L’infezione da Micobatterio Tubercolare nel 2021: dall’epidemiologia alla clinica

Luigi R. CODECASA
Centro di riferimento per la TB-Villa Marelli
ASST Niguarda MILANO

Tubercolosi, malattia della povertà alla ricerca di soluzioni multisettoriali - Un modello di Global Health

- **Global burden**
- **Quali soluzioni nell'era dello sviluppo sostenibile e degli SDG?**

Main messages of the latest Global TB Report 2018

World Health Organization

TUBERCULOSIS

Global Tuberculosis Report 2018

54 million lives saved between 2000 - 2017

TB deaths fell by 33% in the same period

1.6 MILLION TB DEATHS

INCLUDING 0.3 MILLION TB DEATHS AMONG PEOPLE WITH HIV*

TB is the top infectious killer worldwide

TB is also the leading cause of deaths among people with HIV & a major cause of antimicrobial resistance related deaths

MDR-TB crisis with gaps in detection and treatment

Only 1 in 4 needing MDR-TB treatment were enrolled on it

US$ 3.5 BILLION GAP

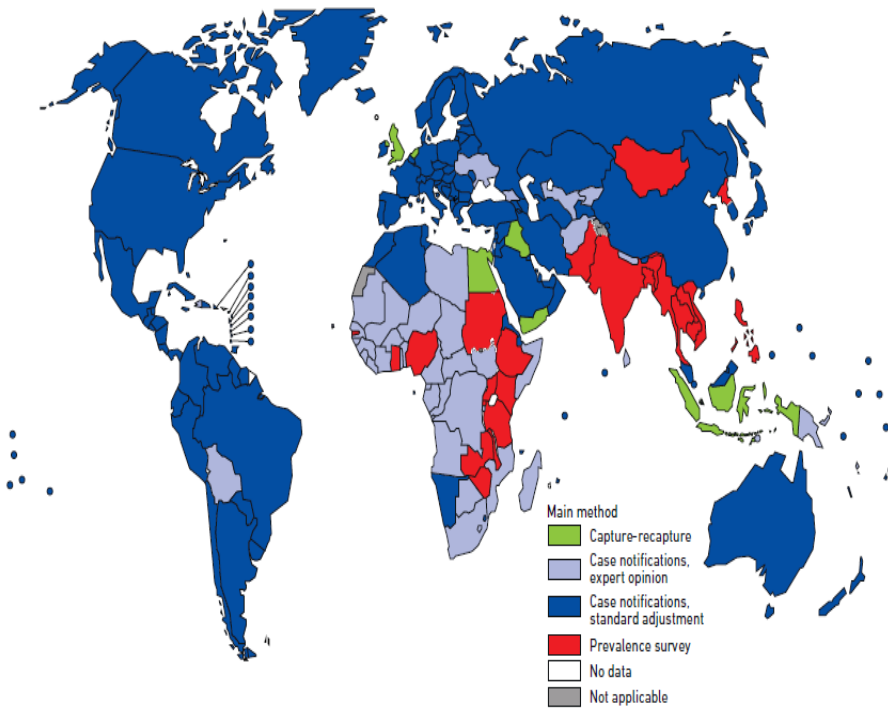
Funding shortfall for TB implementation

Gap of over US$1.3 billion per year for TB research

Data sources, TB burden estimates

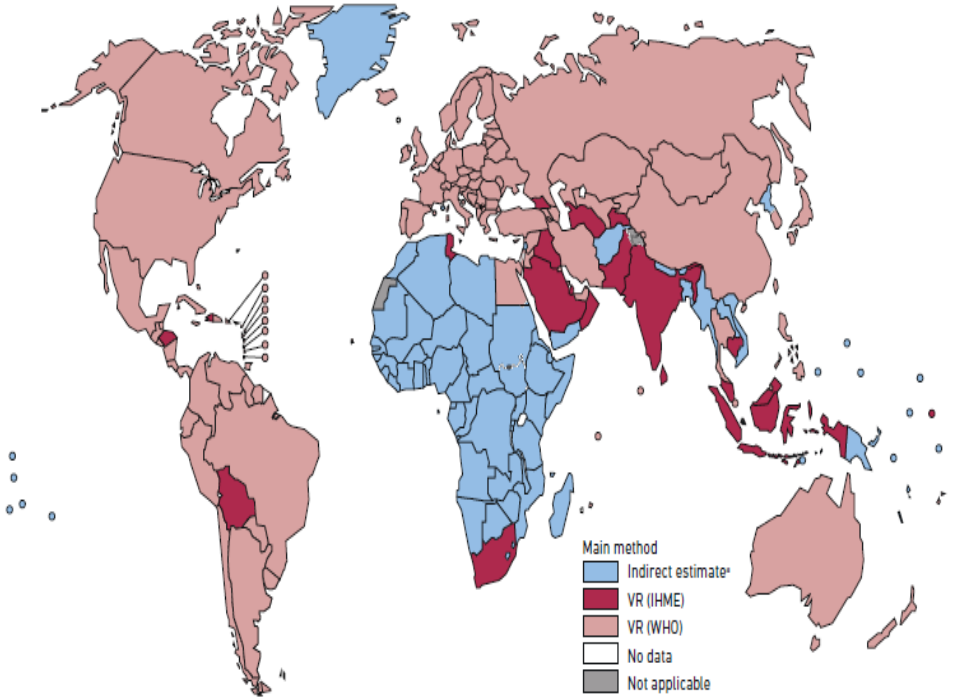
TB incidence

Main methods used to estimate TB incidence



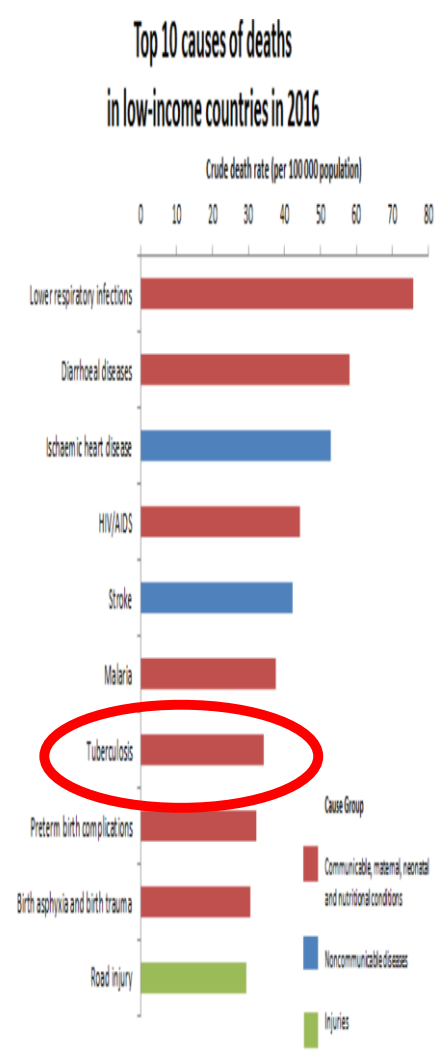
TB mortality

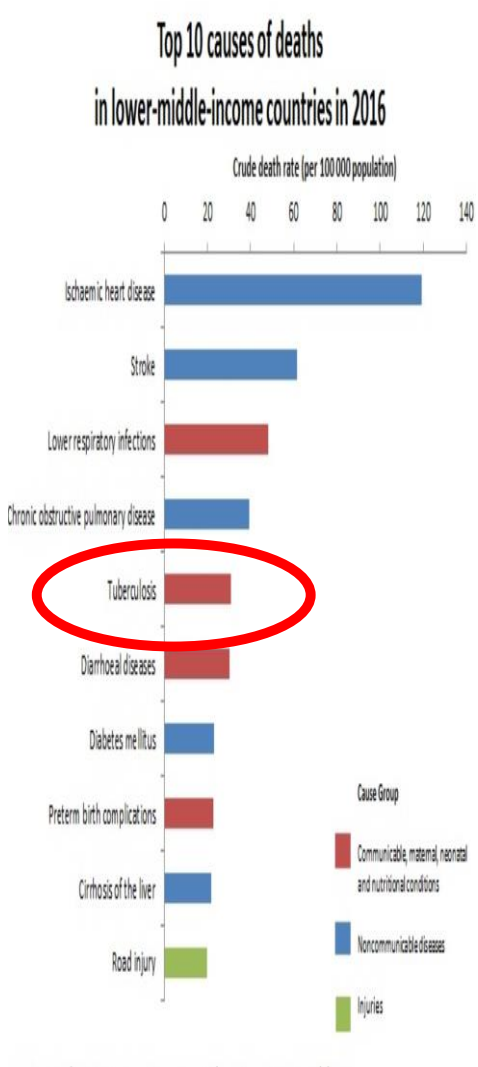
Main methods used to estimate TB mortality in HIV-negative people

