Pulmonary tuberculosis in Switzerland in 2018

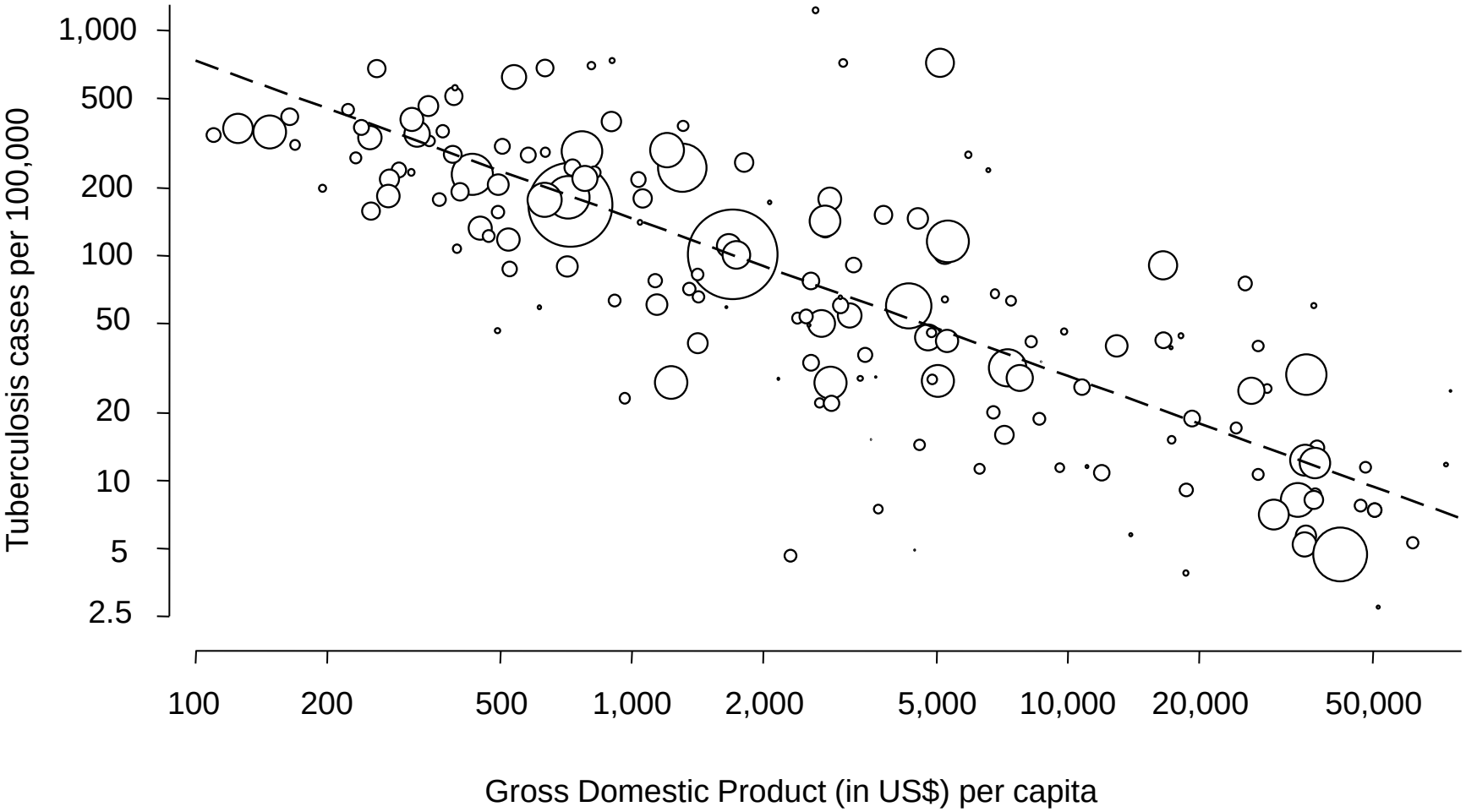
Prof. Jean-Paul Janssens,

Service de Pneumologie, HUG

Hôpitaux Universitaires Genève

Service de Pneumologie

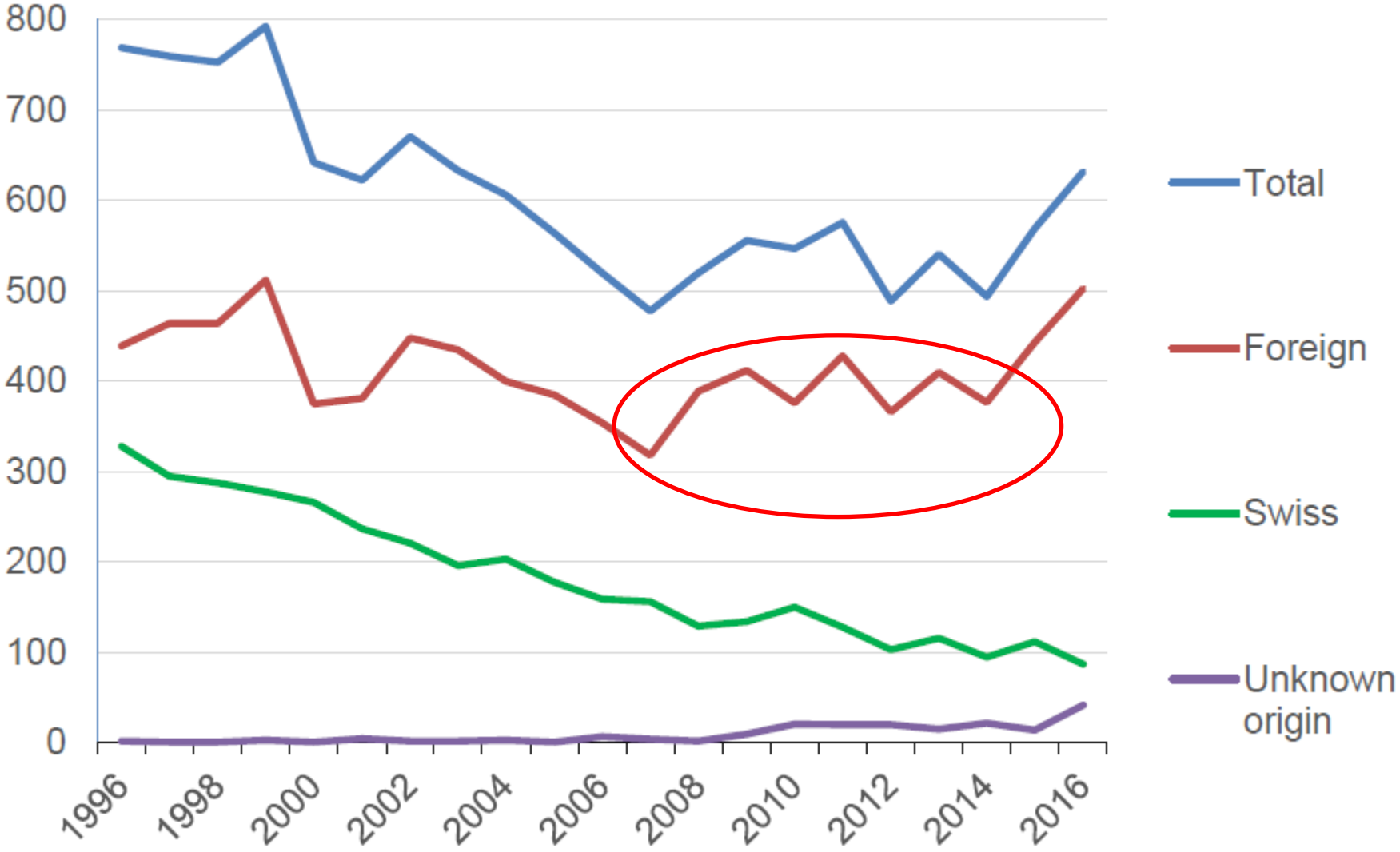
A rainy Sunday afternoon…..



JP Janssens, H Rieder, Eur Respir J 2008

Tuberculosis in Switzerland: epidemiology

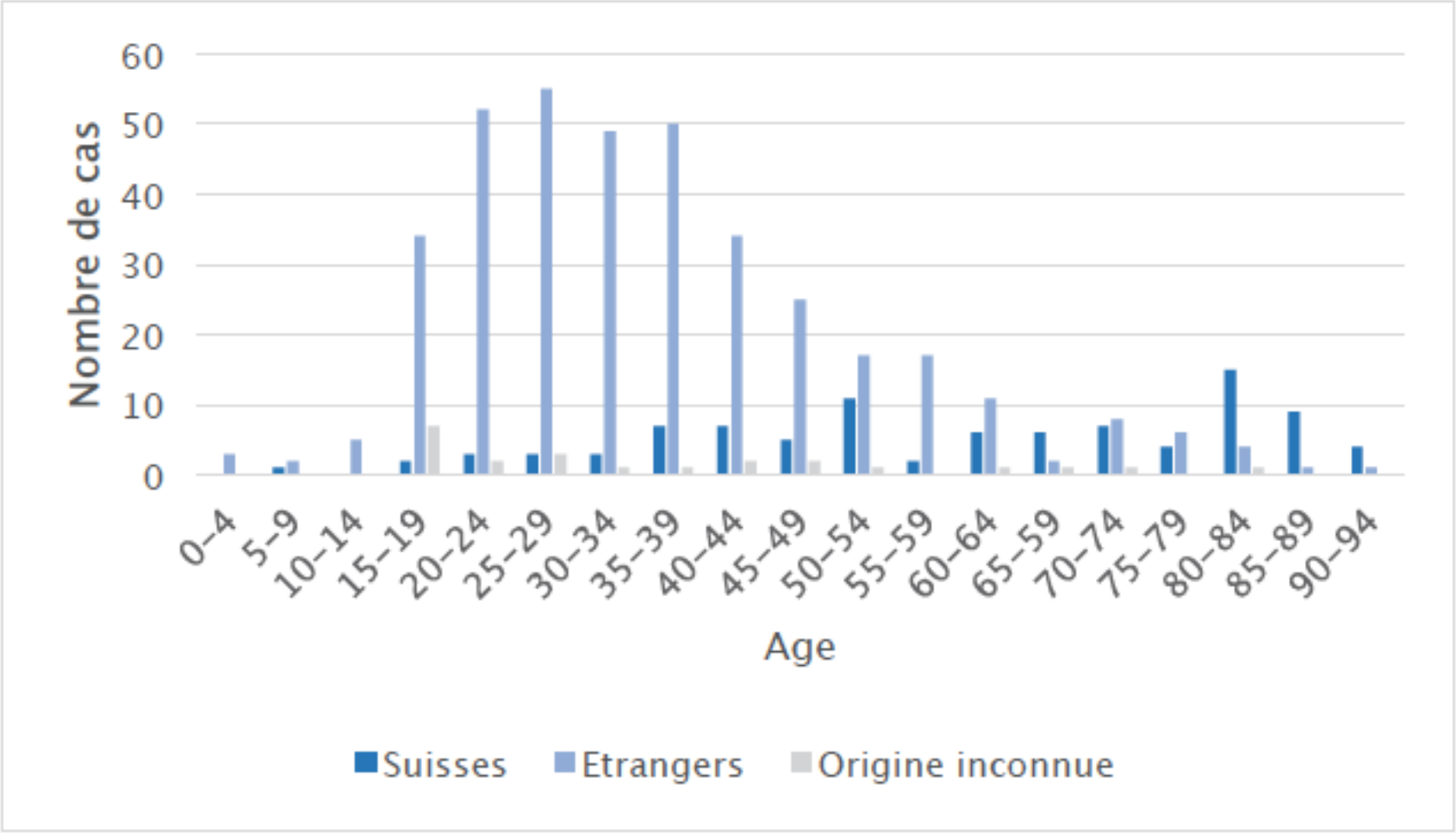
Figure 2-1. Tuberculosis cases notified to the Federal Office of Public Health, by origin, Switzerland, 1996-2016



Manuel de la Tuberculose, 2018

Figure 2 :

tuberculose en Suisse en 2014, répartition par tranche d'âge et selon l'origine



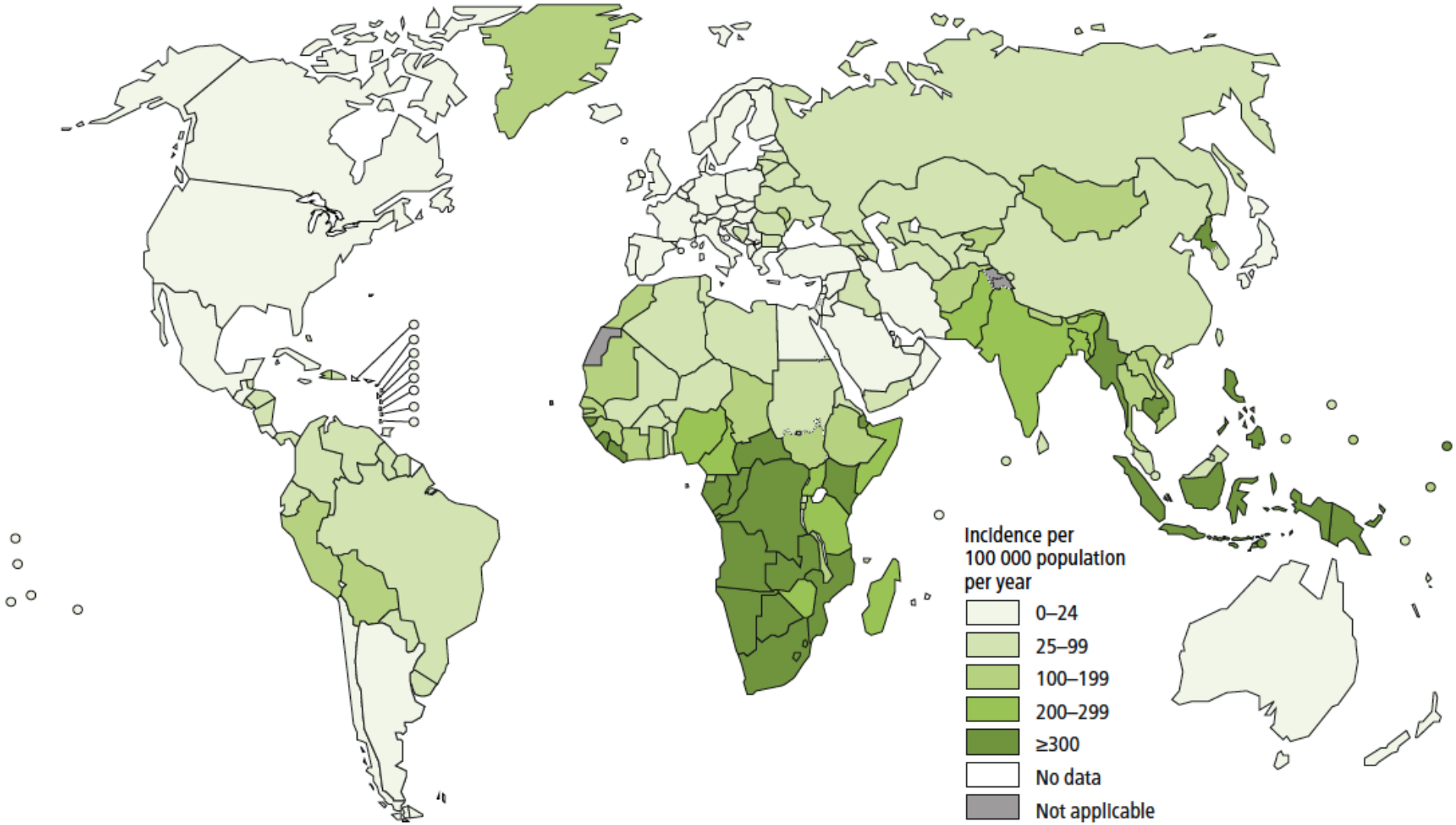
OFSP/BAG 2014

Take-home messages (1)

