UNIVERSITÀ DEGLI STUDI DI FERRARA
- EX LABORE FRUCTUS -

Tubercolosi e Screening tra i Migranti

Delia Goletti
Unità di Ricerca Traslazionale, INMI

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National Institute for Infectious Diseases (INMI) L. Spallanzani, Rome, Italy

- HIV: 5,500-6,000
- HCV: 1,500-2,000
- HBV: 800-1,000
- Active TB: 280-300, LTBI: 200-300

yearly

- Ebola: 2 cases.

Outpatient Clinic of Pneumology

Translational Research Unit

This talk…
Tubercolosi e Screening tra i Migranti

Natural history of TB

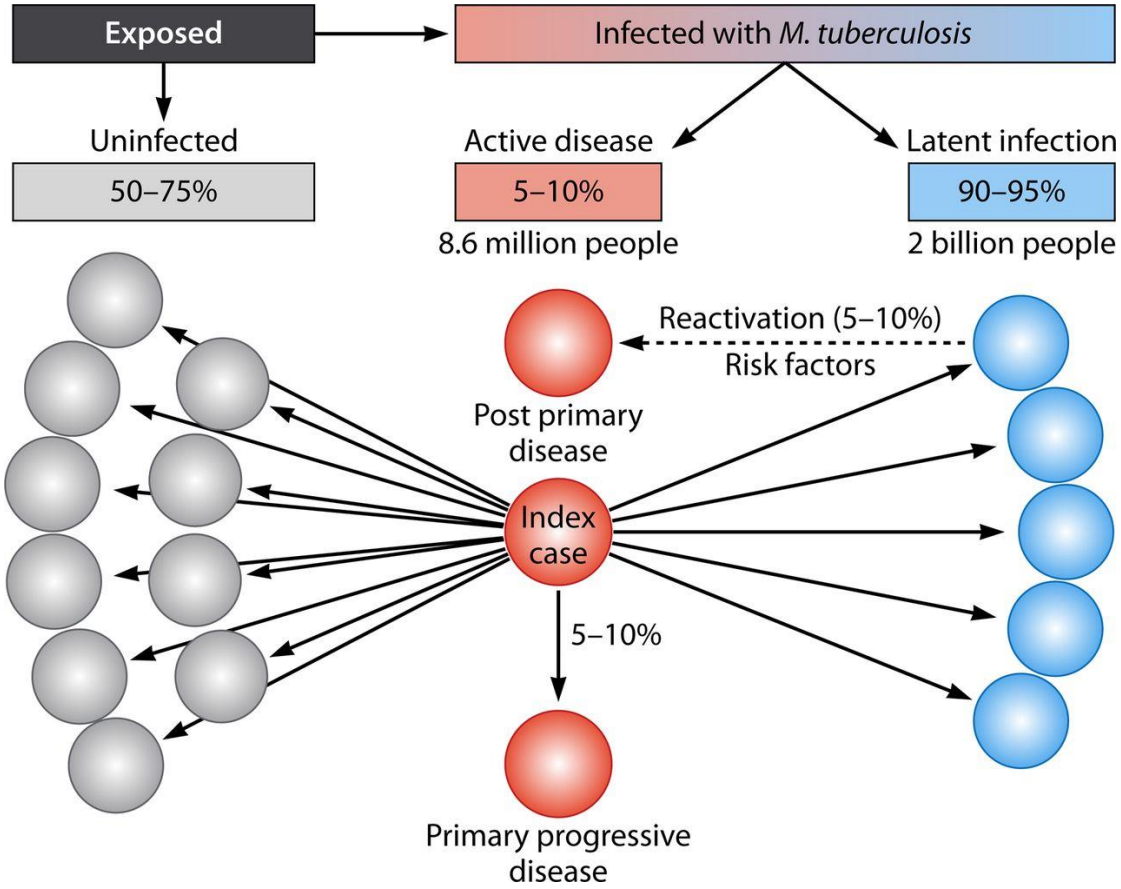
Clinical, microbiological, diagnostic aspects of TB

Screening TB procedures

This talk…

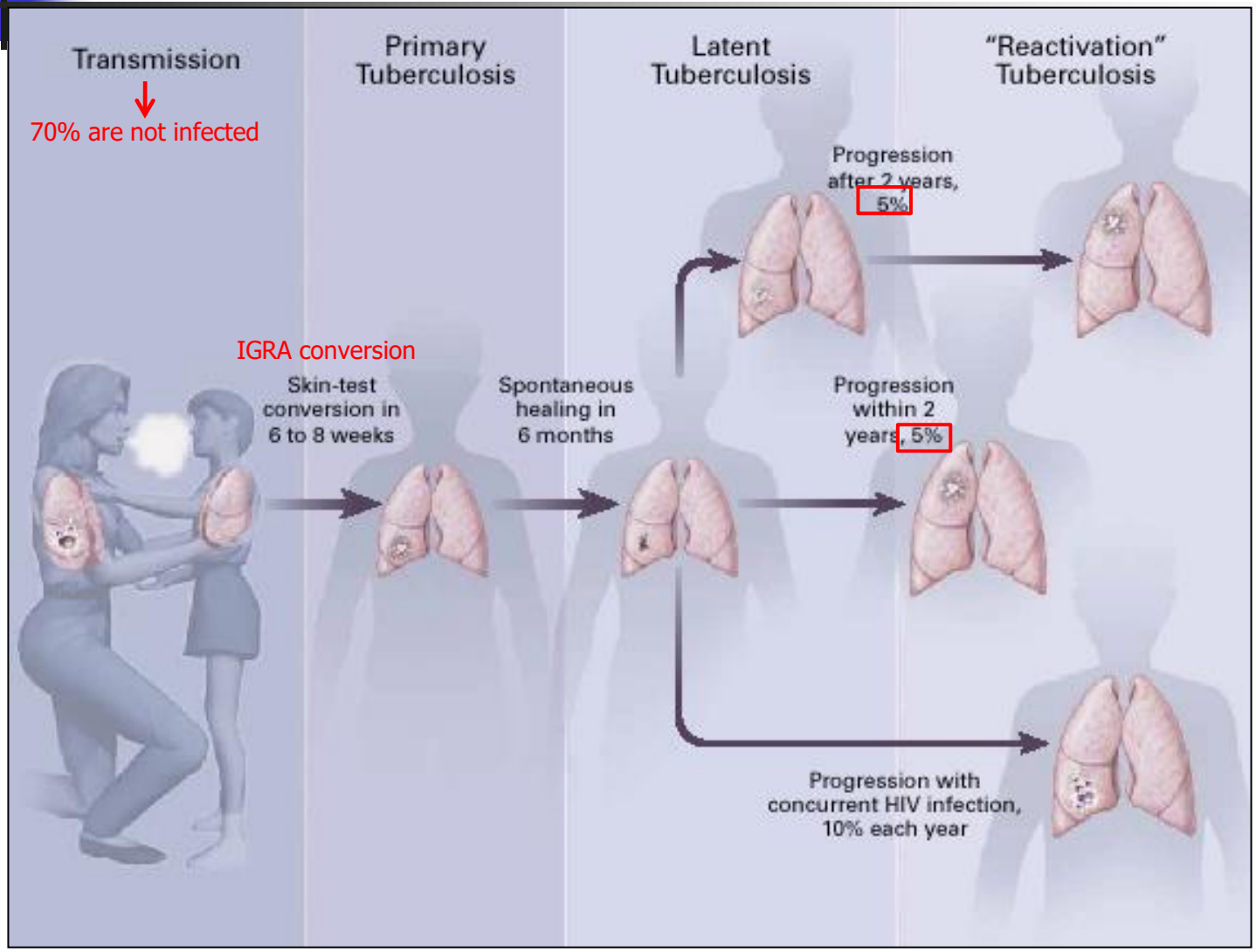
Natural history

Infectious spread of *M. tuberculosis* and resulting disease



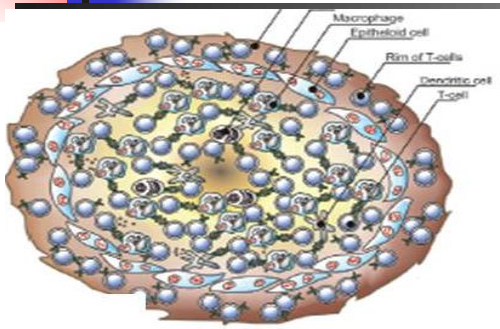
Wlodarska et al. Clin. Microbiol. Rev., 2015

Tuberculosis transmission and progression to active disease from latent infection



Small PM et al, N Engl J Med, 2001

Existence of Mtb inside the granuloma



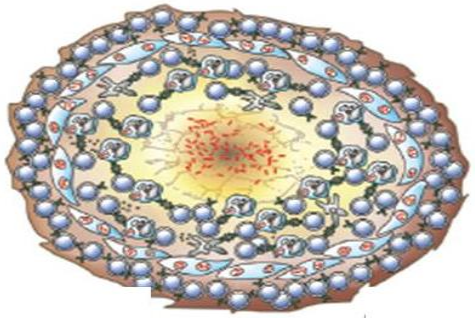
Solid

prevail during LTBI

Fibrotic wall. Outer ring of lymphocytes. In the center mononuclear phagocytes, fibroblasts and DCs.

↓

Mtb: dormancy stage with low metabolic activity



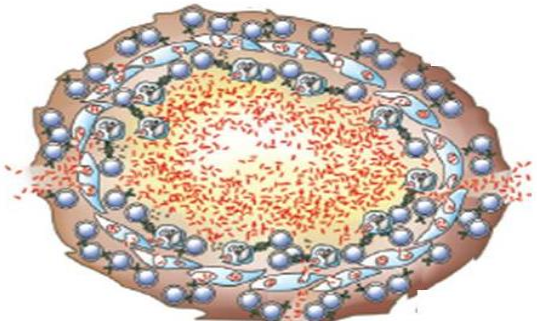
Necrotic

Early stage of TB infection

The center becomes necrotic, composed of solid cell detritus, hypoxic.

↓

Mtb: it starts replicating and becomes metabolically active



Caseous

End stage of severe TB

The center liquefies: cavity formation (neutrophil)

High oxygen content . The caseous material is a source of nutrient.

