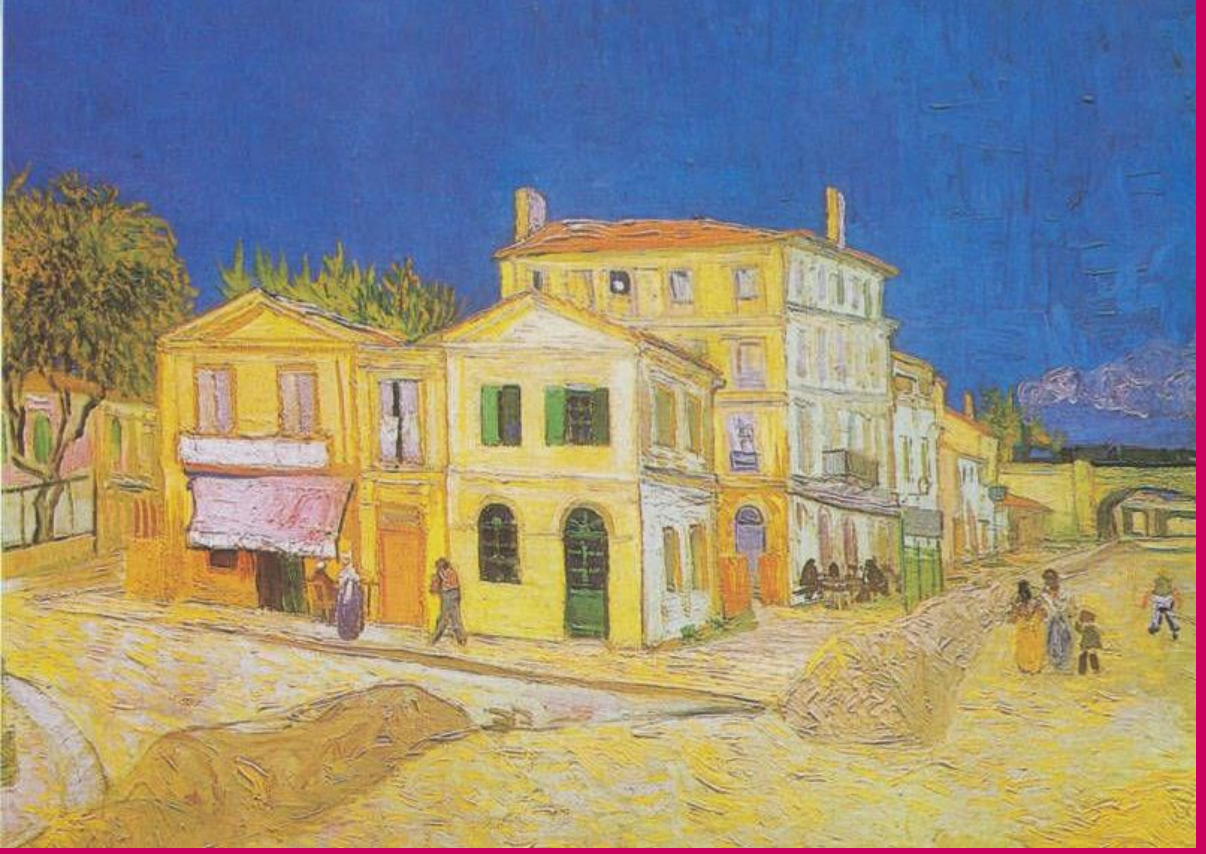
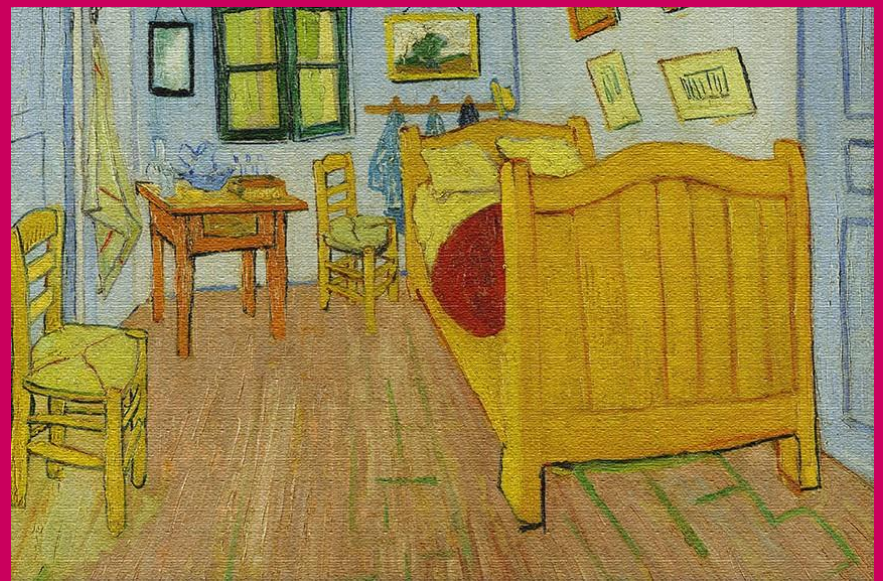




National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Expériences de lutte contre la tuberculose aux Pays-Bas

Gerard de Vries, MD MSc PhD

National Coordinator TB Control, RIVM-CIb

I have no conflict of interest to declare

Gerard de Vries, MD MSc PhD

National Coordinator TB Control

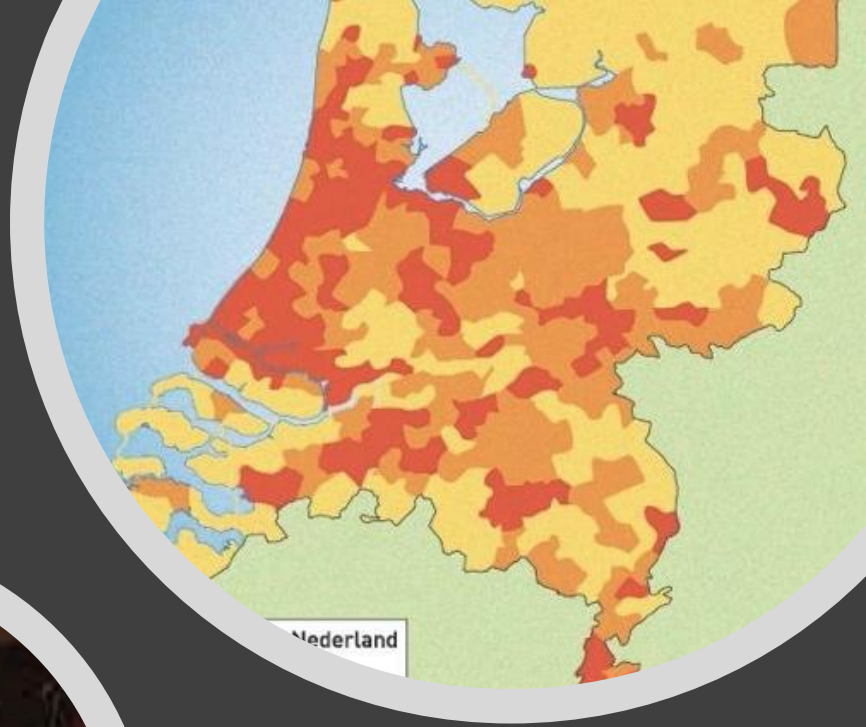
20 September 2021

Outline of presentation

1. The country: The Netherlands
2. Organisation of TB control
3. Dutch National TB Control Plans
4. Epidemiology of TB disease
5. TB control interventions
   - Contact investigation
   - Screening
   - Molecular typing
   - (Latent) TB infection

The Netherlands

- 17.3 million people
- 12 provinces and three small islands in the Caribbean; most densely populated country in the European Union.
- The highest ‘mountain’ is 322 meters; 20% of the country is below sea level.
- Tulips and Dutch painters

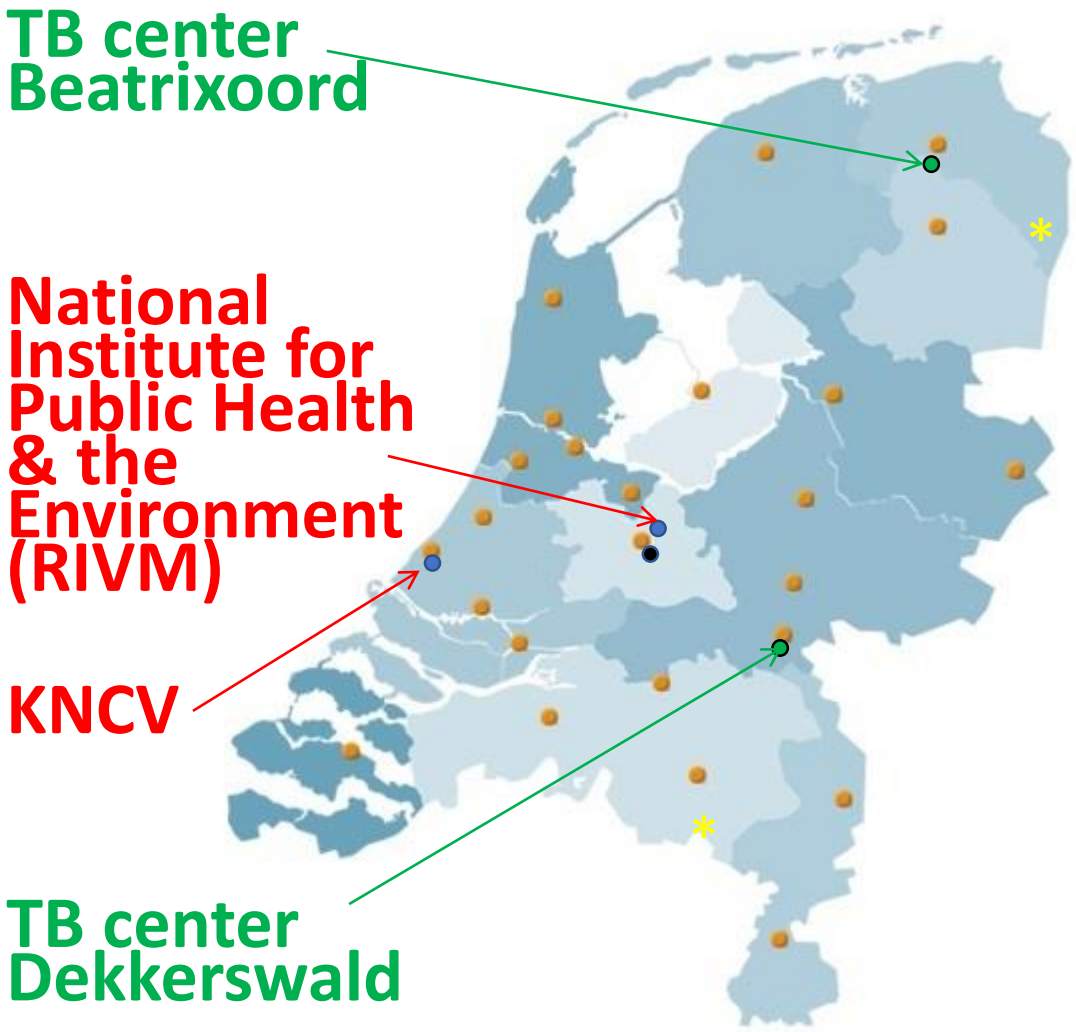


Dutch-French connection

Rembrandts' *Marten & Oopjen*,

alternating on exhibition in Louvres (Paris) and Rijksmuseum (Amsterdam)

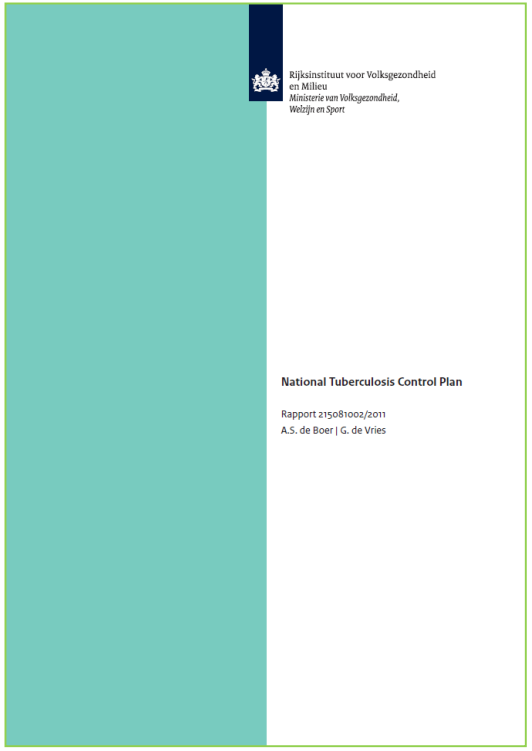
Organisation of TB health services



- 90 hospitals (600 pulmonologists); 2 specialised TB centres
- 29 labs performing *MTBC* cultures
- **25 Municipal Public Health Offices (GGDs)**
  - public health TB doctors
  - TB nurses
  - medical technical assistants
- 2 reception centres for asylum seekers (*)
- ~60 asylum seekers centres
- ~30 prisons

TB strategy

National TB Control Plan 2011-2015

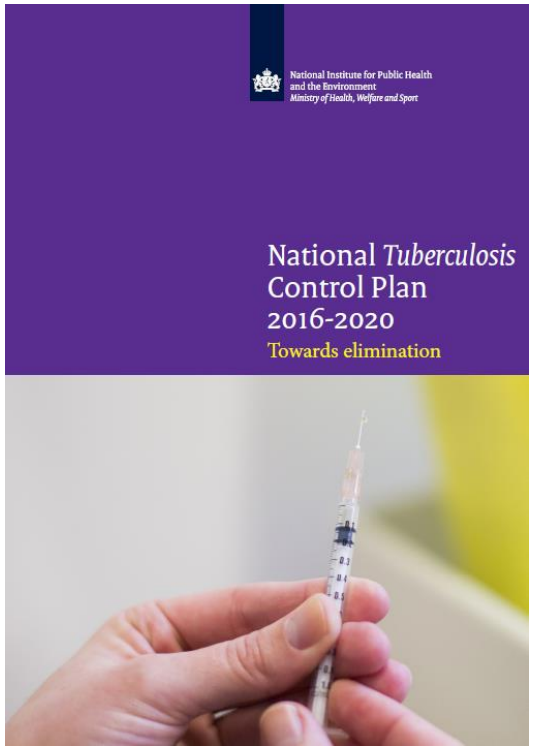


How to sustain an effective and efficient TB programme, while

- Number of TB patients ↓
- Proportion/number of complicated cases ↑
- Workload of health care workers (e.g. chest x-rays, TSTs) ↓
- Knowledge and expertise professionals ↓
- Regional difference (most TB patients in urban areas in the western part of the country)

