Mycobacterium tuberculosis revisited Challenges in 21st Century

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Outline

- Epidemiology
- Control strategies and limitations
- Drug resistance and implications

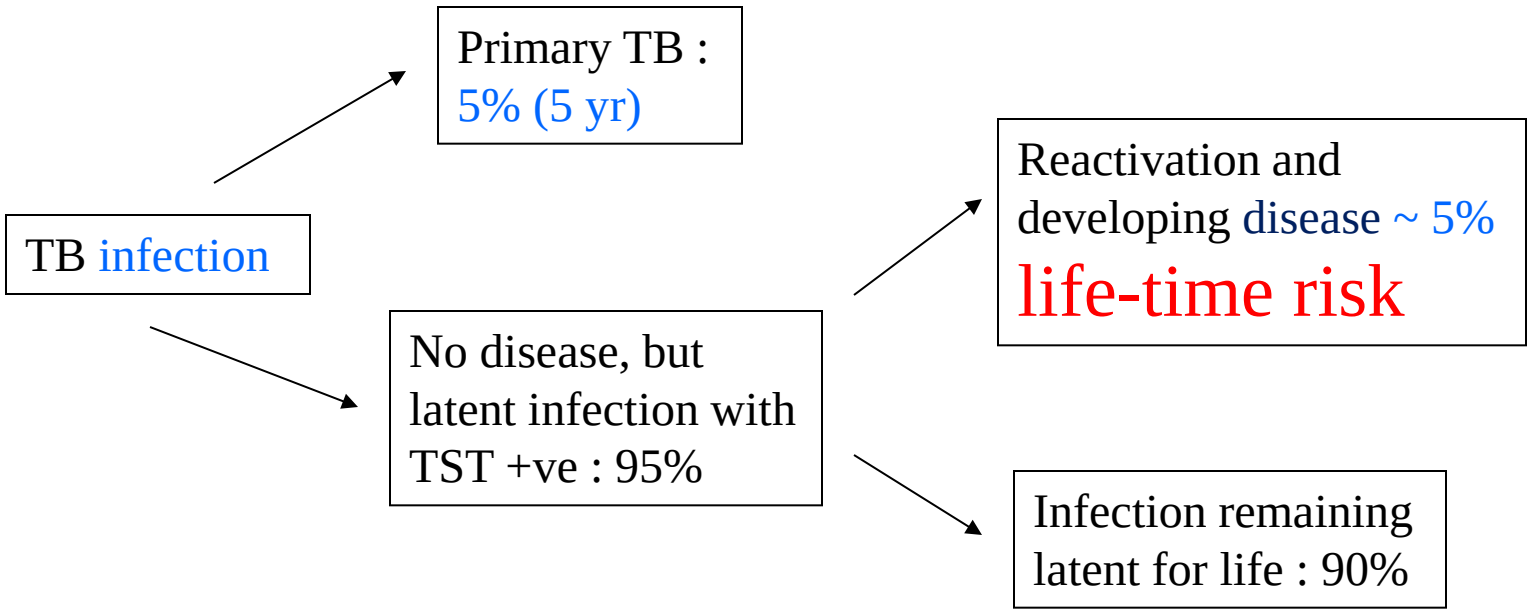
Mycobacterium tuberculosis complex

- Longstanding co-existence
  - Genetic sequence study: 70,000 years of co-evolution with *Homo sapiens* (Comas et al. Nat Genet. 2013;45:1176-82)
  - Fragments of the spinal column from Egyptian mummies show evidence of tuberculosis (TB) over 4000 years ago.

- Large-scale TB epidemics peaking asynchronously in different continents in recent centuries
  - Epidemic curve spanning roughly 300 years in Europe
  - Natural decline observed before chemotherapy
    - TB mortality dropped by 1.71% per year in UK from 1853 to 1910: ? socio-economic improvement and / or natural selection (Davies et al. Int J Tuberc Lung Dis. 1999; 3:1051-4)

Natural history of tuberculosis

Exposure → Infection → Disease

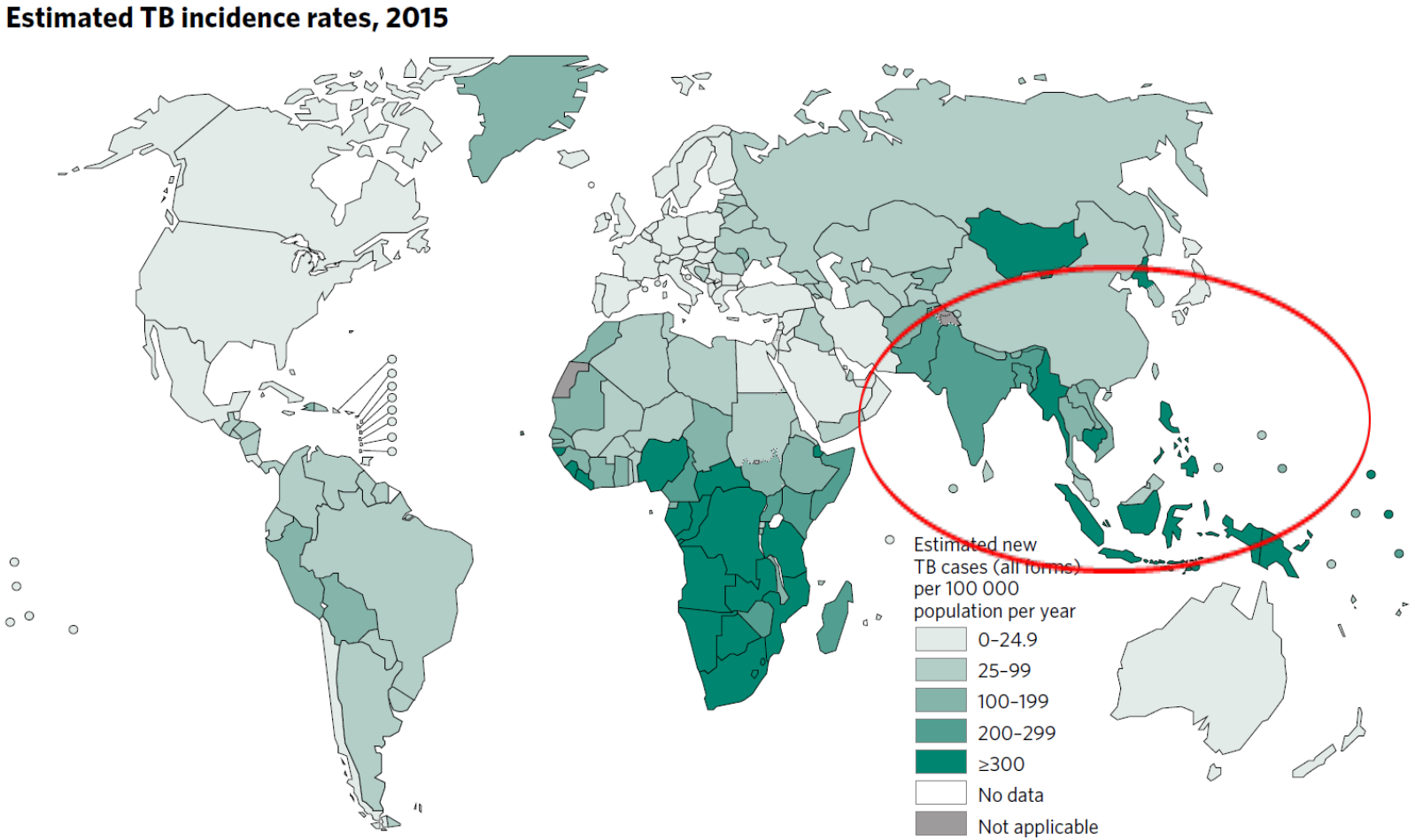


Global TB Burden (2015)

- 10.4 million cases (estimated)
  - Including 1.2 million HIV+TB
  - 60% of TB cases in
    - China, India, Indonesia, Nigeria, Pakistan, South Africa
- 1.8 million deaths
  - Including 0.4 million death in HIV+TB
- Latent TB Infection
  - 1/3 of global population

Global TB Situation 2015

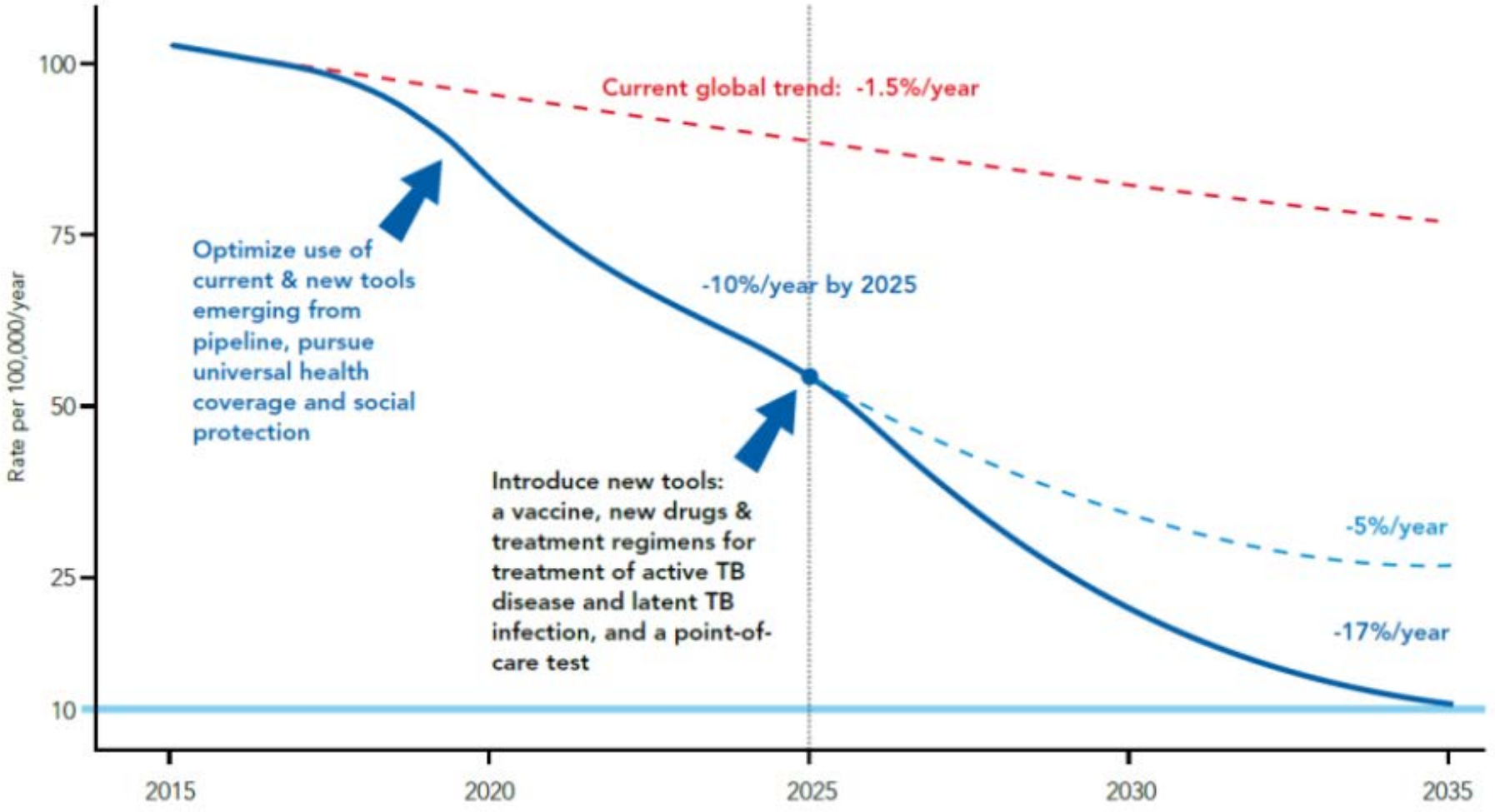
(From WHO Global TB Report 2016)