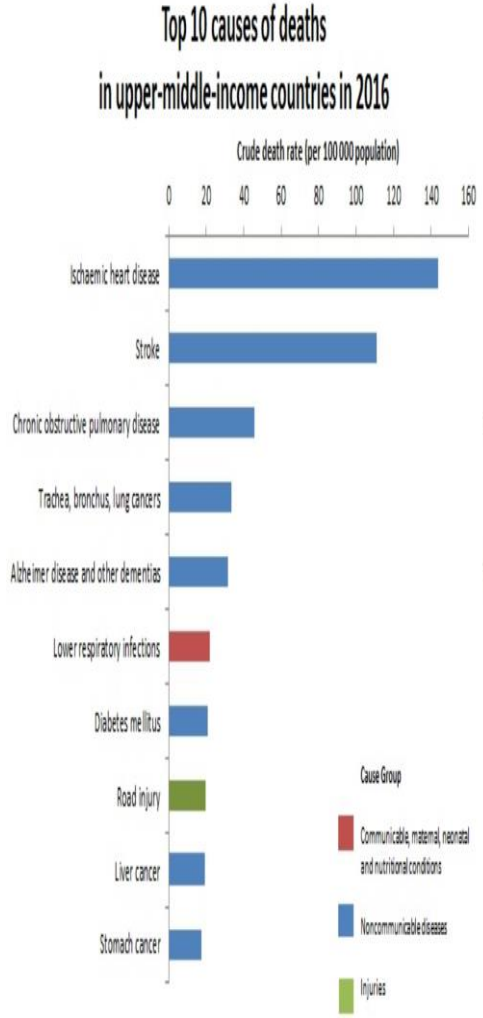


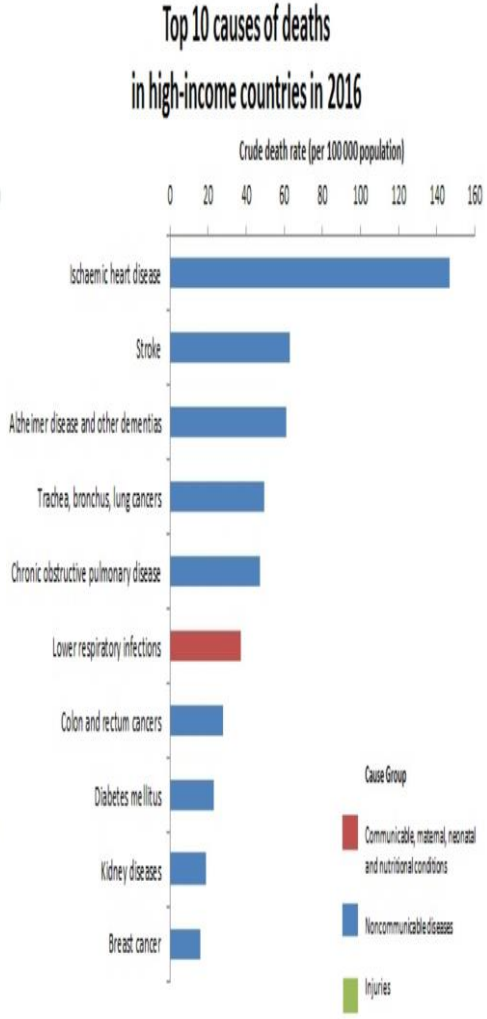
[a] Mortality is estimated as the product of TB incidence and the TB case fatality ratio. Further details are provided in the online technical appendix.

