Leprosy
Hansens disease: whats up

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IC Forum

History of stigma in Leprosy Lep Rev 2014; 85:36-47.

- Chronic disease with long history: described in Egyptian papyrus 1550 BC; India writings 600 BC
- Believed to be brought into Europe from India by the army of Alexander the Great
- Cause of leprosy thought to be a punishment for the sufferers'sins
- This belief persists today in some areas eg. Nepal , Nigeria, Indonesia

Leprosy

- Chronic infectious disease due to *Mycobacterium leprae*
- Neurotropic acid fast bacillus
- Affects mainly the skin and nerves
- Incubation period : up to usually 2-5 years; short incubation: months;

  long incubation period: 10 years

Leprosy

- Spread by
1. Droplet, inhalation of bacilli (nasal mucosa),
2. Via open wound
- Sub-clinical infection on initial exposure (cf Ghon focus in TB)

Evolution of leprosy

Leprosy for medical practitioners and paramedical workers SJ Yawalkar

- Clinical manifestation depends on immune status of the patient
- Disease fails to develop in 95% cases
- Indeterminate leprosy : vague hypopigmented patches
- Indeterminate leprosy (未定類麻風)may either:

1. Heal spontaneously or
2. Persist as indeterminate leprosy or
3. Evolve into definite leprosy (see below)

- Leprosy is divided into two poles depending on the cell-mediated immunity (CMI)

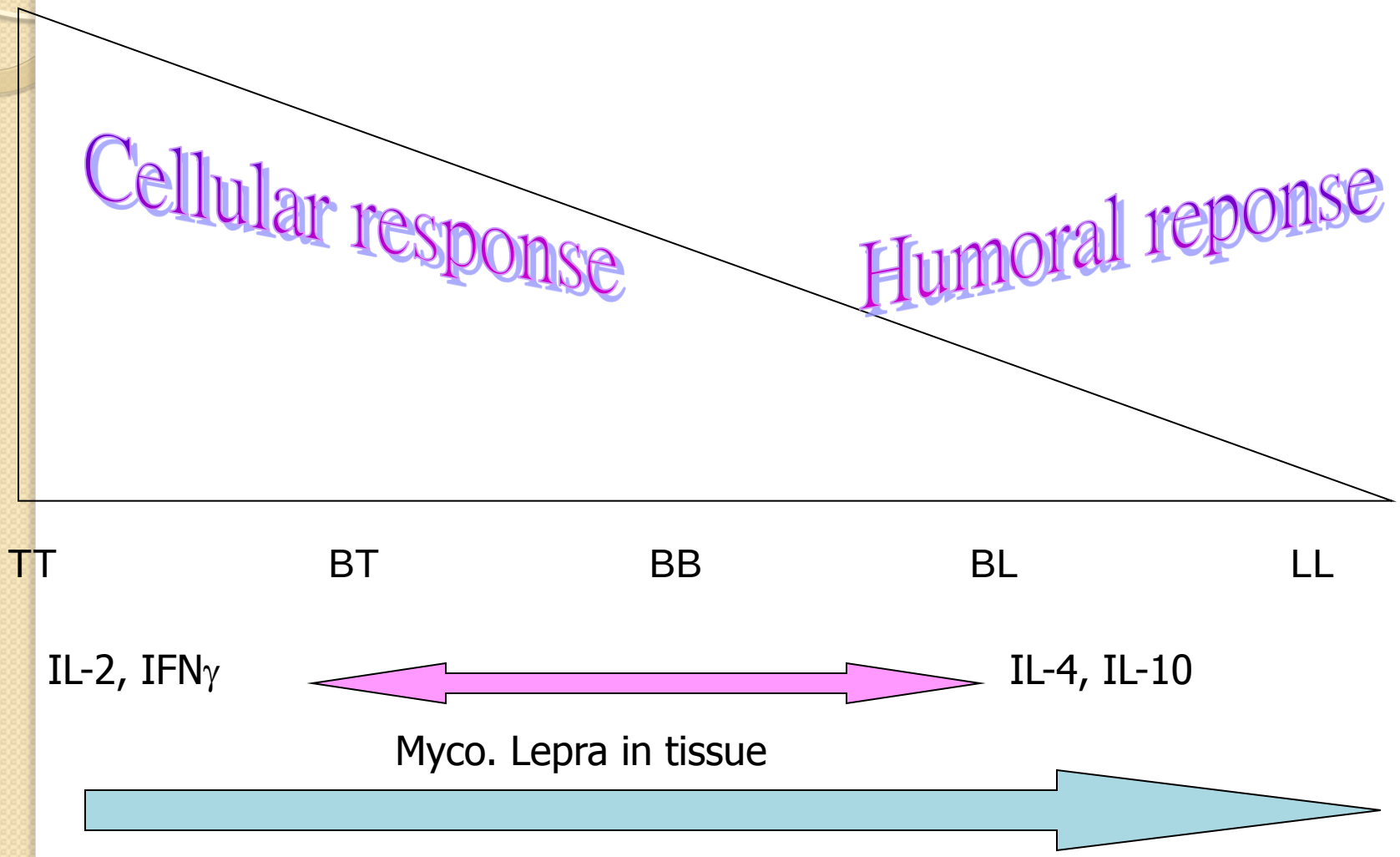
1. PAUCIBACILLARY LEPROSY (PB)少菌型: Strong cell-mediated immunity (CMI)(細胞介導免疫) where no bacilli are seen on skin smear (smear negative).