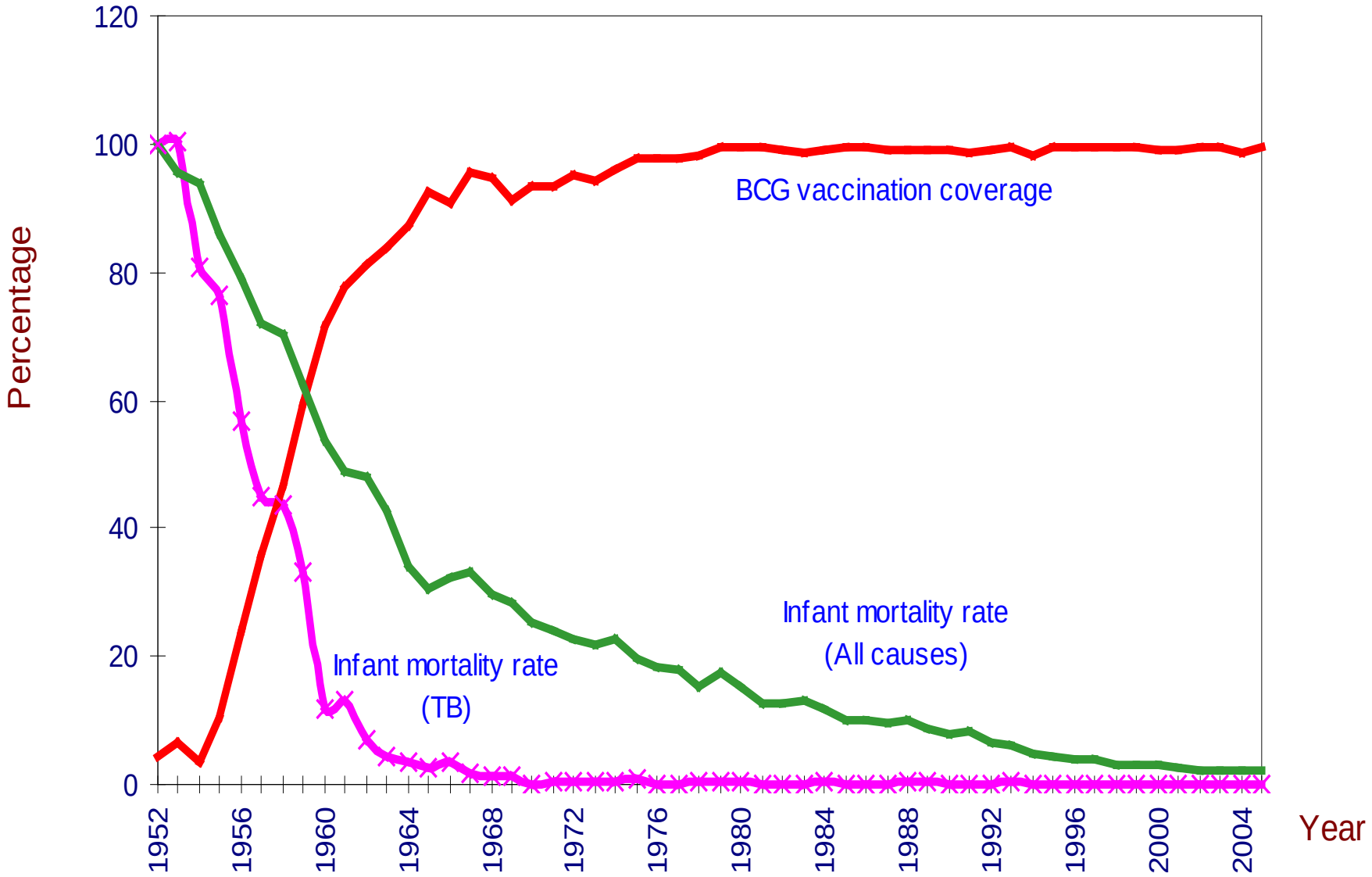
Post-2015 Targets

- 2015 (West Pacific and Southeast Asia)
  - TB death rate: ~ 15 /100 000
  - TB incidence: ~ 135 / 100 000
- 2025
  - 75% reduction in TB deaths
  - 50% reduction in TB incidence (<55 / 100 000)
- 2035
  - 95% reduction in TB deaths
  - 90% reduction in TB incidence (<10 / 100 000)
- 2025 / 2035
  - No affected families face catastrophic costs
- 2050: ?? Elimination (TB incidence < 1 / 1 000 000)

WHO END TB Strategy: Projections



BCG vaccinatiion (Hong Kong)



TB Vaccines

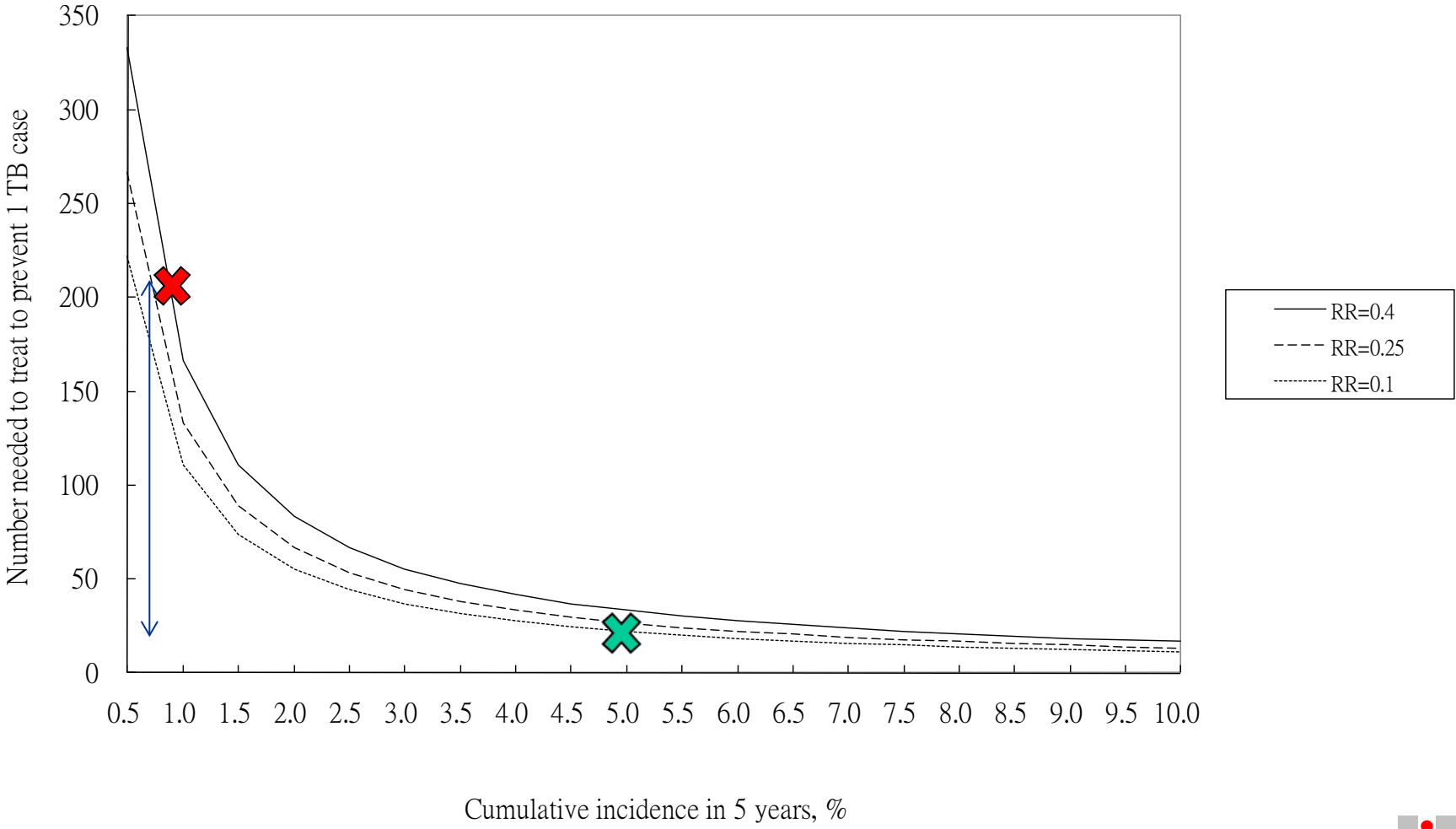
- Vaccines as a control tool
  - Easier to apply on a huge population scale and NOT affected by the emerging drug resistance
- Existing BCG vaccine: partial and unreliable protection against pulmonary TB in adults, the crucial transmission link.
- Require major breakthroughs
  - Natural infection: No long-lasting immunity
  - Conventional “Identify, Inactivate / Attenuate, Administer” approach does NOT work

