fimp Federazione Italiana Medici Pediatri
Sezione di Caserta

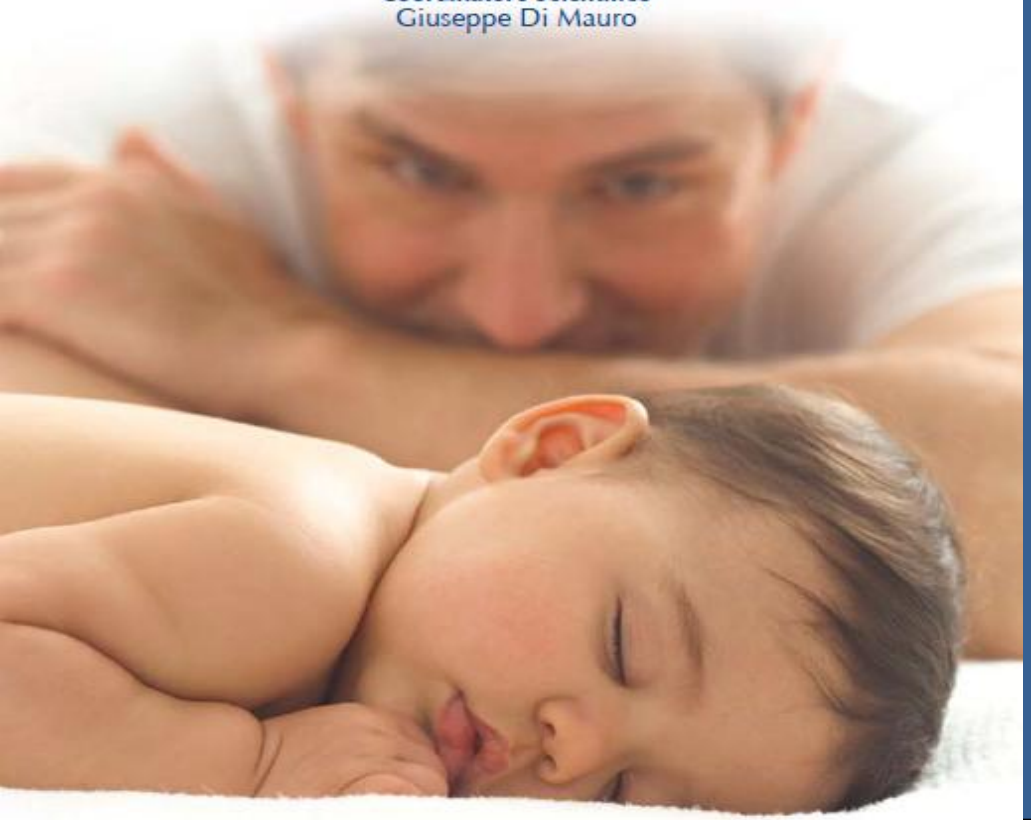
SIPPS & FIMPAGGIORNA 2014

OBIETTIVO PEDIATRIA:
La centralità del bambino tra territorio, ospedale ed università

Il Corso rientra nel programma di Educazione Continua in Medicina del Ministero della Salute

Sede del Corso
PLAZA HOTEL, Via Lamberti - Caserta

Coordinatore Scientifico
Giuseppe Di Mauro



8 Maggio 2014
Prevenzione e cura delle infezioni respiratorie delle alte e basse vie: i contesti, le etiologie e gli effetti della comunicazione

Relatori: *Michele Miraglia Del Giudice, Nicola Principi, Alberto Villani*
Moderatori: *Carlo Capristo, Antonio Campa, Pasquale Femiano*

TUBERCOLOSI PEDIATRICA

Alberto Villani
UOC Pediatria Generale
e Malattie Infettive
Dipartimento di Medicina Pediatrica
Ospedale Pediatrico Bambino Gesù
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alberto.villani@opbg.net

Dipartimento Medicina Pediatrica Casistica 2013
Posti letto: 111

RICOVERI ORDINARI: 5.335

PESO MEDIO: 0,88

DAY HOSPITAL: 14.881

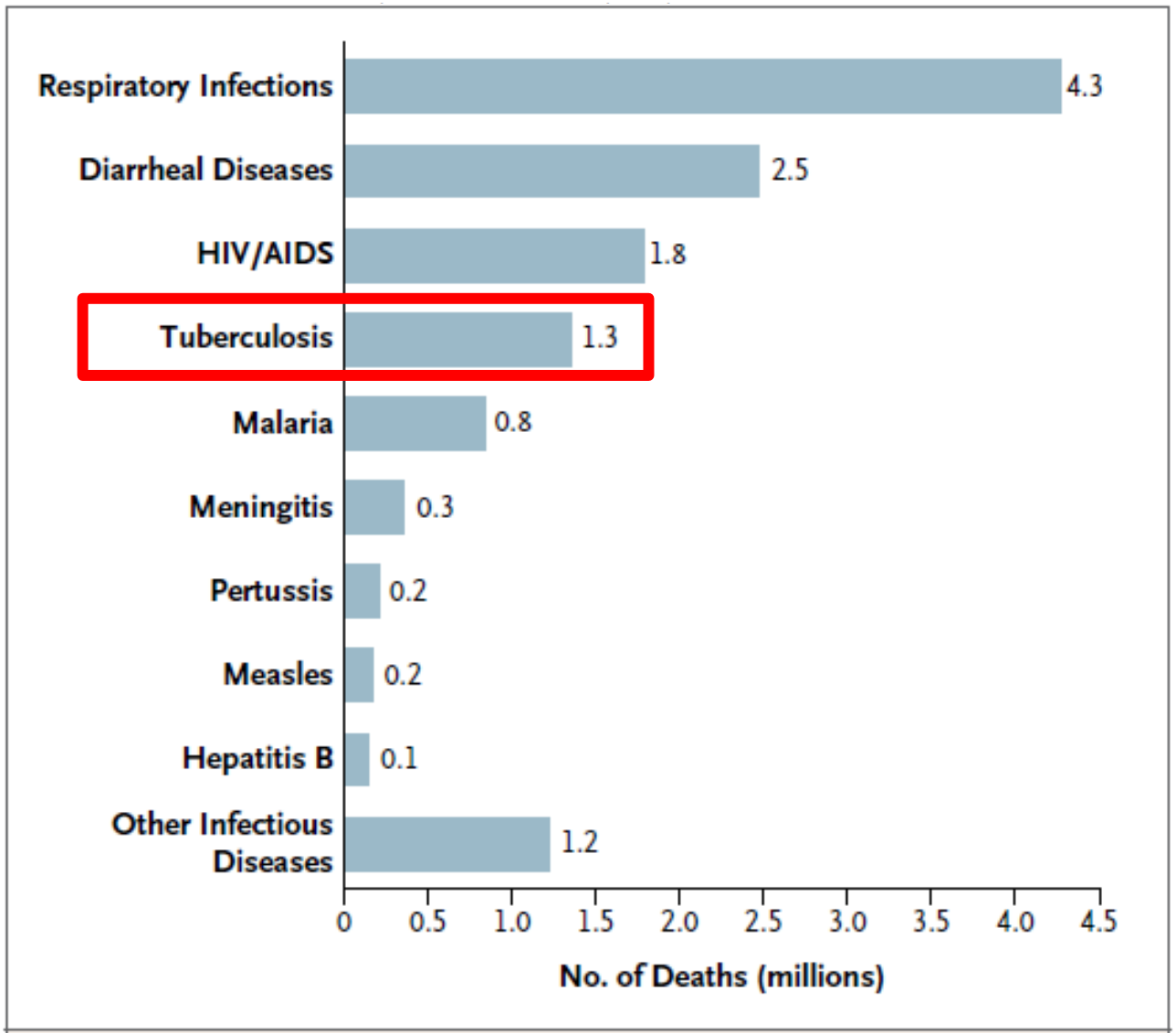
AMBULATORI: 64.378

Attività scientifica DMP 2013

Impact Factor: 415

200 NEJM ANNIVERSARY ARTICLE

The Perpetual Challenge of Infectious Diseases



MULTIRESISTENZA NELLA TUBERCOLOSI PEDIATRICA

Farmaco	Dosaggio Giornaliero (range di dosaggio) in mg/kg Raccomandato dalla WHO
Prima Linea di Agenti orali:	
•Isoniazide	10 – 15
•Rifampicina	10 – 20
•Pirazinamide	30 – 40
•Etambutolo	15 – 25

Classificazione farmaci antitubercolari

Linea	Classe	Categoria	Farmaci
PRIMA	1	Farmaci Essenziali	Rifampicina, Isoniazide, Pirazinamide, Etambutolo
SECONDA	2	Iniettabili	Capreomicina, Kanamicina, Amikacina, Streptomicina
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	5	Farmaci di incerta efficacia	Clofazimina, Linezolid, Amoxicillina/clavulanato, Imipenem/cilastatina

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•Pyrazinamide	30 – 40
•Ethambutol	15 – 25
Agenti Iniettabili:	
•Streptomycin	15 – 20
•Amikacin	15 – 22,5
•Kanamycin	15 – 30
•Capreomycin	15 – 30
Seconda linea batteriostatici orali:	
•Prothionamide	15 – 20
•Ethionamide	15 – 20
•Cycloserine	15 – 20
•Para-aminosalicylic acid	150
Fluoroquinolons:	
•Moxifloxacin	7,5 – 10
•Ciprofloxacin	20 due volte al giorno
•Levoflaxacin	7,5 – 10
•Ofloxacin	15 – 20

DEFINIZIONI

- **MDR-TB** (multidrug resistant tubercolosis): resistente almeno a 1 farmaco tra isoniazide e rifampicina, i due più importanti farmaci di prima linea nel trattamento della tubercolosi. Può manifestarsi in caso di infezione con un batterio farmaco-resistente o può svilupparsi durante un trattamento non ottimale per durata o scelta dei famaci. L'efficacia della cura delle forme resistenti è bassa: 50-70%.
- **XDR-TB** (extensively multidrug resistent tubercolosis): resistente a isoniazide e rifampicina così come a un fluoroquinolone più una farmaco iniettable antitbrcolare di seconda linea (amikacina, kanamicina, capreomicina).

DEFINIZIONI

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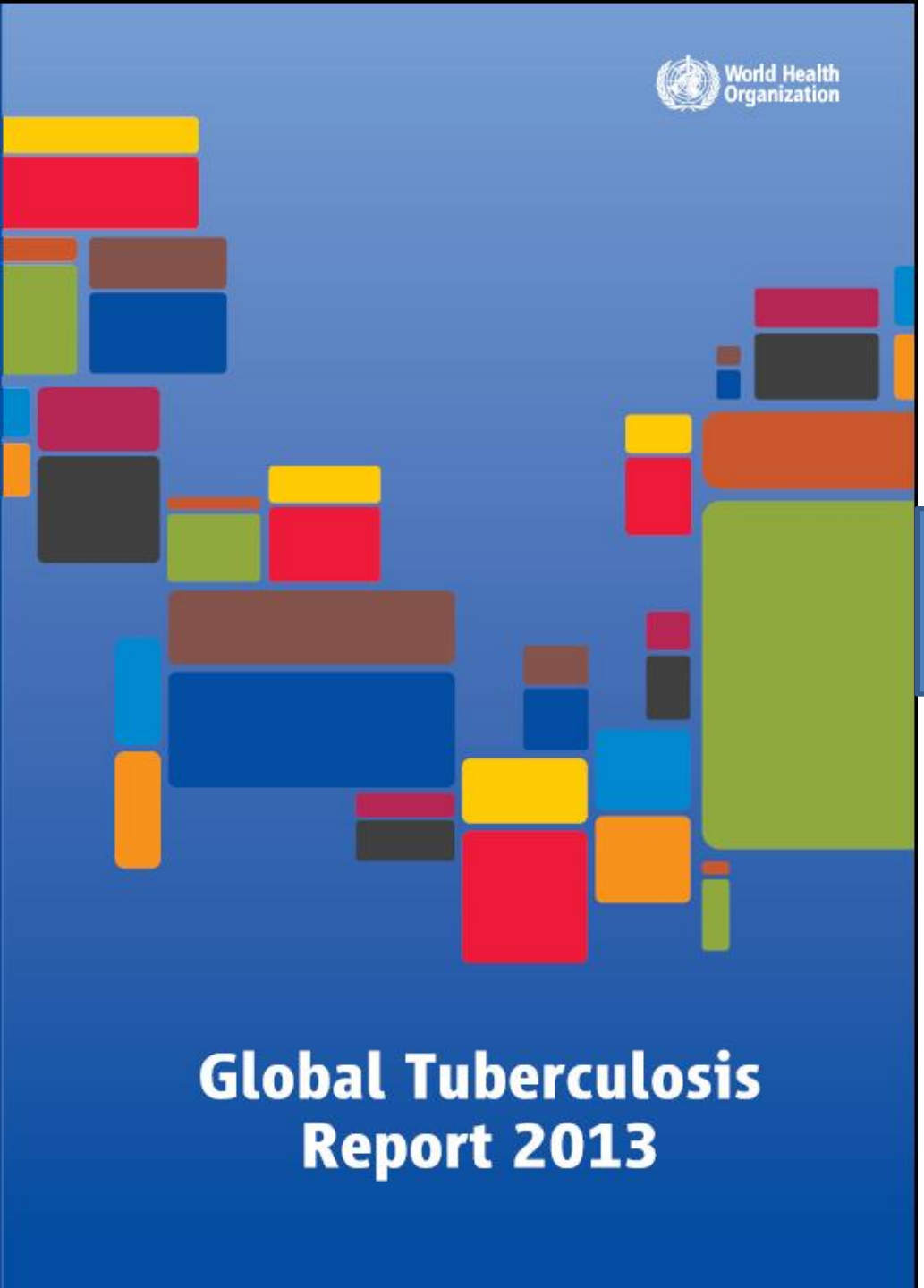
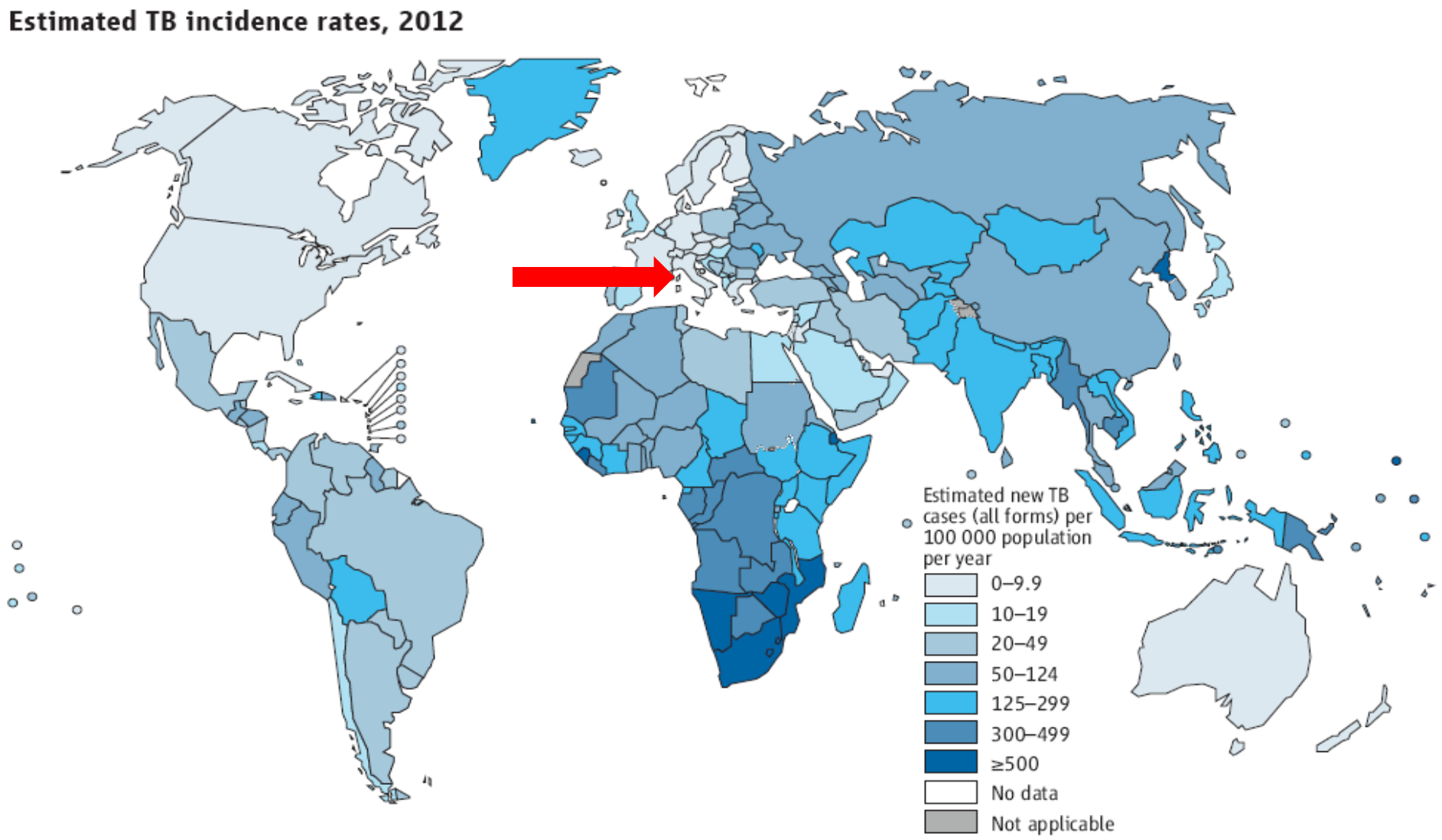
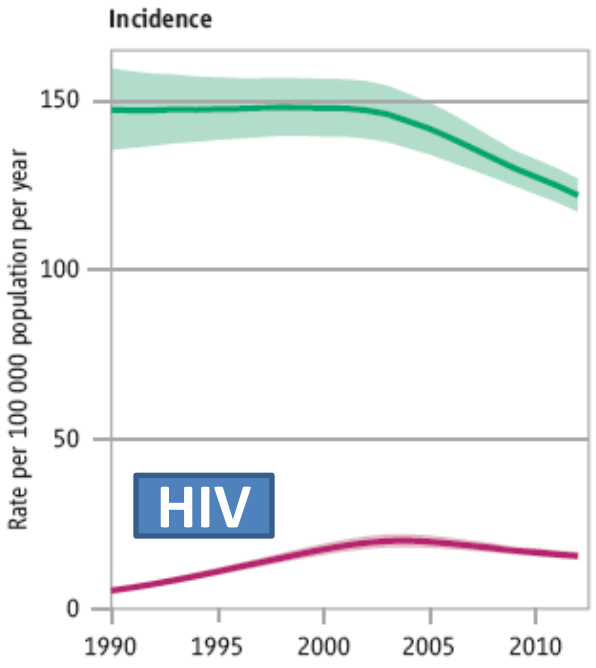