- Spontaneous healing occasionally

2. MULTIBACILLARY LEPROSY (MB)多菌型 cases, CMI is weak and bacilli are seen on skin smear .

3. BORDERLINE SUBTYPES: Unstable forms inbetween the two poles-particularly associated with LEPRA REACTIONS.

Clinico-immunologic spectrum of leprosy



Classification of leprosy (Ridley & Jopling 1966)

- Tuberculoid (TT)結核樣麻風病
- Borderline tuberculoid (BT)界綫類偏結核性麻風
- Borderline (BB)中間界綫麻風
- Borderline lepromatous (BL)界綫類偏瘤型麻風
- Lepromatous (LL)瘤型麻風

Tuberculoid leprosy: clinical features

- Isolated lesions
- Peripheral nerve enlargement
- Isolated anaesthetic patches
- Well-formed granulomas (肉芽腫) :epithelioid cells, Langerhans giant cells, no AFBs present
- Few or no bacilli in the skin lesions: smear negative
- No particular site

Lepromatous leprosy

- Generalised lesions: skin, lung, testes, adrenal glands, upper respiratory system
- granuloma consisting of macrophages containing numerous AFB
- Macrophages that do not differentiate into epithelioid histiocytes that fail to clear AFB
- Numerous bacilli in the lesions: smear often positive
- Papules, macules, plaques,
- Face, arms, earlobes, buttocks

Borderline (diamorphic) leprosy

- Unstable form: changes in immunity can lead to reversal reactions and nerve damage
- Borderline tuberculoid (BT):

1. Resemble tuberculoid leprosy fewer lesions
2. Tuberculoid granuloma, few GC, subepidermal granuloma-free Grenz zone

- Borderline (BB):

1. Annular lesions, asymmetrical
2. Granuloma less well-formed, Grenz zone

Borderline lepromatous leprosy

- Borderline lepromatous (BL):

1. Resemble LL with more extensive less well-defined lesions:
2. Shiny macules, papules, nodules with sloping edges
3. Anaesthesia, decreased sweating in the lesions
4. Grenz zone, foamy macrophages with granular cytoplasm

