bacterial infections Impact on antimicrobial resistance Impact on childhood morbidity and mortality Optimal regimen Affordable measurements for identifying when to stop start prophylaxis
INH prophylaxis	TB unproven in children	Efficacy for TB prophylaxis in children Cost-efficacy Impact on childhood morbidity and mortality Impact on development of INH resistant *M. tuberculosis*
Vaccination		
Pneumococcal vaccine	Invasive pneumococcal disease	Efficacy in HIV-infected children not on antiretrovirals Impact on disease due to non-vaccine serotypes
BCG	Disseminated TB	Efficacy in HIV-infected children Incidence of complications including disseminated BCG
H. influenzae vaccine	Invasive disease due to *H. influenzae*	Incidence of complications Clinical efficacy in HIV-infected children
Pertussis vaccine	Pertussis	Incidence of complications Clinical efficacy in HIV-infected children
Measles vaccine	Measles	Incidence of complications Clinical efficacy in HIV-infected children
Influenza vaccine	Influenza	Incidence of complications Efficacy in HIV-infected children Cost-efficacy
Micronutrient supplementation		
Vitamin A	Measles-associated pneumonia	Efficacy for other causes of pneumonia Impact on mortality and morbidity
Zinc		Efficacy for prevention of pneumonia Impact on mortality and morbidity

CTX = cotrimoxazole; PCP = *Pneumocystis carinii* pneumonia; INH = isoniazid; TB = tuberculosis; HIV = human immunodeficiency virus.

Zar, Int J Tuberc Lung Dis, 2003

cotrimoxazole prophylaxis

- double-blind randomised placebo-controlled trial in children aged 1-14 years with clinical features of HIV infection in Zambia
- median follow-up of 19 months
- 74 (28%) children in the co-trimoxazole group and 112 (42%) in the placebo group had died (hazard ratio [HR] 0.57 [95% CI 0.43-0.77], p=0.0002).
- This benefit applied in children followed up beyond 12 months (n=320, HR 0.48 [0.27-0.84] and across all ages and baseline CD4 counts
- 16 (6%) children in the co-trimoxazole group had grade 3 or 4 adverse events vs with 18 (7%) in the placebo group.
- Pneumocystis carinii was identified by immunofluorescence in only one (placebo) of 73 nasopharyngeal aspirates from children with pneumonia

Chintu et al, Lancet, 2004

the relative cost of PICU

The PICU at KEH has 8 beds and 400 annual admissions (120% occupancy). One bed day costs 1500 rand (£100), an annual course of prophylactic cotrimoxazole costs R34.32 (£2.28), and the average annual income per household is R6157(£410).

Jeena et al, J Med Ethics, 2005

pneumococcal vaccine

Table 2. First Episodes of Invasive Pneumococcal Disease.*

Variable	Vaccinated Group	Control Group	P Value	Vaccine Efficacy (95% CI)
	no. of episodes			*percent*
HIV-negative children				
Invasive pneumococcal disease	11	19	0.2	42 (–28 to 75)
Vaccine-serotype pneumococci	3	17	0.003	83 (39 to 97)
Non–vaccine-serotype pneumococci	4	1	0.38	–300 (–19,599 to 60)
Vaccine-related–serotype pneumococci	4	1	0.38	–300 (–19,599 to 60)
HIV-positive children				
Invasive pneumococcal disease	22	47	0.004	53 (21 to 73)
Vaccine-serotype pneumococci	9	26	0.006	65 (24 to 86)
Non–vaccine-serotype pneumococci	9	8	1	–13 (–235 to 62)
Vaccine-related–serotype pneumococci	6	16	0.05	63 (–1 to 88)
All children				
Invasive pneumococcal disease	33	66	0.001	50 (23 to 68)
Vaccine-serotype pneumococci	12	43	<0.001	72 (46 to 87)
Non–vaccine-serotype pneumococci	13	9	0.52	–44 (–283 to 43)
Vaccine-related–serotype pneumococci	10	17	0.25	41 (–36 to 75)