↓

Mtb: dissemination and transmission

Continuum

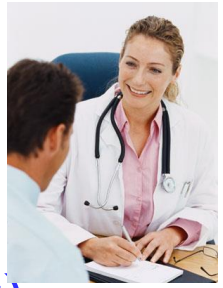
This talk…

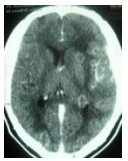
Clinical aspects

Diagnosis

Suspect of active TB

- ANAMNESIS
  - Information regarding TB risks:
    - origin,
    - Contact with smear positive TB cases,
    - immune suppression (HIV, biological therapy, transplants)
- CLINIC
  - General symptoms
  - Specific symptoms (based on the localization)
- IMAGES
  - Images indicative of active TB
- MICROBIOLOGY
  - *M. tuberculosis* isolation

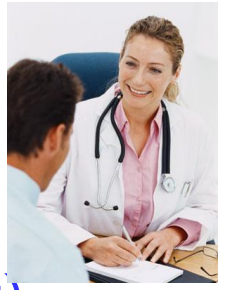






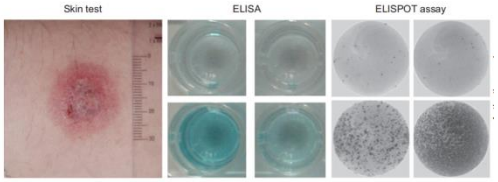

Suspect of LTBI

- ANAMNESIS
  - Information regarding TB risks:
    - origin,
    - Contact with smear positive TB cases,
    - immune suppression (HIV, biological therapy, transplants)



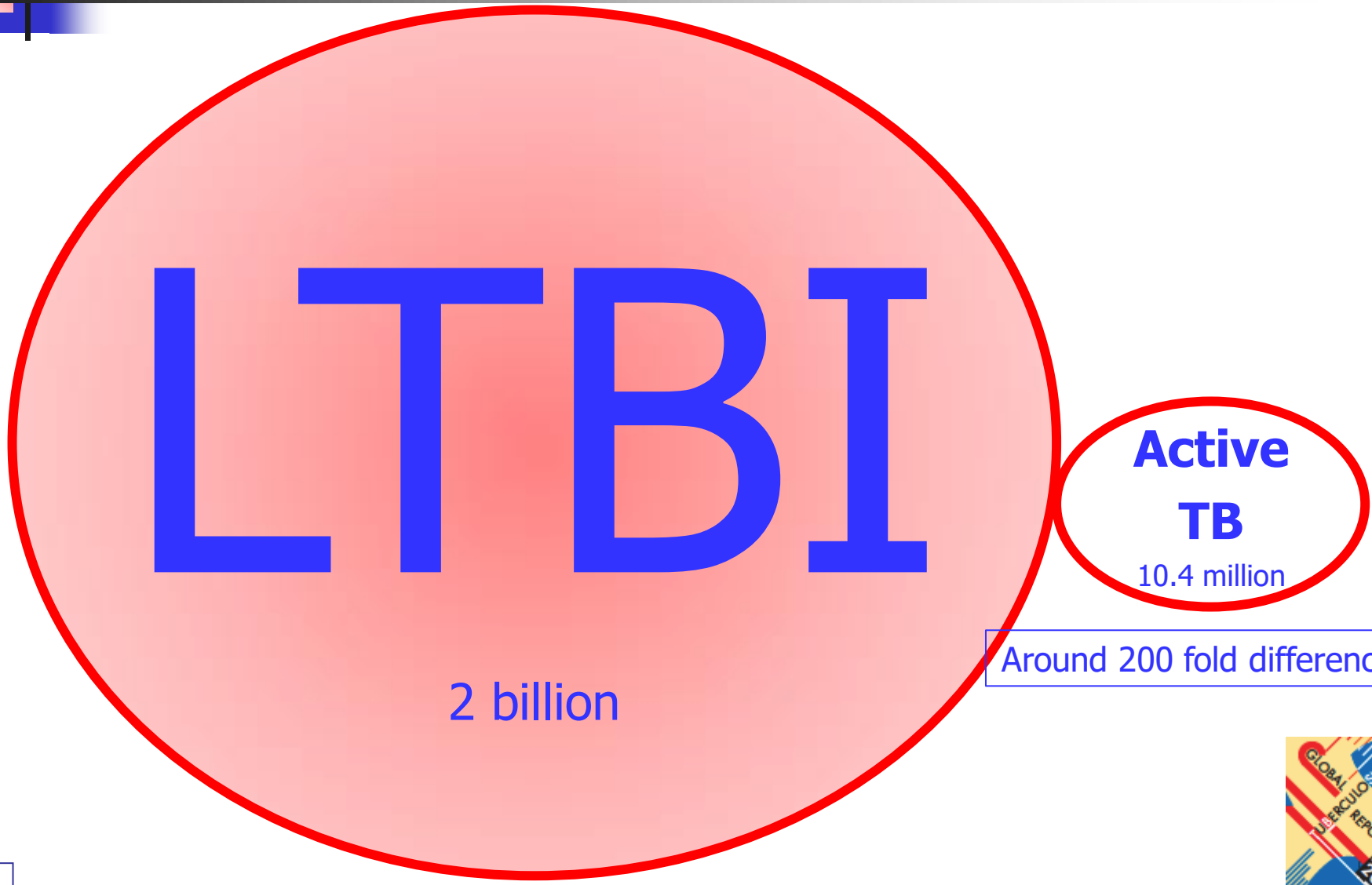
- CLINIC. To exclude:
  - General symptoms
  - Specific symptoms (based on the localization)

- IMMUNE-BASED TESTS
  - TST and/or IGRA

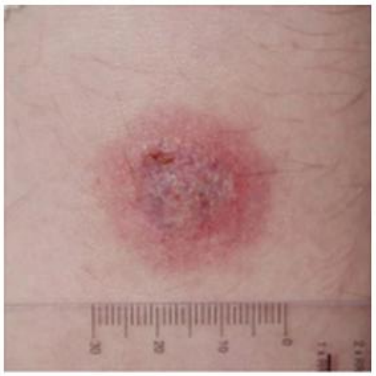


- IMAGES. To exclude specific active lesions:
  - Chest xRay

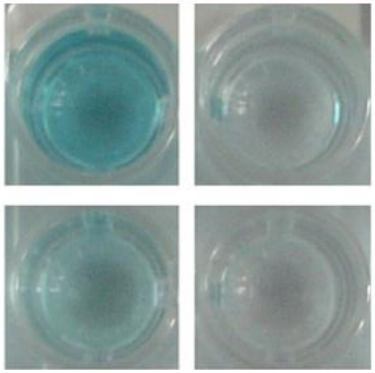
Worldwide LTBI: size of the problem



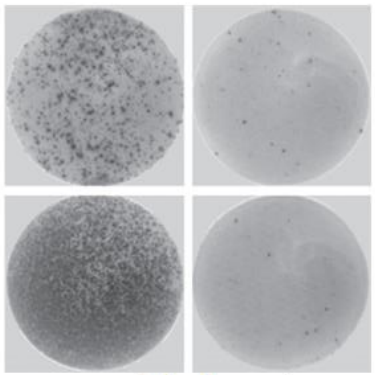
LTBI



Skin test

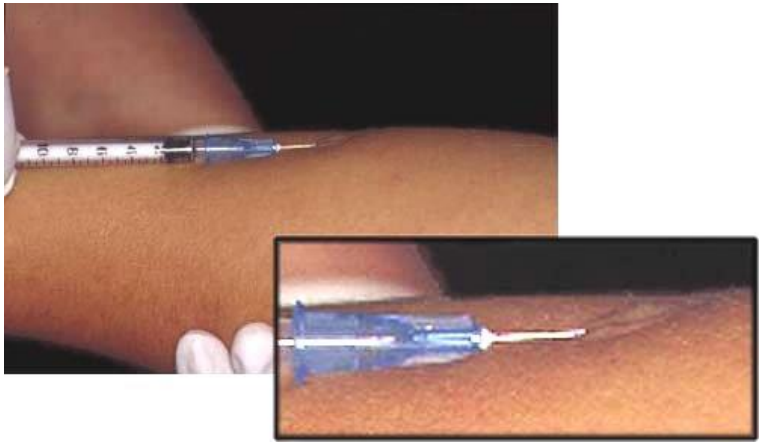


ELISA



ELISPOT assay

Limitations of the TST



- Reagent:
  - Purified protein derivative (PPD) commonly shared among different Mycobacteria (*M.tuberculosis, BCG and atypical mycobacteria*)
- Variability:
  - Reproducibility in giving the test
  - Subjectivity in reading the test
- Logistics
  - Repeat visit needed
  - 3 days before result

Tuberculin skin test (TST)

Positive TST	*M. tuberculosis*	Active TB disease
		Latent TB infection (past exposure to *M. tuberculosis)*
		Latent TB infection (recent exposure to *M. tuberculosis*)
	NTM	Exposure to environmental mycobacteria
	BCG-vaccination	BCG-vaccination

TST does not distinguish among all these different clinical situations

IGRAs: tests for LTBI diagnosis

IFN-γ

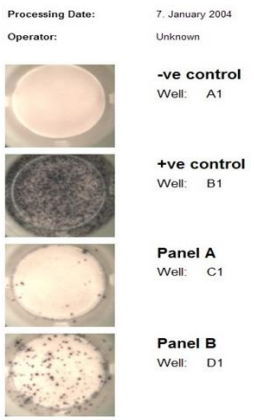
RD1

PBMC

Whole Blood

T SPOT.*TB*

QuantiFERON TB Gold In tube



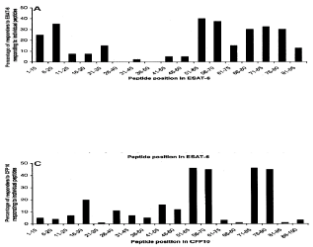


TABLE 1. AMINO ACID SEQUENCES OF OVERLAPPING PEPTIDES FOR ESAT-6 AND CFP-10

Antigen	Amino Acid Sequence
CFP-10	
Peptide 1	MAEMKTDAATLAQEAGNFERISGDL
Peptide 2	GNFERISGDLKTQIDQVESTAGSLQ
Peptide 3	DQVESTAGSLQGQWRGAAGTAAQAAV
Peptide 4	AAGTAAQAAVVRFQEAANKQKQELD
Peptide 5	AANKQKQELDEISTNIRQAGVQYSR
Peptide 6	IRQAGVQYSRADEEQQQALSSQMGF
ESAT-6	
Peptide 1	MTEQQWNFAGIEAAASAIQG
Peptide 2	GIEAAASAIQGNVTSI
Peptide 3	SAIQGNVTSIHSLLDEGKQSLTKLA
Peptide 4	EGKQSLTKLAAAWGGSGSEAYQGVQ
Peptide 5	SGSEAYQGVQQKWDATATELNNALQ
Peptide 6	TATELNNALQNLARTISEAGQAMAS
Peptide 7	NLARTISEAGQAMASTEGNVTGMFA

QuantiFERON TB Gold In tube

- Nil (negative control)
- RD1 peptides (*M. tuberculosis*-specific antigens)
- Mitogen (positive control)

Test Result	Nil	RD1 peptides (*Mtb*-specific Antigen) Cut-off: ≥0.35 UI/ml	Mitogen (PHA) Cut-off: ≥0.5 UI/ml
Indeterminate	–	–	–
Negative	–	–	+
Positive	–	+	+

RD1-IGRA

Positive RD1-IGRA	**BCG-vaccination** **NTM**
	Positive *M. tuberculosis* infection/disease

Mantoux or IGRA? What do I need to use?