History:points to note

- HPI: Duration

Pain, arthralgia, any previous treatment,

PH: liver disease, G6PD, alcohol, blood disorder

DH: drug interaction with MDT

Social history: how long in HK, contacts, country of origin,

FH: family contacts

Physical examination

- Distribution of lesions:
- Localised, well-defined: paucibacillary

- Widespread, ill-defined lesions :multibacillary

- Annular:borderline

Physical examination

- Nerve enlargement sites: check
- Neck:greater auricular nerve
- Arms: ulnar, median, radial nerve
- Leg: lateral popliteal nerve
- Ankle: posterior tibial nerve

- Nerves enlarged in:

1. Tuberculoid leprosy
2. Type I reaction (tender)

Physical examination:deformities

- Eyes: ectropion, lagopthlamos, uveitis
- Hands and feet: claw hand, muscle wasting, neuropathic joint
- Ulceration: chronic neuropathic/trophic ulcers at finger, shins, feet
- Look out for malignant change in chronic ulcers

WHO grading of deformities

Grade	Hands and feet	Eyes
0	No anaesthaesia No visible deformity or damage	Normal vision No damage
1	Anaesthaesia present. No visible deformity	Eyes affected: vision >6/60 or better or patient can count fingers at 6 metres
2	Visible deformity	VA<6/60, unable to count fingers at 6 metres

Investigations

- CBP d/c, reticulocyte count
- RLFT
- G6PD: dapsone in MDT
- EIA-TP
- CXR: look x PTB
- HbsAg
- Skin smear: eyebrows, ears selected skin lesions
- Skin biopsy: to confirm diagnosis