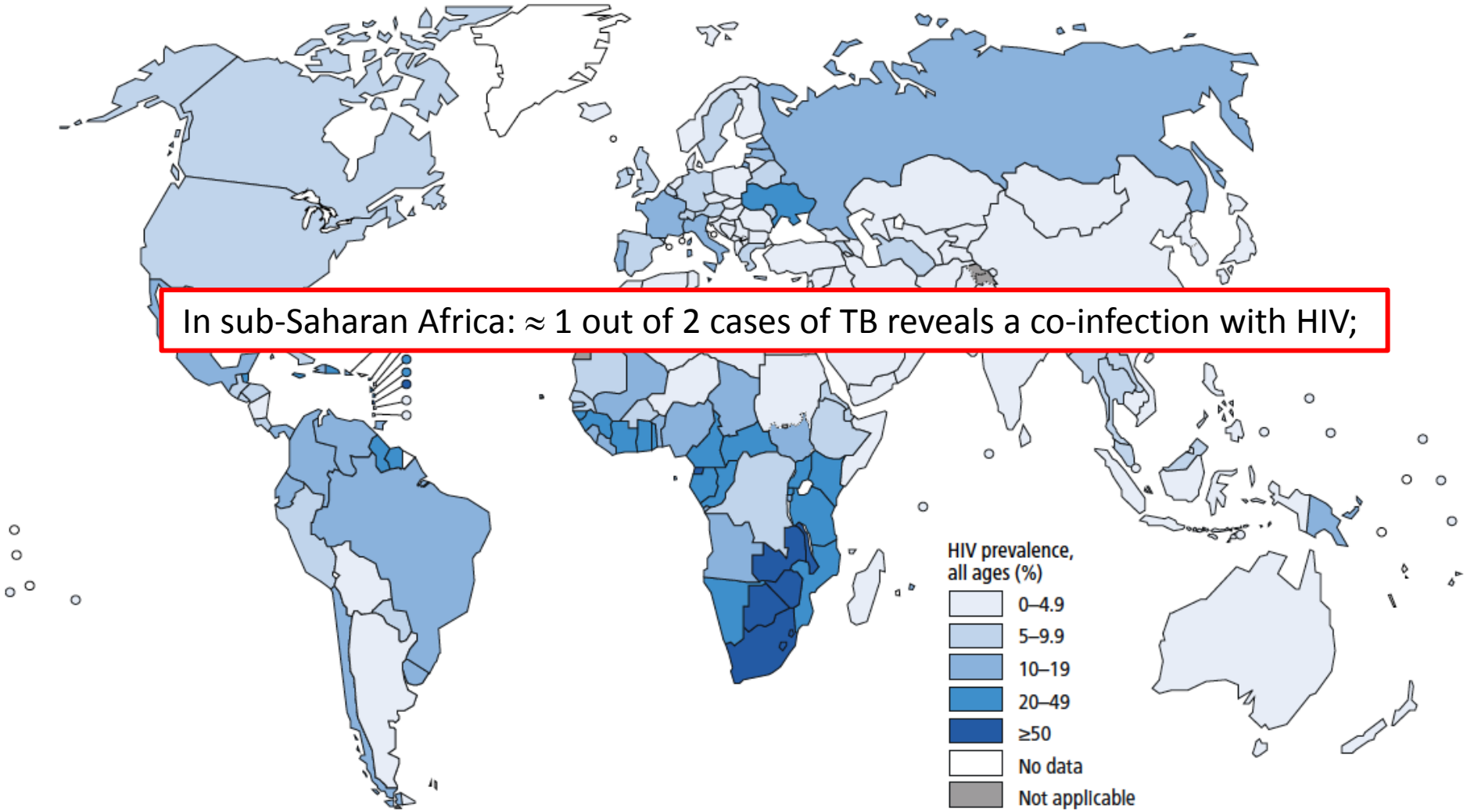
- After decades of a linear decrease, TB incidence is slightly increasing since 2014, although it continues to decrease in the indigenous population
- ≈ 80% of TB cases at a national level are foreign-born; ≈ 25% are related to the asylum procedure
- ≈ 9% have had a prior treatment for tuberculosis (BAG/OFSP 2013)

Estimating clinical probability of TB

Estimated TB incidence rates, 2016



Estimated HIV prevalence in new and relapse TB cases, 2016



In sub-Saharan Africa: ≈ 1 out of 2 cases of TB reveals a co-infection with HIV;

WHO Global report on TB 2017

Exposure

↓

Latent tuberculosis infection

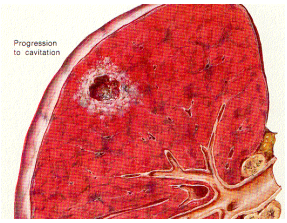
↓

Active tuberculosis

↓

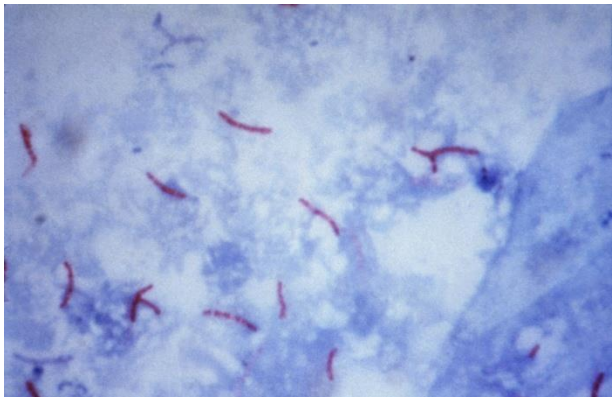
Sequellae of tuberculosis

5 à 10 % of cases
Highest incidence in the 2 years following exposure



Elements associated with the transmission of *M. tuberculosis*

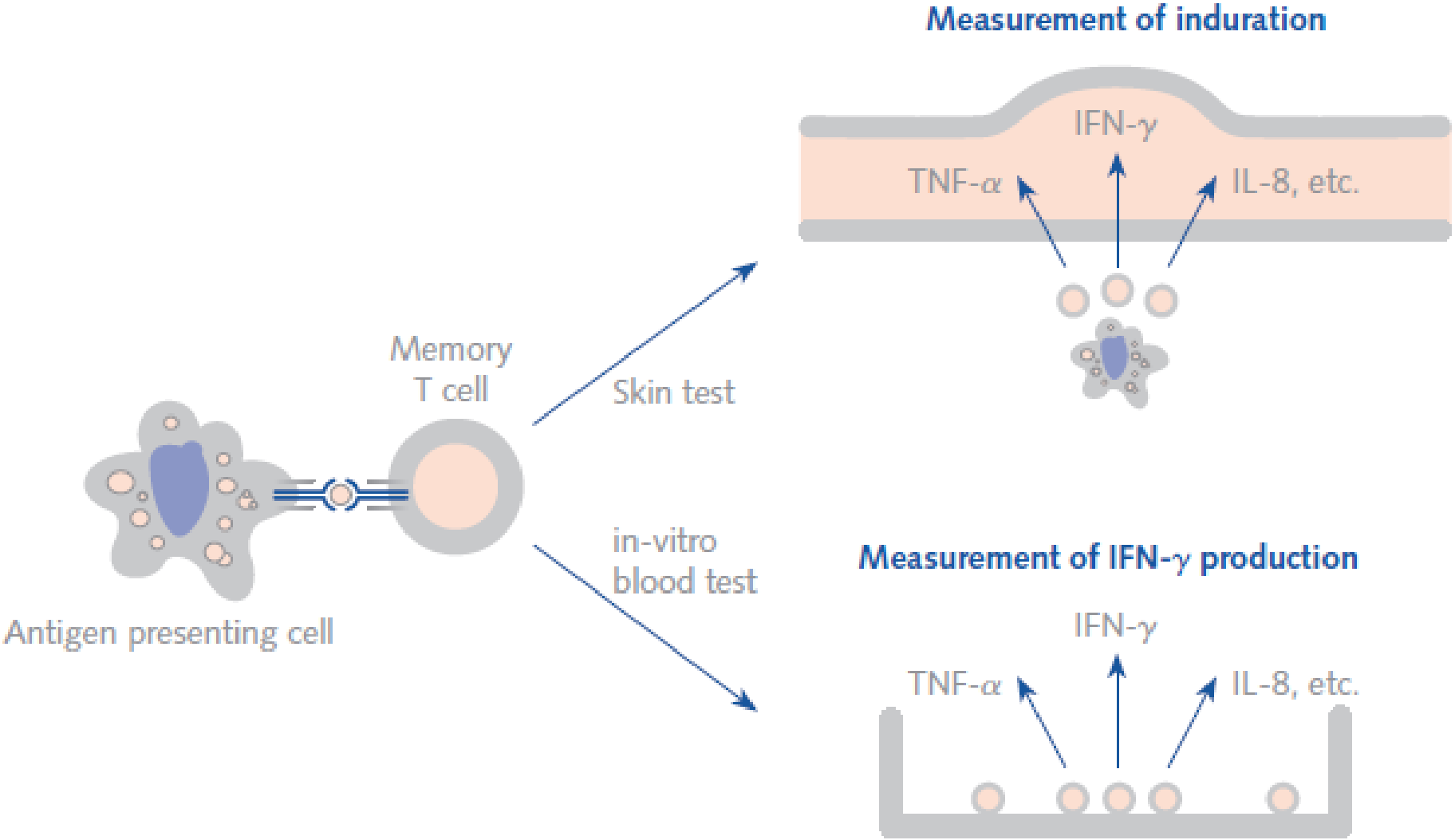
- Cough
- *Time spent with index case (> 8 hours if S+; > 40 hrs if S-)*
- Microscopy
- Environment in which contact(s) occur
- Treatment not yet started

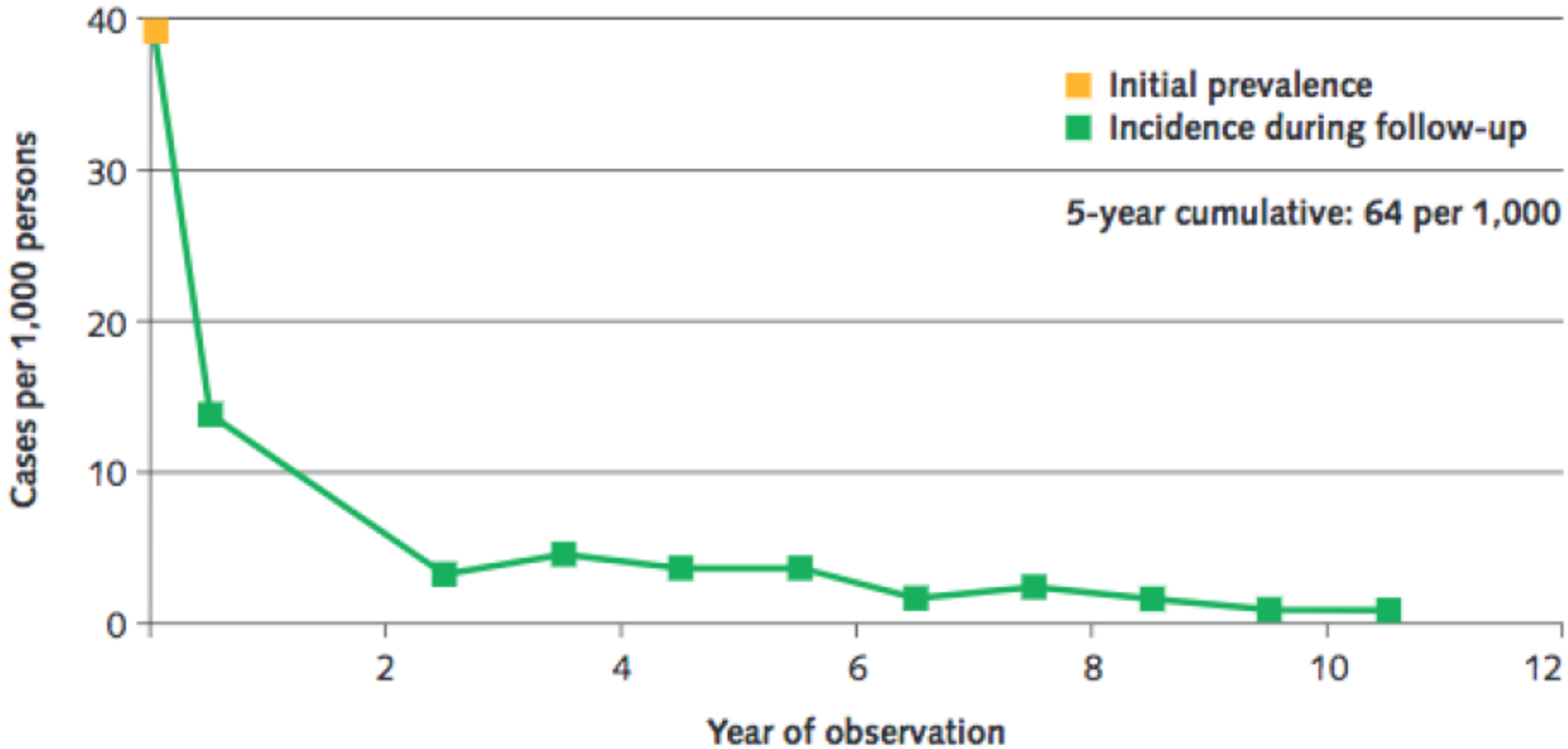


Latent tuberculosis infection

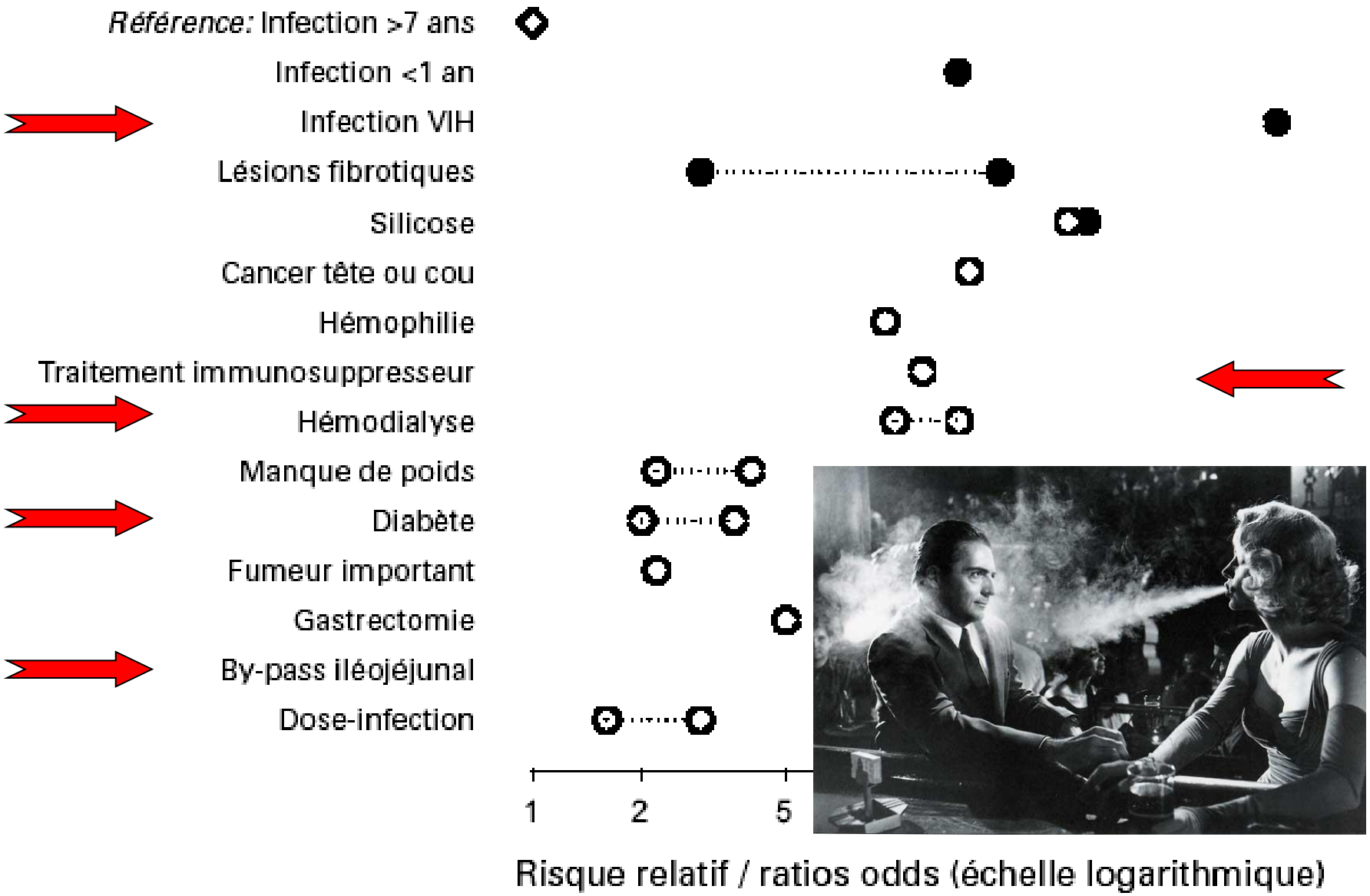
- Is not transmissible
- Is most often asymptomatic
- Is most often not visible on X-rays
- Can be detected by IGRAs (Interferon-gamma release assays) or TST
- *May evolve towards an active TB in 5-10% of cases*
- Risk much higher in small children, HIV infected individuals, or other causes of immunosuppression