BCG-vaccinated → IGRA

BCG-unvaccinated → TST

↓

If available, confermation by IGRA

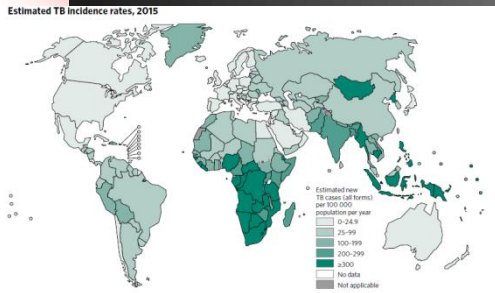
QuantiFERON TB Gold Plus

- Nil
- TB1 (TB Antigen tube of the QuantiFERON TB GOLD In tube)
- TB2 (additional peptides in which there are epitopes recognized by the CD8)
- Mitogen

This talk…

TB epidemiology

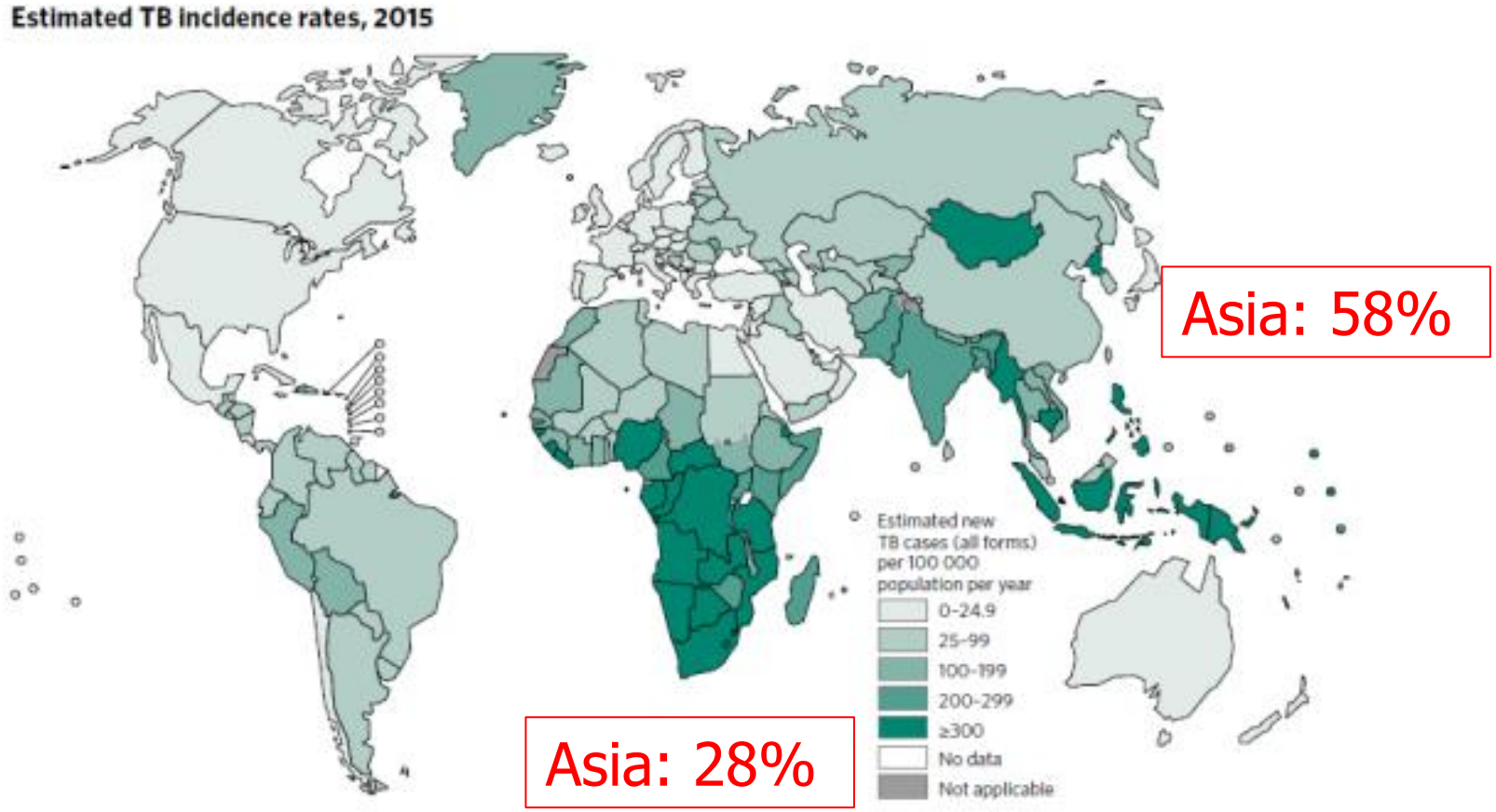
The global burden of TB in 2015



	Estimated number of cases	Estimated number of deaths
All forms of TB	10.4 million 1 m in children (9.6%) 3.5 m in women (33.6%)	1.4 million 0.17 million in children (12%) 0.35 million in women (25%)
HIV-associated TB	1.2 million (11%)	400,000 (28.5%)
Multidrug-resistant TB	480,000 (4.6%) and 100,000 RFP resistant	190,000 (13.5%)