Causes of death by different income level, 2016

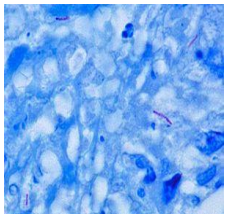


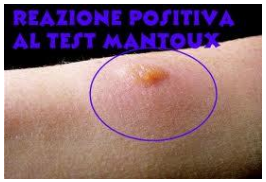


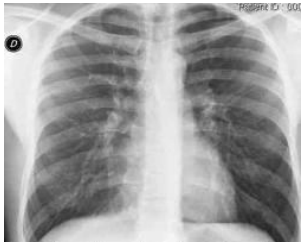




STORIA NATURALE SEMPLIFICATA DELLA TUBERCOLOSI







Fattori rischio di infezione

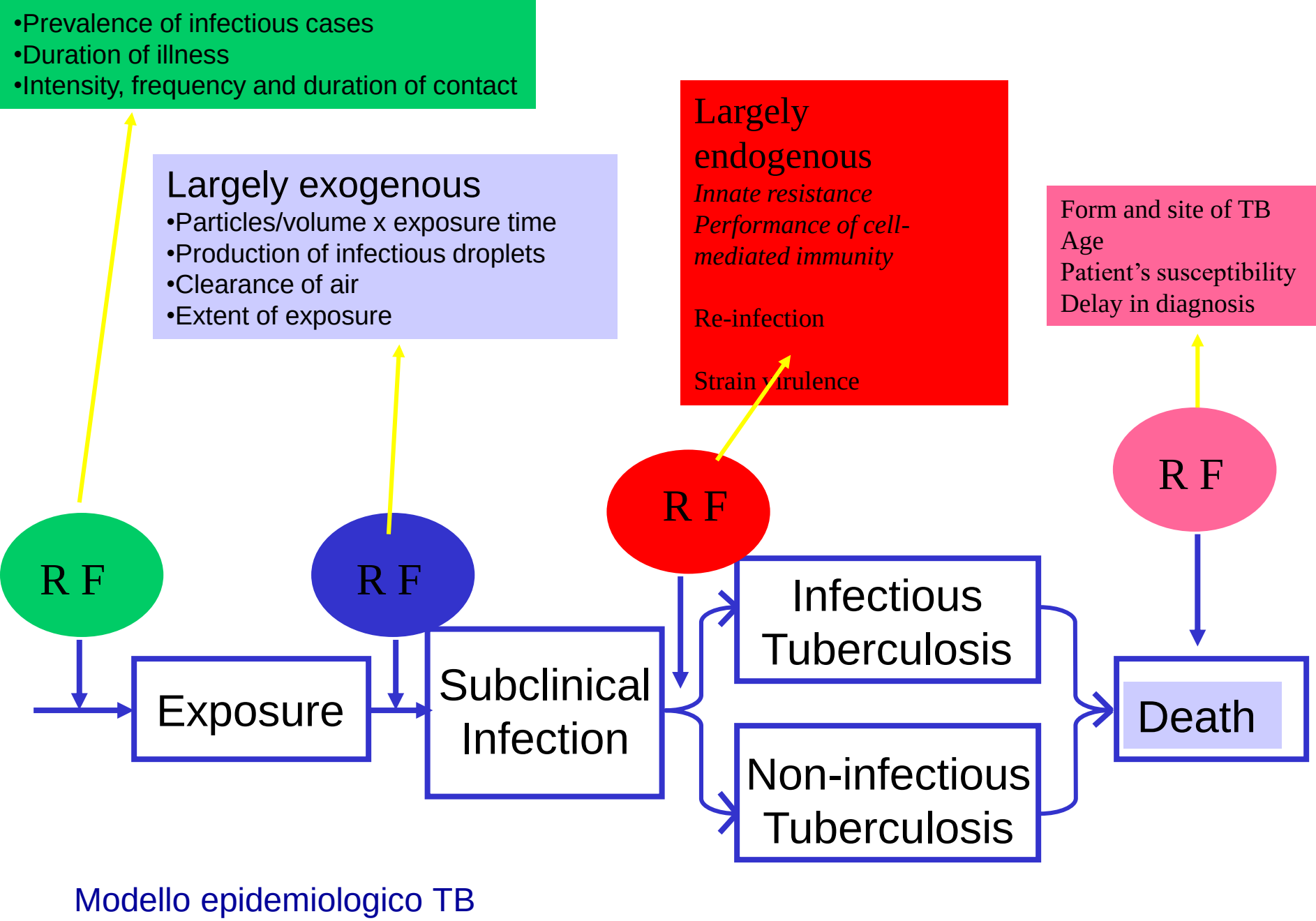
Fattori rischio di malattia

Fattori rischio di MDR

DPI, BCG

TERAPIA PREVENTIVA

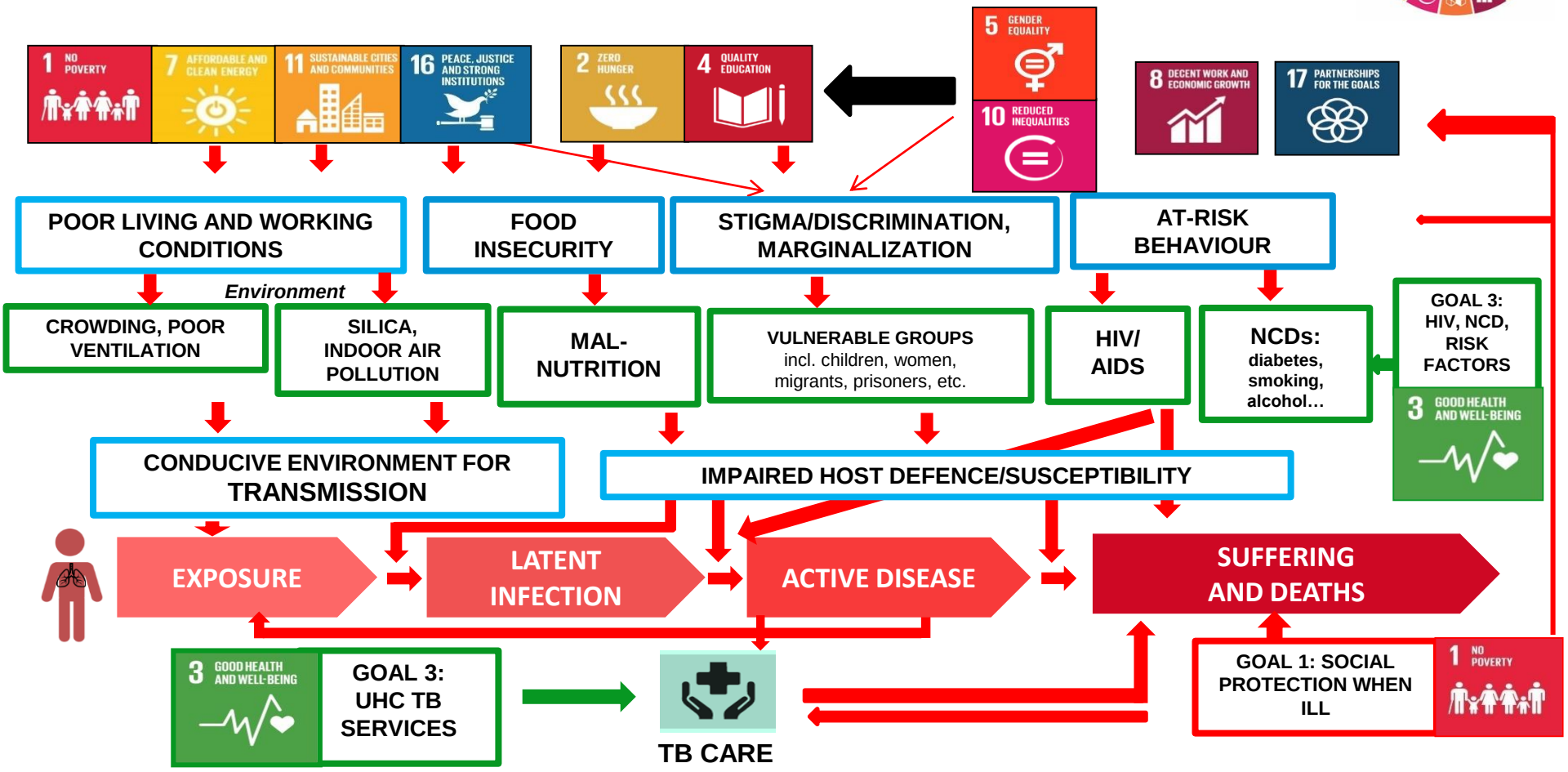
TERAPIA



Modello epidemiologico TB

TUBERCOLOSI:

STORIA NATURALE, DETERMINANTI E INTERVENTI POSSIBILI



The opportunity of the SDG era
to reach the end TB targets

SDG TARGET 3.3 – BY 2030

END THE TB EPIDEMIC

Transformational innovations to End TB

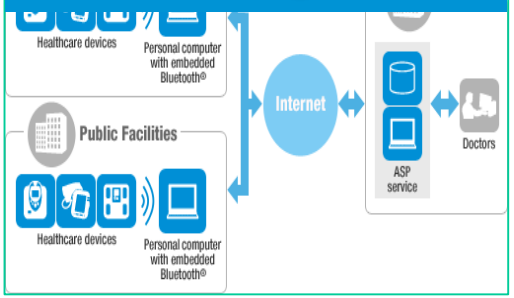
Precision medicine

Genomics

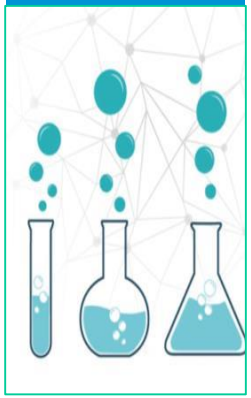
Big data

Digital

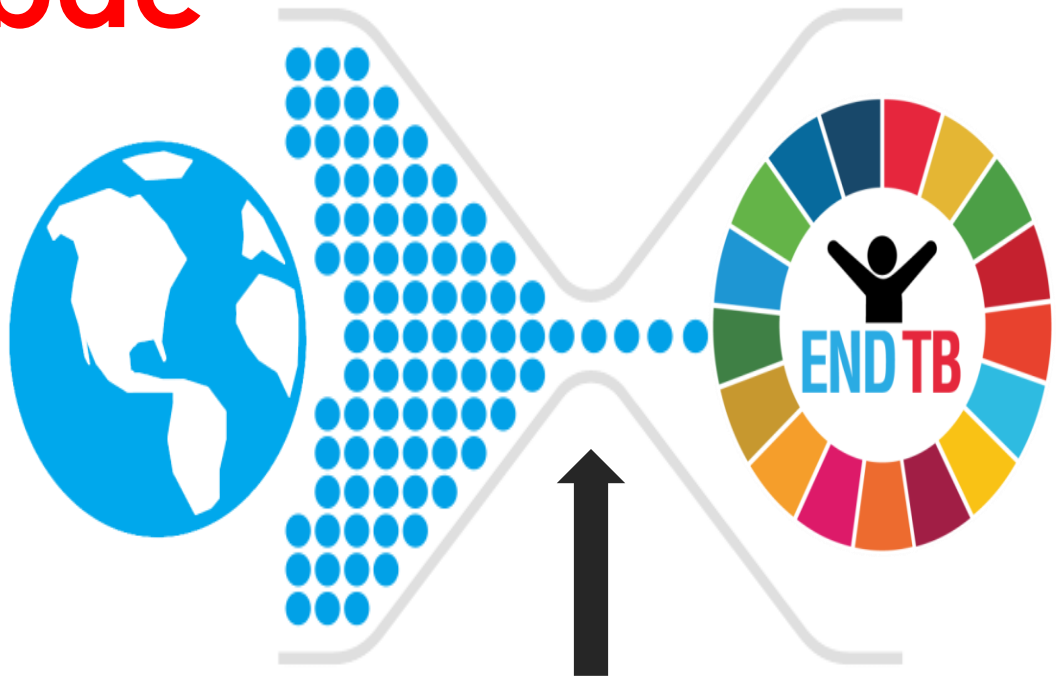
Internet of things



Resea



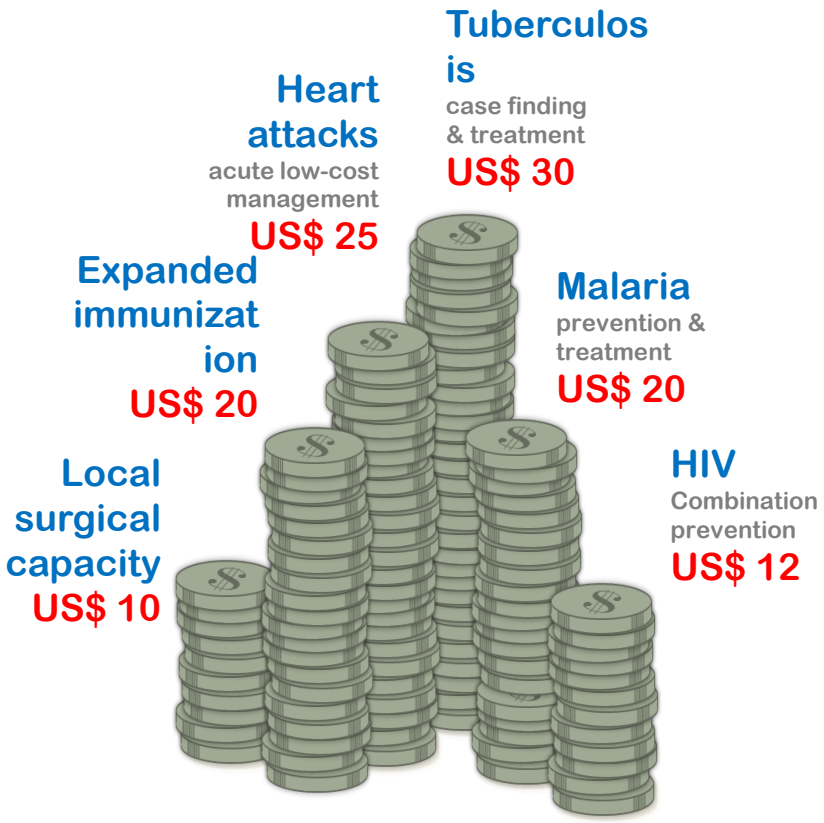
What is holding us bac' ?



The bottlenecks to end TB are fundamentally POLITICAL and FINANCIAL

Why investing towards ending TB?