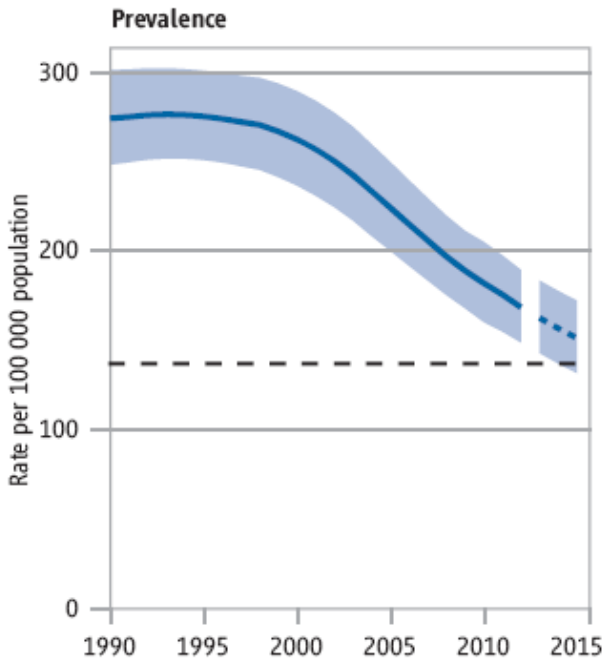
EPIDEMIOLOGIA

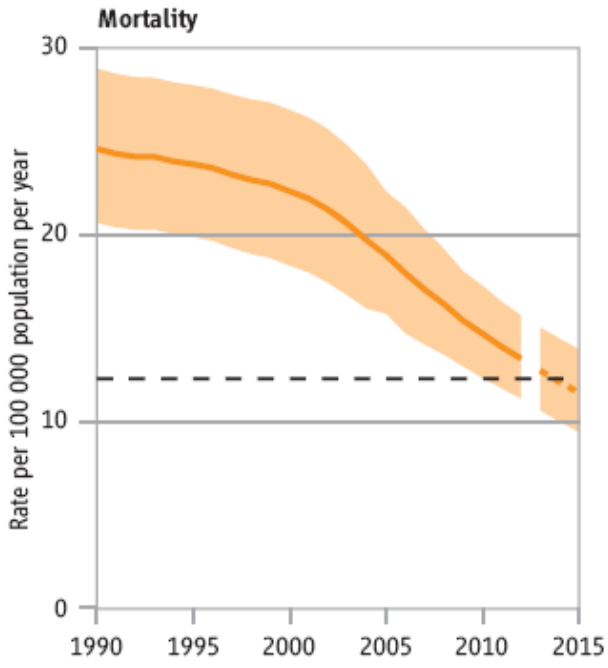
Nuovi casi stimati di tubercolosi (tutte le forme) per 100.000 abitanti per anno. Italia: tra 0 - 9,9.



Andamento dell'incidenza, prevalenza e mortalità per tubercolosi nel mondo.







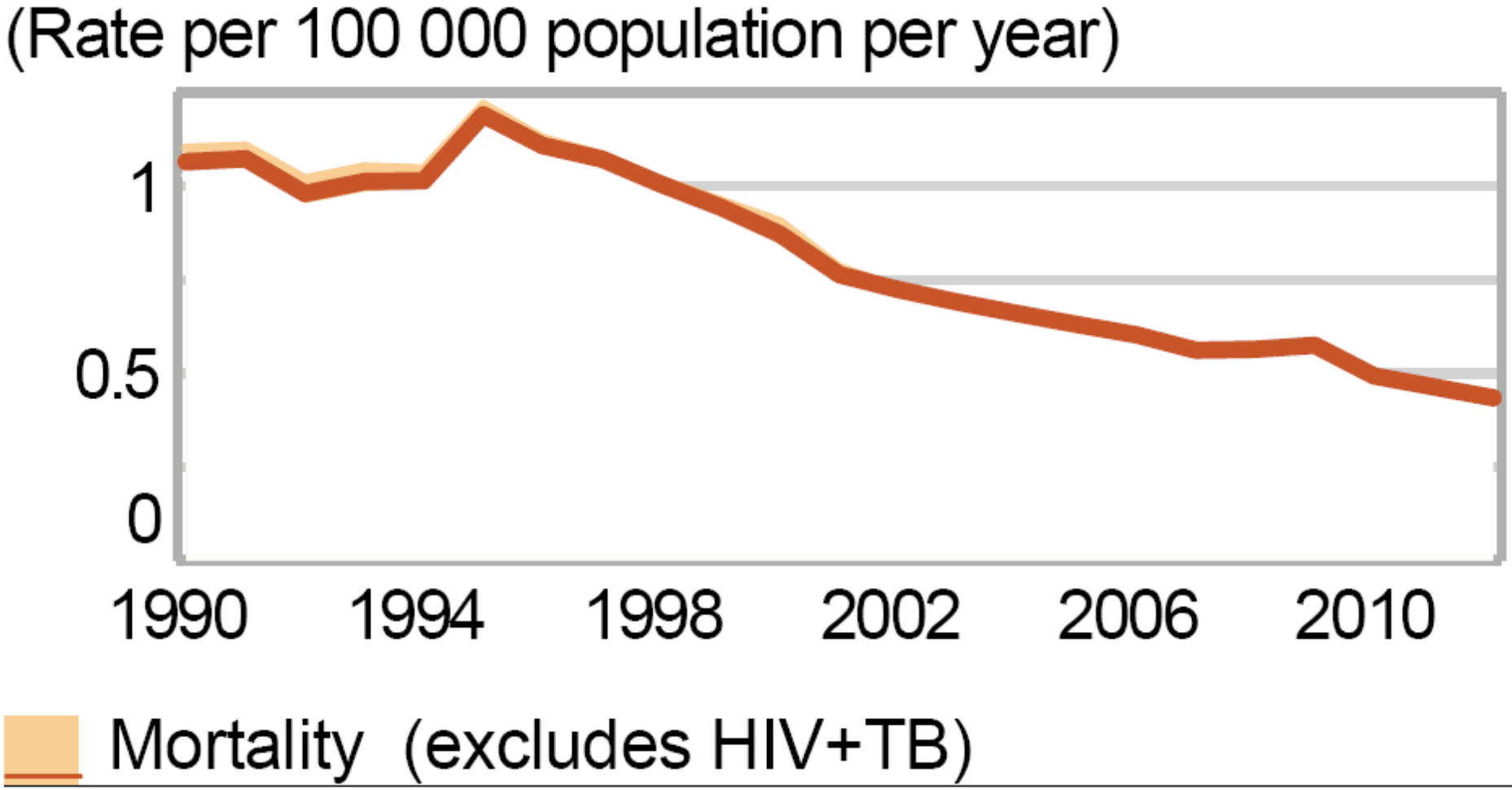
Incidenza: nuovi casi di malattia che compaiono in un determinato lasso di tempo (un anno); stima la probabilità di una persona di ammalarsi della malattia.

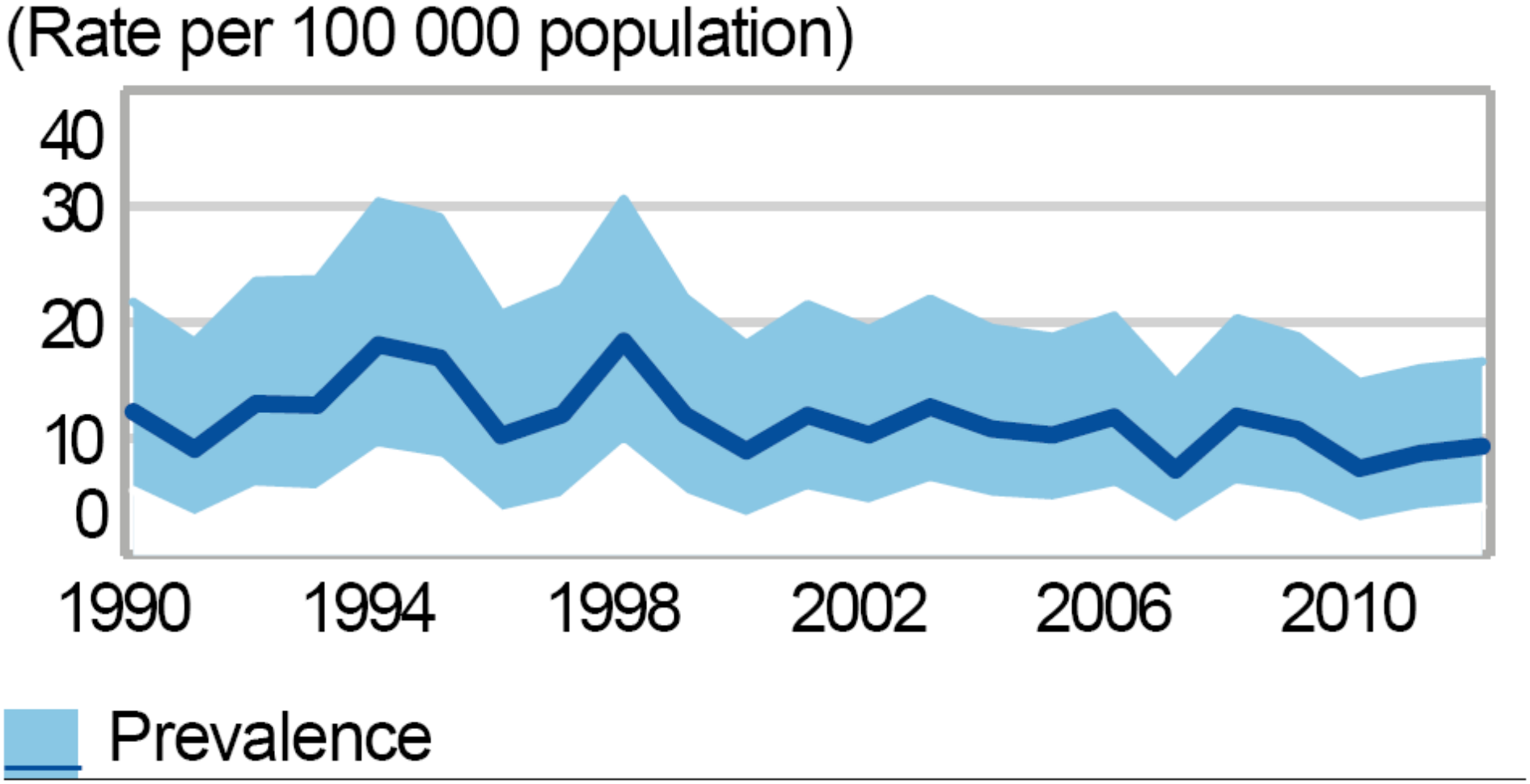
Prevalenza: rapporto fra il numero di casi rilevati nella popolazione in un anno e il numero degli individui della popolazione osservati nello stesso periodo.

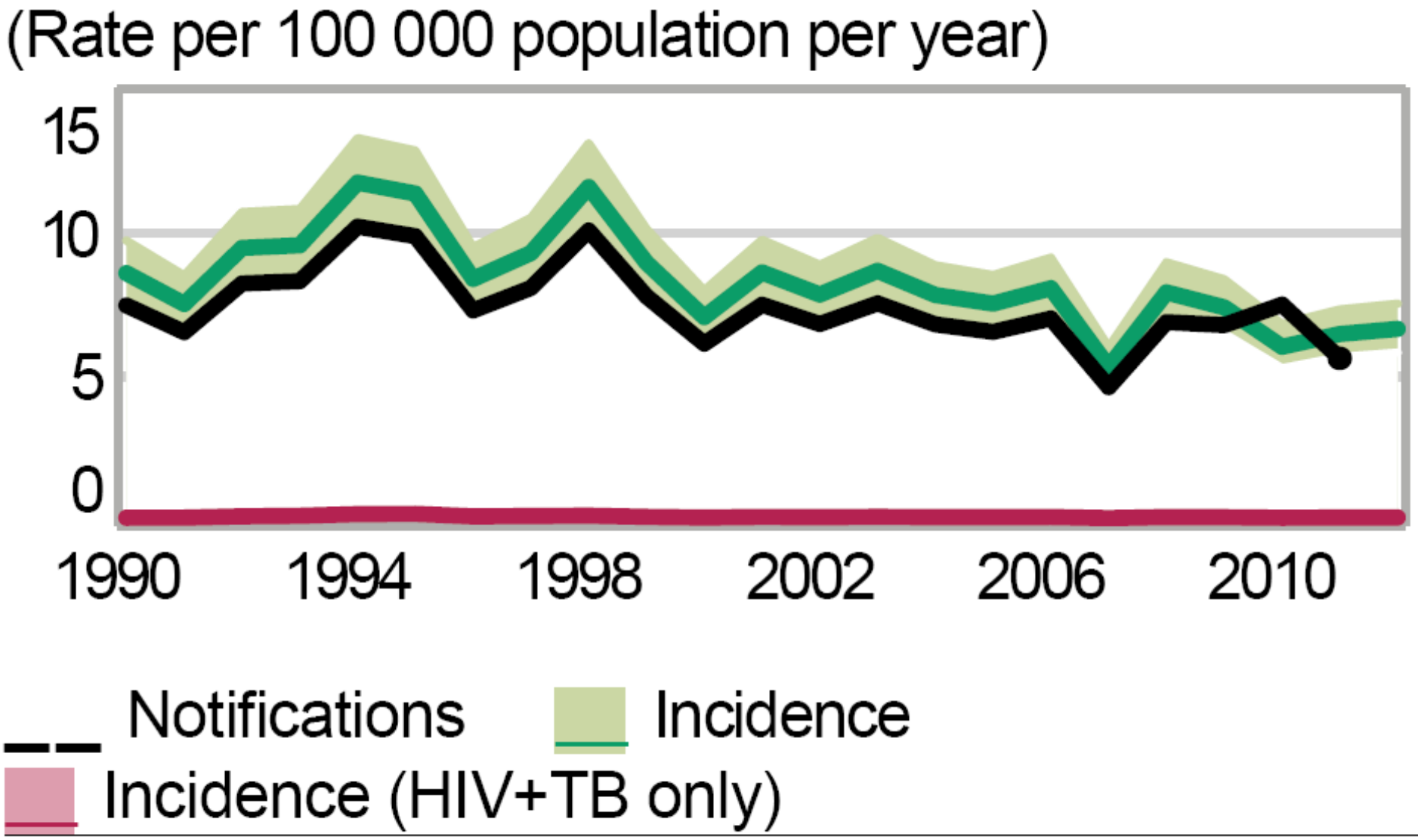
Mortalità: rapporto tra il numero delle morti, durante un periodo di tempo, e la quantità della popolazione media dello stesso periodo.

Andamento dell'incidenza, prevalenza e mortalità per **tubercolosi** e per **HIV** nel mondo (diviso per aree).

Estimated TB incidence rates by WHO region, 1990–2012. Regional trends in estimated TB incidence rates (**green**) and estimated incidence rates of HIV-positive TB (**red**). Shaded areas represent uncertainty bands.