Screening and Treatment of LTBI (HK)

- With the limitations of current diagnostic and treatment tools, a targeted approach is adopted for high-risk groups as defined locally
  - High disease risk / consequence (epidemiological data)
  - To screen = Intention to treat if positive
- TST: varying cutoffs
  - Household contacts (smear+ source), esp<35
    - 15mm, 5mm if under 1 yr
  - HIV (5mm)
  - Silicosis (10mm)
  - Immunosuppression/TNF blocker (10mm before/5mm on Rx)
    - usually not considered necessary after adequate curative TB Rx
- IGRA
  - Selected cases (avoid BCG interference / ? elderly)

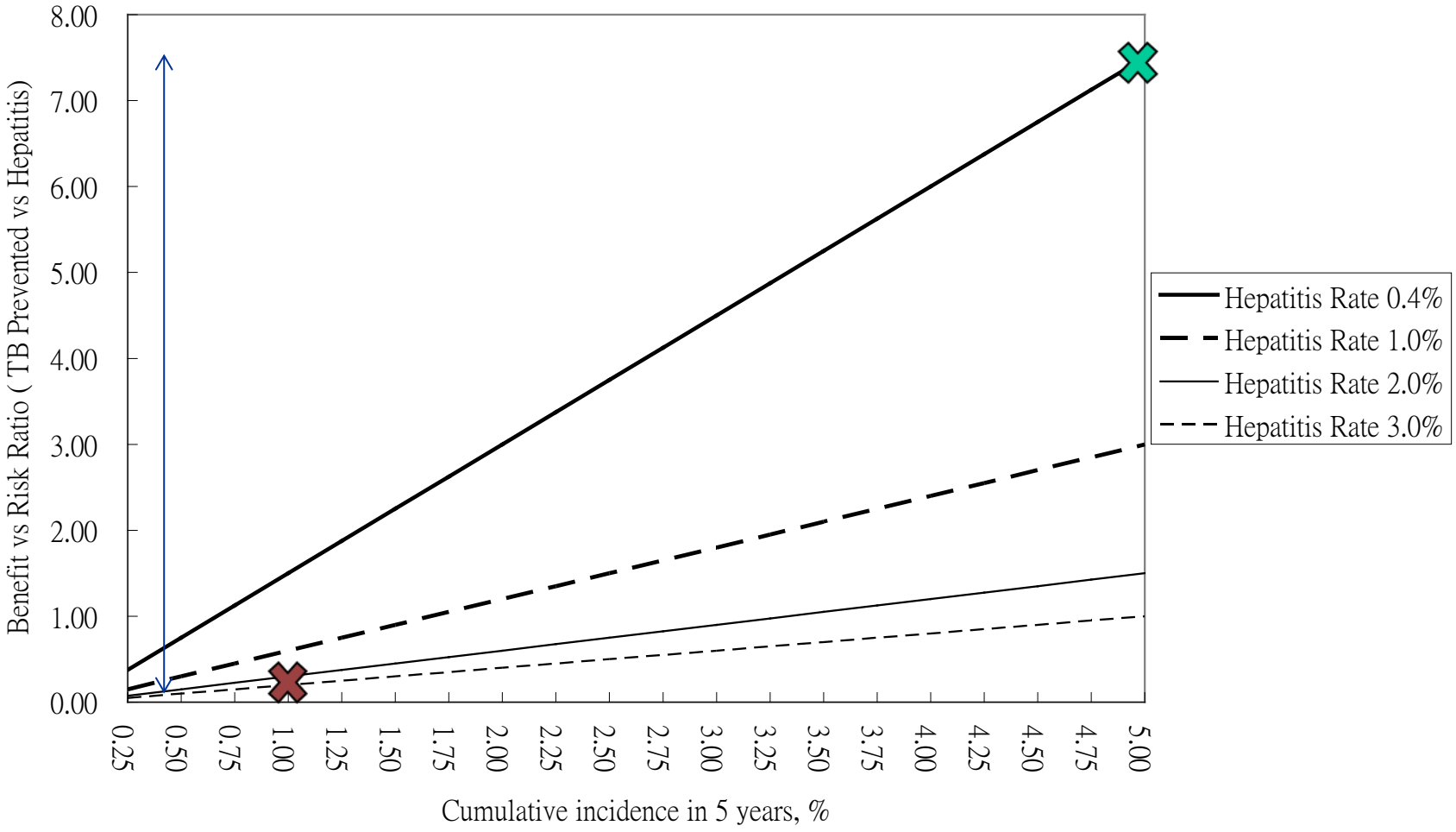
NNT to prevent 1 TB case in 5 years

Leung CC et al. Eur Respir J. 2011;37:690-711



Benefit versus Risk

Leung CC et al. Eur Respir J. 2011;37:690-711



Preventive Treatment

- Targeted screening and treatment of LTBI with the currently available immunodiagnostic tools and treatment regimens aims mainly for personal protection.
- Even with possible future tool refinements, the need to screen the entire global population and treat 1/3 of them would be formidable.

Current Control Strategy

- With limitations in available tools, the current emphasis is on Source Control by Case-finding and Treatment
  - 70% detection of infectious (smear-positive) TB cases and 85% treatment success required to reduce TB burden progressively:
  - Partial treatment
    - Reduces case-fatality but
    - Increases chronic excreters and
    - Emergence of drug resistance

Prompt treatment rapidly controls infectivity

- Quantitative sputum culture for TB patient on treatment (Am Rev Respir Dis 1980)
  - Before treatment: 10^6 to 10^7 bacilli per ml of sputum
  - 7 days → viable bacilli fall by 2 log
  - 14 days; < 10^4 bacilli

- Studies using guinea pigs to quantify the transmission risk in hospital wards demonstrated that effective treatment terminates transmission within days of initiation Riley R, et al. Am Rev Respir Dis 1962; 84: 511–525

- Wells Riley equation

  $P = 1 - e^{-Jqpt/Q}$

  ↓ J = no of infectors

  ↓ q = quantum of infectious particles

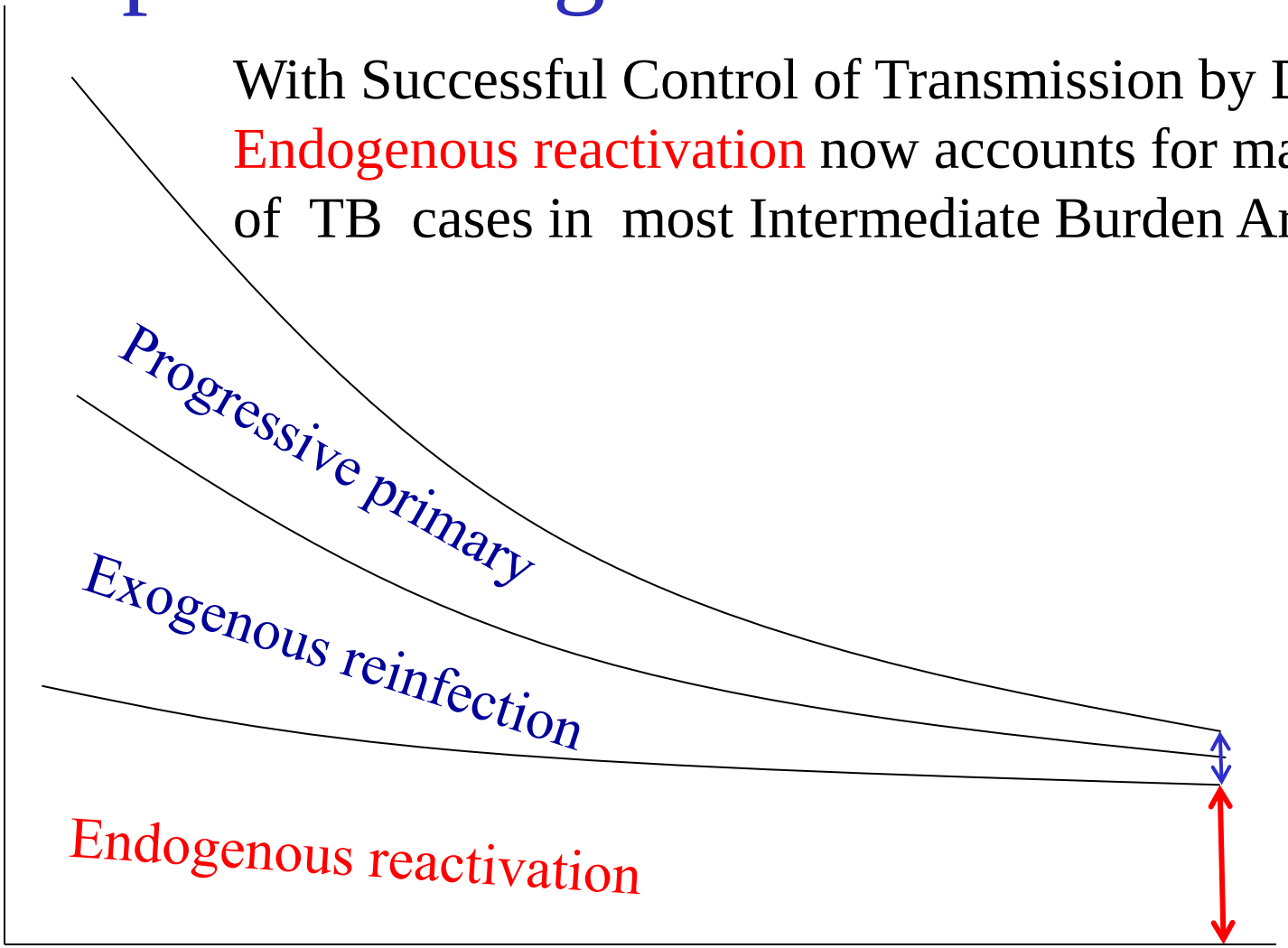
  ↓ t = time

Limitations

- Diagnosis
  - Variable presentation + overlapping clinical and radiological features with other diseases
  - Sputum microscopy lacks sensitivity (~50%)
    - Esp in Children / HIV-infected
  - Conventional culture and drug susceptibility test
    - Slow (4-8 weeks + 2-4 weeks)
- Treatment
  - Long duration and complex regimen
    - adherence problem / medication errors, resulting in failure / relapse and resistance