CHALLENGE: To adapt the organisation to the above changes → 4 Regional Expertise Centra

National TB Control Plan 2016-2020

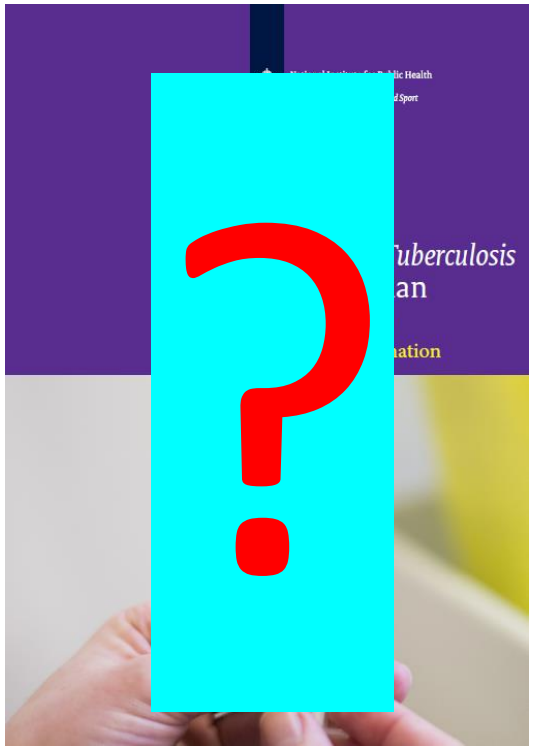


Towards TB elimination

- **Main objectives:**
  - **Reduce TB incidence with 25% in 5 years**
  - **Reduce TB transmission with 25% in 5 years**
- **Main new intervention:** to **screen immigrants and asylum seekers** from **high-incidence countries** for **(latent) TB infection** and **provide TB preventive treatment (TPT).**

http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2016/maart/National_Tuberculosis_Control_Plan_2016_2020_Towards_elimination

National TB Control Plan Update 2021-2025



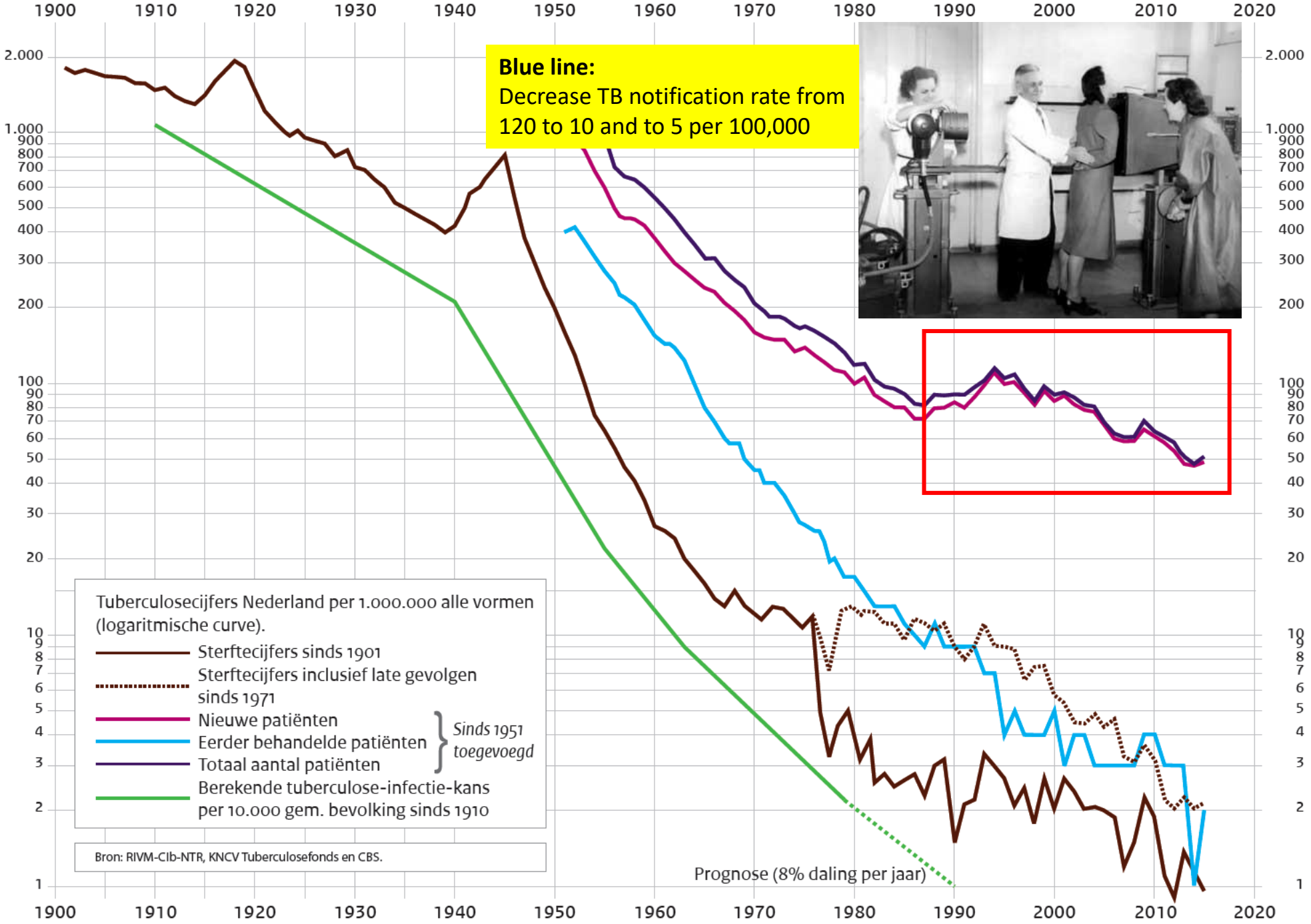
- **Main objectives:**
  - **Reduce TB incidence with 25% in 5 years**
  - **Reduce TB transmission with 25% in 5 years**

TB epidemiology

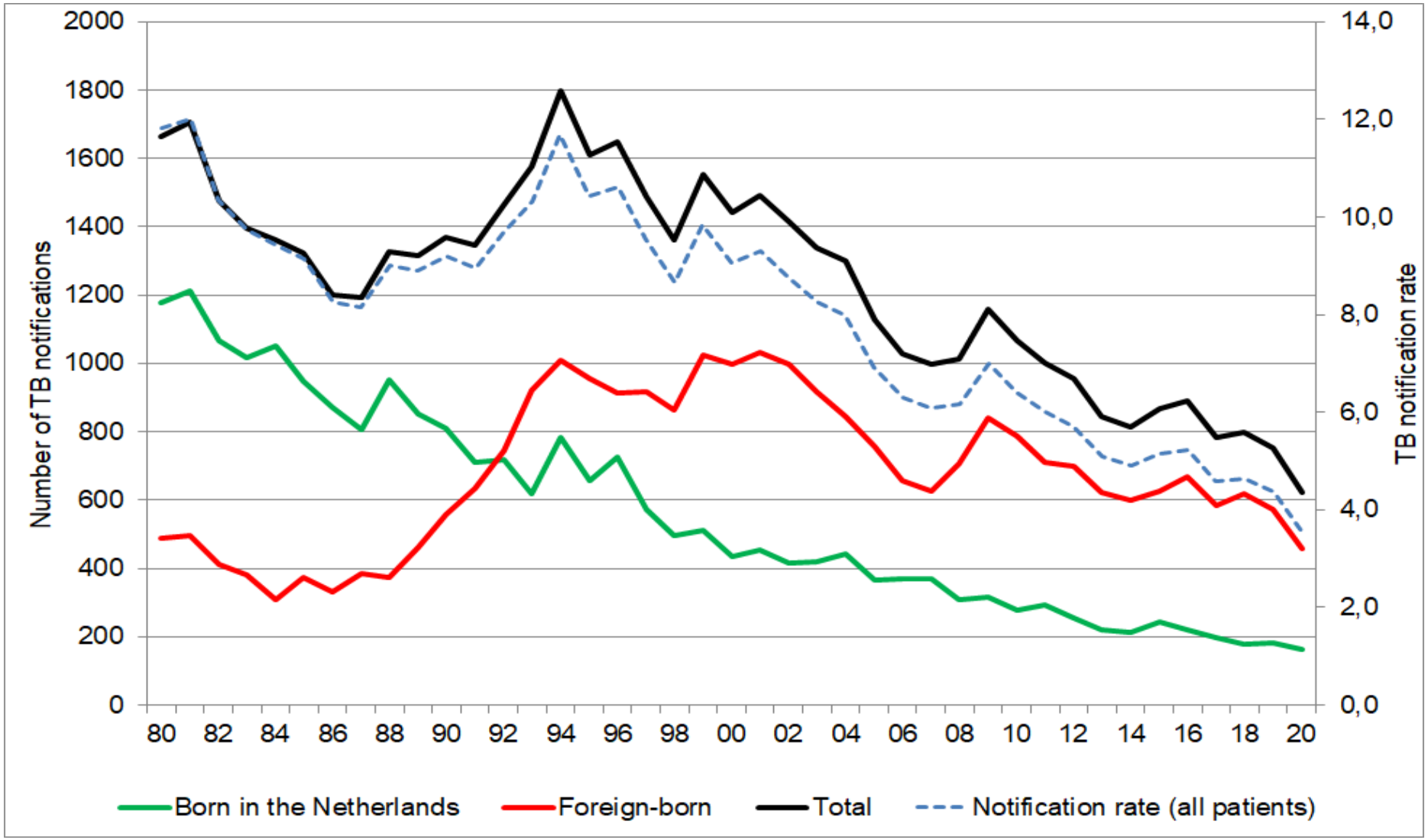
Black line: mortality rate

Dark blue (total) / purple (new) lines : notification rates

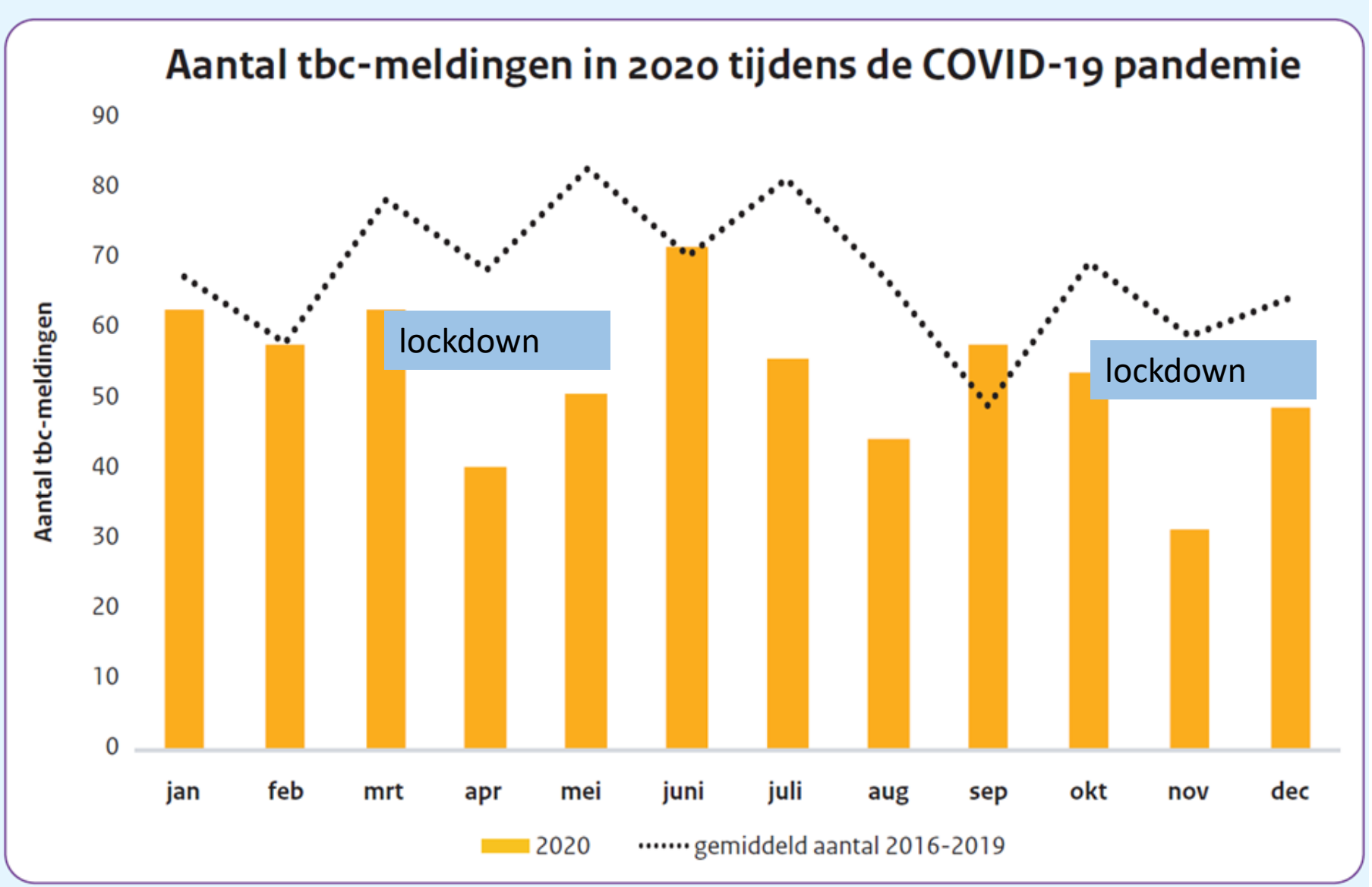
Note: it is a logarithmic scale per million population



