chILD in context:
a global prospective

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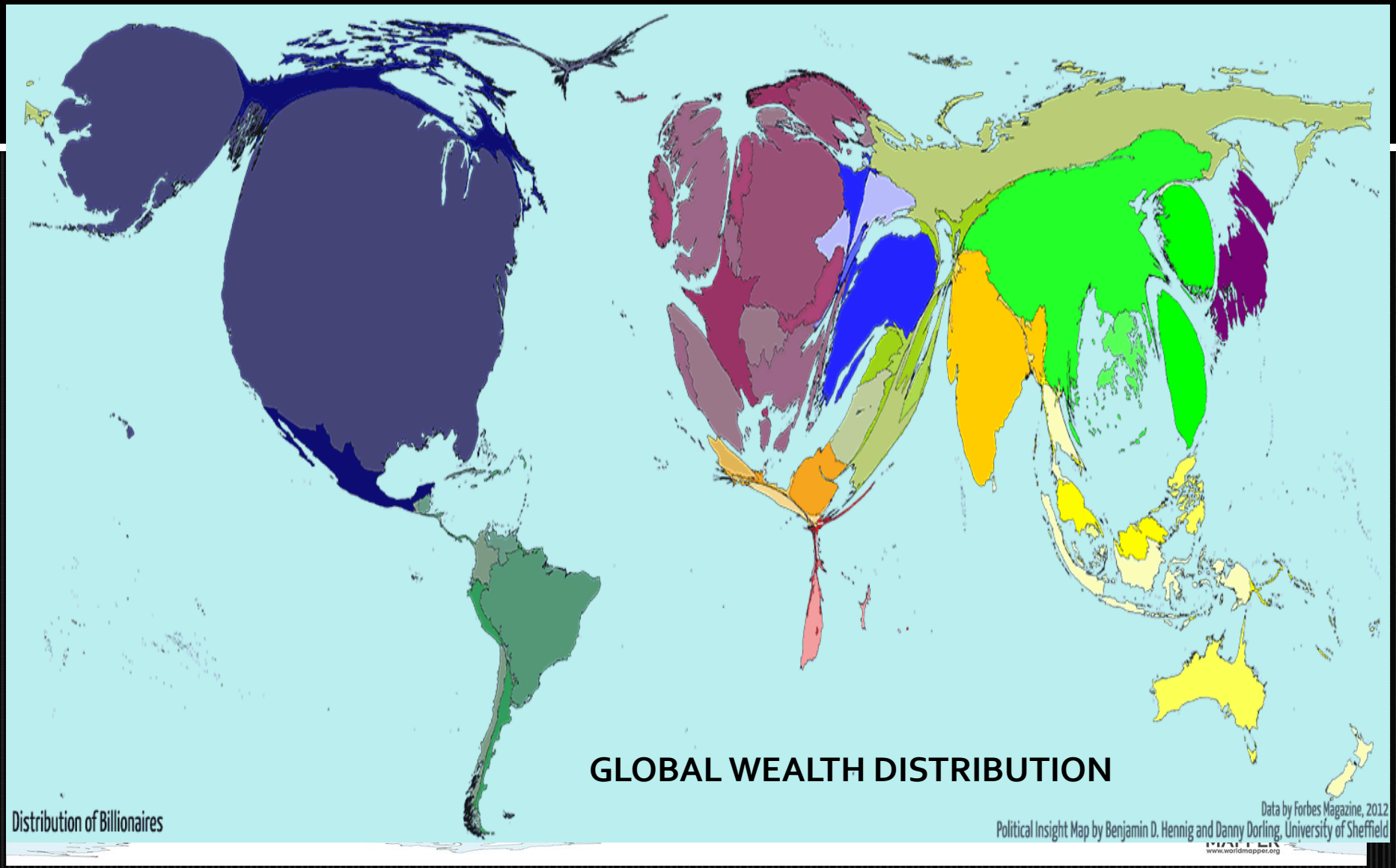
No conflicts of interest; permission for all photos

The BIG picture….

- Many children live in poor places: poverty and high burden of communicable diseases
- Underdeveloped health care resources, fragmented health care
- Resources prioritised for basic primary health care, not specialised care.
- Burden of childhood respiratory illnesses:
  - pneumonia
  - TB
  - HIV
  - Neonatal /prematurity



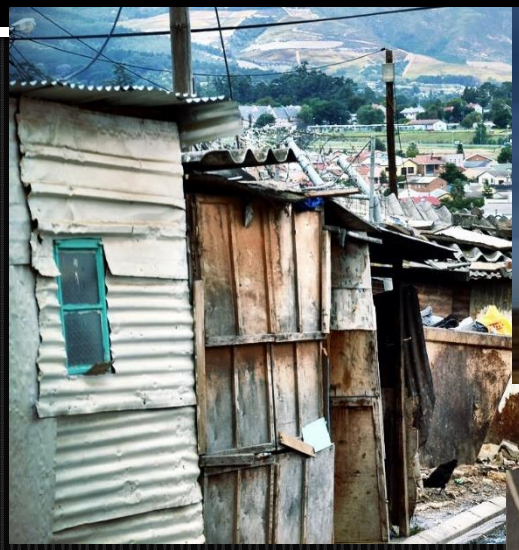
WORLD MAPPER

South Africa…

- Population 56 million
- Unemployment 27%
- Wealth-poverty gap extreme
- Health care distribution unequal, fragmented
- Sophisticated health care infrastructure and resources available in academic facilities and private sector
- HIV infection rate in adults ranges 10-35%. Vertical HIV transmission now < 1% due to effective PMTCT program
- High burden of malnutrition, pneumonia and TB

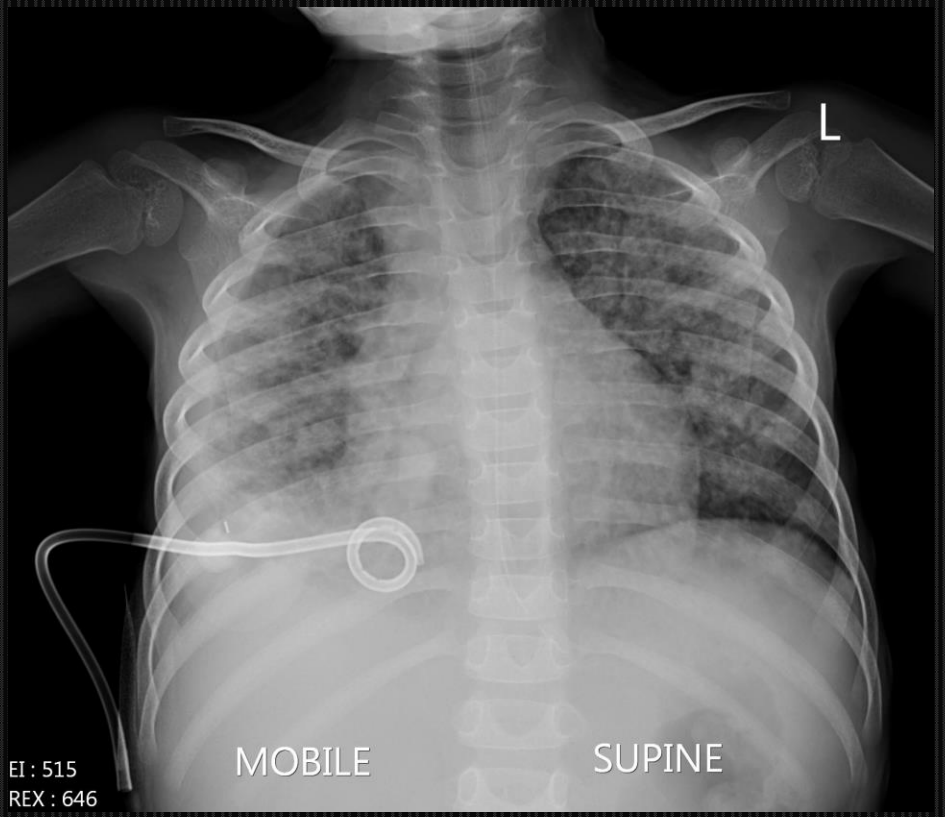
- Estimated 20 paediatric pulmonologists?

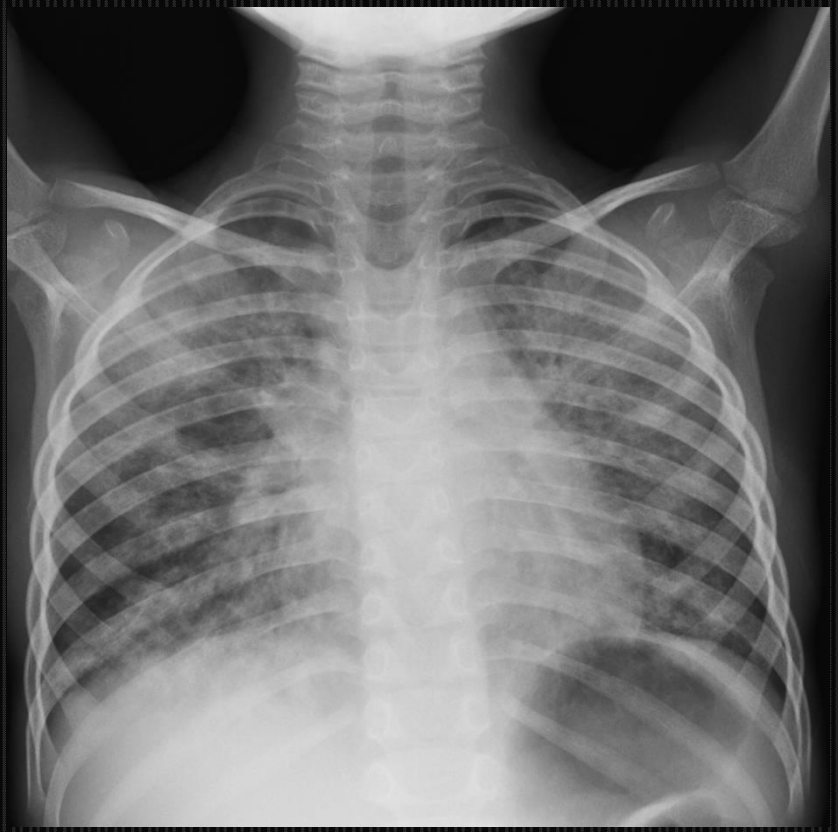
South Africa: a place of extreme beauty and contrasts



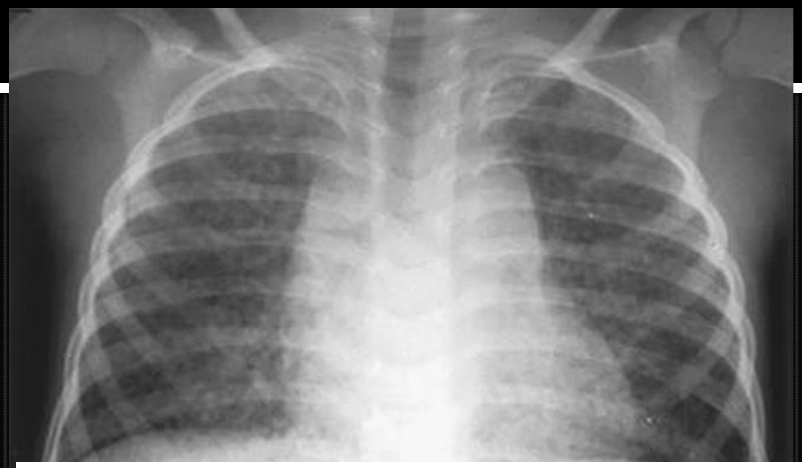
Finding the rare chILD among many similar!