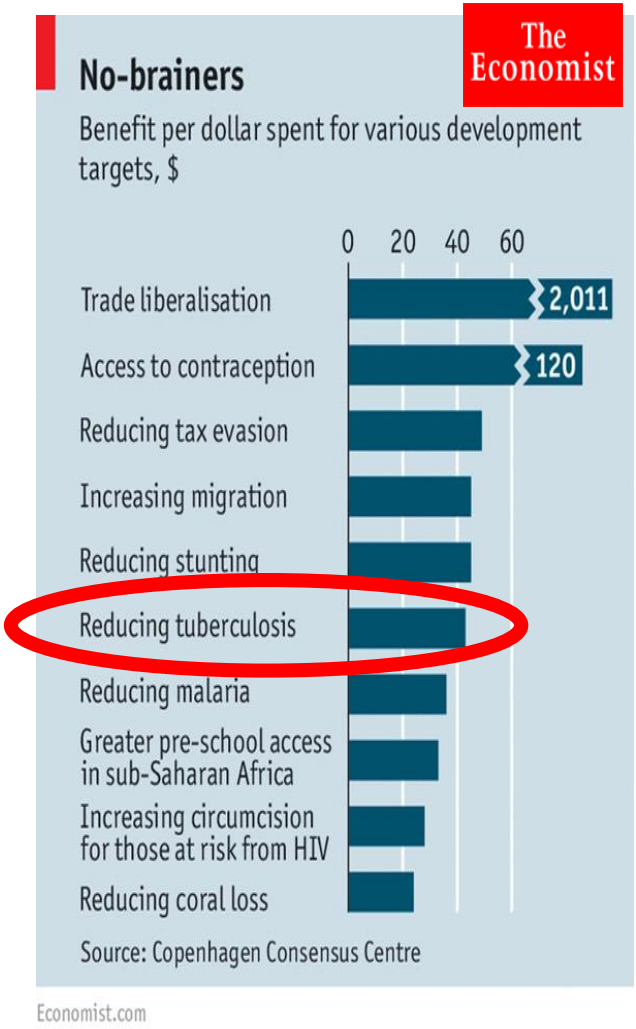
Simply it is the most cost-beneficial health intervention



Return on investment for every one dollar

sp Investing in our future The Global Fund To Fight AIDS, Tuberculosis and Malaria st cost-effective health i e n t i o n s

Report of the High-Level Panel of Eminent Persons on the Post-2015 Development Agenda, 2013



Bottleneck n. 1: Political indifference

Tuberculosis 8

Scale-up of services and research priorities for diagnosis, management, and control of tuberculosis: a call to action

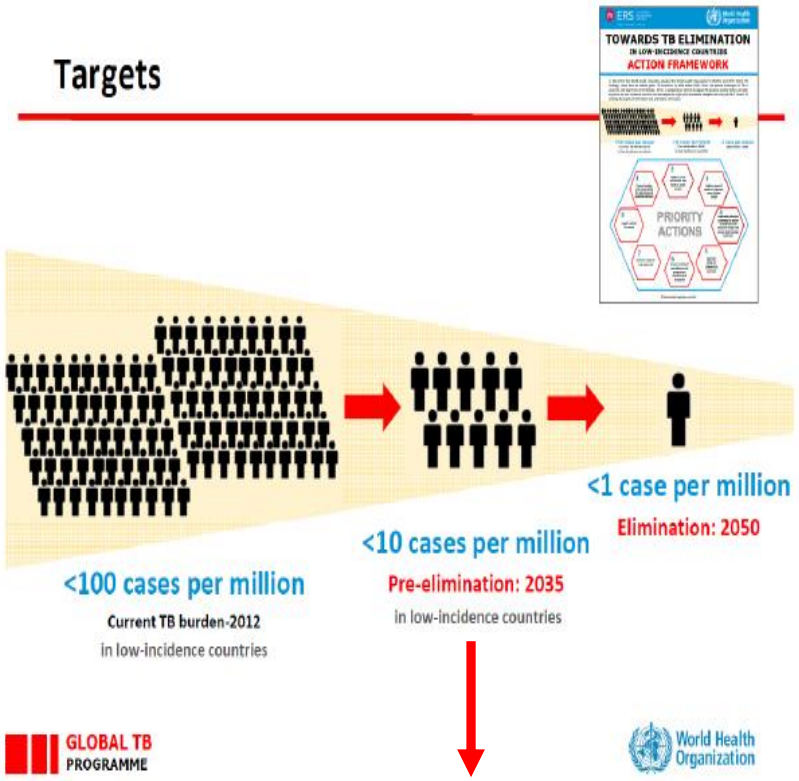
Ben J Marais, Mario C Raviglione*, Peter R Donald, Anthony D Harries, Afranio L Kritski, Stephen M Graham, Wafaa M El-Sadr, Mark Harrington, Gavin Churchyard, Peter Mwaba, Ian Sanne, Stefan H E Kaufmann, Christopher J M Whitty, Rifat Atun, Alimuddin Zumla**

The Millennium Development Goal target for tuberculosis control is to halt the spread of tuberculosis by 2015, and begin to reverse the worldwide incidence. After the introduction of standard control practices in 1995, 36 million people were cured and about 6 million deaths were averted. However, substantial scientific advances and innovative solutions are urgently needed together with creative new strategies. Strong international and national political commitment is essential. Urgent action is needed by national governments to fund their own programmes, and for the G8 countries and other donor governments and organisations to support governmental and non-governmental efforts. To foster the global need for urgent action to control the tuberculosis epidemic, *The Lancet*, in collaboration with the Stop TB Partnership, WHO, Global Fund to Fight AIDS, Tuberculosis and Malaria, and the experts participating in this Series, is launching *The Lancet* TB Observatory, which will assess and monitor progress in tuberculosis control and research, assess domestic and global financing, regularly disseminate information, and advocate for intensified efforts with stakeholders at all levels.

Lancet 2010; 375: 2179–91
Published Online May 19, 2010
DOI:10.1016/S0140-6736(10)60554-5
See Online/Comment DOI:10.1016/S0140-6736(10)60579-X
See Online/Comment DOI:10.1016/S0140-6736(10)60581-8
This is the eighth in a Series of eight papers about tuberculosis

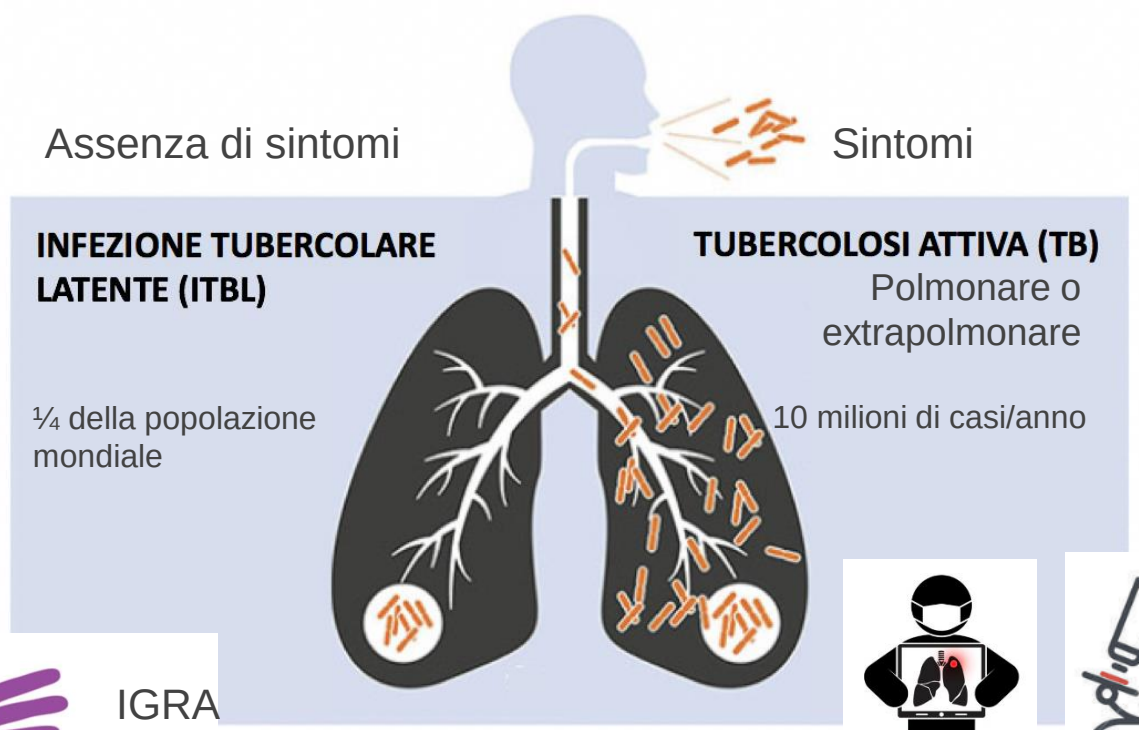
contributions. Creative funding design is no panacea however, and is seldom successful without dedicated political commitment. Fundamentally, what needs to be recognised is that the efforts to control tuberculosis have a severe lack of political commitment at the country and international levels. Funding for tuberculosis is neglected because it is not a special programme of the World Bank, is not a named priority among any UN agency leaders, does not have a special UN programme, is not in UNICEF's portfolio, is not a special presidential initiative in the USA, and does not have strong support from the pharmaceutical industry compared with HIV/AIDS, malaria, and non-communicable diseases. It was even omitted from the formal title of MDG 6 and only listed among its indicators. Yet tuberculosis is a major preventable cause of disease and death, and one of the diseases with the most cost-effective health interventions available today, considering that existing inexpensive interventions, although restricted in their effectiveness, have saved millions of lives. Efforts to