WHO report, 2016

Estimated TB incidence rate in 2015



Asia: 58%

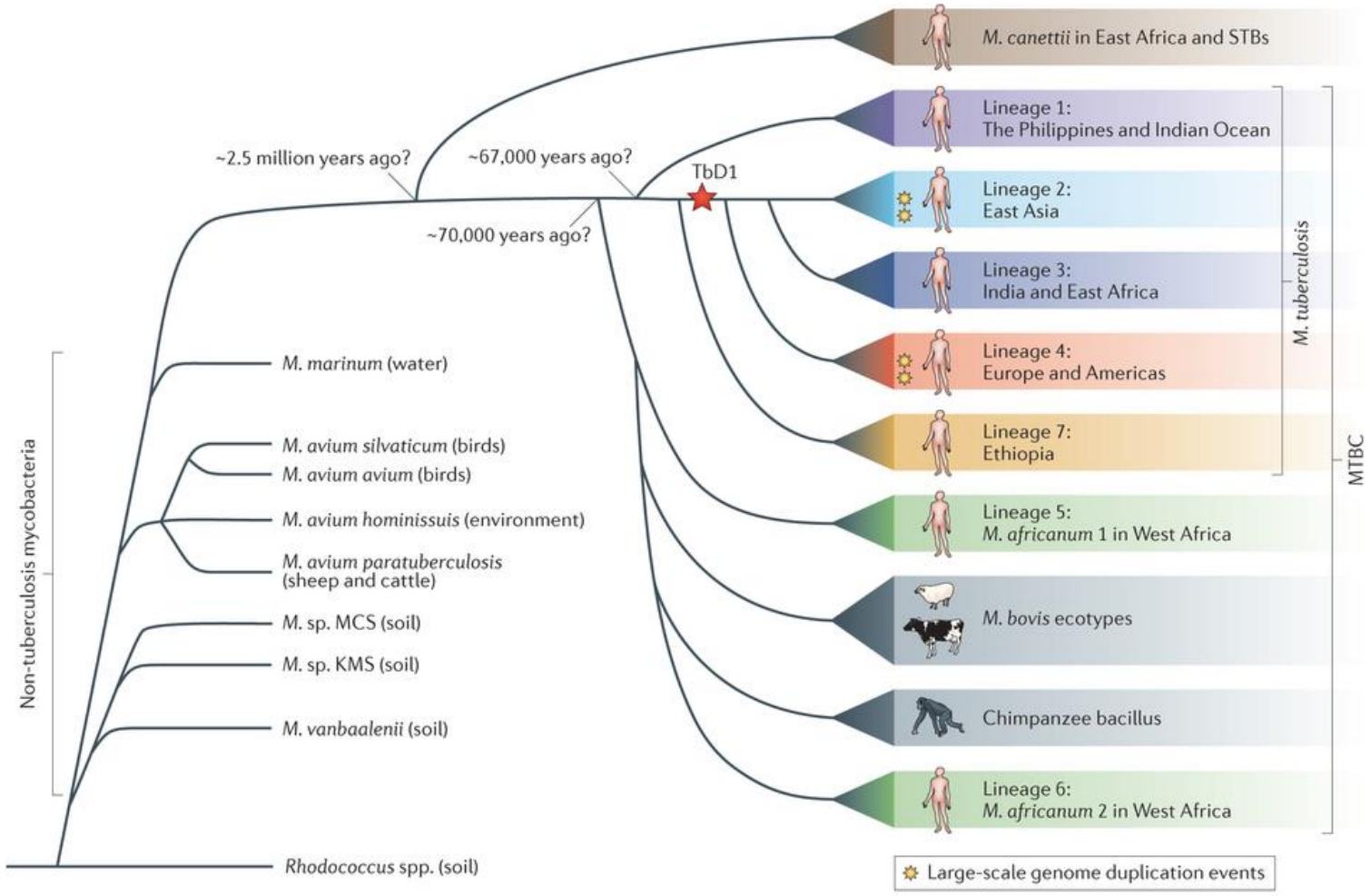
Asia: 28%

WHO report, 2016

This talk…

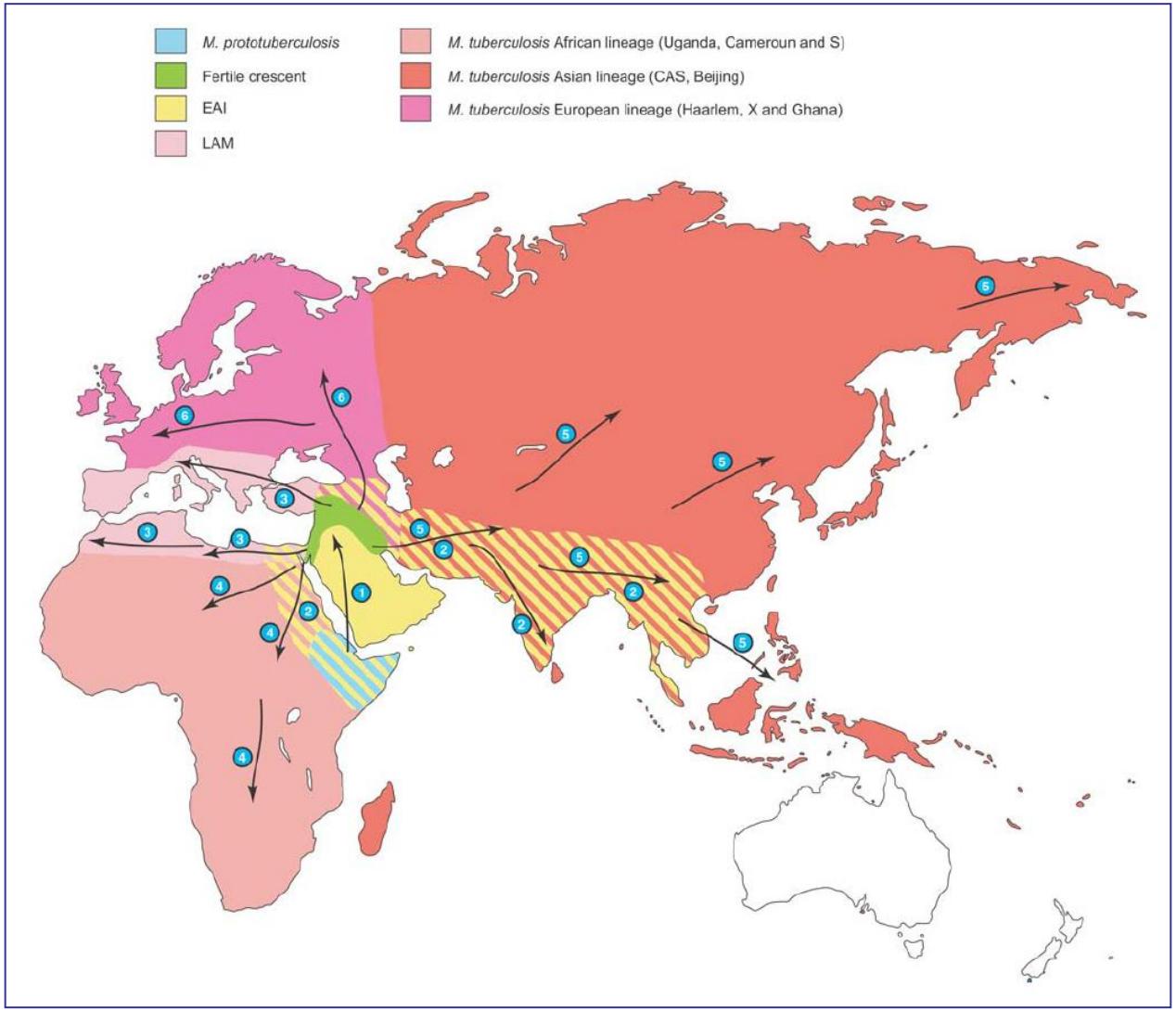
TB microbiology…Mtb lineages

M. tuberculosis evolution



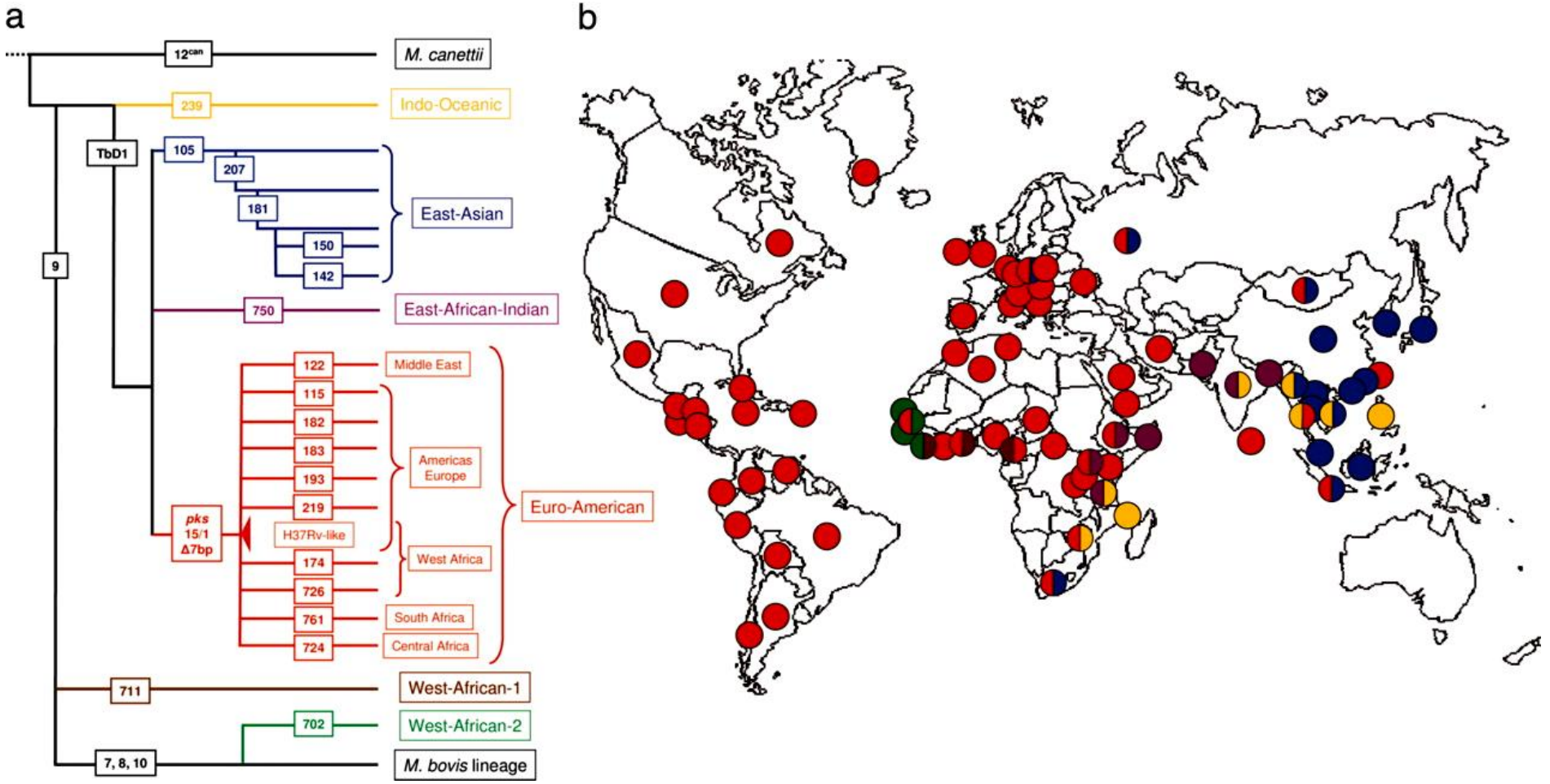
Galagan, Nature Genetics, 2014

M. tuberculosis evolutionary scenario (out of Mesopotamia)



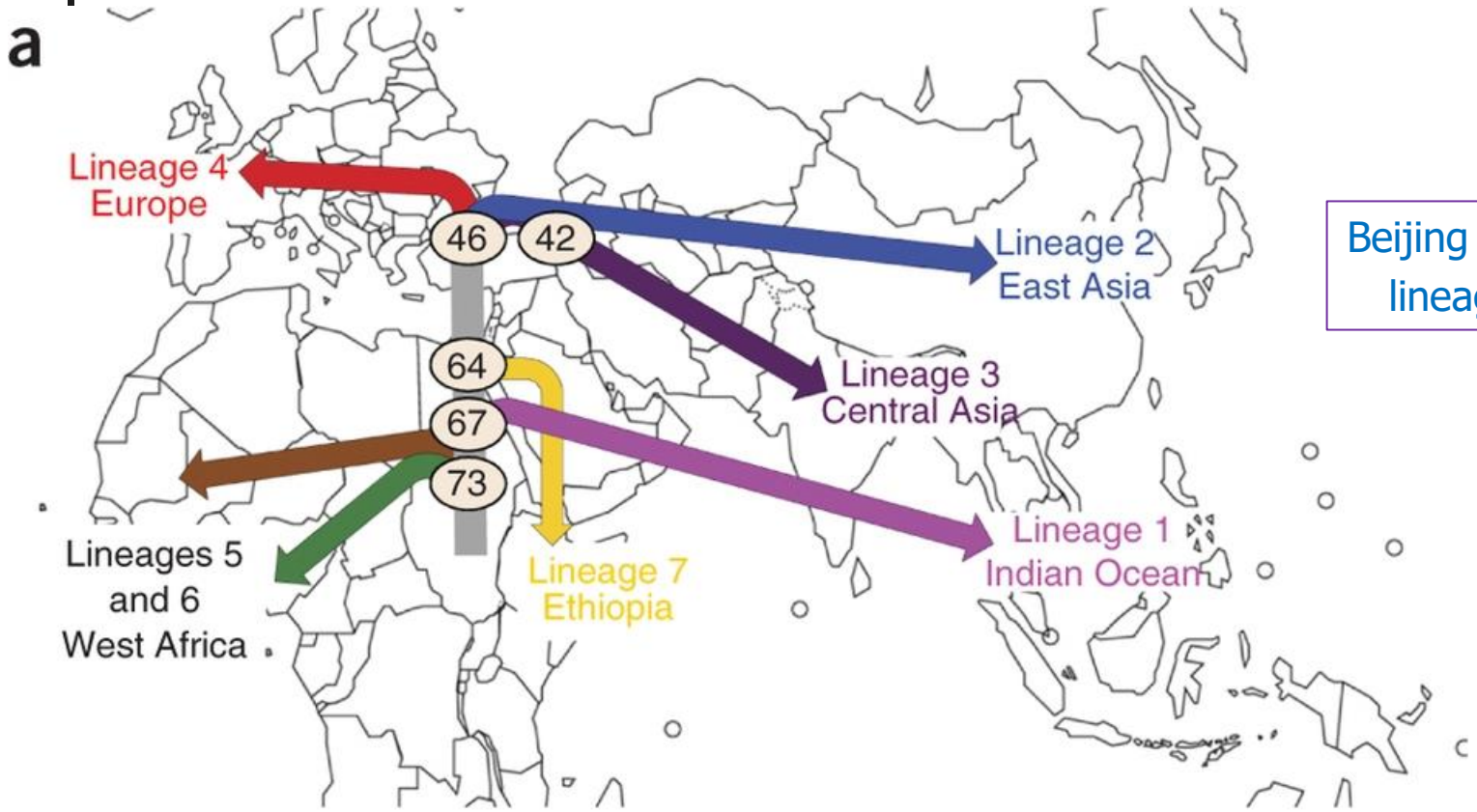
Wirth T, Plos Pathogens, 2008

The global population structure and geographical distribution of *M. tuberculosis*



Gagneux et al, PNAS, 2006

Association between Mtb lineages and ethnic groups underscore the continuous adaptive process between Mtb and its host



Beijing strain, lineage 2

Comas I, Nat Genetics, 2013

Evolution of *M. tuberculosis* in modern age

- Do the strains belonging to different phylogeographic lineages show differences in terms of pathogenicity, virulence, transmissibility, ability to acquire determinants of drug resistance?
- Is the ongoing TB pandemic stable?
- What will be the impact in the future?