Klugman et al, N Engl J Med, 2004

Nature Medicine 10, 811 - 813 (2004)

A role for *Streptococcus pneumoniae* in virus-associated pneumonia

Shabir A Madhi1, Keith P Klugman1, 2 & The Vaccine Trialist Group

Table 2 Percentage efficacy of pneumococcal conjugate vaccine by intent-to-treat analysis

	All children[e]				HIV-uninfected children[f]				HIV-infected children[f]			
Clinical diagnosis	Vaccine $n = 19,922$	Placebo $n = 19,914$	Efficacy (95% CI)	*P* value	Vaccine $n = 18,633$	Placebo $n = 18,626$	Efficacy (95% CI)	*P* value	Vaccine $n = 1,289$	Placebo $n = 1,288$	Efficacy (95% CI)	*P* value
Total number of pneumonia cases[a]	975	1,162	16 (9, 23)	0.00003	566	681	17 (7, 26)	0.0006	379	446	15 (5, 24)	0.004
Pneumonia with alveolar consolidation[b]	356	428	17 (4, 28)	0.01	169	212	20 (3, 35)	0.03	182	209	13 (–4, 28)	0.1
Pneumonia without identified virus[c]	726	845	14 (5, 22)	0.002	385	448	14 (2, 25)	0.03	341	397	14 (3, 24)	0.01
Any identified virus-associated pneumonia[d]	274	353	22 (9, 34)	0.001	195	250	22 (6, 35)	0.009	70	91	23 (–4, 43)	0.09
Influenza A	42	71	41 (13, 60)	0.006	25	41	39 (0, 63)	0.05	15	26	42 (–8, 69)	0.08
RSV	184	208	12 (–8, 27)	0.2	141	161	12 (–10, 30)	0.2	36	40	10 (–40, 42)	0.6
PIV types 1–3	31	55	44 (3, 64)	0.01	18	32	44 (0, 68)	0.05	13	22	41 (–17, 70)	0.1
Adenovirus	16	16	0.0 (–100, 50)	1	10	14	29 (–61, 68)	0.4	6	2	–200 (–1,382, 39)	0.3

[a–f]See **Table 1** for an explanation of the footnotes.

Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study

Lisa M McNally, Prakash M Jeena, Kavitha Gajee, Stanley A Thula, A Willem Sturm, Sharon Cassol, Andrew M Tomkins, Hoosen M Coovadia, David Goldblatt

Lancet 2007; 369: 1440–51

- Durban is the largest city in the Province of KwaZulu-Natal, South Africa
- population 3·09 million
- at the time of the study (2002), the provincial antenatal HIV-1 seroprevalence rate was 36·5%
- antiretrovirals were not available in the public-health care sector.

Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study

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Lancet 2007; 369: 1440–51

- prospective study of 358 children aged 1-59 m with pneumonia / severe pneumonia
- all treated on pen & genta, high dose cotrimoxazole
- 242 (68%) were HIV infected
- 41 (12%) HIV exposed, uninfected
- 75 (21%) HIV uninfected

Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study

Lisa M McNally, Prakash M Jeena, Kavitha Gajee, Stanley A Thula, A Willem Sturm, Sharon Cassol, Andrew M Tomkins, Hoosen M Coovadia, David Goldblatt

- failure to respond by 48 h predicted by
  - age under 1 year (adjusted odds ratio 6·38, 95% CI 2·72–14·91, p<0·0001)
  - very severe disease (2·47, 1·17–5·24, p=0·0181)
  - HIV status
    - HIV infected 10·3, 3·26–32·51
    - HIV exposed but uninfected 6·02, 1·55–23·38; p=0·0003)
  - polymicrobial disease
    - one organism 2·06, 1·05–4·05
    - two organisms 10·75, 4·38–26·36; p<0·0001) on logistic regression analysis