(Rate per 100 000 population per year)
1
0.5
0
1990
1994
1998
2002
2006
2010
Mortality (excludes HIV+TB)


(Rate per 100 000 population)
40
30
20
10
0
1990
1994
1998
2002
2006
2010
Prevalence


(Rate per 100 000 population per year)
15
10
5
0
1990
1994
1998
2002
2006
2010
Notifications
Incidence
Incidence (HIV+TB only)

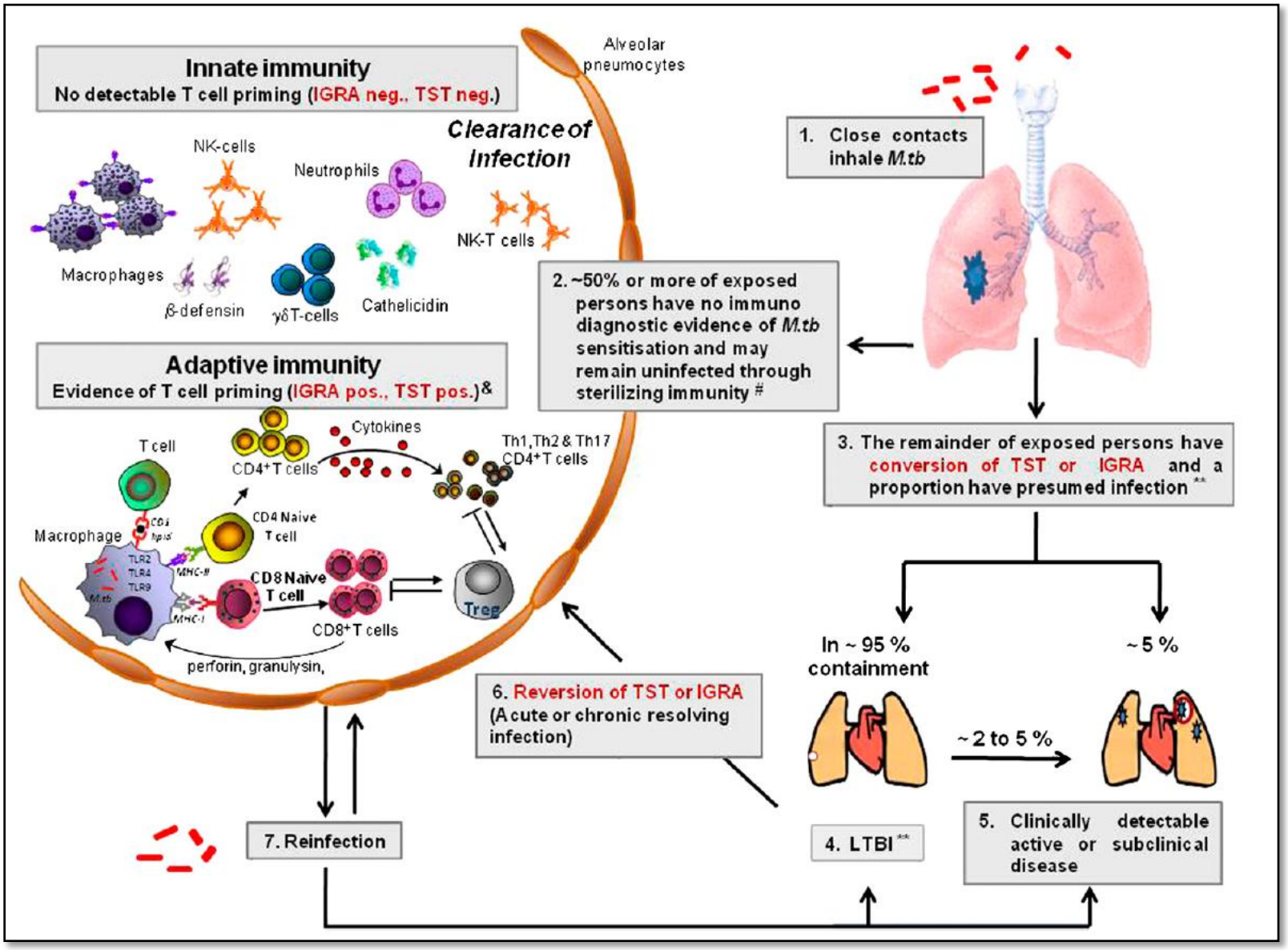
Il punto sull'epidemiologia della TBC

- Problema mondiale molto importante con significativa **mortalità** anche **pediatrica** (**70.000 -130.000 morti/anno**).
- **Italia** paese a **bassa incidenza** (7,66 casi/ 100.000 residenti), ma aumento dell'incidenza tra 0 e 14 anni.
- **Casi notificati in Italia** negli ultimi anni tra **4.000 e 6.000**.

Epidemiologia TBC Pediatrica

- **WHO**: **520.000** (490–550) di casi nel mondo tra i minori di 15 anni
- **15% a 20%** del totale di casi (3% a 25%)
- Elevata percentuale di forme BAAR negativo e extrapolmonare
- Malattia sotto-diagnosticata, poco/sovra notificata
- **70.000 – 130.000** morti/anno

Storia naturale della TBC



Schwander, Dheda. Am J Respir Crit Care Med. 2011 Mar 15; 183(6) : 696-707

Tuberculosis 94 (2014) 8–14

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

COMMENT

A new unifying theory of the pathogenesis of tuberculosis

Ian M. Orme*

Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO 80523, USA

SUMMARY

It is set in stone that *Mycobacterium tuberculosis* is a facultative intracellular bacterial parasite. This axiom drives our knowledge of the host response, the way we design vaccines against the organism by generating protective T cells, and to a lesser extent, the way we try to target anti-microbial drugs. The purpose of this article is to commit total heresy. I believe that *M. tuberculosis* can equally well be regarded as an extracellular pathogen and may in fact spend a large percentage of its human lung "life-cycle" in this environment. It is of course intracellular as well, but this may well be little more than a brief interlude after infection of a new host during which the bacterium must replicate to increase its chances of transmission and physiologically adapt prior to moving back to an extracellular phase. As a result, by focusing almost completely on just the intracellular phase, we may be making serious strategic errors in the way we try to intervene in this pathogenic process. It is my opinion that when a TB bacillus enters the lungs and starts to reside inside an alveolar macrophage, its central driving force is to switch on a process leading to lung necrosis, since it is only by this process that the local lung tissue can be destroyed and the bacillus can be exhaled and transmitted. I present here a new model of the pathogenesis of the disease that attempts to unify the pathogenic process of infection, disease, persistence [rather than latency], and reactivation.

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COMMENT

A new unifying theory of the pathogenesis of tuberculosis

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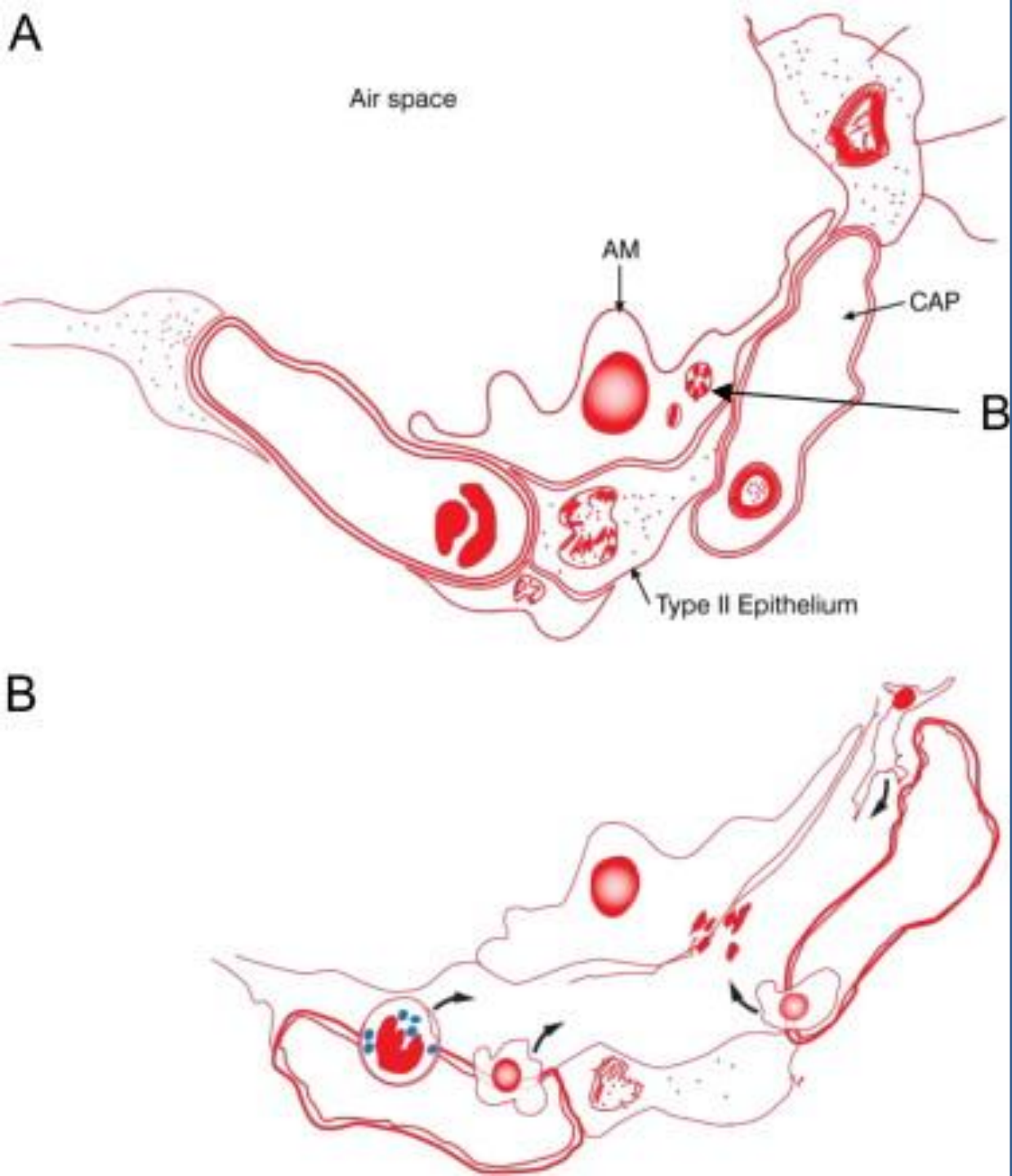
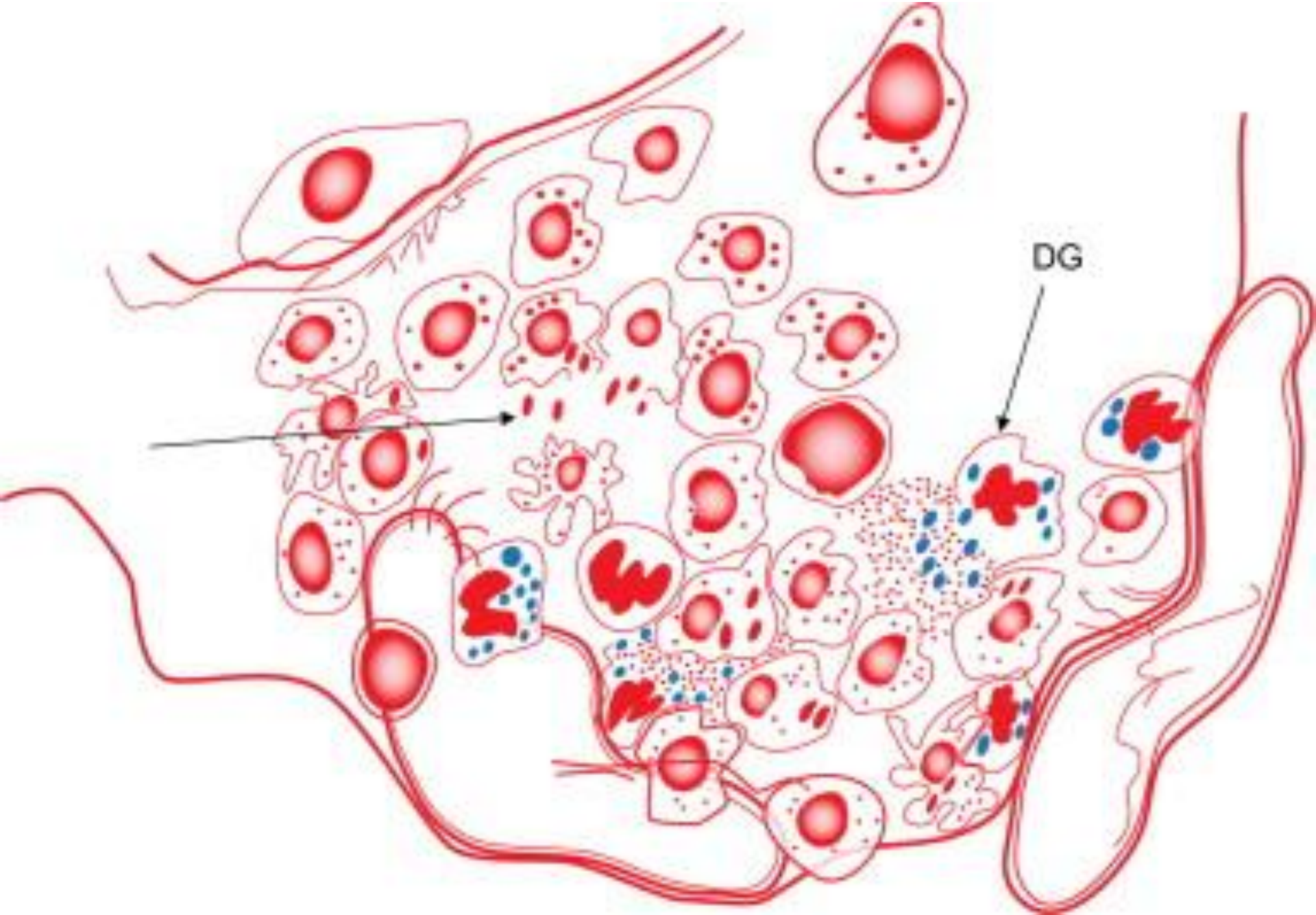
Scopo di questo articolo è quello di commettere un'eresia. Io credo che il Mycobatterium Tuberculosis possa essere ugualmente considerato un **patogeno extracellulare** e può di fatto spendere una larga parte del suo ciclo vitale nel polmone umano nell'ambiente extracellulare.

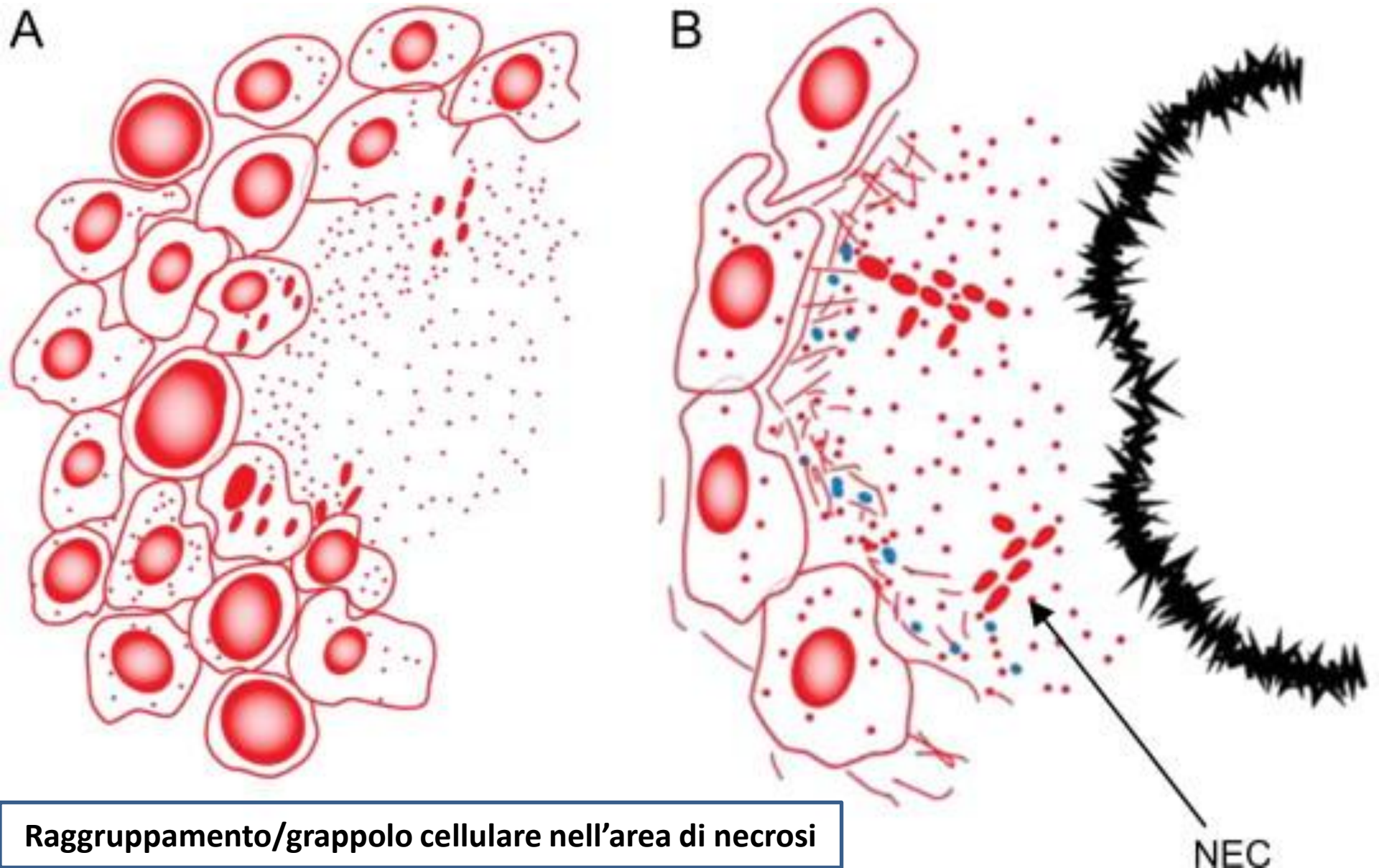


Nella prima fase del processo infettivo **(parte A della figura)** un macrofago alveolare (AM) ingloba il batterio (B). Successivamente **(parte B della figura)** il macrofago alveolare estende il suo citoplasma, alcuni batteri attraversano la membrana basale del macrofago e lo spazio tra macrofago e l'endotelio capillare aumenta. Si determina infiammazione e nella zona arrivano neutrofili e macrofagi dal circolo e celule dendritiche dal parenchima polmonare.

