

# 39th CLINICAL INFECTION & PUBLIC HEALTH FORUM:

## BCG Vaccination related side effects




# ***BCG lymphadenitis & other BCG side effects***

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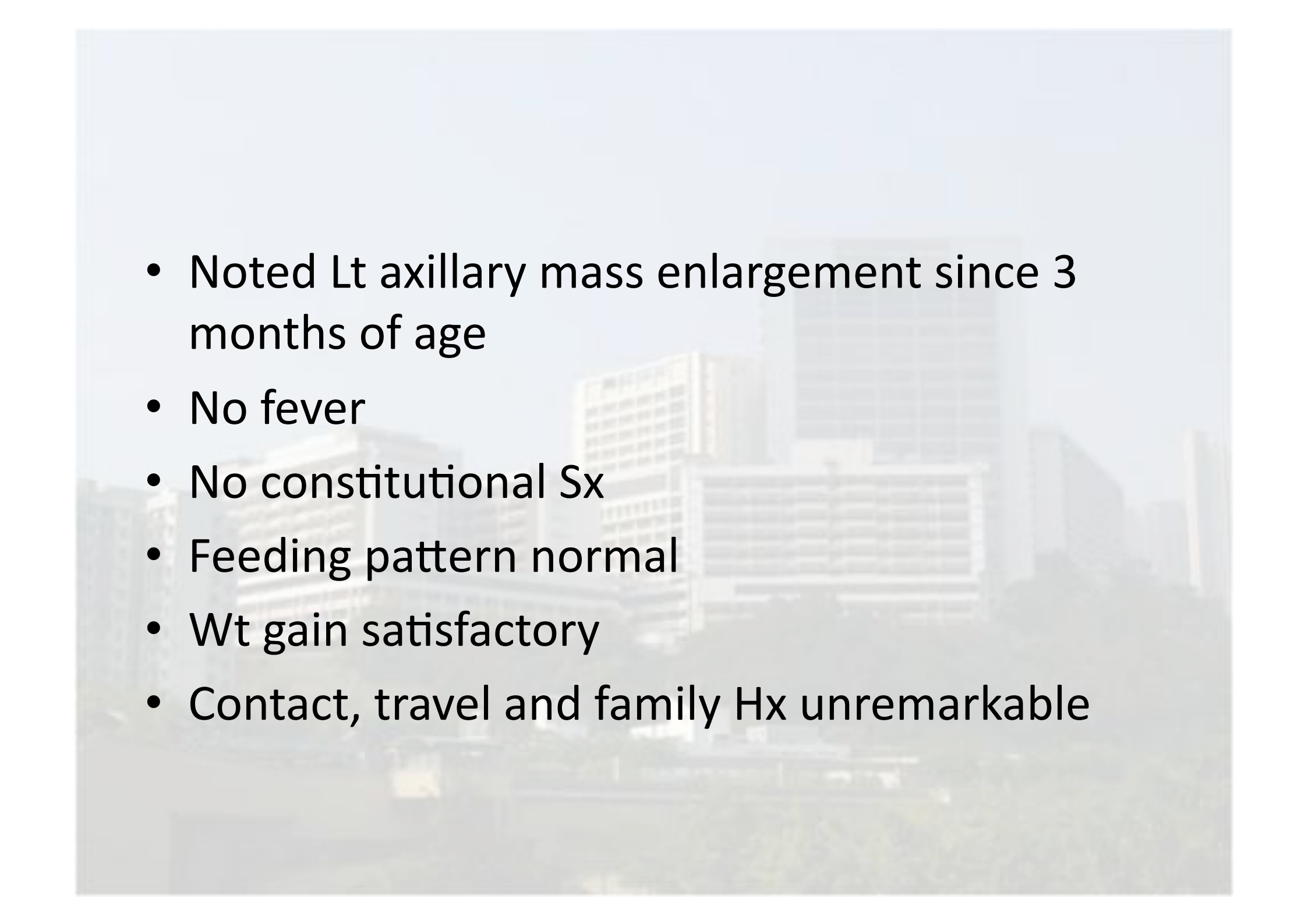
Princess Margaret Hospital






F/5 m.o.

- FT NSD
- Perinatal Hx uneventful
- Immunization UTD

- 
- Noted Lt axillary mass enlargement since 3 months of age
  - No fever
  - No constitutional Sx
  - Feeding pattern normal
  - Wt gain satisfactory
  - Contact, travel and family Hx unremarkable

- 
- ❖ Lt axillary mass gradually enlarged
  - ❖ Noted overlying skin erythema
  - ❖ No discharge
  - ❖ Nontender

# Physical examination

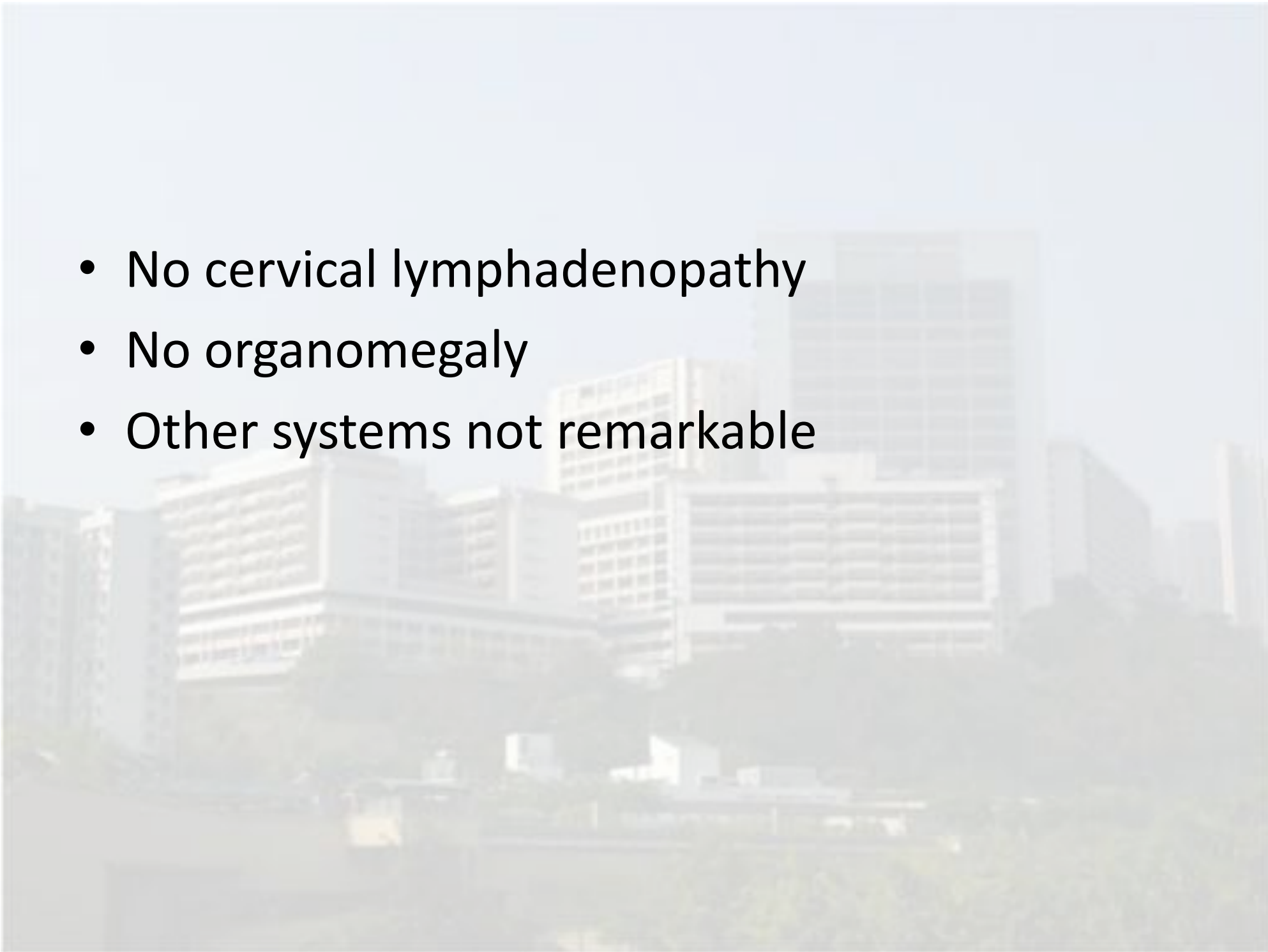
- Afebrile
- Well nourished
- BW 7.6kg
- Ht 65.5cm
- HC 42.5cm
- Along 25<sup>th</sup> centile


