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ITMO Microbiologie
et maladies infectieuses

EDCTP Stakholder Meeting
Tuberculosis
Paris - October 28, 2013

TUBERCULOSIS: REMAINING CHALLENGES

Pr Jean-François DELFRAISSY
Director : ANRS & IMMI/AVIESAN

The French Alliance for Life and Health Sciences: Aviesan

- Created in April 2009
- To coordinate the strategic analysis, the scientific programming and the operational implementation of research
  - **Research operating** agencies :
    - Inserm (ANRS & INCA)
    - CNRS life sciences department
    - CEA (atomic energy commission)
    - Inra (national institute for agricultural research)
    - Inria (computer science and automatic control)
    - IRD (research for development)
    - Pasteur Institute
    - **CIRAD, Fondation Mérieux, IRBA**
  - **Universities**
  - **Hospitals**

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Aviesan - Alliance nationale pour les Sciences de la Vie et de la Santé

Ten Thematic Institutes

Genetics, Genomics Bioinformatics	**Cell Biology Development**	**Neurosciences Cognitive Sciences Neurology, Psychiatry** *Alzheimer*	**Immunology Hematology Respiratory diseases**	**Microbiology Infectious Diseases** *ANRS*
Molecular and Structural Biology	**Nutrition Circulation Metabolism**	**Cancer** *INCa*	**Public Health** *IReSP*	**Health Technologies**

Main Research Institutes in the field

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

National Institute for Health and Medical Research
Total budget: €750m

INSTITUT PASTEUR

Institut Pasteur
Total Budget: €250m

cnrs
dépasser les frontières

National Center for Scientific Research
Total budget: €3,415bn for 7 institutes

IRD
Institut de recherche pour le développement

Institute for Research for Development
Total budget: €233m

cirad
LA RECHERCHE AGRONOMIQUE POUR LE DÉVELOPPEMENT

Agricultural Research Center for Development
Total budget: €214m

Project Funding/year: infectious diseases

PHRC: Clinical Research Hospital Programme
€16m/year

National Research Agency
€22m/year

National Research Agency for AIDS & Hepatitis
€39m/year

EP7, EDCTP1, IMI, JPI
ERANET €40m/year

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€1.5bn

INSTITUT PASTEUR

ANR

IBEID
Institut Pasteur

ECOFECT

Ecrin
French Clinical Research Infrastructure Network

cirad
LA RECHERCHE AGRONOMIQUE POUR LE DÉVELOPPEMENT

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

BIOASTER

REIVAC
Réseau national d'investigation clinique en VACcinologie

IRD
institut de recherche pour le développement

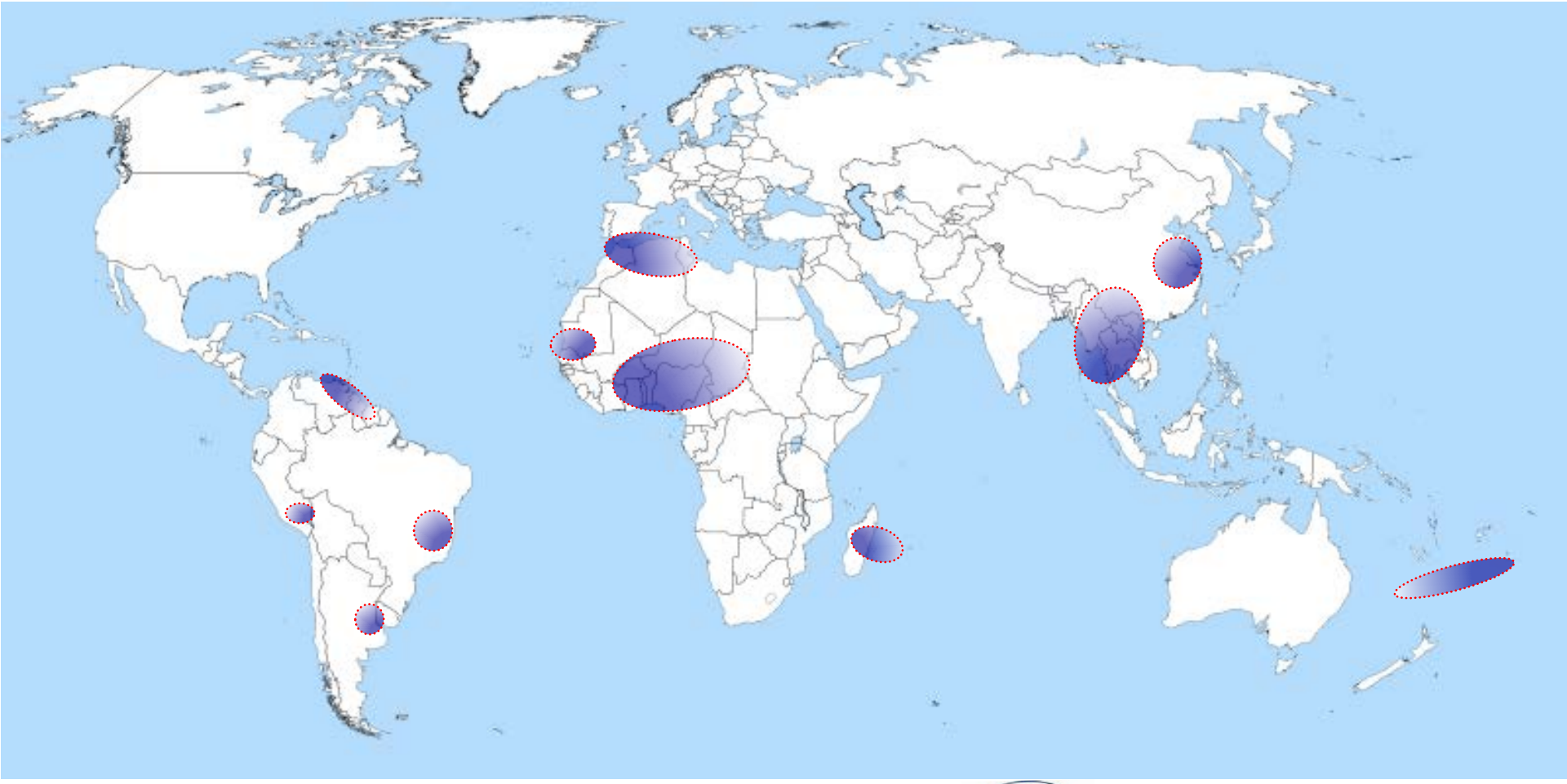
Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