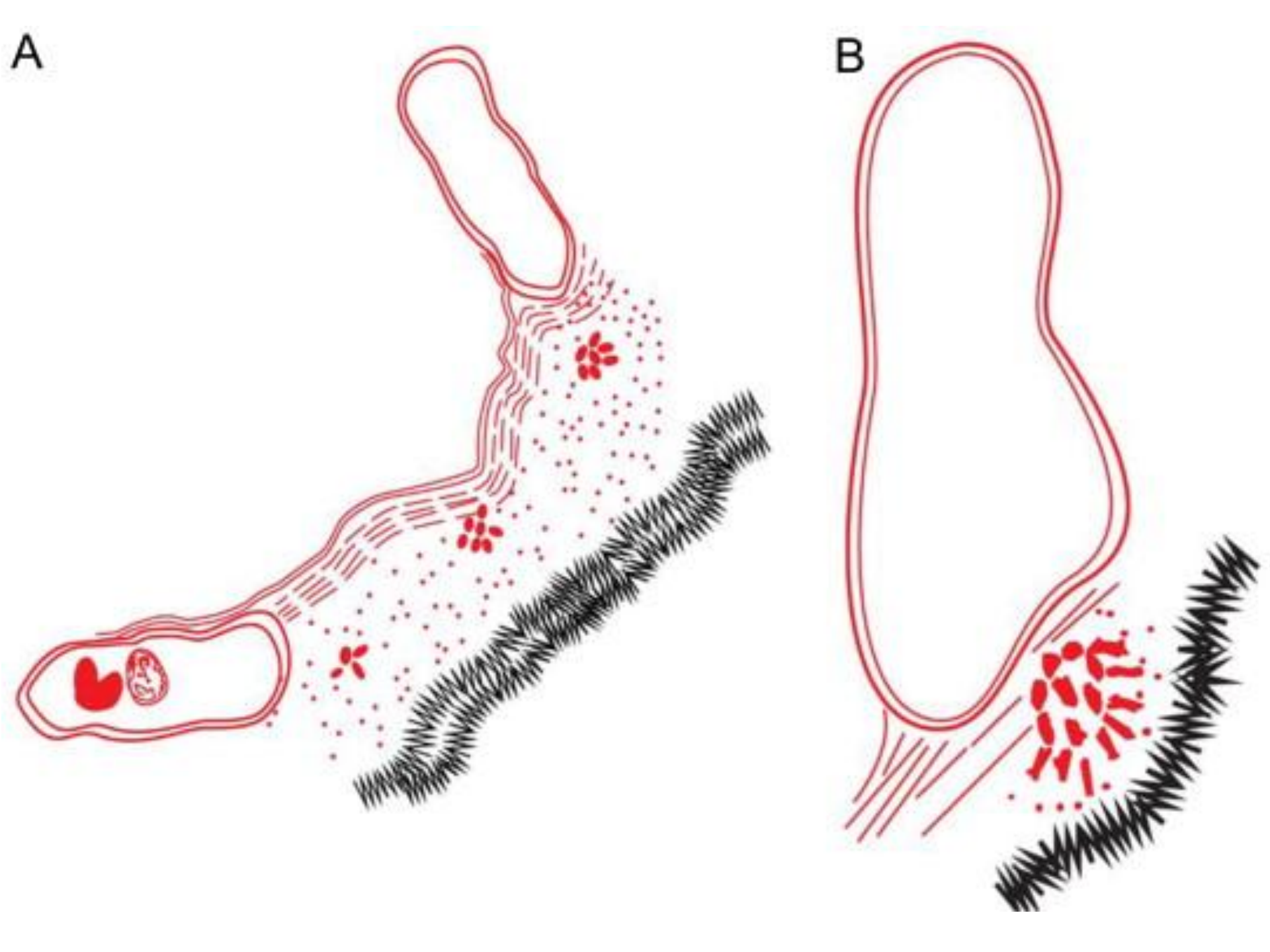
L’infiammazione determina morte di alcune cellule e l’inizio di aree di necrosi

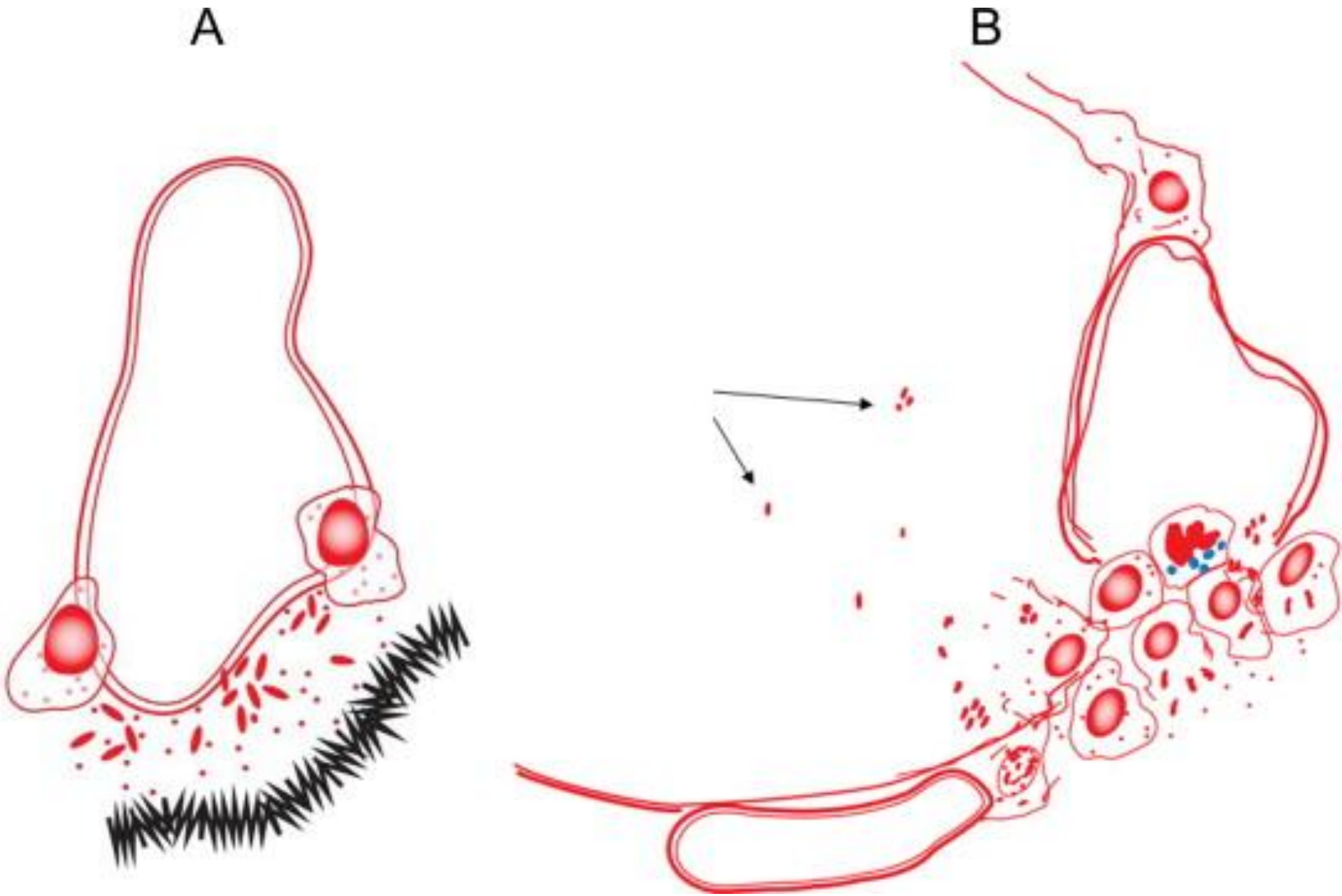


Ha inizio la formazione del granuloma con i bacilli che si adattano a sopravvivere nell'area di necrosi
(NEC: Necrosis-associated Extracellular Cluster)

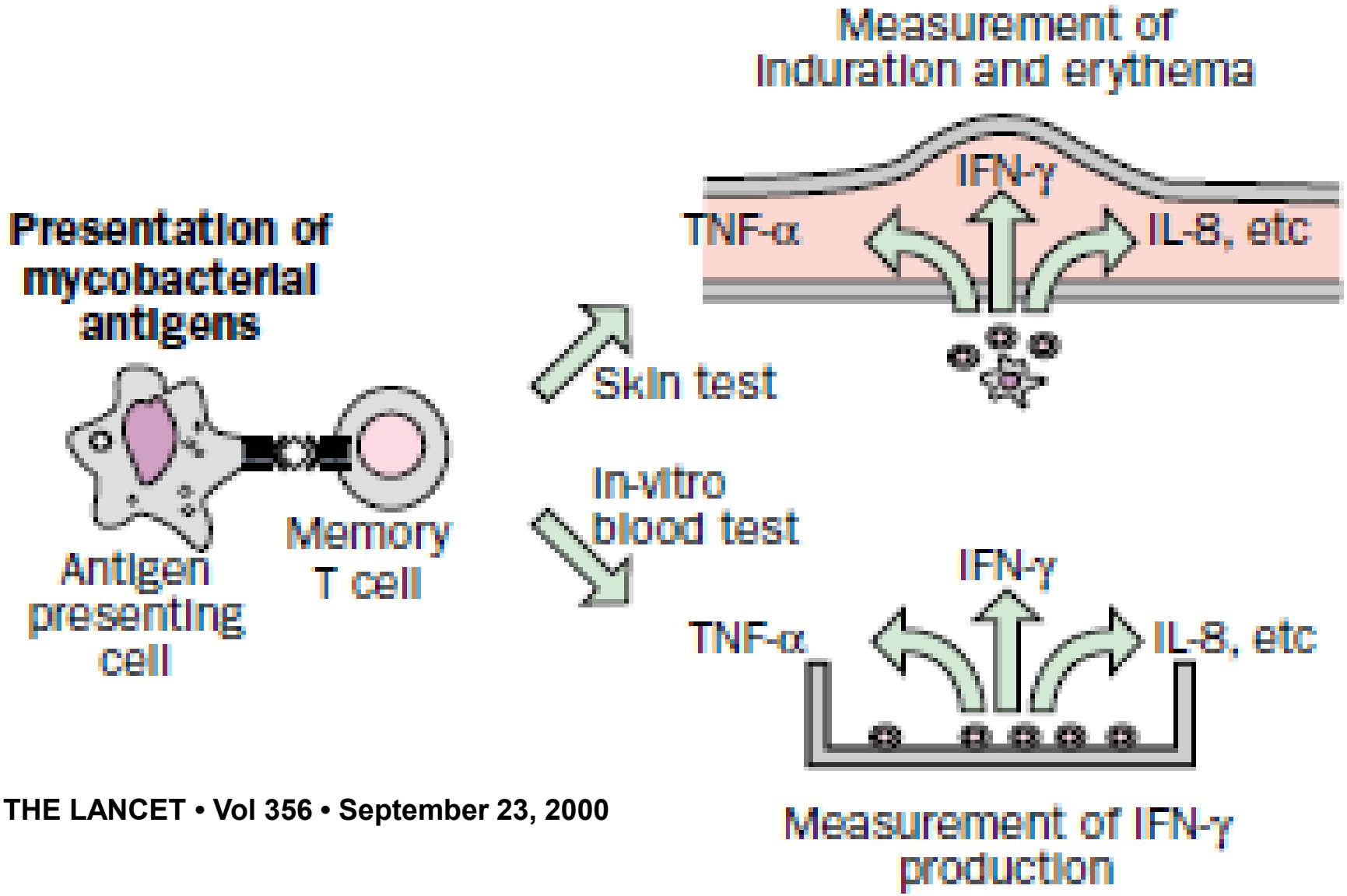


Raggruppamento/grappolo cellulare nell'area di necrosi


A
B


A
B

Interferon Gamma Release Assay



THE LANCET • Vol 356 • September 23, 2000

Caratteristiche test diagnostici

	TST	QTF-Gold	T-SPOT
Esecuzione	*In vivo*	*In vitro*	*In vitro*
Visita di ritorno	Si	No	No
Cross-reattività BCG MOTT	 si si	 no no	 no no
Effetto *booster*	si	no	no
Antigeni usati	PPD	Esat-6/Cfp-10	Esat-6/Cfp-10
Tipo di risposta	Ipersensibilità ritardata	Produzione di IFN gamma	Produzione di IFN gamma
Tipo di risultato	Infiltrato cutaneo	Concentrazione di IFN	Numero linfociti Ag-specifici
Sensibilità Popolazione generale	75-90%	90%	92-96%
Specificità Popolazione generale	35 % bassa	98%	92%

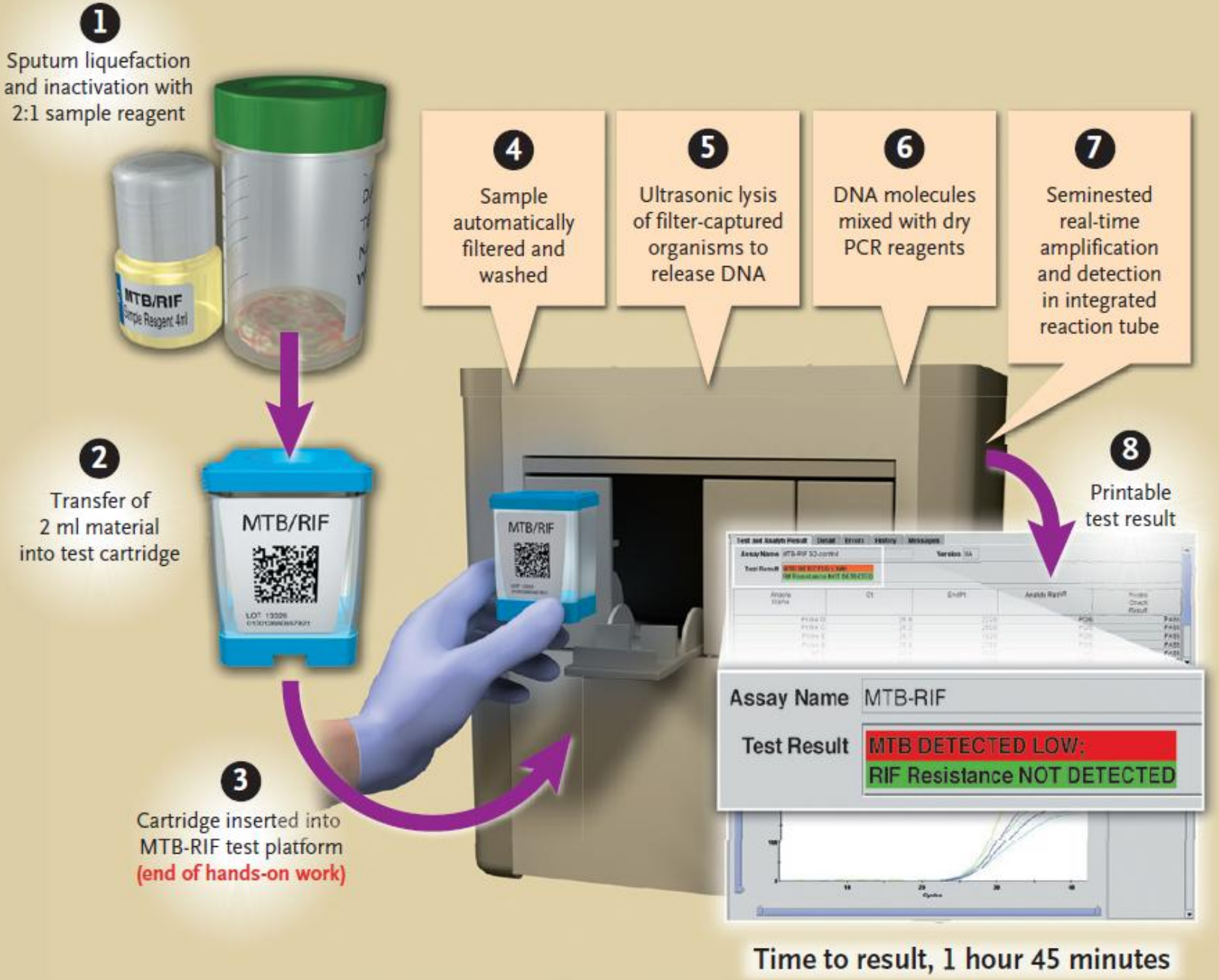
Pai M. et al. Lancet Infect Dis 2004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.