- Lt axillary LN enlargement
- LN 2x2cm diameter
  - Fluctuation +ve
  - Nontender
  - Overlying skin erythema +ve





- No cervical lymphadenopathy
- No organomegaly
- Other systems not remarkable

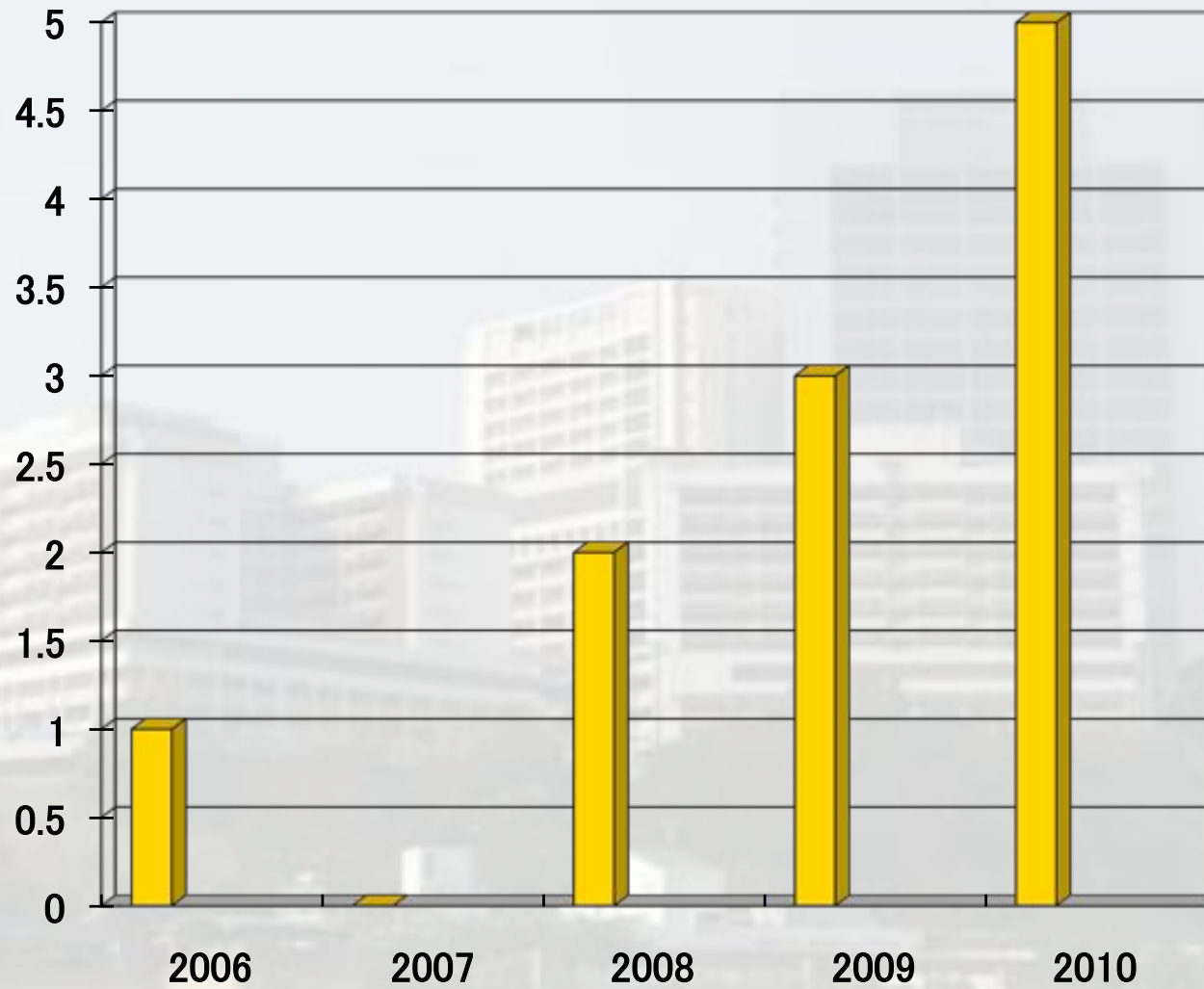


- 
- What is the Dx?
  - What is the clinical approach?

# Similar cases

- Presented with isolated Lt axillary lymphadenitis
- Admitted Paed PMH
- From 2006-2010