cnrs
dépasser les frontières

MÉDITERRANÉE INFECTION

anRS

French Network



Institut Pasteur

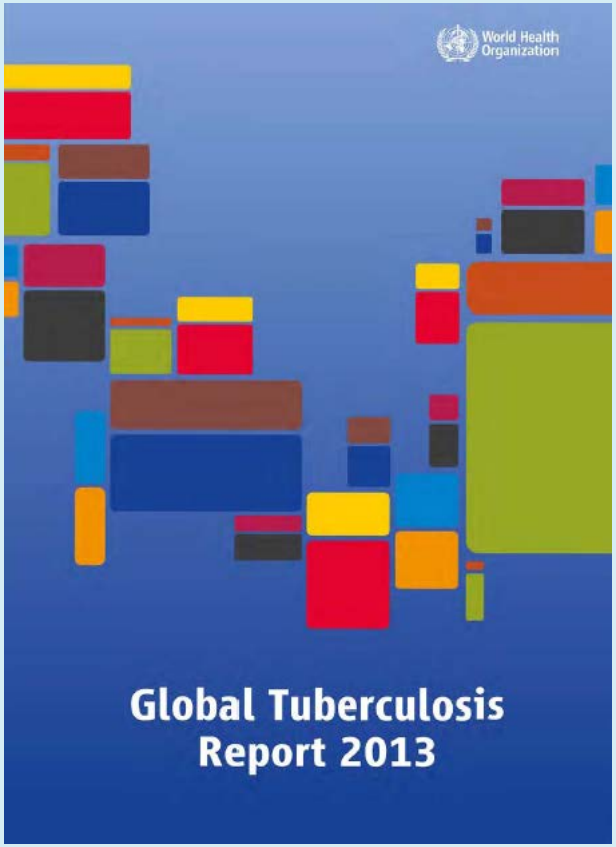
IRD
Institut de recherche pour le développement

anRS
Agence nationale de recherches sur le sida et les hépatites virales

Fondation Mérieux

cirad
LA RECHERCHE AGRONOMIQUE POUR LE DÉVELOPPEMENT

Tuberculosis: key figures in 2013



World Health Organization

8.6 million incident cases [8.3-9.0], incl. 0.45 million MDR-TB [0.30-0.60]

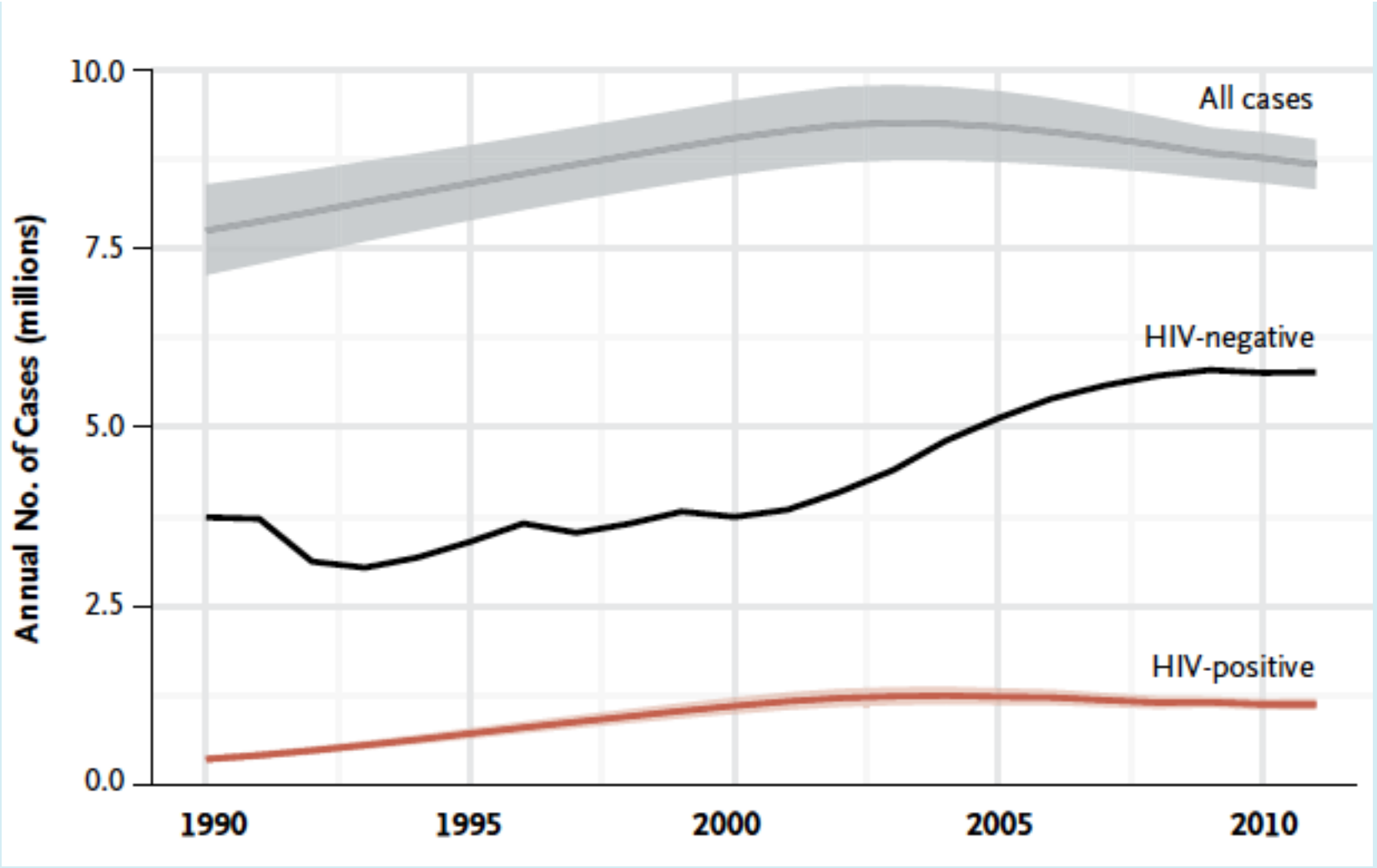
12 million prevalent cases [11-13]