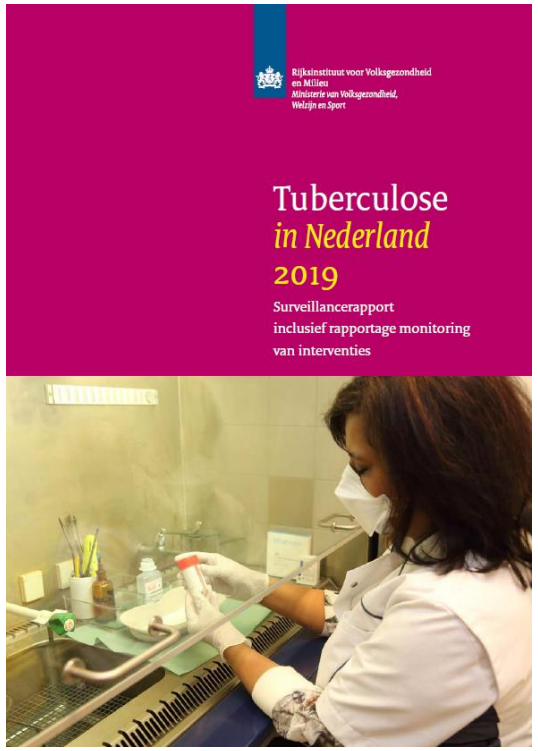
TB notifications 1980-2020



Impact of COVID-19 measures on TB notifications



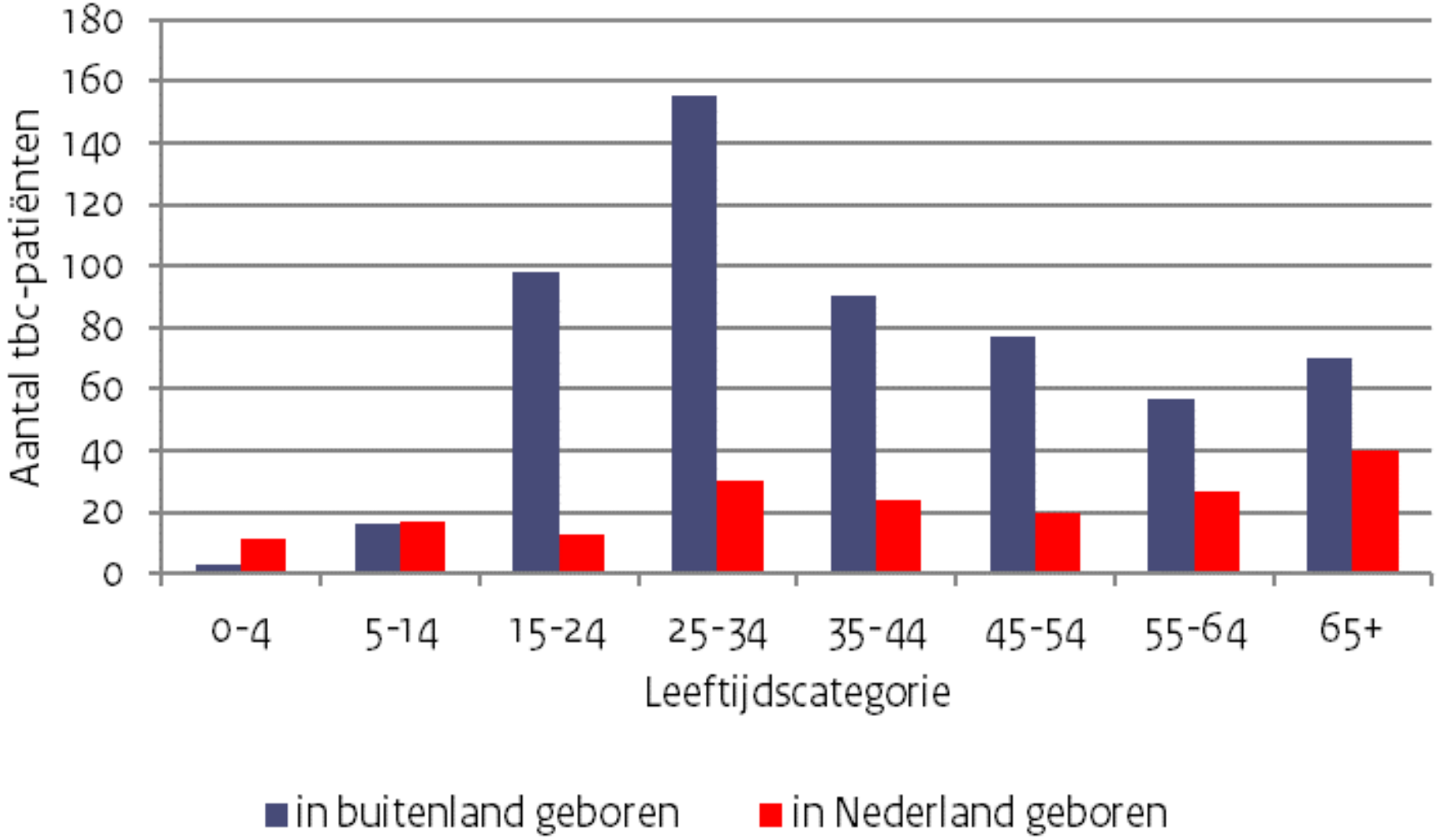
TB Surveillance report 2019

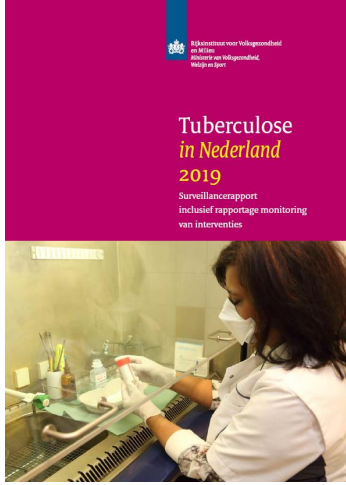


Key characteristics	2019 - N (%)	2020 - N (%)
Number (incidence rate)	754 (4.3)	623 (3.6)
Age <15 years	37 (4.9)	36 (5.8)
Age ≥65 years	112 (15)	90 (14%)
Male/female ratio	1.4	1.3
Foreign-born	570 (76)	453 (73)
Pulmonary TB (PTB & EPTB)	444 (59)	344 (55)
Extrapulmonary TB	310 (41)	279 (45)
Culture-confirmed	503 (67)	423 (68)
RR/MDR/XDR	9 (1.8)*	12 (2.8)*
Previous TB	33 (4.4)	30 (4.8)
HIV co-infection	21 (3.5)	14 (2.9)
Treatment completion **	87%	not yet available

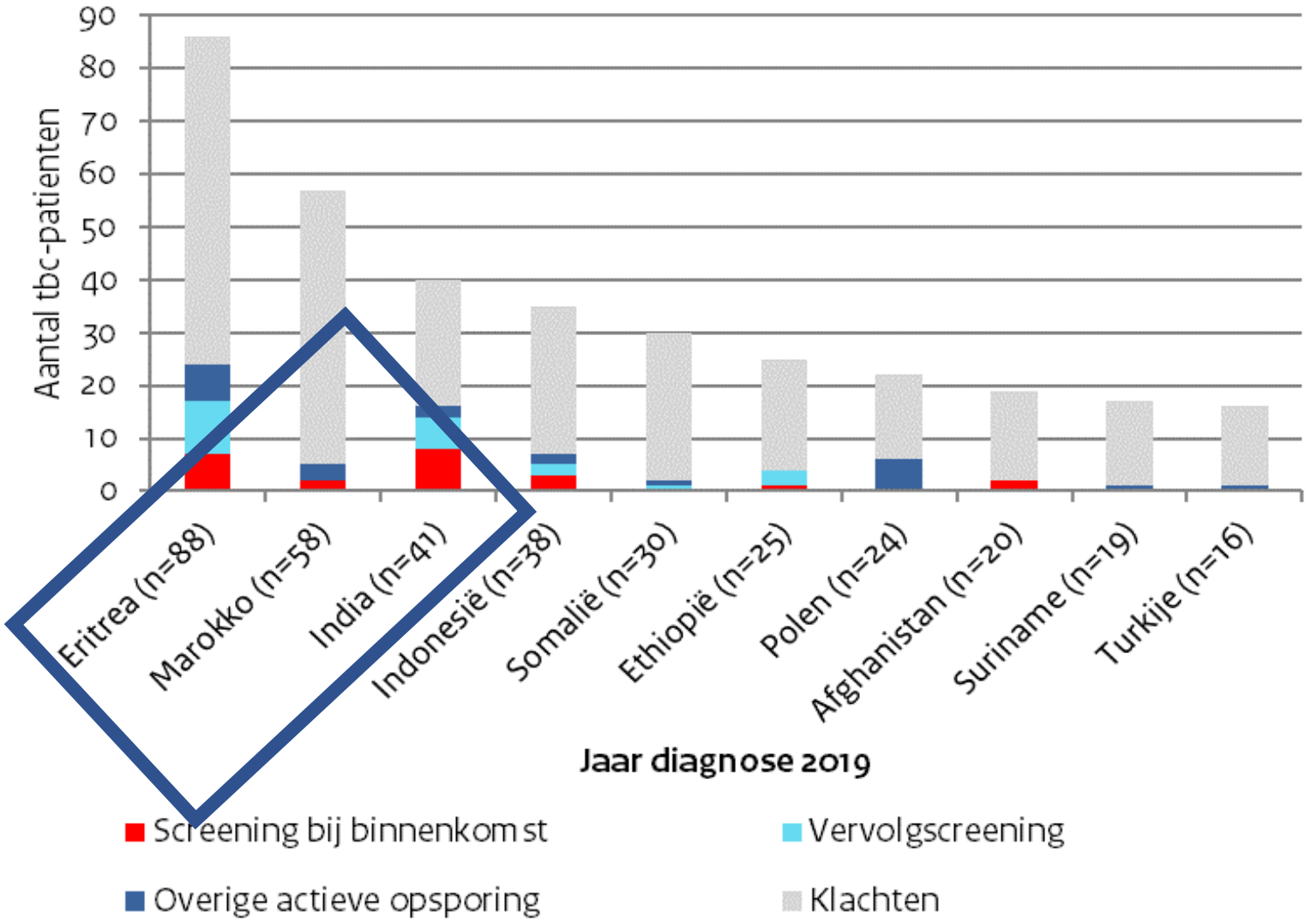
* Percentage of culture-confirmed cases
** only cases without rifampicin resistance

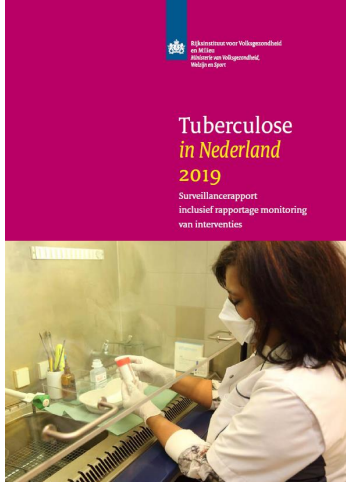
TB cases by country of origin, 2019, age



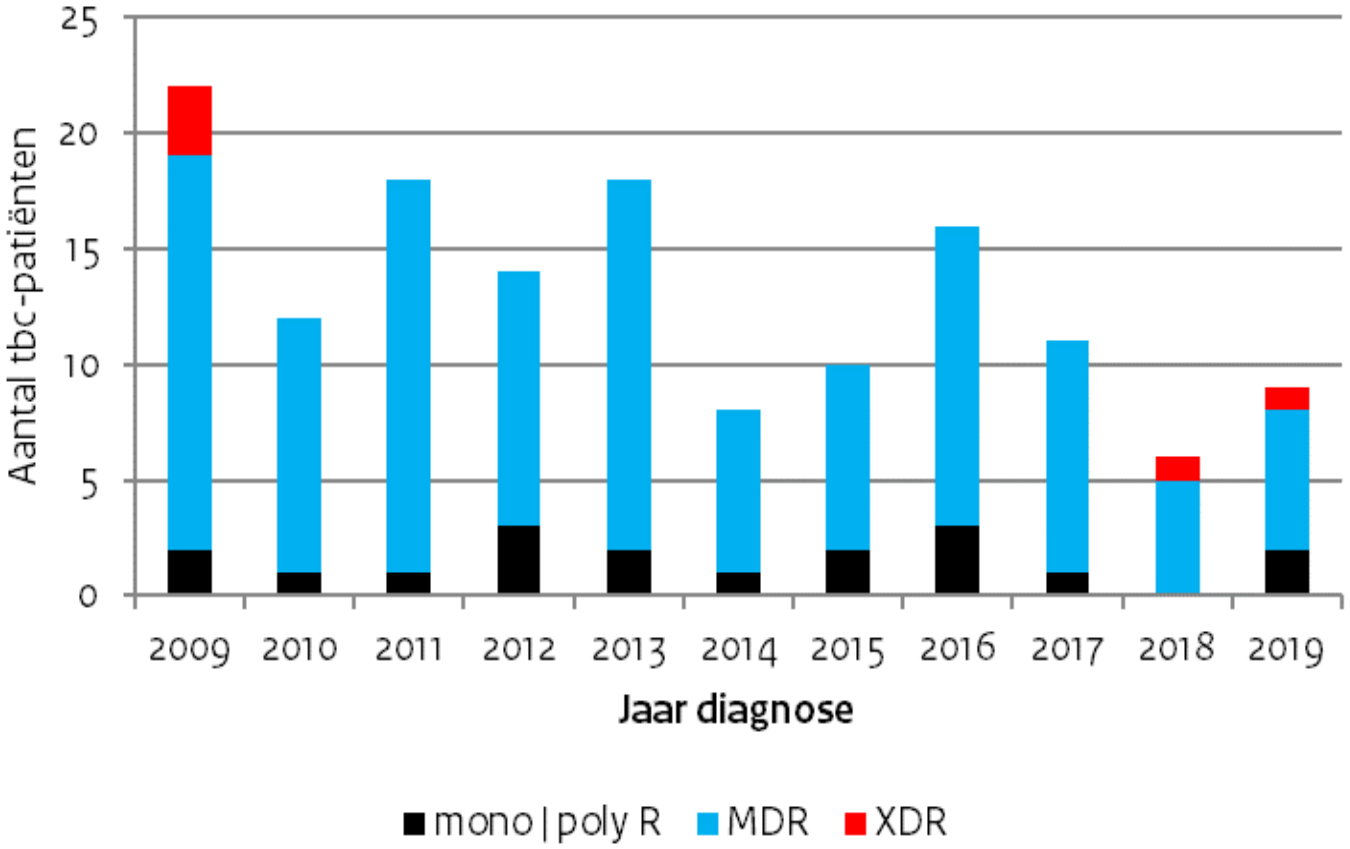


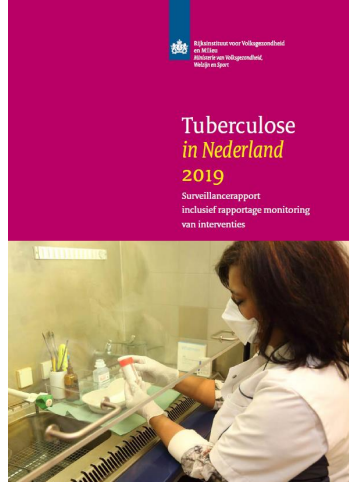
TB cases by country of origin, 2019, top 10