	48 h treatment failure	Cumulative treatment failure	In-hospital mortality
Age younger than 1 year	3·44 (1·78–6·40)	2·24 (1·32–3·82)	3·37 (1·41–10·25)
HIV-1 ELISA positive	2·55 (1·33–4·96)	3·22 (1·73–6·07)	8·06 (2·02–69·74)
Very severe disease	3·53 (1·94–6·49)	3·55 (2·05–6·17)	6·13 (2·05–23·93)
Maternal tuberculosis	6·53 (1·93–27·97)	4·53 (1·36–19·4)	4·36 (1·42–13·24)
Loose stools	1·55 (0·94–2·56)	1·68 (1·03–2·74)	1·47 (0·76–2·83)
Seen health-care worker	2·02 (1·11–3·72)	2·09 (1·19–3·7)	2·59 (1·04–7·68)
Weight for age <2 SD	1·28 (0·81–2·03)	1·66 (1·06–2·60)	1·4 (0·75–2·59)
Hypoxia	3·28 (1·81–6·0)	3·02 (1·89–4·84)	6·02 (2·1–23)
Admission organisms			
One	1	1	1
Two	1·98 (1·02–3·89)	2·28 (1·24–4·21)	1·47 (0·59–3·74)
Three	7·82(3·45–17·94)	7·43 (3·33–16·76)	3·23 (1·16–9·15)
Four	..	..	3·59 (0·06–49)

All data are odds ratio (95% CI). WCC=white cell count. Up-to-date immunisation, severe malnutrition, alar flare, heart rate, temperature, haemoglobin, and platelet count all had no effect on outcome.

Table 2: Predictors of poor outcome on univariate analysis

McNally et al, Lancet, 2007

	Younger than 1 year				1 year and older			All children (n=358)
	HIV+ (n=170)	HIV^{EU} (n=41)	HIV- (n=49)	All under 1 year (n=260)	HIV+ (n=72)	HIV- (n=26)	All over 1 year (n=98)	
Streptococcus pneumoniae	12 (7%)	0	1 (2%)	13 (5%)	12 (17%)	1 (4%)	13 (13%)	26 (7%)
Staphylococcus aureus	7 (4%)	2 (5%)	2 (4%)	11 (4%)	4 (6%)	1 (4%)	5 (5%)	16 (5%)
Viridans group streptococci	6 (4%)	3 (7%)	2 (4%)	11 (4%)	2 (3%)	2 (8%)	4 (4%)	15 (4%)
Streptococcus milleri	2 (1%)	0	0	2 (1%)	1 (1%)	0	1 (1%)	3 (1%)
Enterococcus faecalis	0	0	1 (2%)	1 (<1%)	1 (1%)	0	1 (1%)	2 (1%)
Other streptococci	5 (3%)	2 (5%)	4 (8%)	11 (4%)	1 (1%)	0	1 (1%)	12 (3%)
Escherichia coli	2 (1%)	1 (2%)	0	3 (1%)	0	0	0	3 (1%)
Haemophilus influenzae	1 (<1%)	1 (2%)	0	2 (1%)	0	0	0	2 (1%)
Klebsiella pneumoniae	1 (<1%)	1 (2%)	0	2 (1%)	0	0	0	2 (1%)
Serratia marcescens	1 (<1%)	0	0	1 (<1%)	0	0	0	1 (<1%)
Pseudomonas aeruginosa	0	1 (2%)	0	1 (<1%)	0	0	0	1 (<1%)
Acinetobacter baumii	1 (<1%)	0 (0)	0	1 (<1%)	0	0	0	1 (<1%)

All data are number (%). HIV-1^{-}=HIV uninfected. HIV-1^{EU}=HIV exposed, uninfected. HIV-1^{+}=HIV infected. *Eight children had two organisms isolated from their admission blood culture. Therefore numbers do not add up to 358.