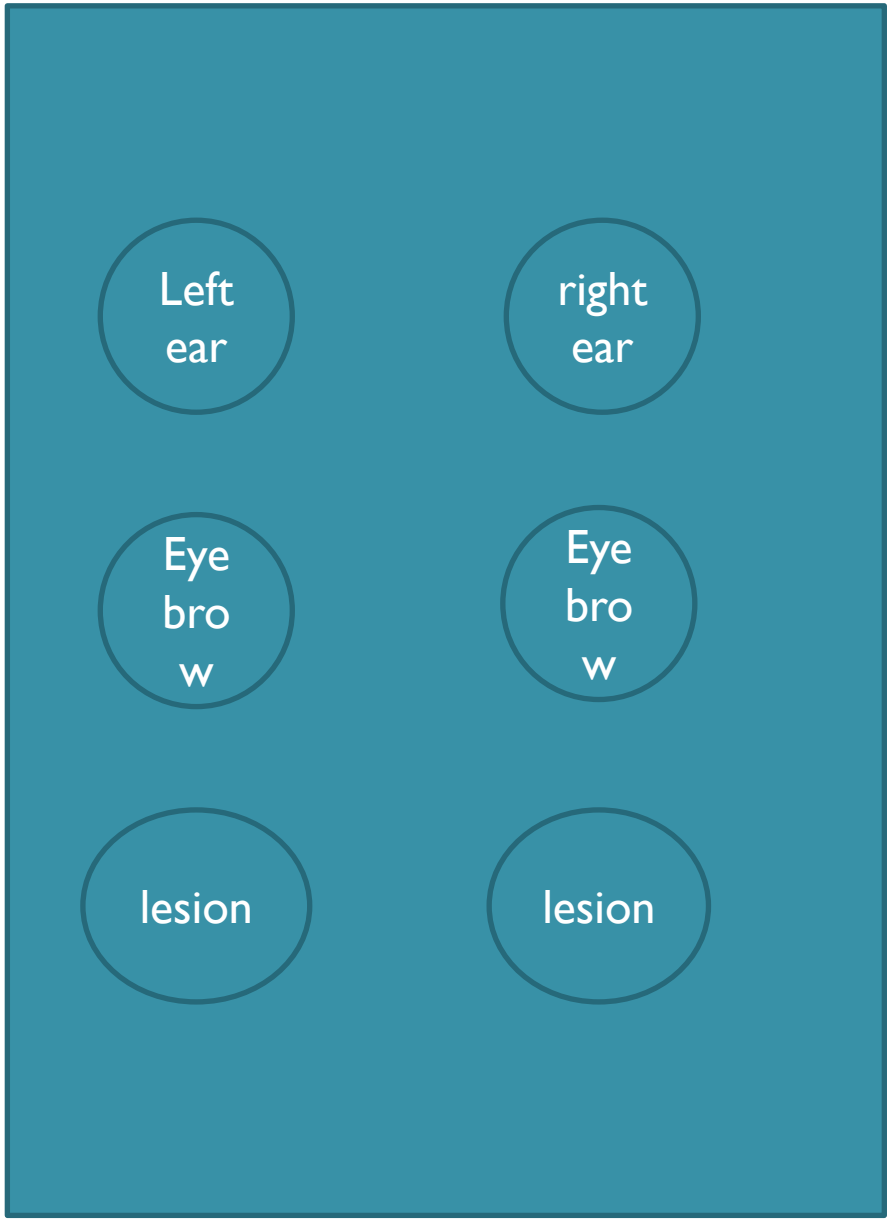
Skin smear

- Index case:
- Both ears; eyebrow; skin lesion, ENL lesions

- Contact case: both ears both eyebrows

Skin smear

- Pinch sampling site
- Incision with no.15 blade (1mm deep, 3-5 mm long
- Scrape the sides of the incision with the blade
- Transfer the serum onto the glass slide
- Avoid contamination with blood
- Stain glass slide with Ziehl Neelson method



Skin smear: Bacteriological index

- Bacteriological index : density of bacilli (living (solid staining) and dead (fragmented)
- Logarithmic index 0 (no bacilli in any of 100 oil-immersion fields) >> 6 (>1000 bacilli on average in immersion field)
- Average index of examined sites/number of sites=BI

Skin smear: Morphological index

- Morphological index:% of living bacilli to the total number of bacilli
- Calculated by examining 200 free standing bacilli
- Indicates response to treatment and infectivity

WHO MDT

- **Paucibacillary(PB) leprosy MDT**

1. Dapsone 100mg/day
2. Rifampicin 600mg/month

- For six months

- May be given as WHO-MDT blister packs

WHO MDT

- **Multibacillary (MB) leprosy**
- For adults the standard regimen is:

1. Rifampicin: 600 mg once a month
2. Dapsone: 100 mg daily
3. Clofazimine: 50 mg daily
4. Clofazimine 300 mg once a month

Duration= 24 months.

WHO MDT children

1. PB MDT

a. Child (10 - 14 years)	Dapsone 50 mg daily Given daily	Rifampicin 450 mg/ month Given once a month under supervision
b. Child < 10 years. Under supervision:	Dapsone 25 mg daily Rifampicin 300 mg/month	

2. MB-MDT

a. Child (10-14 years) Under supervision:	Dapsone 50 mg daily Rifampicin 450 mg /month	Clofazimine 50 mg daily Clofazimine 150 mg /month
b. Child <10 years. Under supervision:	Dapsone 25 mg daily Clofazimine 50 mg given twice a week, and Clofazimine 100 mg /month under supervision	Rifampicin 300 mg /month

Treatment

- MDT 2nd line:

1. Ofloxacin 400mg /day
2. Minocin 100mg/day
3. Klacid 250mgbd

Monitoring of treatment

- Monitor for ↑LFT,renal function ↓CBP especially at start of MDT
- Monitor for dapsone hypersensitivity syndrome:fever, rash, hepatitis, lymphadenopathy,hepatomegaly (Thailand: incidence DDS hypersensitivity:1982-1988:3.6%)

Counselling

- Important part of the management
- Establishes basis for patient compliance and contact referral

Counselling:major points

- Leprosy used to be untreatable leading to deformities via nerve damage and loss of sensation
- The leprosy bacilli do not lead to deformity directly