1
Sputum liquefaction and inactivation with 2:1 sample reagent
MTB/RIF
Sample Reagent 4ml
2
Transfer of 2 ml material into test cartridge
MTB/RIF
3
Cartridge inserted into MTB-RIF test platform
(end of hands-on work)
4
Sample automatically filtered and washed
5
Ultrasonic lysis of filter-captured organisms to release DNA
6
DNA molecules mixed with dry PCR reagents
7
Seminested real-time amplification and detection in integrated reaction tube
8
Printable test result
Assay Name
MTB-RIF
Test Result
MTB DETECTED LOW:
RIF Resistance NOT DETECTED
Time to result, 1 hour 45 minutes

Farmaco	Dosaggio Giornaliero (range di dosaggio) in mg/kg Raccomandato dalla WHO
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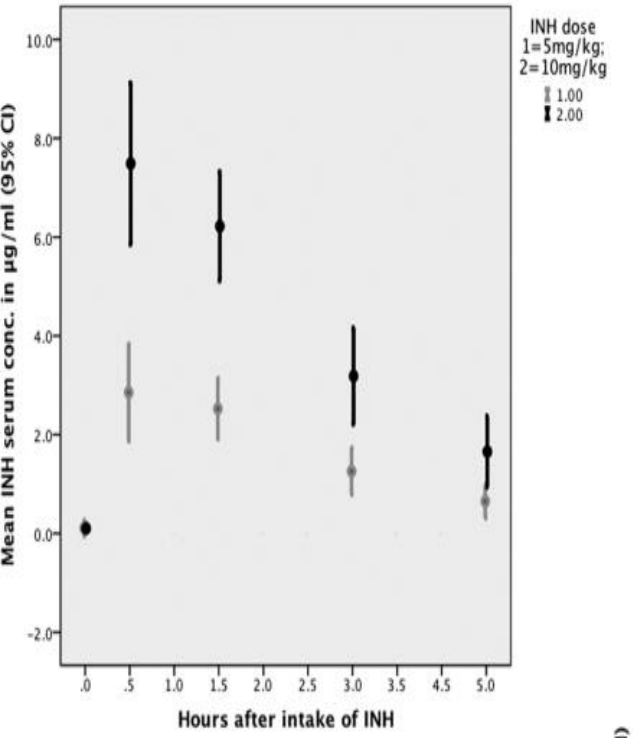
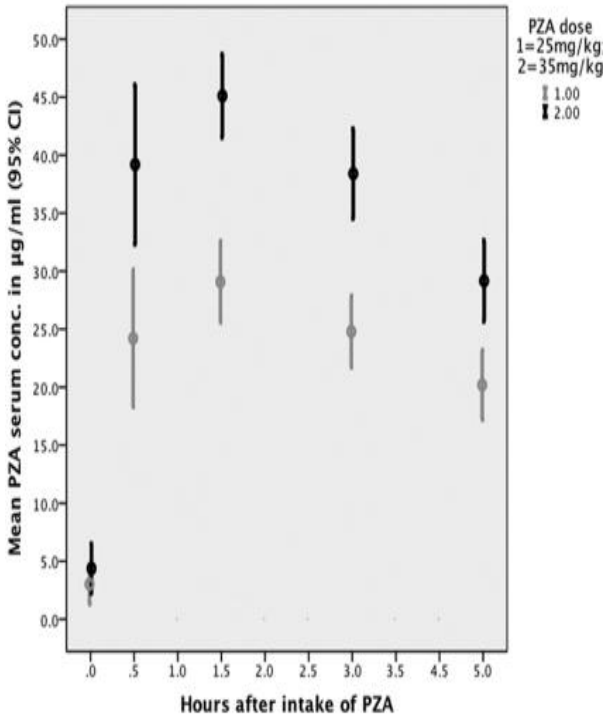
•Rifampicina	10 – 20
•Pirazinamide	30 – 40
•Etambutolo	15 – 25

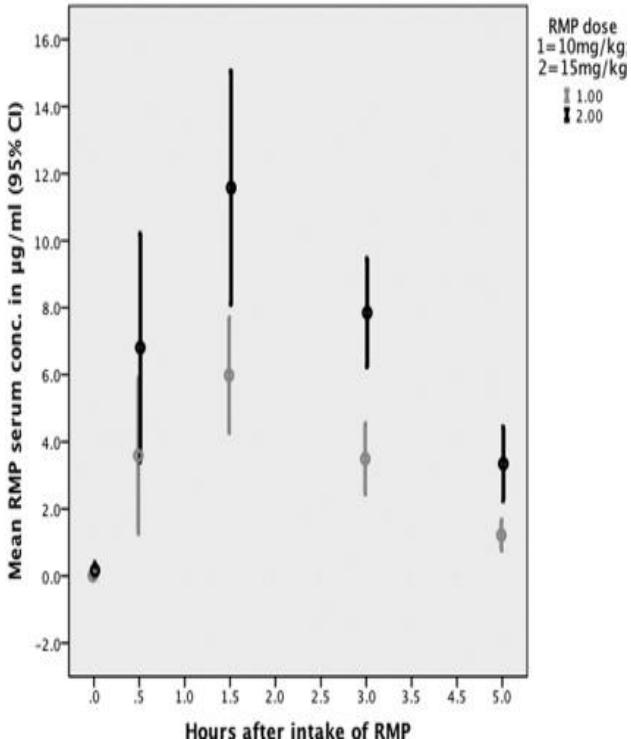
a. INH serum concentrations



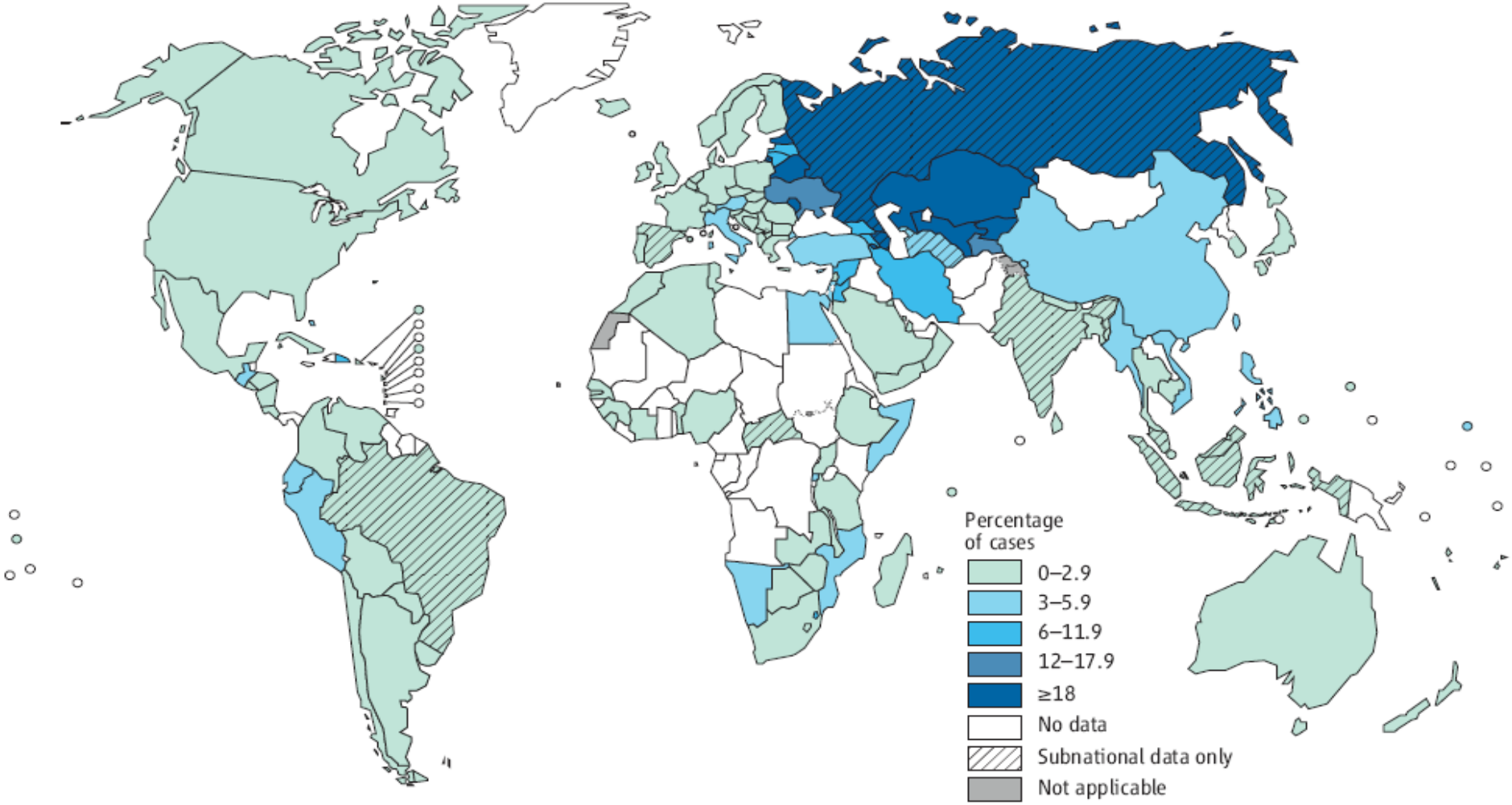
b. PZA serum concentrations



c. RMP serum concentrations



Percentage of new TB cases with MDR-TB[a]



[a] Figures are based on the most recent year for which data have been reported, which varies among countries.

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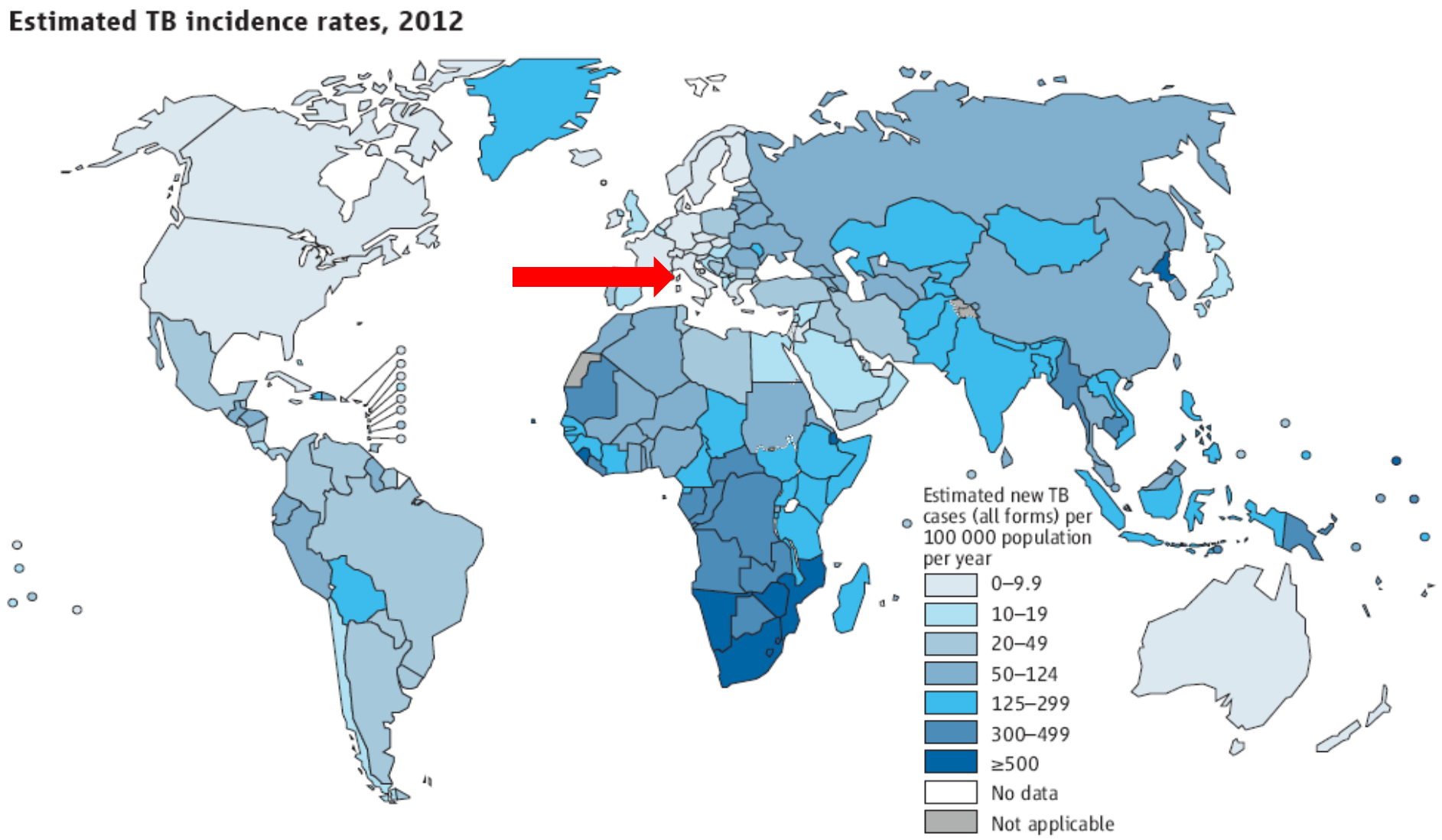
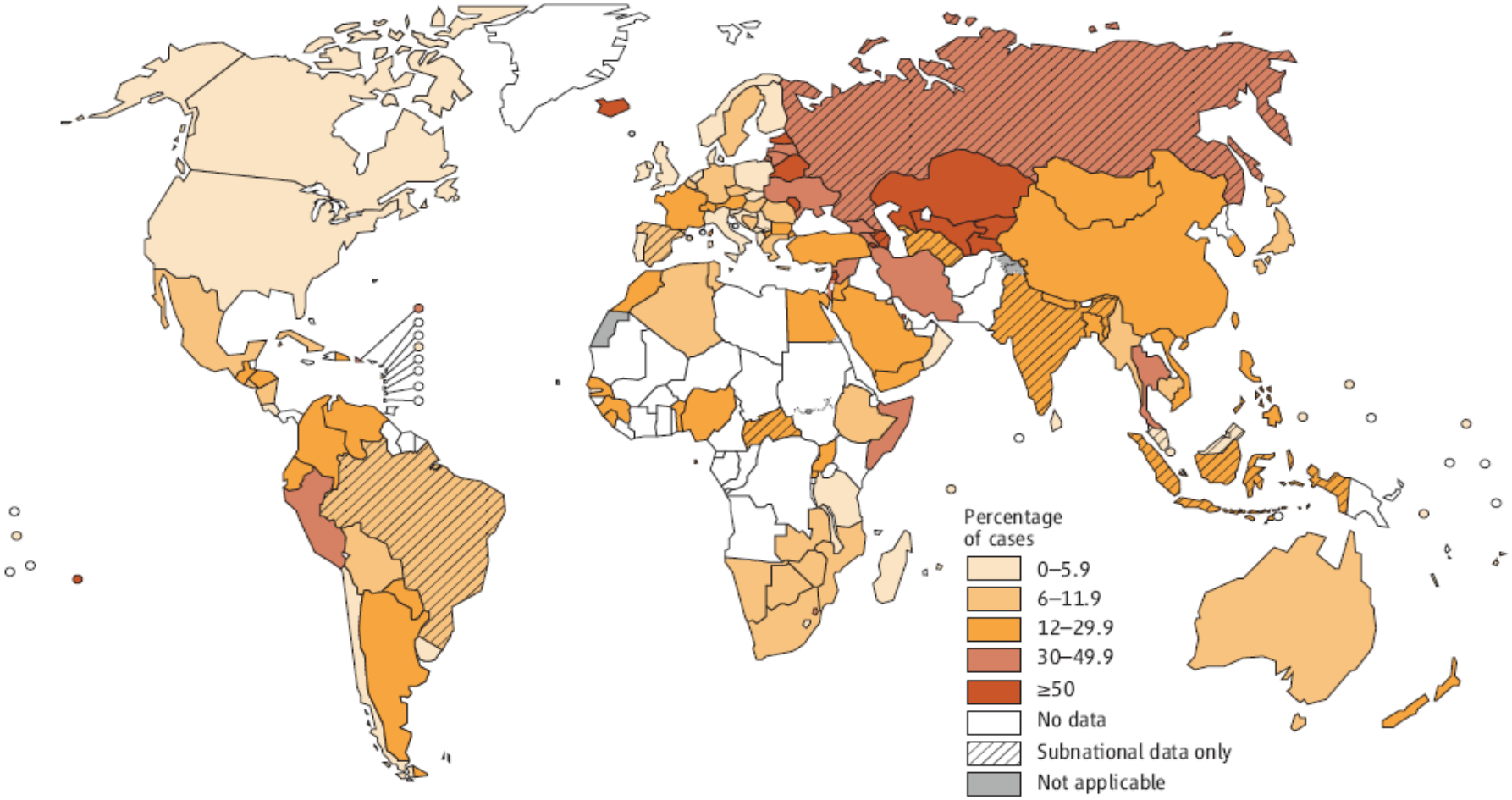
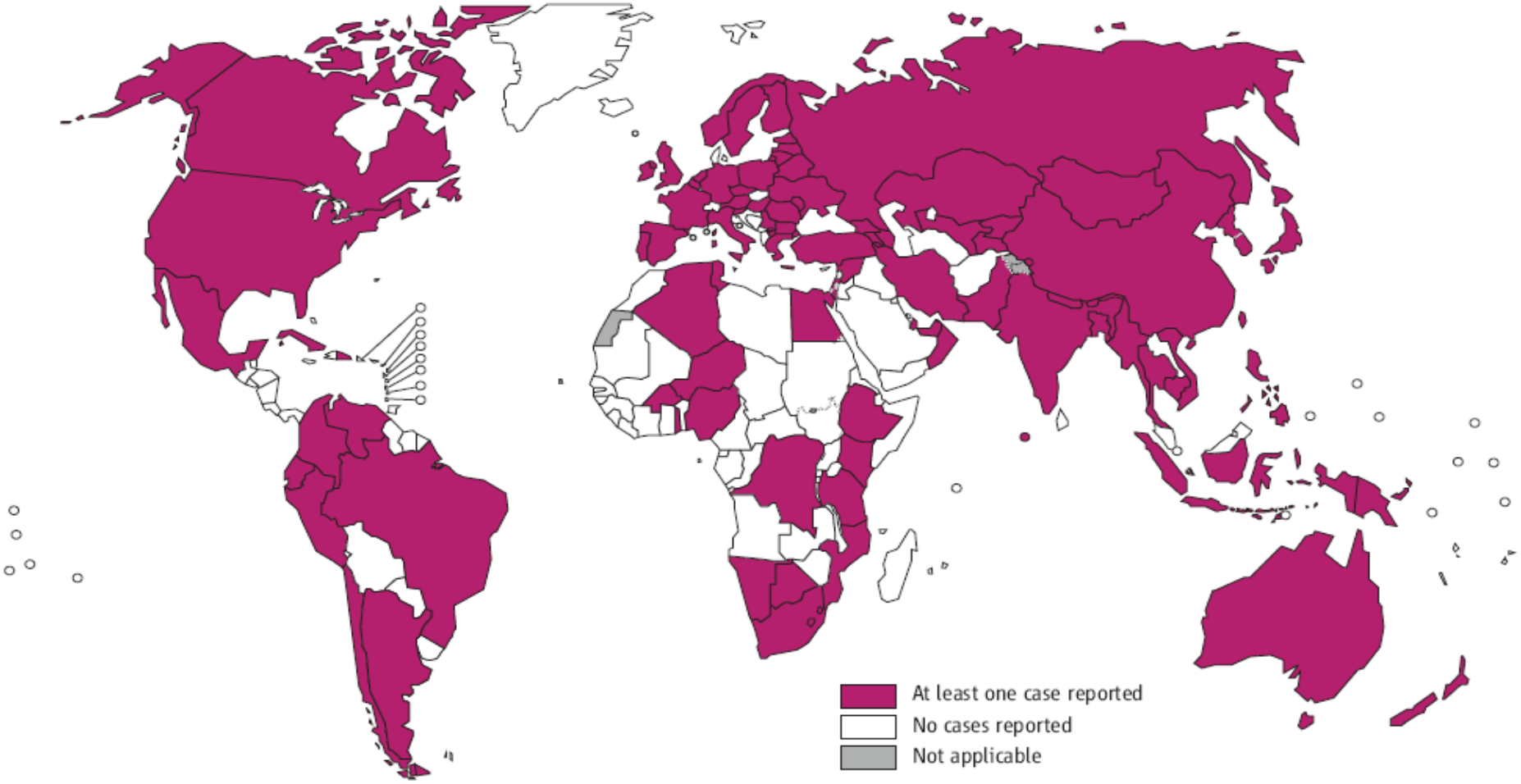