DLD presentation

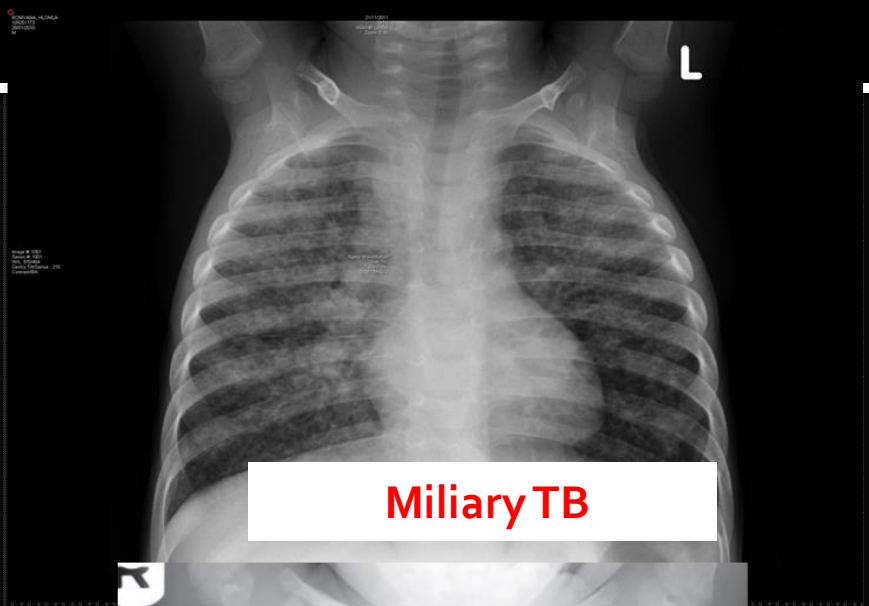




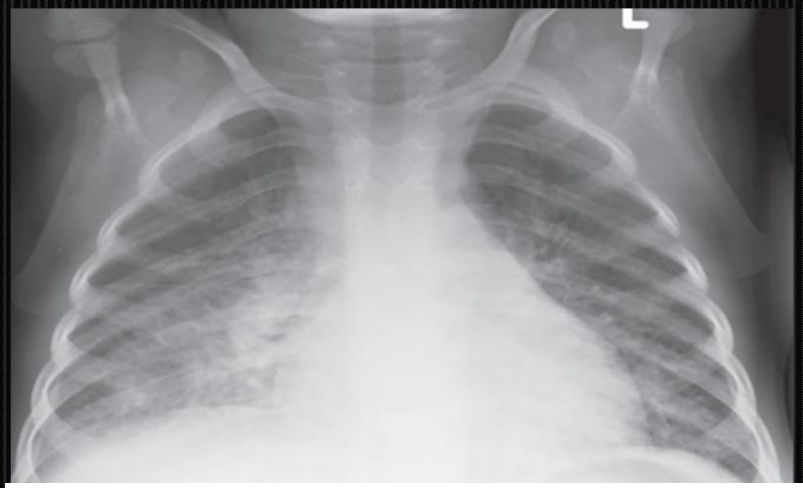
Diffuse lung disease in HIV infection: pre-ART



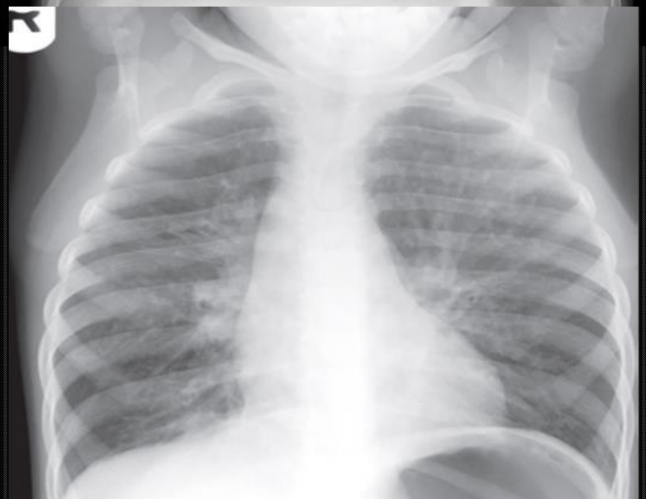
Lymphoid interstitial pneumonitis



Miliary TB

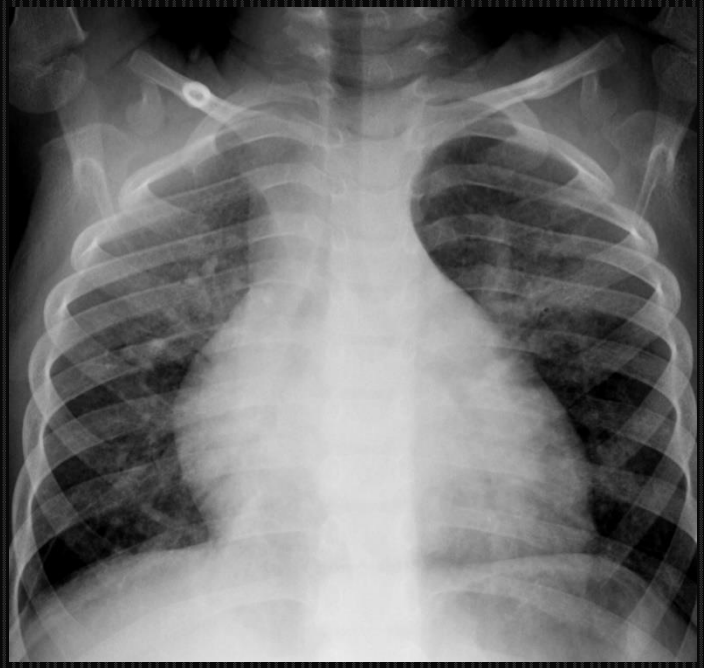


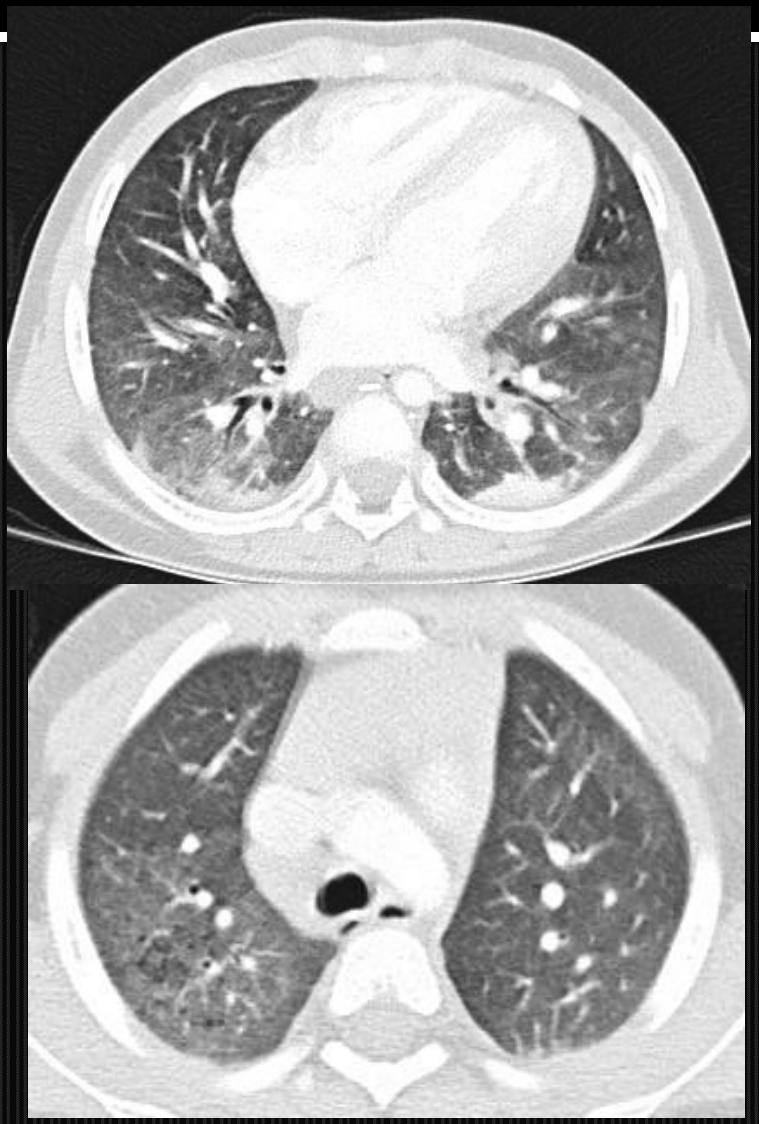
Kaposi sarcoma



bronchiolitis obliterans bronchiectasis (BOB)

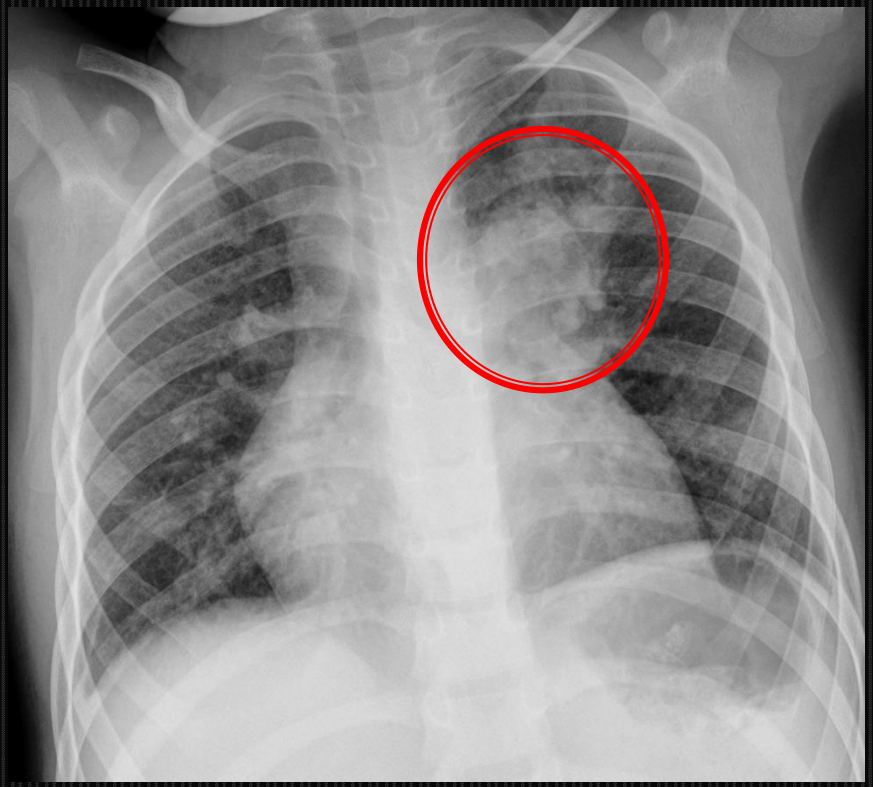
DLD in HIV infection : post-ART



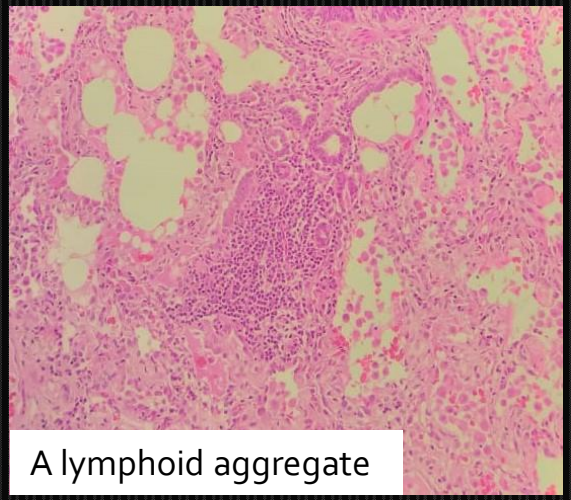


3 year old HIV+ on ART , virally suppressed
Persistent tachypnea and reticular nodular infiltrates
Patchy ground glass opacification and cysts on CT

Lymphoid interstitial pneumonitis



B- lymphocyte aggregates

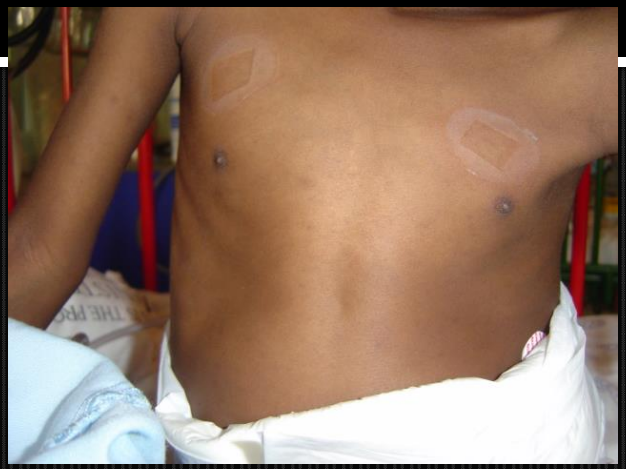


A lymphoid aggregate

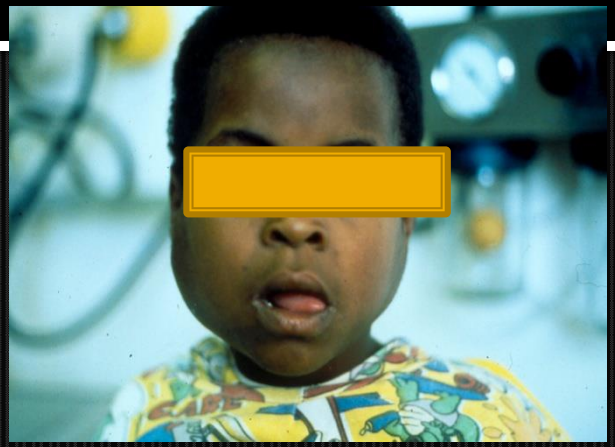
T- lymphocytes

LIP: pre-ART clinical features

Digital clubbing



Chest deformity



Parotid enlargement

- Lymphocytic proliferation in lymphoreticular organs > generalised lymphadenopathy, parotitis, tonsillar and adenoidal hypertrophy, hepatosplenomegaly
- Auscultation findings vary
- Repeated respiratory infections eventually > bronchiectasis > cor pulmonale
- As HIV advances and CD_4 count diminishes, less lymphoproliferation may result in disappearance of these features including pulmonary infiltrates
- Treatment: ART ± systemic corticosteroids