- Deformities can be avoided with timely treatment
- Most people are unaware of this; leprosy remains a feared and stigmatized disease

Counselling

- Leprosy is transmissible but the infectivity rate is not high
- Close contacts are recommended to come for screening
- Contact referral is done by the patient voluntarily
- The diagnosis of leprosy will not be disclosed by our clinic

Type I (reversal) reaction

- Type I: swelling, eythema, oedema, tenderness in pre-existing lesions, +/-fever
- Ulceration, necrosis if severe
- Look for painful swollen nerves, oedema of hands, face, feet
- May lead to permanent nerve damage if not treated promptly →claw hand, foot drop, facial palsy
- May present with sudden onset of numbness without skin signs

Type I reaction

- More common in borderline leprosy :BT, BB,BL: unstable forms
- Upgrading reaction (→ TT pole) usually in the first **6/12 of Tx** in BT, BB cases
- Downgrading (→LL pole) in **untreated cases**, or if treatment interrupted
- Due to alteration (increase or decrease) in CMI

Type I reaction: management

- Systemic steroids: prednisolone 40-60mg/day
- (ACTH(Cortrosyn) injections used to be given in KH)
- Efficacy of lamprene in reversal reaction not definite, may be helpful
- MDT continued

Type I reaction

- Gradually tail down systemic steroids by 5-10 mg every 2-4 weeks according to response
- Final dose prednisolone 5mg/day for at least 2/52

- Usually 3-6/12 systemic steroids required

Reversal reaction vs relapse

Characteristic	Reversal reaction	Relapse
Onset	Sudden onset	Slow onset
Time of presentation	During Tx or <6/12 of stopping Tx	Onset months after Tx stopped
Clinical lesions	Pre-existing lesions may become swollen, shiny, erythematous; new lesions may occur	Edges of lesions may become erythematous
Ulceration	Occasional	Unusual
Corticosteroids	Good response	Not indicated; lesions may resolve but recur
Nerve involvement	Nerves rapidly become painful; rapid onset of nerve deficit	Neurological damage occurs insidiously

Type II reaction/ENL

- LL cases, occ BL
- Immune complex Ag/Ab complexes
- Said to occur later in the course of Tx as compared to reversal reaction
- Crops of erythematous/pink nodules EN-like but generalised distribution
- Fever, malaise common
- May be intermittent or continuous

Type II (cont)

- ENL may be assoc with oedema of face, hands, feet
- Paralysis may occur
- Nerve damage not as rapid as reversal reaction
- Assoc with uveitis, orchitis, joint pain, bone pain (tibia), proteinuria, lymphadenitis, muscle pain, epistaxis

Management

- Examination: EN-like nodules on the limbs, check
- the eyes etc to look for involvement of other organs
- nerve enlargement
- Start Prednisolone 20-40mg/day
- Gradually taper off over the next few weeks depending on response

Management: ENL

- Continue MDT
- If prednisolone does not control the ENL,
- may add lamprene up to 300 mg/day for up to 3/12
- Thalidomide for resistant cases

Management ENL

- Thalidomide: for resistant cases: s/e teratogenicity, peripheral neuropathy, drowsiness, thromobembolism
- need nerve conduction studies
- Chloroquine, analgesics, rest helpful in mild intermittent cases

Current issues

- Continuing prejudice, discimination: patients therefore unwilling to refer contacts or receive treatment
- Leprosy now uncommon, easily missed diagnosis
- Drug resistance: need to ensure that treatment is completed

Drug resistance

- Dapsone resistance: first cases detected in 1964 : two single nucleotide polymorphisms (SNPs) in the gene *folP 1*
- Rifampin resistance: mutations in gene *rpoB*
- Ofloxacin resistance: SNPs in *gyrA* and *gyrB*

Drug and Multidrug Resistance among *Mycobacterium leprae* Isolates from Brazilian Relapsed Leprosy Patients J Clin Microbiol. 2012 Jun; 50(6): 1912–1917.