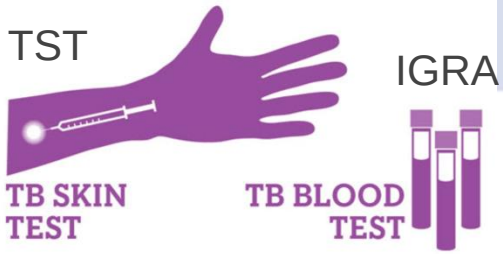
TB elimination strategy in low TB endemic countries



<10/100,000 <1/100,000 <0.1/100,000

TUBERCOLOSI IN UN FLASH:
EPIDEMIOLOGIA, CLINICA, SCREENING E DIAGNOSI

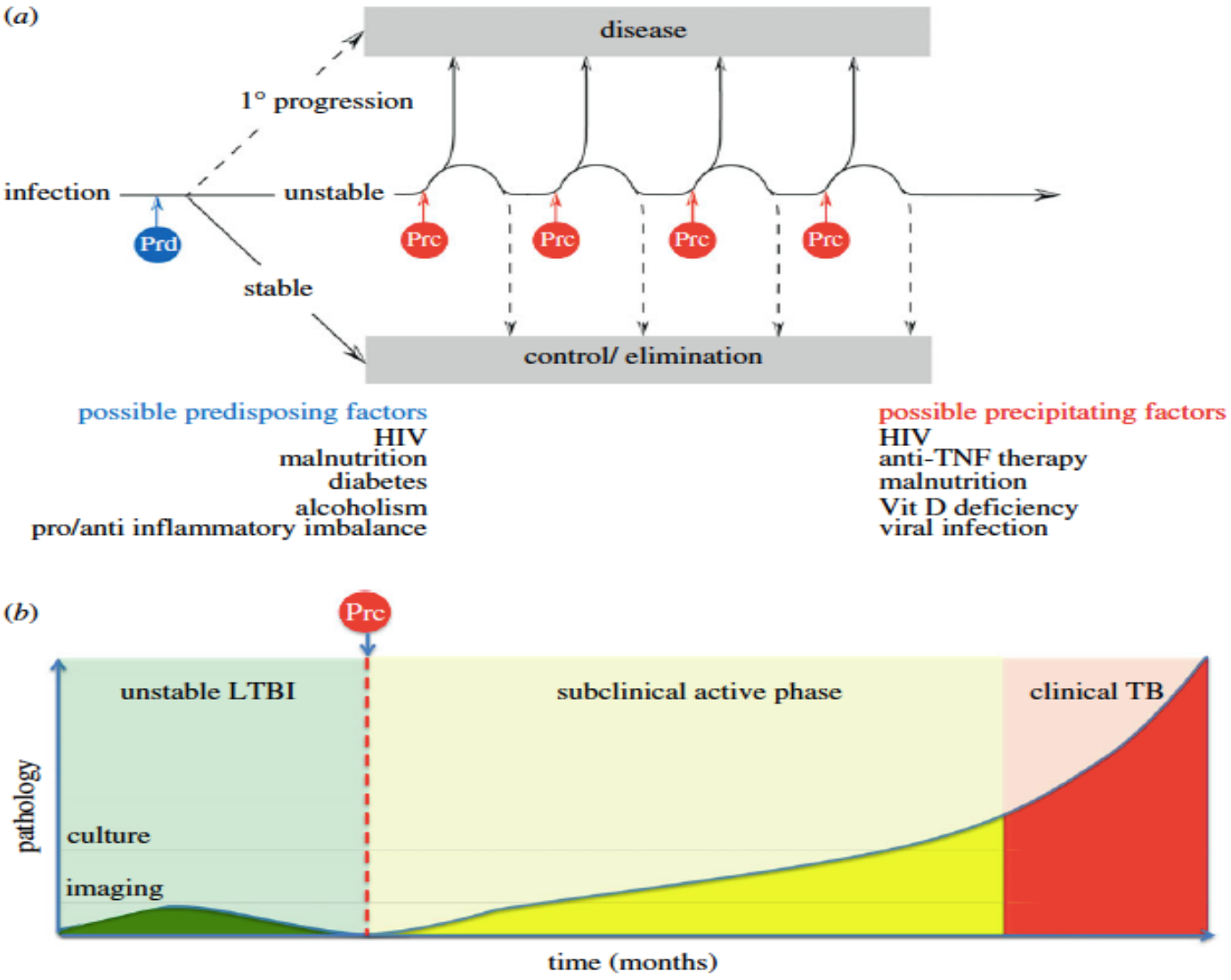


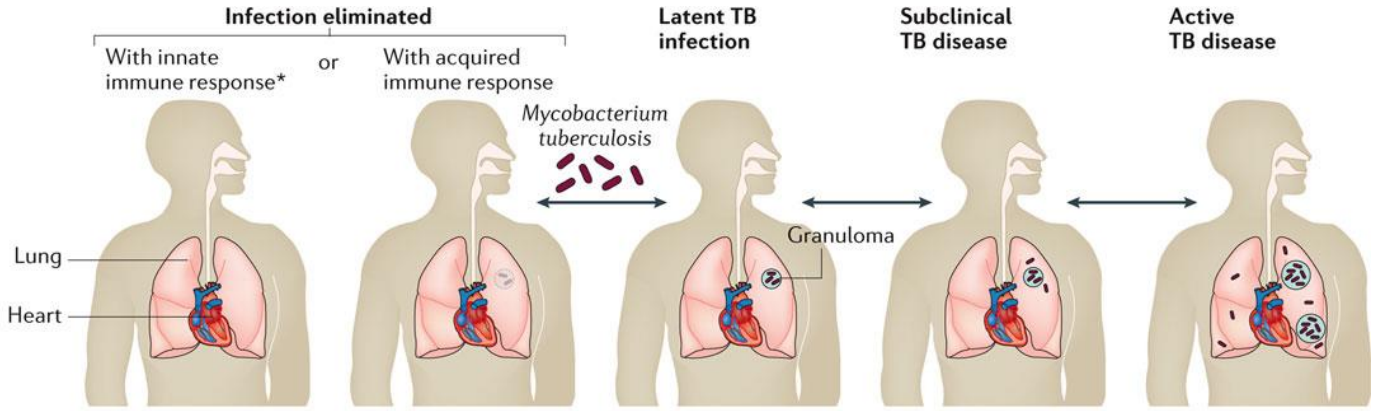


RX torace

Esami microbiologici:

- NAA technology;
- Microscopia;
- Coltura.

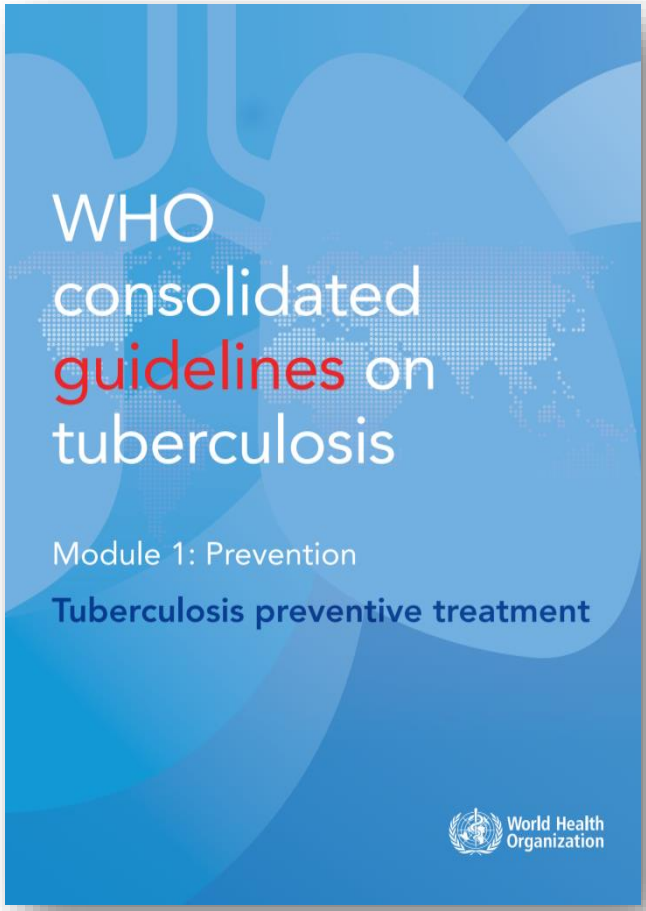

(a)
disease
1° progression
infection
unstable
Prd
Prc
Prc
Prc
Prc
stable
control/ elimination
possible predisposing factors
HIV
malnutrition
diabetes
alcoholism
pro/anti inflammatory imbalance
possible precipitating factors
HIV
anti-TNF therapy
malnutrition
Vit D deficiency
viral infection
(b)
Prc
unstable LTBI
subclinical active phase
clinical TB
pathology
culture
imaging
time (months)