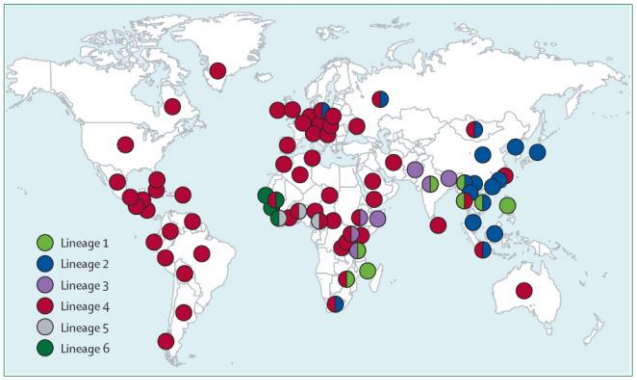


Figure 2: **Global phylogeography of *M tuberculosis***
Dots indicate the dominant lineage in country as sampled in Gagneux et al[86] with additional data from Filliol et al.[48]
Adapted with permission from Gagneux et al,[86] copyright (2006) National Academy of Sciences USA.

Migrants and TB

- Tuberculosis (TB) burden in high-income countries is primarily amongst the foreign-born, migrant population
- The reasons underlying this burden are the interaction of migration from high TB burden countries and the reactivation of remotely acquire latent tuberculosis infection in the first five years after arrival
- Genotyping data suggests that there is relatively little transmission in migrant communities in the receiving country
- Methods of TB control in migrant population have historically focused on identifying active tuberculosis but the yields for this remain relatively low

This talk…

TB screening

Migrants and TB in Europe

- In 2014, 219,00 migrants and refugees reached Europe by land and sea
- In 2015, more than 1 million migrants and refugees reached Europe by land and sea
- In 2016, January-April, 181,673 migrants and refugees reached Europe with 1,261 deaths.
- Among those arrived by the Mediterranean see, 82% came from 10 countries, mainly:
  - Syrian Arabic Republic (43%)
  - Afghanistan (23%)
  - Iraq (14%), Pakistan (4%), Iran (4%)

Dara et al., ERJ, 2016

Percentage of tuberculosis notifications in the foreign-born for selected OECD high-income countries

Italy (around 60%)

Italy

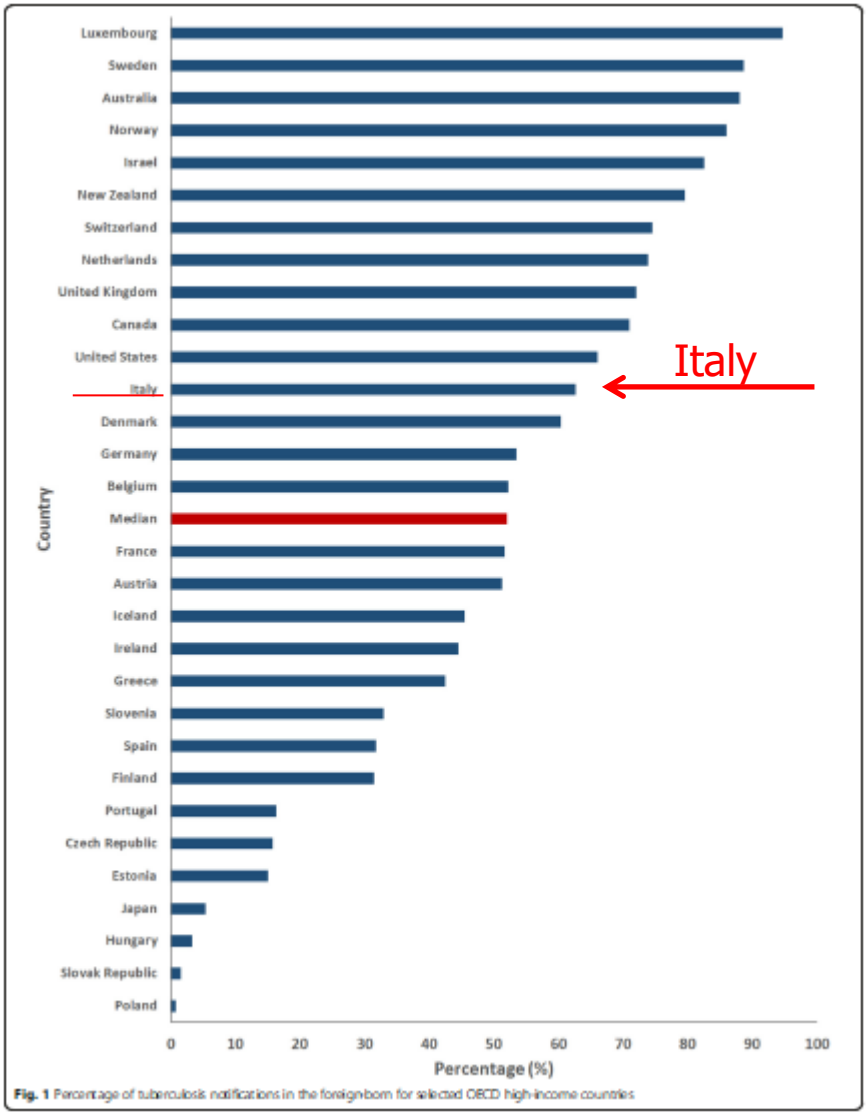


Fig. 1 Percentage of tuberculosis notifications in the foreign-born for selected OECD high-income countries

Pareek et al., BMC Medicine, 2016

TB burden in migrants: why?

The TB burden observed in foreign-born individuals occurs due to one of three reasons:

- Migrants from overseas must either have active TB on arrival (very rare, 0.35%)
- Migrants have remotely-acquired latent TB infection which reactivates post-arrival (5-72%, it correlates with TB incidence in the country of origin and age)
- Migrants acquire TB, following arrival, through local transmission

Pareek et al., BMC Medicine, 2016

Meccanismi responsabili dello sviluppo di tubercolosi nel migrante

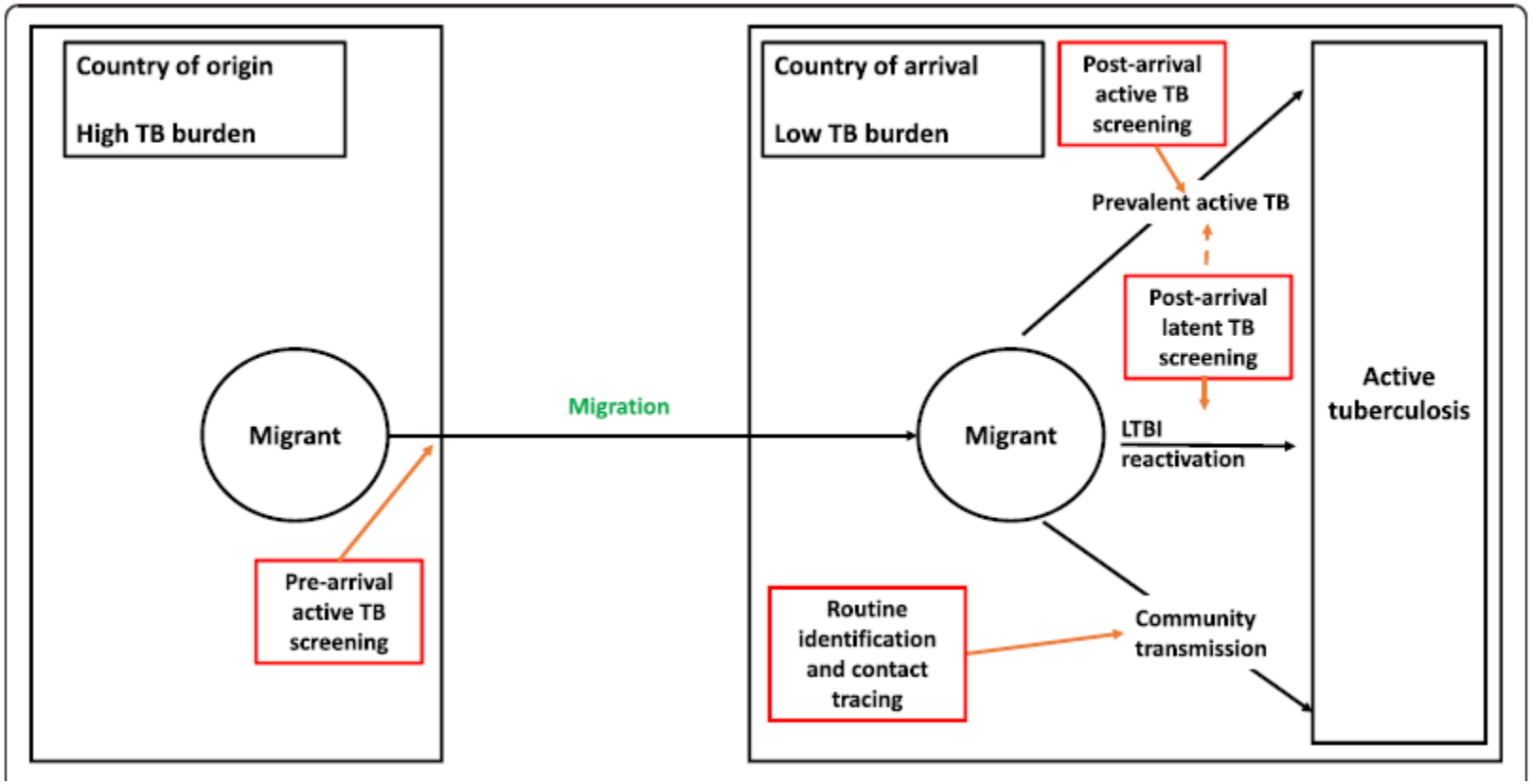
Riattivazione dell'infezione tubercolare latente (LTBI)

- Incidenza di TB nel paese di origine
- infezione da HIV
- Diabete
- Malattie renali croniche
- emarginazione sociale
- variazioni dietetiche, malnutrizione
- stress emotivo
- alcolismo
- droga

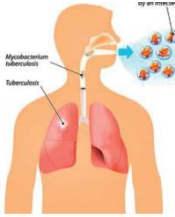
Nuova infezione esogena

- alta prevalenza di forme tubercolari bacillifere in comunità
- precarie condizioni di vita
- cofattori (HIV, tossicodipendenza)

Schematic diagram of migration, factors determining how incident active tuberculosis occurs and methods of screening migrants



Pareek et al., BMC Medicine, 2016



Different approaches for the migrant screening process methods

Table 3 Potential strengths and weaknesses of different migrant screening methods

	Screening methodology	
	Screening for active tuberculosis	Screening for latent tuberculosis infection
Screening tool used	Chest x-ray	Tuberculin skin test
		Interferon gamma release assay
Screening location	Pre-arrival	Post-arrival
	At arrival	
	Post-arrival	
Strengths	Able to identify active TB	Identifies latent TB before reactivation occurs
	Able to identify infectious individuals	Can be built into community programmes
	Can be integrated into immigration processes	Targeted screening likely to be cost-effective
Weaknesses	Low yields for active TB	Programmatically difficult to implement
	Uncertain cost-effectiveness (unless screening targeted)	Numbers accepting and completing treatment may be suboptimal
	Does not identify patients with latent TB who can go on to reactivate	