Interferon gamma release assays: IGRAs
QuantiFERON-Gold-In-tube; Oxford Immunotec





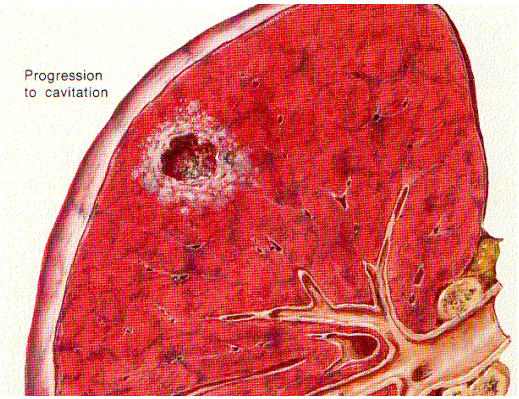
Ferebee S H, Mount F W. Am Rev Respir Dis 1962;85:490-521
Ferebee S H. Adv Tuberc Res 1970;17:28-106


Référence: Infection >7 ans
Infection <1 an
Infection VIH
Lésions fibrotiques
Silicose
Cancer tête ou cou
Hémophilie
Traitement immunosuppresseur
Hémodialyse
Manque de poids
Diabète
Fumeur important
Gastrectomie
By-pass iléojéjunal
Dose-infection
1
2
5
Risque relatif / ratios odds (échelle logarithmique)

Take-home messages (2)

- Risk of active TB after acquiring latent tuberculosis is not linear: it is maximal during the 2 years following infection
- Tobacco is an important risk factor for transmission and reactivation
- Smoking also delays sputum conversion

Active tuberculosis

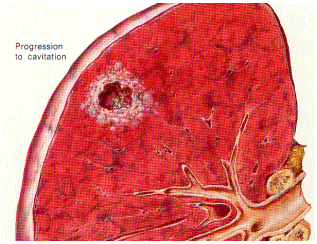


- Active TB is pulmonary in ≈ 70 %* of cases and extra-pulmonary in ≈ 30% of cases
- Extra-thoracic involvement is more frequent in HIV infected subjects, and in non-Caucasian populations
- 31% of pulmonary TB cases have a positive microscopy (S+); 84% are confirmed by culture (BAG/OFSP 2013)

*: indicative

Tableau 3
Organes atteints des cas de tuberculose entre 2005 et 2009

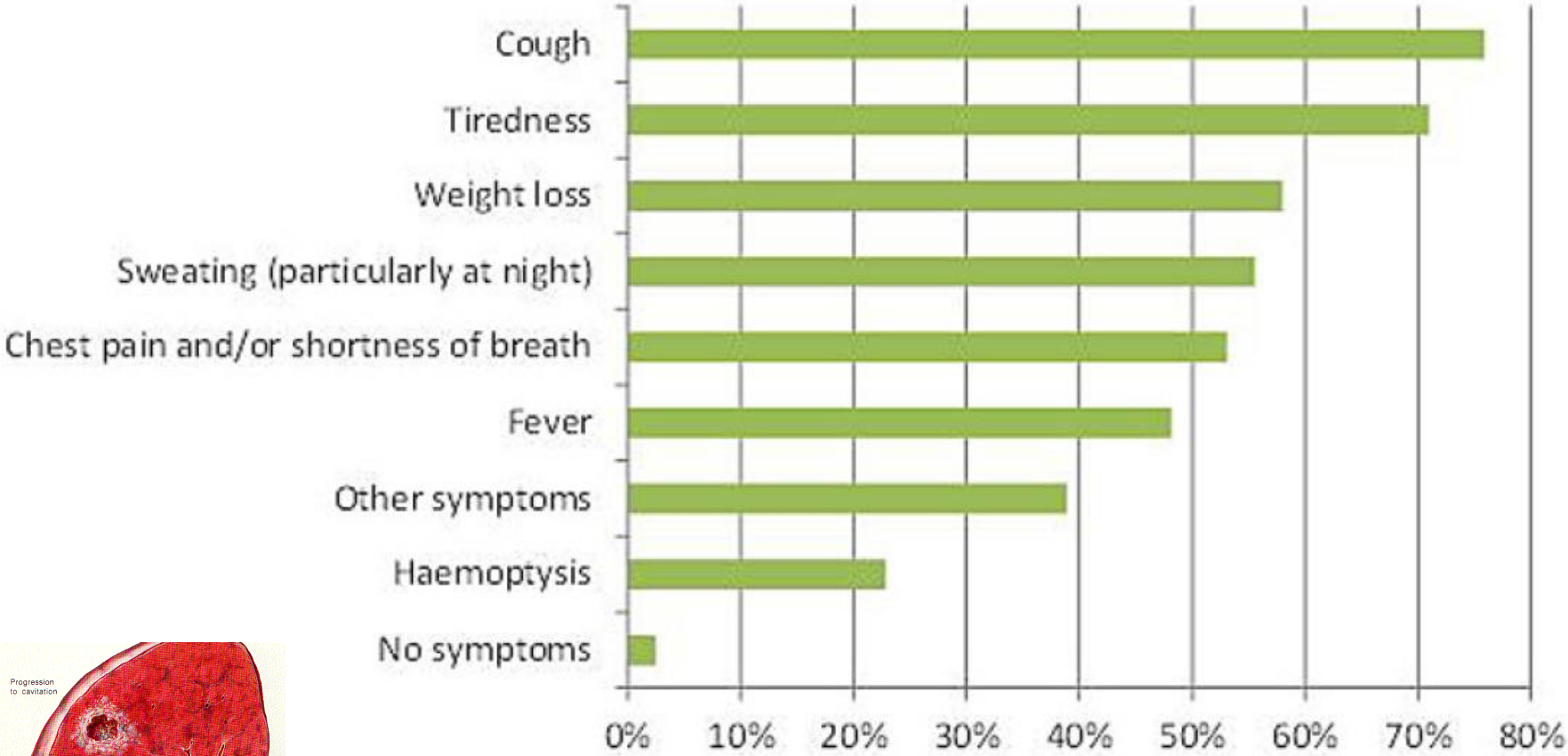
	n	%
Nombre total de cas	2637	
Poumons	1888	72%
Nb. d'expectorations positives à la microscopie déclarées	552	
Culture positive (tout échantillon clinique)	1579	
Ganglions extrathoraciques	380	14%
Plèvre	183	7%
Ganglions intrathoraciques	201	8%
Tractus urogénital	83	3%
Tuberculose disséminée (miliaire ou touchant plus de deux organes)	126	5%
Péritoine	87	3%
Colonne vertébrale	51	2%
Os (hors colonne vertébrale)	37	1%
Système nerveux central	42	2%
Autres organes	77	3%

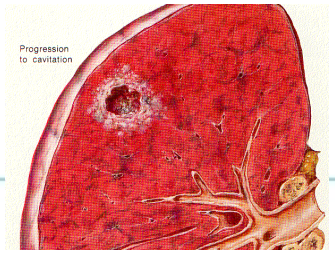


OFSP/BAG

Active pulmonary tuberculosis: presentation

Figure 2: Frequency of symptoms among the 162 tuberculosis patients.

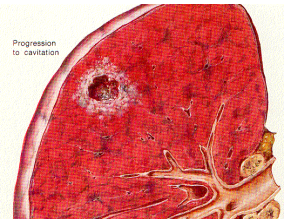




C Auer et al, SMW 2018

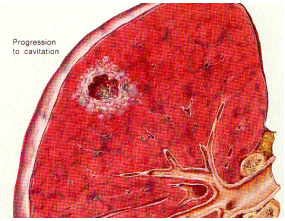
Active pulmonary tuberculosis: Radiology

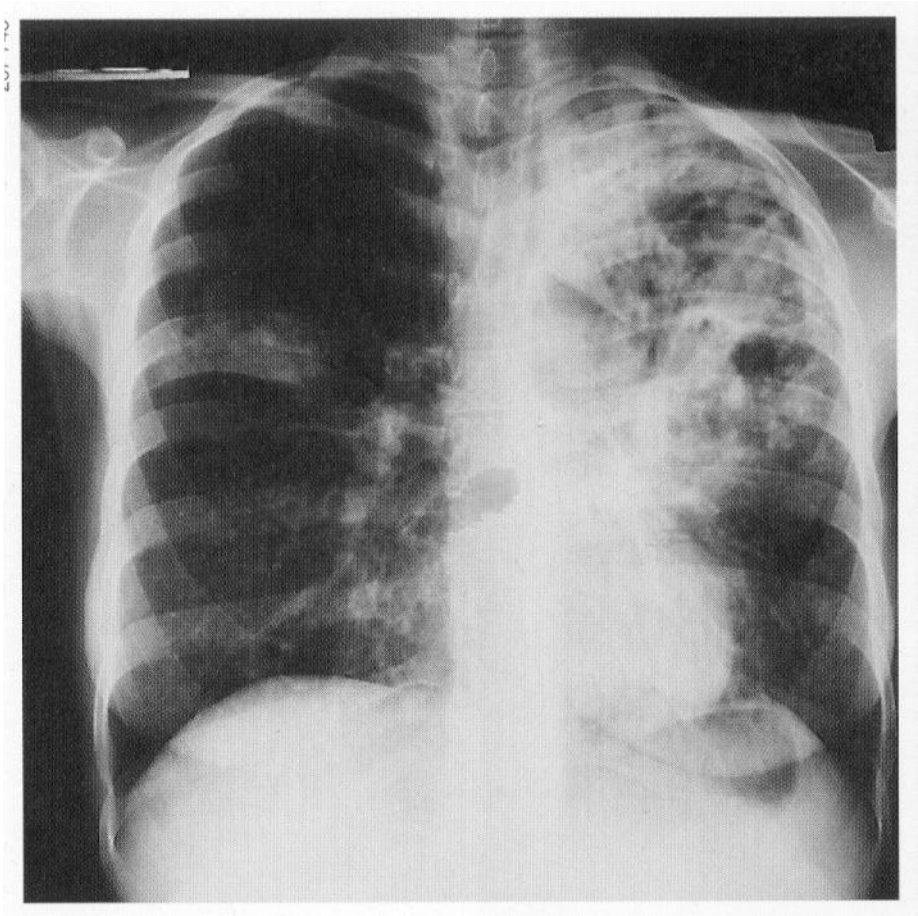
- Suggestive images more frequent in upper lobes
- Cavitation suggestive, but infrequent, and frequently absent in elderly or HIV co-infected individuals
- Older patients tend to have more frequent involvement of middle and lower lobes and less cavitation
- « Tree-in-bud » appearance is *compatible* with mycobacterial infection but is basically a sign of bronchiolitis (not specific)
- **CT is helpful** for a more precise evaluation of extension and follow-up under treatment; CT also shows mediastinal/hilar involvement

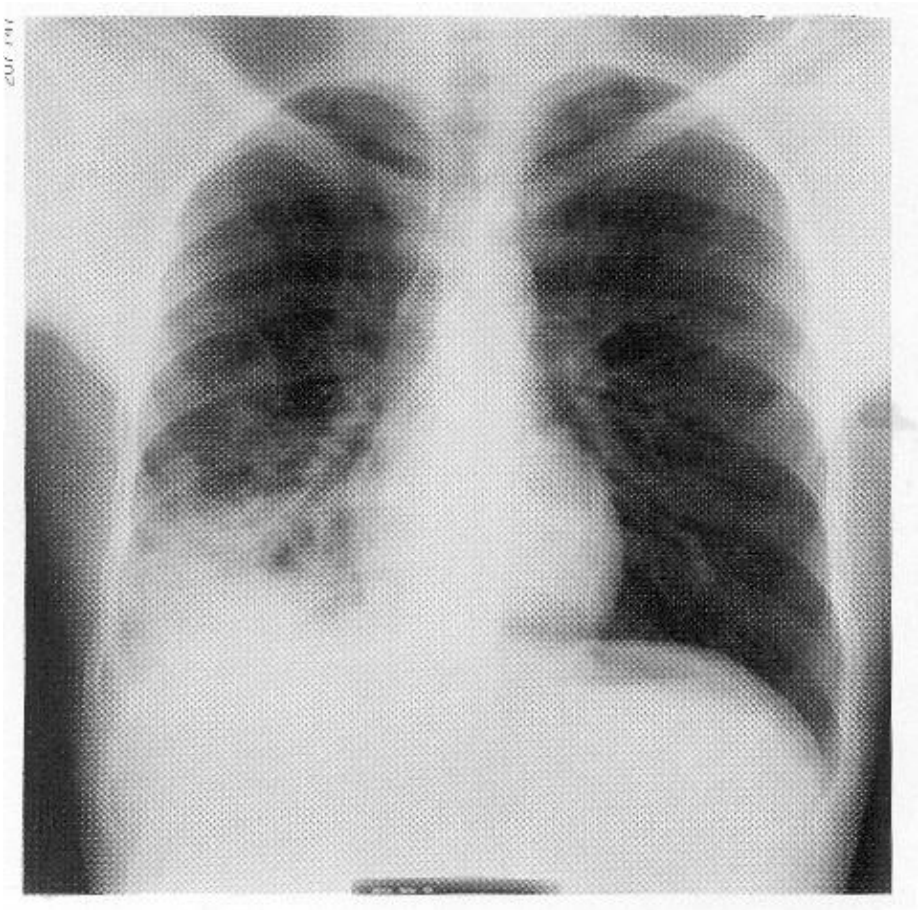


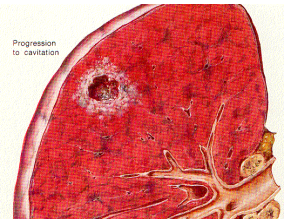
Active pulmonary tuberculosis: are IGRAs useful?