About 13% of TB cases occur among people living with HIV

Geography:
Asia: 58%, Africa: 27%

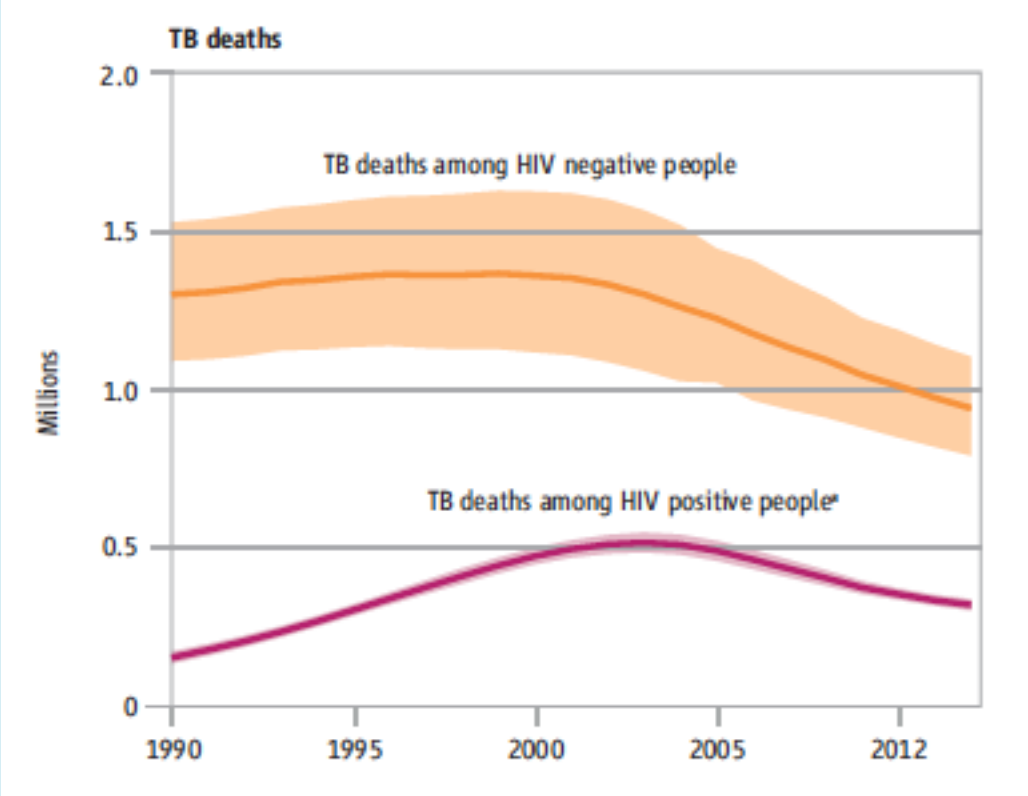
Mortality:
HIV-negative: 0.94 million [0.79-1.10]
HIV-positive: 0.32 million [0.30-0.34]