Pareek et al., BMC Medicine, 2016

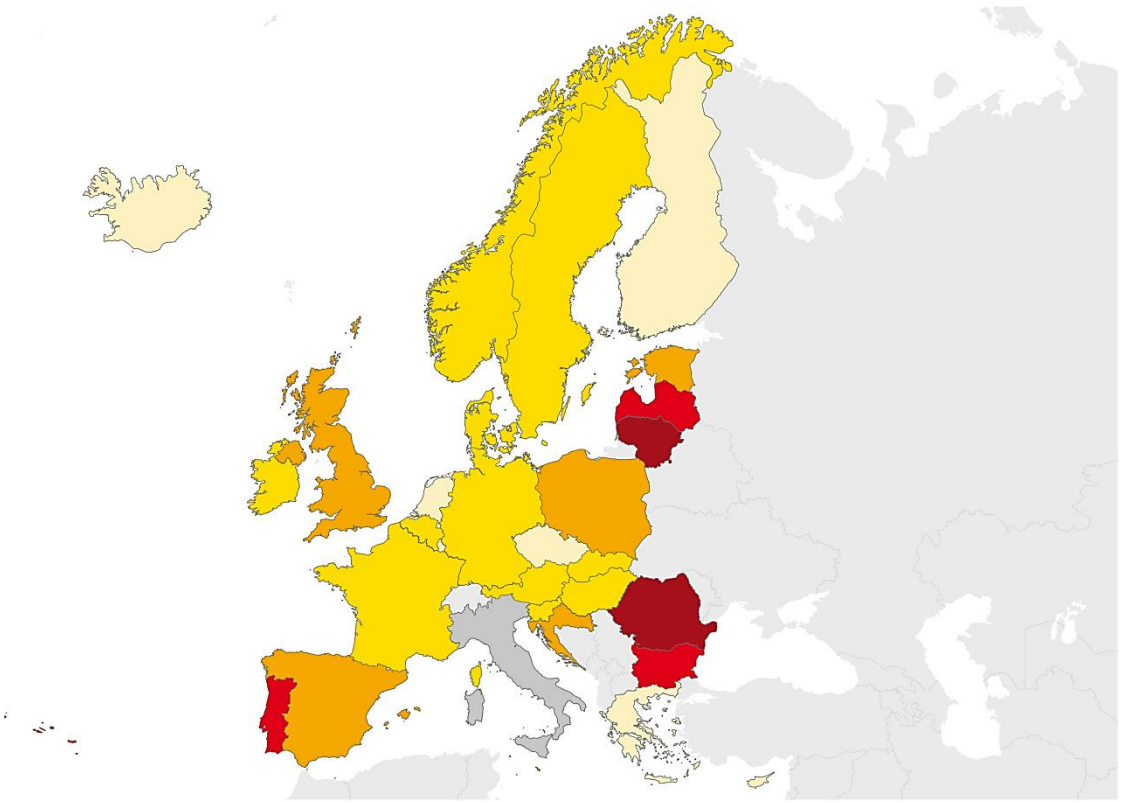
Yields for active tuberculosis from previous meta-analyses

Author	Year	Yield for active tuberculosis (%)		
		Overall	Pre-arrival	At/post-arrival
Klinkenberg [19]	2009	0.35	1.21	0.31
		0.51		
Arshad [18]	2010	0.35	-	0.35
Aldridge [71]	2014	0.22	0.22	-

Pareek et al., BMC Medicine, 2016

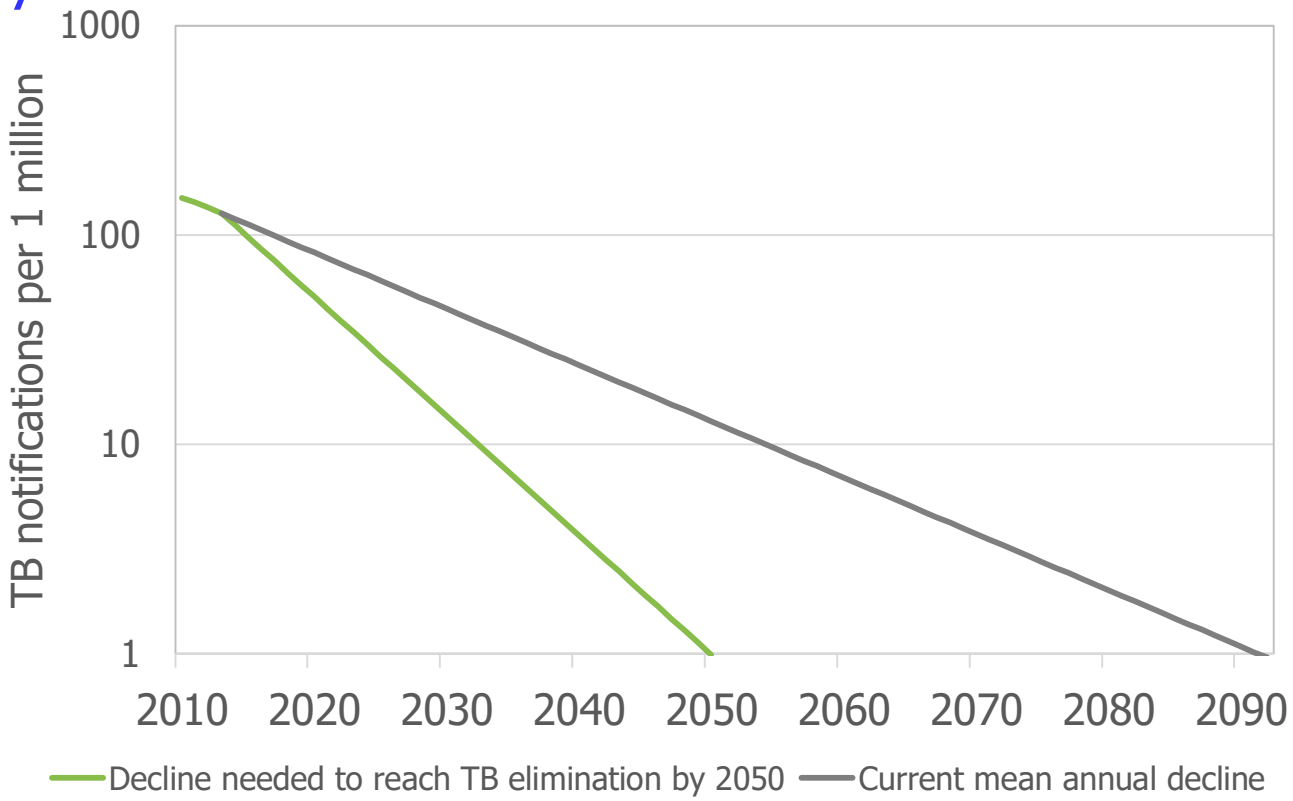
Background
TB notifications by country, EU/EEA, 2014

- 58 008 TB cases in 29 EU/EEA countries
  - 12.8 per 100 000 population (range 2.5–79.7)



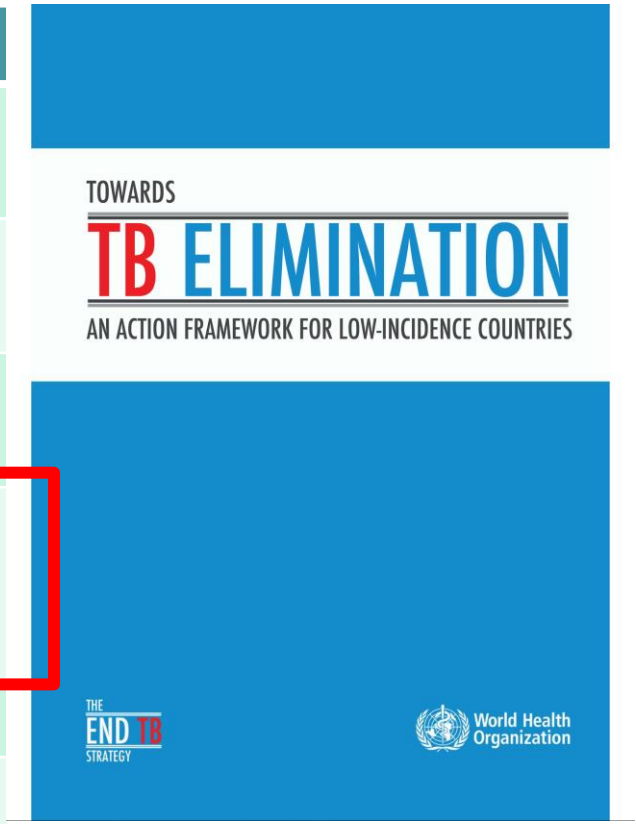
Background
Towards TB elimination in EU/EEA

- With current mean annual change in the TB notification rate (-6%), the EU/EEA will achieve TB elimination by 2092.
- To reach elimination by 2050, TB rates need to decline by 12% annually.



Towards TB elimination: An action framework for low-incidence countries

Priority action area
1. Ensure political commitment, funding and stewardship for planning and essential services of high quality.
2. Address the most vulnerable and hard-to-reach groups.
3. Address special needs of migrants and cross-border issues.
4. Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups, and provide appropriate treatment.
5. Optimize the prevention and care of drug-resistant TB.
6. Ensure continued surveillance, programme monitoring and evaluation and case based-data management.
7. Invest in research and new tools.
8. Support global TB prevention, care and control.