Epidemiological Transition

With Successful Control of Transmission by DOTS, Endogenous reactivation now accounts for majority of TB cases in most Intermediate Burden Areas



TB from Recent Transmission

JOURNAL OF CLINICAL MICROBIOLOGY, June 2003, p. 2706–2708 Vol. 41, No. 6
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.6.2706–2708.2003

Molecular and Conventional Epidemiology of Tuberculosis in Hong Kong: a Population-Based Prospective Study

Moira Chan-Yeung,[1]* Cheuk-Ming Tam,[2] Harriet Wong,[1] Chi-Chiu Leung,[2] Julie Wang,[1] Wing-Wai Yew,[3] Chak-Wah Lam,[4] and Kai-Man Kam[5]

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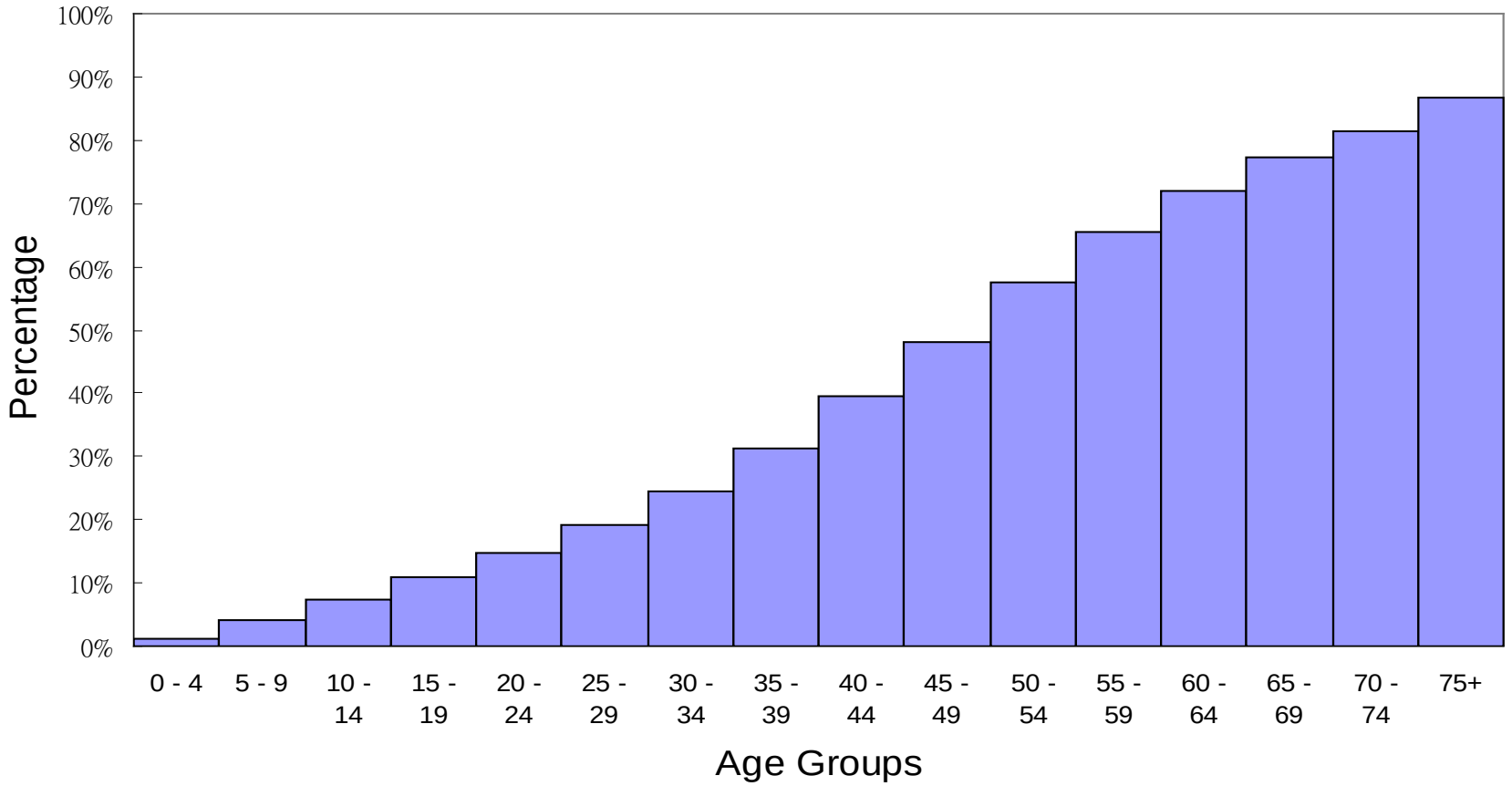
Received 12 November 2002/Returned for modification 16 January 2003/Accepted 24 February 2003

A prospective population-based molecular and conventional epidemiological study of 65.4% of bacteriologically confirmed cases of tuberculosis was carried out on the island of Hong Kong from May 1999 to Oct 2000 by the IS*6110*-based restriction fragment length polymorphism technique. Eleven of the isolates had five or fewer bands; 24.5% of the remaining 691 isolates belonged to clusters. The estimated proportion of recently transmitted disease was 15 to 20%.

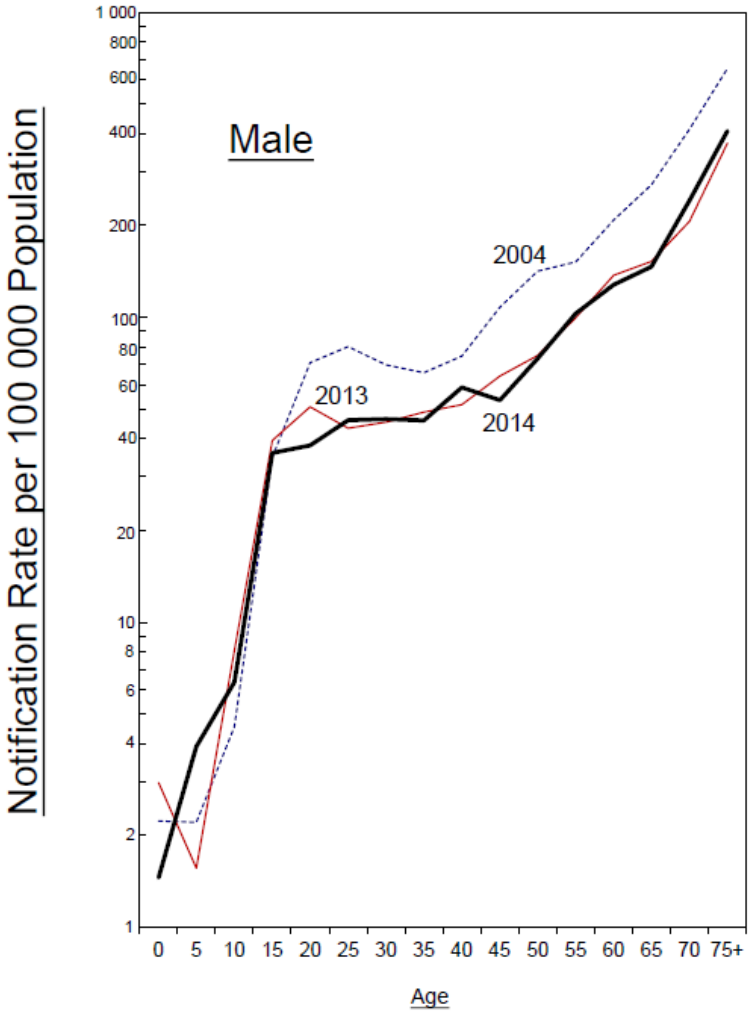
Estimated Infection Rate (HK)

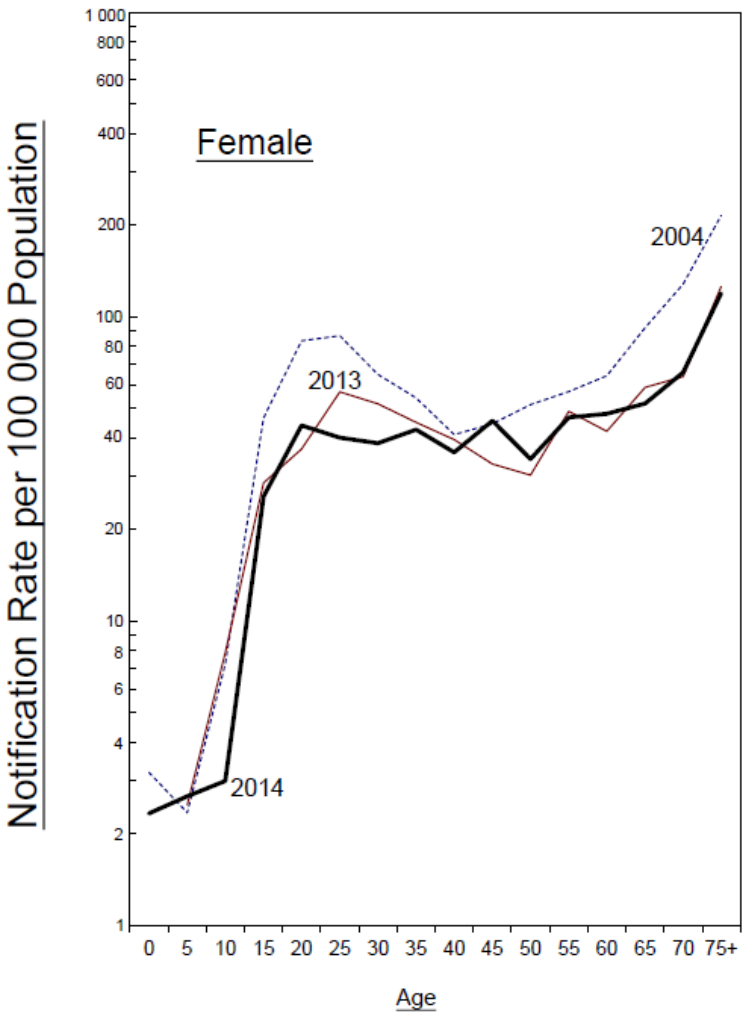


*Estimation based on: Incidence (smear-positive cases) = ARI * Styblo ratio

Notification by Gender &Age

TB Notification Rate by Age & Sex 2004, 2013 & 2014





Co-existing medical diseases

(Leung CC el. al.J Am Geriatr Soc. 2002 ;50:1219-26)