Estimated incidence of TB

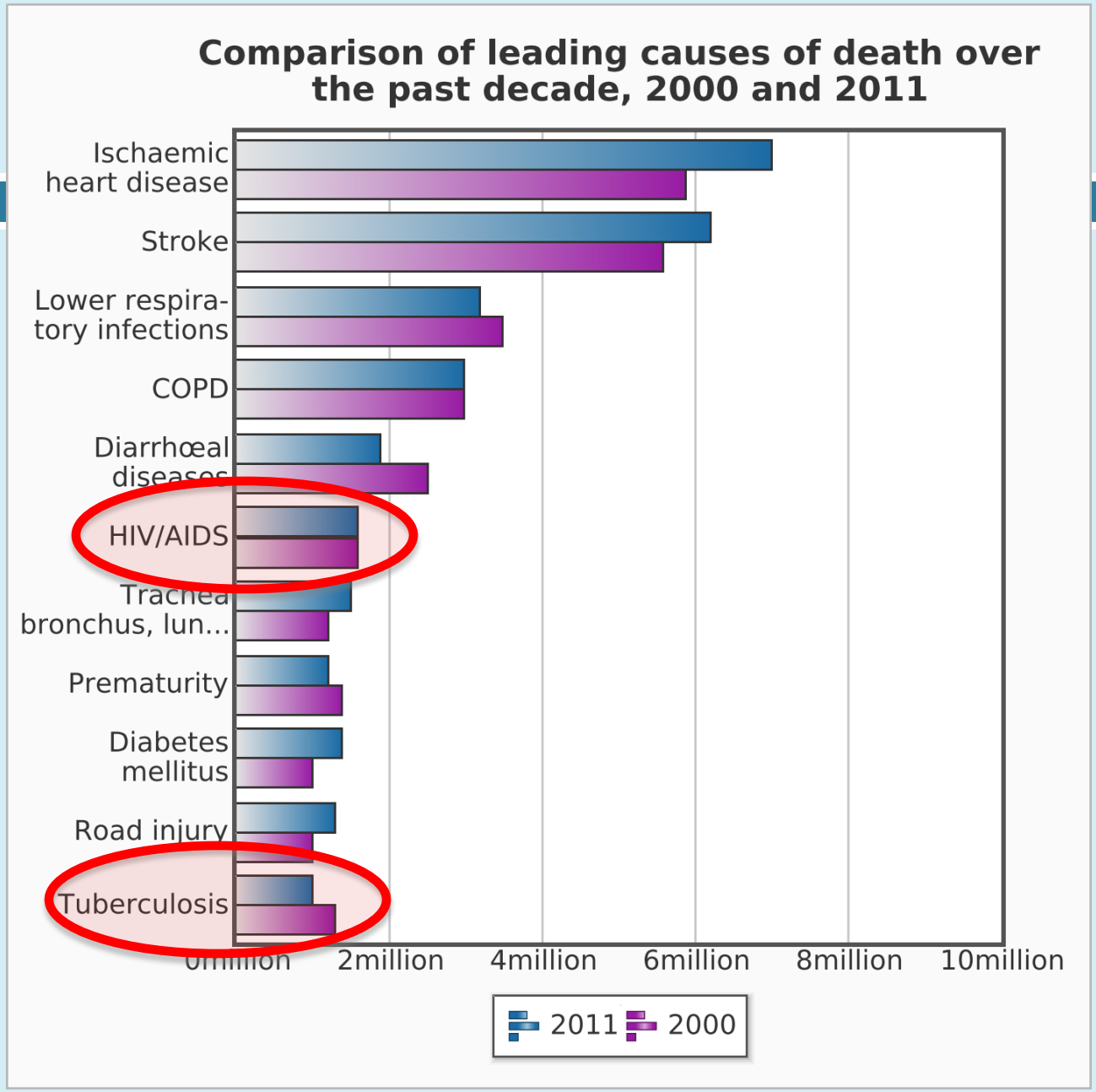


Zumla A. *et al.*, NEJM 2013; 368: 745-55

TB deaths, 1990-2012

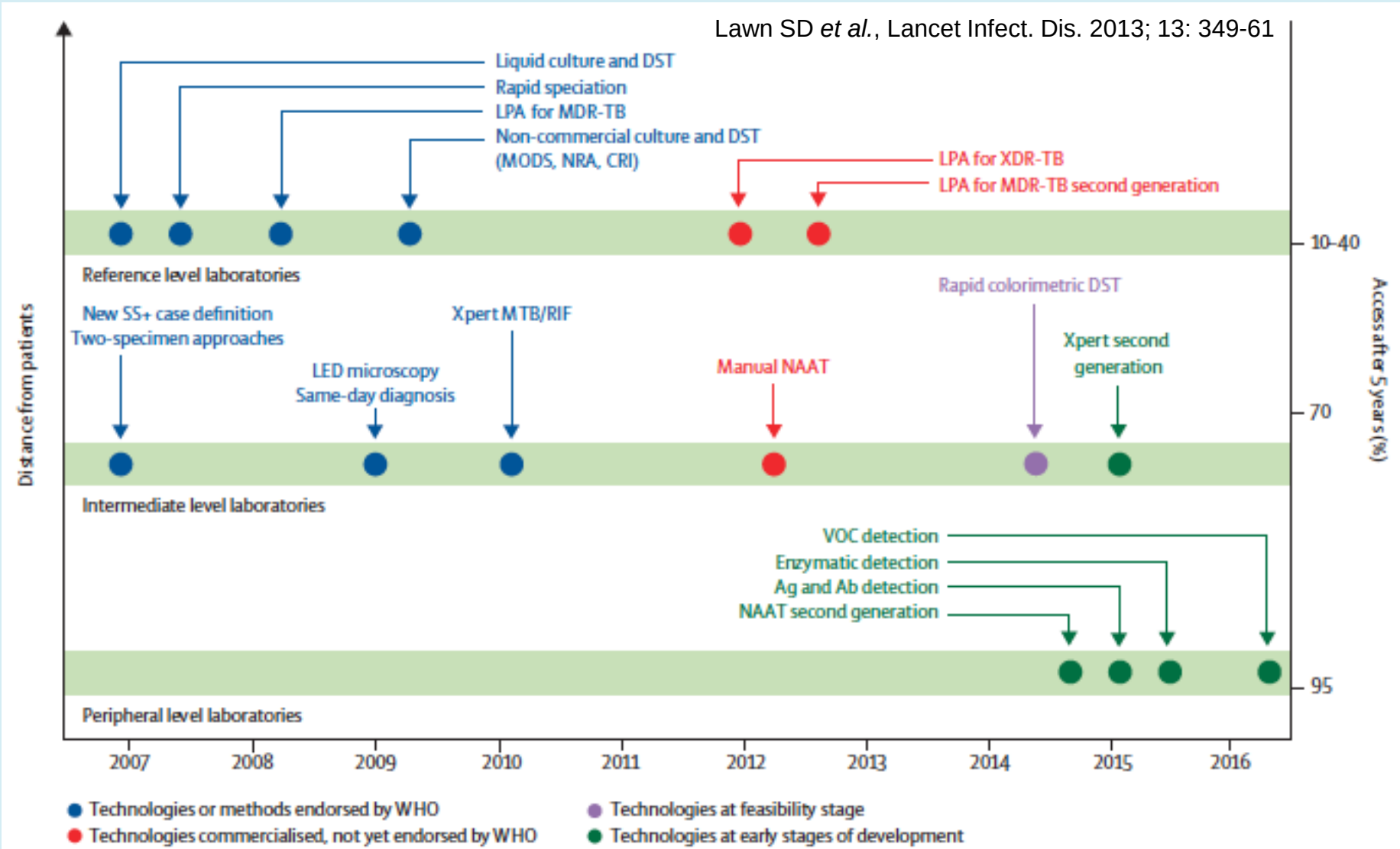


WHO global tuberculosis report 2013



World Health Organization

Development pipeline for new TB Δg



TB diagnostics

Technologies in early development[a]

Volatile organic compounds
- BreathLink, Menssana Research, USA
- Prototype breath analyzer device, Next Dimensions Technology, USA

Molecular technologies
- Alere Q, Alere, USA
- B-SMART, LabCorp, USA
- Gendrive MTB/RIF ID, Epistem, UK
- LATE-PCR, Brandeis University, USA
- GeneXpert XDR cartridge, Cepheid, USA
- TruArray MDR-TB, Akkoni, USA
- INFINITIMTB Assay, AutoGenomics, USA

Culture-based technologies
- BNP Middlebrook, NanoLogix, USA
- MDR-XDR TB Color Test, FIND, Switzerland/Imperial College, UK
- TREK Sensititre MYCOTB MIC plate, Trek Diagnostic Systems/Thermo Fisher Scientific, USA

Other technologies
- TB Rapid Screen, Global BioDiagnostics, USA
- TBDx, Signature Mapping Medical Sciences, USA

Evaluated by WHO but not yet endorsed due to insufficient evidence

Molecular technologies
- TB LAMP, Eiken, Japan
- Genotype MTBDRsl, Hain Lifescience, Germany

On the market but evidence for use not yet submitted to WHO for evaluation

Molecular technologies
- iCubate System, iCubate, USA
- TB drug resistance array, Capital Bio, China
- EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China
- Truelab/Truenat MTB, Molbio/bigtec Diagnostics, India