# No. of Cases in PMH



**Table 1. Characteristics and outcome of 11 infants with suppurative BCG lymphadenitis**

LN: lymph node

N/A: not recorded or not available

PCR: polymerase chain reaction

I&D: incision and drainage

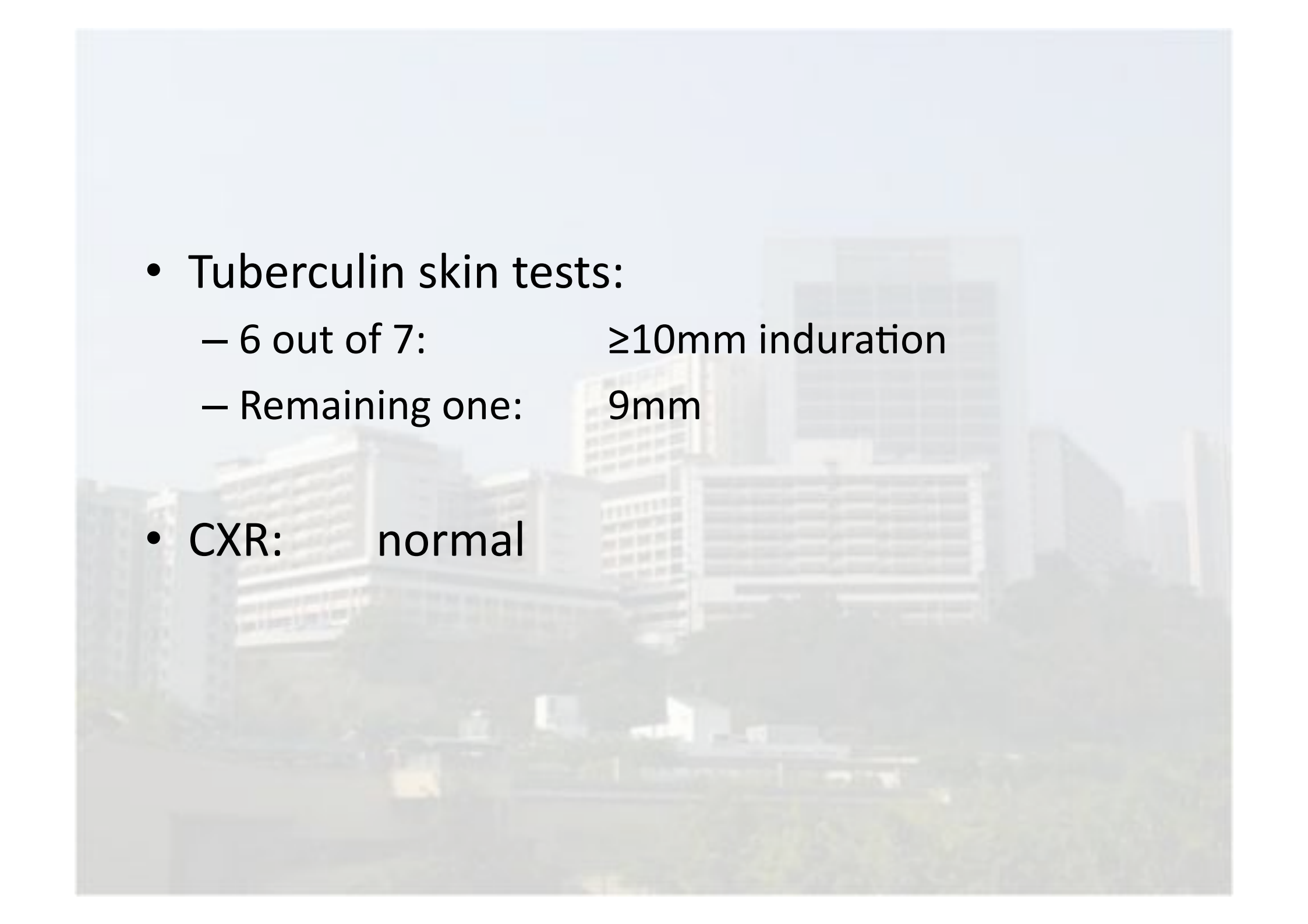
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Sex	F	M	M	M	M	M	F	M	M	F	F
DOB	Nov 2005	Dec 2006	Nov 2006	Aug 2006	Jul 2006	Aug 2009	Sep 2009	Dec 2009	Feb 2009	Apr 2010	May 2009
Age at presentation (months)	2	2	3	3	3	3	4	3	11	4	3
Duration after vaccination (months)	2	2	3	3	3	3	4	3	2	4	3
Size of L1 axillary LN at presentation (cm)	3	3x1.5	2.5	2.3x2.5	1.3	1.3x1.5	2x1	1x2	3x4	1.5	1.5x1.5
Max size of fluctuation (cm)	4x5	2x1.5	2x1	1	1	2x2	1	1.5x2.5	2x1.5	1.5	2.4x1.8
Appearance of BCG injection site at presentation	Normal scar	Normal scar	Normal scar	Normal scar	Normal scar	Normal scar	Normal scar	Scabbed	Normal scar	Normal scar	Normal scar
Mantoux Test (2 units)	N/A	13mm	21mm	23mm	18mm	8mm	18mm	N/A	18mm	N/A	N/A
CXR	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Bacteriologic investigation of LN content	M. bovis isolated from culture	M. bovis isolated from culture	Culture -ve for mycobacteria	Not performed by referring doctor	M. bovis isolated from culture	M. bovis isolated from culture	M. bovis isolated from culture	M. bovis isolated from culture	M. bovis isolated from culture	M. bovis isolated from culture	N/A
Management	I&D prior to referral	I&D prior to referral	I&D prior to referral	I&D prior to referral	I&D performed twice for failed needle aspiration	Needle aspiration	Needle aspiration	Needle aspiration	Needle aspiration	Needle aspiration	Spontaneous rupture 1 month after presentation
Wound care	Daily wound toilet and dressing until complete wound healing					None	None	None	None	None	Dressing for 2 weeks
Outcome	Wound healed with irregular scar and 1 cm keloid in 4 months	Wound healed with 1 cm irregular scar in 3 months  Isolated L1 supraclavicular lymphadenitis shortly after resolution of axillary lymphadenitis	Wound healed with 1 cm irregular scar in 6 months	Wound healed in 4 months  1cm keloid requiring plastic surgical excision	Wound healed with 2 cm irregular scar in 3 months	Complete resolution in 1 month  Spontaneous rupture of adjacent LN	Complete resolution in 0.5 month  Spontaneous rupture of adjacent LN	LN almost completely resolved (0.2cm at 5 months)	LN resolving (0.5cm at 6 months)	LN resolving (0.4cm at 3 months)	Wound healed in 2 weeks with 3mm depressed scar. LN resolved in 4 months

# Demographic data

- Total =11
- M:F        7:4
- Chinese
- BCG vaccine
  - 10 at birth
  - 1 at 11months

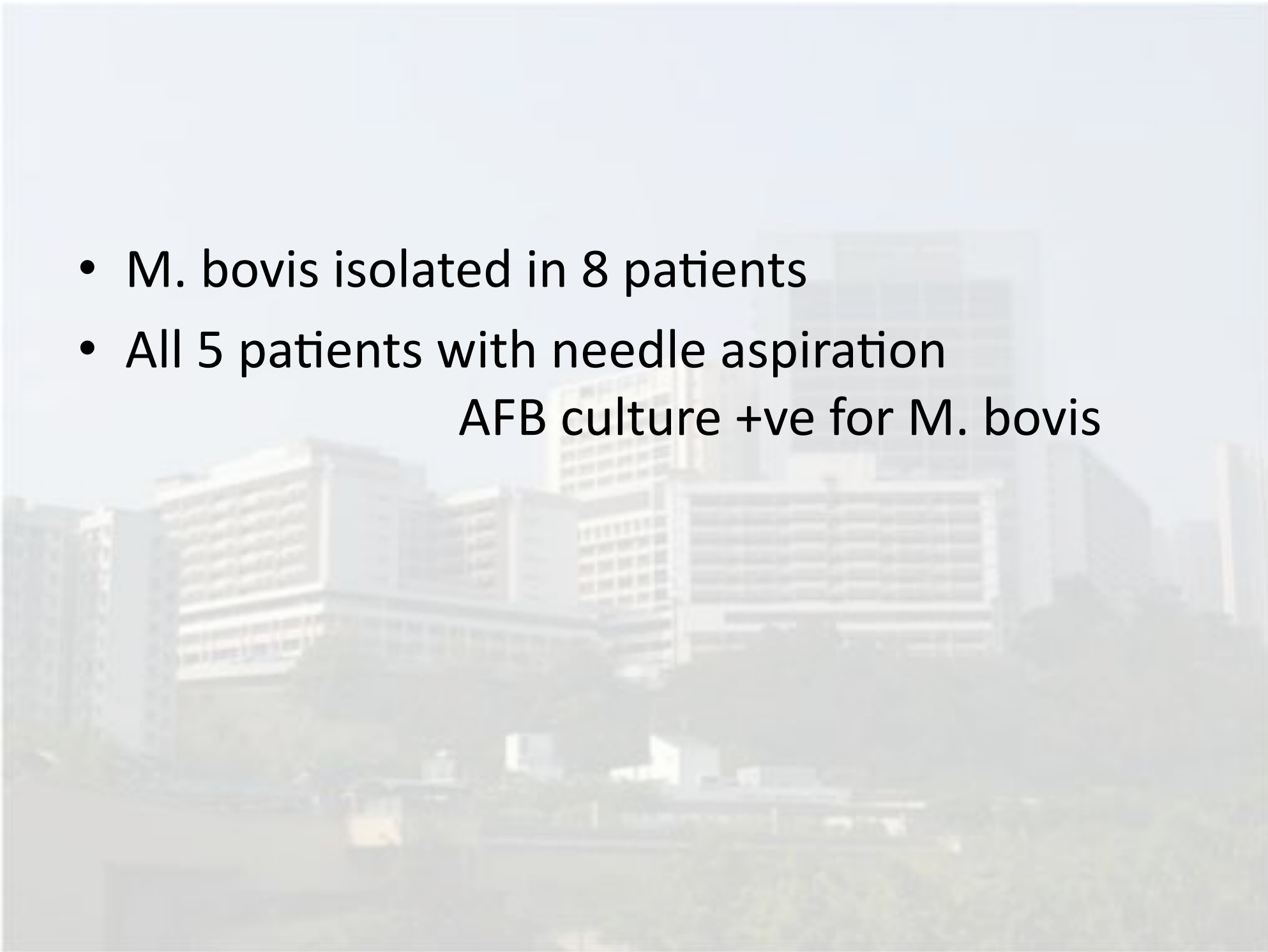
# Clinical features


- All presented with Lt axillary mass
  - Mean age: 3.5 months (after vaccination)
  - Range: 2-5 months
  - 1 patient also developed Lt supraclavicular mass (also suppurative)
- None had fever / constitutional Sx