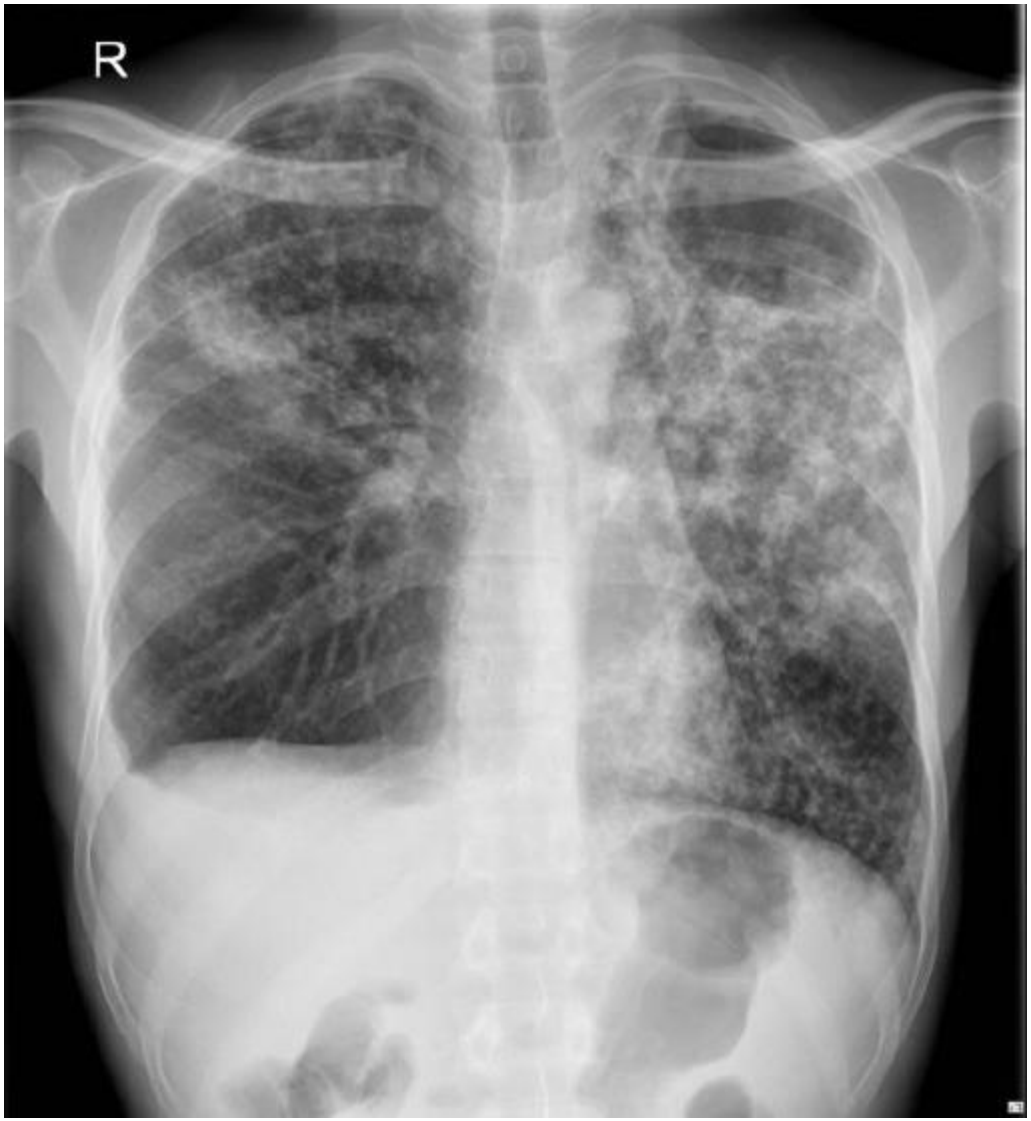
- QuantiFERON-Gold-in-tube and T-SPOT.TB are ***useless*** for the diagnosis of active TB
- Their sensitivity is too low to exclude TB; their specificity is low because they do not allow to distinguish between active and latent TB
- In elderly patients or in subjects who come from countries with a high prevalence of TB, in whom probability of exposure to MTB is high, IGRAs have no diagnostic value

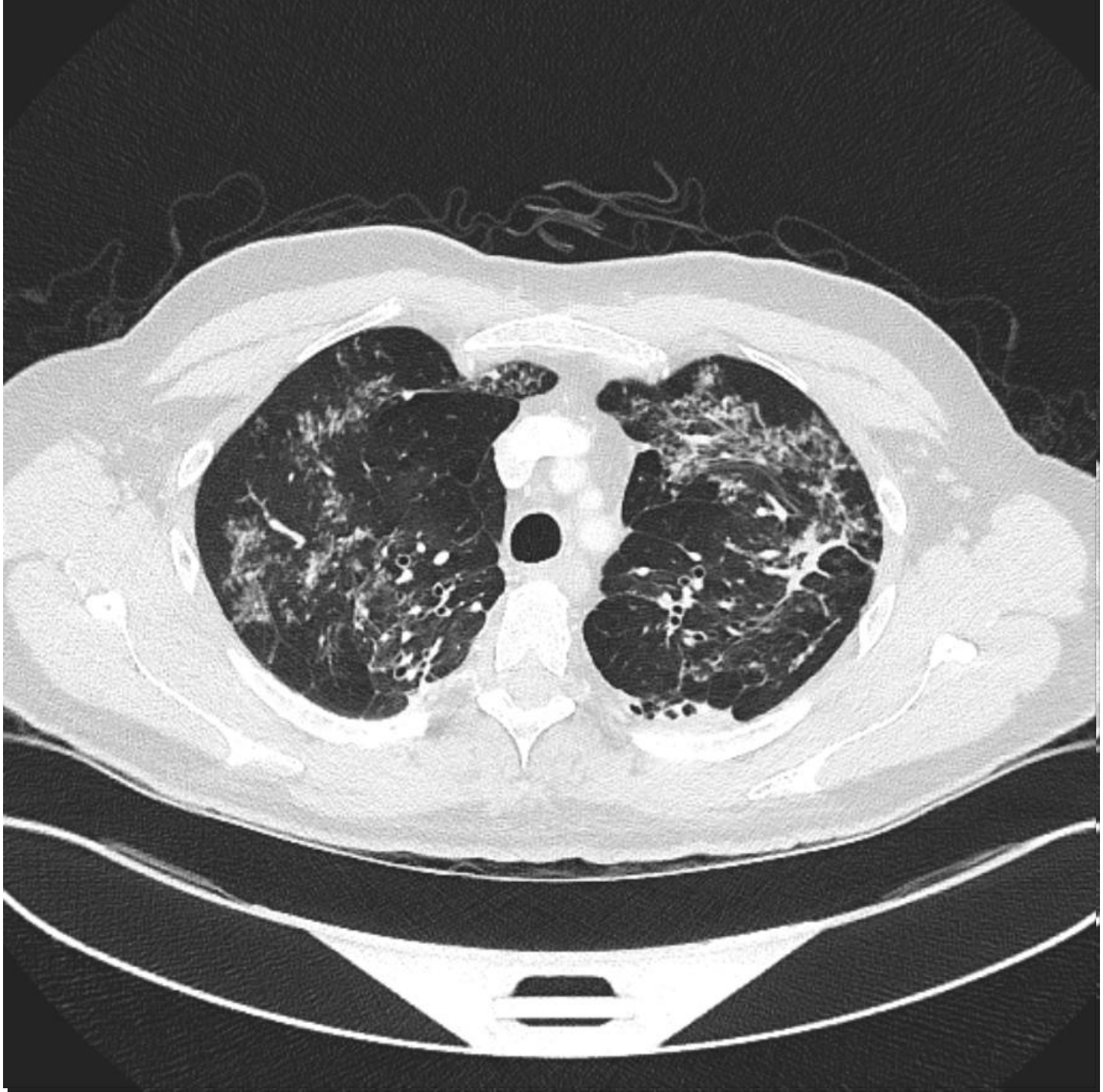







Progression
to cavitation


R



Sputum analysis

- Patients suspect of pulmonary TB and admitted to a hospital/emergency room *should be isolated* (Airborne infection isolation procedures)
- Sputum analysis can be spontaneous or induced
- Whenever possible, Xpert MTB/RIF tests or UltraXpert tests should be used
- Two negative sputum samples for PCR reasonnably exclude a contagious form of pulmonary TB
- Sputum analyses can be collected on the same day, a few hours apart

Diagnostic tools in 2018

Figure 2. Appareils GeneXpert avec 1, 2, 4 et 16 modules

Xpert MTB/RIF test

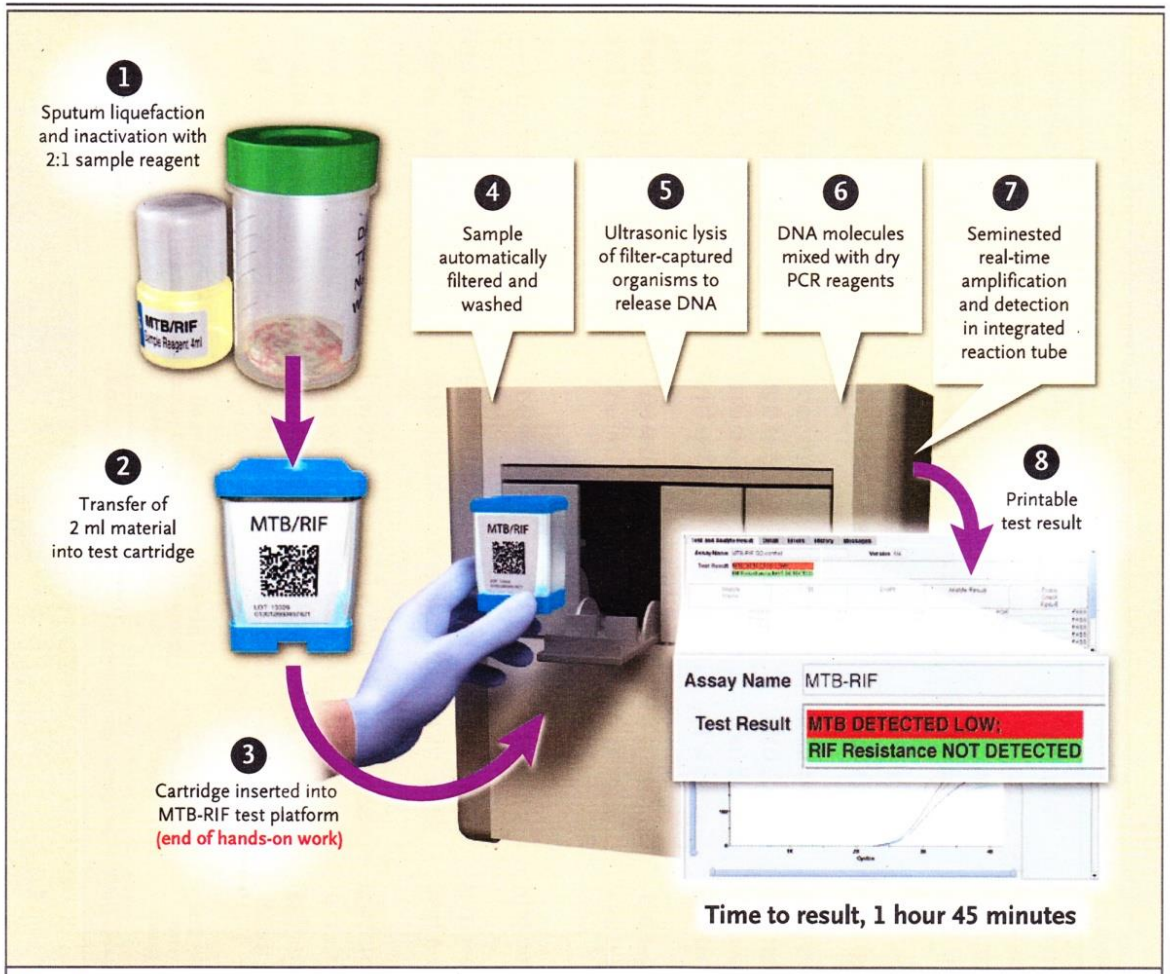


Figure 2. Assay Procedure for the MTB/RIF Test.
Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected; RIF resistance not detected." PCR denotes polymerase chain reaction.

C. Boehme et al. Sept. 2010. New Engl J Med

Table 3. **Sensitivity and specificity of different diagnostic tests from systematic reviews, using culture-confirmed pulmonary tuberculosis (TB) as the gold standard**

Diagnostic test	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)
Liquid culture (gold standard)	100	100
Conventional sputum-smear microscopy[50,51]	61 (31–89)	98 (93–100)
Xpert MTB/RIF[49]		
Clinical diagnosis[52 a]	24 (10–51)	94 (79–97)

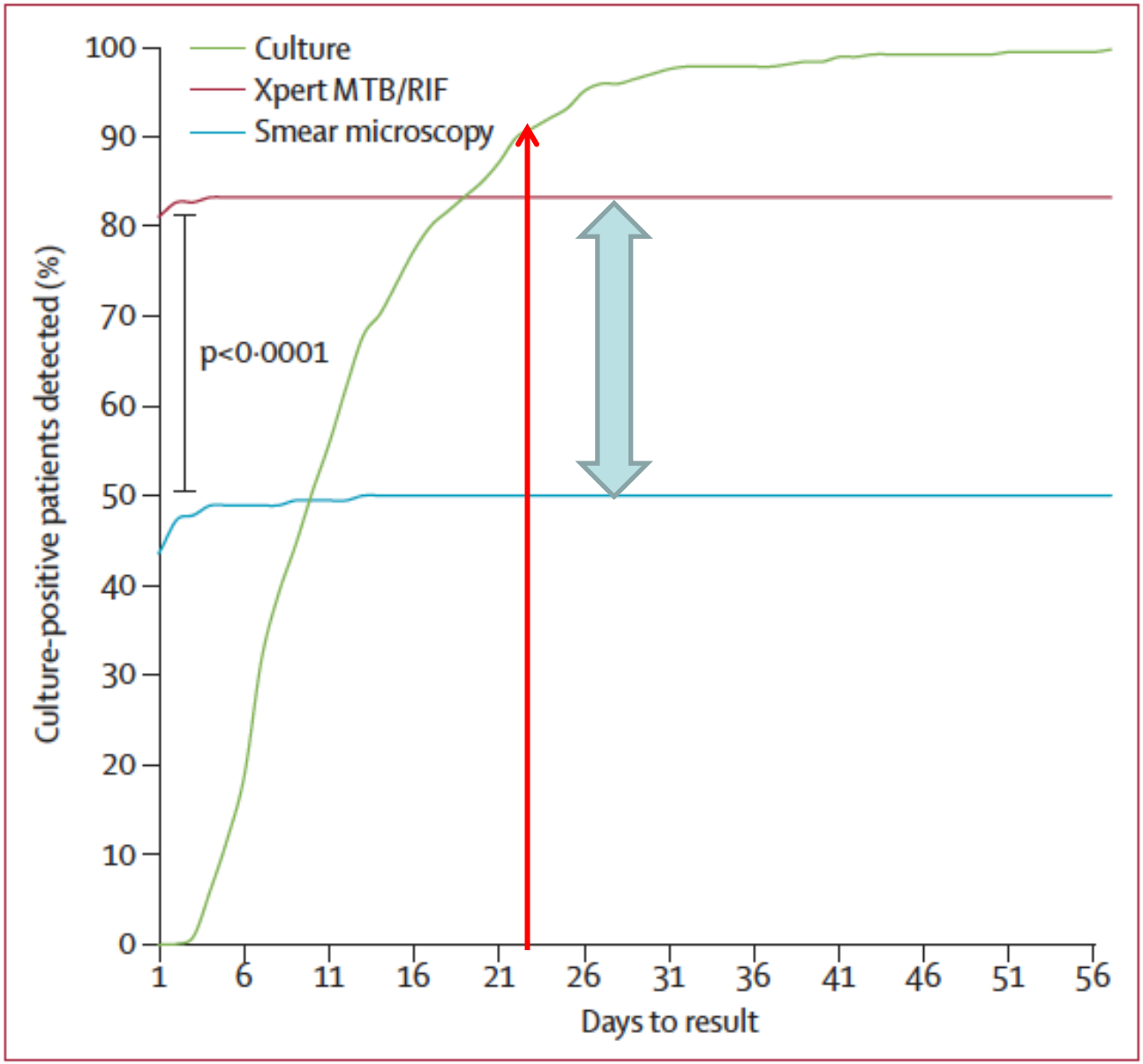


Figure 2: **Time to diagnosis by smear microscopy, Xpert MTB/RIF, or liquid culture in culture-positive patients**

*One patient's culture obtained at recruitment was positive after 59 days.