Percentage of previously treated TB cases with MDR-TB[a]

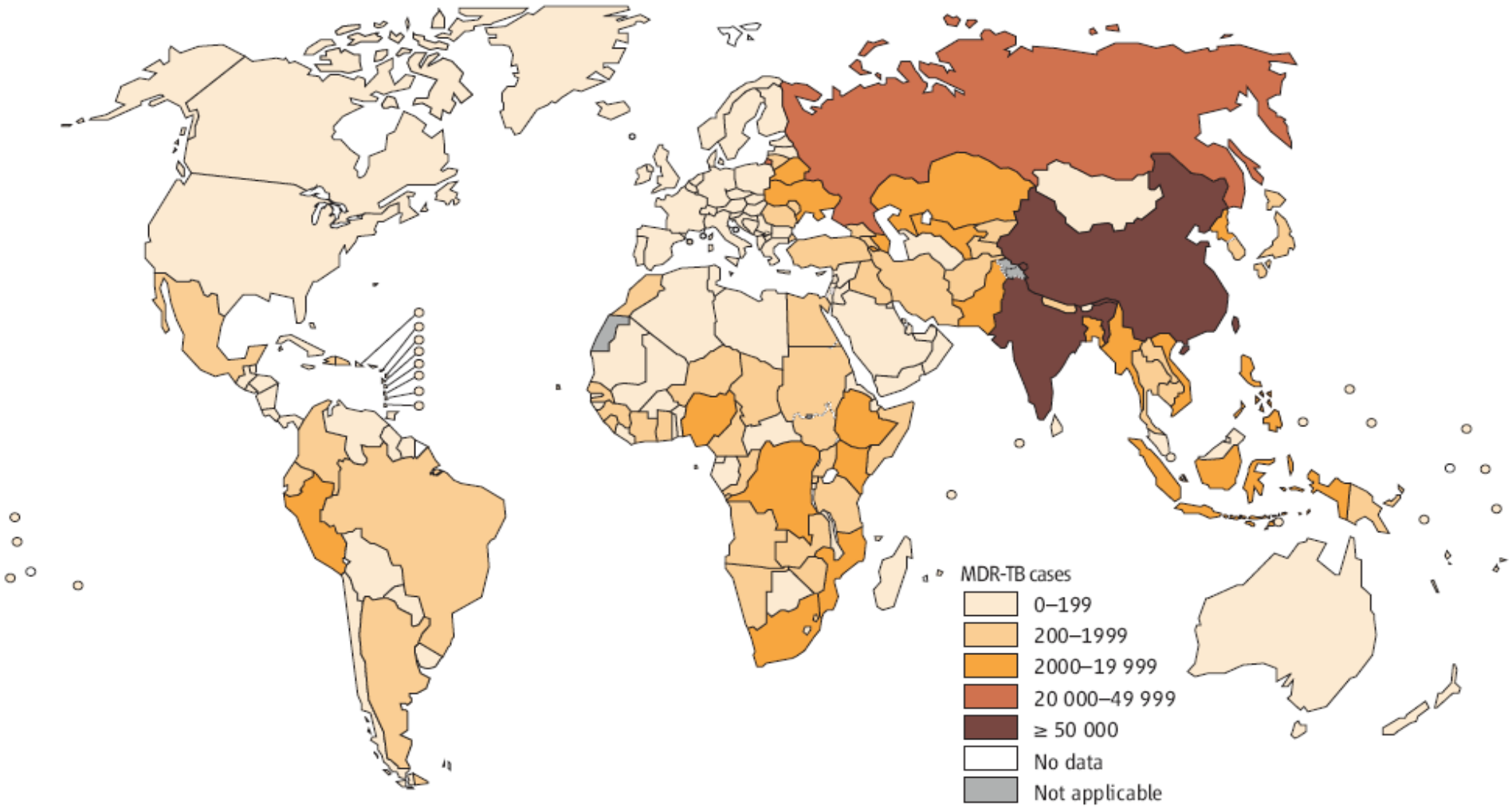


[a] Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (< 10).

Countries that had notified at least one case of XDR-TB by the end of 2012



Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2012



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•Para-aminosalicylic acid	150
Fluoroquinolons:	
•Moxifloxacin	7,5 – 10
•Ciprofloxacin	20 due volte al giorno
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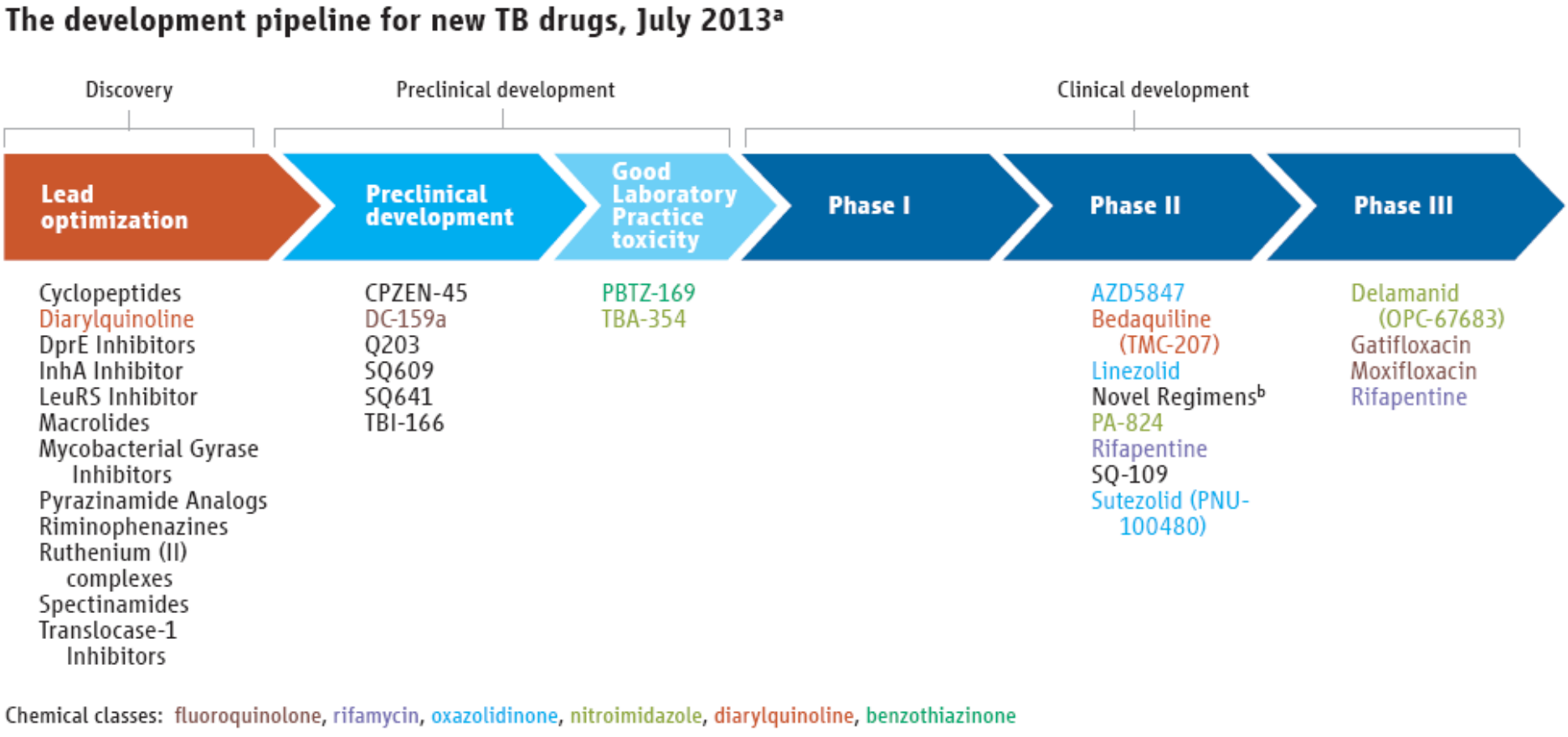
•Levoflaxacin	7,5 – 10
•Ofloxacin	15 – 20

Infezione	Condizioni	Terapia Anti-TB	
		Fase Intensiva	Fase di Mantenimento
Miliare o estesa a tutto il polmone	Qualsiasi	**2 HRZE**	**4 HR**
Polmonare da media a moderata	HIV o alta resistenza alla Isoniazide	**2 HRZE**	**4 HR**
Polmonare da media a moderata	HIV o bassa resistenza alla isoniazide	**2 HRZ**	**4 HR**
Linfadenite	HIV o alta resistenza alla isoniazide	**2 HRZE**	**4 HR**
Linfadenite	HIV o bassa resistenza alla isoniazide	**2 HRZ**	**4 HR**
Meningite	Qualsiasi	**2 HRZE**	**4 HR**
Osteoarticolare	Qualsiasi	**2 HRZE**	**4 HR**

Categoria di Infezione	Terapia Anti-TB	
	Fase Intensiva	Fase di Mantenimento
Polmonare, Extrapolmonare moderata	2 HRZ	4 HR
Extrapolmonare grave	2 HRZ	7-10 HR
Meningite TB	2 HRZA o 2 HRZP	7-10 HR
MDR	Terapia Individuale	
Infezione HIV	2 HRZ	7-10 HR