- 
- Tuberculin skin tests:
    - 6 out of 7:  $\geq 10\text{mm}$  induration
    - Remaining one: 9mm
  - CXR: normal



- M. bovis isolated in 8 patients
- All 5 patients with needle aspiration  
AFB culture +ve for M. bovis





# BCG, BCG lymphadenitis & its side effects

Review & Discussion

# BCG vaccine



- Bacillus Calmette-Guérin (BCG) vaccine:
  - oldest vaccine still widely used
  - live attenuated
    - in vitro attenuation of an isolate of *Mycobacterium bovis* specially cultured in an artificial medium for years
  - named after its discoverers
    - French bacteriologist Albert Calmette
    - veterinarian Camille Guérin
  - propagate the vaccine strain under different conditions
  - The marketed strains from different pharmaceutical companies are now bacteriologically different.<sup>1</sup>

1. Fine PE. The BCG story: lessons from the past and implications for the future. *Rev. Infect. Dis.* 1989;11 Suppl 2:S353-359.

- Protects esp infants & children
  - Disseminated TB (efficacy 78%)
  - TB meningitis 64% <sup>2</sup>
- Role of protection against pulmonary TB remains unclear <sup>3</sup>
- Most cost effective
  - HK\$1,600 per life-year gain <sup>4</sup>

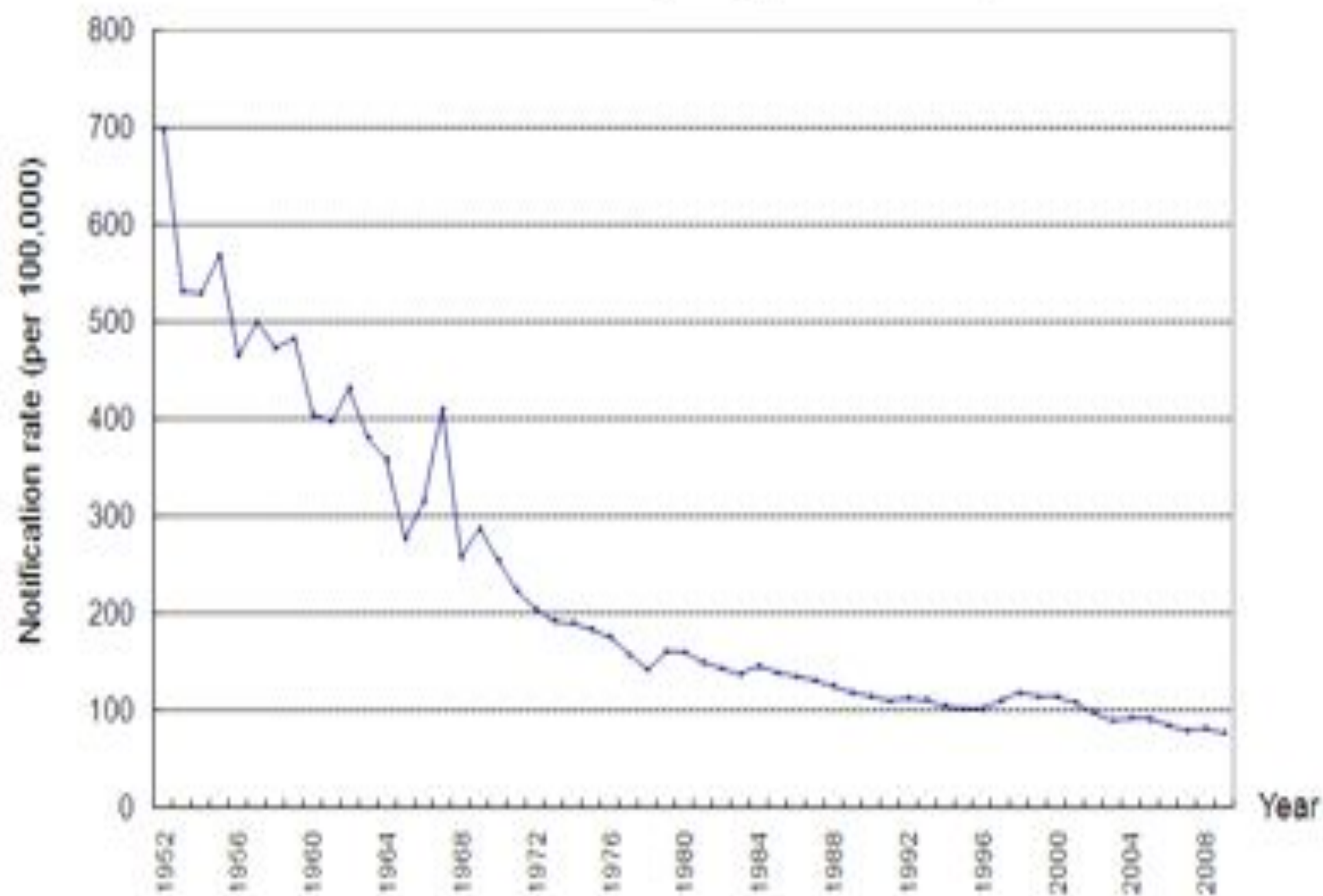
2. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG Vaccine in the Prevention of Tuberculosis: Meta-analysis of the Published Literature. *JAMA*. 1994;271(9):698-702.

3. Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of bacillus Calmette-Guérin vaccine. *Clin. Infect. Dis*. 1995;20(4):982-991.

4. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and military tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006;367(9517):1173-1180.

- Hong Kong
  - Universal neonatal BCG immunization program introduced since Apr 1952
  - Followed by dramatic decline of TB notification
  - Coverage around 99% since 1980

TB notification in Hong Kong (1952 - 2009)



# Complications of BCG

- Safe
- Low incidence of serious adverse reactions<sup>6,7</sup>

6. Lotte A, Wasz-Hockert, Poisson N, et al. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bulletin of the International Union Against Tuberculosis and Lung Diseases* 1988;63:47-59

7. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull World Health Organ* 1990;68:93-108

- **Most common Cx:** 8-10
  - Local reaction
    - Erythema, induration, papule, discharging ulcers, abscess
  - Regional lymphadenopathy
    - Ipsilateral
    - Usually axillary, rarely lower cervical chains
    - Spontaneously resolved
    - Occasionally became suppurative