Non-molecular technologies
- Alere Determine TB-LAM, Alere, USA

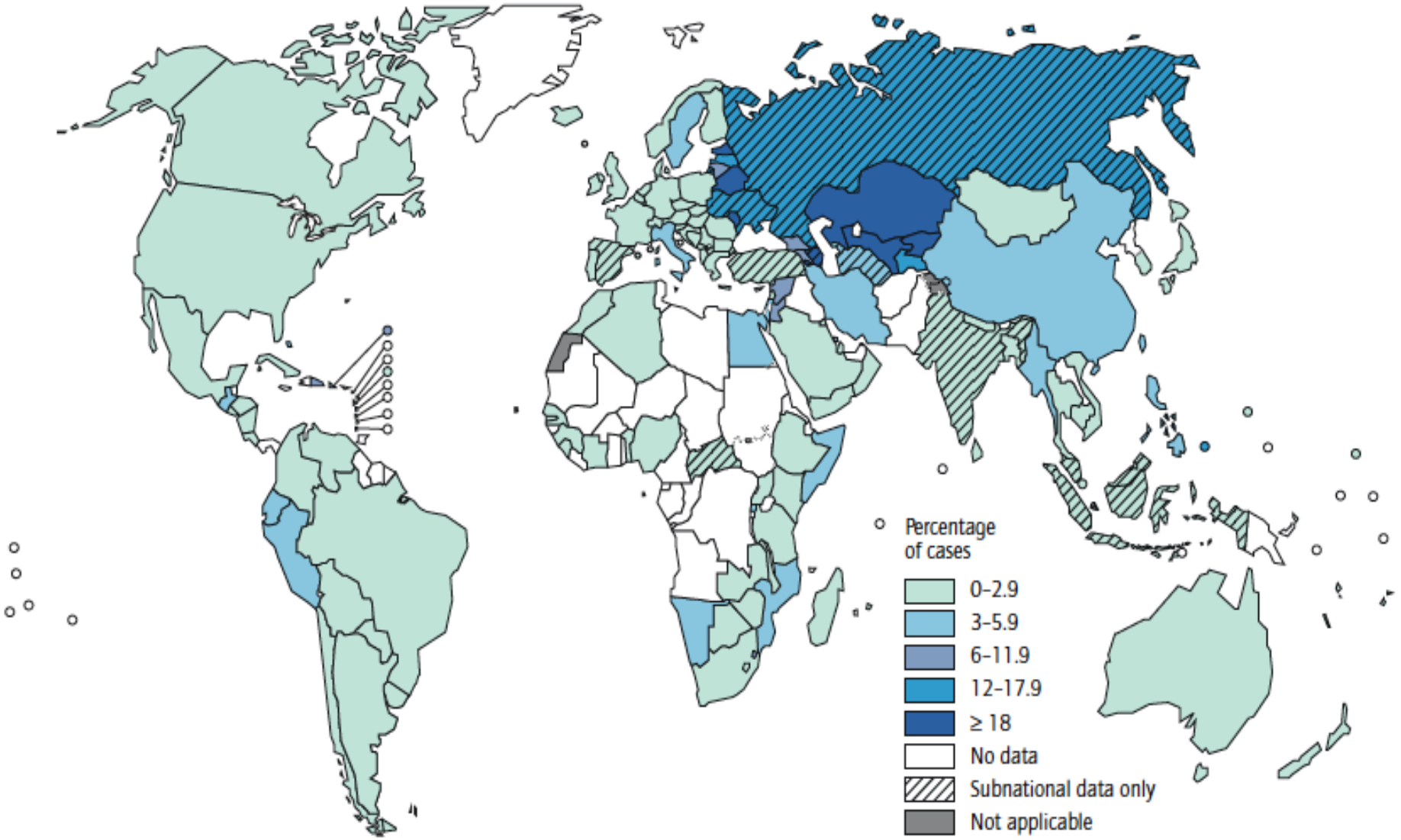
Technologies endorsed by WHO

Molecular technologies
- Xpert MTB/RIF[b]
- Line probe assays (acid-fast bacilli smear-positive sputum specimens or culture-positive specimens)

Microscopy
- Ziehl-Neelsen and fluorescence microscopy methods

Culture-based technologies
- Commercial liquid culture systems and rapid speciation
- Non-commercial culture and drug susceptibility testing methods