	Age ≥ 65 (n = 457)	Age < 65 (n = 413)	P value
Diabetes mellitus	67 (14.7%)	38 (9.2%)	.014
Neoplasm	43 (9.4%)	5 (1.2%)	< .001
Chronic renal failure	19 (4.2%)	2 (0.5%)	< .001
Ischemic heart disease	43 (9.4%)	3 (0.7%)	< .001
Cerebro-vascular disease	25 (5.5%)	3 (0.7%)	< .001
Chronic liver disease	8 (1.8%)	4 (1.0%)	.486
COPD* / silicosis	87 (19.0%)	26 (6.3%)	< .001
Hypertension	45 (9.8%)	15 (3.6%)	< .001
Peptic ulcer	18 (3.9%)	4 (1.0%)	.010
Dementia	14 (3.1%)	0 (0%)	.001
Parkinson's disease	8 (1.8%)	0 (0%)	.008
Gout	9 (2.0%)	2 (0.5%)	.098
Anemia	10 (2.2%)	2 (0.5%)	.062
Collagen vascular disease	2 (0.4%)	4 (1.0%)	.431
Thyroid disease	2 (0.4%)	3 (0.7%)	.673

Field Hurdles

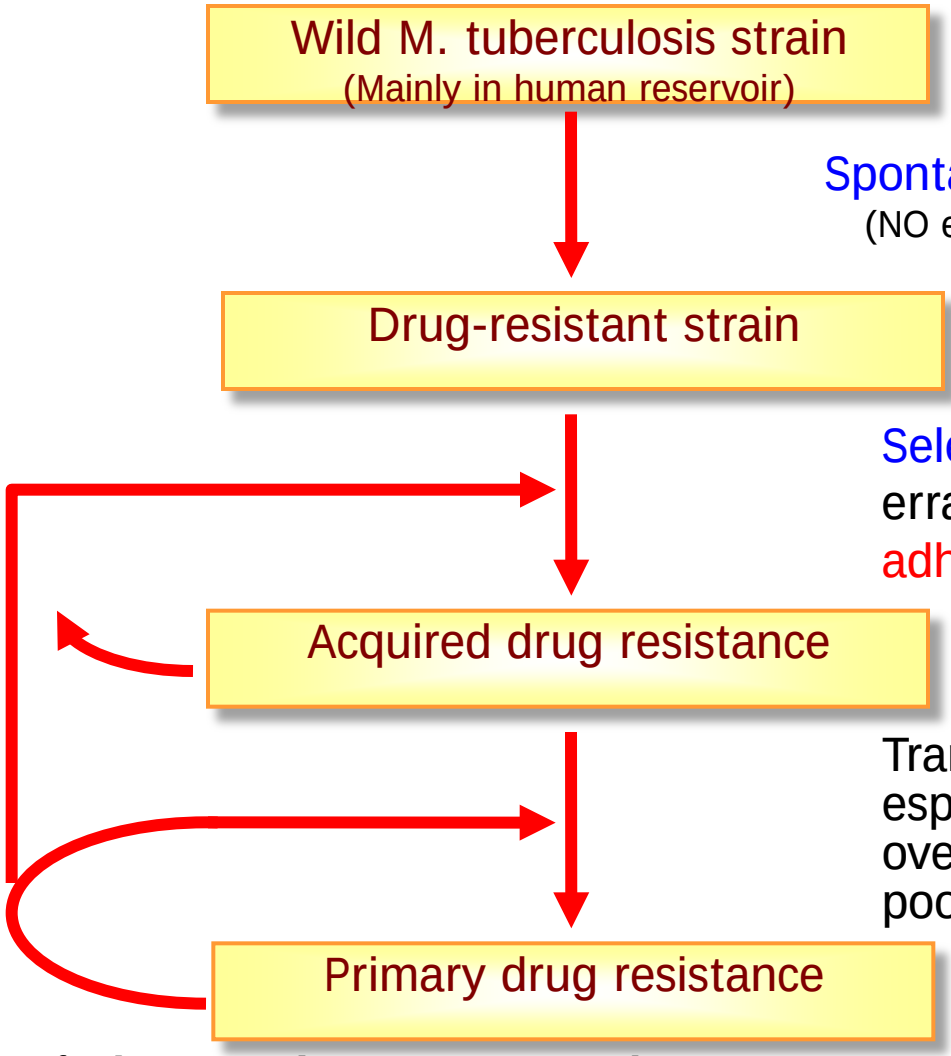
- Social determinants
  - Social and economic disparities / health inequities between and within countries
  - Mobile populations (migrants/refugees/?travellers)
  - HIV and other risk factors

- Drug resistance complicates control
  - MXR-TB and XDR-TB

Global: Drug Resistant TB

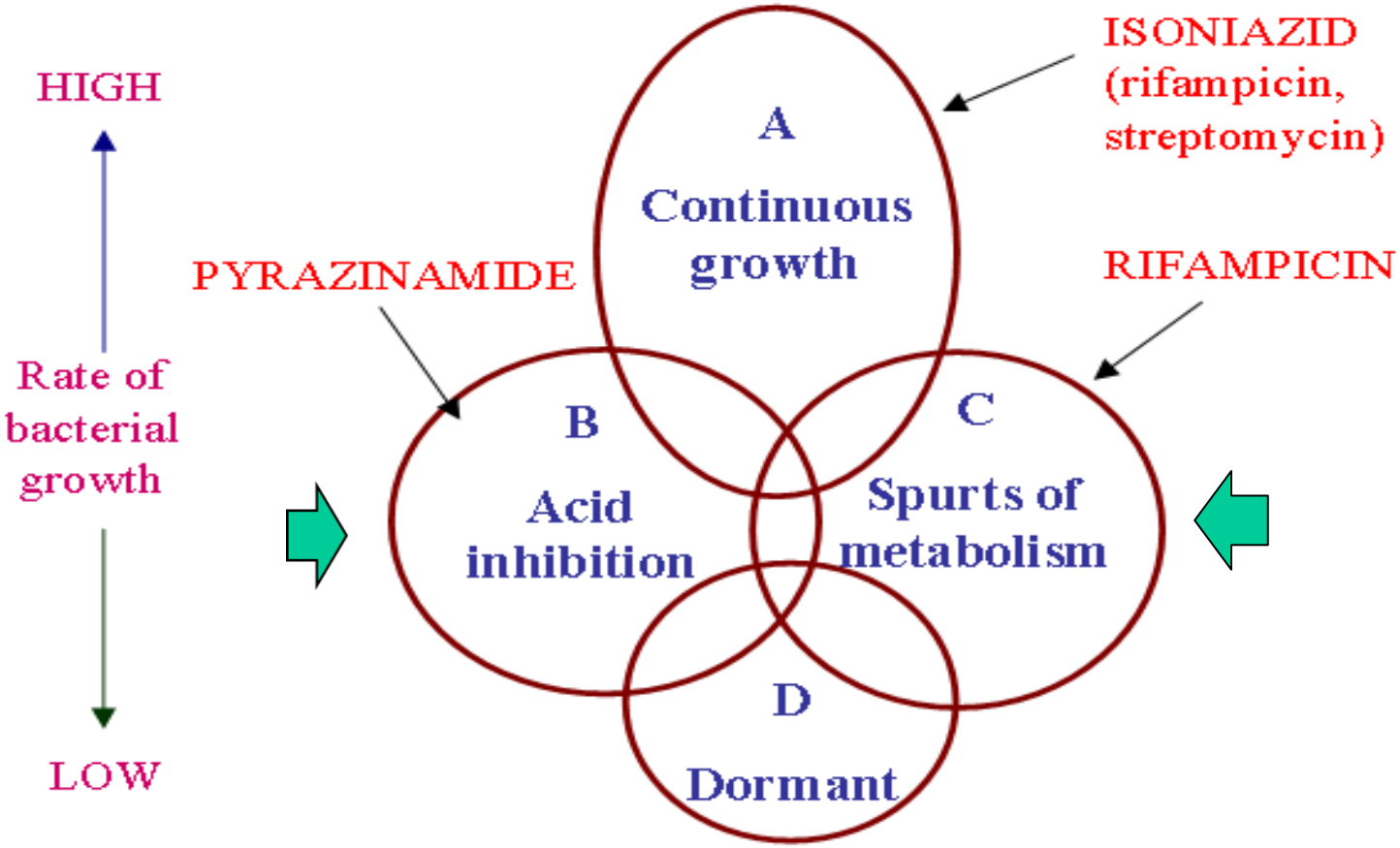
- MDR/RR-TB
  - 580000 (MDR-TB: 480 000 + RR-TB:100000)
    - 45% in India, China and Russian Federation.
  - New cases: 3.9% ; Previously treated: 21%
- Extensively drug-resistant (XDR-)TB:
  - MDR-TB with additional resistance to any fluoroquinolone and at least one of the second line injectables
    - Reported in 117 WHO member states
    - 9.5% of MDR-TB

Clinical drug resistance: Man-made phenomenon



Ref: Zhang Y and Yew WW. Int J Tuberc Lung Dis 2009;13(11):1320–1330

Hypothetical bacterial populations



Factors Affecting Response to Treatment

- Unimportant:
  - rest
  - sanatorium accommodation
  - diet
  - nursing care
- Relatively important:
  - severity of disease
  - initial or acquired drug resistance
- Important:
  - Chemotherapy
  - Compliance

Lancet. 2014 Jun 14;383(9934):2057-64. doi: 10.1016/S0140-6736(13)62639-2. Epub 2014 Mar 18.

Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data.

Wang L[1], Zhang H[1], Ruan Y[1], Chin DP[2], Xia Y[1], Cheng S[1], Chen M[1], Zhao Y[1], Jiang S[1], Du X[1], He G[1], Li J[1], Wang S[1], Chen W[1], Xu C[1], Huang F[1], Liu X[1], Wang Y[3].