8. Romanus V et al *Acta Paediatr.* 1993 Dec;82(12):1043-52

9. Szczuka I. *Przegl Epidemiol* 2002;56(2):205-16

10. Daoud W. *Respirology* 2003 Sep;8(3):376-8

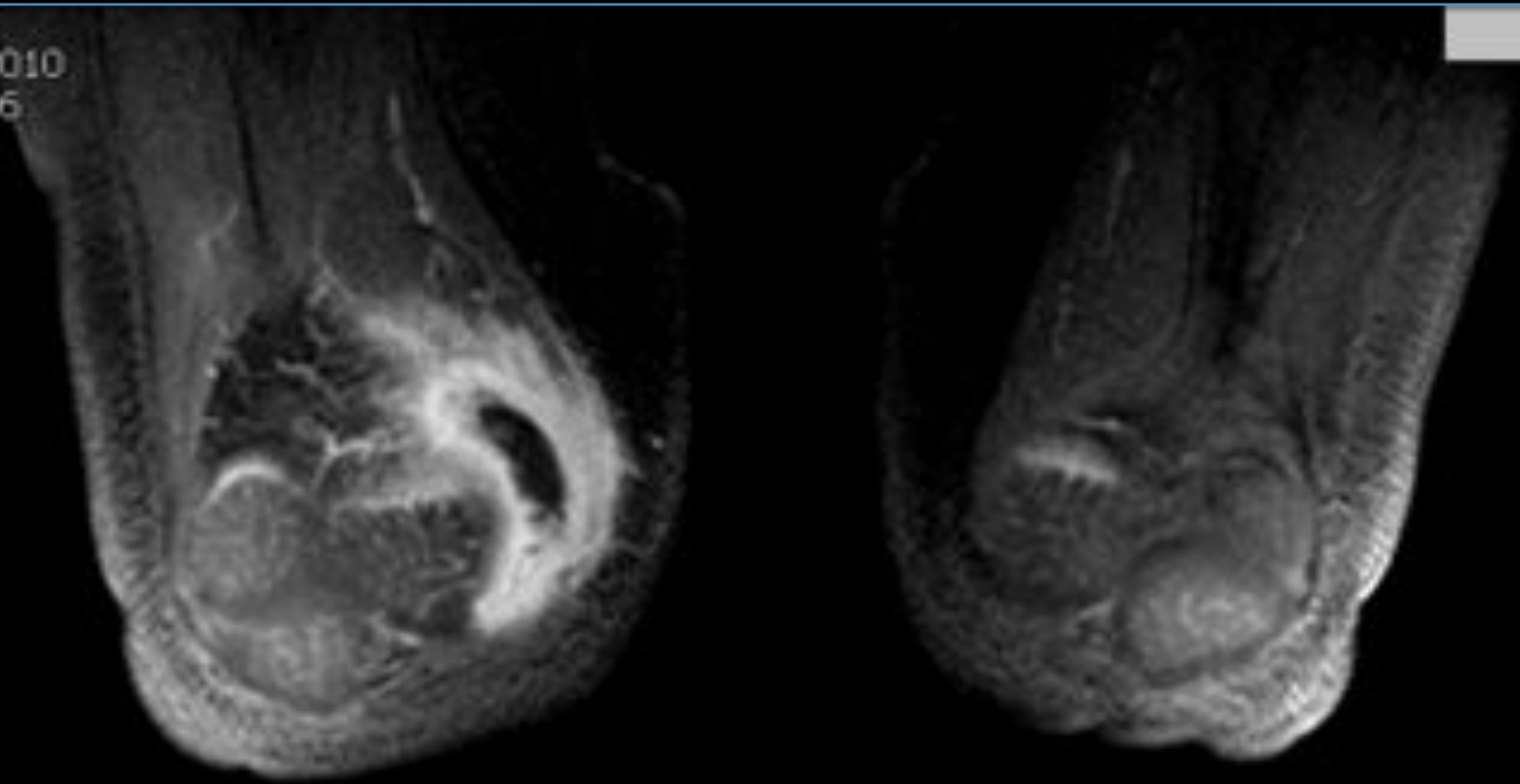


- Serious Cx
  - osteomyelitis,
  - disseminated BCGiosis
- extremely rare
- Impaired immunity<sup>11</sup>
  - e.g. HIVS or primary immunodeficiencies



Study 1  
08/07/2010  
11:37:56  
12 IMA

RPF



SL 2  
TE 2.73  
TR 6.89  
Comment: RECON 2 MM



SP A84.1  
FoV 159\*159  
384 \*384  
Cor>Tra(13.8)>Sag(-7.1)  
W: 542  
C: 383

Study 1  
08/07/2010  
11:37:56  
7 IMA

ARF

SL 2  
TE 2.73  
TR 6.89  
Comment: REFORM 2MM+C

AL

SP R5.7  
FoV 159\*159  
384 \*384  
Sag>Cor(17.4)>Tra(-2.2)  
W: 542  
C: 383

PCR - M bovis/BCG

-ve control

M tb suspension

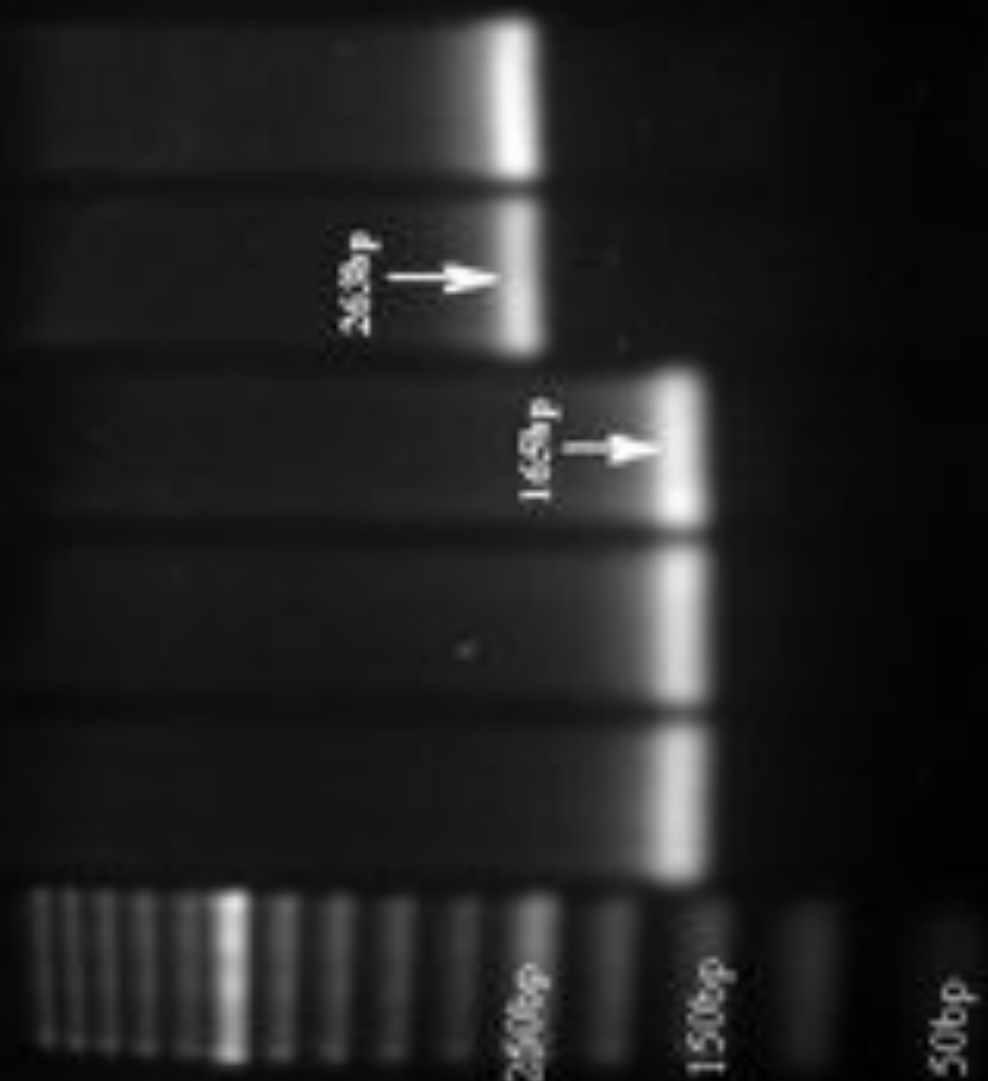
ZN+ 70x (M tb)

BCG

ST315648

ST315648

50bp ladder



Duplicate Copy

PRINCE OF WALES HOSPITAL  
MICROBIOLOGY

MICROBIOLOGY  
10B018050-4

[REDACTED]

F/10M

i Hang Assunta

Date Collected: 28/07/10 09:40  
Date Arrived: 28/07/10 11:29  
Specimen:- TISSUE  
Site:- Soft tissue, medial side of right knee

**ZN Stain** : No ACID ALCOHOL FAST BACILLI seen

**AFB culture** :-

Organism 1 : Mycobacterium bovis isolated

Please consult the Duty Microbiologist before treatment if clinically indicated.