Rifampicin resistant TB





INT J TUBERC LUNG DIS 19(4):406–412
© 2015 The Union
http://dx.doi.org/10.5588/ijtld.14.0838

Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000–2009

- 113 patients
- 96% born outside the Netherlands
- Median age 29 years
- 14 (12%) HIV co-infected
- 104 started MDR-TB treatment
- 86% successful treatment outcome
- HIV associated with poor outcome

TB control interventions

Basics of TB control

1. “Passive case finding” (80% of notified patients) – *‘Think TB’*
2. Case holding / patient support
3. Active case finding (TB disease / TB infection)
   - Contact investigation (~6-8% of TB notifications)
   - Screening vulnerable populations (immigrants/asylum seekers, prisoners, homeless persons) (~8-10% of TB notifications)
   - Screening clinical risk groups (HIV, pre-TNF medication, pre-transplantation) – mainly focussed on (latent) TB infection
4. (Selective BCG vaccination)

Contact investigation

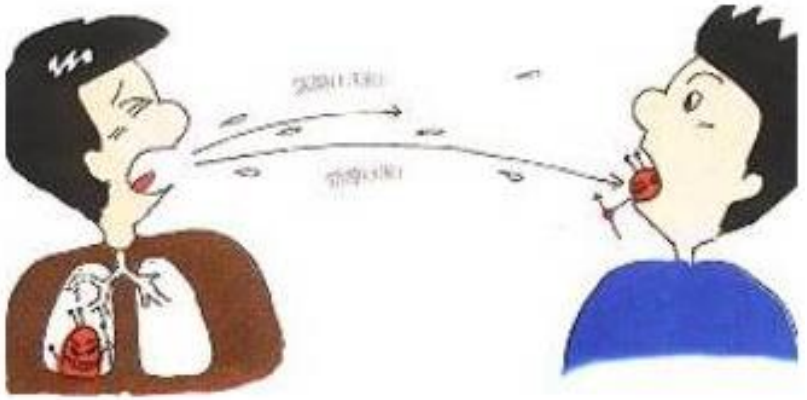
Factors to take into consideration

1. Infectiousness of the index patient (sputum smear microscopy, cavities on chest X-ray, cough hygiene)
2. Infectious period (duration of symptoms)

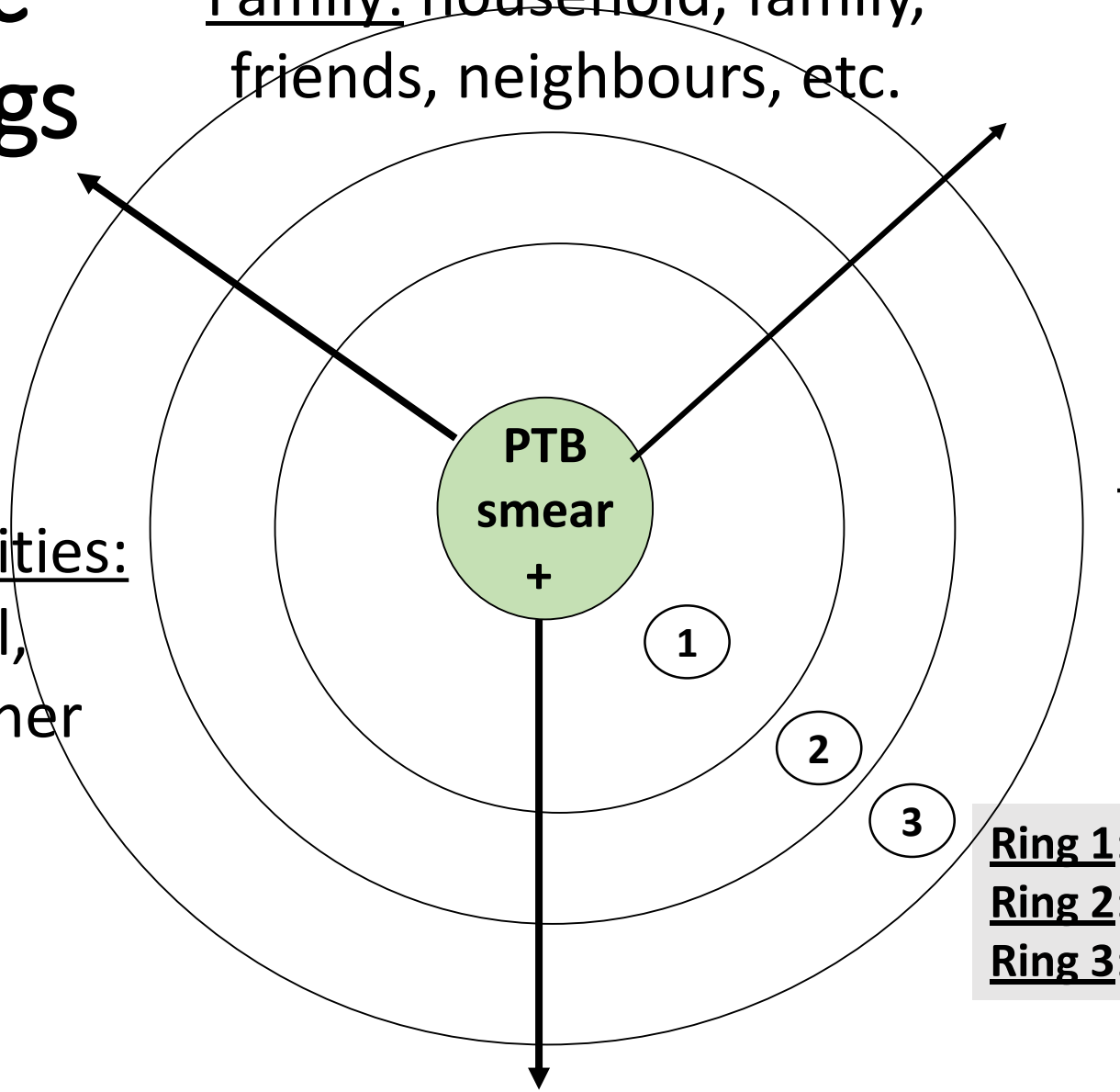
Contact investigation

Factors to take into consideration

1. Infectiousness of the index patient (sputum smear microscopy, cavities on chest x-ray, cough hygiene)
2. Infectious period (duration of symptoms)
3. Risk of transmission
   - Closeness to index patient (household/close contacts)
   - Exposure time
   - Environmental factors (size of the room, ventilation)



Concentric circles/rings approach



Ring 1: close/long contact
Ring 2: less close/long contact
Ring 3: casual contact

Operationalisation exposure

Intensity	**Environment**		**Duration**			
			Long	Short		
			Daily or >48 hour	Weekly or 6-48 hour	Occasional or 1-6 hour	Sporadic or <1 hour
Close	Car	<5 m^3	Ring 1	Ring 1 or 2	Ring 2	Ring 2
	Room	10-30 m^3	Ring 1	Ring 2	Ring 2	Ring 2 or 3
Less close	Class/office	100-200 m^3	Ring 2	Ring 2 or 3	Ring 3	Ring 3
	Large closed area	>200 m^3	Ring 2	Ring 3	Ring 3	None

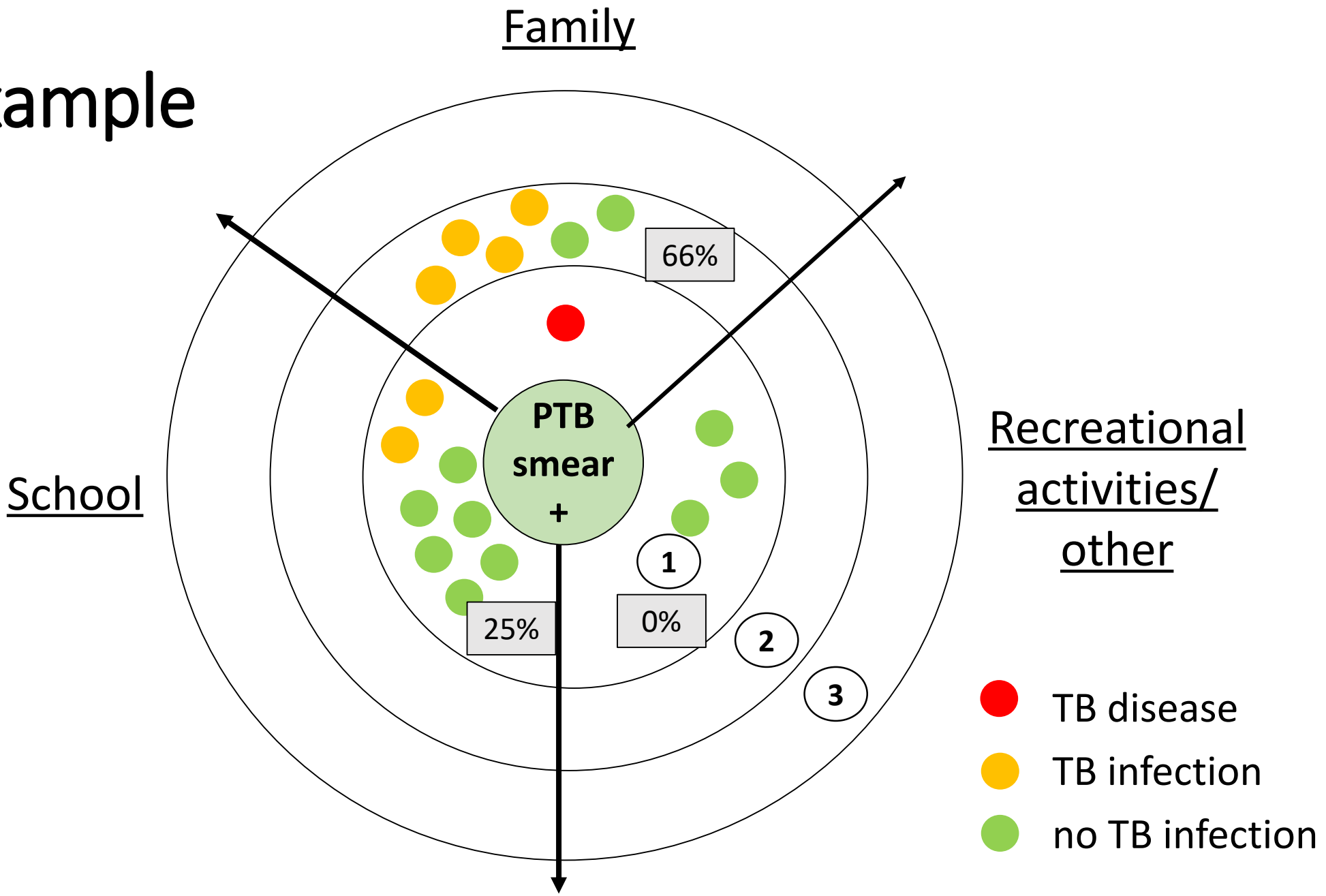
Source: Dutch guideline on TB contact investigation, 2019

Contact investigation

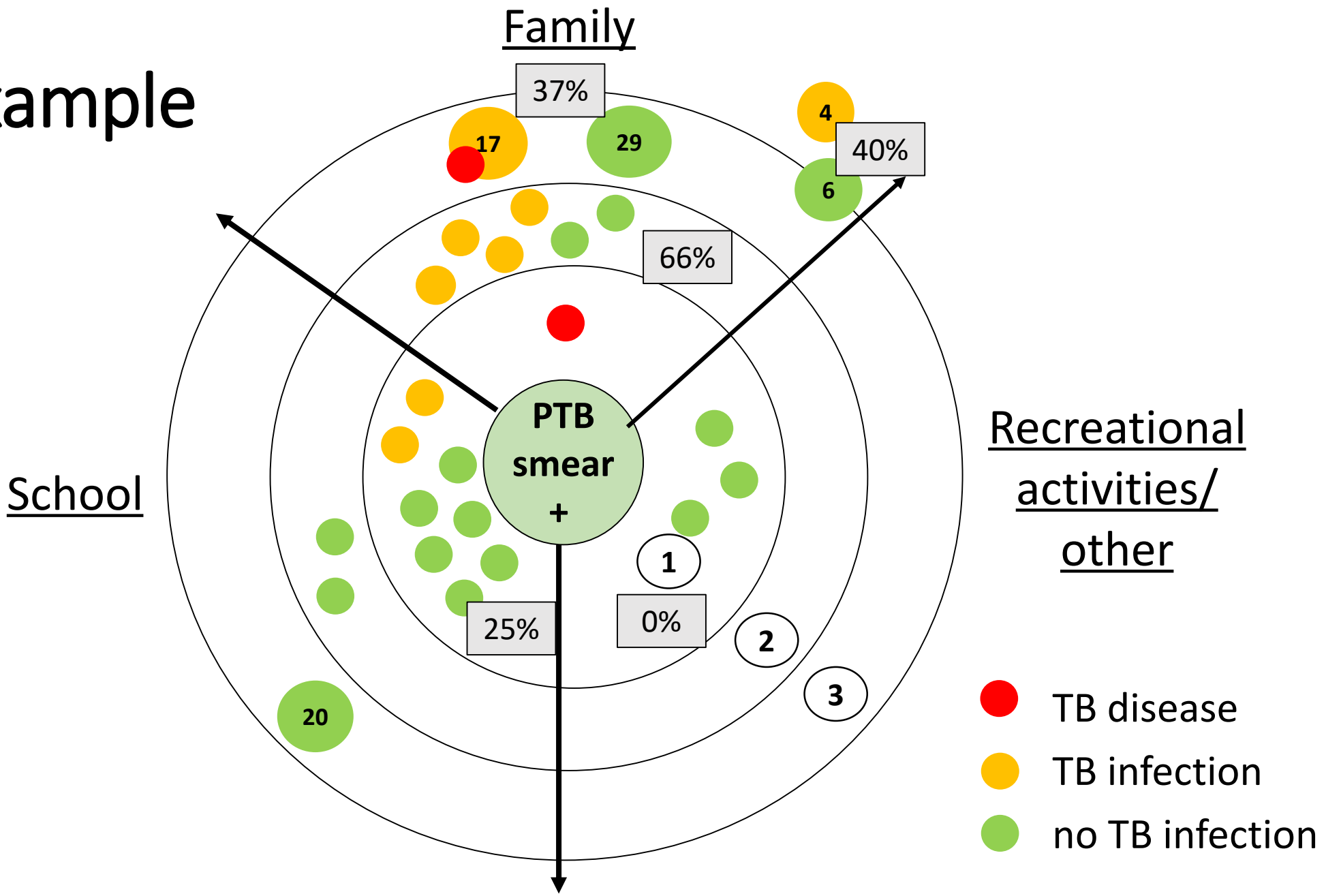
Factors to take into consideration

1. Infectiousness of the index patient (sputum smear microscopy, cavities on chest x-ray, cough hygiene)
2. Infectious period (duration of symptoms)
3. Risk of transmission
   - Closeness to index patient (household/close contacts)
   - Exposure time
   - Environmental factors (size room, ventilation)
4. Susceptibility of contacts (young children, HIV, immunosuppressive drugs (anti-TNF medication, organ transplants) → **prioritise**
5. Confirmed transmission (‘*stone-in-the-pond principle*’) → **extend contact investigation**