DLD – The Spectrum

Children's Interstitial Lung Disease (chILD) Network Classification of Diffuse Lung Disease in Children (Adapted from Deutsch et al.[8])

DISORDERS MORE PREVALENT IN INFANCY

- **Diffuse developmental disorders**
  - Acinar dysplasia
  - Congenital alveolar dysplasia
  - Alveolar capillary dysplasia with misalignment of pulmonary veins
- **Growth abnormalities reflecting deficient alveolarization**
  - Pulmonary hypoplasia
  - Chronic neonatal lung disease (prematurity)
  - Related to chromosomal disorders
  - Related to congenital heart disease
- **Specific conditions of uncertain etiology**
  - Neuroendocrine cell hyperplasia of infancy
  - Pulmonary interstitial glycogenosis
- **Surfactant dysfunction disorders**
  - Surfactant protein B (*SFTPB*) mutations
  - Surfactant protein C (*SFTPC*) mutations
  - *ABCA3* mutations
  - Surfactant dysfunction disorders without known genetic aetiology
    - Pulmonary alveolar proteinosis
    - Chronic pneumonitis of infancy
    - Desquamative interstitial pneumonia
    - Non-specific interstitial pneumonia

DISORDERS RELATED TO SYSTEMIC DISEASE PROCESSES

- Immune-mediated/collagen vascular disorders
- Storage disease
- Sarcoidosis
- Langerhans cell histiocytosis
- Malignant infiltrates

DISORDERS OF THE NORMAL HOST (NON-IMMUNOCOMPROMISED)

- Infectious/Post-infectious processes
- Related to environmental agents
- Hypersensitivity pneumonitis; Toxic inhalation
- Aspiration syndromes
- Eosinophilic pneumonia

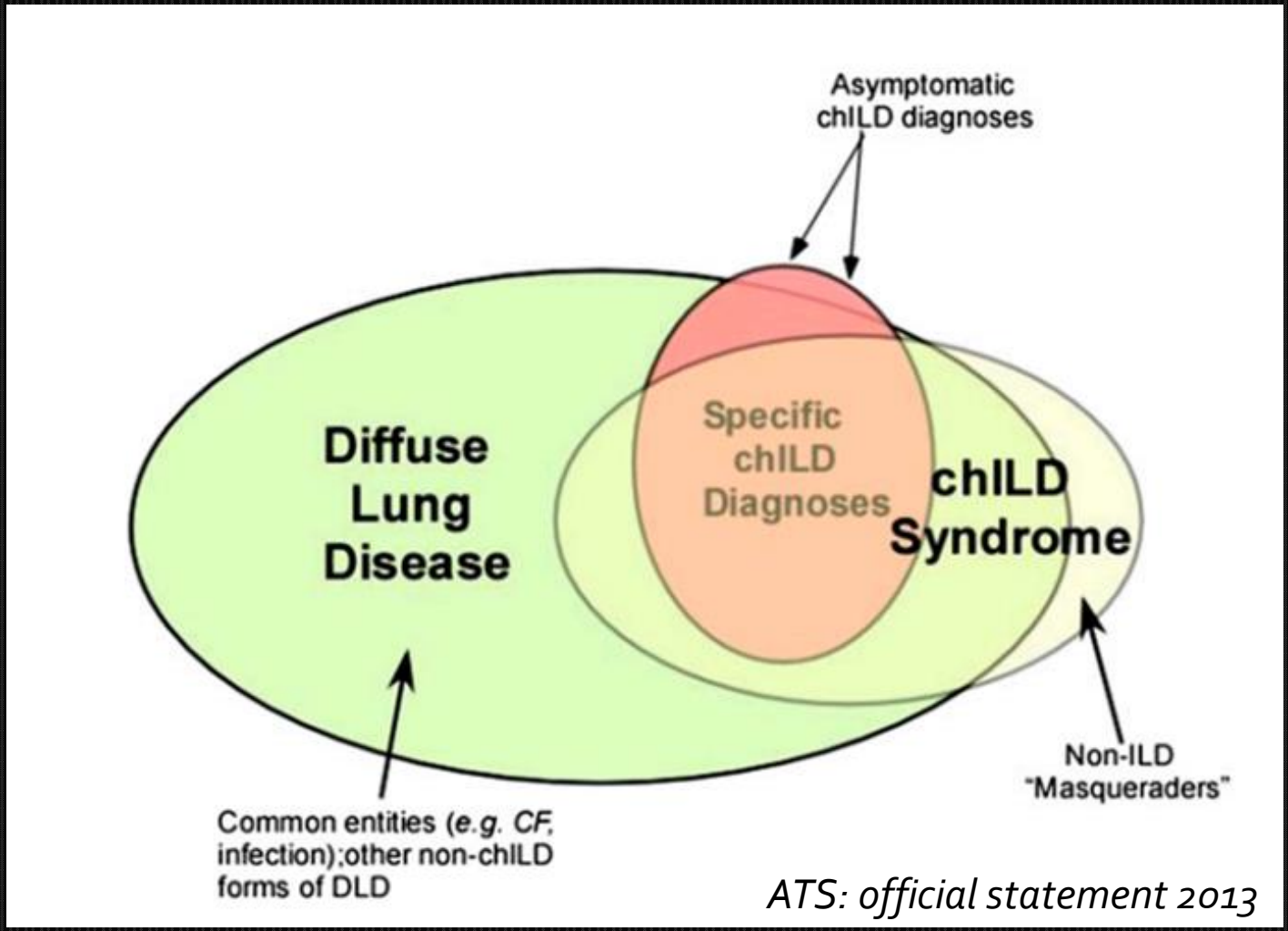
DISORDERS OF THE IMMUNOCOMPROMISED HOST

- Opportunistic infections
- Related to therapeutic intervention
- Related to transplantation and rejection
- Diffuse alveolar damage, unknown aetiology

DISORDERS MASQUERADING AS INTERSTITIAL LUNG DISEASE

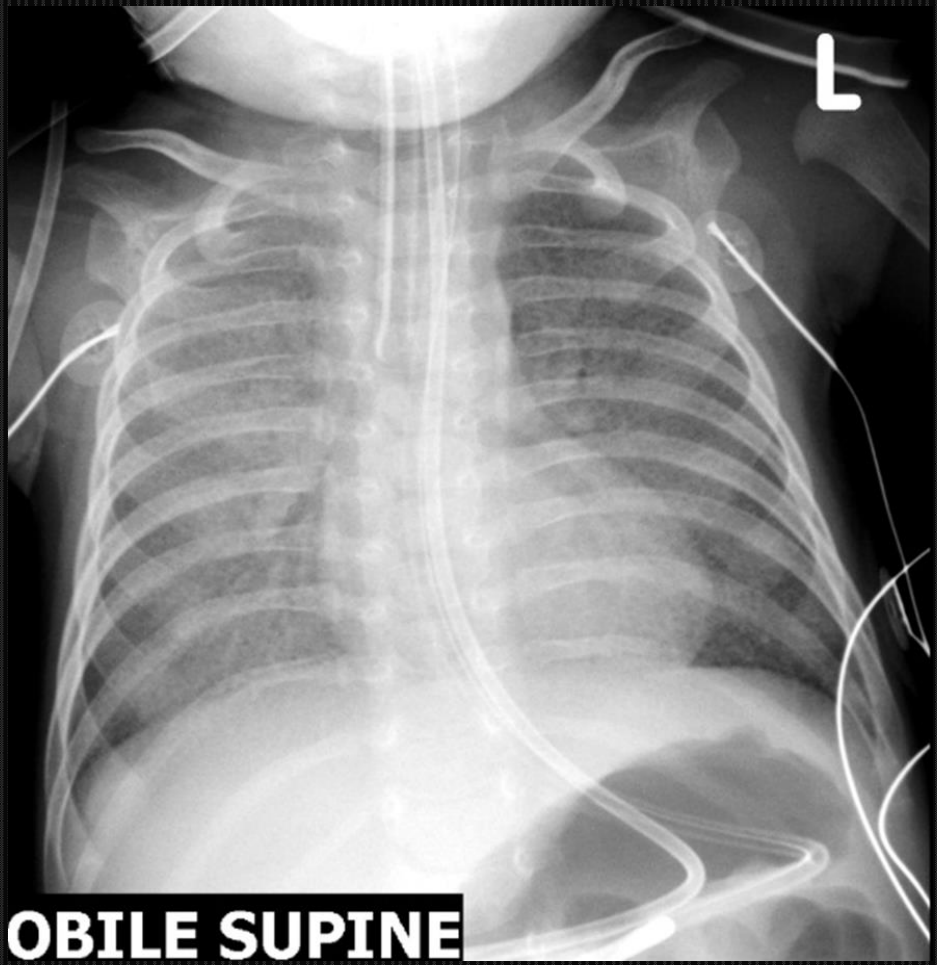
- Arterial hypertensive vasculopathy
- Congestive changes related to cardiac dysfunction
- Veno-occlusive disease
- Lymphatic disorders

Investigating DLD in South Africa:

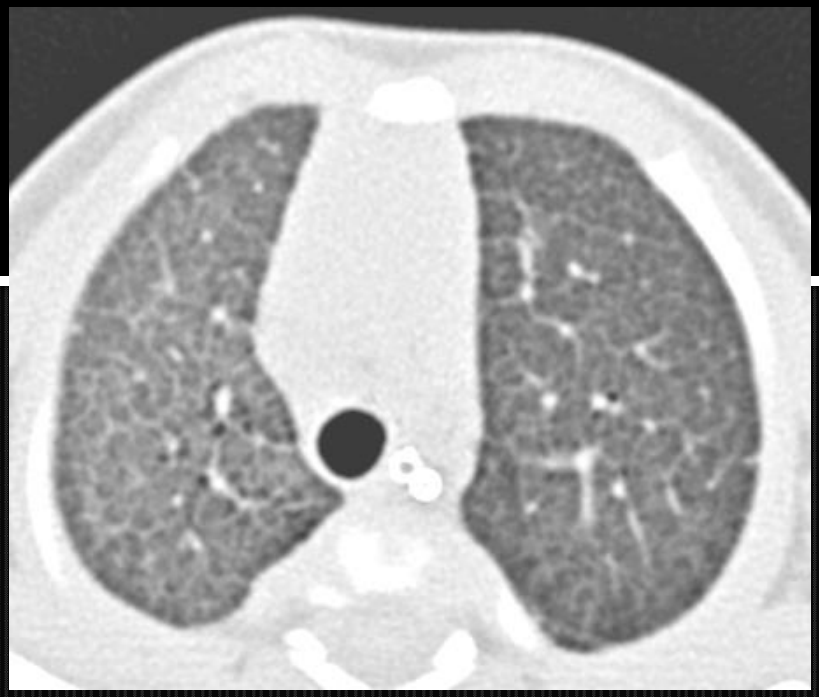


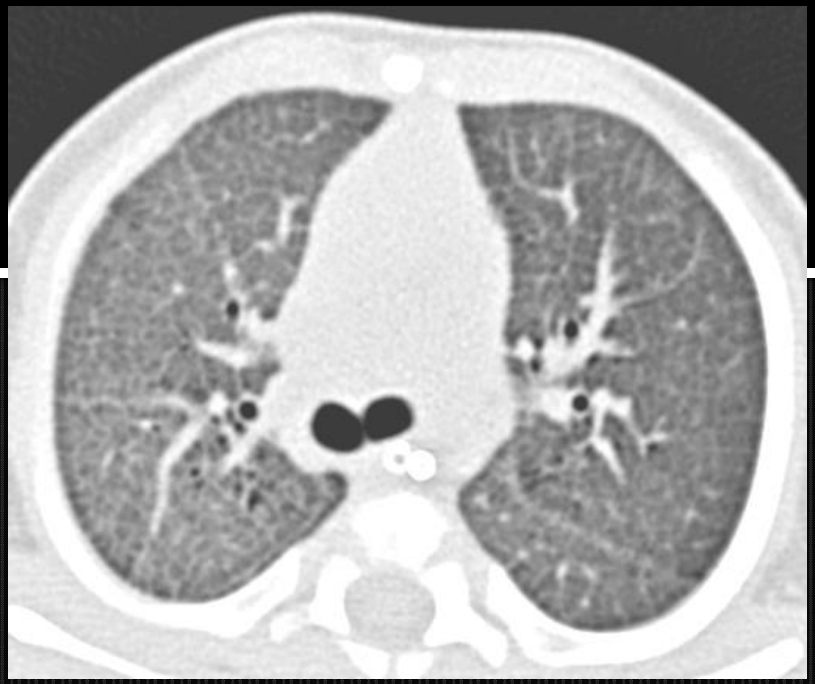
ATS: official statement 2013

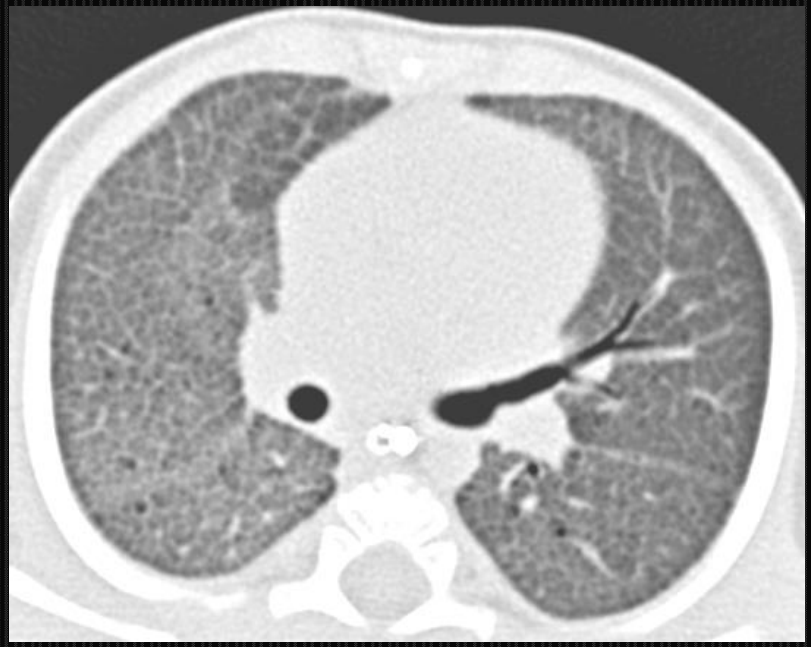
Every now and then….



- 6 weeks old
- Mother HIV infected. ART, Suppressed Viral load; Child HIV uninfected
- No sibling or family history
- Hypoxic respiratory failure
- Too unwell for more invasive investigations
- Poor response to drugs
- Palliation







- post mortem lung biopsy
- findings- consistent with probable surfactant dysfunction disorder

Investigating DLD

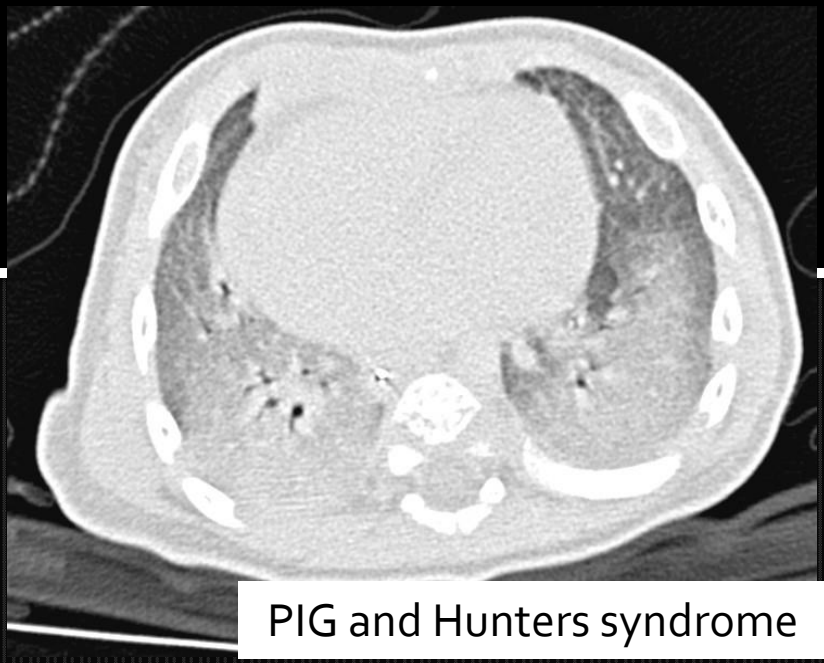
- Clinical evaluation and environmental exposures, underlying risk factors
- Routine blood and other relevant investigations
- Imaging: CT scan
- Flexible bronchoscopy
- Lung biopsy
- Genetic testing
- Management

Routine blood and other relevant investigations for DLD

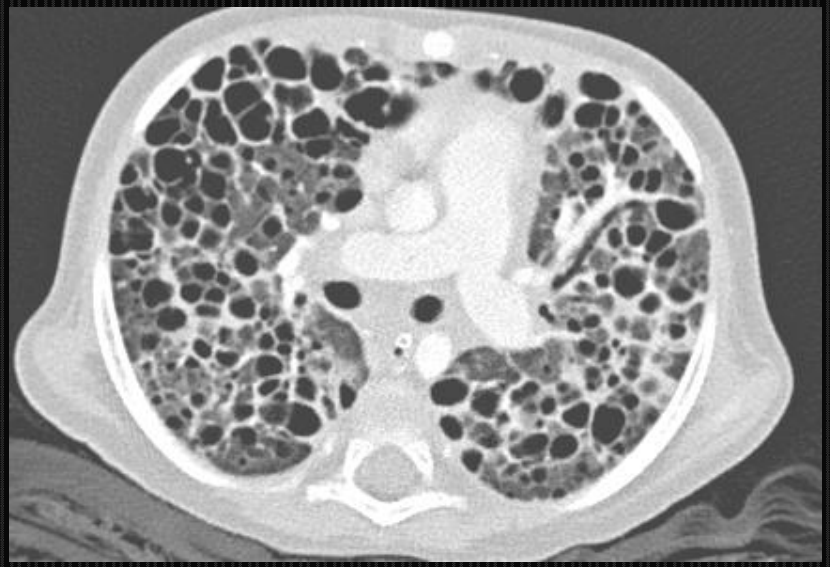
Investigation	value	Availability	
		South Africa	Other Africa
Full blood count differential	Infection, anaemia, eosinophilia	**yes**	**yes**
HIV	Exclude HIV	**yes**	**yes**
Basic primary immune deficiency	Exclude PID infections	**yes**	**some**
Microbiology e.g. Xpert , PCP, Viral studies	On blood culture, NPA, induced sputum, BAL .	**yes**	**some**
Cardiac echo	exclude CHD, cardiovascular pathology, PHT	**yes**	**some**
Aspiration studies	Exclude aspiration syndromes	**yes**	**rarely**
Sweat test	CF	**yes**	**no**

CT scan

- Generally available
- HOWEVER: paediatric protocols rarely used, many poor quality HRCTs being performed.
- Controlled ventilation studies under GA rarely possible
- Only handful of paediatric radiologists in Africa– all in South Africa
- Lung biopsy at times guided only by clinical and CXR findings



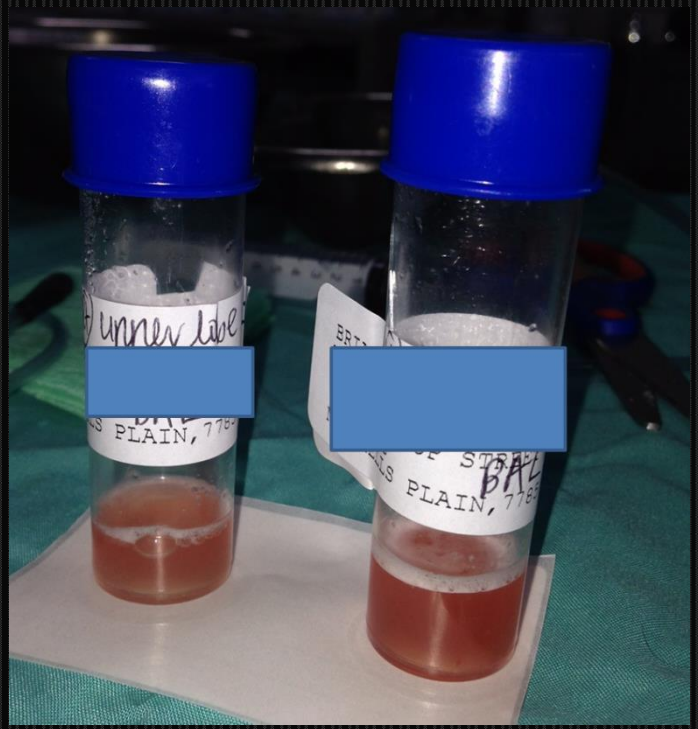
PIG and Hunters syndrome



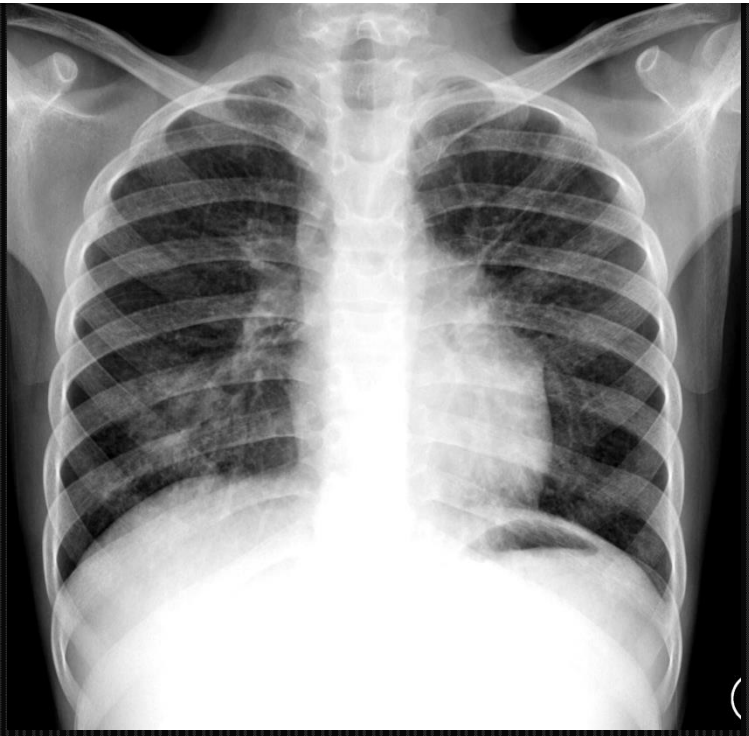
Miliary TB , ARDS and Pulmonary interstitial emphysema?