Identification and sensitivity test is performed by Public Health Laboratory Centre.

PHLC test results may be available in ePR before they have been reviewed by the laboratory.

# BCG lymphadenitis

- Ipsilateral LN enlargement
- Axillary, supraclavicular, lower cervical chains
- After BCG vaccination
- Arouse concern from caretaker

# Risk factors for BCG lymphadenitis

- Host related <sup>13, 16, 17</sup>
  - Age
    - neonatal period
  - Immunogenicity
    - Immunodeficiency e.g. SCID
    - AIDS
  - Administration
    - subcutaneous
  - Race

13. Victoria MS, Shah BR. Bacillus Calmette-Guerin lymphadenitis: a case report and review of the literature. *Pediatr Infect Dis J* 1985;4:295-6

16. Gołebowska M et al. Adverse events following BCG vaccination in infants and children up to 36 months of age. Przegl Epidemiol. 2008;62(1):71-5

17. Talbot EA, Perkins MD, Silva SFM, et al. Disseminated Bacille Calmette Guérin disease after vaccination: case report and review. *Clin Infect Dis* 1997;24:1139-46



- Vaccine related <sup>11</sup>
  - Dosage
  - Strain virulence
  - Viability (proportion of live & dead bacilli)
    - Storage condition e.g. cold chain

# Clinical features

- Challenging to differentiate
  - BCG related
  - vs bacterial, tuberculous or nontuberculous mycobacterial infection

# Suggesting BCG related<sup>14,19</sup>

- Hx of BCG vaccination on ipsilateral arm
- Onset 2-4 months after BCG vaccination
  - may ranged from 2 weeks to 2 years
- Absence or minimal local tenderness
- >95% ipsilateral axillary LNs
  - ~5% Supraclavicular or lower cervical chains
  - +/- axillary LN
- Usually 1-2 discrete LNs
  - Rarely matted

14. Helmick CG, D'Souza AJ, Goddard RN. An outbreak of severe BCG axillary lymphadenitis in Saint Lucia, 1982-1983. *West Indies Med J* 1986;35:12-7

19. Noah PK, Pande D, Johnson B, et al. Evaluation of oral erythromycin and local isoniazid instillation therapy in infants with *Bacillus Calmette-Guerin* lymphadenitis and abscesses. *Pediatr Infect Dis J* 1993;12:136-9

# Types of BCG lymphadenitis

- Non-suppurative (simple) form <sup>14,20,21</sup>
  - Benign clinical course
  - Resolves spontaneously
  - Without any sequelae over weeks

14. Helmick CG, D'Souza AJ, Goddard RN. An outbreak of severe BCG axillary lymphadenitis in Saint Lucia, 1982-1983. *West Indies Med J* 1986;35:12-7

20. Lotte A, Wasz-Hockert, Poisson N, et al. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bulletin of the International Union Against Tuberculosis and Lung Diseases* 1988;63:47-59

21. Singla A et al *Pediatr Infect Dis J* 2002 May;21(5):446-8





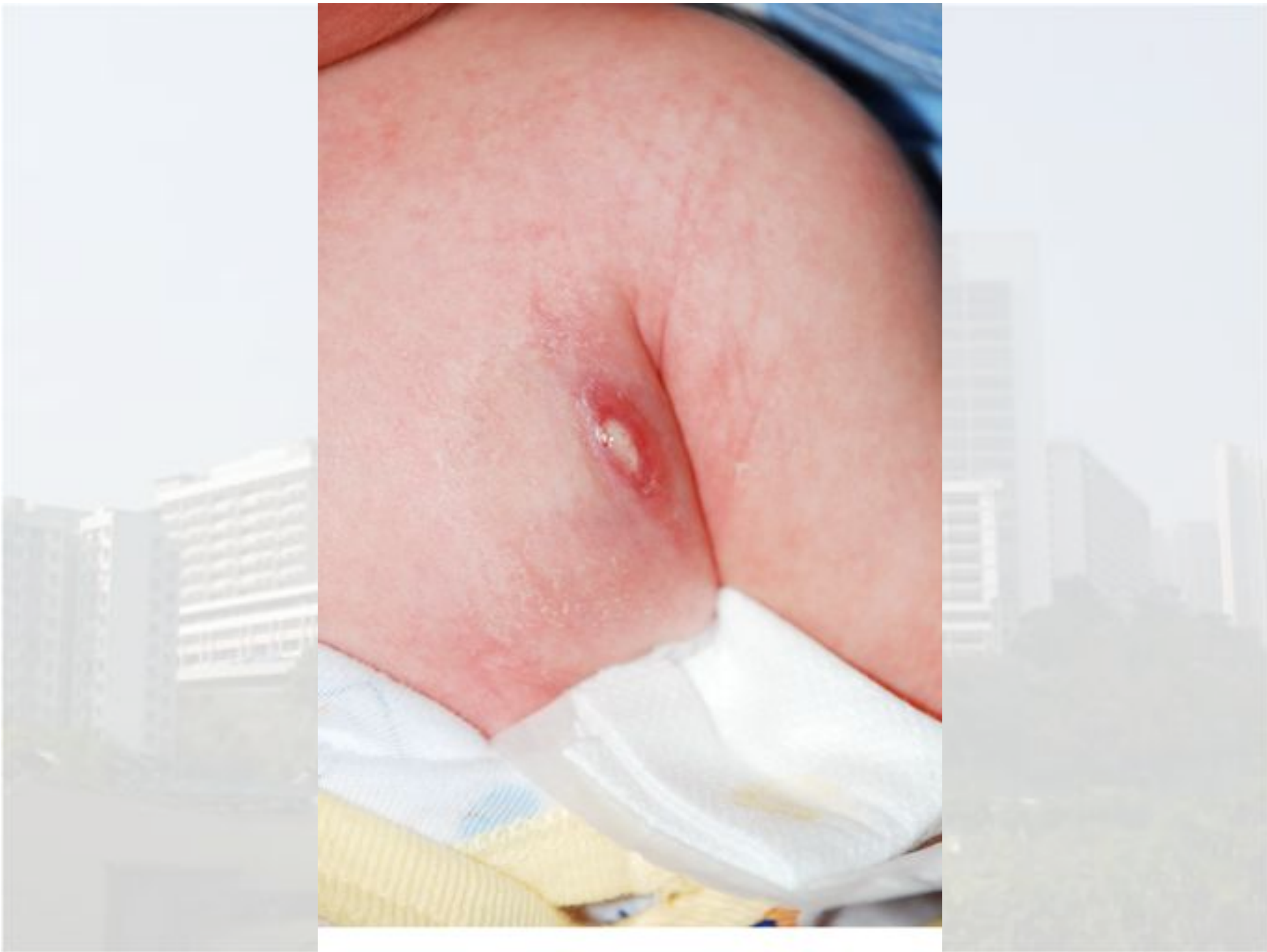
- Suppurative form<sup>22</sup>
  - Progressive enlargement of LNs
  - Collection of fluctuating material
  - Overlying skin change (universal)
    - Erythema
    - Edema
    - Pigmentation
    - Pustule formation







0000 3 26



# Diagnosis

- Basically clinical<sup>14,19</sup>
- Universal BCG vaccination at birth in HK
- Commonest age of presentation 2-5 months
  - Almost all Dx <2 y.o.
- Isolated TB axillary lymphadenitis extremely rare.