An example


Family
School
Recreational activities/ other
PTB smear +
66%
25%
0%
1
2
3
TB disease
TB infection
no TB infection

An example


Family
37%
17
29
4
40%
6
66%
PTB smear +
School
Recreational activities/ other
1
0%
2
3
25%
20
TB disease
TB infection
no TB infection

Tests

- **Tuberculin Skin Test (TST; Mantoux) PPD SSI RT23 ®**
- **Interferon Gamma Release Assay (IGRA)**
  - QuantiFERON®-TB Gold Plus (QFT-PLUS)
  - T-SPOT®.TB
- Both IGRA tests contain TB-specific antigens (ESAT-6 and CFP-10)

The Netherlands: two-step approach

Evaluation of screening / contact investigation

Bron- en contactonderzoek bij tuberculosepatiënten in Nederland
2011-2016
Evaluatierapport

KNCV TUBERCULOSEFONDS

52,000 contacts examined

Tabel 10. Opbrengst voor actieve tuberculose en latente tbc-infectie per contactring

Patients	**1154**		**773**		**217**		**1072**		**3,216**	
	ZN-positieve longtuberculose		Kweek positieve longtuberculose		Kweek negatieve longtuberculose		Extrapulmonale tuberculose		Totaal	
	N	%	N	%	N	%	N	%	N	%
Tuberculose										
Eerste ring	227	2,1%	23	0,6%	0	0,0%	28	0,8%	278	1,5%
Tweede ring	57	0,3%	8	0,2%	1	0,2%	0	0,0%	66	0,3%
Derde ring	8	0,1%	0	0,0%	0	0,0%	0	0,0%	8	0,1%
Totaal	292	0,8%	31	0,4%	1	0,1%	28	0,6%	352	0,7%
Latente tbc-infectie										
Eerste ring	1770	18,0%	318	9,3%	54	6,8%	332	11,1%	2495	14,6%
Tweede ring	1197	6,8%	150	3,8%	13	3,2%	39	6,0%	1408	6,2%
Derde ring	330	3,9%	12	3,7%	0	0,0%	1	5,6%	343	3,9%
Totaal	3297	9,2%	480	6,2%	67	5,5%	372	10,2%	4246	8,8%

ZN = Ziehl-Neelsen/auraminekleuring

Lessons learned contact investigation

- **Contact investigation is very effective when targeted at high-risk contacts, e.g. 1-2% of close contacts of smear positive patients had TB disease and 15-20% TB infection.**
- **It should be prioritised to people at highest risk (close contacts, young children, people with immunosuppression)**
- **Extension of contact investigation to large groups is rarely useful/ necessary.**

TB screening prisoners

- From 1994-2010, all new prison inmates were screened with a mobile X-ray unit (MXU).

TB screening prisoners

- From 1994-2010, all new prison inmates were screened with a mobile X-ray unit.
- 2010: more selective screening of new prison inmates.

Towards selective tuberculosis screening of people in prison in a low-incidence country

De Vries et al, ERJ, 2020

TABLE 1 Number of new entrants in prisons, prisoners screened, tuberculosis (TB) among prisoners (identified by screening or otherwise), screening yield and prevalence of TB among prisoners in the Netherlands, 2001–2018

Year	New entrants in prison n	Prisoners screened n	Coverage of screening	TB among prisoners n	TB diagnosed by MXU screening n	Yield of screening per 100 000	TB not diagnosed by MXU screening n	Prevalence per 100 000
2001	35 000#	26 158	75%	28	17	65	11	80
2002	33 100	25 730	78%	36	25	97	11	109
2003	37 750	29 079	77%	36	26	89	10	95
2004	45 379	37 752	83%	42	32	85	10	93
2005	54 790	46 702	85%	25	25	54	0	46
2006	54 851	44 546	81%	46	46	103	0	84
2007	51 366	42 467	83%	13	13	31	0	25
2008	48 078	40 248	84%	21	15	37	6	44
2009	46 285	39 072	84%	33	27	69	6	71
2010	46 052	37 464	81%	29	23	61	6	63
Total 2001–2010	**452 651**	**369 218**	**82%**	**309**	**249**	**67**	**60**	68
2011	46 231	22 779	49%	30	22	97	8	65
2012	44 352	20 412	46%	22	17	83	5	50
2013	43 307	18 494	43%	20	17	92	3	46
2014	44 218	15 309	35%	16	13	85	3	36
2015	40 587	14 200	35%	6	4	28	2	15
2016	35 957	12 222	34%	15	13	106	2	42
2017	35 664	10 466	29%	20	13	124	7	56
2018	35 241	9 929	28%	7	7	71	0	20
Total 2011–2018	**325 557**	**123 811**	**38%**	**136**	**106**	**86**	**30**	42
Total	**778 208**	**493 029**	**63%**	**445**	**355**	**72**	**90**	57

MXU: mobile radiography unit. #: estimated number.

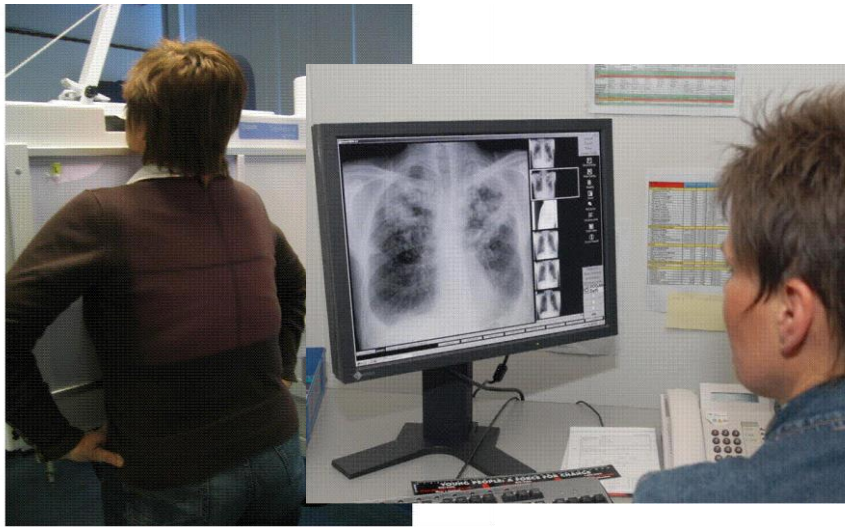
TB screening prisoners

- From 1994-2010, all new prison inmates were screened with a mobile X-ray unit.
- 2010: more selective screening of new prison inmates.
- Now: screening prisoners from countries with TB incidence >10/100,000 (about 40% of new prison entrants eligible).

➢ **Lesson learned: important to systematically evaluate interventions**

TB screening immigrants – 2 pathways

1. **‘Regular’ immigrants**
   - Reason migration: work, study, family reunification.
   - Screening is mandatory by Immigration Law, if intended stay is >3 months and from country with TB incidence >100/100,000.
   - Screening is done by GGD within 1-2 months after arrival.
2. **Asylum seekers/refugees**
   - Screening is mandatory by Immigration Law, if person is from country with TB incidence >50/100,000.
   - Screening is done by 2 GGDs within 2 days after arrival at the two reception centres.



Evaluation screening immigrants to the NL, 2011-2015 (excluding asylum seekers)

TB incidence country of origin	Number	TB found by screening	Yield per 100,000 (+ Conf. Interval)
~~≤50~~	~~26,101~~	~~7~~	~~27 (11-55)~~
51-100	37,787	11	29 (15-52)
101-200	36,548	41	112 (80-152)
>200	13,028	38	292 (206-400)
unknown	2,837	0	-
Total	**116,301**	**97**	**83 (67-100)**

- Screening immigrants from countries with a TB incidence ≤50/100,000 was discontinued per 1/1/2015 (Van den Berg, Eur Resp J 2017)
- **Based on this evaluation screening was also stopped per 1/4/2019 for immigrants from countries with TB incidence 50-100 per 100,000, e.g. China, Russia.**

Low yield of screening asylum seekers from countries with a tuberculosis incidence of <50 per 100 000 population

Gerard de Vries[1,2], Job van Rest[1], Wieneke Meijer[3], Bert Wolters[4] and Rob van Hest[4,5]

Eur Respir J 2016; 47: 1870–1872

TABLE 1 Results of screening asylum seekers in the Netherlands from countries with a tuberculosis (TB) incidence <50 per 100 000 people, 2011–September 2015

	Number screened	TB identified *via* screening	TB prevalence of screening per 100 000	95% CI
TB incidence in the country of origin per 100 000[#]				
0–9.9	423			
10.0–19.9	34 825	8	23.0	10.7–43.6
20.0–29.9	3496			
30.0–39.9	166			
40.0–49.9	6529	4	61.3	19.5–147
Total	45 439	12	26.4	14.3–44.9
Top 5 countries[#]				
Syria[¶]	31 470	7	22.2	9.7–44.0
Iraq[+]	5327	3	56.3	14.3–153
Iran[§]	3086			
Former non-European Union Yugoslav countries[f,##]	2051	2	97.5	16.4–322
Albania[¶¶]	547			

Data are presented as n, unless otherwise stated. [#]: TB incidence according to the World Health Organization in 2013 [12]; [¶]: incidence 15 per 100 000; [+]: incidence 45 per 100 000; [§]: incidence 22 per 100 000; [f]: TB incidence of Bosnia and Herzegovina, Macedonia, Montenegro and Serbia were weighted according to population; [##]: incidence 25 per 100 000; [¶¶]: incidence 18 per 100 000.

NNS for Syrian asylum seekers: 31,470 / 7 = 3,787

NNS (number needed to screen = inverse of prevalence)

High TB incidence rates in NL among asylum seekers from Eritrea (blue) and Somalia (red) in first 5 years after arrival