TB screening in Europe

ORIGINAL ARTICLE
TUBERCULOSIS

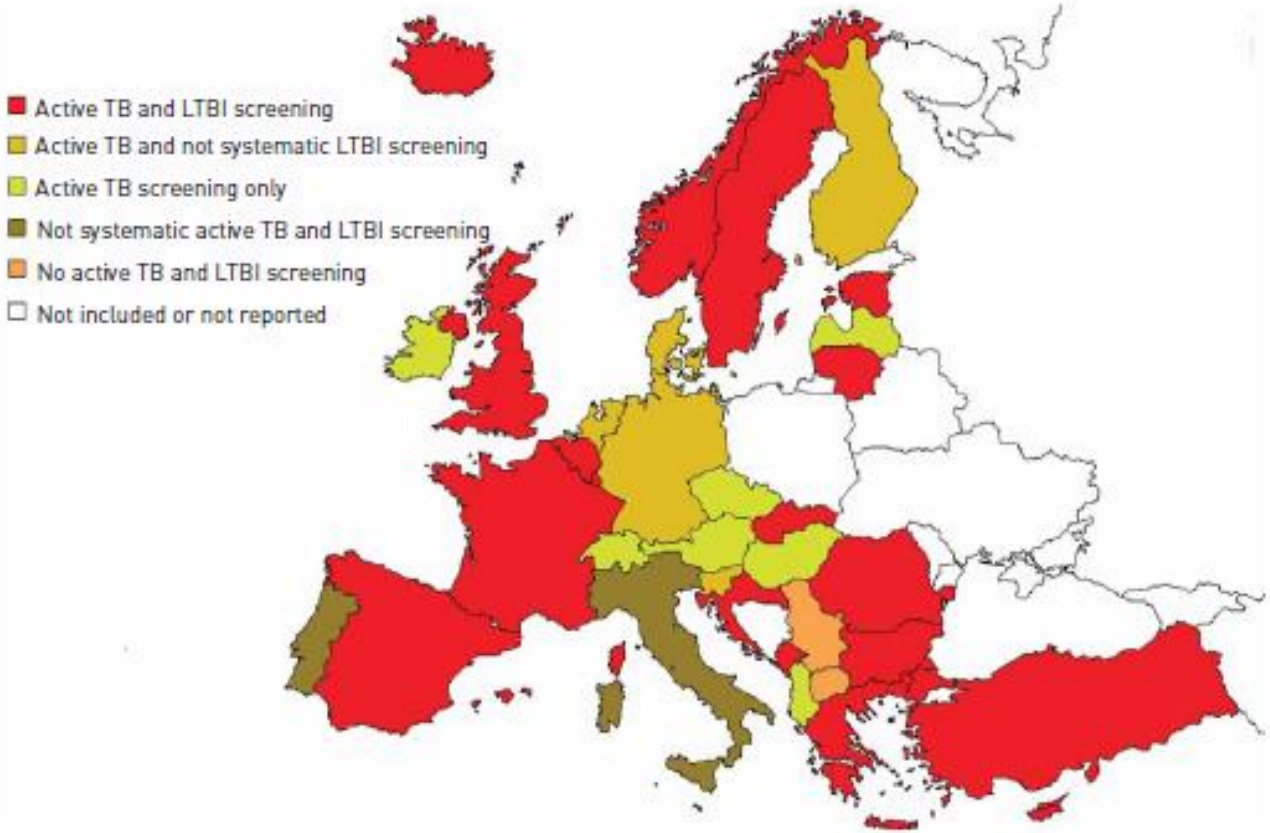
Tuberculosis care among refugees arriving in Europe: a ERS/WHO Europe Region survey of current practices

Masoud Dara[1,15], Ivan Solovic[2,15], Giovanni Sotgiu[3,15], Lia D'Ambrosio[4,5,15], Rosella Centis[4,15], Richard Tran[1,15], Delia Goletti[6], Raquel Duarte[7], Stefano Aliberti[8], Fernando Maria de Benedictis[9], Graham Bothamley[10], Tom Schaberg[11], Ibrahim Abubakar[12], Vitor Teixeira[13], Brian Ward[13], Christina Gratziou[14] and Giovanni Battista Migliori[4]

- A questionnaire investigating screening and management practices among refugees was sent to 38 national TB programme representatives of low and intermediate TB incidence European countries/ territories of the WHO European Region.

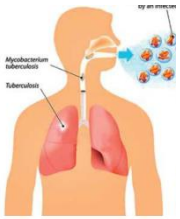
- Out of 36 responding countries, 31 (86.1%) reported screening for active TB, 19 for LTBI, and 8 (22.2%) reporting outcomes of LTBI treatment.

TB screening in Europe



Dara et al, ERJ 2016

Active TB screening in migrants in Europe




Screening for TB is performed with algorithms using different combinations of :

- symptom-based questionnaires and/or
- sputum smear/culture collection and/or
- Chest radiography

Dara, ERJ, 2016

Procedures if active tuberculosis is diagnosed

Procedures if active tuberculosis is diagnosed

- No: refusal of asylum: 34/36 (94.4%)
- Yes: obligation to undergo treatment: 24/36 (66.6%)
- Other: 10/36 (27.7%)
- Not applicable: 2/36 (5.5%)

Obligation to undergo treatment

Where

- Treatment in hospital: 24/36 (66.6%)
- Not applicable: 8/36 (22.2%)
- Not answered: 4/36 (11.1%)

When

- Treatment immediately started after diagnosis: 26/36 (72.2%)
- Not answered 2/36 (5.5%)
- Not applicable: 8/36 (22.2%)

Funding

- Governmental funds: 26/36 (72.2%)
- Not answered: 2/36 (5.5%)
- Not applicable: 8/36 (22.2%)

Dara et al, ERJ 2016

Screening for LTBI: Migrants and TB

To screen by TST or IGRA

- Who? Only those coming from high TB endemic countries (definition: above 150 for 100,000 inhabitants, like in UK; or above 30 for 100,000 inhabitants, like in Canada)

- After the screening, what to do? Offer a preventive therapy; ensure completion of treatment

Dara et al., ERJ, 2016

Procedures if LTBI is diagnosed

Procedures if latent tuberculosis infection is diagnosed

- No, refusal of asylum: 20/36 (55.5%)
- Yes, obligation to undergo preventive therapy: 8/36 (22.2%)
- Other: 18/36 (50%); Not applicable: 8/36 (22.2%)

Obligation to undergo preventive therapy

Proposed to all positive for latent tuberculosis infection

- Proposed to all positive for latent tuberculosis infection: 3/36 (8.3%)
- No, proposed for specific groups and ages only: 7/36 (19.4%)
- Not applicable: 24/36 (66.6%); Not answered: 1/36 (2.7%)

Same procedure as native nationals positive for latent tuberculosis infection

- Same procedure as native nationals positive for latent tuberculosis infection: 7/36(19.4%)
- Not applicable: 24/36(66.6%); Not answered: 5/36 (13.8%)

Therapy delivery

Therapy delivered at chest/directly observed treatment/tuberculosis centres/tuberculosis

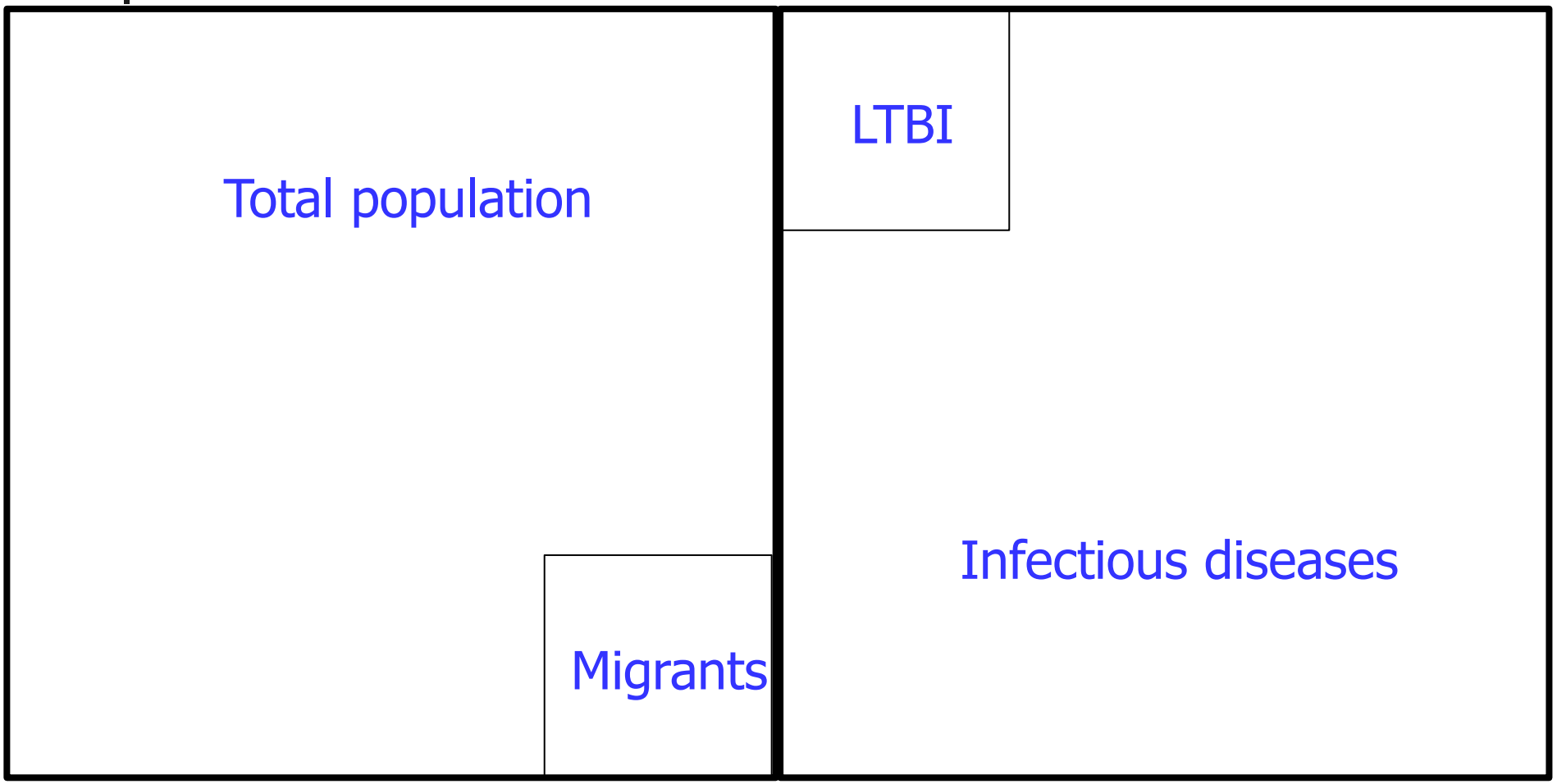
- specialists: 7/36 (19.4%); Not applicable: 23/36(63.8%); Not answered: 6/36 (16.6%)