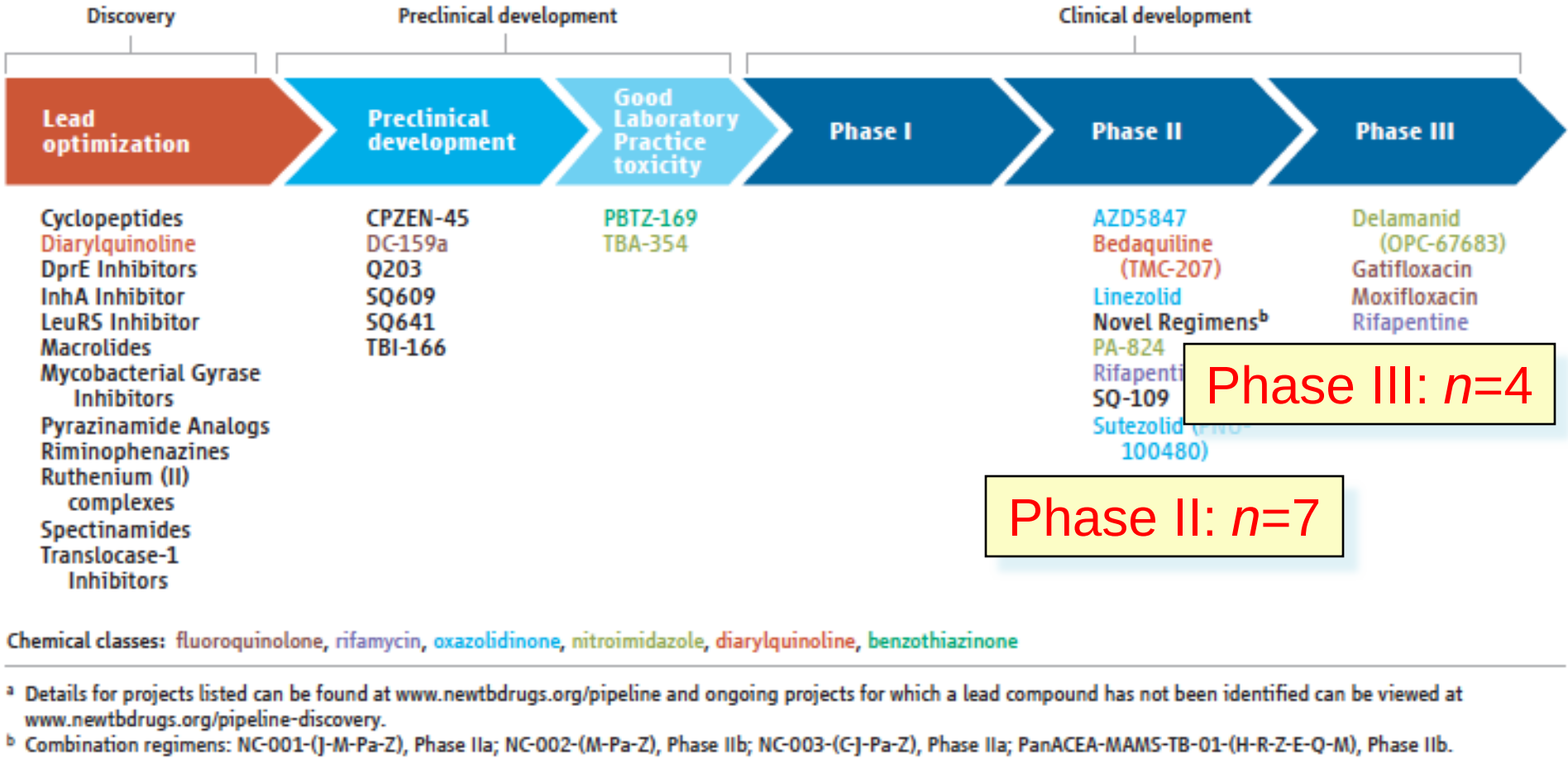
Percentage of new TB cases with MDR-TB



Global tuberculosis report 2012

World Health Organization

Development pipeline for new TB drugs



[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.

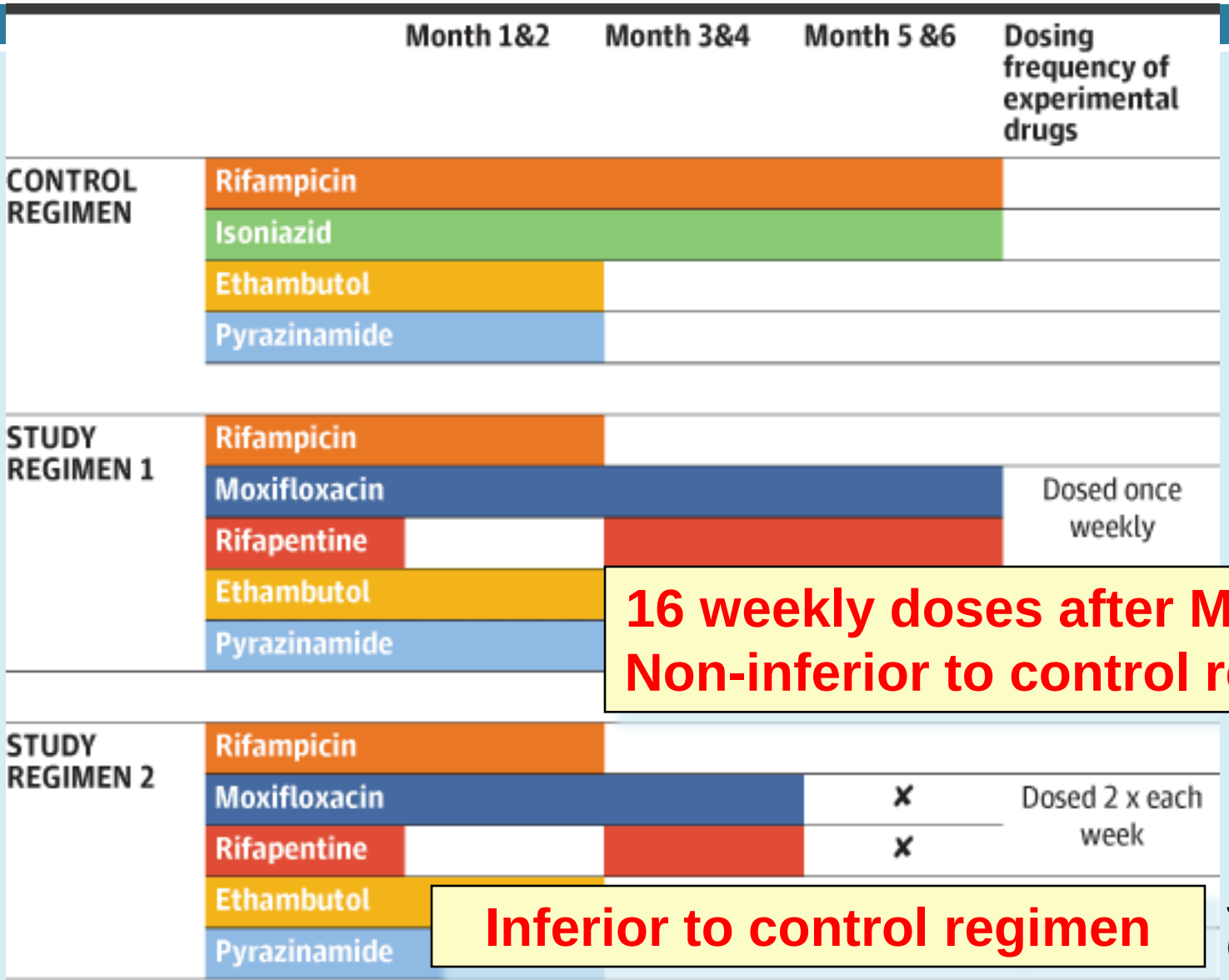
[b] Combination regimens: NC-001-(J-M-Pa-Z), Phase IIa; NC-002-(M-Pa-Z), Phase IIb; NC-003-(C-J-Pa-Z), Phase IIa; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), Phase IIb.