14. Helmick CG, D'Souza AJ, Goddard RN. An outbreak of severe BCG axillary lymphadenitis in Saint Lucia, 1982-1983. *West Indies Med J* 1986;35:12-7

19. Noah PK, Pande D, Johnson B, et al. Evaluation of oral erythromycin and local isoniazid instillation therapy in infants with *Bacillus Calmette-Guerin* lymphadenitis and abscesses. *Pediatr Infect Dis J* 1993;12:136-9

# Investigations

- Limited value
  - MT2:
    - should be +ve if normal immune function
    - Possible immune deficiency if -ve
  - CXR: no involvement in BCG related lymphadenitis



- Pus aspirate
  - Gram smear
  - Culture
  - AFB smear
  - AFB culture
  - Gene analysis
    - MTB PCR complex cannot differentiate MTB from BCG strain<sup>24</sup>

# Management

- 3 Rx options
  - Antibiotics
  - Needle aspiration
  - Surgical excision

# Antibiotics

- Anti-TB Rx & several antibiotics including erythromycin have been tried
- Well controlled trials:<sup>28,32</sup>
  - Cannot prevent suppuration
  - Cannot shorten the duration of healing
  - Indicated only if other bacterial superinfection

28. Caglayan S, Yegin O, Kayran K, et al. Is medical therapy effective for regional lymphadenitis following BCG vaccination? Am J Dis Child 1987;141:1213-4

31. Baki A, Oncü M, Usta S, Yildiz K, Karagüzel A Therapy of regional lymphadenitis following BCG vaccination. Infection. 1991 Nov-Dec;19(6):414-6

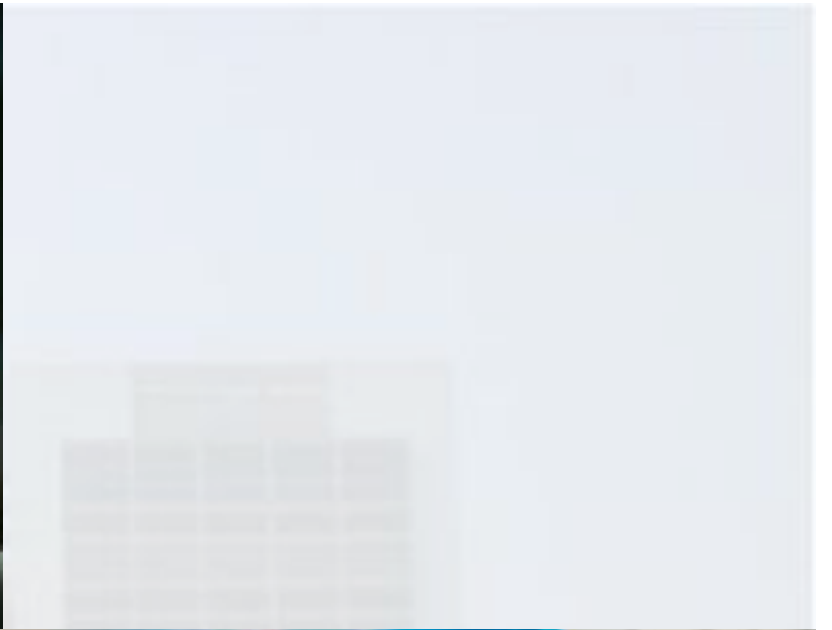
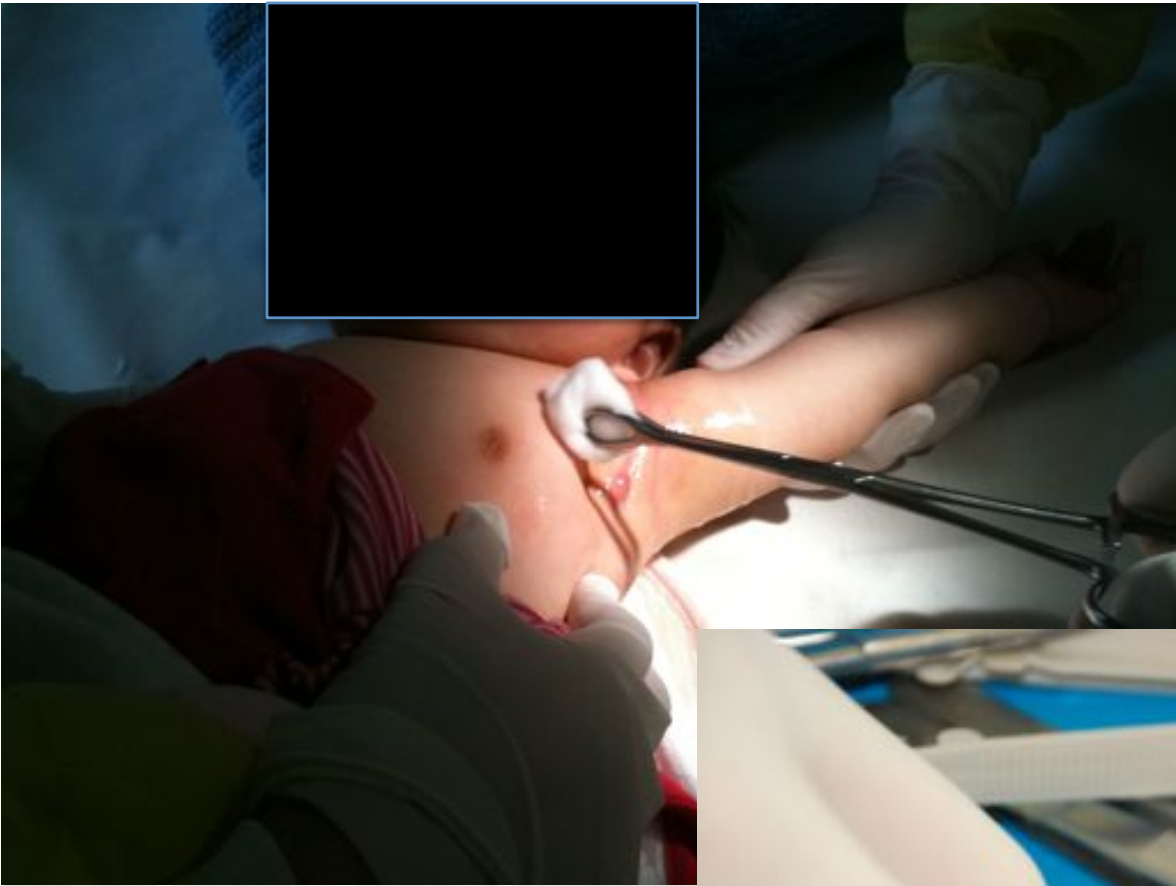
# Needle aspiration

- For suppurative type
- Prevent universal development of perforation & sinus formation (causing excessive scarring)<sup>33-35</sup>
- Shorten duration of healing
- Offer diagnostic information

33. Cagalayn S, Arikan A, Yaprak I, et al. Management of suppuration in regional lymph nodes secondary to BCG vaccination. *Acta Paediatr Jpn* 1991;33:699-702

35. Sataynarayana S, Mathur AD, Verma Y, Pradhan S, Bhandari MK. Needle aspiration as a diagnostic tool and therapeutic modality in suppurative lymphadenitis following Bacillus Calmette Guerin vaccination. *J Assoc Physicians India*. 2002 Jun; 50:788-91