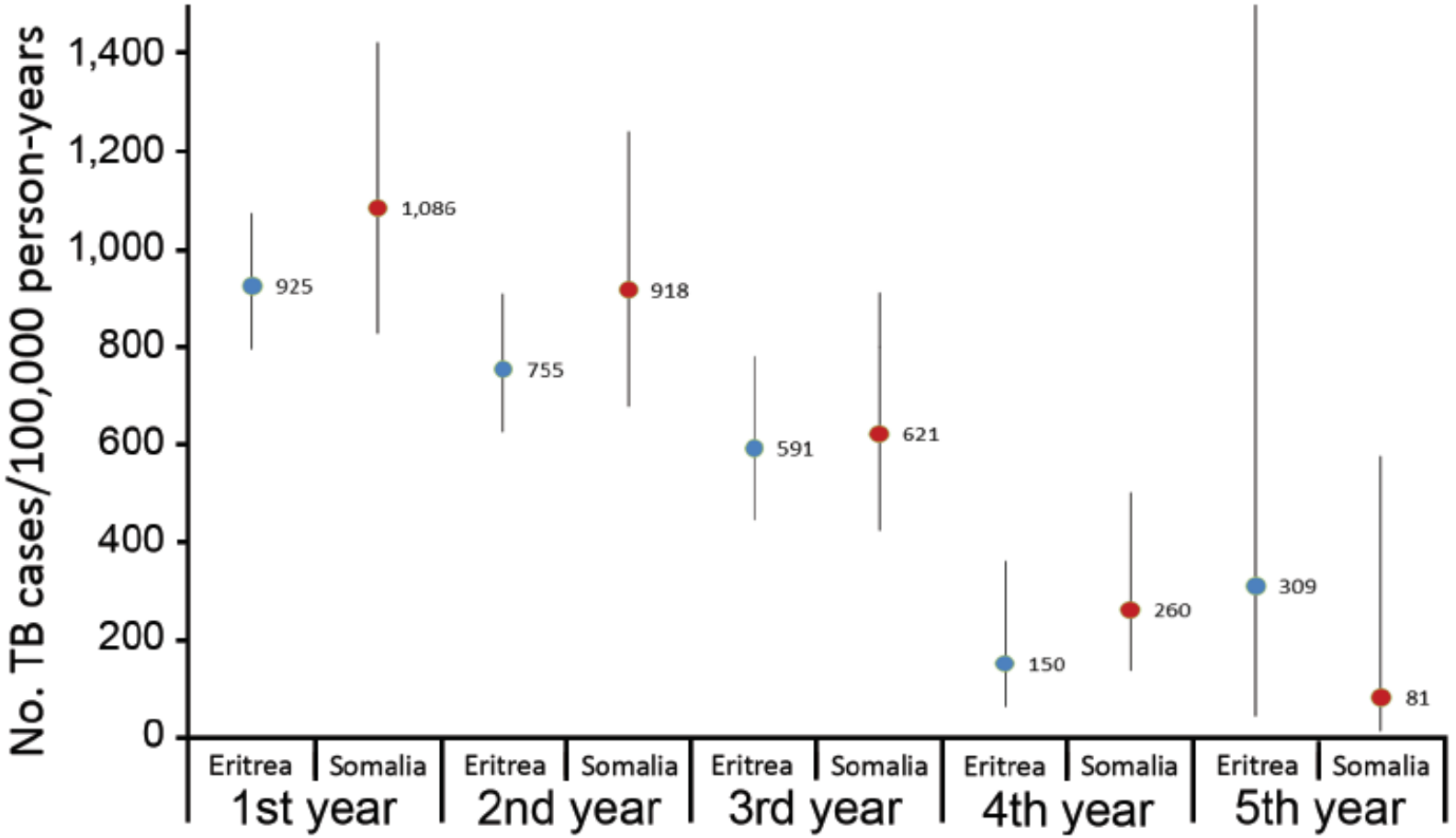
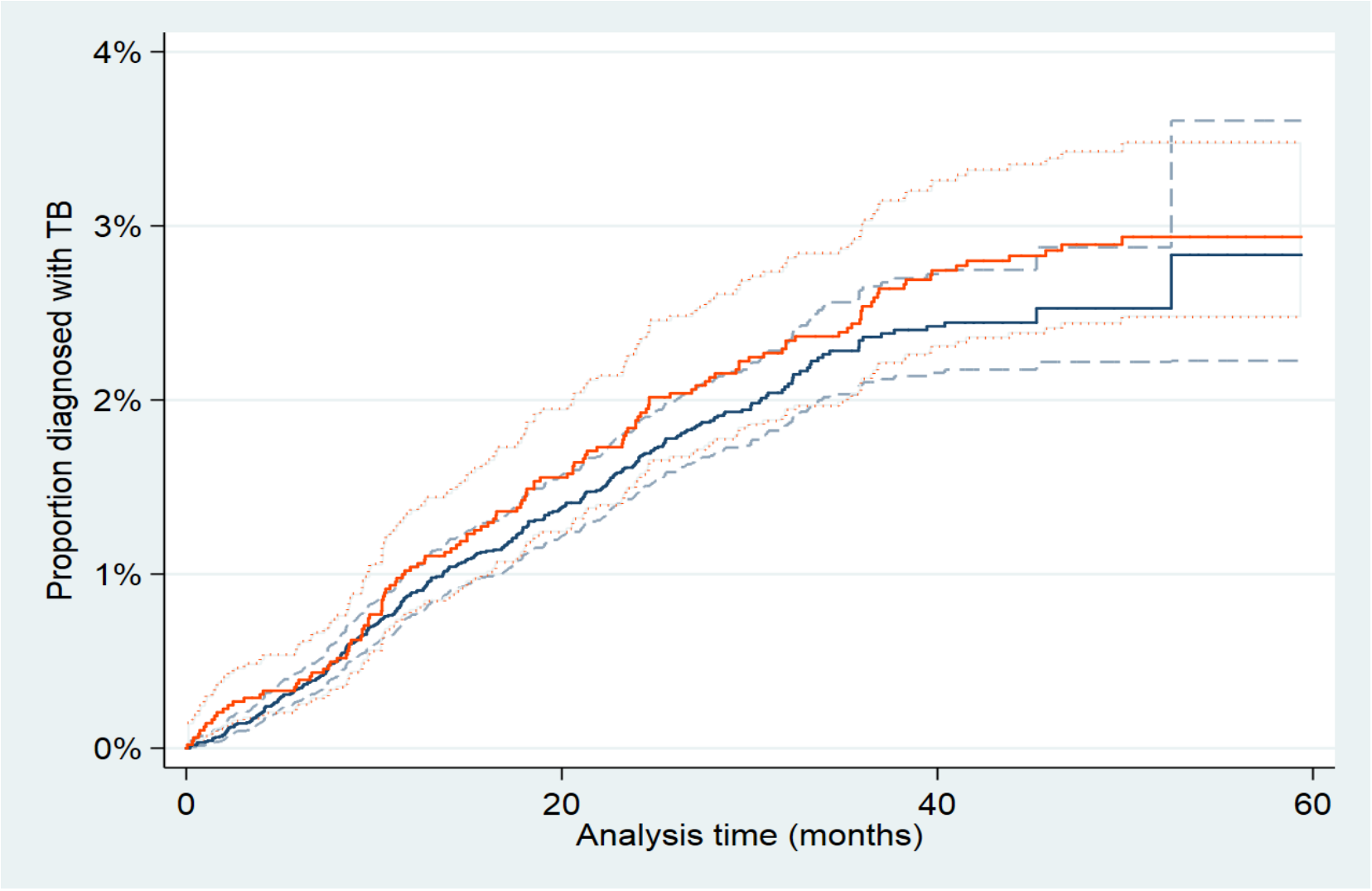


Figure 1. Trend of TB incidence rates (cases/100,000 person-years) of asylum seekers arriving from Eritrea and Somalia in the Netherlands, 2013–2017, by year after arrival. Error bars indicate 95% CIs; upper limit of the 95% CI for persons from Eritrea in the fifth year after arrival (2017) is 2,195. TB, tuberculosis.

Van den Boogaard, Emerging Infect. Dis, 2020

High TB incidence rates in NL among asylum seekers from Eritrea (blue) and Somalia (red) in first 5 years after arrival



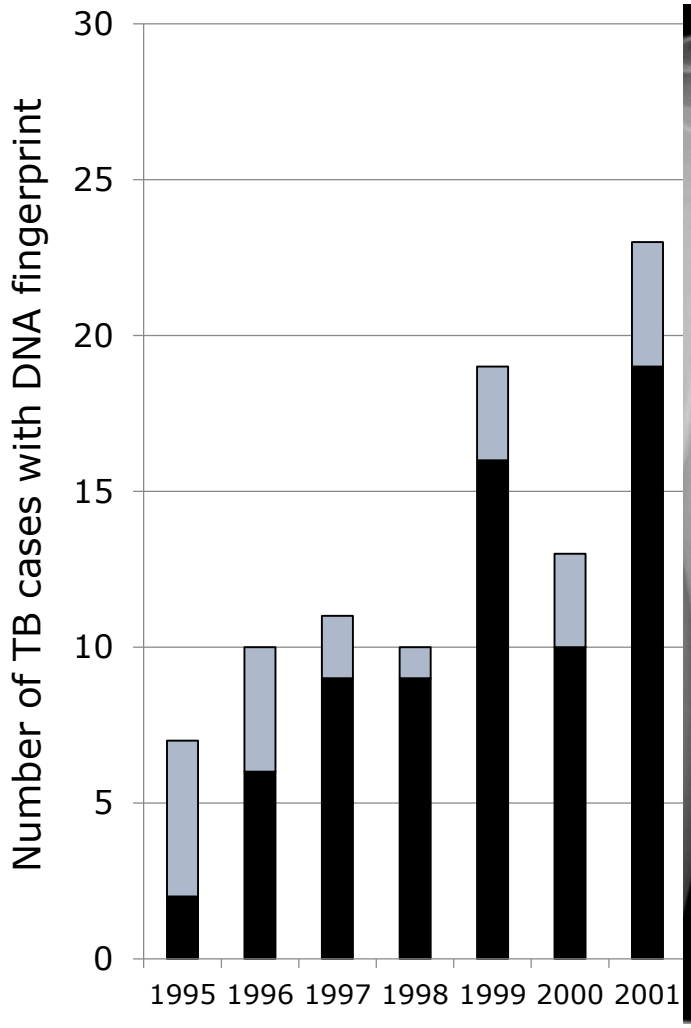
Excluding cases found at screening at arrival (prevalence about 300/100,000)

Van den Boogaard, Emerging Infect. Dis, 2020

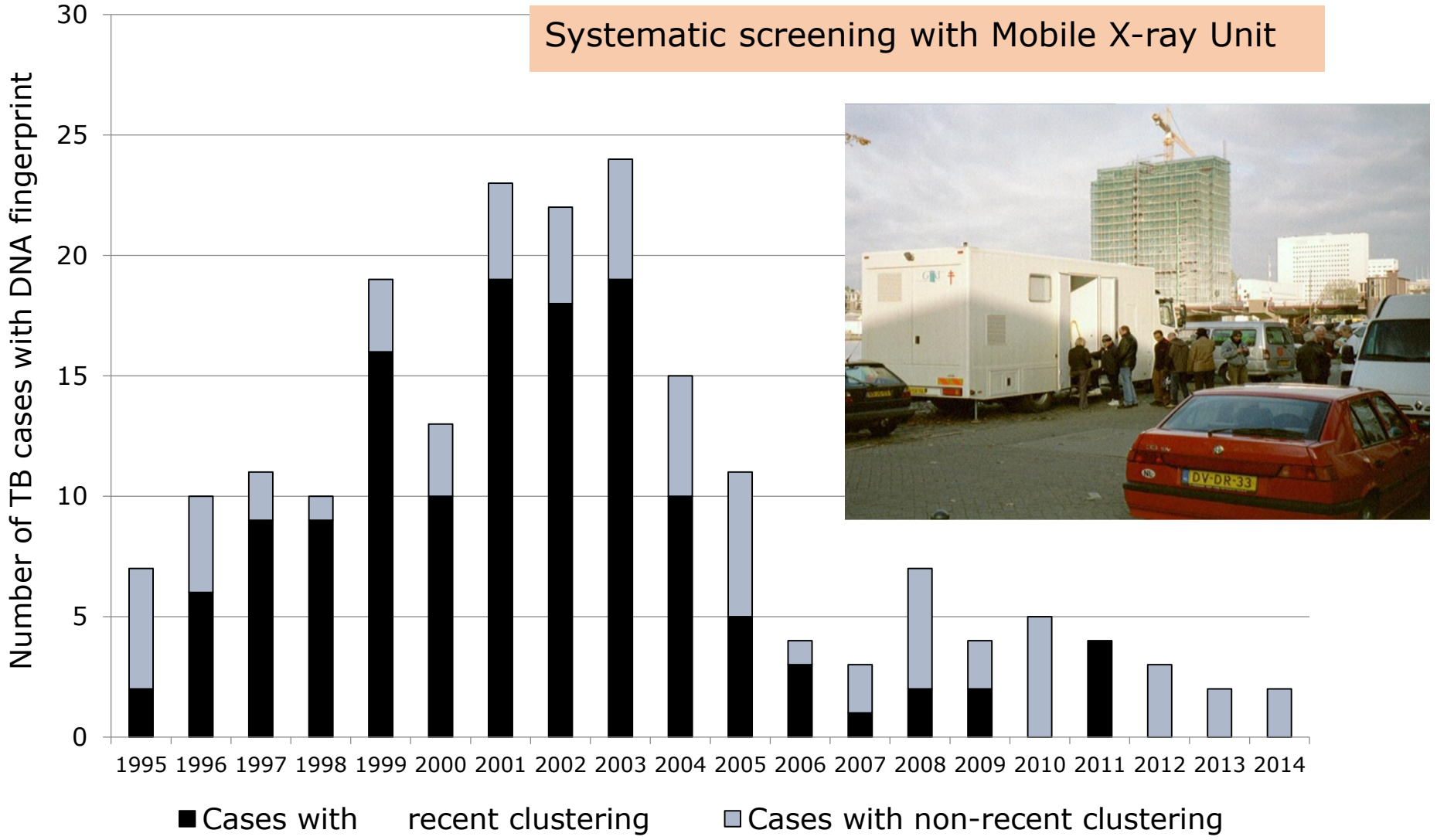
Lessons learned screening immigrants

- **A monitoring and evaluation framework is essential to regularly assess the yield/‘the number needed to screen’.**
- **Large differences in the yield of screening; related to country of origin of migrant and the migration route/reason.**
- **Screening efficiency can be increased by targeting those at highest risk.**
- **Substantial part of immigrants have normal chest X-ray at entry screening but develop TB later. Need to screen for TB infection.**

TB among homeless/drug users in Rotterdam



TB among homeless/drug users in Rotterdam



Lessons learned screening homeless/drug users

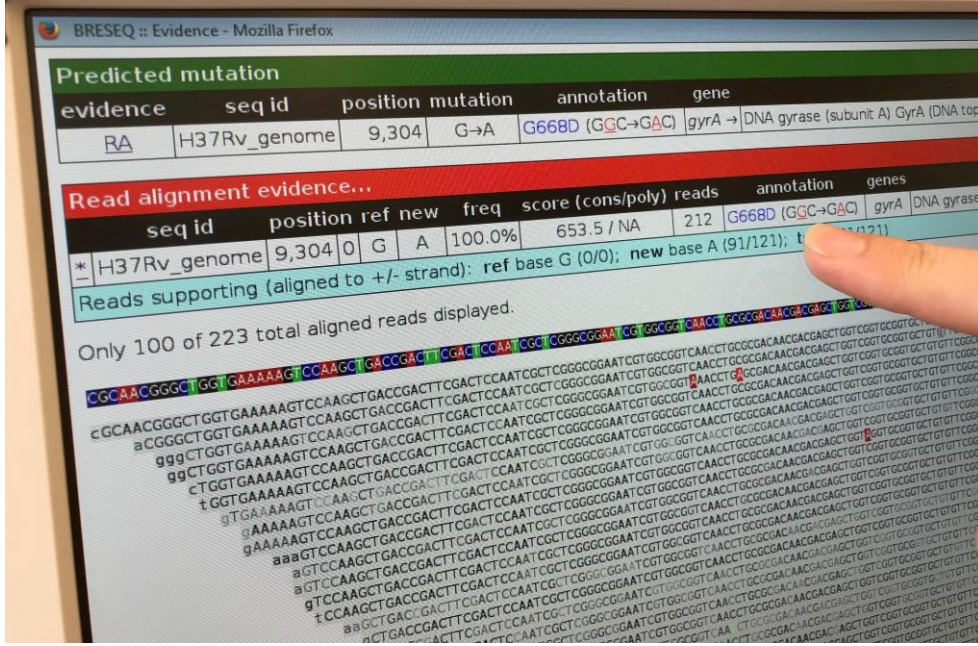
- **Molecular typing/DNA fingerprinting identified an outbreak.**
- **Systematic screening (2x per year) reduced TB, and controlled transmission of the outbreak strain (De Vries, AJRCCM, 2007).**
- **Patient support was essential to complete treatment ('find & treat').**
- **Informed by (molecular) epidemiology and screening results, screening was gradually reduced and eventually stopped because of low yield (and high NNS) (Van Hest, ERJ, 2016).**

TABLE 1 Number of tuberculosis (TB) cases in Rotterdam May 2002–2014

	TB cases in Rotterdam (a)	Homeless/illicit drug-using TB cases in Rotterdam (b)	Proportion homeless/illicit drug-using TB cases (b/a)	TB cases identified by MDXU TB screening (c)	Number of screenings (d)	Number needed to screen (d/c)	Yield (of target population) (c/b)
May–December 2002	100	17	17.0%	11	1615		
2003	171	25	14.6%	10	2789		
2004	164	18	11.0%	1	2430		
2005	130	11	8.5%	6	2265		
Outbreak management	**565**	**71**	**12.6%**	**28**	**9099**	**325**	**39.4%**
2006	127	5	3.9%	2	1951		
2007	109	4	3.7%	0	1567		
2008	100	10	10.0%	1	1308		
2009	129	6	4.7%	0	1231		
2010	110	5	4.5%	1	839		
2011	89	4	4.5%	0	814		
2012	98	4	4.1%	0	370		
2013	81	2	2.5%	0	272		
2014	68	2	2.9%	0	366		
Post-outbreak period	**911**	**42**	**4.6%**	**4**	**8718**	**2180**	**9.5%**

Annual number of all homeless persons and illicit drug users notified with TB in Rotterdam, annual proportion of homeless or drug using TB cases relative to the total caseload, annual number of homeless or drug using TB cases identified by the mobile digital X-ray Unit (MDXU), annual number of screenings, annual efficiency (number needed to screen) and annual yield (proportion of homeless persons and illicit drug users identified by the MDXU relative to the total number of homeless or drug using TB cases (target population) of the intervention.

DNA fingerprinting



RFLP
1993-2008

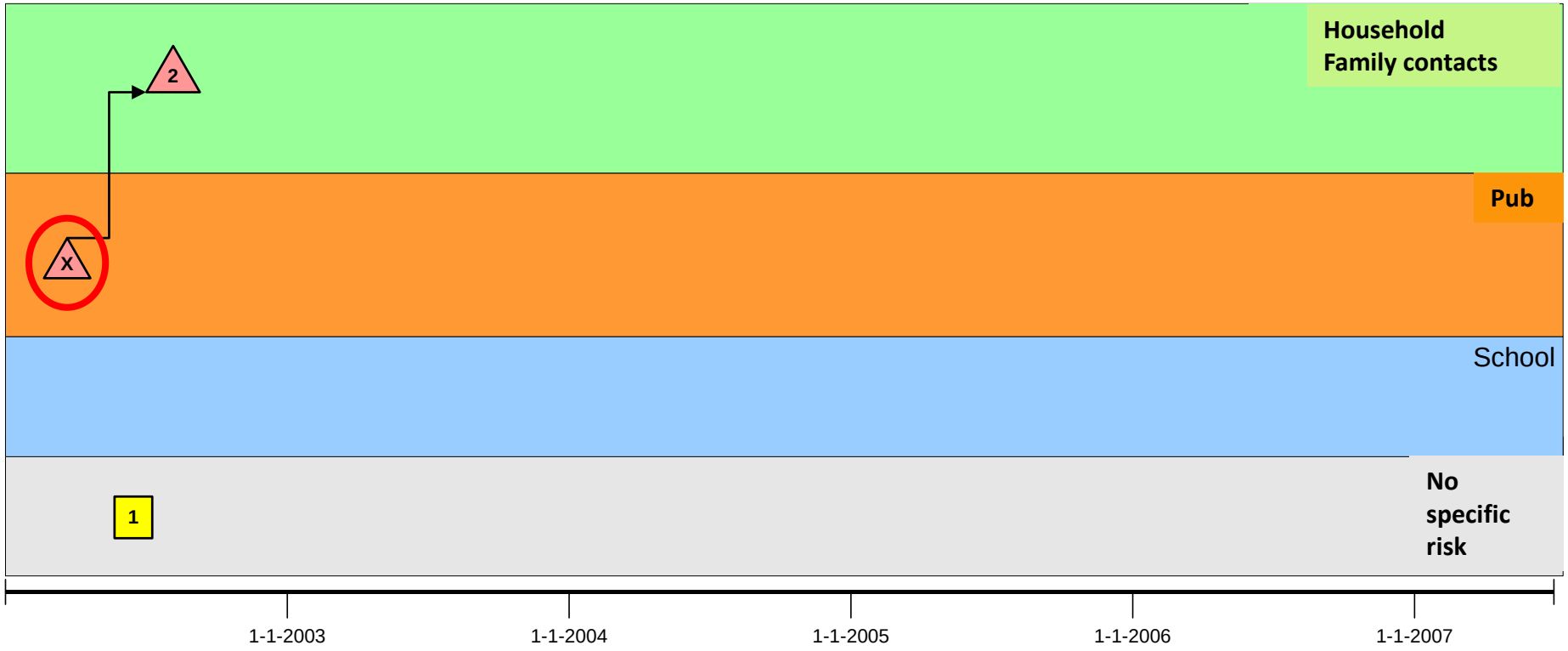
2004-2008

VNTR
2009-2018

2016-2018

WGS
2019-now

Outbreak in a Rotterdam pub



1-1-2002

1-7-2007

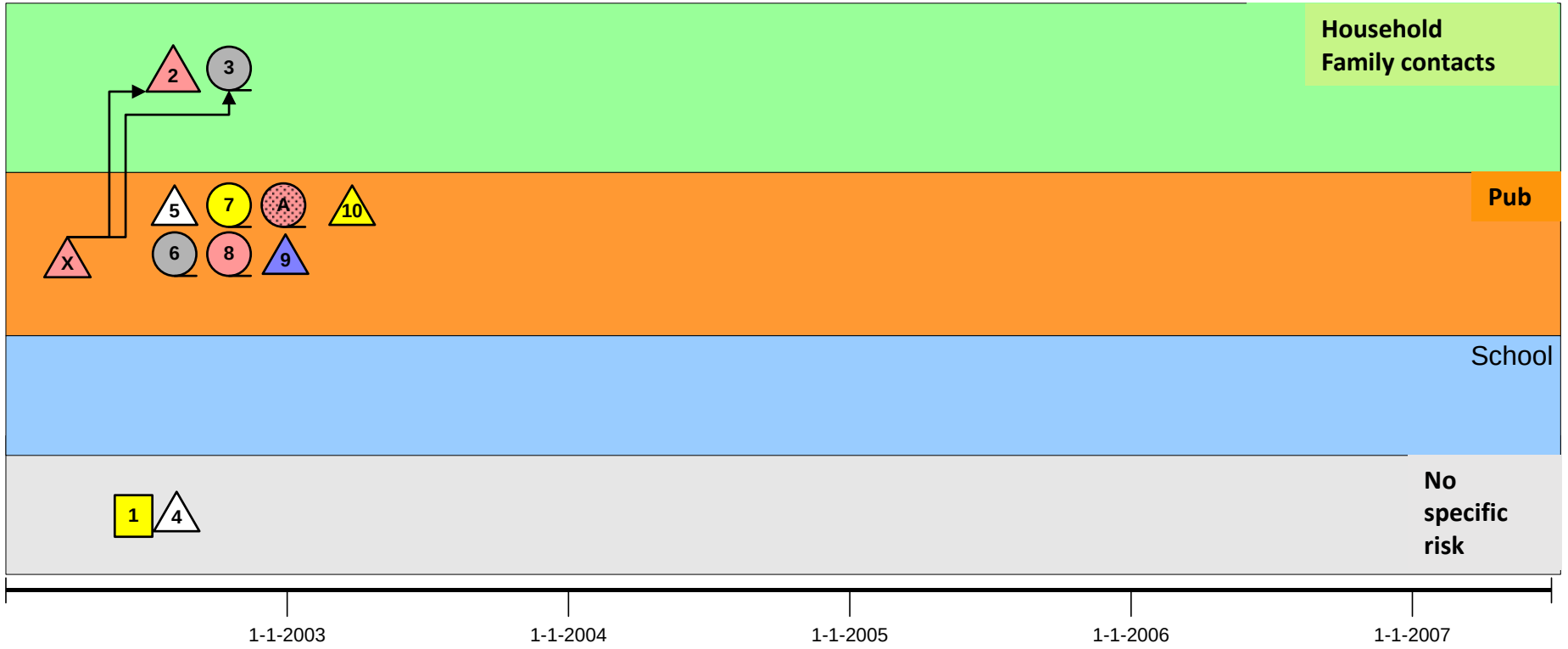
Type of tuberculosis

- Pulmonary TB (smear positive)
- Pulmonary TB (smear negative)
- Extrapulmonary TB

Ethnic background

- Joegoslavië
- Suriname
- Marokko
- Nederland
- Andere

Outbreak in a Rotterdam pub



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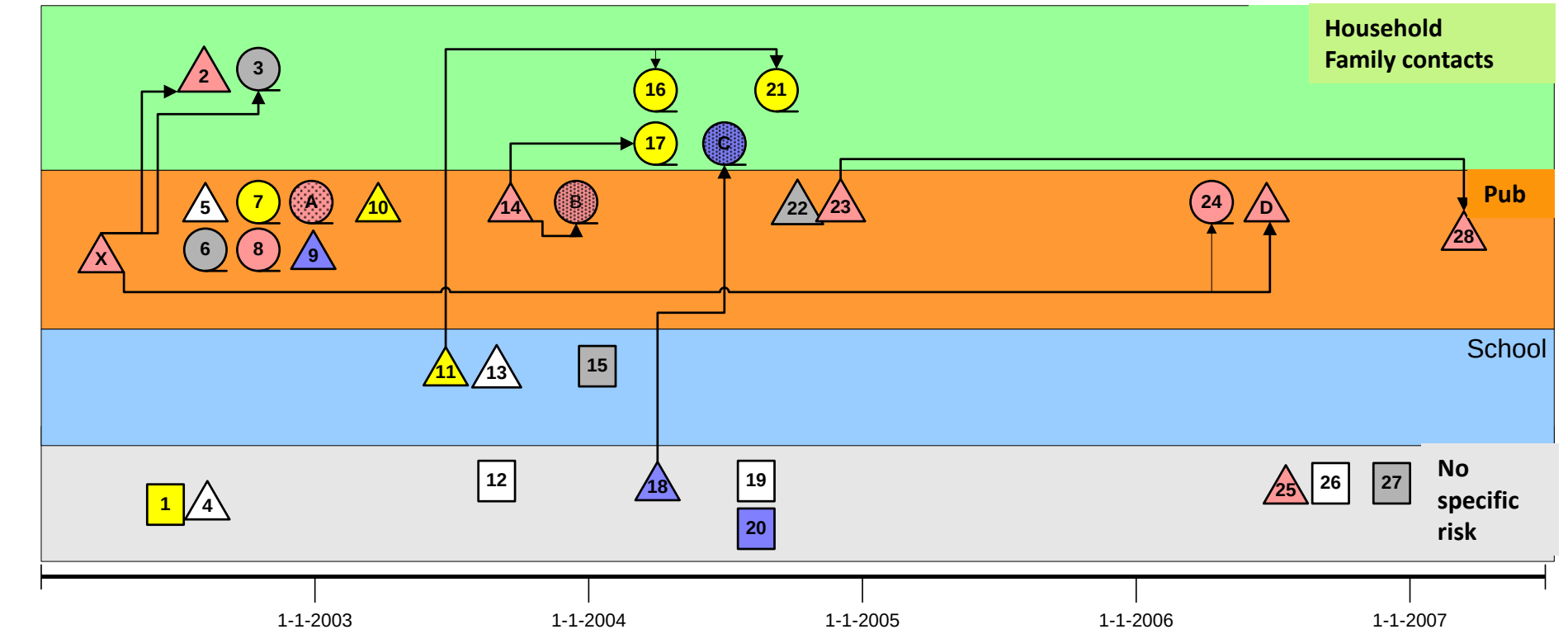
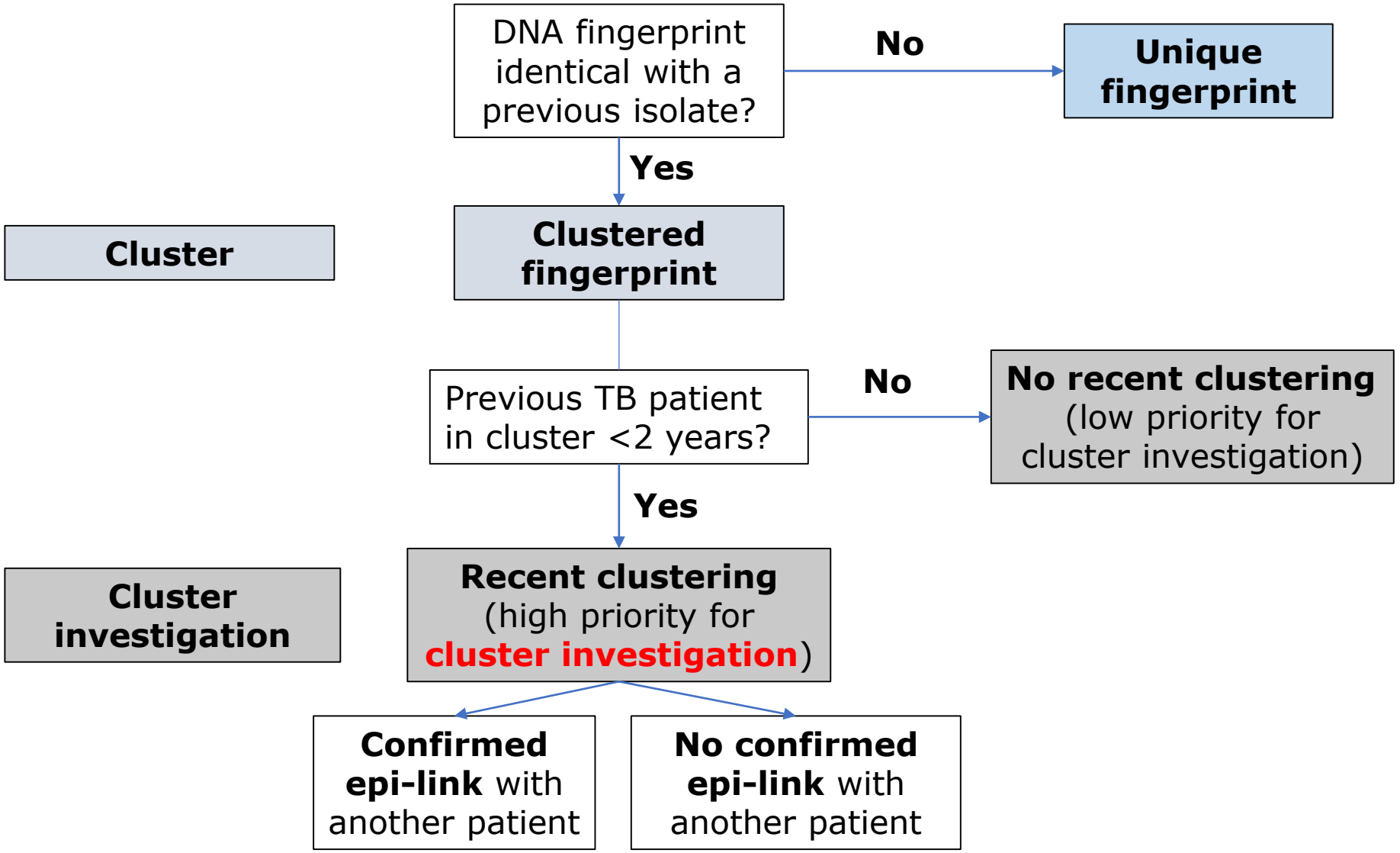


De Vries. BMC Infect Dis. 2009

Algorithm for cluster investigation



Lessons learned from DNA fingerprinting

- **Powerful tool to identify outbreaks.**
- **Nowadays in the Netherlands, good instrument to document absence of transmission (in 2020 only 4 clusters increased with ≥3 cases).**
- **It helps to identify nosocomial transmission.**
- **WGS also provides information on drug-resistance mutations. RIVM replaced per 1/1/2020 routine phenotypic drug-susceptibility testing by detection of resistant mutation genes in WGS.**

TB infection
previously latent TB infection (LTBI)

Policy and practice of programmatic management of latent tuberculosis infection in The Netherlands

Gerard de Vries[a,b,*], Rob van Hest[c,d], Marleen Bakker[e], Connie Erkens[a], Susan van den Hof[a,f], Wieneke Meijer[g], Karen Oud[h], Erika Slump[b], Jaap van Dissel[b]

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 7 (2017) 40–48

Table 1
Latent tuberculosis infection indicators in The Netherlands, 2015.

Target group for LTBI screening in the Netherlands	Number eligible for LTBI screening	Number screened for LTBI	Screening coverage	Number LTBI cases diagnosed and reported to NTR	Number cases that initiated LTBI treatment	LTBI treatment coverage	Number completed LTBI treatment (2014)	LTBI completion rate (2014)	Number with active TB reported to NTR	TB incidence among target group (per 100,000)
All contacts of TB patients	*	*	*	867	679	78%	505/575	88%	65	
People living with HIV	865 ‡	Unknown	–	3	3	100%	4/4	100%	36	
Patients initiating / on TNF-alpha blocking treatment	Unknown	Unknown	–	192**	177**	92%	151/169**	89%	14	
Patients preparing for (or with) organ or hematologic transplantation	Unknown	Unknown	–						5	
Health care workers	Unknown	Unknown	–	21	17	81%	27/29	93%	6	
Travelers	Unknown	Unknown	–	22	18	82%	20/20	100%		
Others***	Unknown	Unknown	–	328	234	79%	194/216	90%		
Total	Unknown	Unknown	–	**1433**	**1128**	**79%**	**901/1013**	**89%**		

Note: There is no policy in the Netherlands to screen patients with renal insufficiency/ dialysis or with silicosis for LTBI.
LTBI: latent tuberculosis infection; NTR: Netherlands Tuberculosis Register; TB: tuberculosis.

* Data is available of the number of contacts eligible for TB examination in source tracing and contact investigation (n = 7162) related to a TB patient diagnosed in 2014, the number of contacts actually screened for LTBI (n = 5446) and the screening coverage (76%). The dataset allows a breakdown in intensity of contacts, i.e. household and close contacts, but not (yet) for age group, such as children.

** LTBI screening data in the NTR has been combined for patients initiating TNF-alpha blocking therapy and preparing for transplantation.

*** Others: mainly pre-employment, pre-travel and other low-risk LTBI screening.

How to screen for (and treat) TB infection?

How to screen?

1. Two-step approach, initial TST testing and if TST ≥5 mm (or 10 mm) than IGRA.
2. In clinical risk groups both tests are used at the same time to increase sensitivity.

How to treat (TPT)?

1. 3HR
2. 6H
3. 4R
4. (rifapentine not available)

Monitoring latent tuberculosis infection diagnosis and management in the Netherlands

Connie G.M. Erkens[1], Erika Slump[2], Maurits Verhagen[3], Henrieke Schimmel[2], Gerard de Vries[1,2], Frank Cobelens[1,4] and Susan van den Hof[1,4]

Eur Respir J 2016; 47: 1492–1501

1993-2013 (21 years):

- 37,729 LTBI cases reported;
- 28,931 (77%) started preventive treatment;
- 85% completed treatment

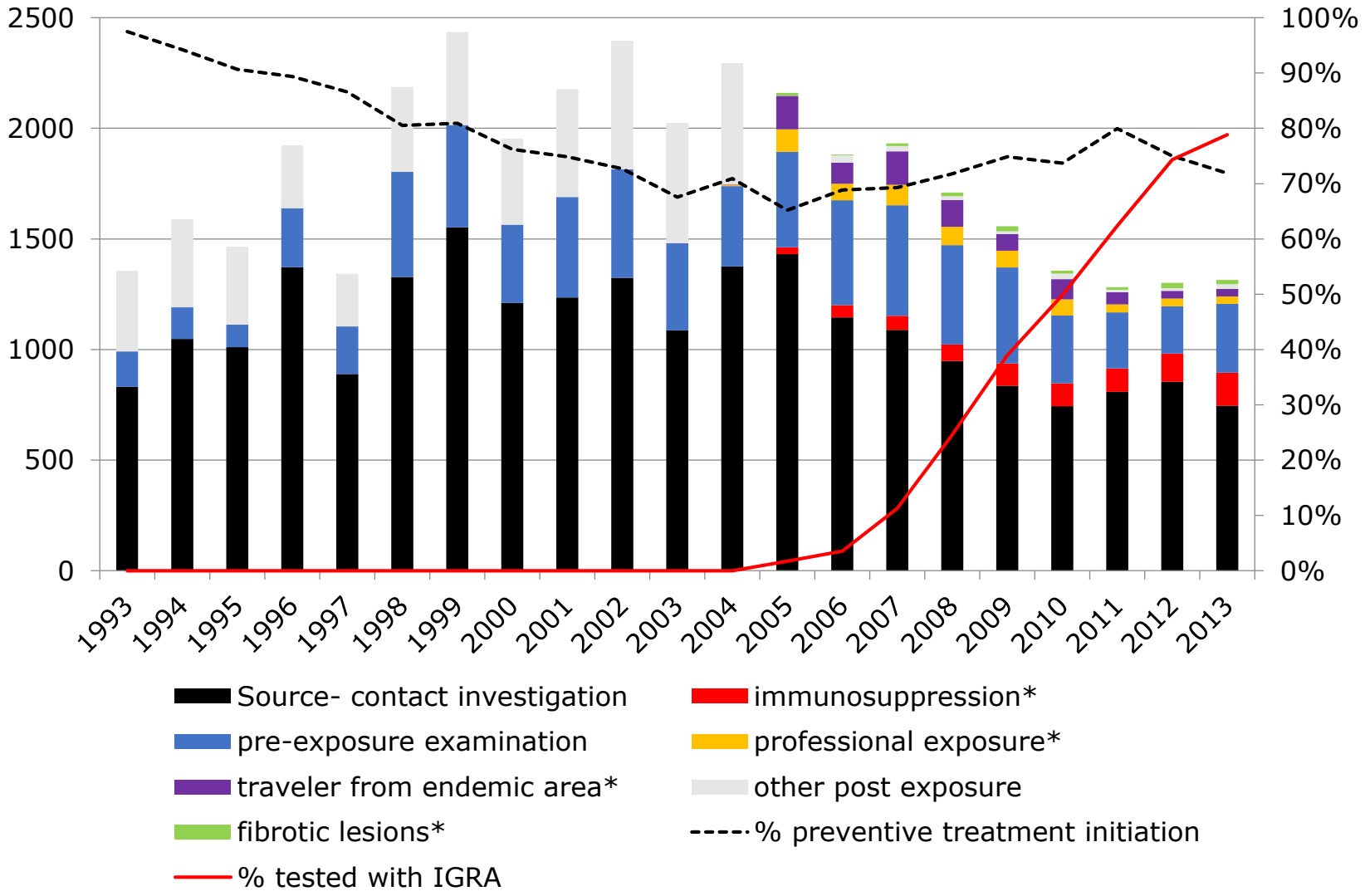


FIGURE 1 Number of cases with latent tuberculosis infection by target group for screening, and percentage screened with interferon-γ release assay (IGRA) and preventive treatment initiation (1993–2013). #: reported since 2005.

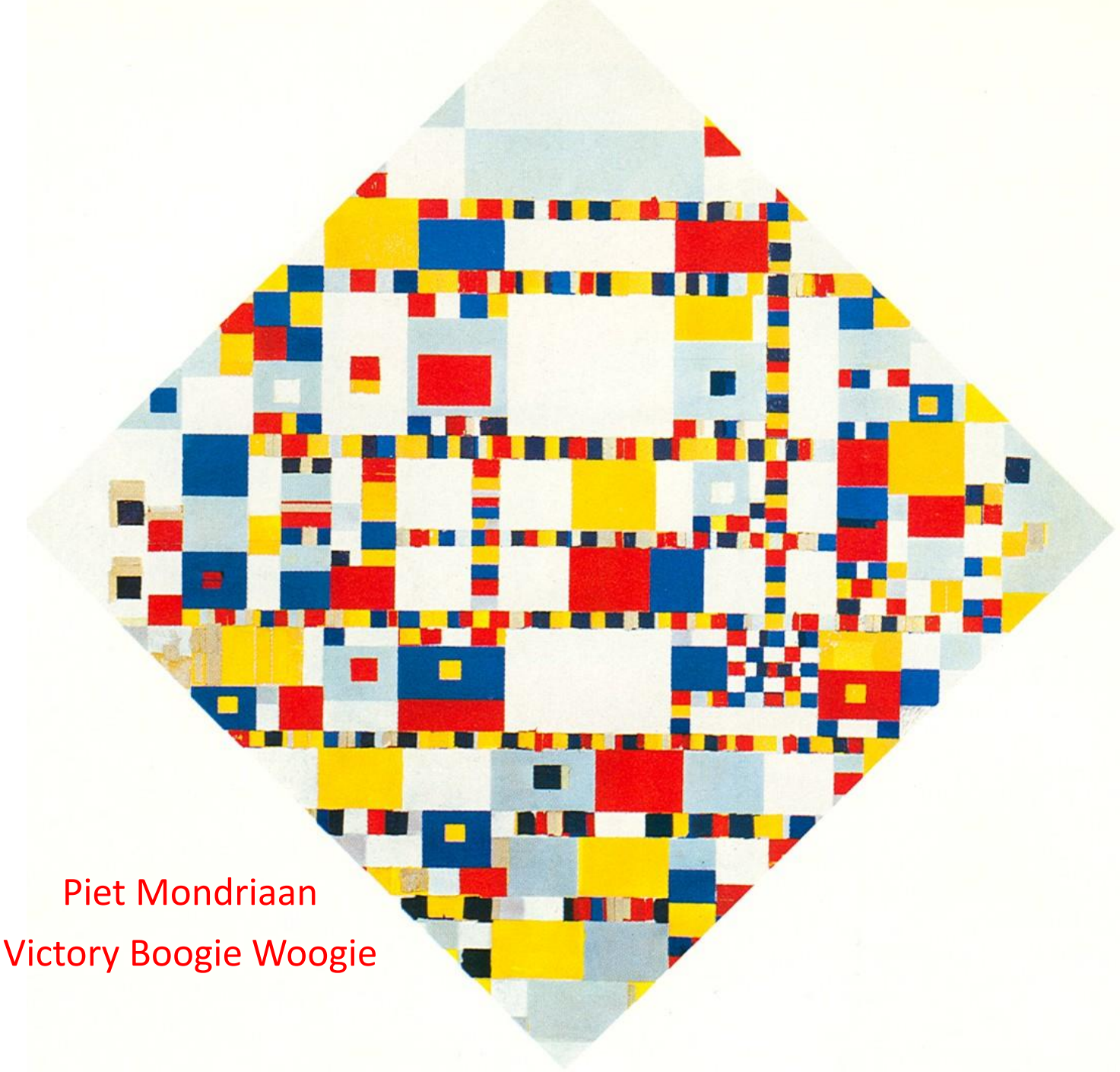
Studies on screening (im)migrants for TB infection

	Screened	TB infection /TB disease	Started Rx	Completed Rx	Publication
Immigrants (all ages)	566	94 (17%) **+ 3 TB**	49 (52%)	34 (69%)	Spruijt, PloS One, 2019
Asylum seekers ≥12 from TB high-incidence countries	719	178 (25%) **+ 4 TB**	149 (84%)	129 (87%)	Spruijt, ERJ, 2019
Migrant community (Eritrea)	257	30 (12%) **+ 1 TB**	29 (97%)	28 (97%)	Spruijt, BMC Public Health, 2020

Changes in TB screening algorithms immigrants

Age	TB incidence in country of origin	'Regular' immigrants	Asylum seekers
<12 years			LTBI test to replace CXR (not yet implemented)
<18 years		LTBI test replaced CXR (2015/2016)	
≥18 years (≥12 years asylum seekers)	50-100	n/a	CXR
	100-200	CXR	CXR
	≥200	CXR + LTBI test (2019)	CXR + LTBI test (2019)

Merci



Piet Mondriaan

Victory Boogie Woogie