The New Xpert MTB/RIF Ultra: Improving Detection of *Mycobacterium tuberculosis* and Resistance to Rifampin in an Assay Suitable for Point-of-Care Testing

Soumitesh Chakravorty,[a] Ann Marie Simmons,[b] Mazhgan Rowneki,[a] Heta Parmar,[a] Yuan Cao,[a] Jamie Ryan,[b] Padmapriya P. Banada,[a] Srinidhi Deshpande,[a] Shubhada Shenai,[a] Alexander Gall,[c] Jennifer Glass,[b] Barry Krieswirth,[d] Samuel G. Schumacher,[e] Pamela Nabeta,[e] Nestani Tukvadze,[f] Camilla Rodrigues,[g] Alena Skrahina,[h] Elisa Tagliani,[i] Daniela M. Cirillo,[i] Amy Davidow,[j] Claudia M. Denkinger,[e] David Persing,[b] Robert Kwiatkowski,[b] Martin Jones,[b] David Alland[a]

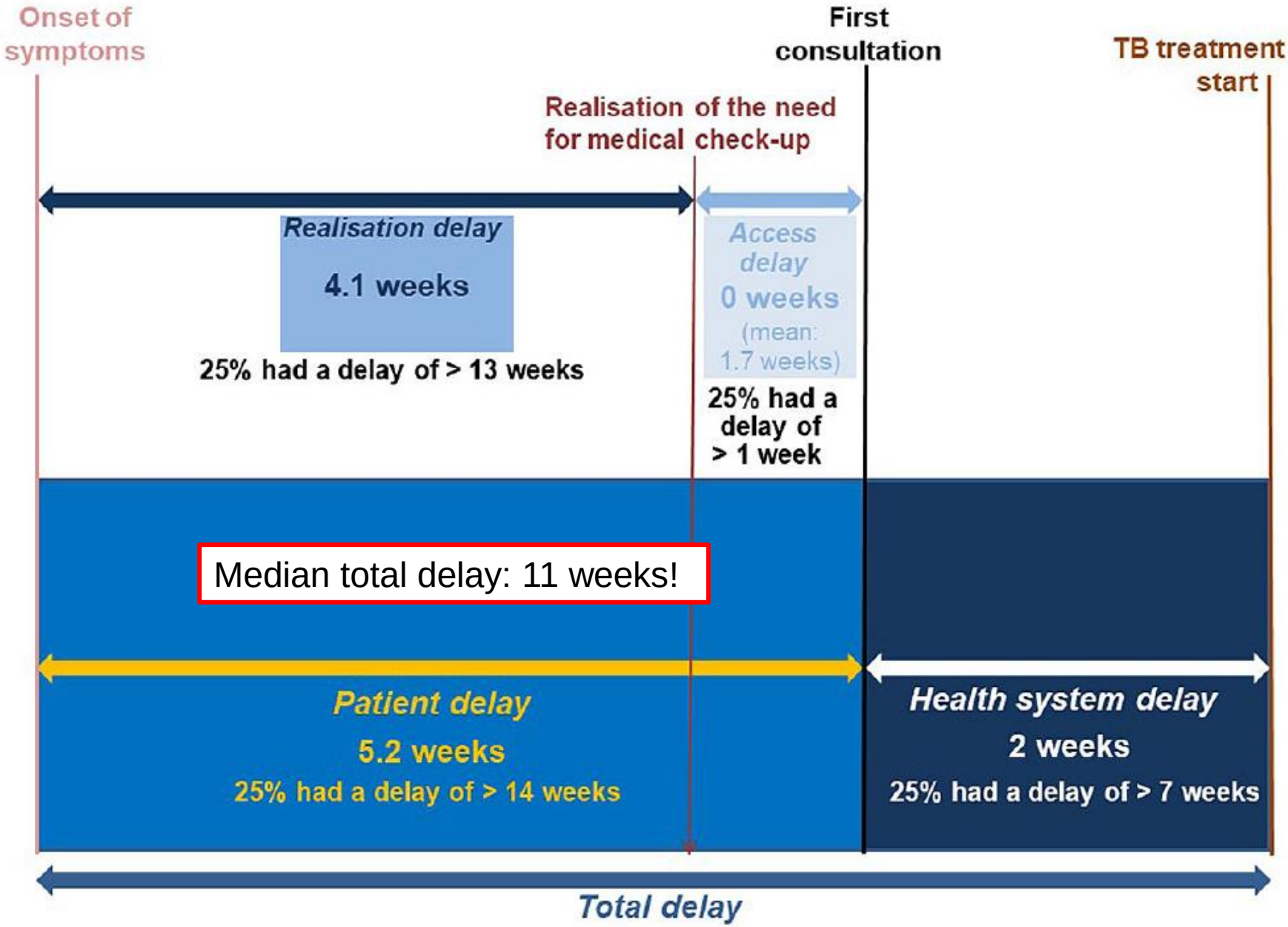
AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

TABLE 2 Comparative performance of Ultra and Xpert assay on clinical sputum samples

	Tuberculosis detection			Rifampin resistance detection	
	% sensitivity (95% CI)				
Assay	All culture-positive specimens (n = 200)	Smear-negative specimens (n = 109)	% specificity (95% CI) (n = 77)	% sensitivity (95% CI) (n = 41)	% specificity (95% CI) (n = 98)
Xpert	81.0 (74.9, 86.2)	66.1 (56.4, 74.9)	98.7 (93.0, 100)	92.7 (80.1, 98.5)	99.0 (94.4, 100)
Ultra	87.5 (82.1, 91.7)	78.9 (70.0, 86.1)	98.7 (93.0, 100)	92.7 (80.1, 98.5)	98.0[a] (92.8, 99.9)

[a]One sample was detected as RIF resistant by Ultra but was detected as RIF susceptible by both phenotypic susceptibility testing and Xpert. Upon Sanger sequencing, this sample was found to be hetero-resistant with a mixture of the wild type and an *rpoB* S531L mutant. Reclassifying this sample as RIF resistant would change the sensitivity and specificity for RIF-R detection for Ultra to 92.9% (95% CI, 80.5, 98.5) and 99.0% (95% CI, 94.4, 100), respectively, and would change the sensitivity and specificity for RIF-R for Xpert to 90.5% (95% CI, 77.4, 97.3) and 99.0% (95% CI, 94.4, 100), respectively. Note that Ultra provided RIF resistance results for 20 samples that tested *M. tuberculosis* negative by Xpert and are excluded from the analysis of RIF resistance to provide accuracy estimates on the same sample set. Xpert was performed on a fresh sputum aliquot, and Ultra was tested retrospectively on a frozen aliquot of the same sputum sample.

Figure 3: Overview of the various delays (median) and their extent.



Take-home messages (3)

- Estimating clinical probability is very important in diagnosing TB
- IGRAs are <u>not</u> diagnostic tests for active pulmonary TB
- Sensitivity of PCR based technologies has the potential to reduce substantially time to diagnosis
- Sputum analysis by X-pert techniques (or when indicated by bronchoscopy) is now the standard approach in our country

Treating pulmonary tuberculosis

- Four drugs for initial treatment of non-MDR TB
- Isoniazide (H), rifampicine (R), ethambutol (E), and pyrazinamide (Z)
- 2HRZE; 4HR; if cavitary TB and S+/C+ after 2 months, continuation phase may be prolonged to a total of 9 months
- Vit B6 40 mg/day
- Liver tests (ASAT, ALAT) initially then monthly « by default » (3-5 x increase tolerated)

MDR/XDR-TB in Switzerland

550 cases of TB/year

↓

Since 2011, 3% are MDR /year (≈ 15 cases/year)

↓

Max: 1-2 cas of XDR/year

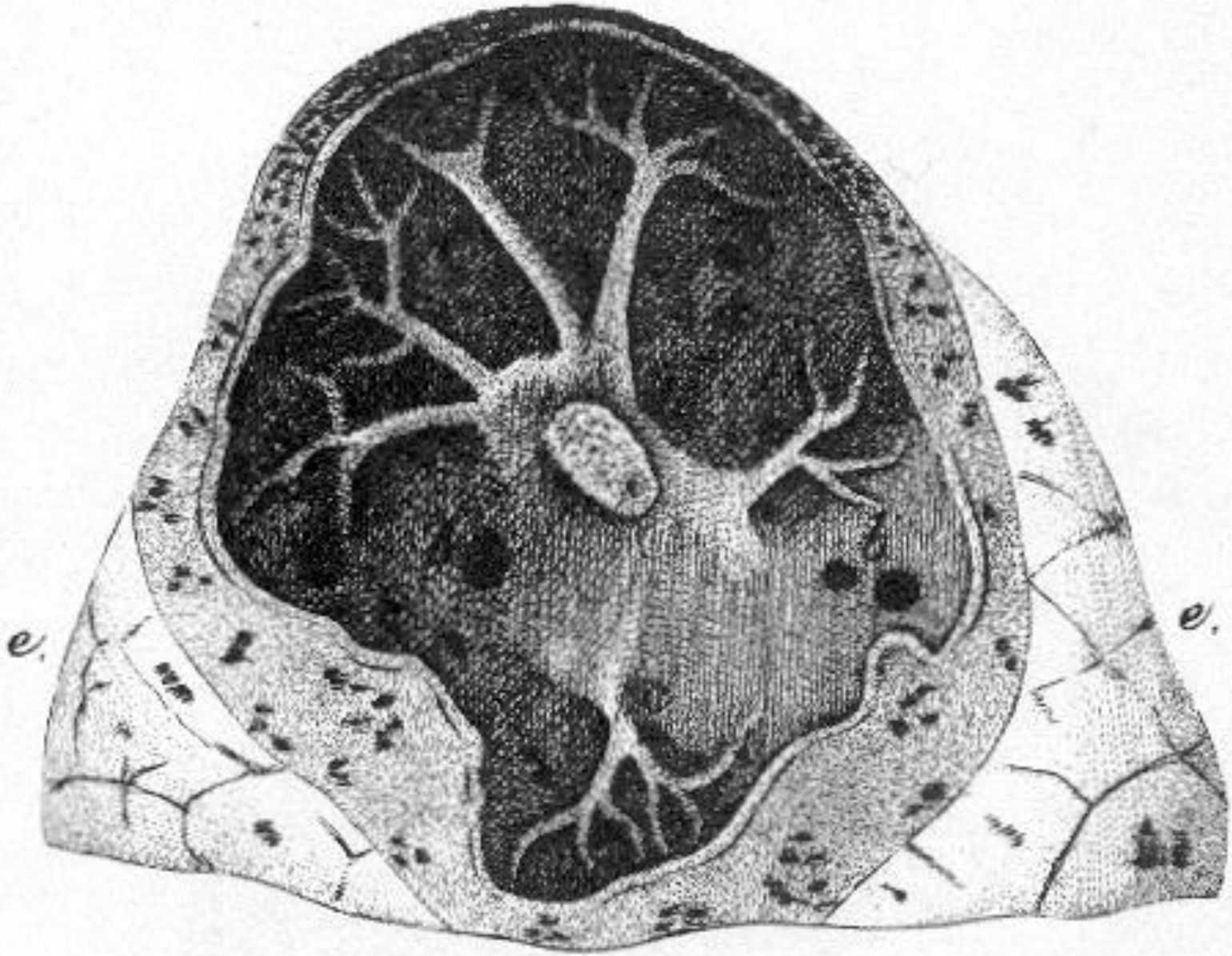
Risk factors for MDR/XDR TB

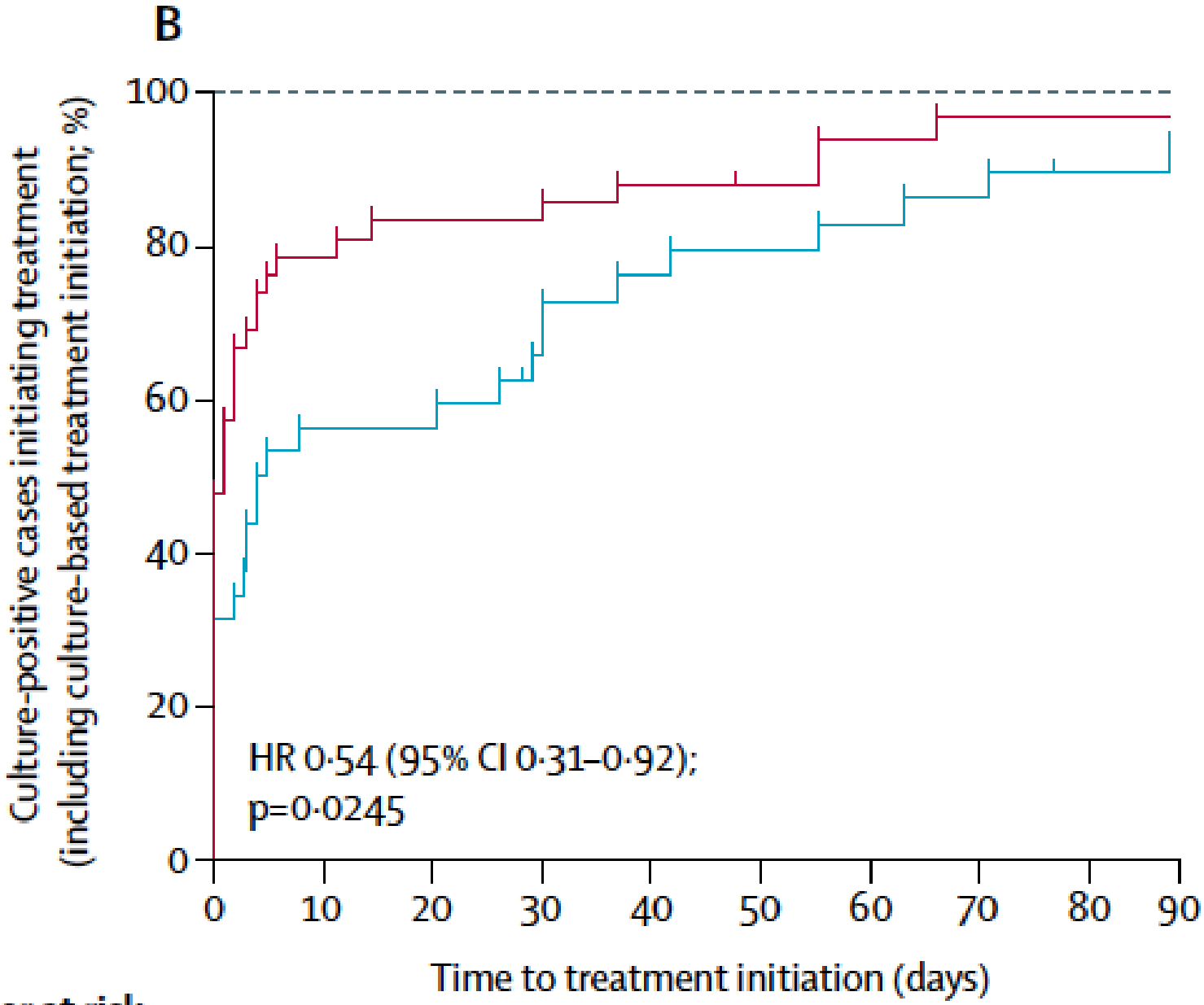
- *Prior treatment for TB with uncertain compliance to treatment*
- *Origin: coming from a high incidence country for MDR*
- Detainment in prisons of the ex Soviet Union
- Being homeless; HIV…