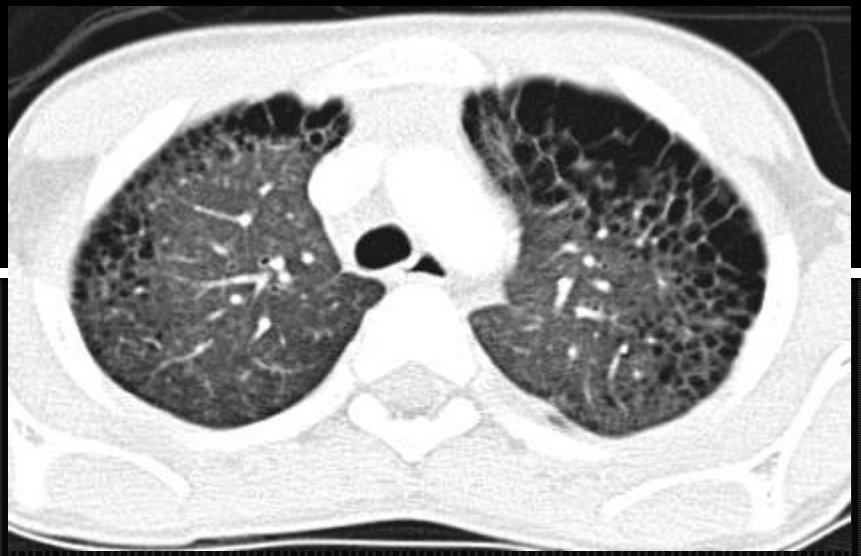
Flexible bronchoscopy

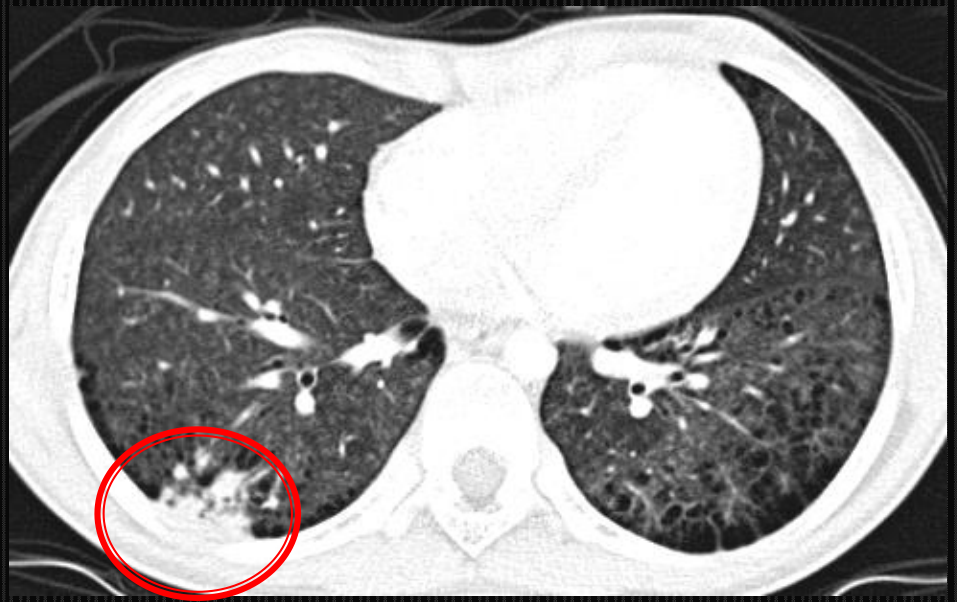
- Currently performed in only a few specialist centres in Africa
- Requires General anaesthesia/ conscious sedation
- essential first line investigation to exclude infections, other pathologies, pulmonary haemorrhage disorders or PAP/surfactant disorders
- CD_4/CD_8 (sarcoid, LIP)
- Ideally guided by CT but <u>blind BAL</u> (through ETT) in diffuse disease recommended in flexible bronchoscopy not available



CT guided BAL



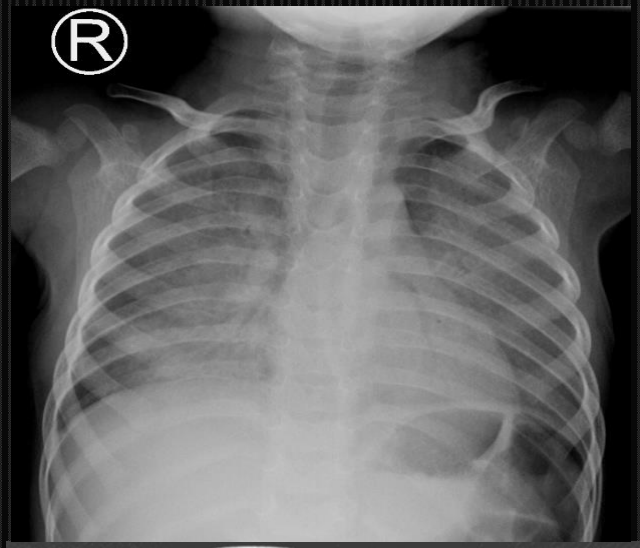


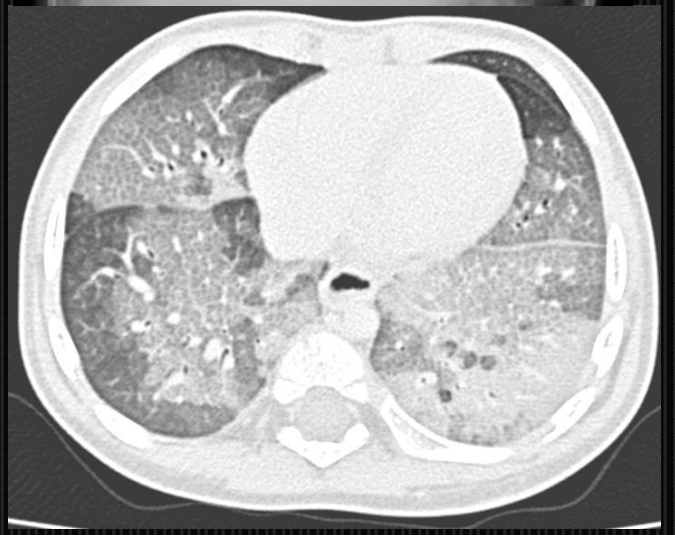


- 7 year old chronic hypersensitivity pneumonitis (Pigeon)
- BAL RLL: GXpert positive = pulm TB

Flexible bronchoscopy and BAL

- diagnostic and therapeutic value
- Case series (n=12) of otherwise healthy infants (2-11 months) with DLD resembling PAP:
- All Zimbabwean immigrant parents
- HIV uninfected
- Some with poor growth
- No feeding difficulties
- No family history or consanguinity
- Very similar pattern; mid-lower zone ground glass opacification with geographic distribution ; crazy paving

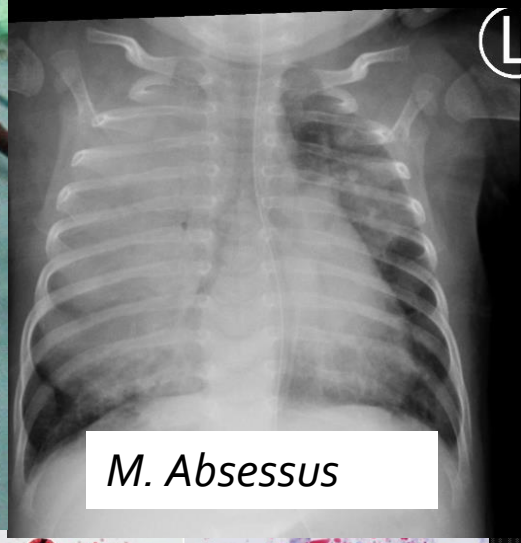


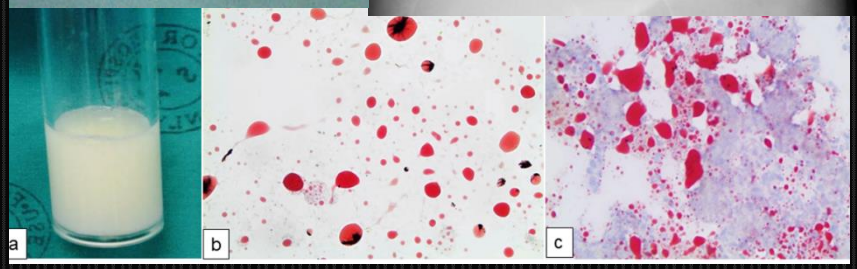


Zimbabwean infants

- BAL: creamy/milky fluid
- Co-infections with viruses in 50% cases
- Co-infection with NTM (*M. Absessus*) in 2/12.
- Diagnosis:

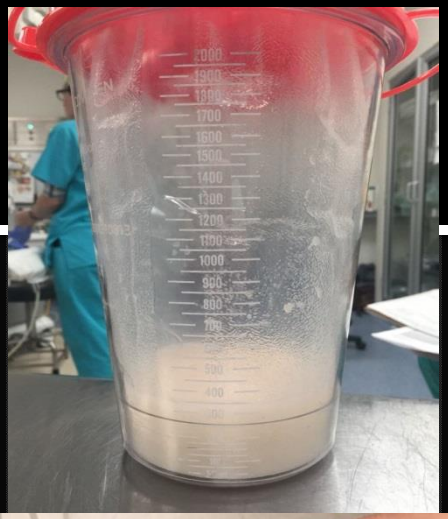
  EXOGENOUS LIPOID PNEUMONIA
- *Further inquiries: Daily cooking oil (2-3 tsp daily) from birth to aid digestion : a common cultural practice in Zimbabwean communities*





Sudan Red stain: abundant intra and extracellular lipid

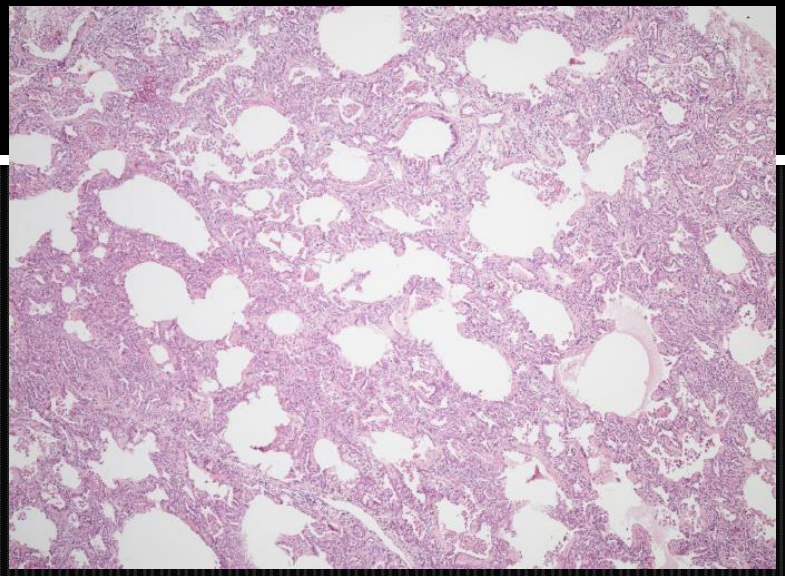
Exogenous lipid pneumonia: management

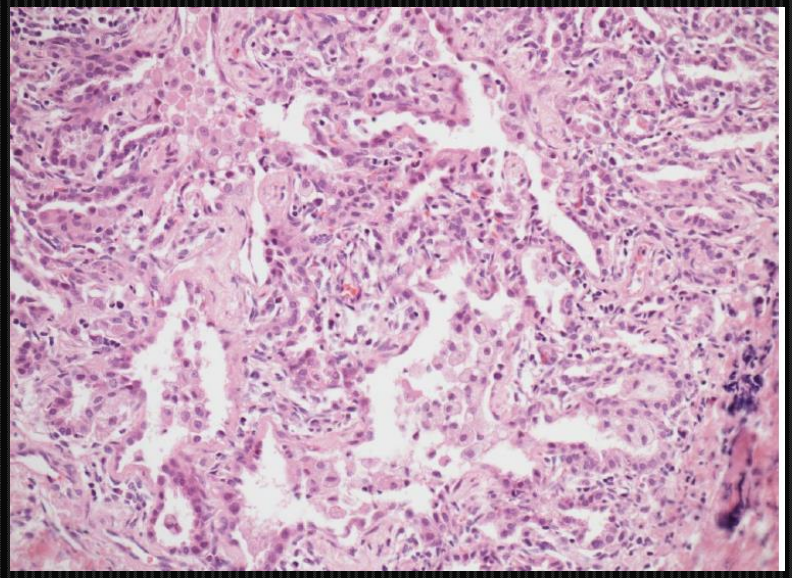


- Mostly resolved spontaneously with discontinuation of oil, radiology changes persist for months
- 5/12 need single or multiple therapeutic partial lung lavage to improve oxygenation
- Corticosteroids in a few ? effect
- NTM treatment if NTM disease

Lung biopsy

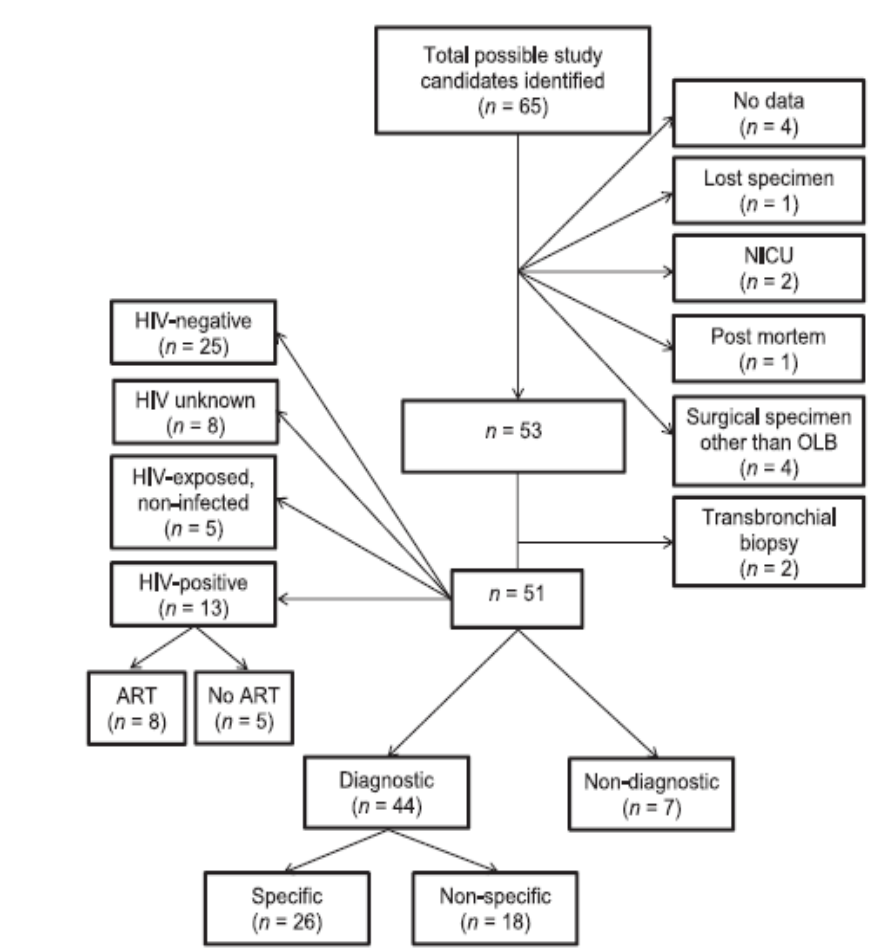
- Important investigation is absence of advanced molecular genetics.
- However, few centres in Africa with expertise to perform and interpret lung paediatric lung biopsies
- SA : 3 pathologists with expertise. None in rest of Africa?
- Open mostly, VATS possible in few centres
- Requires PICU/high care facilities.
- EM available in few centres in SA.
- Infants: *Chronic pneumonitis of infancy* common pattern, presumed underlying SP dysfunction , ABCA 3, SPC