- 92 relapse leprosy cases in Brazil
- Sequence analysis of part of the genes associated with *Mycobacterium leprae* drug resistance in skin biopsy samples
- 4 of 92 cases (4.3%) : Single nucleotide polymorphisms in genes associated with drug resistance in *M. leprae*

1. 1 case with a mutation in *rpoB* (RIF resistasnce)
2. 1 case sample with SNPs in both *folP1* (DDS) and *rpoB* (RIF)
3. Multidrug resistance: 2 cases with mutations in *folP1*, *rpoB*, and *gyrA* (RIF, DDS, OFL)

Drug resistant cases: WHO recommendations

- Dapsone resistance: continue MB-MDT

- Rifampicin or Rifampicin + Dapsone resistance: for Ofloxacin 400 mg om, clofazimine 50 mg om, minocycline 100 mg om for 6 months FOLLOWED BY
- Clofazimine 50 mg om, ofloxacin 400 mg om, OR minocycline 100 mg om for 6 months for at least another 18 months

Global leprosy update 2015

Elimination of Leprosy 2016;82:8, WHO Leprosy Fact sheet. who.int

- 94% new cases reported from 14 countries
- Global new case burden:

1. India: 60% (127,326 new cases)
2. Brazil 13% (26,395 new cases)
3. Indonesia 8% (17,202 new cases)

Incidence of new cases globally

WHO leprosy fact sheet who.int

Year	New cases reported globally
2015	211,978
2014	213,899
2013	215,656

Stigma in leprosy

- Stigma developed from centuries of misconception superstition and fear of leprosy
- Discriminatory laws against leprosy sufferers were passed in some countries in the past (leprosy constitutes grounds for divorce m.timesofindia.com); many countries have abolished such laws
- Education of the public of the new situation of this condition and of the improved outlook is needed

Global situation

- Around 214, 000 new leprosy cases detected each year
- Elimination defined as prevalence rate <1 case/10,000 population
- Need to monitor:

1. The incidence of new cases with Grade 2 disability
2. New child cases of leprosy

WHO Global Leprosy Strategy 2016-2020

1. **Focus on early case detection before visible disabilities** occur. For earlier detection and reduction of patients with grade-2 disabilities (G2D) at the time of diagnosis. The target of G2D rate is less than one per million population.
2. **Special focus will be on children** as a way to reduce disabilities and reduce transmission. The target is zero disabilities among new paediatric patients by 2020.
3. **Target detection among higher risk groups** : conducting campaigns in endemic areas or communities; and improving coverage for marginalized populations. Develop national plans to ensure screening of all close contacts, especially household contacts.
4. **Shorter, uniform treatment regimen** promoted for all types of leprosy based on clinical data
5. **Incorporate specific interventions against stigma** and discrimination due to leprosy by establishing effective collaboration and networks to address relevant technical, operational and social issues which will benefit persons affected by leprosy.

WHO new recommendation

- Since 1998, WHO MB-MDT shortened to one year
- PB-MDT unchanged (six month regimen)

Single-dose ROM trial for paucibacillary leprosy

- Single dose (ROM)
- has been used to treat skin smear negative PB cases also recommended by WHO:

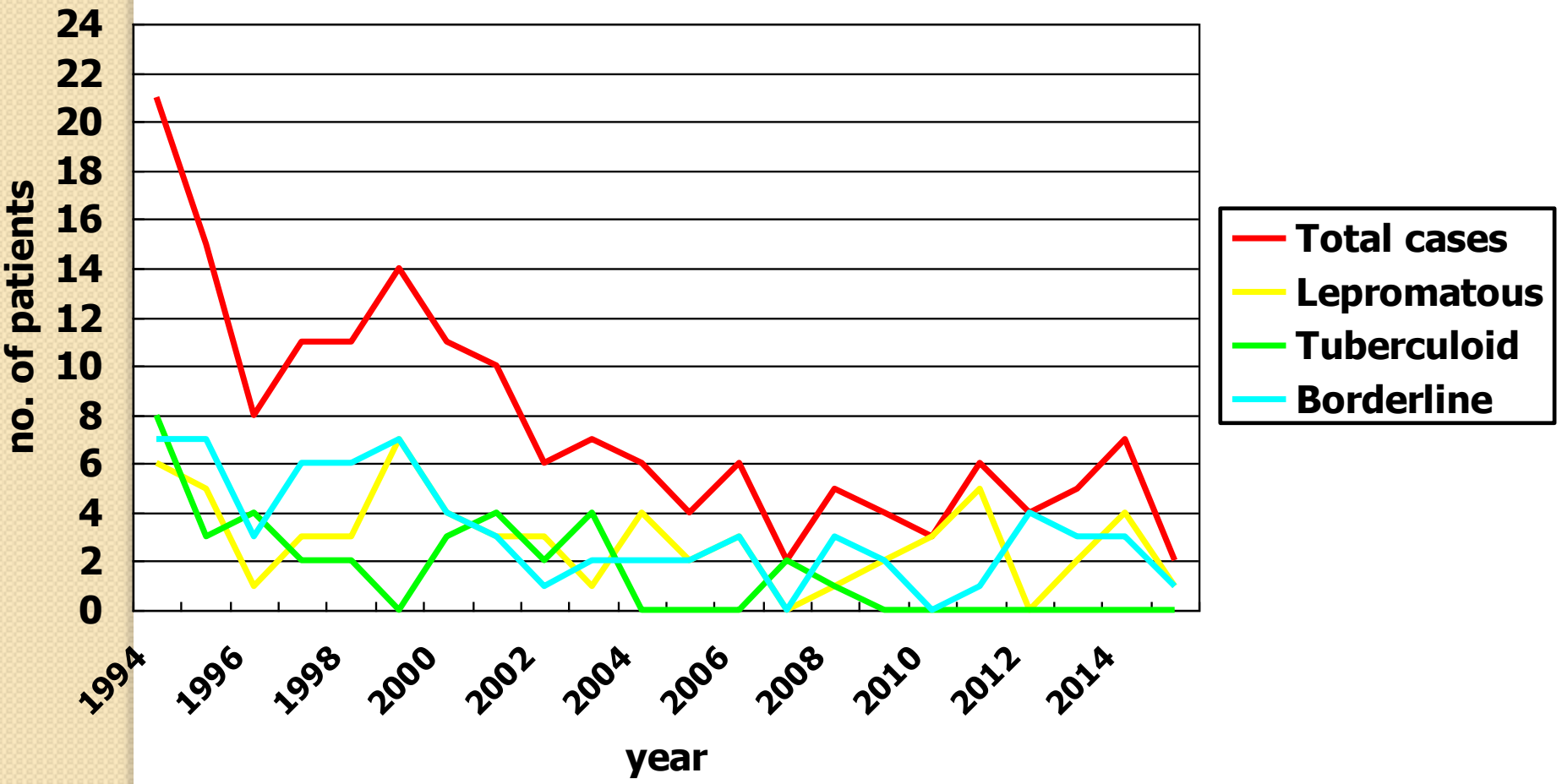
1. Rifampicin 600 mg
2. Ofloxacin 400 mg
3. Minocycline 100 mg

Hong Kong leprosy new cases

- Prevalence rate/Detection rate <1/10, 000 population since mid-1980s
- In the past 5 years, new leprosy cases mainly from:

1. Indonesia
2. Philippines
3. China

Annual incidence of leprosy in SHS



Summary

- Leprosy is now treatable
- The incidence of leprosy globally is under control at present
- Drug resistance and continued stigmatization may compromise leprosy control
- Leprosy is uncommon in HK

THANK YOU