Table 3: Admission blood culture results by HIV status and age*

McNally et al, Lancet, 2007

	Younger than 1 year				1 year or older		
	Total (n=90)	Infected (n=74)	Exposed uninfected (n=9)	Uninfected (n=7)	Total (n=20)	Infected (n=13)	Uninfected (n=7)
Pneumocystis jirovecii	29 (32%)	26 (35%)	3 (33%)	0	0	0	0
Mycobacterium tuberculosis	15 (17%)	13 (18%)	0	2 (29%)	9 (45%)	5 (39%)	4 (57%)
Cytomegalovirus	40 (45%)	37 (51%)	2 (22%)	1 (14%)	4 (20%)	3 (23%)	1 (14%)
Streptococcus pneumoniae	9 (10%)	7 (9%)	0	2 (29%)	3 (15%)	3 (23%)	0
Staphylococcus aureus	13 (14%)	11 (15%)	2 (22%)	1 (14%)	6 (30%)	4 (31%)	2 (29%)
Other gram positive	6 (7%)	5 (7%)	0	1 (14%)	3 (15%)	3 (23%)	0
Haemophilus influenzae	5 (6%)	3 (4%)	1 (11%)	1 (14%)	4 (20%)	2 (15%)	2 (29%)
Adenovirus	6 (7%)	4 (5%)	0	2 (28%)	3 (15%)	2 (15%)	1 (14%)
Respiratory syncytial virus	11 (12%)	8 (11%)	3 (33%)	0	2 (10%)	0	2 (29%)
Other virus	8 (9%)	6 (8%)	1 (11%)	1 (14%)	3 (15%)	3 (23%)	0
Aspergillus spp	0	0	0	0	1 (5%)	1 (8%)	0
Streptomyces spp	1 (<1%)*	1 (<1%)	0	0	0	0	0
Sacchromyces spp	0	0	0	0	1 (5%)	1 (8%)	0

All data are number (%). *Only children who had all study investigations and failed therapy are included (admission and non-responder blood culture; admission nasopharyngeal aspirate and NB-BAL or lung aspirate for viral immunofluorescence; and culture, induced sputum, and NB-BAL or lung aspirate for *P jirovecii* pneumonia and tuberculosis; gastric washings for tuberculosis; NB-BAL, lung aspirate, or pleural aspirate for bacteria). Bacteria isolated from nasopharyngeal swabs or induced sputa are not regarded as significant and therefore not included.

Table 5: Organisms isolated from children who were investigated for failing to respond by HIV status and age

McNally et al, Lancet, 2007

thus …

- co-infection with multiple organisms a common cause for treatment failure
- viral pathogens an important component
- CMV an important component
- Tuberculosis in high incidence areas

HIV and croup

- 54 children with croup required endotracheal intubation during the 5 year study period (average follow-up 18 months - range 3 to 48 months)

- 38 children HIV negative
  - all were successfully extubated and did not require tracheostomy.

- 16 children HIV positive
  - only 2 were successfully extubated,
  - 14 requiring tracheostomy
  - of these 14 children
    - 3 had been previously identified as being HIV positive and started on Anti-Retroviral Therapy (ART).

    - all were started on ART once their HIV status was confirmed by PCR testing.