Diagnosing diffuse lung disease in children in a middle-income country: the role of open lung biopsy

A. G. Gie,* J. Morrison,* R. P. Gie,* P. Schubert,† J. Jansen,‡ S. Kling,* P. Goussard*



- Retrospective review of OLB 2004-2011 (early ARV era)
- N=51 ;Median age 7 months
- DLD on oxygen or mechanical ventilation
- 66% severe malnutrition; 30% HIV infected (half on ART)
- OLB diagnostic in 44
  - 86 % ; HIV+ 77%; HIV– 48%
  - 25: pneumonia: CMV, PCP, virus
  - 5 : undiagnosed TB
  - 4: non –infectious (SPC, LCH, IPH, lymphangiectasia
  - 10 non-specific

INT J TUBERC LUNG DIS 21(8):869–874

Utility of lung biopsy at RCCH (*unpublished*)

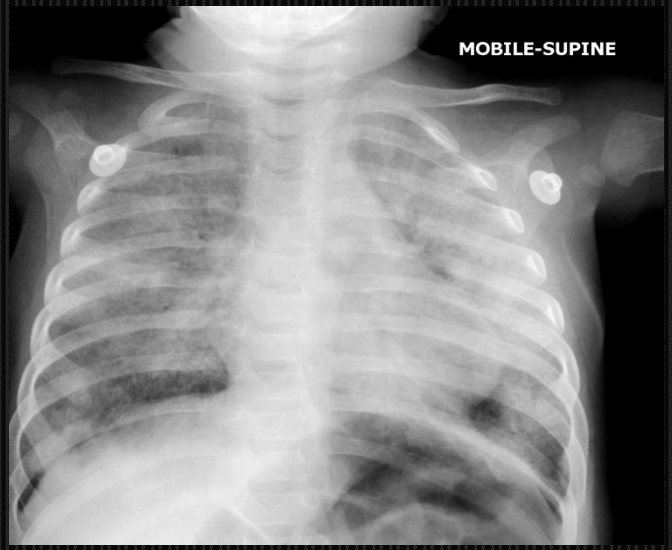
- 36 lung biopsies for DLD 2013-2018; 35 diagnostic; 2 post mortem
- Median age 52 months (range 1-164)
- 19 (< 2 years age)
- 25 (69%) VATS

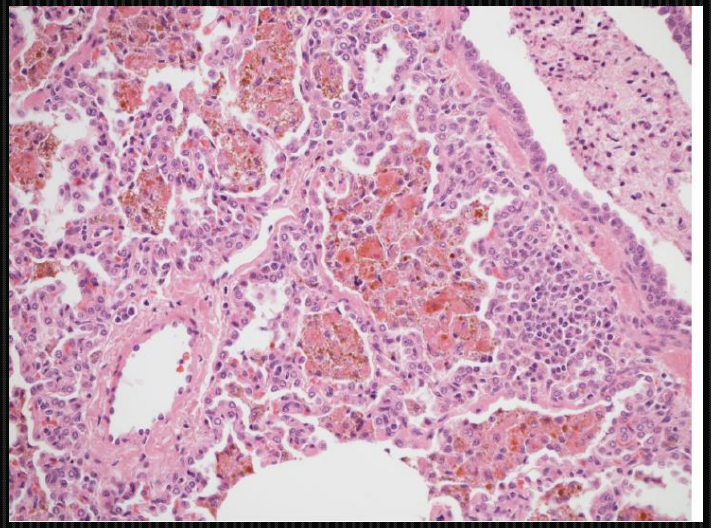
< 2 years (n=19)	> 2 years (n=17)
Alveolar haemorrhage syndrome 7 (37%)	Alveolaer haemorrhage syndrome 9 (53%)
Probably surfactant dysfunction 4 (21%)	Other 8 (47%)
Other 7 (37%), including two PIG.	*infections, lymphactiectasia, hypersensitivity pneumonitis, DIP*

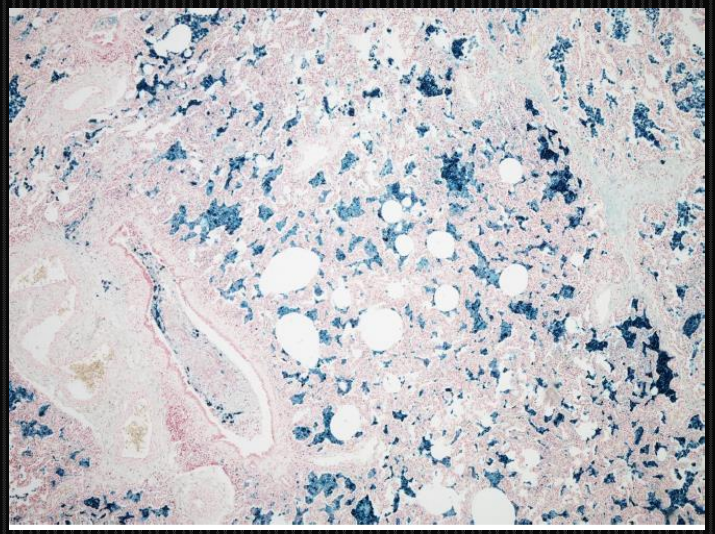
Intervention involved increase or addition of immunosuppressive 20/35 (57%), discontinuation of therapy 6/35 (17%), palliation 2/35 (6%) and addition of other treatment (7/35 (20%).such as antibiotics, immunoglobulins, ganciclovir and sirolimus

Alveolar haemorrhage syndromes idiopathic or immune mediated?

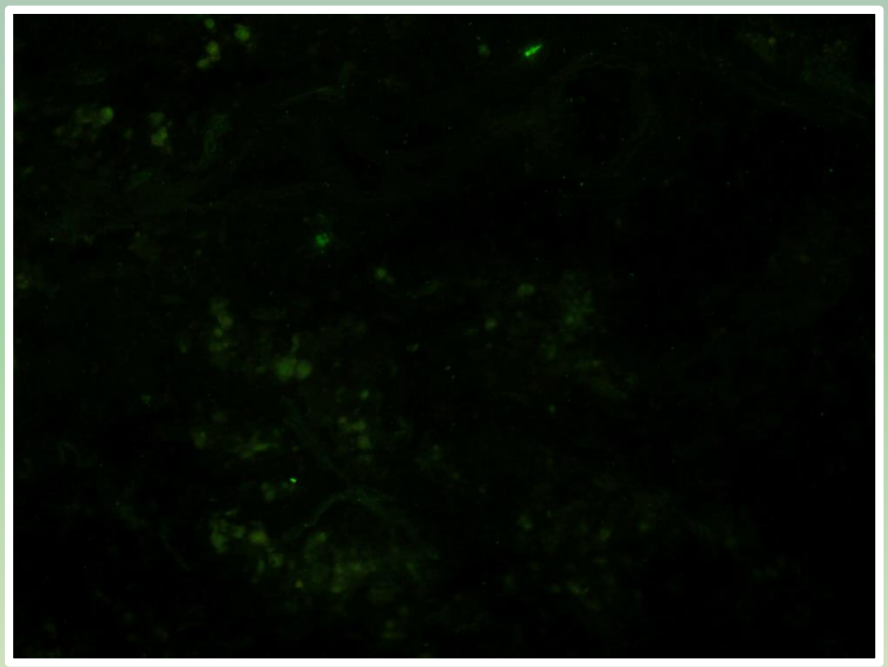
- present with chronic respiratory symptoms, hypoxia, recurrent or persistent anaemia
- Diffuse lung disease clinically and imaging
- Most auto-antibody negative, no renal disease.
- No histology evidence of capillaritis
- Respond well to corticosteroids and chloroquine
- Add azathioprine, RITUXIMAB



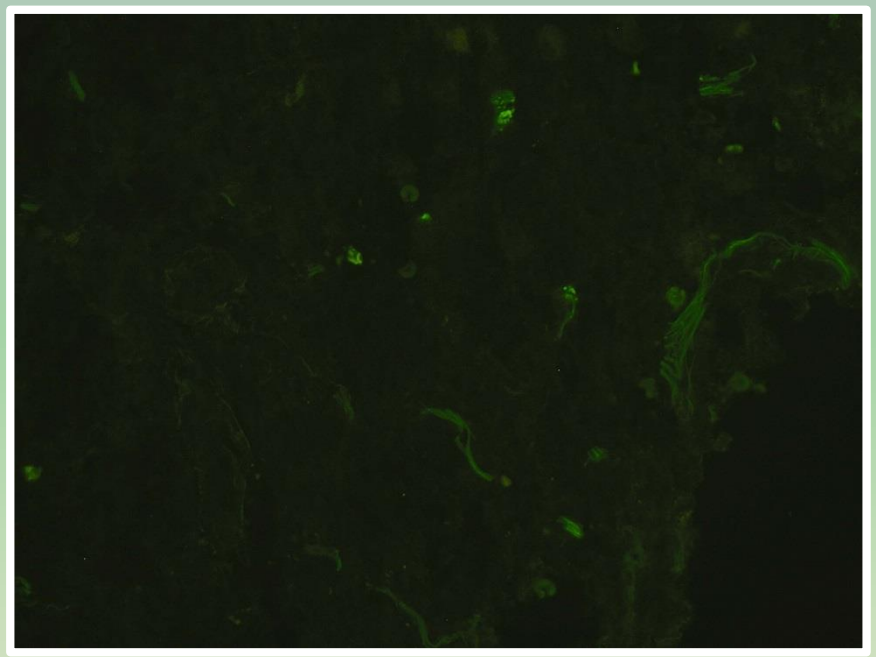




Immune complex disease ?

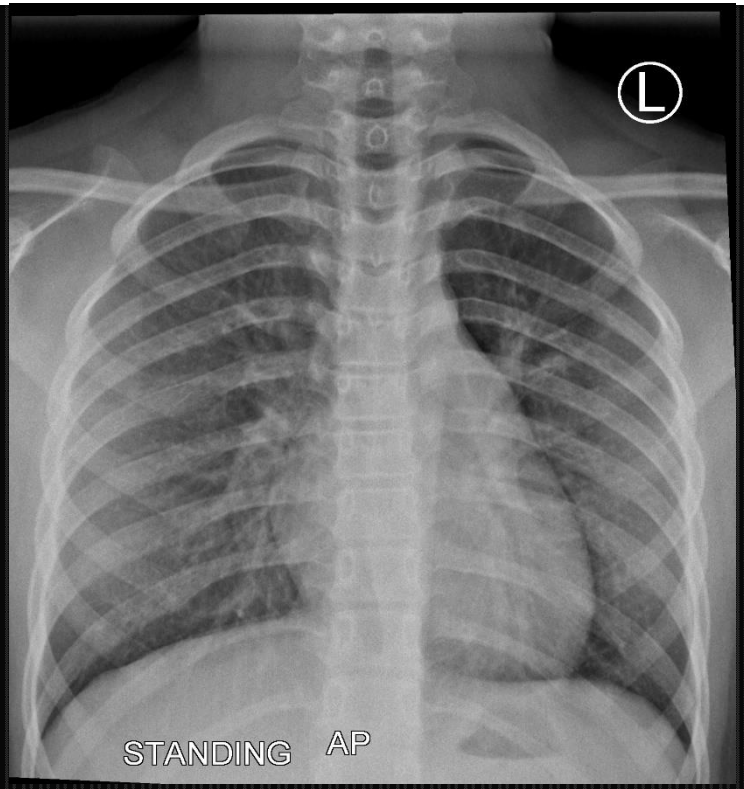


Ig A

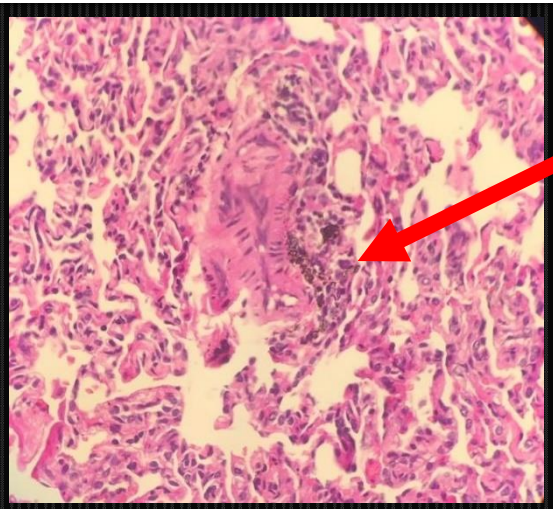


Ig Gb

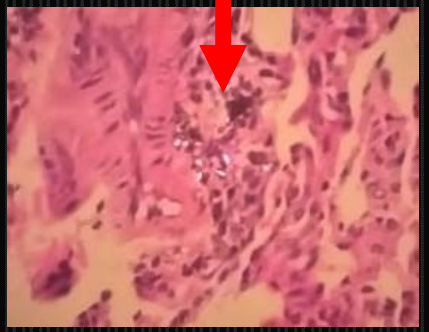
ILD and pollution /environment: more than we know?