Funding

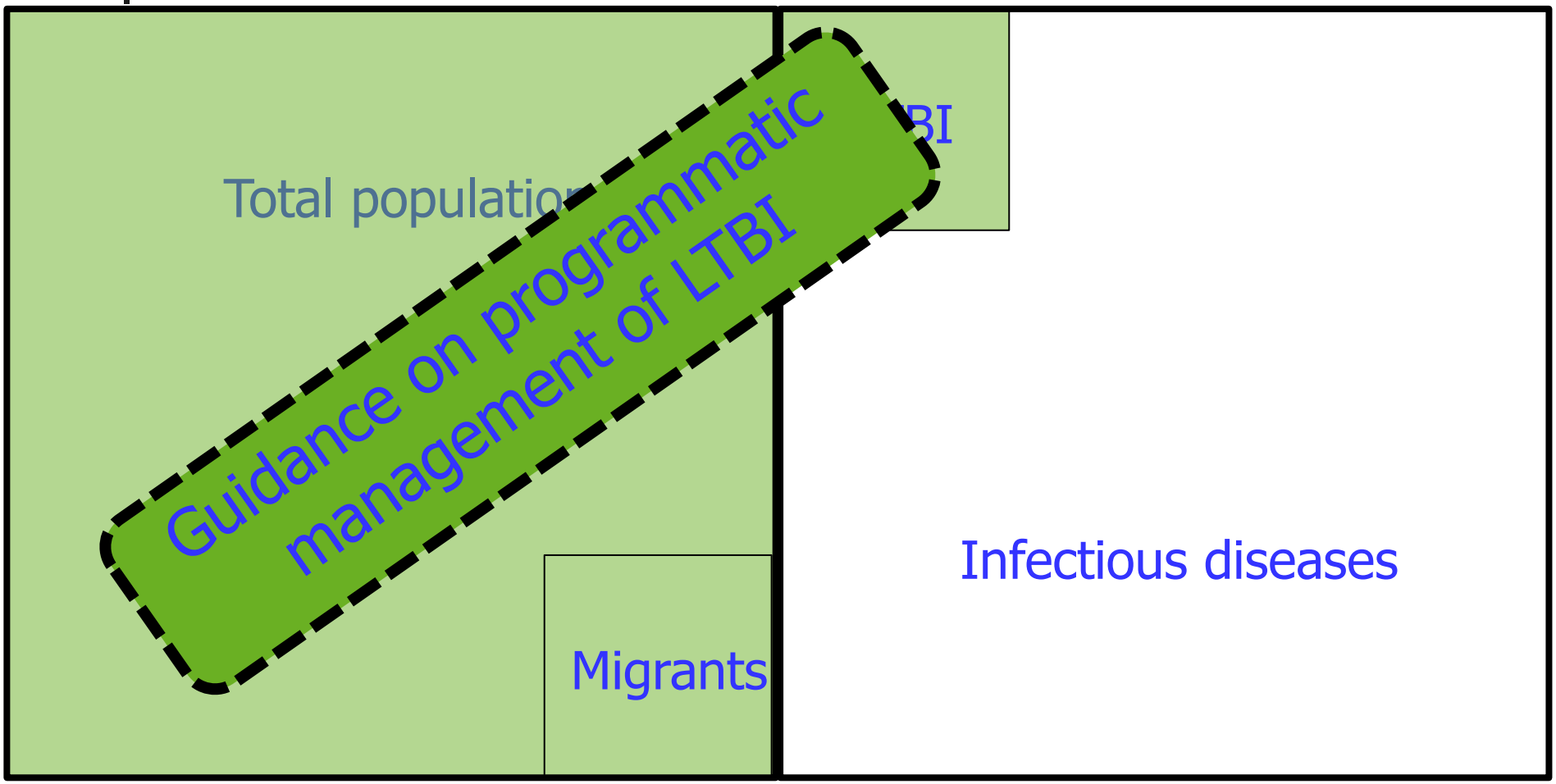
- Government budget: 9/36 (25%)
- Not applicable: 23/36 (63.8%); Not answered: 4/36 (11.1%)

Dara et al, ERJ 2016

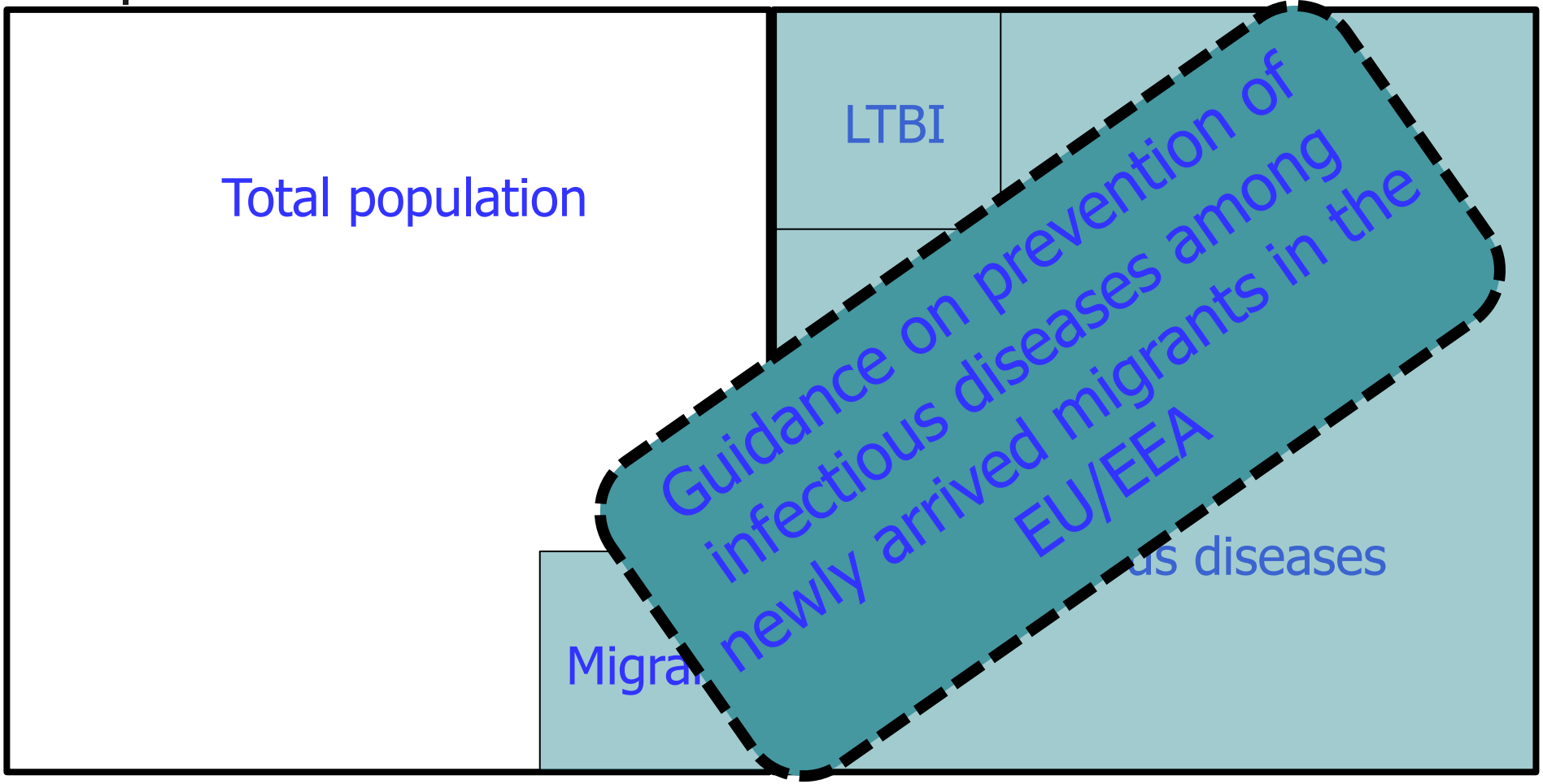
ECDC guidance: Applicability for TB control in migrants



ECDC guidance: Applicability for TB control in migrants



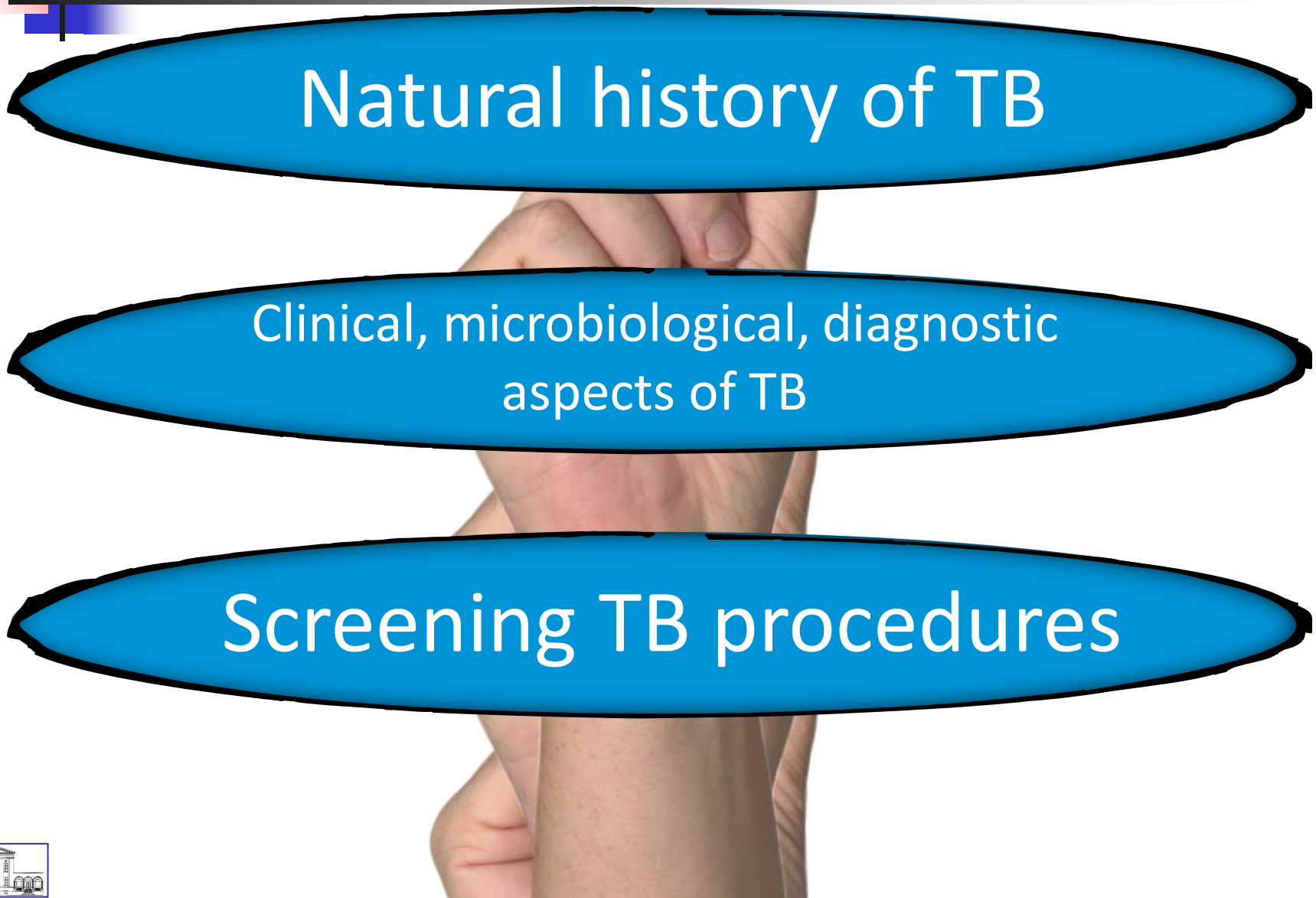
ECDC guidance: Applicability for TB control in migrants



My thanks …

- Giovanni Battista Migliori, Fondazione S. Maugeri IRCCS, Tradate, Italy
- Marieke J van der Werf, eCDC, Stockholm, Sweden
- Giuseppe Ippolito, National institute for Infectious Diseases, Rome, Italy

This talk…


Natural history of TB
Clinical, microbiological, diagnostic aspects of TB
Screening TB procedures