- Randomized controlled trial by Banani et al:<sup>34</sup>
  - Significant higher chance of wound healing without surgical excision (95% vs 68%)
  - Shorter duration of recovery (6.7wks vs 11.8wks)
- Local instillation of isoniazid during needle aspiration<sup>19</sup>
  - Efficacy remains to be confirmed

34. Banani SA, Alborzi A. Needle aspiration for suppurative post-BCG adenitis. Arch Dis Child 1994;71:446-7

19. Noah PK, Pande D, Johnson B, et al. Evaluation of oral erythromycin and local isoniazid instillation therapy in infants with Bacillus Calmette-Guerin lymphadenitis and abscesses. Pediatr Infect Dis J 1993;12:136-9

- 
- Repeated aspirates are usually required
  - Wider bored needles preferred
    - Thick caseating material difficult to aspirate



# Surgical excision<sup>37</sup>

- Definitive removal of affected LNs
- Promote early cure
- Better wound healing c.f. I&D
- Risk of GA in infants and children
- As last resort for those multiloculated or matted LNs

# Incision & drainage

- Incision & drainage not recommended<sup>33, 37</sup>
  - Poor wound healing
  - Persistent discharge
  - Sinus formation
  - Scarring
  - Delayed recovery

33. Cagalayn S, Arikan A, Yaprak I, et al. Management of suppuration in regional lymph nodes secondary to BCG vaccination. *Acta Paediatr Jpn* 1991;33:699-702

37. Oguz F, Sidal M, Alper G, et al. Treatment of Bacillus Calmette-Guérin-associated lymphadenitis. *Pediatr Infect Dis J* 1992;10:887-8



	Non-suppurative	Suppurative
Clinical feature	Non fluctuant	Fluctuant
Clinical course	Benign	Prone to rupture
Management	Conservative	Needle Aspiration / Total Surgical Excision





Case Presentation  
continues...

# Progress of our patient

- CXR clear
- MT2 9mm induration
- Bedside Needle aspiration performed



- 0.5ml thick caseating material aspirated
  - Gram smear & culture –ve
  - AFB smear –ve
  - AFB culture *Mycobacterium bovis* +ve
- Wound healed soon after aspiration
- Daily dressing is not necessary
- Suppurative LN resolved in 2 weeks




Rx results

# Incision & Drainage

- Total N =5
  - Keloid formation =2
  - Scarring =5
    - Max scar 2cm diameter
    - Irregular
  - Wound healing (no further discharge)
    - Mean duration 4months
    - Range 3-6 months

# Needle Aspiration

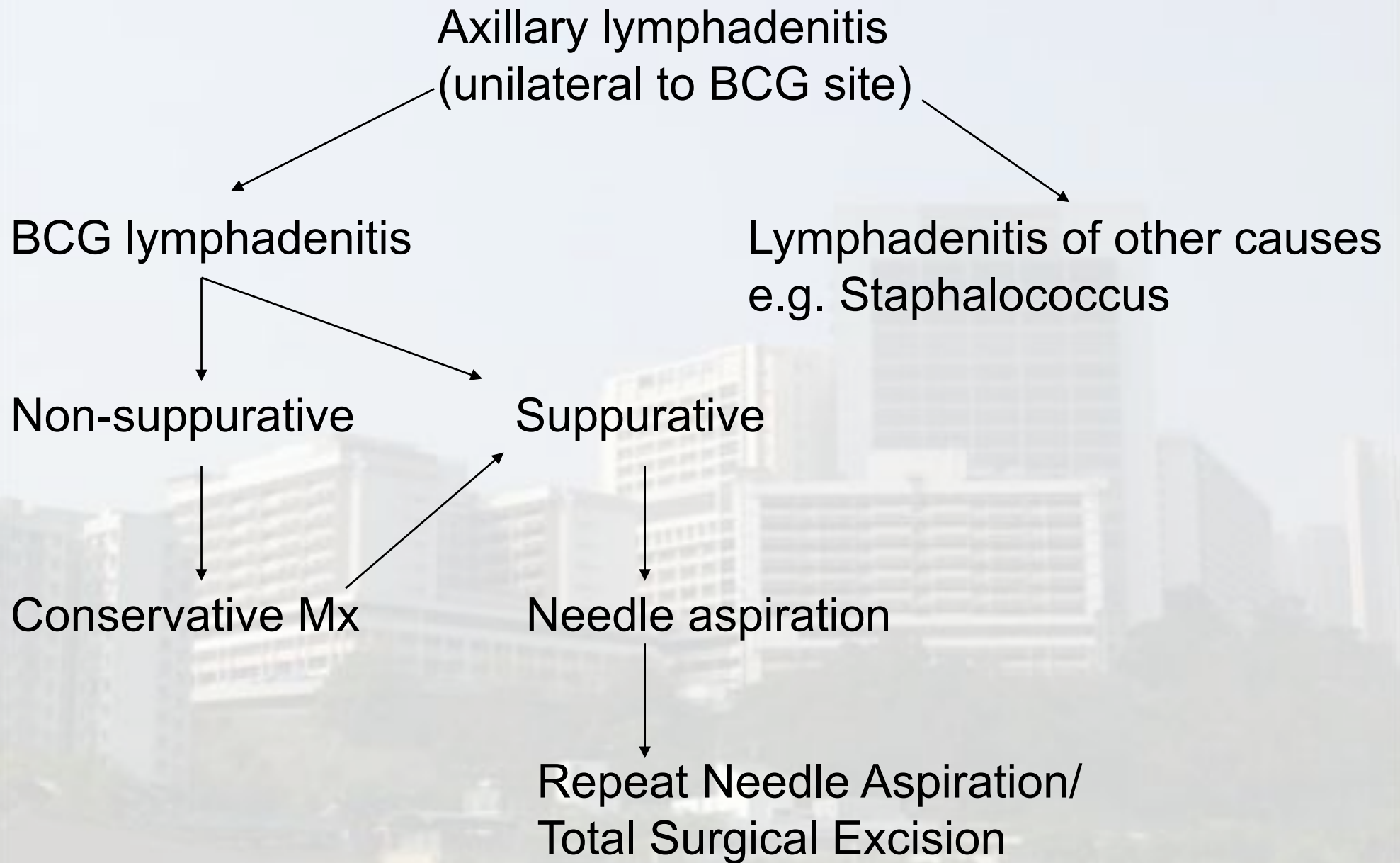
- Total N=6
- Complete resolution =2
  - In 2-4/52
  - No scarring
- LN resolving =3
  - 2.5 -> 0.2cm at 5 months
  - 1.5 -> 0.4cm at 3 months
  - 2 -> 0.5cm at 6 months
- Rupture of adjacent LNs =2
  - Spontaneously healed in 2-4 wks
  - Daily dressing

- 
- The background of the slide is a faded, light-colored photograph of a large, multi-story hospital building with many windows. The building is set against a clear sky, and there are some trees and a fence in the foreground, though they are also faded.
- Failed aspiration =1 (dry tap)
    - Referred for surgical excision
    - But I&D performed instead
    - Scarring ~2cm



# Spontaneous Rupture

- N = 1
  - Minimal discharge
  - Complete wound healing in 2/52
  - 3mm depressed scar



*Clinical Approach for BCG Lymphadenitis*

# Take home messages

- BCG lymphadenitis **clinical Dx**
  - Hx **BCG** vaccination
  - **Ipsilateral axillary** /cervical
  - **2-4 months** after BCG
  - **No fever / constitutional Sx**
  - **Minimal local** tenderness
- **Incision & drainage** should be **avoided**
- **Needle aspiration** vs total surgical excision
  - Needle aspiration prevent surgical & anaesthetic Cx in infants

# Acknowledgement

Patients & Parents

Dr. C W Leung

Consultant and Head, PID Team

Dr. Y W Kwan

Associate Consultant, PID Team

Nursing staff



Thank you