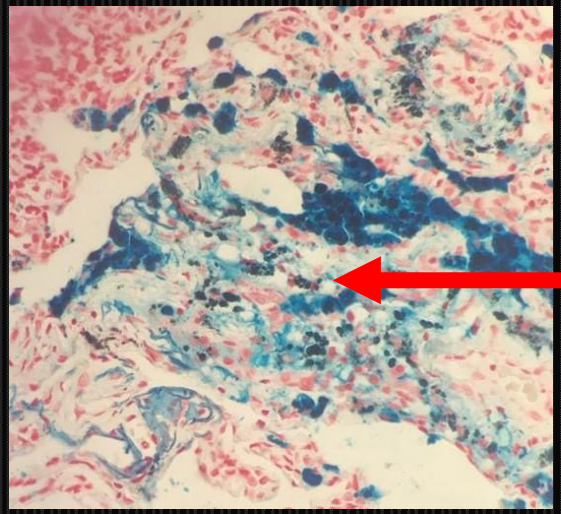


- 11 yr old from rural district diagnosed and treated for Idiopathic pulmonary hemorrhage for many years
- Well controlled on corticosteroids and chloroquine
- Lung biopsy performed to guide future drug management



Carbon and silica particles in peri-bronchial distribution





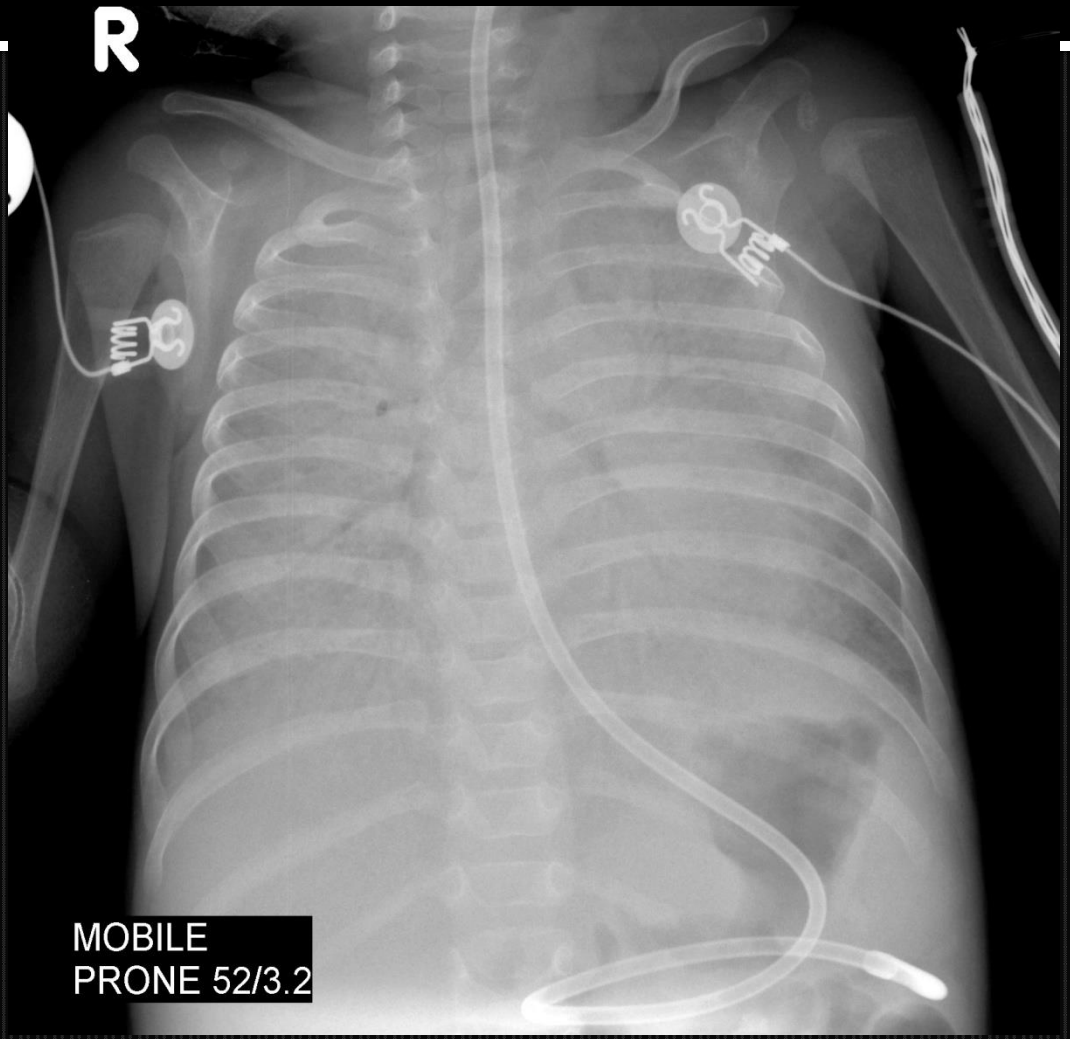
Haemosiderosis is same distribution

Genetic investigations

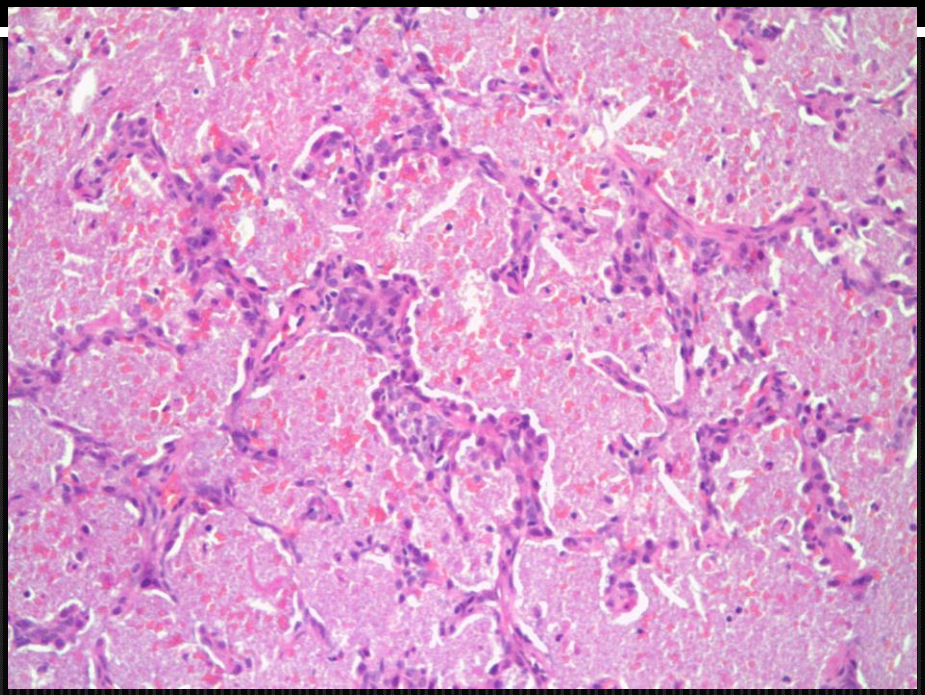
- not routinely available in most centres due to cost , expertise and rare disease status
- Commercial panels offered by private or international laboratories for a fee .
- Likely to be high prevalence of novel of unknown significance mutations in indigenous populations
- Best practice to store DNA in all children with suspected genetic chILD
- Collaboration with international partners is essential and best approach.

SA family- Xhosa ancestry

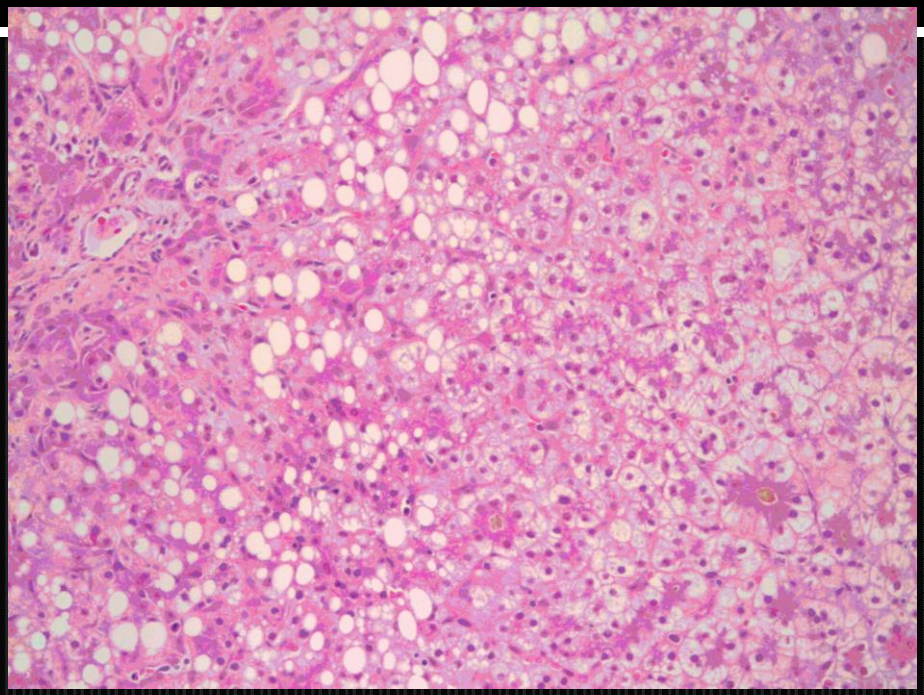
- Sib 1: DOB 2005
- Presented with severe pneumonia needing prolonged ventilation
- Tracheostomy done
- PAP diagnosed on CT, BAL and lung biopsy
- Severe FTT, hepatomegaly, GORD
- Nissans and gastrostomy
- Died age 6-7 m
- No cause found