FINDINGS: From 1990 to 2010, the **prevalence** of smear-positive **tuberculosis** decreased from 170 cases (95% CI 166-174) to 59 cases (49-72) per 100,000 population. During the 1990s, smear-positive **prevalence** fell only in the provinces with the DOTS programme; after 2000, **prevalence** decreased in all provinces. The percentage reduction in smear-positive **prevalence** was greater for the decade after 2000 than the decade before (57% vs 19%; p<0.0001). 70% of the total reduction in smear-positive **prevalence** (78 of 111 cases per 100,000 population) occurred after 2000. Of these cases, 68 (87%) were in known cases-ie, cases diagnosed with **tuberculosis** before the **survey**. Of the known cases, the proportion treated by the public health system (using the DOTS strategy) increased from 59 (15%) of 370 cases in 2000 to 79 (66%) of 123 cases in 2010, contributing to reduced proportions of treatment default (from 163 [43%] of 370 cases to 35 [22%] of 123 cases) and retreatment cases (from 312 [84%] of 374 cases to 48 [31%] of 137 cases; both p<0.0001).

National survey of drug-resistant tuberculosis in Mainland China

	New cases	Previously treated
MDR-TB	5.7% (4.5%-7.0%)	25.6% (21.5%-29.8%)
XDR-TB	0.5% (0.2%-0.8%)	2.1% (0.6%-3.5%)

95% confidence interval in brackets

Ref: Zhao Y et al. N Engl J Med 2012;366:2161-70.

Apparent Paradox: Possible Reasons

- Irregular treatment before effective coverage of quality DOTS in national programme: emergence of isoniazid and rifampin resistance
- No regular culture / DST-guided use of secondline drugs: MDR-TB not detected or effectively treated
- ? Standard 5-drug retreatment programme amplified resistance, especially in failure cases
- ? Uncontrolled use of secondline drugs outside programme settings: XDR-TB
- Transmission of drug-resistant TB within community

Immigrants and TB (HK)

Immigrants and tuberculosis in Hong Kong

CC Leung *, CK Chan, KC Chang, WS Law, SN Lee, LB Tai, Eric CC Leung, CM Tam

ABSTRACT

Objective: To examine the impact of immigrant populations on the epidemiology of tuberculosis in Hong Kong.

Design: Longitudinal cohort study.

Setting: Hong Kong.

Participants: Socio-demographic and disease characteristics of all tuberculosis notifications in 2006 were captured from the statutory tuberculosis registry and central tuberculosis reference laboratory. Using 2006 By-census population data, indirect sex- and age-standardised incidence ratios by place of birth were calculated. Treatment outcome at 12 months was ascertained from government tuberculosis programme record forms, and tuberculosis relapse was tracked through the notification registry and death registry up to 30 June 2013.

Results: Moderately higher sex- and age-standardised incidence ratios were observed among various immigrant groups: 1.06 (Mainland China), 2.02 (India, Pakistan, Bangladesh), 1.59 (Philippines, Thailand, Indonesia, Nepal), and 3.11 (Vietnam). Recent Mainland migrants had a lower sex- and age-standardised incidence ratio (0.51 vs 1.09) than those who immigrated 7 years ago or earlier. Age younger than 65 years, birth in the Mainland or the above Asian countries, and previous treatment were independently associated with resistance to isoniazid and/or rifampicin. Older age, birth in the above Asian countries, non-permanent residents, previous history of treatment, and resistance to isoniazid and/or rifampicin were independently associated with poor treatment outcome (other than cure/treatment completion) at 1 year. Birth outside Hong Kong was an independent predictor of relapse following successful completion of treatment (adjusted hazard ratio=1.76; 95% confidence interval, 1.07-2.89; P=0.025).

Conclusion: Immigrants carry with them a higher tuberculosis incidence and/or drug resistance rate from their place of origin. The higher drug resistance rate, poorer treatment outcome, and excess relapse risk raise concern over secondary transmission of drug-resistant tuberculosis within the local community.

Hong Kong Med J 2015;21:318–26
DOI: 10.12809/hkmj144492

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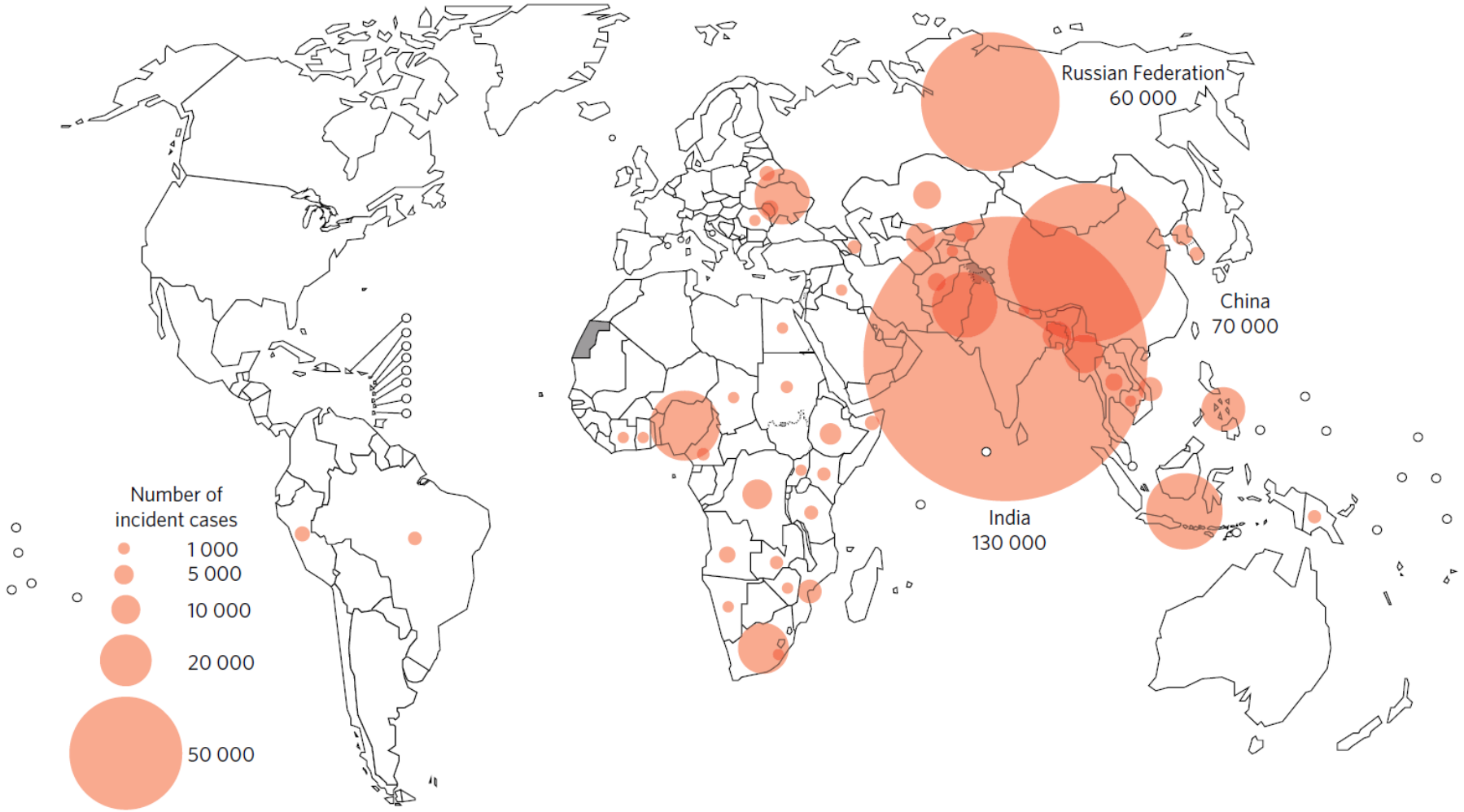
Incident MDR/RR-TB cases in 2015

(From WHO Global TB Report 2016)



Rate of Drug-resistant Tuberculosis

Among cases (mainly cases seen at chest clinics) registered during the period January to December 2012 (Data from Programme Forms)

Age Group	Category	% resistance to				* % resistance to			MDR-TB	# Total % resistance	Total no. of cases analysed
		E	R	H	S	1 drug	2 drugs	≥ 3 drugs			
0 - 19	New cases	1.32	2.63	7.89	9.21	6.58	1.32	3.95	2.63	11.84	76
	Previously treated cases	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1
	Overall	1.30	2.60	7.79	9.09	6.49	1.30	3.90	2.60	11.69	77
20 - 39	New cases	0.34	1.02	3.75	10.56	10.22	1.70	0.68	0.85	12.61	587
	Previously treated cases	9.68	16.13	16.13	16.13	6.45	3.23	12.90	12.90	22.58	31
	Overall	0.81	1.78	4.37	10.84	10.03	1.78	1.29	1.46	13.11	618
40 - 59	New cases	1.01	1.44	5.60	10.49	9.05	2.87	1.01	1.29	12.93	696
	Previously treated cases	2.63	5.26	13.16	21.05	17.11	2.63	6.58	5.26	26.32	76
	Overall	1.17	1.81	6.35	11.53	9.84	2.85	1.55	1.68	14.25	772
60 up	New cases	0.66	0.47	4.32	8.26	7.50	2.35	0.47	0.19	10.32	1066
	Previously treated cases	0.00	1.61	8.60	10.75	10.22	3.76	1.08	1.61	15.05	186
	Overall	0.56	0.64	4.95	8.63	7.91	2.56	0.56	0.40	11.02	1252
All	New cases	0.70	0.95	4.66	9.48	8.58	2.31	0.78	0.74	11.67	2425
	Previously treated cases	1.70	4.08	10.54	13.95	11.56	3.40	3.74	3.74	18.71	294
	Overall	0.81	1.29	5.30	9.97	8.90	2.43	1.10	1.07	12.43	2719

Notes: E = ethambutol; R = rifampicin; H = isoniazid; S = streptomycin
* % resistant to one, two or more than two of the four drugs E, R, H and S
# total % resistance: resistant to at least one of the four drugs E, R, H and S
New cases: for cases with no past history of anti-tuberculosis treatment
Previously treated cases: for cases with past history of anti-tuberculosis treatment
Overall: for all cases

Critical Concern: Drug-Resistant TB

- Major (5 or more fold) risk differentials of MDR-TB between HK and some neighboring areas
- Increasing use of secondline drugs outside programme settings:
  - Rapidly emerging resistance to injectibles, fluoroquinolones and pyazinamide (besides isoniazid and rifampicin)
  - Cases resistant to ALL first and secondline drugs
- Intensified population movements affecting drug adherence and promoting cross transmission across all age bands including children and elderly
- Overcrowded local environment and institutions including schools, elderly homes and hospitals.

Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city

(Leung EC, et al. Eur Respir J. 2013;41:901-8)

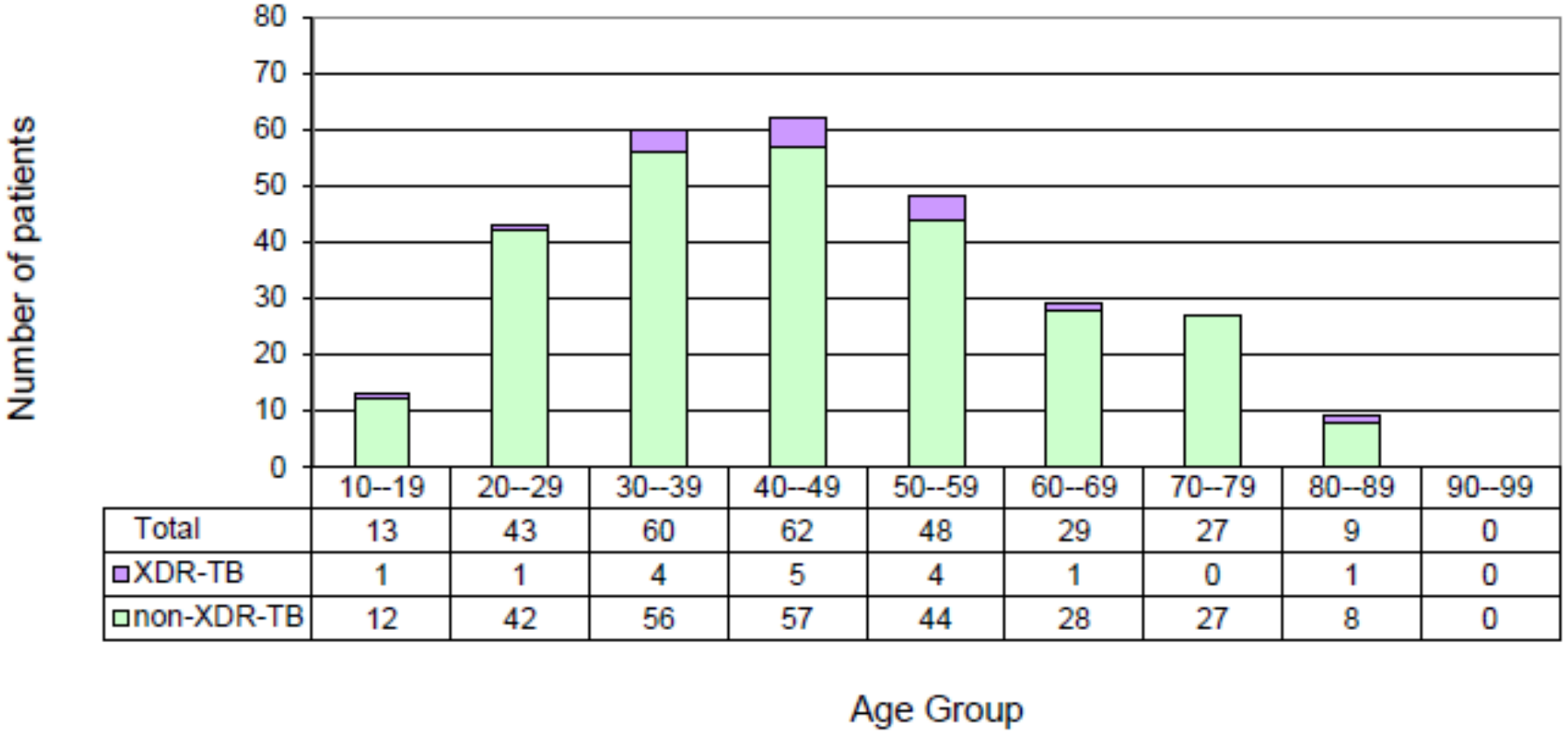
ABSTRACT: Multidrug-resistant (MDR)- tuberculosis (TB) and extensively drug resistant (XDR)-TB reportedly lead to increased household transmission.

This is a retrospective cohort study of active TB occurring among household contacts exposed to MDR-TB.

Of 704 contacts in 246 households, initial screening identified 12 (1.7%) TB cases (prevalent cases) and 17 (2.4%) contacts that subsequently developed active TB (secondary cases) after a median (range) duration of 17 (5–62.5) months. Eight prevalent cases and three secondary cases had MDR-TB. TB incidence rates per 100 000 person-years were 254.9 overall and 45.0 for MDR-TB. XDR-TB in the index MDR-TB patient significantly increased the odds of identifying a prevalent TB case to 4.8 (95% CI 1.02–22.5), and the hazard of finding a secondary TB case to 4.7 (95% CI 1.7–13.5). Molecular fingerprinting confirmed household transmission of MDR-TB. Of 20 retrievable isolates from 27 XDR-TB index cases, restriction fragment length polymorphism analysis showed clustering among 13 (65%), with 11 (55%) due to recent transmission by n-1 method and an identifiable household source in only three (27.2%) of the 11 cases.

XDR-TB relative to MDR-TB significantly increases household transmission of TB, probably reflecting prolonged/higher infectivity, and indicating a need for prolonged household surveillance. XDR-TB may largely transmit outside of the household settings.

Age Profile: MDR-TB 2005-2014



	10--19	20--29	30--39	40--49	50--59	60--69	70--79	80--89	90--99
Total	13	43	60	62	48	29	27	9	0
XDR-TB	1	1	4	5	4	1	0	1	0
non-XDR-TB	12	42	56	57	44	28	27	8	0

Notification Sources (2004-2014)

Origin	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
East Kowloon Chest Clinic	121	132	86	121	129	100	99	105	101	83	83
Kowloon Chest Clinic	330	287	231	220	184	171	165	122	154	167	127
Sai Ying Pun Chest Clinic	148	112	92	108	86	69	80	71	89	79	70
Shaukiwan Chest Clinic	138	111	104	128	105	80	72	74	65	74	66
Shaukiwan Pneumoconiosis	29	10	15	13	13	16	6	9	10	2	9
Shek Kip Mei Chest Clinic	157	140	96	111	127	92	87	90	101	95	80
South Kwai Chung Chest Clinic	261	282	224	187	200	158	166	146	158	122	127
Tai Po Chest Clinic	112	101	92	79	81	63	71	86	82	93	64
Wanchai Chest Clinic	223	214	191	169	168	170	143	118	110	113	95
Yan Oi Chest Clinic	290	263	238	165	179	172	152	173	144	146	104
Yaumatei Chest Clinic	203	249	204	151	137	139	131	128	132	112	101
Yuen Chau Kok Chest Clinic	181	148	136	122	116	124	131	112	108	110	98
Yung Fung Shee Chest Clinic	178	174	148	120	147	118	131	112	116	86	92
Castle Peak Hospital (Chest Clinic)	5	3	3	4	5	0	0	0	2	0	0
Cheung Chau Chest Clinic	2	3	1	1	2	1	1	1	1	0	0
Sai Kung Chest Clinic	7	4	9	5	9	1	3	6	4	4	2
Sheung Shui Chest Clinic	54	64	61	53	45	42	63	33	21	30	33
Tung Chung Chest Clinic	16	11	15	12	9	7	11	13	9	11	11
Yuen Long Chest Clinic	80	93	69	64	67	73	80	48	39	66	51
Sub-total	2 535	2 401	2 015	1 833	1 809	1 596	1 592	1 447	1 446	1 393	1 213
Grantham Hospital	257	165	176	215	209	214	180	163	138	148	140
Haven of Hope Hospital	137	127	124	124	87	103	65	80	68	77	95
Kowloon Hospital	205	113	142	108	120	84	108	92	97	64	74
Ruttonjee Hospital	263	256	264	218	165	183	170	176	165	127	140
Wong Tai Sin Hospital	189	184	140	90	104	82	105	57	58	86	69
Other Govt. Institutions (a)	87	84	60	66	78	54	64	62	54	51	61
Other H.A. Hospitals	2 301	2 543	2 538	2 530	2 648	2 472	2 425	2 364	2 497	2 377	2 578
Private Practitioners	136	156	164	90	83	57	101	100	109	118	129
Private Hospitals	116	131	143	189	332	348	283	253	226	223	206
Total	6 226	6 160	5 766	5 463	5 635	5 193	5 093	4 794	4 858	4 664	4 705
% of cases from Chest Clinics among the total	40.7	39.0	34.9	33.6	32.1	30.7	31.3	30.2	29.8	29.9	25.8
% from Chest Hospitals (b)	16.9	13.7	14.7	13.8	12.2	12.8	12.3	11.8	10.8	10.8	11.0
% from Other Public Hospitals	38.4	42.6	45.1	47.5	48.4	48.6	48.9	50.6	52.5	52.1	56.1
% from Private Sector	4.0	4.7	5.3	5.1	7.4	7.8	7.5	7.4	6.9	7.3	7.1

Infection control for TB in HCF

(CDC MMWR1994)

Hierarchy of controls

1. Administrative controls
   - Assessment of risk
   - Infection control plan
   - HCW training
   - Early identification, diagnosis, isolation, and treatment
   - Patient education
   - Triage
   - Evaluation of infection control programme
2. Engineering controls
   - Maximise natural ventilation
   - Mechanical ventilation
   - UV (germicidal) light
   - HEPA filters
3. Personal controls
   - Masks and respirators
   - BCG vaccination
   - TST/ preventive therapy

Early diagnosis and treatment leads to rapid fall of sputum bacillary count. This MAY NOT APPLY to MDR- or XDR-TB and early detection of rifampicin resistance is therefore crucial in high risk settings.