Mulwafu et al, Int Pediatr Otorhhinolaryngol, 2007

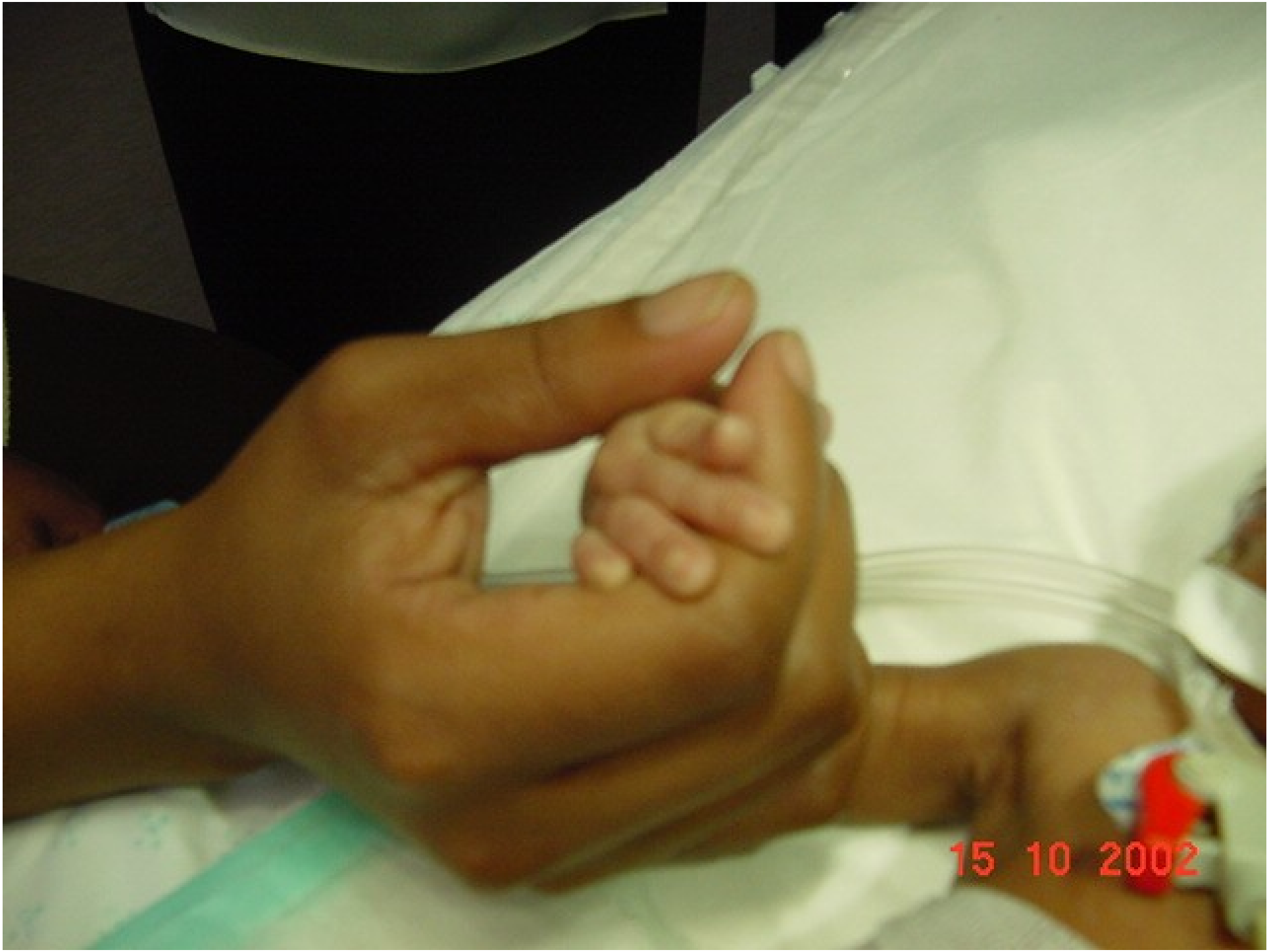
HIV and croup

- 2 died of severe lung disease before discharge from hospital.
- remainder transferred from ICU after an average length of stay in the ICU of 17.9 days (range 4 - 56 days).
- two children decannulated while still in hospital, the remainder being discharged into the Tracheostomy Home Care Program
- to date another 4 children have been decannulated and one child has died of severe pneumonia,
- 6 children are still cannulated.
  - Of these six children, 4 have undergone micro-laryngoscopy
    - 3 post intubation fibrotic furrows and fibrotic stenosis of the subglottis
    - 1 unilateral vocal cord paralysis (the reason for ongoing airway obstruction was not clear).

Mulwafu et al, Int Pediatr Otorhhinolaryngol, 2007

conclusions

- HIV disease in children should be eliminated
- HIV exposed but non-infected children have increased incidence of lung disease
- there is a higher incidence of both viral and bacterial disease
- even in the presence of HIV respiratory infections can be reduced
- failure of therapy often related to presence of multiple organisms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