Sib 1



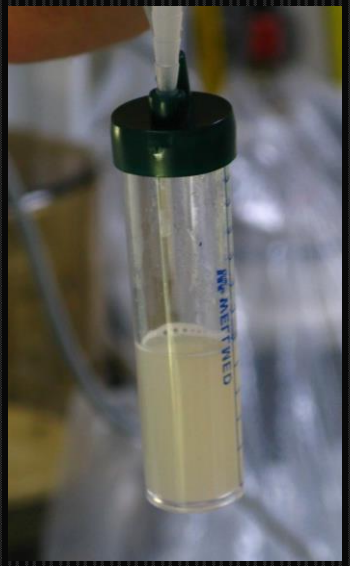
Lung biopsy: PAP

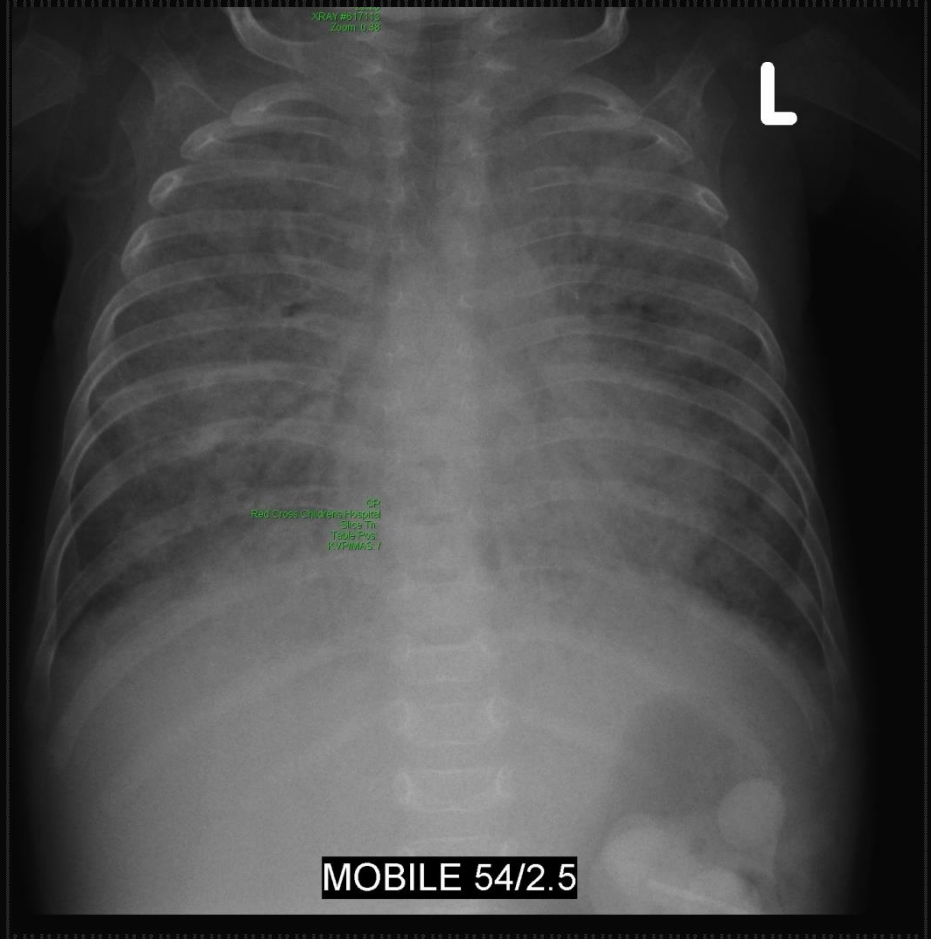


Liver biopsy; steatosis, ? Inborn error of metabolism

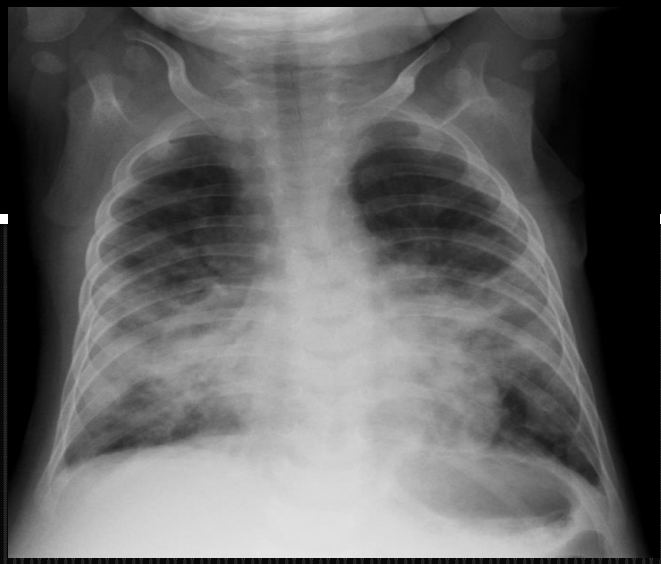
Sib 2

- Identical presentation
- Severe GORD, FTT
- Needed Nissans and PEG
- Progressive hypoxia despite partial lung lavage
- Died 9 months with infection

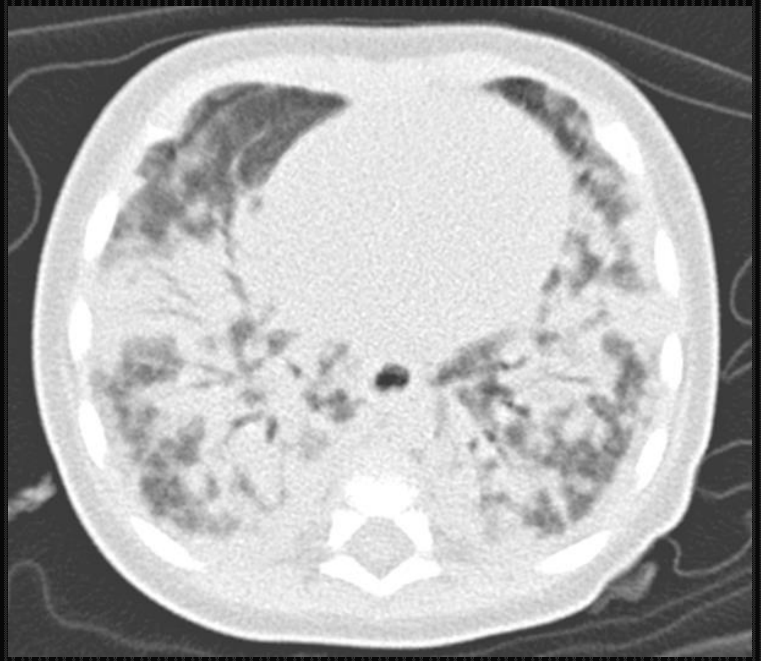




3rd male sibling



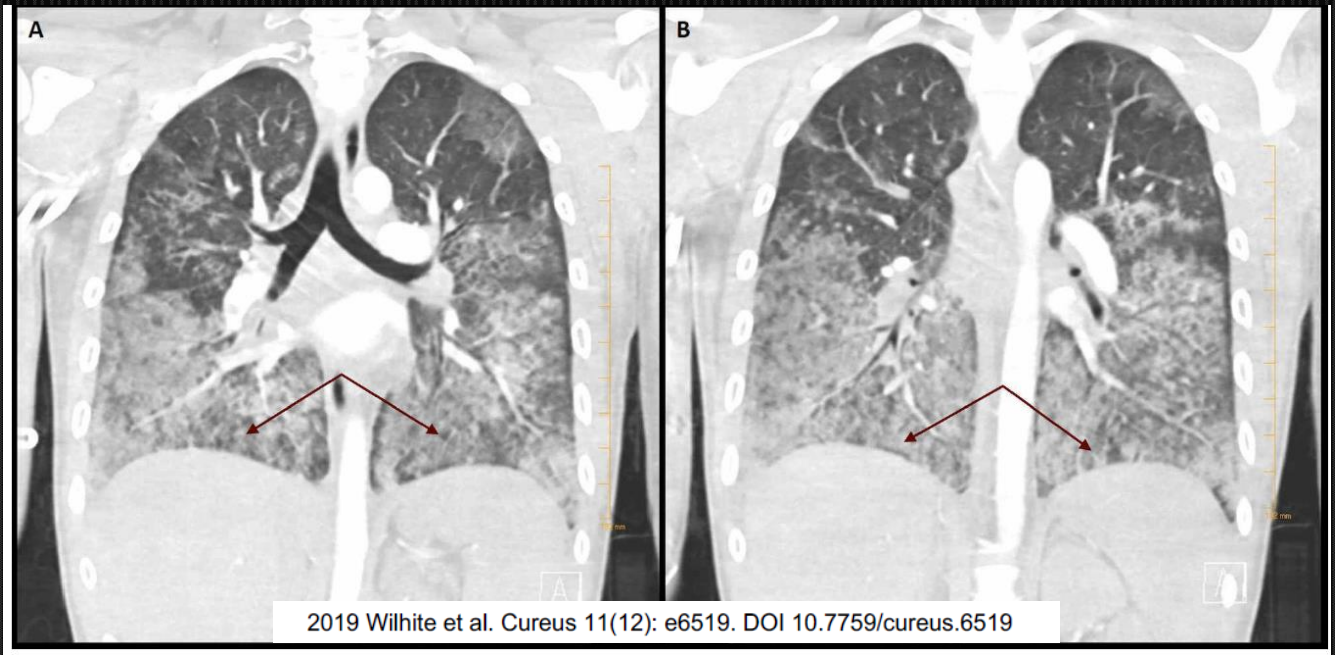
- 3 affected boys, 1 healthy girl (? X-linked disorder)
- Onset in early infancy, normal at birth
- GORD, FTT , high WCC and low albumin with hepatomegaly in all
- DNA:
- No mutations found for SP-B, SP-C, ABCA3, NKX2.1 gene defects
- Methionyl-tRNA synthetase (MARS) variant identified- likely pathogenic
- Sib 3 did well with partial whole lung lavages, corticosteroids and azithromycin, domiciliary O2, eventually weaned O2 and alive today.



Emerging causes of DLD..

Diffuse Alveolar Hemorrhage: An Uncommon Manifestation of Vaping-associated Lung Injury

Rodger Wilhite [1] , Tarang Patel [2] , Ethan Karle [2] , Shyam Shankar [1] , Armin Krvavac [3]



2019 Wilhite et al. Cureus 11(12): e6519. DOI 10.7759/cureus.6519

- E-cigarette/vaping Induced Lung Injury (EVALI)
- > 2000 cases reported to CDC in 2019 and nearly 50 deaths

Update: Interim Guidance for Health Care Providers for Managing Patients with Suspected E-cigarette, or Vaping, Product Use–Associated Lung Injury — United States, November 2019

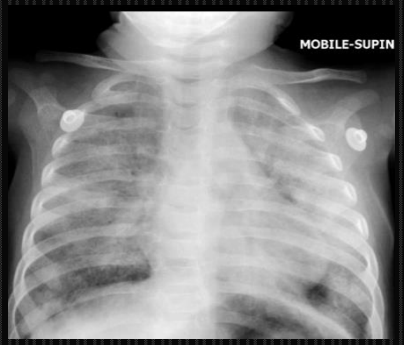
MMWR / November 22, 2019 / Vol. 68 / No. 46

Diagnostic approach diagram

DLD

Empiric antibiotic Rx:

- Broad spectrum
- PJP
- CMV
- TB
- Atypical infections(macrolide)



History and first line Investigations:

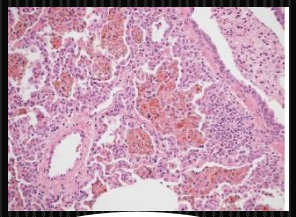
- Family history/sibling deaths
- Neonatal history/illness
- Syndrome or developmental disorders?
- Cardiac assessment, pulmonary hypertension?
- Connective tissue disorder± screen
- Aspiration risk and feeding practices e.g. oil
- HIV and PID screen.
- Full blood count (severe Fe deficiency anemia)
- TB investigations (Induced sputum, mantoux)
- Respiratory viruses, CMV viral load
- Thyroid function

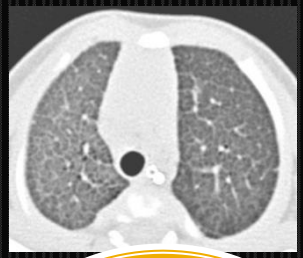
Re-evaluate

* Elective intubation and *blind* BAL

BAL

infections, blood, alveolar proteinosis, lipid, cell profile immunohistochemistry





Lung biopsy

Routine HE
Periodic acid Schiff
Iron stains
Lipid stains
EM
Immunohistology

Make friends with an anesthetist!

CT chest: volume controlled

- Consult and plan biopsy with pathologist and experts
- Share histology tissue with experts

Special investigations:
- genetic tests for hereditary chILD
Store DNA

Management of ILD with fewer resources

- Drugs: mostly accessible in including IVIG , chloroquine/hydroxychloroquine and immunosuppressives (azathioprine, cyclophosphamide, tacrolimus, rituximab)
- *Empiric treatment* with corticosteroids if NO special investigations possible and confident that infection aetiology unlikely , especially TB ; INH and PJP prophylaxis recommended
- Domiciliary oxygen if available but rarely in other poor countries
- Gastrostomy or nasogastric feeds and nutritional support
- Long term ventilation mostly not feasible
- PICU or high dependency care scare resource
- Paediatric lung transplant not performed in SA
- Palliative care approach .

Ethical challenges

- Prioritisation of scare resources
- Choosing investigations, especially invasive ones must be appropriate in context of what care or interventions are available, and likelihood that investigations will impact on management decisions.
- Recognition of futility of investigations or treatments is important and so that appropriate palliative care is initiated

In summary

- Like other rare diseases, chILD in poor countries probably overlooked, misdiagnosed
- Overwhelming burden of other childhood illnesses , infections prioritise resources and overwhelm diagnostic strategies.
- We have still lots to learn and understand about chILD in low middle income … unique causes, disease patterns and probably novel/different mutations
- Collaboration with international partners is key.

Thank you!

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