Combating Drug Resistance

- Control at SOURCE
  - Early detection of TB and drug resistance through deployment of rapid molecular tools, especially in high risk scenarios
  - Prompt initiation of APPROPRIATE treatment
    - Drug-sensitive TB: avoid fluoroquinolone unless rifampicin resistance excluded
    - Rifampicin-resistant TB: genotypic test for further resistance isoniazid, fluoroquinolone and injectible, followed by phenotypic test +/- MIC / TDM to guide choice of drugs (including also repurposed or new drugs)
- Prevent further drug resistance
  - Seeking appropriate source of advice for difficult scenarios
  - Do not add a single drug to a failing regimen (addition phenomenon)
  - Intensified case-holding efforts till treatment completion
    - DOT and defaulter tracing
    - Cross-jurisdiction notification
    - Statutory enforcement (generally as last resort)

Genetic basis of DR-TB

Table Mechanisms of drug resistance in *M. tuberculosis*

Drug (year of discovery)	MIC µg/ml	Gene(s) involved in resistance	Gene function	Role	Mechanism of action	Mutation frequency %
Isoniazid (1952)	0.02–0.2	*katG* *inhA*	Catalase-peroxidase Enoyl ACP reductase	Pro-drug conversion Drug target	Inhibition of mycolic acid biosynthesis and other multiple effects	50–95 8–43
Rifampicin (1966)	0.05–1	*rpoB*	β subunit of RNA polymerase	Drug target	Inhibition of RNA synthesis	95
Pyrazinamide (1952)	16–50 (pH 5.5)	*pncA*	Nicotinamidase/pyrazinamidase	Pro-drug conversion	Depletion of membrane energy	72–97
Ethambutol (1961)	1–5	*embB*	Arabinosyl transferase	Drug target	Inhibition of arabinogalactan synthesis	47–65
Streptomycin (1944)	2–8	*rpsL* *rrs* *gidB*	S12 ribosomal protein 16S rRNA rRNA methyltransferase (G527 in 530 loop)	Drug target Drug target Drug target	Inhibition of protein synthesis	52–59 8–21 ?
Amikacin/kanamycin (1957)	2–4	*rrs*	16S rRNA 16S rRNA	Drug target	Inhibition of protein synthesis	76
Capreomycin (1960)		*tlyA*	2′-O-methyltransferase			
Quinolones (1963)	0.5–2.5	*gyrA* *gyrB*	DNA gyrase subunit A DNA gyrase subunit B	Drug target	Inhibition of DNA gyrase	75–94
Ethionamide (1956)	2.5–10	*etaA/ethA* *inhA*	Flavin monooxygenase	Prodrug conversion Drug target	Inhibition of mycolic acid synthesis	37 56
PAS (1946)	1–8	*thyA*	Thymidylate synthase	Drug activation?	Inhibition of folic acid and iron metabolism?	36

MIC = minimum inhibitory concentration; ACP = acyl carrier protein; PAS = para-aminosalicylic acid.

Ref: Chang KC, Yew WW, Zhang Y. Expert Opin Med Diagn 2009; 3(2):1-24

Examples of commercial products

- *rpoB* mutations
  - INNO-LiPA Rif.TB
  - Xpert MTB/RIF:
    - automated
    - heminested real-time PCR assay
    - molecular beacons for probing *rpoB* mutations
- *rpoB* and *katG* mutations
  - GenoType MTBDR (Hain test)
- *rpoB, katG, and inhA* mutations
  - GenoType MTBDR*plus*
- *gyrA*, *rrs*, and *embB / gyr B*, *eis* mutations
  - GenoType MTBDRsl (v1 / v2)

Phenotypic DST for TB

Bottger EC. Clin Microbiol Infect 2011; 17: 1128–1134

- Classifies clinical isolates as either drug-‘resistant’ or drug-‘susceptible’ by their ability to grow in the presence of a ‘critical concentration’ (lowest concentration of drug that inhibits 95% of wild-type strains of bacilli, not related to achievable serum level) of the test drug.
- Drug resistance in *M. tuberculosis* is heterogeneous:
  - low-level, moderate-level and high-level drug resistance phenotypes, associated with different mutations
  - Decrease in drug susceptibility does not inevitably exclude the drug from treatment regimens
- Quantitative measures, e.g. MIC, may help to:
  - reflect the biological complexity of drug resistance,
  - optimally exploit the compounds available for treatment.

Therapeutic Drug Monitoring (TDM)

Drugs. 2014;74:839-54 & Clin Pharmacokinet. 2014;53:873-90.

- Individual pharmacokinetic variability: difficult to predict without TDM
- Methods:
  - One or two samples:
    - 2-h post-dose sample: approximates peak serum drug concentration (Cmax)
    - 6-h sample: distinguish between delayed absorption and malabsorption.
  - Promptly centrifuged, serum harvested and frozen
    - Isoniazid and ethionamide not stable at room temperature
  - Dried blood spots and prepackaged multidrug plates for MIC: ↑ access
- Clinical role requires further validation:
  - Concentration response seen in vitro and animal model data
  - In human studies, standard dosing not consistently achieving target concentrations for first-line drugs, but not necessarily associated with poor response

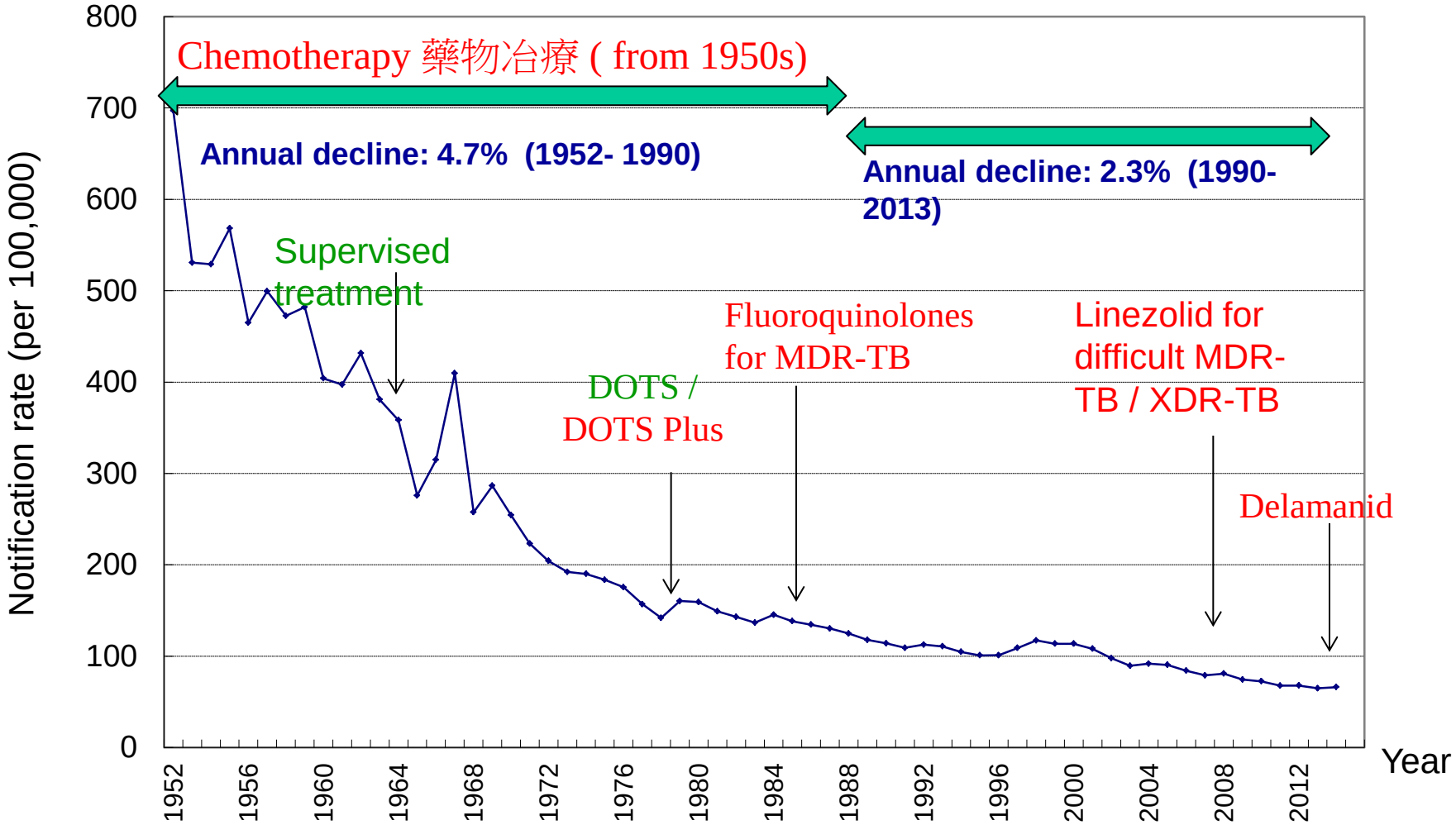
TB Drug Groups

(WHO. Treatment of Tuberculosis Guidelines 4th edn)

- First-line anti-TB drugs
  - Group 1(oral first-line drugs): isoniazid, rifampicin (rifapentine or rifabutin), pyrazinamide, ethambutol,
- Second-line anti-TB drugs
  - Group 2 (injectables): aminoglycosides (streptomycin, kanamycin, amikacin) and injectable polypeptides (capreomycin, viomycin)
  - Group 3 (oral and injectable fluoroquinolones): ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin.
  - Group 4 (oral bacteriostatic): para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide.
- Third-line anti-TB drugs
  - Group 5 (unclear role): clofazimine*, linezolid*, high dose isoniazid*, thioacetazone, amoxicillin plus clavulanate, imipenem plus cilastatin, clarithromycin.

* Recent evidences supporting use of these drugs for difficult MDR-TB

TB Chemotherapy in Hong Kong



Fluoroquinolone (FQ): a word of caution

- Essential for treatment of MDR-TB
  - Inadvertent FQ monotherapy should be avoided
    - With the relatively high TB incidence in HK, there is a need to exclude TB when FQ is used for common chest infections
    - Avoid using FQ as supplementary fourth drug (like ethambutol or streptomycin) in firstline regimen unless rifampicin resistance reasonably excluded.
  - Beware of food and drug interactions
    - absorption of fluoroquinolones is reduced by dairy products, and drugs (antacids, sucralfate, chewable didanosine, vitamins) containing divalent cations (such as Zn, Fe, Ca, Mg)

Thank You