Treating pulmonary tuberculosis

- For all cases of pulmonary TB, *contact tracing procedures* must be discussed with a specialized center
- All cases of TB must be declared (form on the site of Swiss Pulmonary League: https://www.lungenliga.ch/de/startseite.html)
- Small children and immunosuppressed individuals must be rapidly referred to experienced physicians/pediatricians

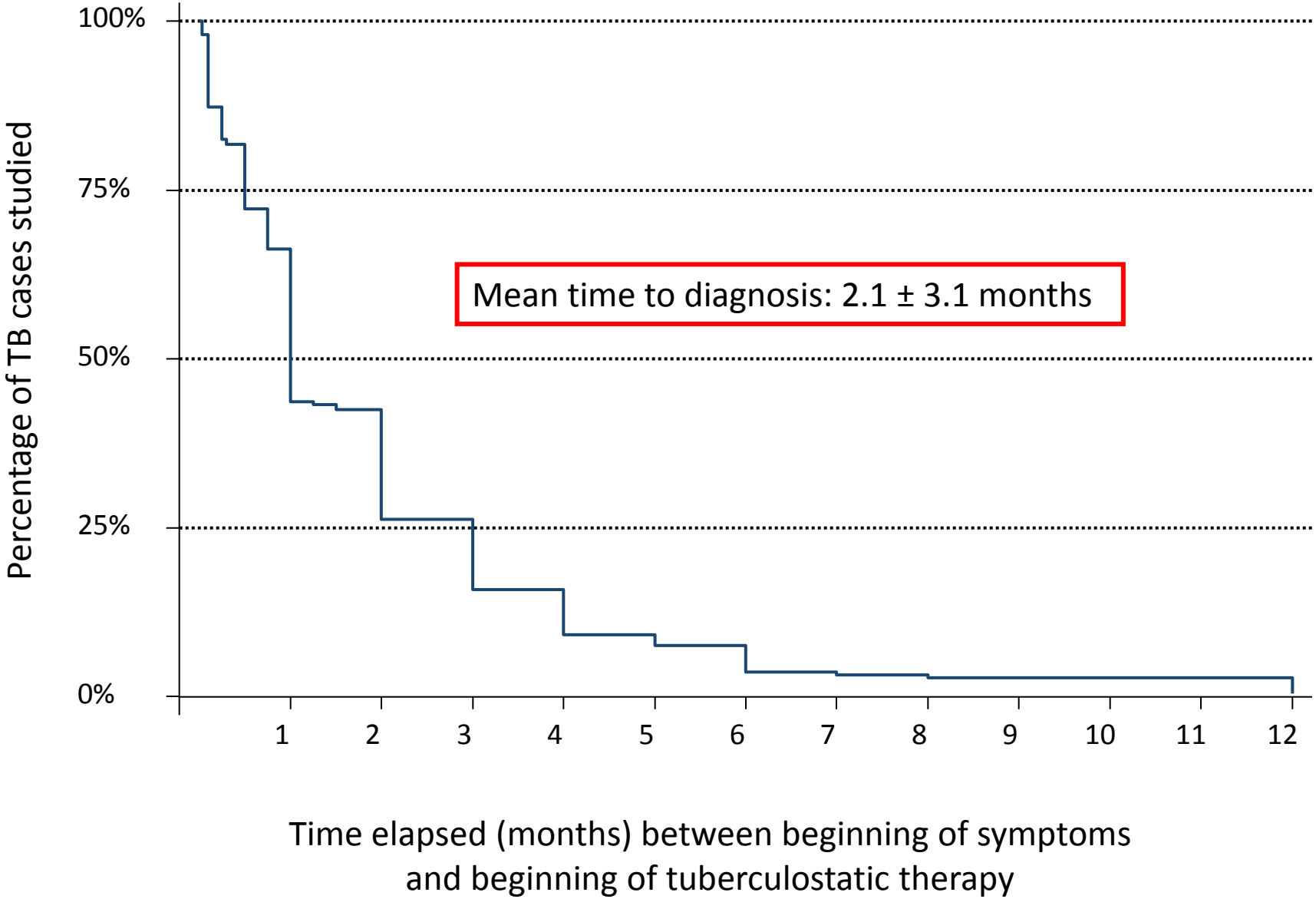
Merci pour votre attention!





Number at risk

Routine	32	14	14	11	7	6	5	4	2	2
Novel	42	9	7	7	5	4	2	1	1	1



O Kherad et al; BMC Infect Dis; 2009

TB and HIV…

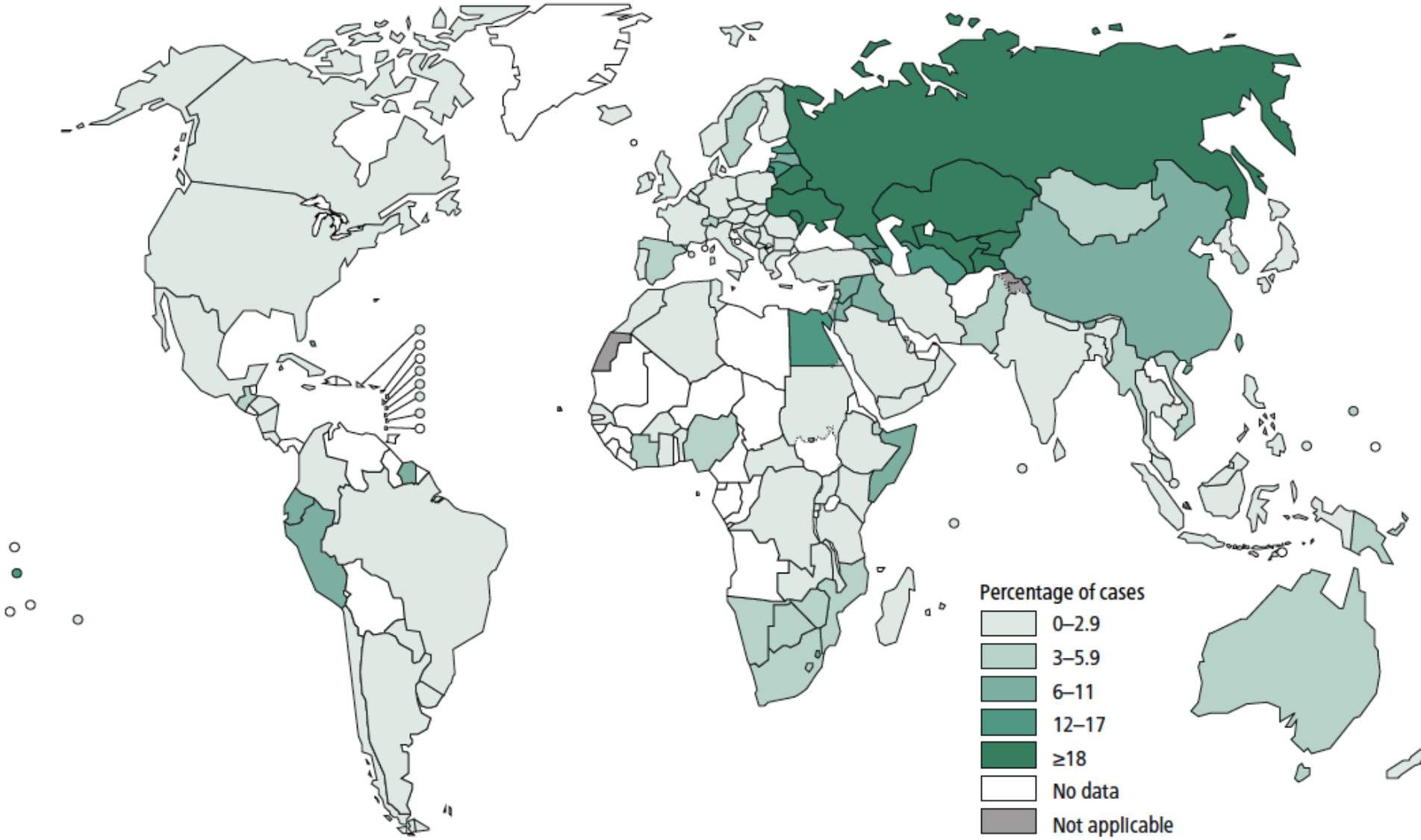
Recommendation:

1.4.1. ART should be started in all TB patients living with HIV regardless of their CD4 cell count (Strong recommendation, high certainty in the evidence).

1.4.2. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty in the evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment.

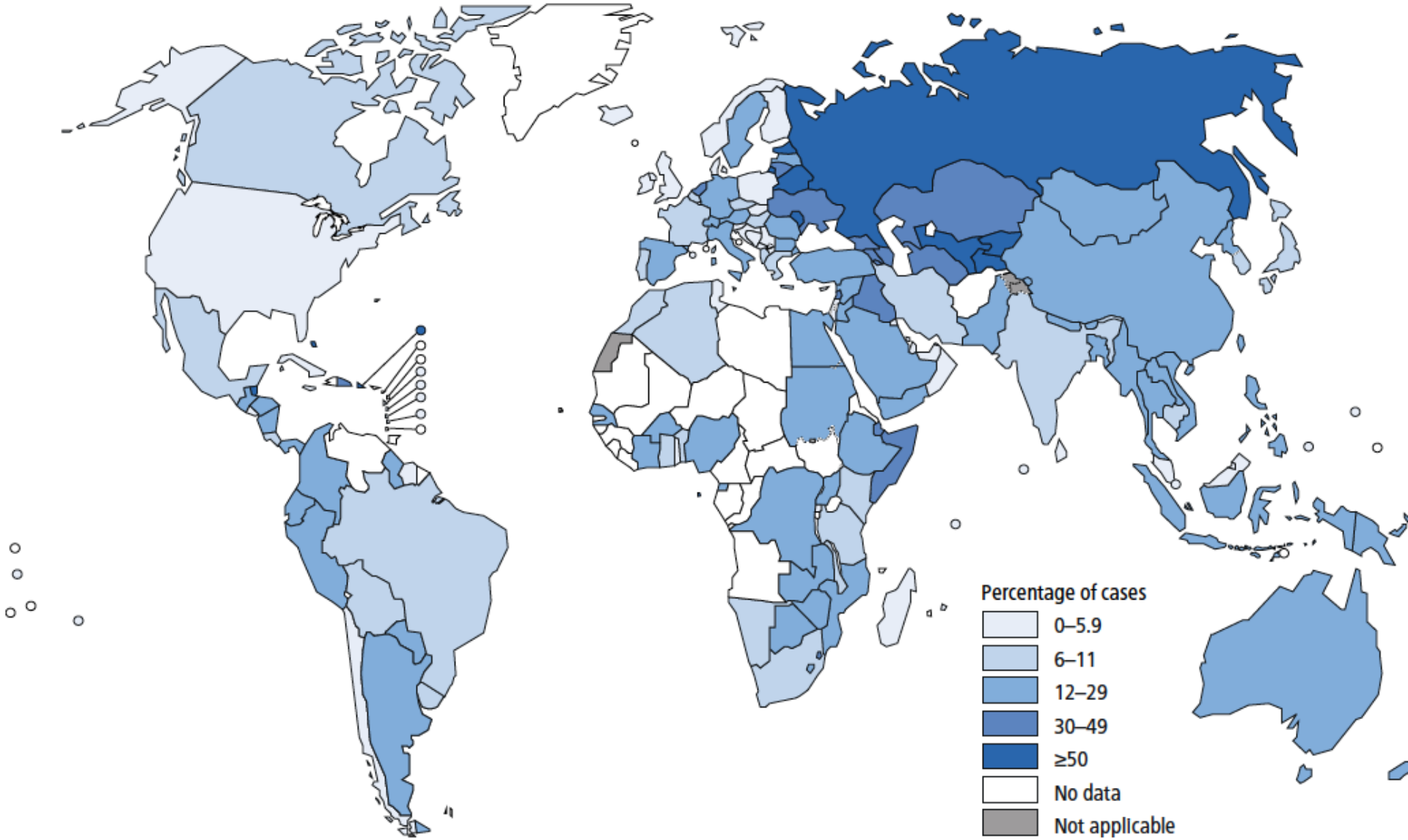
FIG. 3.20

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



[a] Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before 2002 are not shown.

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



Outils diagnostiques: commentaires (1)

- Les systèmes de culture liquide MGIT ont permis de raccourcir la durée de mise en évidence de M-TB: la majorité des cultures est + après 4 semaines
- Les systèmes Xpert sont indispensables pour le diagnostic des TB pulmonaires et extra-thoraciques. Ils sont en particulier recommandés pour le LCR.
- La sensibilité des systèmes Xpert dans les prélèvements non-respiratoires reste inférieure à celle des échantillons d'origine pulmonaire

Outils diagnostiques: commentaires (2)

- Dans un environnement où le risque de MDR-TB est faible, un résultat + pour une mutation du gène rpoB a jusqu'à 40% de chances d'être un faux +.
- L'attitude clinique doit être dictée par la probabilité à priori de MDR-TB.
- L'échantillon doit être adressé au Laboratoire de référence à Zurich pour séquençage at antibiogramme genotypique
- La technique de référence est l'antibiogramme phenotypique.

Outils diagnostiques: commentaires (3)

- D’un commun accord avec le Laboratoire de Bactériologie, les systèmes Xpert ne sont utilisés **que pour le diagnostic**, et ne seront plus utilisés une fois qu’un résultat + a été obtenu sauf sur demande d’un(e) pneumologue ou infectiologue
- L’utilisation des systèmes Ultra-Xpert comporte un risque de faux + en particulier lors de mise em évidence de DNA en faible quantitié (“traces”) à intégrer dans le contexte clinique

Et pour conclure: le futur?