Phase III trial: RIFAQUIN results

- **Continuation phase: combination of rifapentine and moxifloxacin once a week**
- Primary endpoints: relapse during follow-up to 18 months after treatment initiation & occurrence of grade 3 or 4 adverse events
- *n*=730 with newly diagnosed smear-positive TB
- 28% HIV-positive (median CD4: 312 cells/mm^3)

Jindani A, CROI 2013

Phase III trial: RIFAQUIN results



Jindani A, CROI 2013

Other phase III trials

- **OFLOTUB:** gatifloxacin instead of ethambutol, 4 months

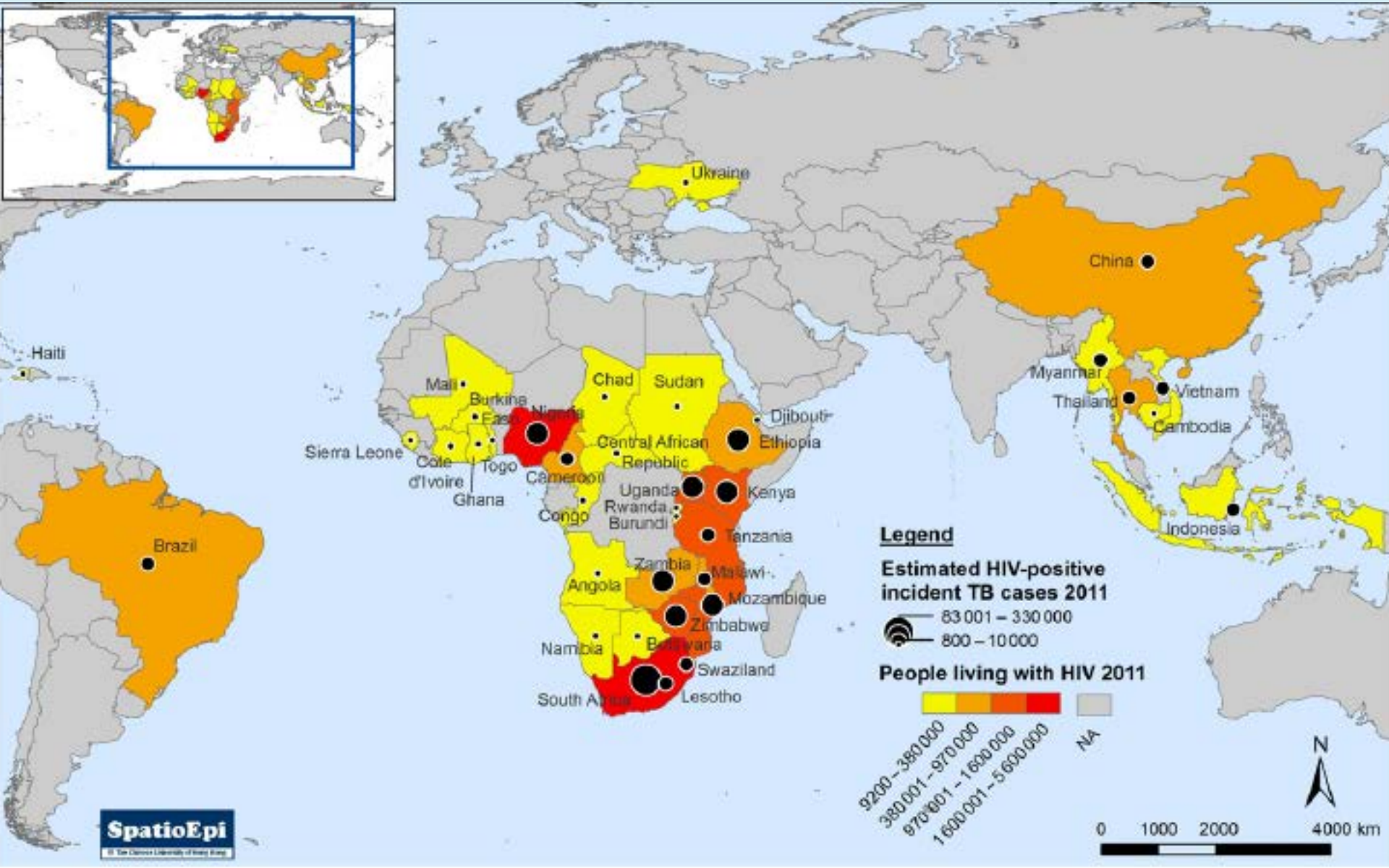
Efficacy and safety results will be presented by Merle C *et al.*, The Union/CDC late-breaker session, 3 Nov. 2013, 44th Union World Conference on Lung Health, Paris

- **ReMOX:** moxifloxacin instead of ethambutol or isoniazid, 4 months

(+ delamanid for MDR-TB)

Remaining challenges: TB & NTM

- **TB prevention:** IPT, TB vaccine
- **TB control:**
  - New molecular tools, incl. better detection of drug resist.
- **TB treatment:**
  - New regimen
  - Shortened duration
  - Less drug-drug interactions
  - MDR-TB, XDR-TB
- **NTM:** which regimen for which patient? Colonization *vs.* disease? Treatment outcomes? Need to reduce drug toxicity!



Respirology (2013) **18**, 912–922
doi: 10.1111/resp.12120

TB-HIV: some remaining challenges

- TB and HIV: 'cursed duet', 'deadly combination' → still a challenge in 2013
- **TB remains the most frequent life-threatening OI and a leading cause of death among PLWH**
- Diagnosis: how to use Xpert MTB/RIF? POC test???
- Urine LAM: interesting alternative → more data needed
- Treatment:
- IRIS: definition/Δg, treatment, predictive factors (score)
- IPT: 6 or 36 months? Or lifelong??? Intermittent?????