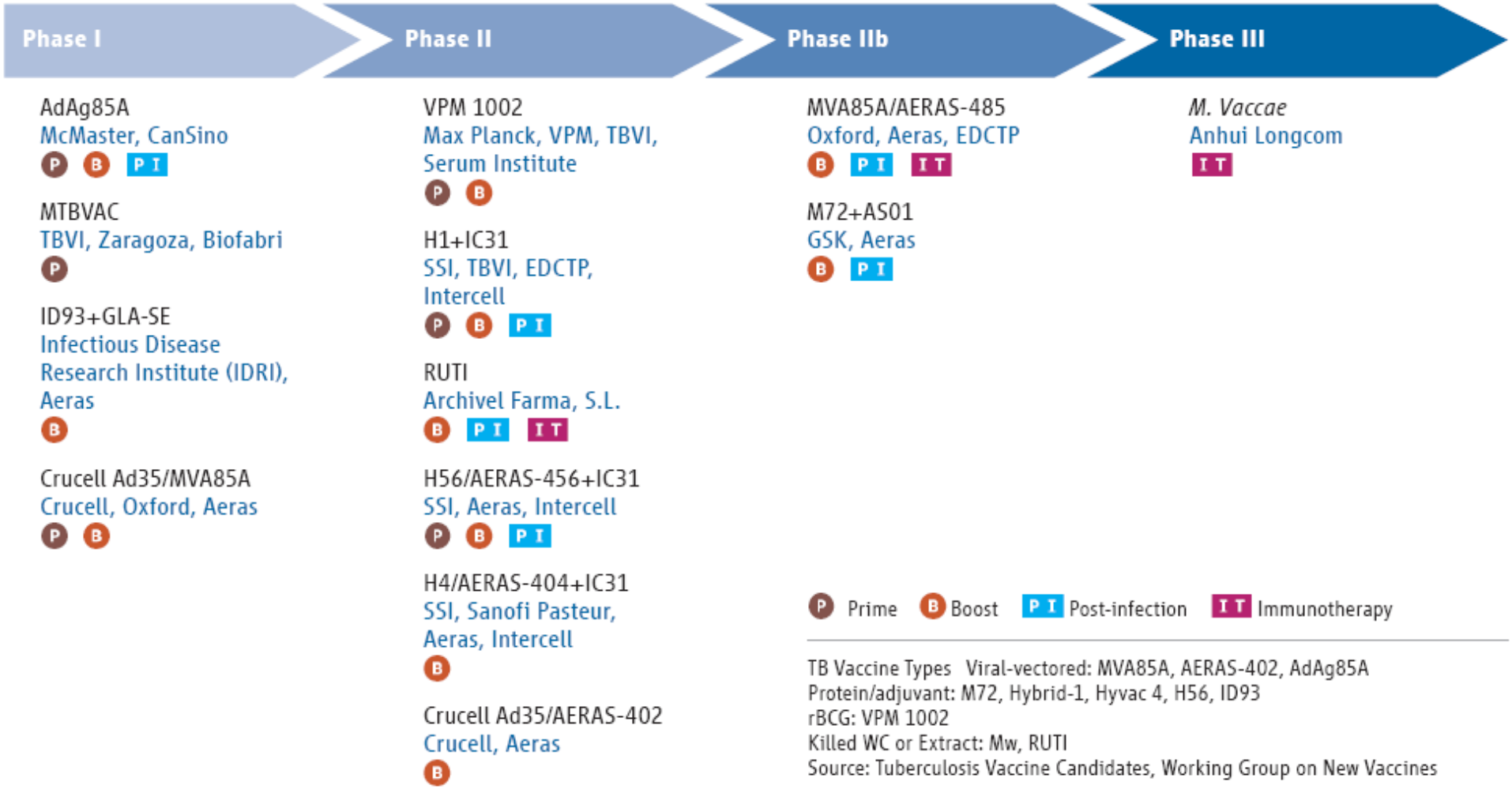
RESISTENZA ALLA TERAPIA ANTITUBERCOLARE
STIMOLO PER LA RICERCA DI NUOVI FARMACI



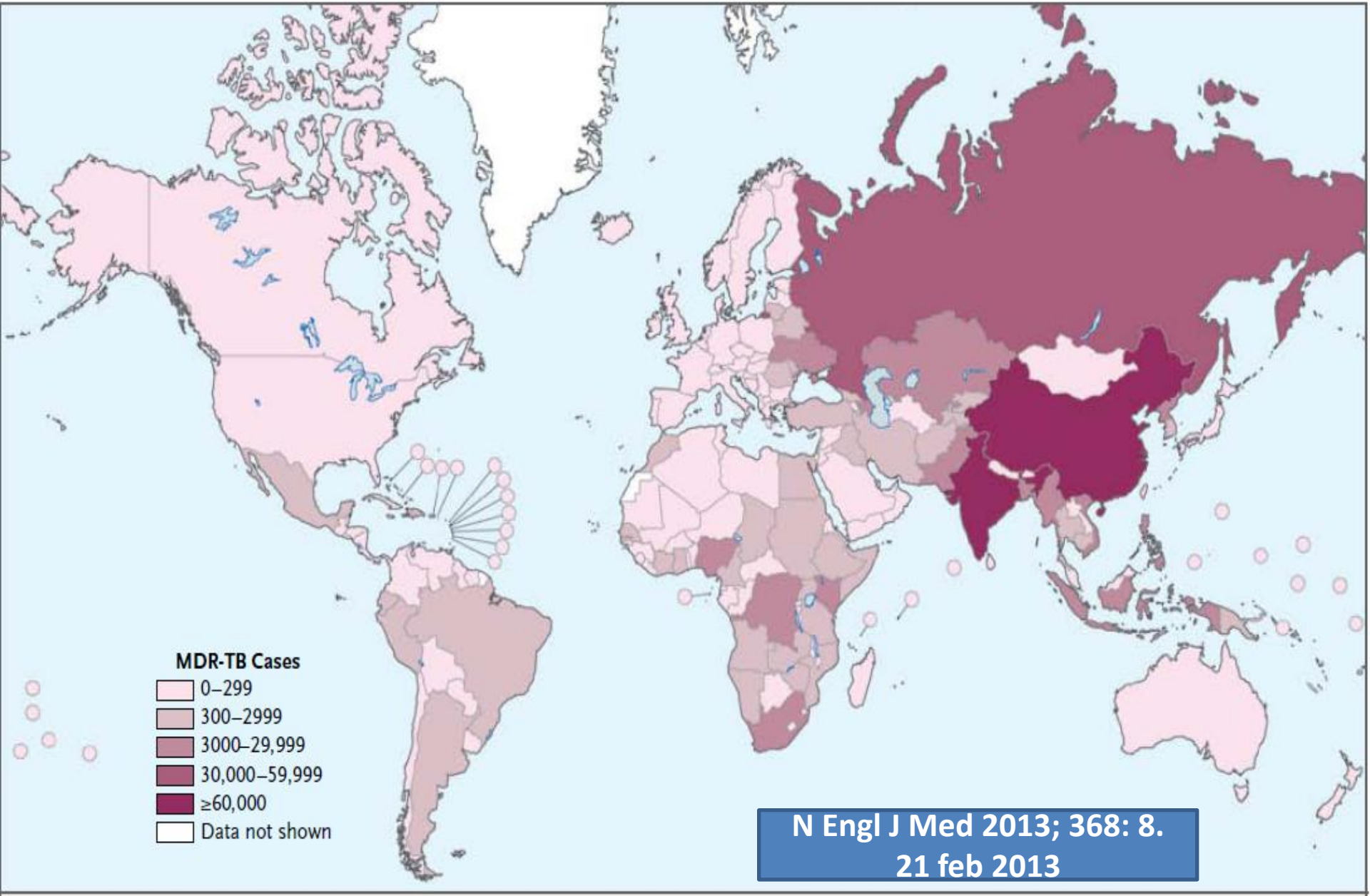
[a] Details for projects listed can be found at www.newtbdrugs.org/pipeline and ongoing projects for which a lead compound has not been identified can be viewed at www.newtbdrugs.org/pipeline-discovery.

[b] Combination regimens: NC-001-(-)-M-Pa-Z), Phase IIa; NC-002-(M-Pa-Z), Phase IIb; NC-003-(C-)-Pa-Z), Phase IIa; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), Phase IIb.

The development pipeline for new TB vaccines, July 2013



TB Vaccine Types Viral-vectored: MVA85A, AERAS-402, AdAg85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93
rBCG: VPM 1002
Killed WC or Extract: Mw, RUTI
Source: Tuberculosis Vaccine Candidates, Working Group on New Vaccines



N Engl J Med 2013; 368: 8.
21 feb 2013

Figure 2. Global Numbers of Cases of Multidrug-Resistant Tuberculosis.

Shown are the estimated numbers of cases of multidrug-resistant disease (including extensively drug-resistant disease) among cases of pulmonary tuberculosis that were officially reported in 2011.

Box 1. Treatment of tuberculosis

Treatment of TB consists of a standardized 6- or 8-month chemotherapy for new or previously treated cases, respectively. In countries where DST is routinely performed, MDR-TB treatment is individualized. Otherwise, MDR-TB is often treated using standardized drug regimens; however, these may vary between countries.

New TB cases

- Two months of isoniazid, rifampicin, pyrazinamide, and ethambutol (intensive phase).
- Four months of isoniazid and rifampicin (continuation phase).

Previously treated TB cases

- Two months of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin (intensive phase).
- One month of isoniazid, rifampicin, pyrazinamide, and ethambutol (intensive phase).
- Five months of isoniazid, rifampicin, and ethambutol (continuation phase).

MDR-TB cases

- At least four drugs likely to be effective must be included.
- Any first-line oral agents likely to be effective should be included (e.g., pyrazinamide or ethambutol).
- One effective injectable aminoglycoside or polypeptide drug should be included (kanamycin, amikacin, capreomycin, or streptomycin).
- One fluoroquinolone should be included.
- Intensive-phase therapy, including the injectable drug, should last for at least 6 months. Total duration of therapy should be at least 18 months.

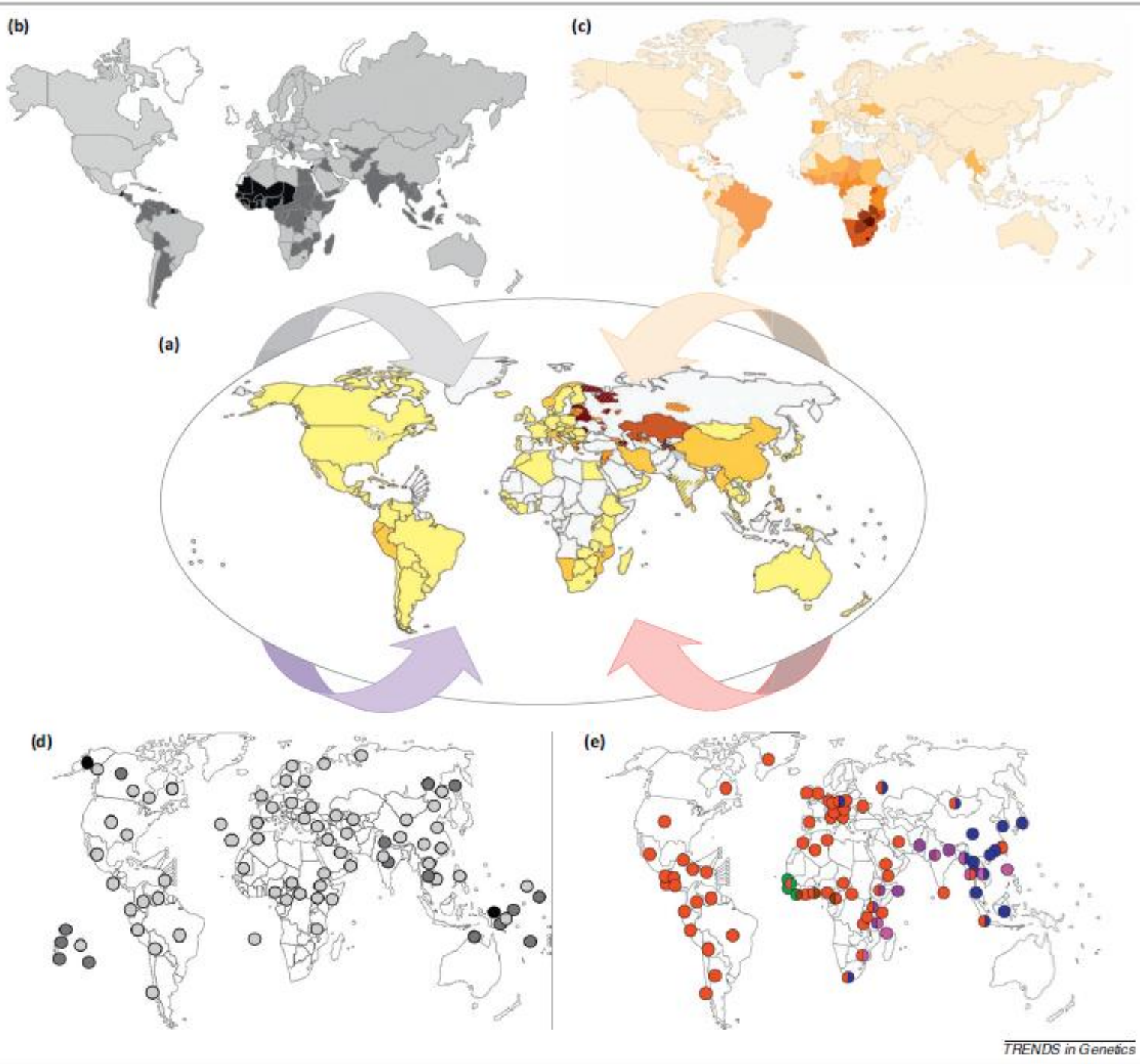
Review

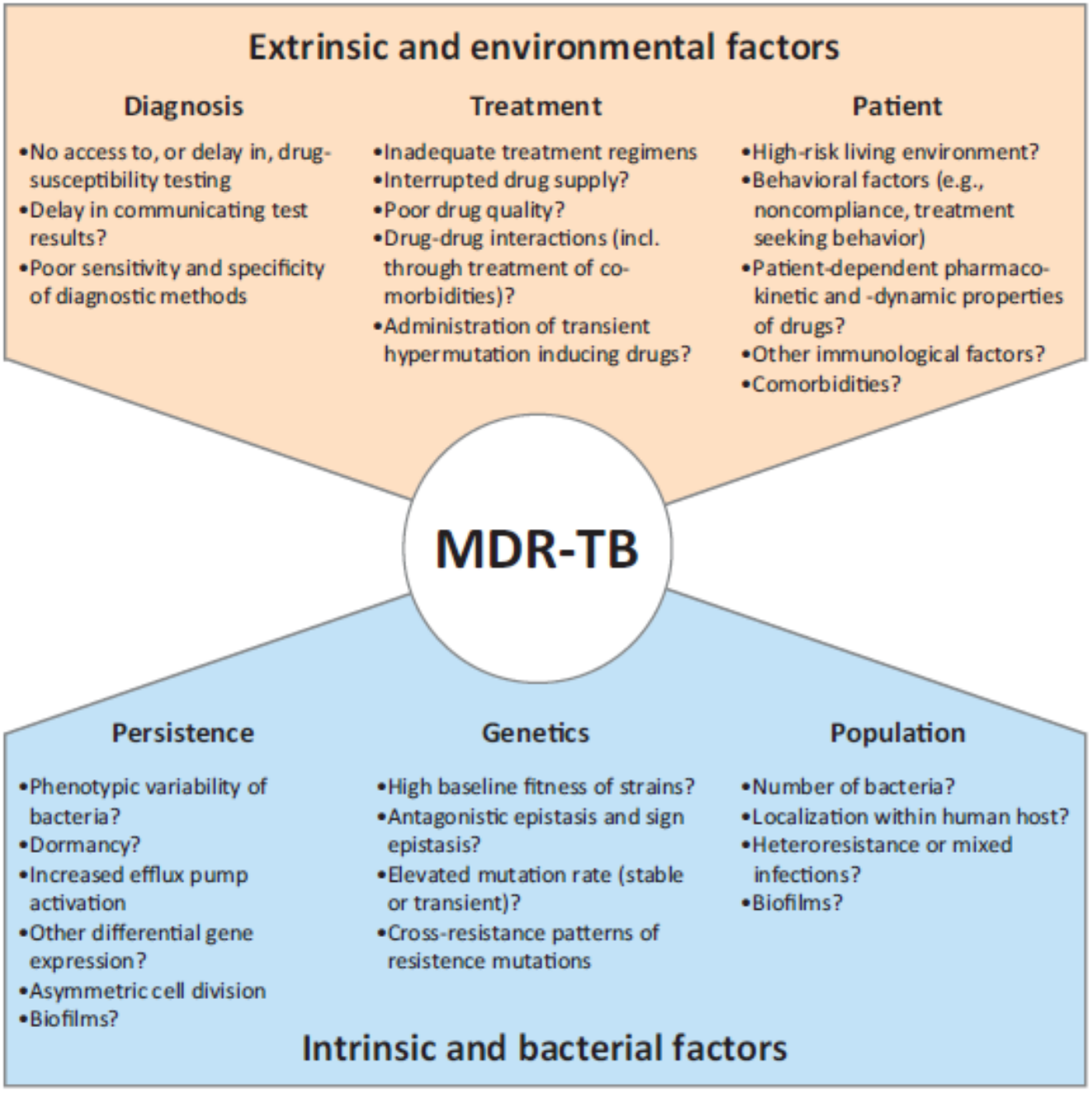
Cell PRESS

The heterogeneous evolution of multidrug-resistant *Mycobacterium tuberculosis*

Borna Müller[1,2], Sonia Borrell[1,2], Graham Rose[3], and Sebastien Gagneux[1,2]

[1] Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Basel, Switzerland
[2] University of Basel, Basel, Switzerland
[3] Division of Mycobacterial Research, Medical Research Council, National Institute for Medical Research, London, UK


(b)
(c)
(a)
(d)
(e)
TRENDS in Genetics



TRENDS in Genetics

Caring for Children with Drug-Resistant Tuberculosis

Practice-based Recommendations

James A. Seddon[1,2], Jennifer J. Furin[3], Marianne Gale[4], Hernan Del Castillo Barrientos[5,6], Rocío M. Hurtado[7,8,9], Farhana Amanullah[10], Nathan Ford[11], Jeffrey R. Starke[12], and H. Simon Schaaf[1,13]; on behalf of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis

TABLE 2. STUDIES DESCRIBING DRUG-RESISTANT TUBERCULOSIS TREATMENT IN CHILDREN

First Author	Year of Study	Location	Number of Children Included	Number Culture-Confirmed	Treatment Success (%)	Adverse Events
Seddon (23)	2003–2008	Cape Town, South Africa	111	111	88 (79)	NS
Leimane (60)	1998–2006	Latvia	76	NS	70 (92)	26
Schaaf (21)	1998–2001	Cape Town, South Africa	39	39	21 (54)	20
Drobac (35)	1999–2003	Lima, Peru	38	28	36 (95)	16
Feja (19)	1995–2003	NY	20	6	16 (80)	4
Satti (20)	2007–2011	Lesotho	19	5	15/17 (88)	18
Fairlie (22)	2008	Johannesburg, South Africa	13	13	7 (54)	2
Granich (118)	1994–2003	CA	10	NS	9 (90)	NS
Mendez Echevarria (36)	1994–2005	Madrid, Spain	8	5	8 (100)	4
Padayatchi (24)	1992–2003	Durban, South Africa	8	8	1 (13)	NS
Rose (28)	2007–2012	Cape Town, South Africa	7	7	4/4 (100)	3
Kjöllerström (27)	2011*	Lisbon, Portugal	4	4	4 (100)	3
Thomas (61)	2006–2007	Tuglea Ferry, South Africa	4	4	4 (100)	2
Schluger (25)	1983–1993	NY	2	2	2 (100)	NS
Pinon (55)	2010*	Turin, Italy	2	NS	1 (50)	0
Suessmuth (26)	2005	Hannover, Germany	1	1	1 (100)	NS

Paediatric Respiratory Reviews 12 (2011) 31–38

Contents lists available at ScienceDirect

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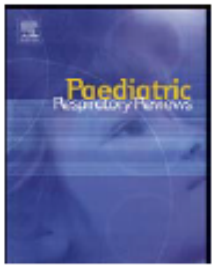