FIG. 8.2

The global development pipeline for new anti-TB drugs and regimens, August 2017

Phase I[a]	Phase II[a]	Phase III[a]
GSK-3036656[b] OPC-167832[b] Q203[b]	Delpazolid (LCB01-0371) PBTZ169[b] SQ109[b] Sutezolid	Bedaquiline Delamanid Pretomanid
	Levofloxacin Linezolid Nitazoxanide Rifampicin (high dose) Rifapentine	Clofazimine Rifampicin (high dose) Rifapentine
	Bedaquiline and delamanid (ACTG 5343 DELIBERATE trial) Bedaquiline – Pretomanid – Pyrazinamide regimen Bedaquiline – Pretomanid – Moxifloxacin – Pyrazinamide regimen Delamanid – Linezolid – Levofloxacin – Pyrazinamide regimen (MDR-END trial)	Bedaquiline – Pretomanid – Linezolid, with or without moxifloxacin or clofazimine for MDR-TB or XDR-TB (TB PRACTECAL trial) Bedaquiline – Pretomanid – Linezolid (NiX-TB trial) Bedaquiline with two optimised background regimens (oral, 9 months; with oral and injectables, 6 months) (STREAM trial) Bedaquiline – Linezolid with optimized background regimen for MDR-TB (NExT trial) Bedaquiline and delamanid with various existing regimens for MDR-TB and XDR-TB (endTB trial) Rifapentine – Moxifloxacin for drug-susceptible TB (TB Trial Consortium Study 31/A5349)

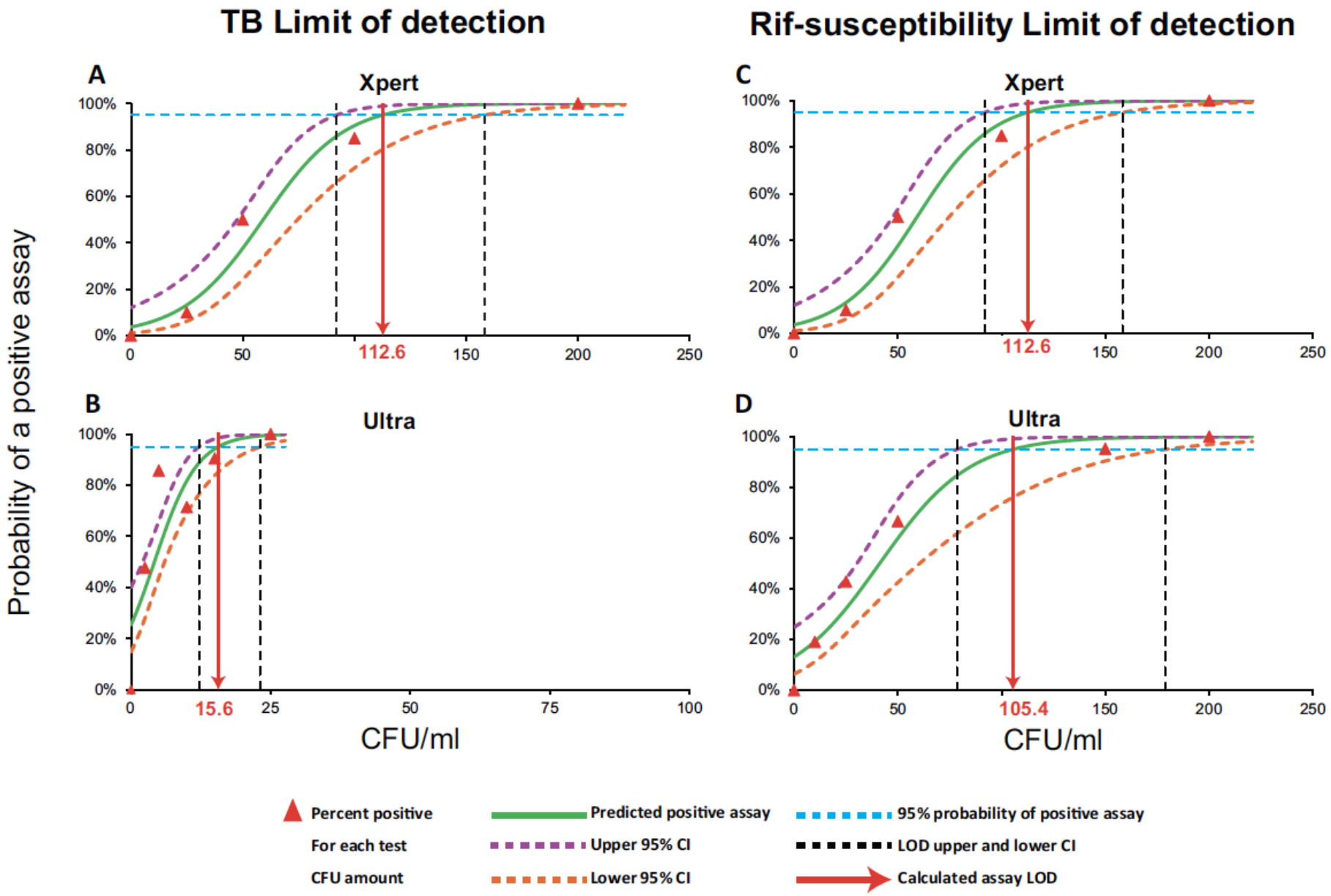
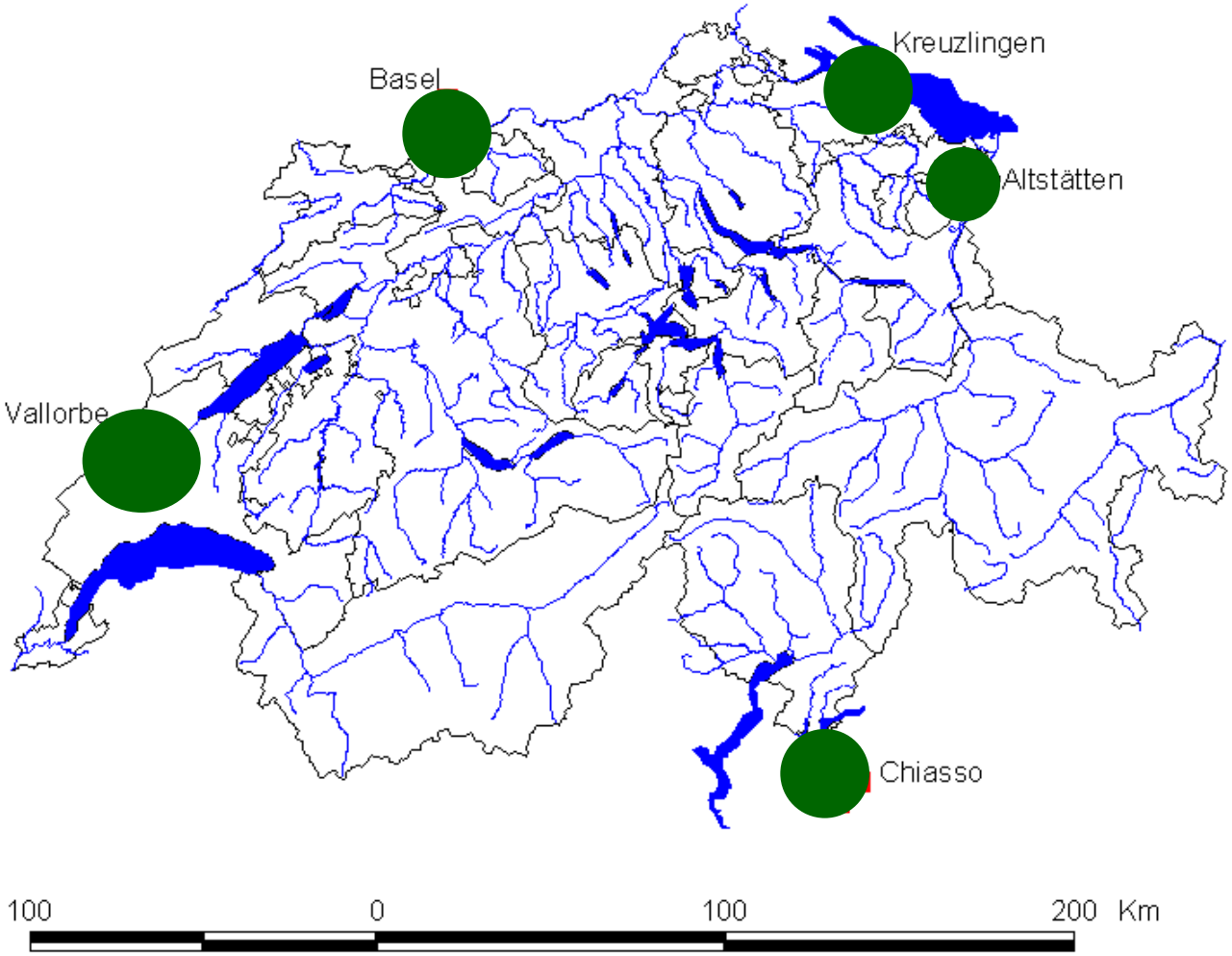
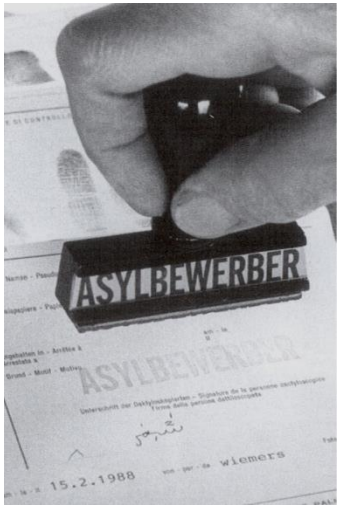


FIG 1 Limit of detection for *M. tuberculosis* H37Rv. The limit of detection of tuberculosis detection is shown for Xpert (A) versus Ultra (B). The limit of detection for generating a rifampin susceptibility rather than an indeterminate result is shown for Xpert (C) versus Ultra (D).

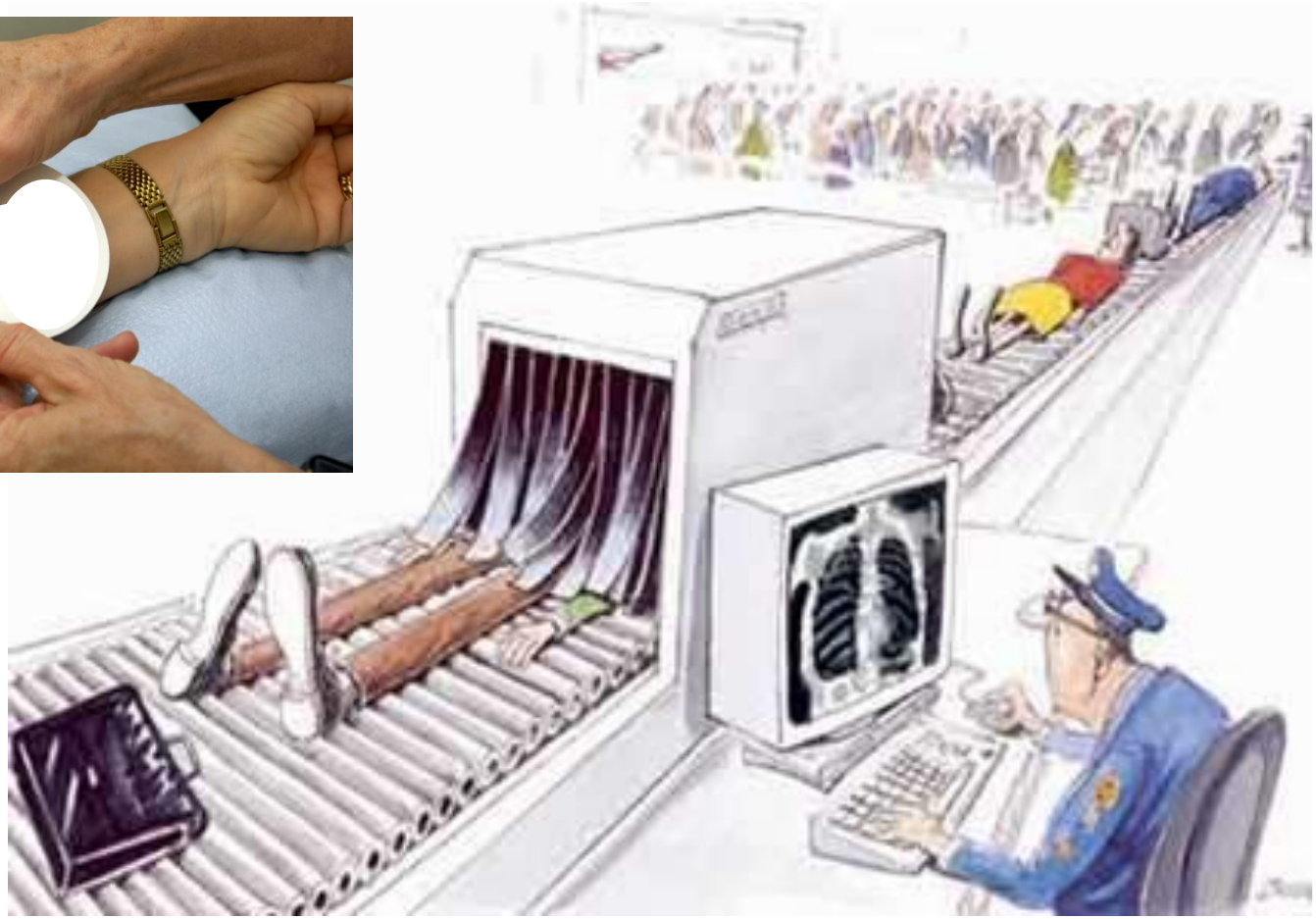
Faut-il 1, 2, 5, 10 expectorations induites?

- Expectorations: recommandations OMS:
- Spot – Morning – Spot ou
- Spot – Morning
- Les critères de validité de la Mayo Clinic ne s’appliquent à priori pas