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

2020 TPT guidelines – TPT options

- 6 or 9 months of daily isoniazid*
- 3 month regimen of weekly rifapentine plus isoniazid*
- 3 month regimen of daily isoniazid plus rifampicin*
- 4 months of daily rifampicin alone
- 1 month regimen of daily isoniazid plus rifapentine
- 36 months of daily isoniazid preventive treatment in PLHIV >10y in settings with high TB transmission
- 6 months regimen of levofloxacine for MDR-TB contacts



** Strong recommendation*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2019 VOL. 380 NO. 11

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

Availability of rifapentine

Rifapentine available in the U.S., Canada, South Africa and a few more high burden countries

Track for accreditation at EMA not yet started

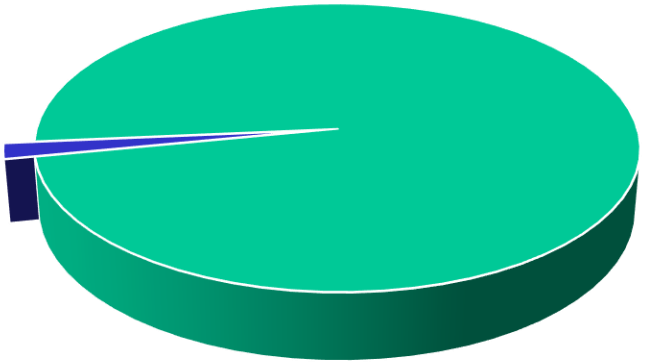
Where are we with preventive therapy

- 1.7 billion people estimated to live with TB infection in the world

(Houben et al PLoS Medicine 2016)

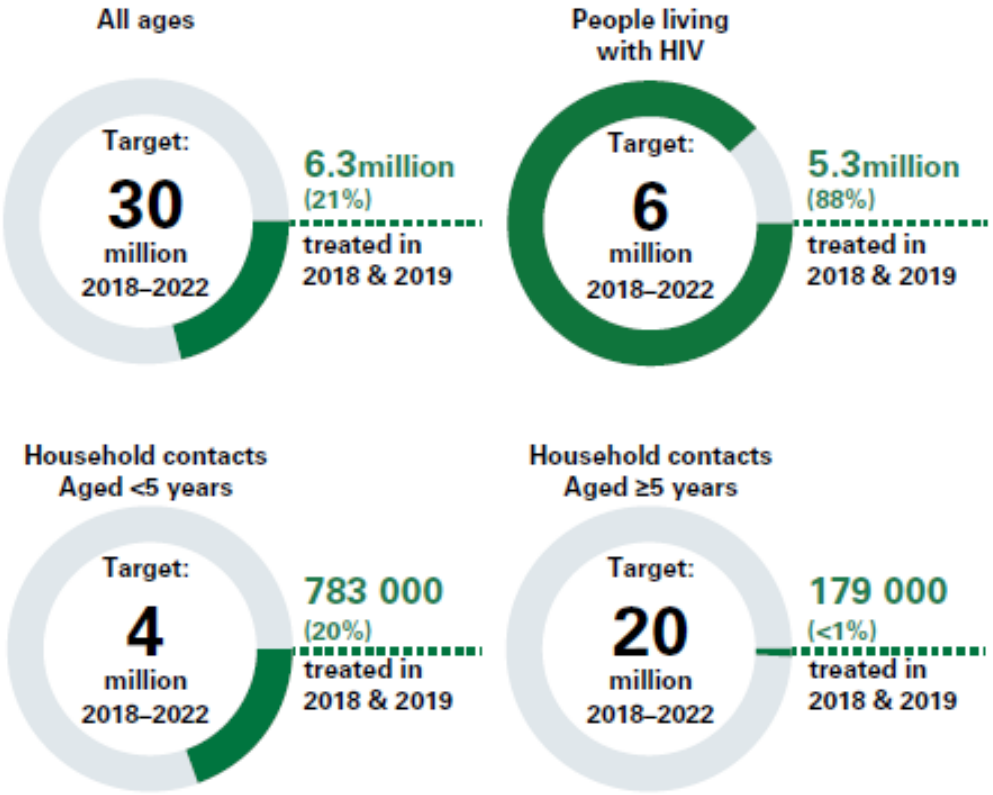
- At the UN high-level meeting on TB in 2018, Member States committed to provide TB reventive treatment to at least 30 million people globally between 2018 and 2022

This represents 1.8% of the infected pool



Global progress in scaling up TPT

2018-2019 vs. 2018–2022 targets



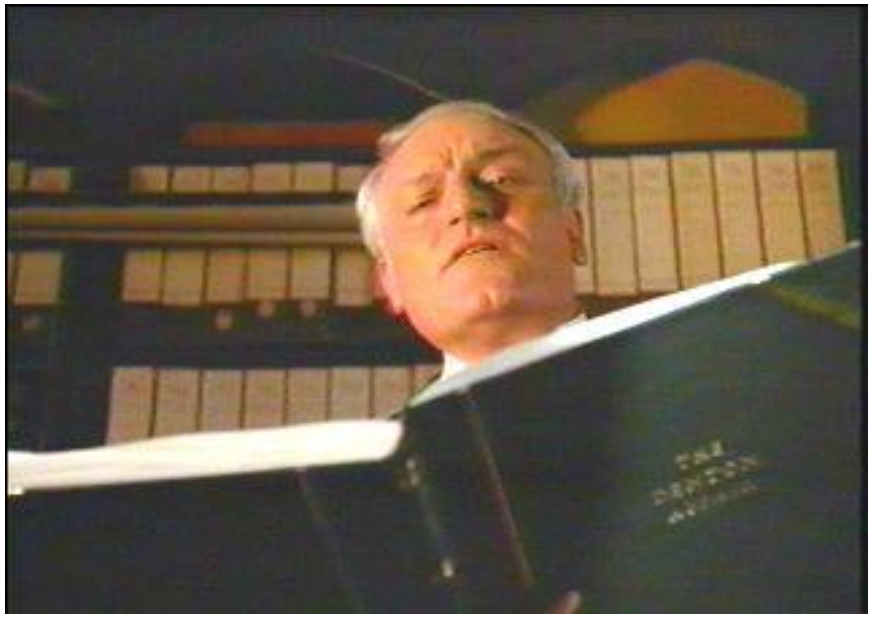
TB treatment	recommendation	Rapid Diagnostic challenge
DS TB treatment (strong)	***New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (strong recommendation, high certainty evidence)***	WRD for R and H and interpretative criteria Z and E require sequencing
DS TB treatment ***(conditional recommendation, moderate certainty evidence) – new***	***Patients aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide***	Unclear interpretative criteria for Rifapentin Requires upfront testing for moxi (?) and Z
MDR treatment (strong)	Group A + Group B (+ Group C)	FQs ok with WRDs B sequencing + CC mic? Best available option: tNGS on SM+; early WGS from MGIT Reporting XDR
XDR; preXDR	NIX-TB regimen including pretomanid	Testing for bedaquiline, surveillance for pretomanid, lineage

..e siccome “POTREBBE ANCHE PIOVERE”…

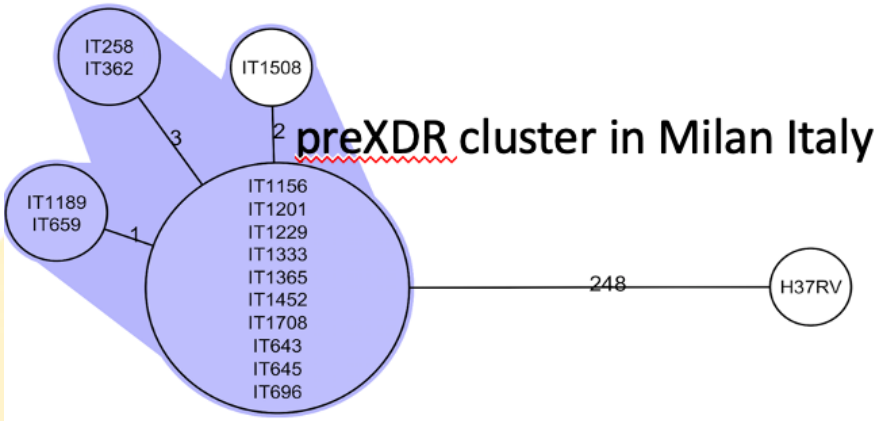
MDR *M. tuberculosis* outbreak clone in Eswatini missed by Xpert has elevated bedaquiline resistance dated to the pre-treatment era.

Beckert, P., Sanchez-Padilla, E.,
Merker, M. *et al.*

Genome Med **12,** 104 (2020).
https://doi.org/10.1186/s13073-020-00793-8



I would like, if I may, to take you in a strange journey…



Pre-XDR-TB

Protocollo: IT-1708 — Allegato al Referto del: na
Lineage: Euro American Superlineage (Lineage: 4.8)
Coverage medio: 86.34 — Cluster: Isolato IN in cluster*
*Database di riferimento includono tutti gli isolati sequenziati presso Emerging Bacterial Pathogens Unit- IRCCS San Raffaele – Milano

Pag. 1 / 2

Farmaco	Regione	Gene	Mutazione [aminoac.]	Interpretazione*	Altre Informazioni**
Rifampicina	Rv0667	*rpoB*	**Ser450Leu**	**Resistente**	
Isoniazide	Rv1483	*inhA*	**c-15t**	**Resistente**	
	Rv1908c	*katG*	**Ser315Thr**		
Etambutolo	Rv3795	*embB*	**Met306Ile**	**Resistente**	
	Rv3794	*embA*	/		
Pirazinamide	Rv2043c	*pncA*	**Ala146Val**	**Resistente**	
Fluorochinoloni (MXF;LEV;OFL)	Rv0006	*gyrA*	Glu21Gln Asp94Tyr	Resistente	
	Rv0005	*gyrB*	/		
Amikacina	Rvnr01	*rrs*	/	Sensibile	
	Rv2416c	*eis*	/		
Kanamicina	Rvnr01	*rrs*	/	Sensibile	
	Rv2416c	*eis*	/		
Capreomicina	Rvnr01	*rrs*	/	Sensibile	Mutazioni silenti;
	Rv1694	*tlyA*	Leu11Leu		
Etionamide	Rv3854	*ethA*	4326082_T _INS	**Resistente**	
	Rv3855	*ethR*	/		
	Rv1483	*inhA*	**c-15t**		
Bedaquilina	Rv1305	*atpE*	/	Sensibile	Non ci sono evidenze che le mutazioni siano associate a farmacoresistenza; si raccomanda test fenotipico di conferma;
	Rv0678		Ala59Val		
Delamanid	Rv3261	*fbiA*	/	Sensibile	
	Rv3262	*fbiB*	/		
	Rv1173	*fbiC*	/		
	Rv0407	*fgd1*	/		
	Rv3547	*ddn*	/		
Linezolid	Rv0701	*rplC*	/		
Linezolid	Rvnr02	*rrl*	/		
Clofazimine	Rv0678		Ala59Val	Sensibile	

Mod. ERP DMA 10

XDR-TB requiring therapy adjustment

Protocollo: IT-1245/IT-1201 — Allegato al Referto del: na
Lineage: Euro American Superlineage (Lineage: 4.8)
Coverage medio: 66.50 — Cluster: Isolato IN cluster*
*Database di riferimento includono tutti gli isolati sequenziati presso Emerging Bacterial Pathogens Unit- IRCCS San Raffaele – Milano

Pag. 1 / 2

Farmaco	Regione	Gene	Mutazione [aminoac.]	Interpretazione*	Altre Informazioni**
Rifampicina	Rv0667	*rpoB*	**Ser450Leu**	**Resistente**	
Isoniazide	Rv1483	*inhA*	c-15t	**Resistente**	
	Rv1908c	*katG*	**Ser315Thr**		
Etambutolo	Rv3795	*embB*	**Met306Ile**	**Resistente**	
	Rv3794	*embA*	/		
Pirazinamide	Rv2043c	*pncA*	**Ala146Val**	**Resistente**	
Fluorochinoloni (MXF;LEV;OFL)	Rv0006	*gyrA*	Glu21Gln Asp94Tyr	Resistente	
	Rv0005	*gyrB*	/		
Amikacina	Rvnr01	*rrs*	/	Sensibile	
	Rv2416c	*eis*	/		
Kanamicina	Rvnr01	*rrs*	/	Sensibile	
	Rv2416c	*eis*	/		
Capreomicina	Rvnr01	*rrs*	/	Sensibile	Mutazioni silenti;
	Rv1694	*tlyA*	Leu11Leu		
Etionamide	Rv3854	*ethA*	4326082_T _INS	**Resistente**	
	Rv3855	*ethR*	/		
	Rv1483	*inhA*	**c-15t**		
Bedaquilina	Rv1305	*atpE*	/	Resistente	Delezione di 87.3% del gene/regione Rv0678. Interpretazione finalizzata; si raccomanda test fenotipico di conferma;
	Rv0678		del (0,127)		
Delamanid	Rv3261	*fbiA*	/	Sensibile	
	Rv3262	*fbiB*	/		
	Rv1173	*fbiC*	/		
	Rv0407	*fgd1*	/		
	Rv3547	*ddn*	/		
Linezolid	Rv0701	*rplC*	/		
Linezolid	Rvnr02	*rrl*	/		
Clofazimine	Rv0678		del (0,127)	Resistente	

Mod. ERP DMA 10

Villa et al ERJ 2021

Inpatient and ambulatory treatment

Inpatient treatment is not mandatory, but patients may be hospitalized at the initiation of MDR-TB treatment for a short period of time to ensure that patients can tolerate the regimen. It may also be advisable for specific groups and for very ill people, for instance during the initiation of treatment or when adverse events occur during treatment.

Ambulatory treatment from the outset without initial hospitalization may be feasible in settings where management of MDR-TB in the community is strong.

OBIETTIVI DELLO STUDIO

1. Studiare le caratteristiche della popolazione richiedente asilo (RA) sul territorio milanese in termini di:
   - Incidenza della tubercolosi (TB)
   - Prevalenza dell'infezione tubercolare latente (ITBL)
   - Trasmissione TB all'interno dei centri d'accoglienza (CAS/*Hub*)
1.
2. Valutare l'impatto degli interventi e individuare eventuali misure correttive per
1. quanto riguarda:
2.
   - Adesione e aderenza alla terapia preventiva per l'ITBL
3. Descrivere la sorveglianza congiunta ATS-VM dell'ITBL nelle caratteristiche di:
   - Qualità dei dati (completezza interna e validità esterna)
   - Successo terapeutico anti-TB
   - Tempistiche degli interventi

ATS
Città Metropolitana Milano

Villa Marelli

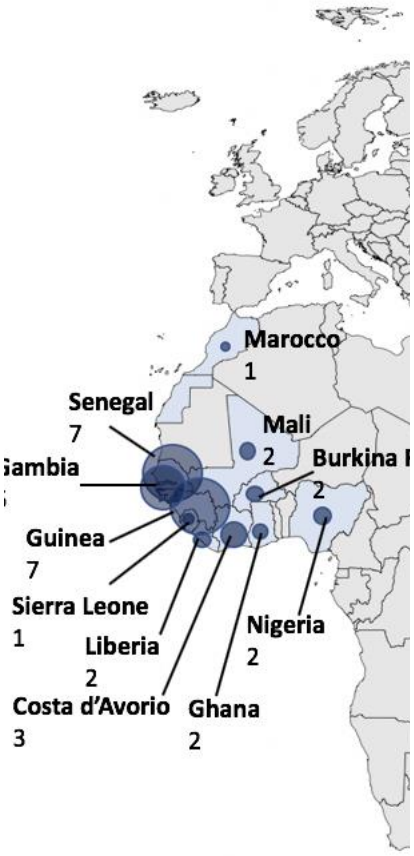
Regione Lombardia
(sistema MAINF)

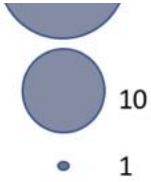
RISULTATI:

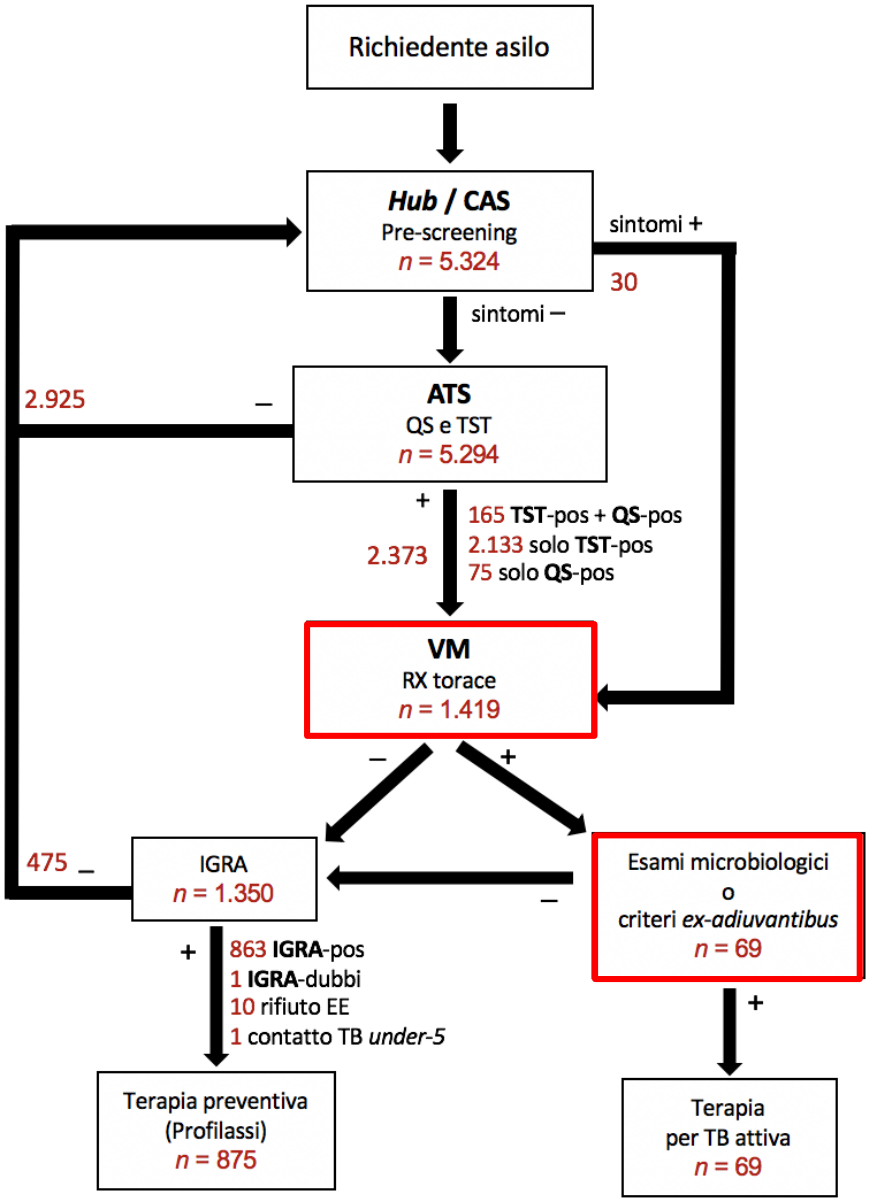
CASI TB (*n* = 69)

	Casi TB *n* (%)
Sesso	
M	61 (88,41 %)
F	8 (11,59 %)
Classi d'età	
0 – 9	1 (1,45 %)
10 – 19	20 (28,98 %)
20 – 29	42 (60,87 %)
30 – 39	4 (5,80 %)
≥ 40	2 (2,90 %)
Permanenza in Italia§, *mesi (range min. ; max)*	6 (0,5 ; 36)
Presenza di sintomi	57 (82,61 %)
Esecuzione TST	39 (56,52 %)
Latenza diagnostica, *giorni (Q1;Q3)*	36 (13 ; 80)

§ Dato disponibile per 53 pazienti (76,81 %)







Dopo i fondamentali…ecco i risultati del gioco di squadra

5.324 richiedenti asilo valutati

- 69 casi di TB con prevalenza di 1.236 x 100.000
- Prevalenza ITBL del 28%

Outcomes treatment

- 85% casi di TB trattati con successo, 9% persi al follow up, 6% trasferiti
- 875 soggetti candidati a terapia preventiva: 92.4% hanno iniziato la terapia preventiva, 4.3% persi al follow up, 3.3% rifiuto terapia
- 760 soggetti (94%) hanno completato la terapia preventiva, 6% interrotta per eventi avversi

Progetto Camper

Centro Antitubercolare Mobile Per Milano

Sistema Socio Sanitario
Regione Lombardia
ATS Milano
Città Metropolitana

OSPEDALE NIGUARDA
CA' GRANDA
Sistema Sanitario Regione Lombardia

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

CONVENZIONE DI GINEVRA 22 AGOSTO 1864
Croce Rossa Italiana

stop TB

UNIVERSITAS STUDIORUM MEDIOLANENSIS


CROCE ROSSA ITALIANA
LIPOMO
CROCE ROSSA ITALIANA - LIPOMO

Il lavoro fino alla pandemia….

Dal settembre 2019 al febbraio 2020 erano stati visitati e testati con Mantoux 509 soggetti,

di cui 180 (35,3%) sottoposti a test di conferma per l'infezione latente (39,4% POSITIVI)

mentre 271 hanno effettuato una Rx torace (53,2%) con riscontro di

6 TBC in atto,

14 TBC pregresse,

4 altre patologie (tumori etc).

2021 TB reprise

CAMPER VECCHIO

12/1 RSA Don Leone Porta 78 operatori sanitari+ospiti
26 e 29/1 Centro Accoglienza Cascina Gobba 72 ospiti
9/2 via Saponaro 44 ospiti
12/3/2021 Ditta MARKAS (mensa Gaetano Pini) 30 dipendenti

INTERMEZZO E CAMPER NUOVO (Ducato): no RX torace esterne

30/4 Centro Accoglienza Aquila 14 ospiti
23/4 Centro Accoglienza Fantoli 10 ospiti
29/4 Centro Dialisi NephroCare 20 pazienti
7/5 Centro Accoglienza Sicomoro 18 ospiti
21/5 Ditta MARKAS (2° controllo) 20 dipendenti
25/5 RSA Quarenghi 11 ospiti

27/5/ RSA Baroni 20 ospiti
4 e 8/6 Centro Accoglienza Corelli 43 ospiti+operatori
17 e 22/6 Scuola Pareto 40 insegnanti+studenti
29/6 Scuola Mattei (Pioltello) 25 insegnanti+studenti
1/7 Accademia Formativa Martesana (Gorgonzola) 29 insegnanti+studenti
2 e 6/7 Centro Accoglienza Aquila 42 ospiti
7 e 8/7 Azienda Agricola San Maurizio (Pozzolo Martesana) 40 dipendenti
9/7 Football Club Brera (Peschiera Borromeo) 10 contatti
27 e 29/7 Ditta Bags (Trezzano S/N) Italia 43 dipendenti
25 e 31/8 e 9/9 via Saponaro 75 ospiti
26/8 Azienda Agricola San Maurizio (Pozzolo Martesana) (2° controllo) 21 dipendenti
7/9 Accademia Formativa Martesana (Gorgonzola) (2° controllo) 29 insegnati+studenti
15 e 16/9 Centro Accoglienza CRI Bresso 70 ospiti
21/9 Scuola Mattei (Pioltello) (2° controllo) 24 insegnanti+studenti
22 e 23/9 Centro Accoglienza CRI Bresso 68 ospiti
28 e 30/9 Scuola Pareto (2° controllo) 43 insegnanti+studenti
TBD ottobre Centro Accoglienza Corelli 200 ospiti

2021 TB reprise

Al momento, nonostante le molte difficoltà, sono state effettuate 37 uscite con 939 screening (+ 200 da programmare ai primi di ottobre).

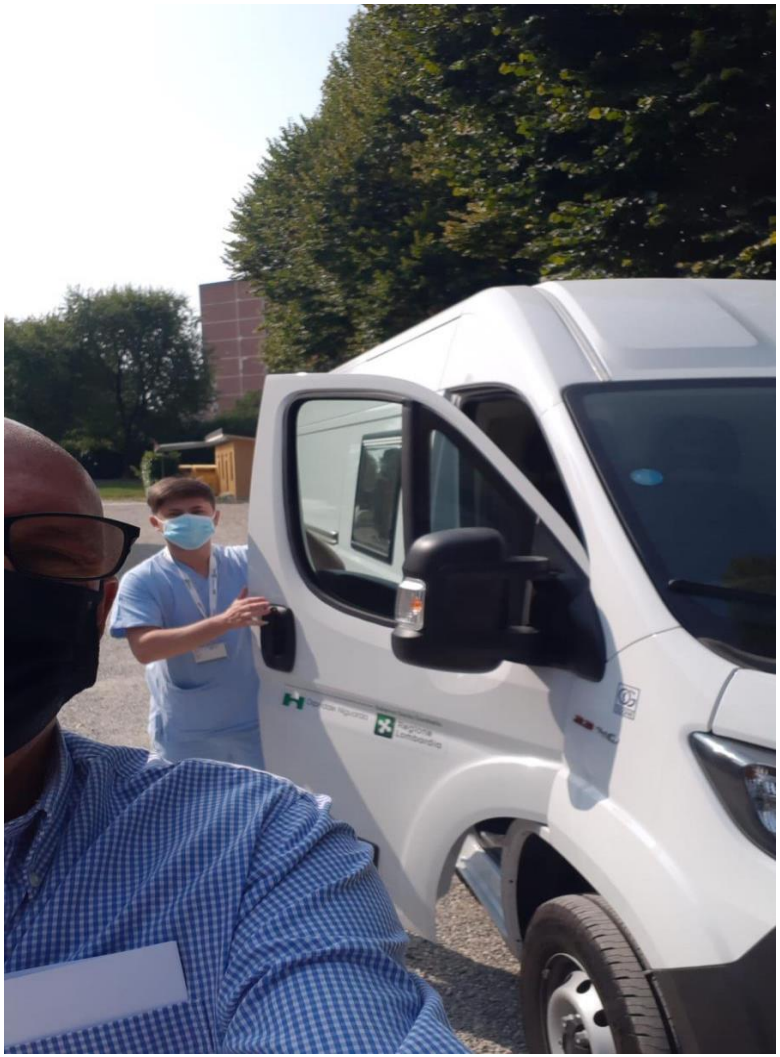
Dei 536 soggetti testati, 419 sono risultati QFT- e 117 QFT+ di cui al momento:

2 soggetti affetti da Tb attiva

109 già in TITL

Purtroppo abbiamo dovuto dirottare altri interventi all'interno di Villa Marelli per cui il dato avrebbe potuto essere maggiore.

Noi continuiamo a provarci!
Grazie dell’attenzione.



..Le attività in Africa: CORSO ANNUALE PER SPECIALIZZANDI IN SENEGAL

Iscrivetevi e sostenete Stop TB Italia

www.stoptb.it