Mini-symposium: Childhood TB in 2010

Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians

H. Simon Schaaf *, Ben J Marais

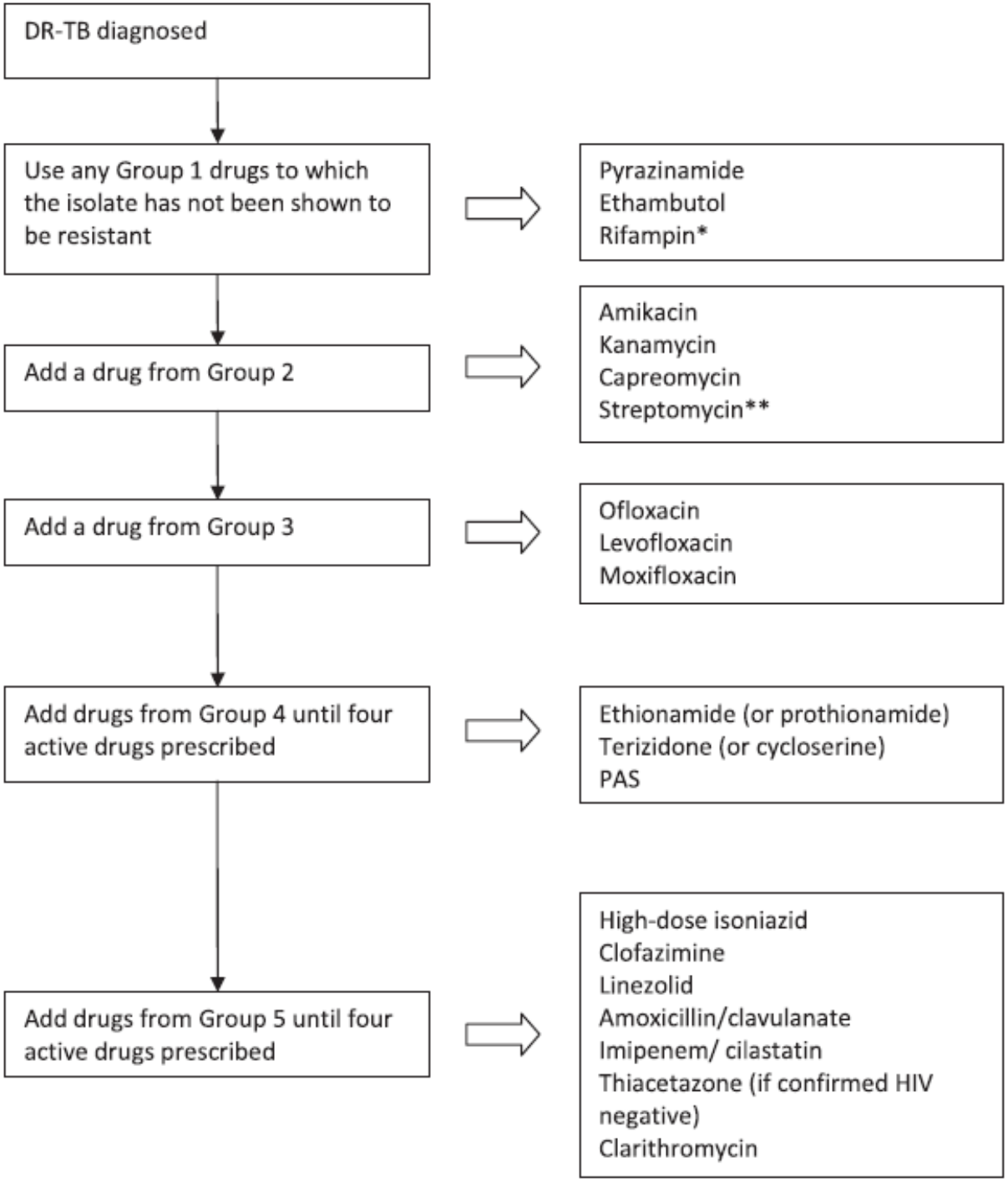
Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, and Tygerberg Children's Hospital, Cape Town, South Africa

Pediatric Infectious Disease 2012 April–June
Volume 4, Number 2; pp. 41–42

Editorial

Drug-resistance in childhood tuberculosis—invisible and unnoticed

Soumya Swaminathan


DR-TB diagnosed
Use any Group 1 drugs to which the isolate has not been shown to be resistant
Pyrazinamide
Ethambutol
Rifampin*
Add a drug from Group 2
Amikacin
Kanamycin
Capreomycin
Streptomycin**
Add a drug from Group 3
Ofloxacin
Levofloxacin
Moxifloxacin
Add drugs from Group 4 until four active drugs prescribed
Ethionamide (or prothionamide)
Terizidone (or cycloserine)
PAS
Add drugs from Group 5 until four active drugs prescribed
High-dose isoniazid
Clofazimine
Linezolid
Amoxicillin/clavulanate
Imipenem/ cilastatin
Thiacetazone (if confirmed HIV negative)
Clarithromycin

Situazione italiana

«The spread of drug-resistant tuberculosis in children: an Italian case series»

Mignone F., Codecasa L.R., Scolfaro C., Raffaldi I., Lancella L., Ferrarese M., Garazzino S., Marabotto C., Esposito S., Gabiano C., Lipreri R., Tovo P.A.

Epidemiol Infect, 2013 Dec 19: 1-8

Dal giugno 2006 al luglio 2010

22 pazienti pediatrici

17 resistenti a 1 o più farmaci

5 multidrug-resistant

Mycobatterio
o
Mycobatteri?

THORAX

Ethnicity and mycobacterial lineage as determinants of tuberculosis disease phenotype

Manish Pareek, Jason Evans, John Innes, et al.

Thorax 2013 68: 221-229 originally published online September 27, 2012
doi: 10.1136/thoraxjnl-2012-201824

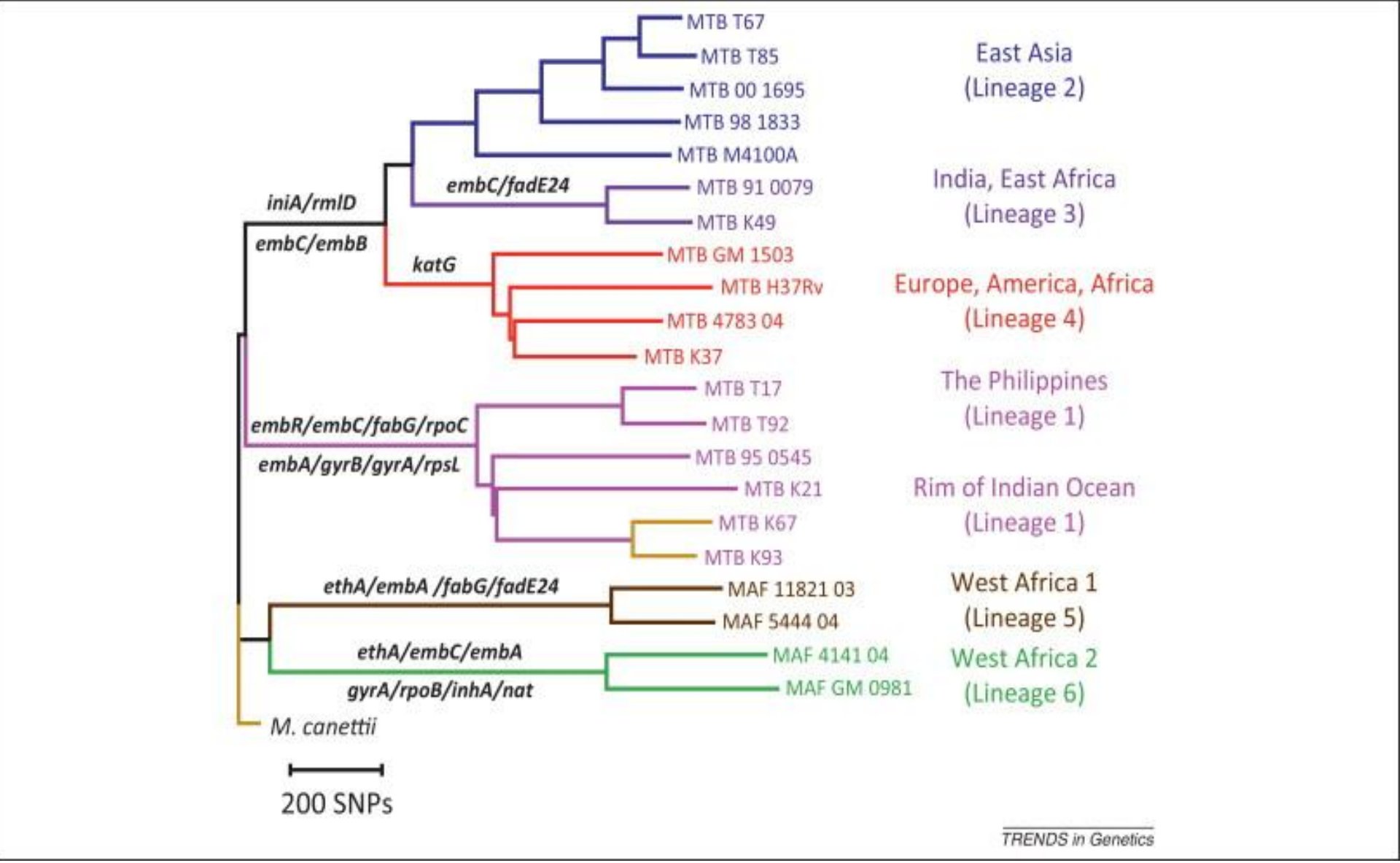
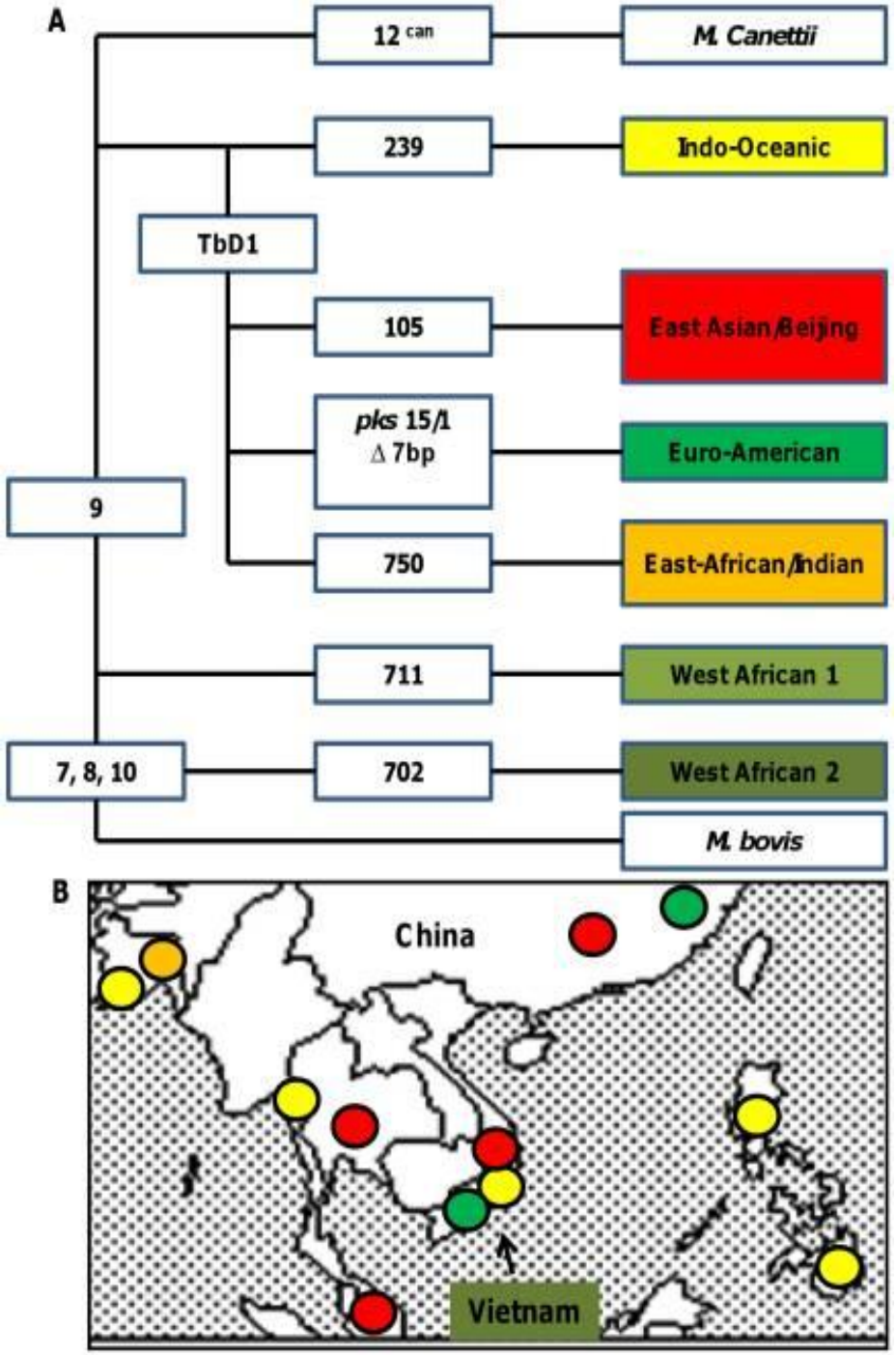
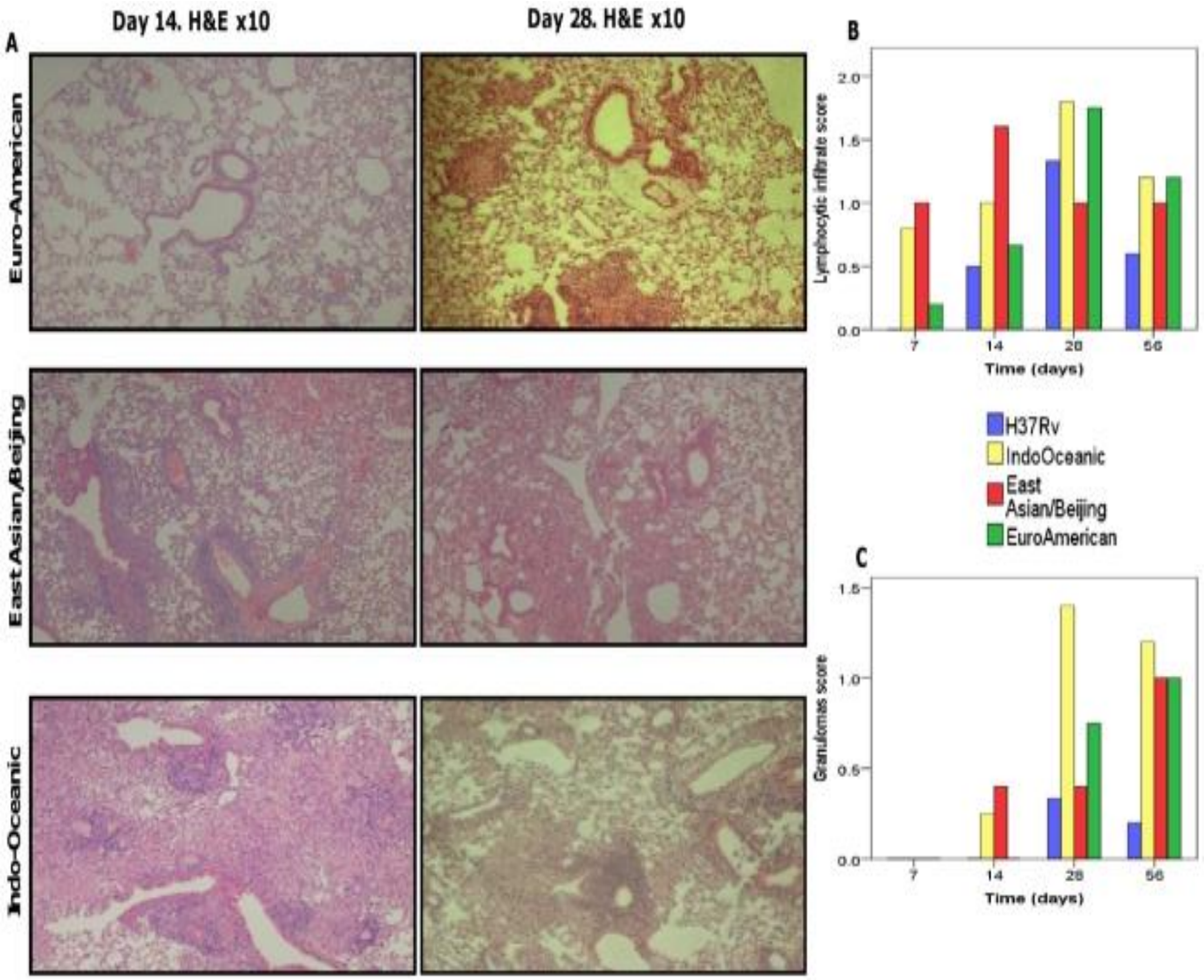


Figure 4. Drug resistance-associated genes containing *Mycobacterium tuberculosis* lineage-specific mutations. Phylogenetic tree of the six main lineages of *M. tuberculosis* associated with human tuberculosis (TB), based on 21 whole-genome sequences [81]. Genes indicated are associated with drug resistance (Table 1, main text) and harbor lineage-defining, nonsynonymous substitutions. This creates the potential for epistatic interactions between the genetic background of a given strain and specific drug resistance-conferring mutations. Abbreviation: SNPs, single nucleotide polymorphisms.

The phylogeny of *M. tuberculosis* in South East Asia. Large sequence polymorphisms define six major lineages of *M. tuberculosis* (A) which are strongly associated with specific geographical regions (B). In Vietnam, three lineages cause the majority of disease: the East Asian/Beijing, the Indo-Oceanic, and the Euro-American (adapted from reference 1). Numercial values in the figure represent regions of deletions (RD) that define each of the lineages.





Histology of lungs infected with different lineages of *M. tuberculosis*.
Sections of the lungs were stained with H&E stain. Representative lung sections for each *M. tuberculosis* infected group at day 14 and day 28 post-infection are displayed (A). Lung sections were scored (blind to the strain lineage) for lymphocytic infiltrates (B) and granulomas (C) and mean scores for each group presented. A score of 0 = normal lung; a score of 2 = moderate lymphocytic infiltrate/granuloma formation seen; a score of 3 = extensive lymphocytic infiltrate/granuloma formation seen. The displayed histology images are from one experiment only.

Casistica Ospedale Bambino Gesù 2001-2013

TOTALE casi TBC	225
SENSIBILE	**189** (88,29%)
MONO-RESISTENTE	**25** (8,29%)
POLI-RESISTENTE	**8** (2,92%)
ESTENSIVAMENTE-RESISTENTE	

CONCLUSIONI

- La terapia tradizionale per la tubercolosi in Italia è ancora valida ed efficace.
- Le forme multiresisitenti o estesamente multiresistenti in Italia, in particolare in età pediatrica, sono molto rare.
- E’ importante seguire i cambiamenti del Mycobaterium e lo sviluppo delle resistenze.
- La Tubercolosi non è una malattia sconfitta e merita ancora molta attenzione