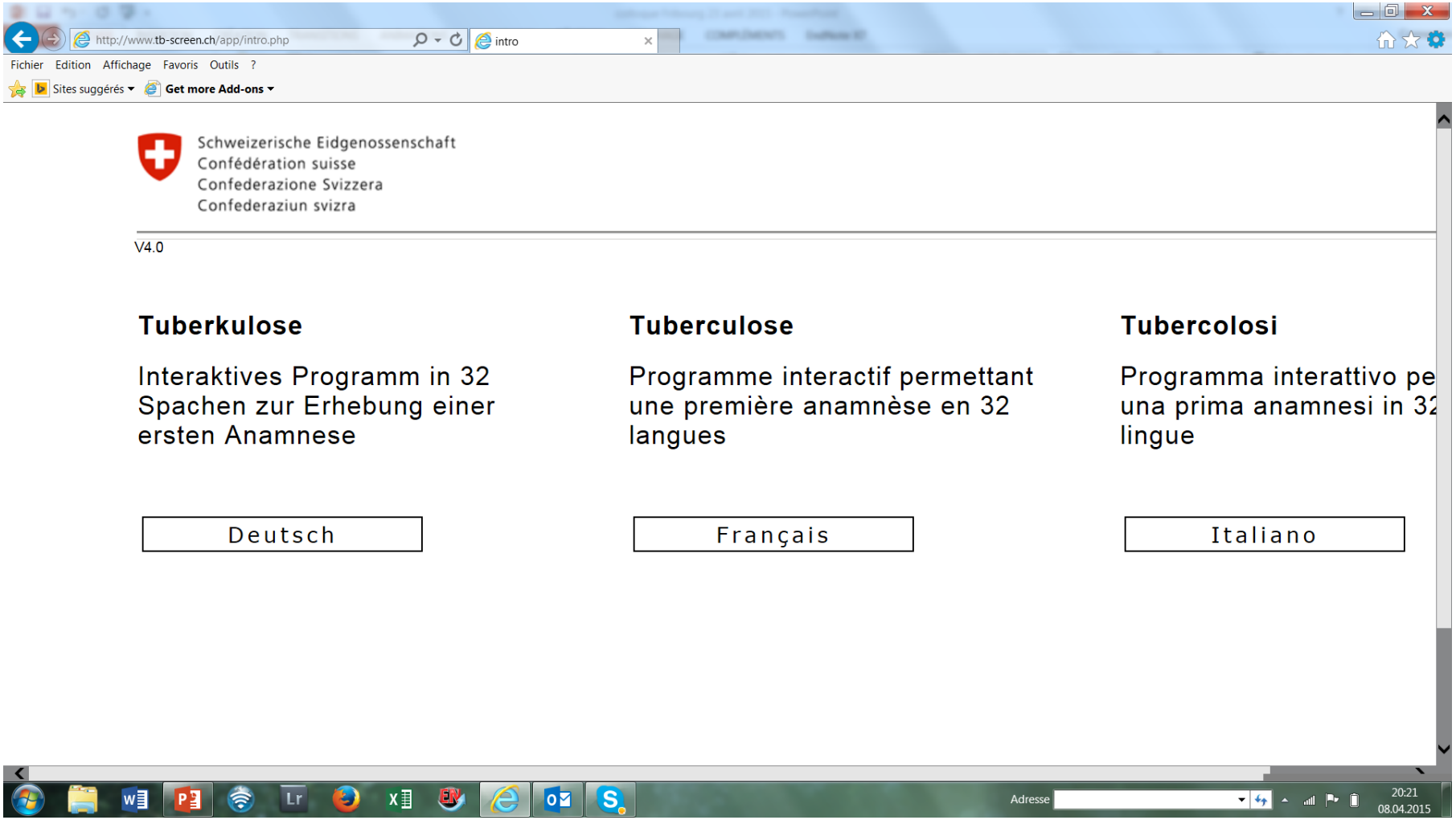

Kreuzlingen
Basel
Altstätten
Vallorbe
Chiasso
100
0
100
200 Km


ASYLBEWERBER
15.2.1988

Migrants et tuberculose:
Procédure jusqu‘au 31.12.2005

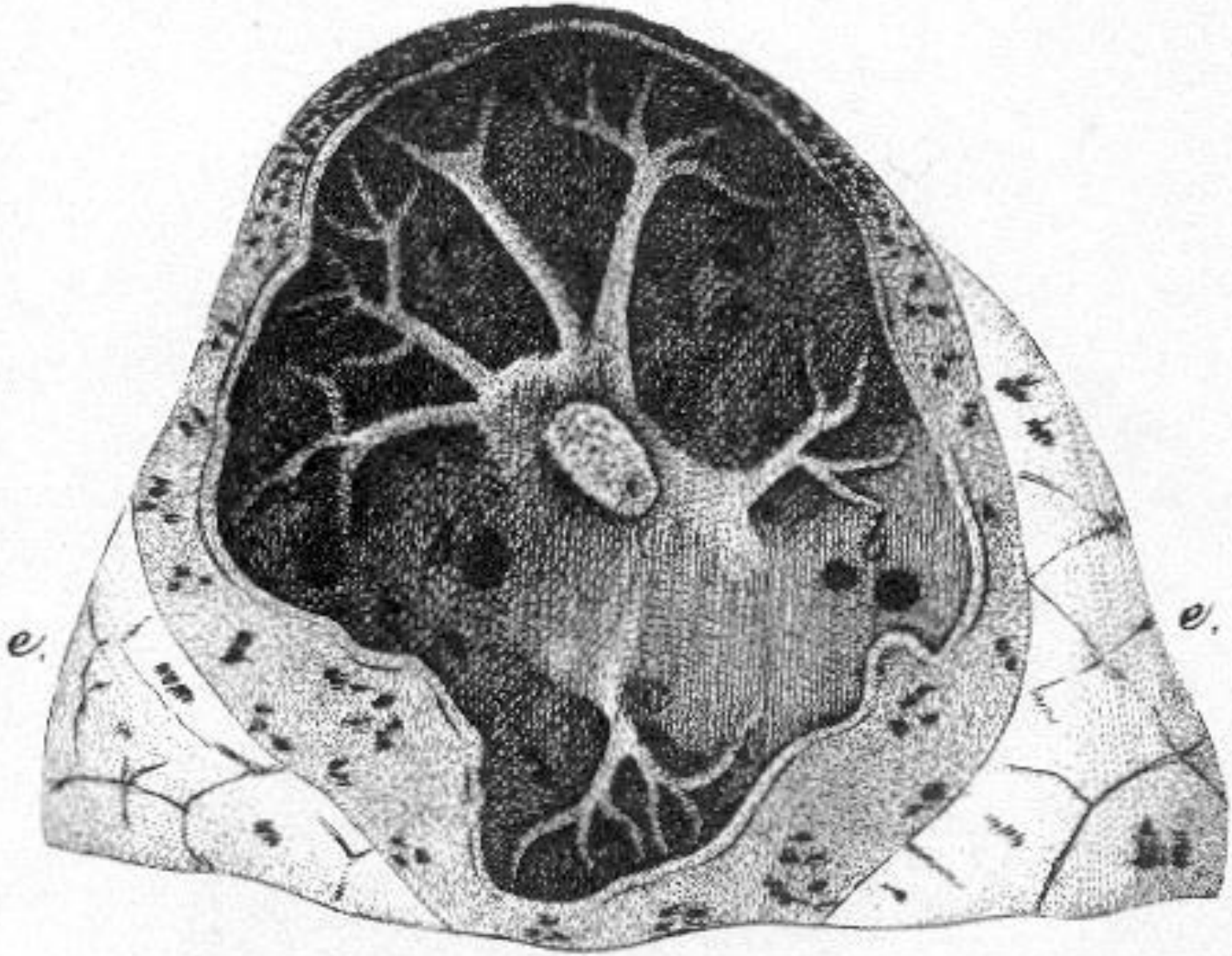


http://www.tb-screen.ch/app/intro.php



In the main study, 1,520 persons with signs and symptoms of TB were enrolled. Overall, sensitivity of the Ultra was 5% higher than that of Xpert MTB/RIF (95%CI +2.7, +7.8) but specificity was 3.2% lower (95%CI -2.1, -4.7). Sensitivity increases were highest among smear-negative culture-positive patients (+17%, 95%CI +10, +25) and among HIV-infected patients (+12%, 95%CI +4.9, +21). Specificity-decreases were higher in patients with a history of TB (-5.4%, 95%CI -9.1, -3.1) than in patients with no history of TB (-2.4%, 95%CI -4.0, -1.3).

Merci pour votre attention!



- http://www.rts.ch/archives/tv/culture/calendrier-de-l-histoire/5834254-guerir-grace-au-soleil.html

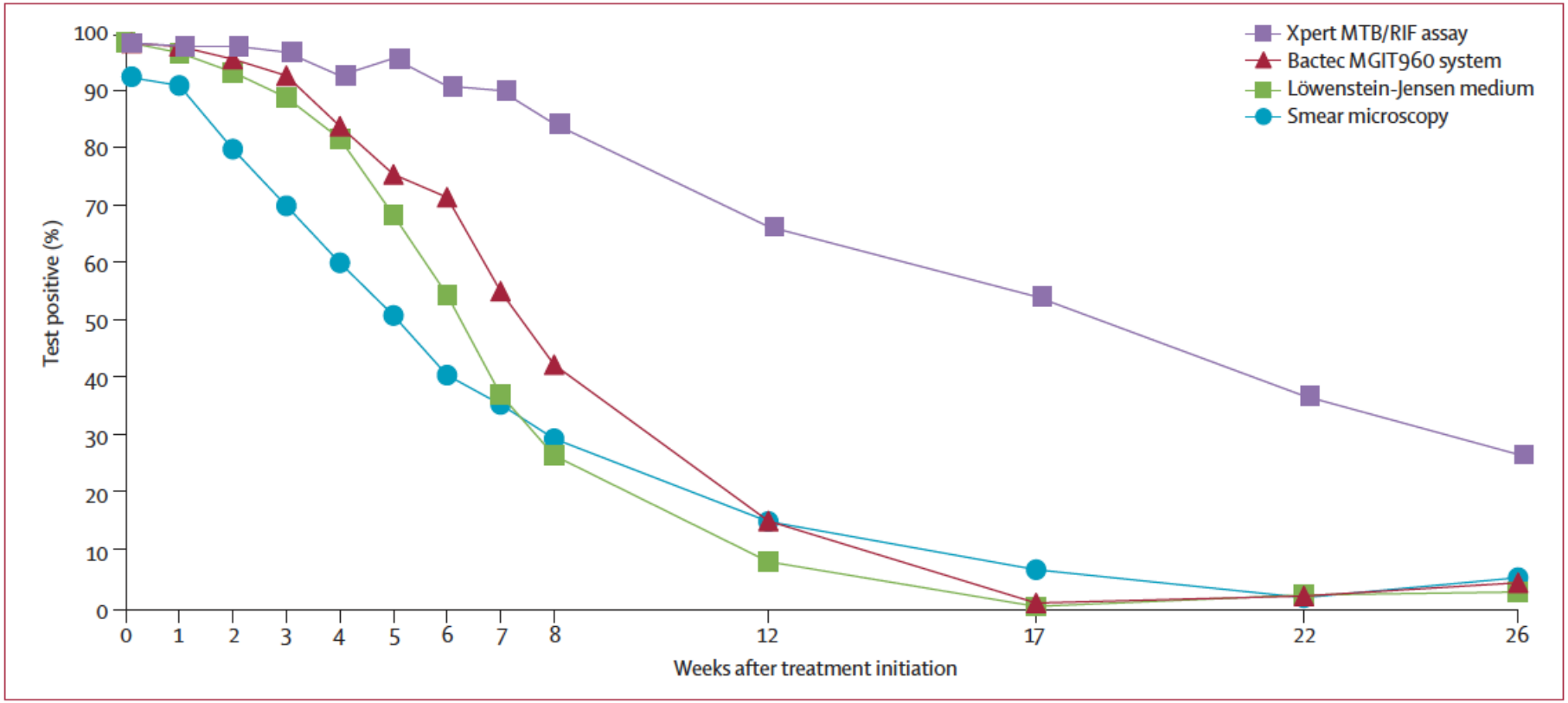
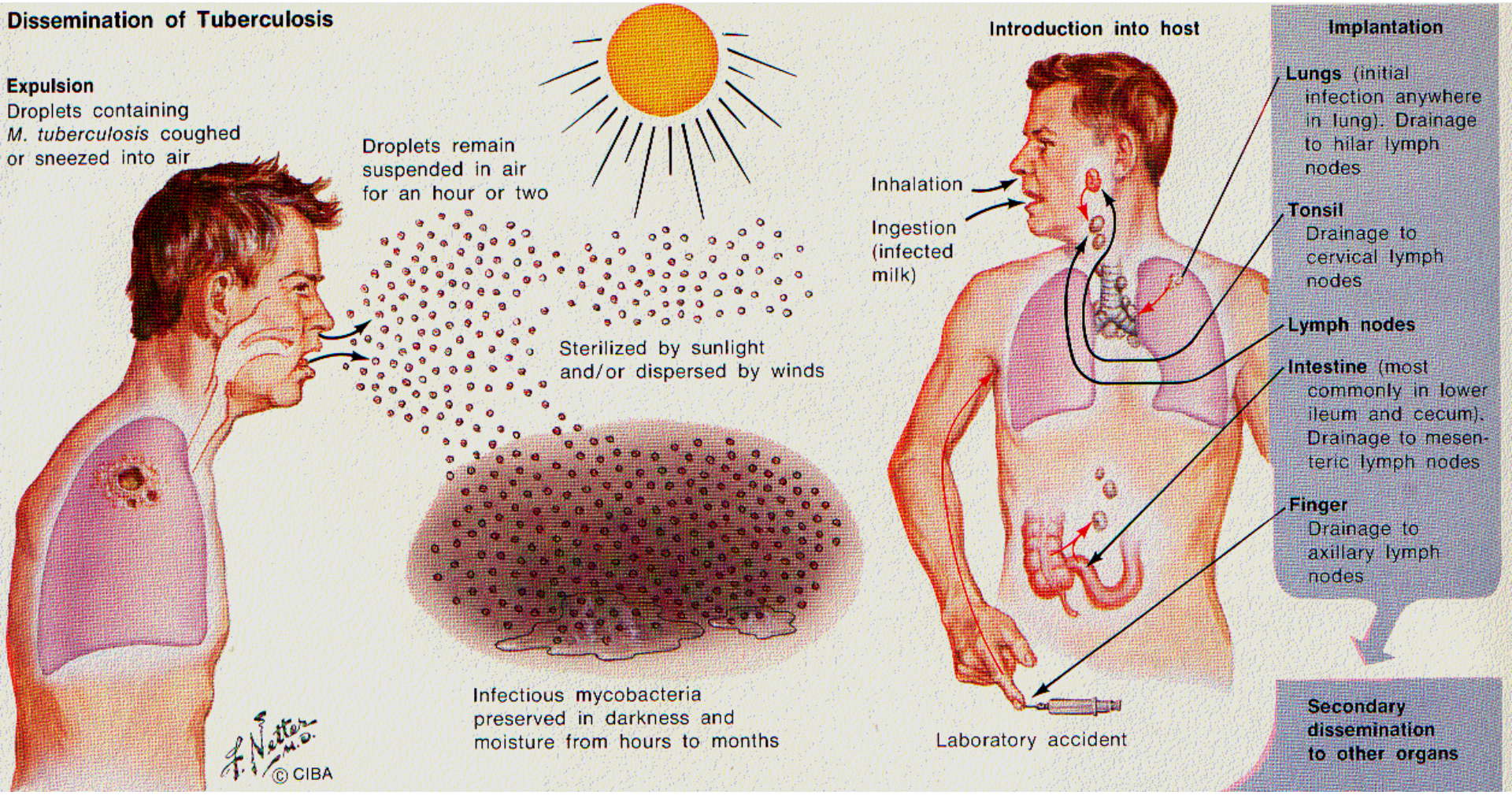


Figure 1: **Qualitative data for all tests at baseline and follow-up visits**


Dissemination of Tuberculosis
Expulsion
Droplets containing
M. tuberculosis coughed
or sneezed into air
Droplets remain
suspended in air
for an hour or two
Sterilized by sunlight
and/or dispersed by winds
Infectious mycobacteria
preserved in darkness and
moisture from hours to months
F. Netter M.D.
© CIBA
Introduction into host
Inhalation
Ingestion
(infected
milk)
Laboratory accident
Implantation
Lungs (initial
infection anywhere
in lung). Drainage
to hilar lymph
nodes
Tonsil
Drainage to
cervical lymph
nodes
Lymph nodes
Intestine (most
commonly in lower
ileum and cecum).
Drainage to mesen-
teric lymph nodes
Finger
Drainage to
axillary lymph
nodes
Secondary
dissemination
to other organs

Active pulmonary tuberculosis: presentation

- Cough
- Fatigue
- Weight loss; T°
- Nocturnal sweating
- Blood-tainted sputum, hemoptysis (typical, but infrequent)
- Chronicity of symptoms (> 3 weeks)
- Absence of clinical improvement with a trial of antibiotics
- *May present without symptoms!*

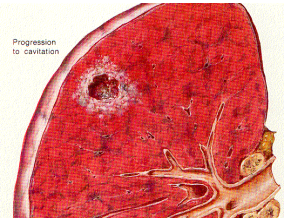


Tableau 7-1. Doses recommandées (Organisation mondiale de la Santé) pour quatre médicaments de première ligne

	Dose journalière (valeurs minimales et maximales) en mg par kg		Dose journalière maximale (mg)	Phase de continuation intermittente (3 fois par semaine)
	Adultes	Enfants		Adultes seulement
Isoniazide	5 (4–6)	10 (7–15)	300	10 (8–12)
Rifampicine	10 (8–12)	15 (10–20)	600	10 (8–12)
Pyrazinamide	25 (10–30)	35 (30–40)	Non spécifiée	Non indiqué
Ethambutol	15 (15–20)	20 (15–25)	Non spécifiée	Non indiqué

WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF