



Extent and origin of resistance in *M. tuberculosis* in the Netherlands

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The 'royal touch'





Background

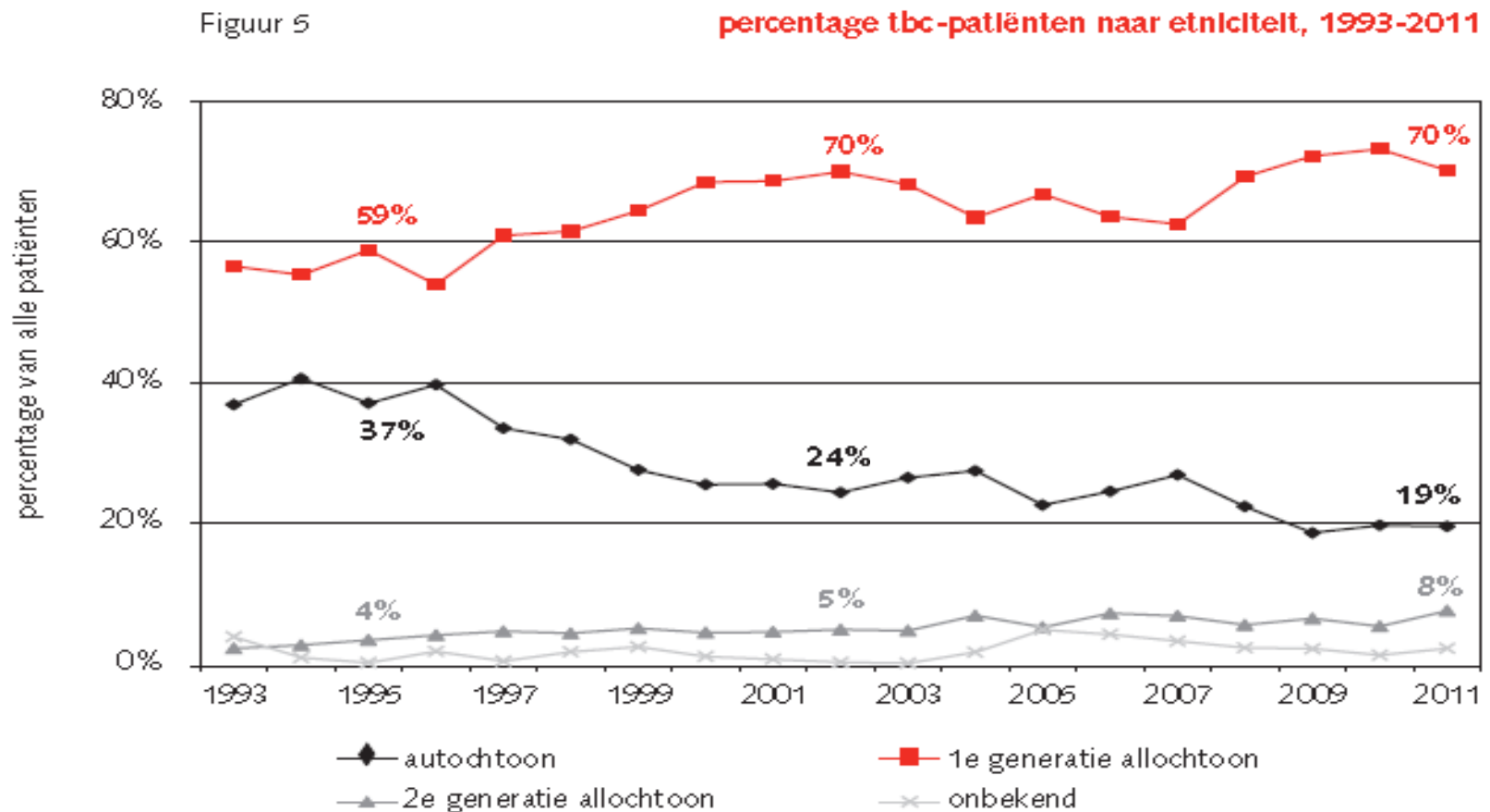
Origin and management of primary and acquired drug-resistant tuberculosis in The Netherlands: the truth behind the rates

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M. M. G. G. Sebek,* D. van Soolingen[‡]

- The majority of the resistant cases in the Netherlands were found in immigrants
- Small proportion of drug-resistant (DR) cases resulted from recent infection or treatment in the Netherlands

Background

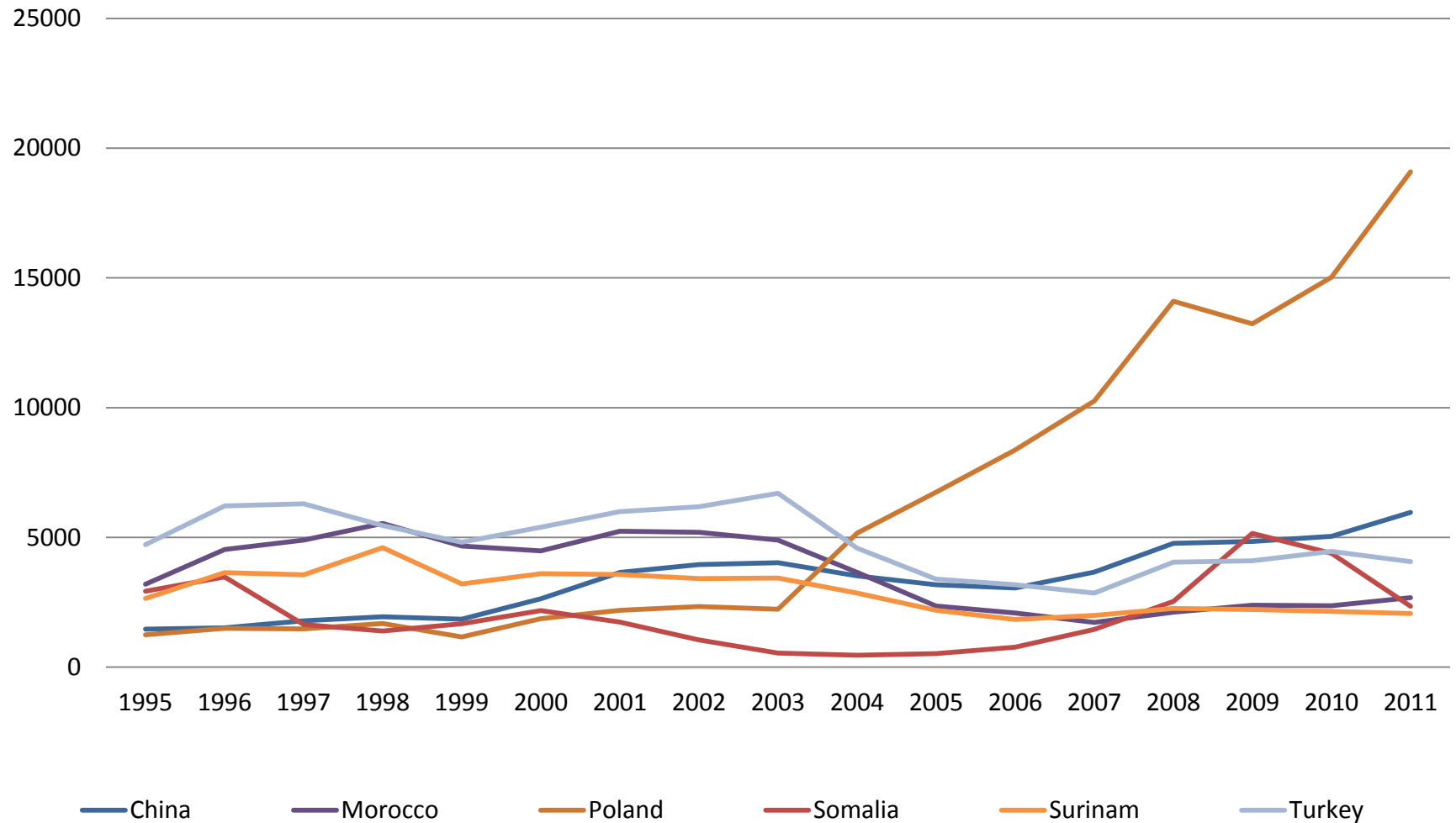
- Proportion of immigrants among TB patients have increased



Background



- Immigration trends have changed





Research questions

- What are the trends in resistance in *M. tuberculosis* in the Netherlands from 1993-2011?
- To what extent has drug resistance been acquired or transmitted in the Netherlands?



Methods

- Data was collected from 3 sources:
 1. Netherlands Tuberculosis Register (NTR): data on treatment history, case finding, patient characteristics, demographics and case management
 2. DNA fingerprint surveillance data from the NRL
 3. Epilink data: information routinely collected by TB public health nurses on the relationship between TB patients
- All patients notified with TB between 1993 and 2011 →
 - selection of all cases with *M. tuberculosis* positive cultures (n=14959)



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RESULTS – TRENDS IN RESISTANCE

Isolates **18294 (100%)**

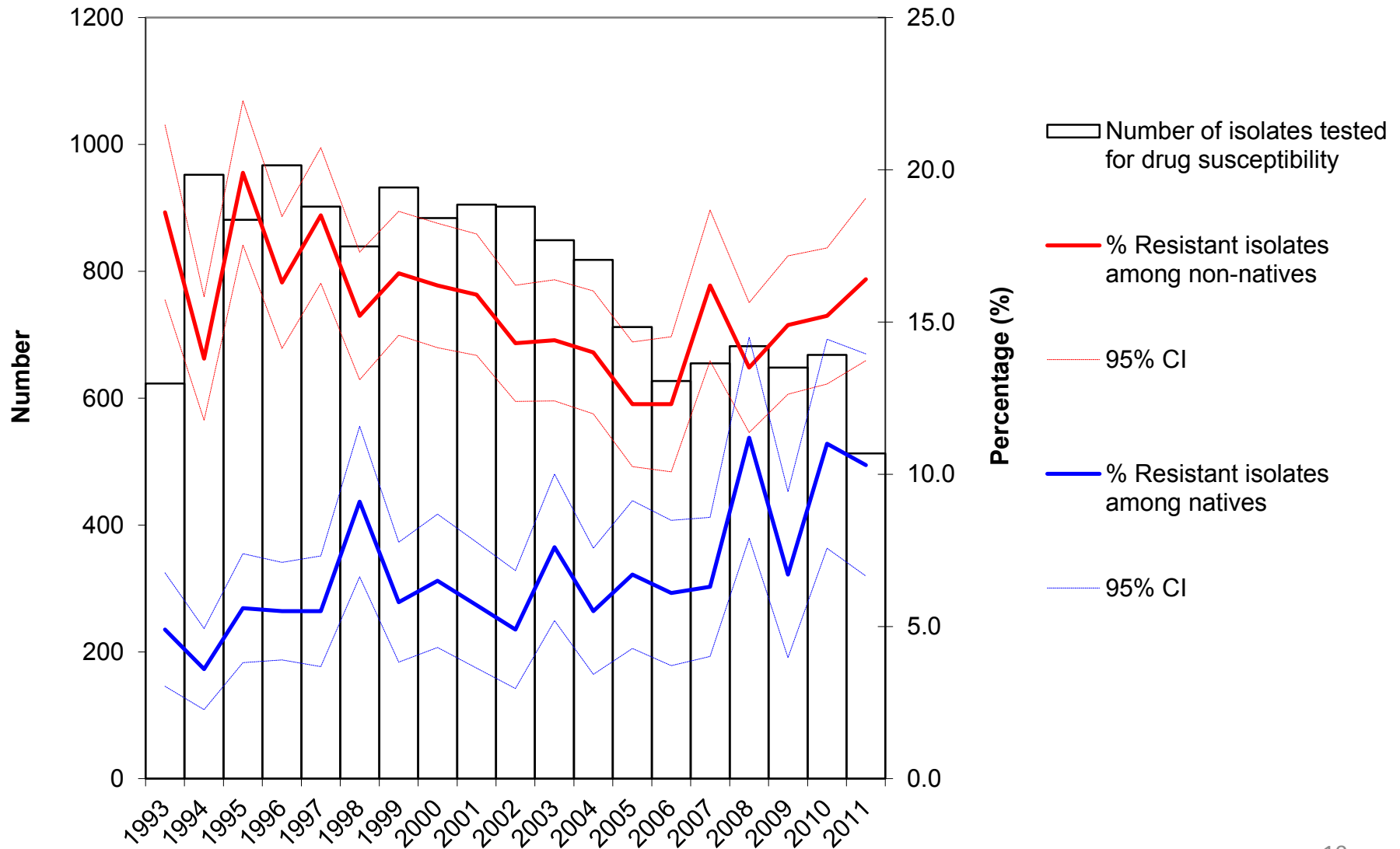
'Match with NTR' **15601 (85%)**

M. Tuberculosis strains,
confirmed by culture
14959 (96%)

Isolates tested for
susceptibility
14820 (99%)

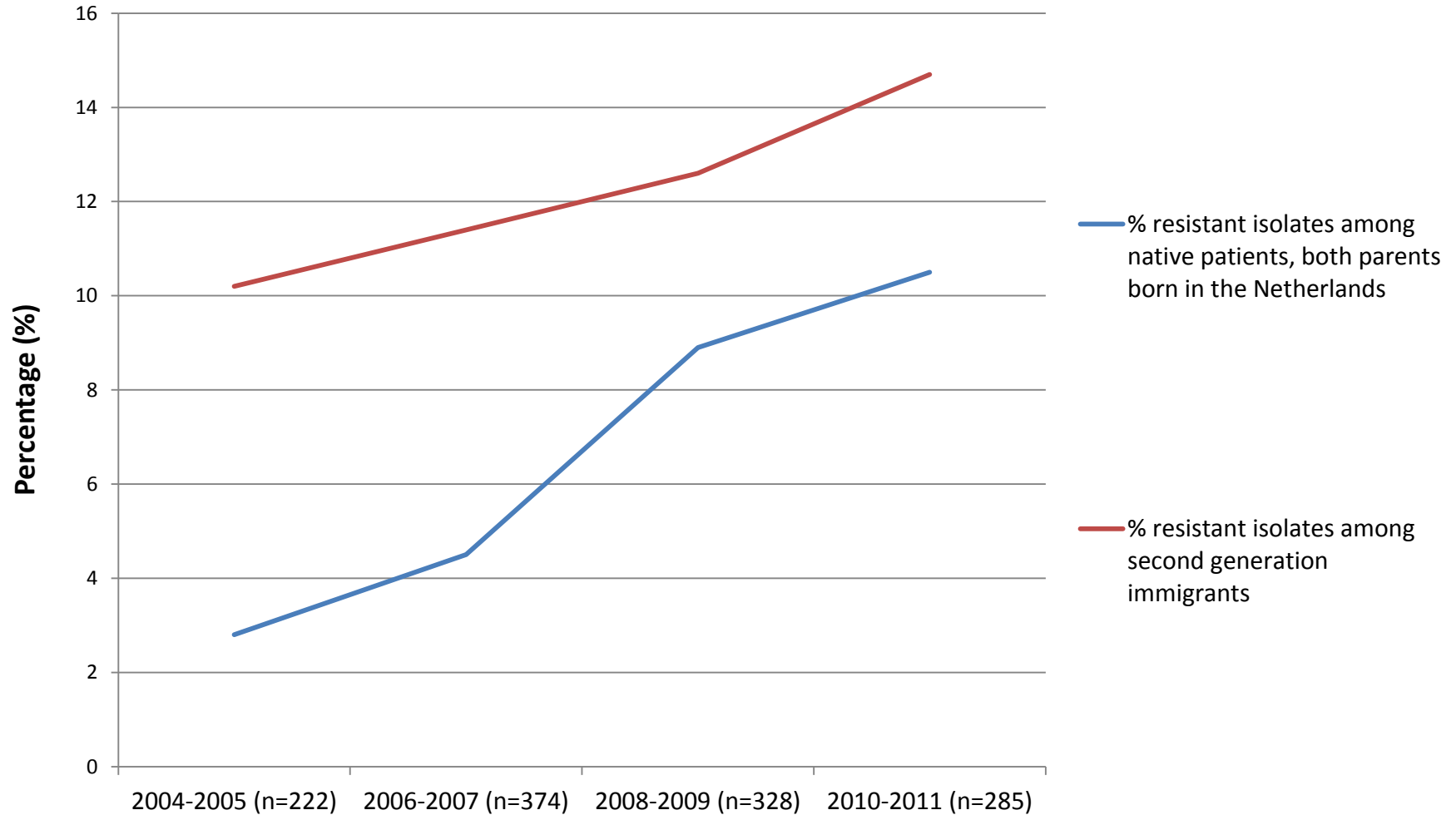
Isolates resistant to
≥1 drug
1890 (12.8%)

Percentage isolates with resistance to at least one drug



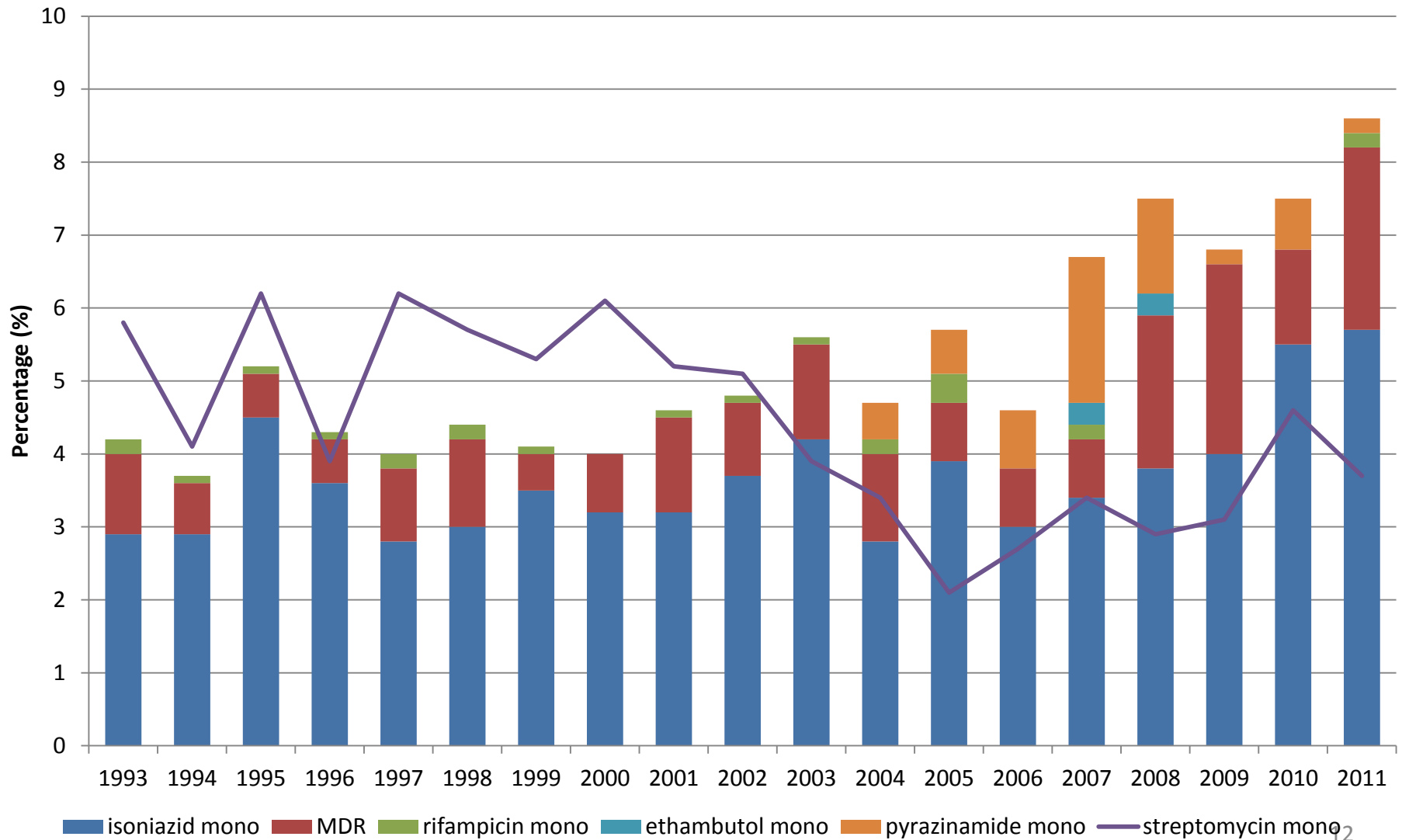


Trends in resistance among natives





Drug-specific trends in resistance

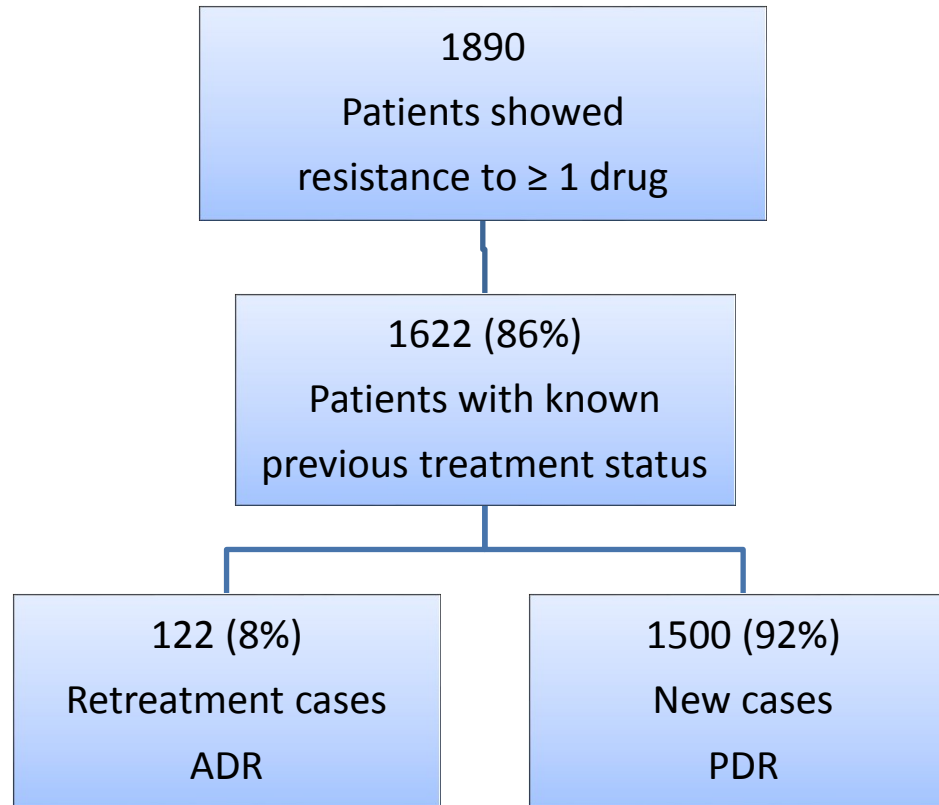




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RESULTS – ORIGIN OF RESISTANCE

Acquired or primary drug resistance?



- 92% of the resistant cases were PDR and 8% ADR
- This corresponds to 10% and 0.8% of all



Origin of resistance in 106 foreign-born ADR cases

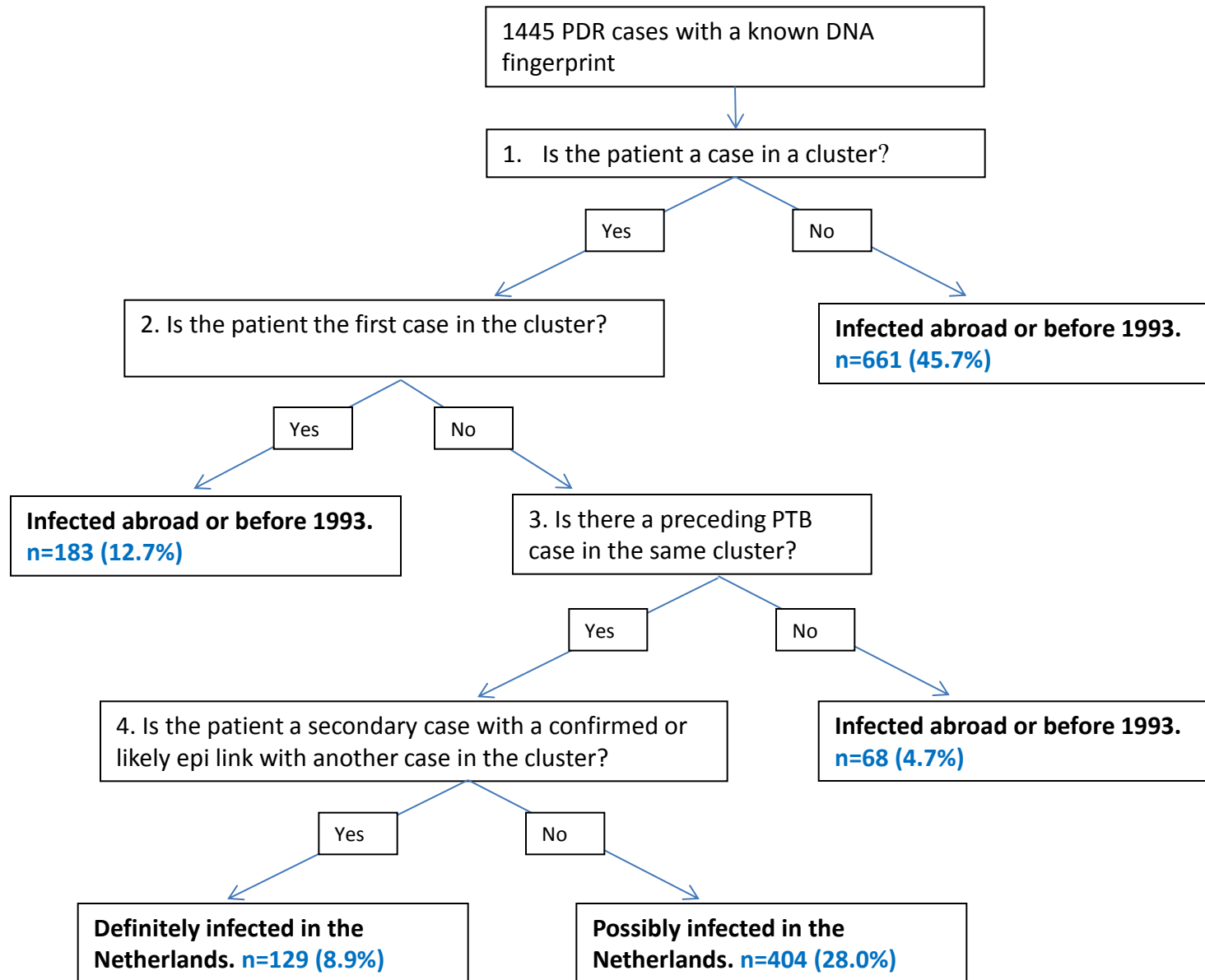
- 49 ADR patients (46%) acquired drug resistance abroad
- 29 ADR patients (27%) acquired drug resistance in the Netherlands
- Unknown for 28 ADR patients (26%)
- $29 + 16 = 45$ patients acquired drug resistance in the Netherlands



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RESULTS – TRANSMISSION OF RESISTANCE

Transmission classification tree for PDR cases





Summary

- Unexpected increasing trend in resistance among Dutch-born TB patients
- Resistance was mainly due to transmission of a resistant strain instead of acquired
- Transmission of resistance happened mostly abroad, but also in the Netherlands
- Acquired drug resistance occurred in the Netherlands in 45 cases

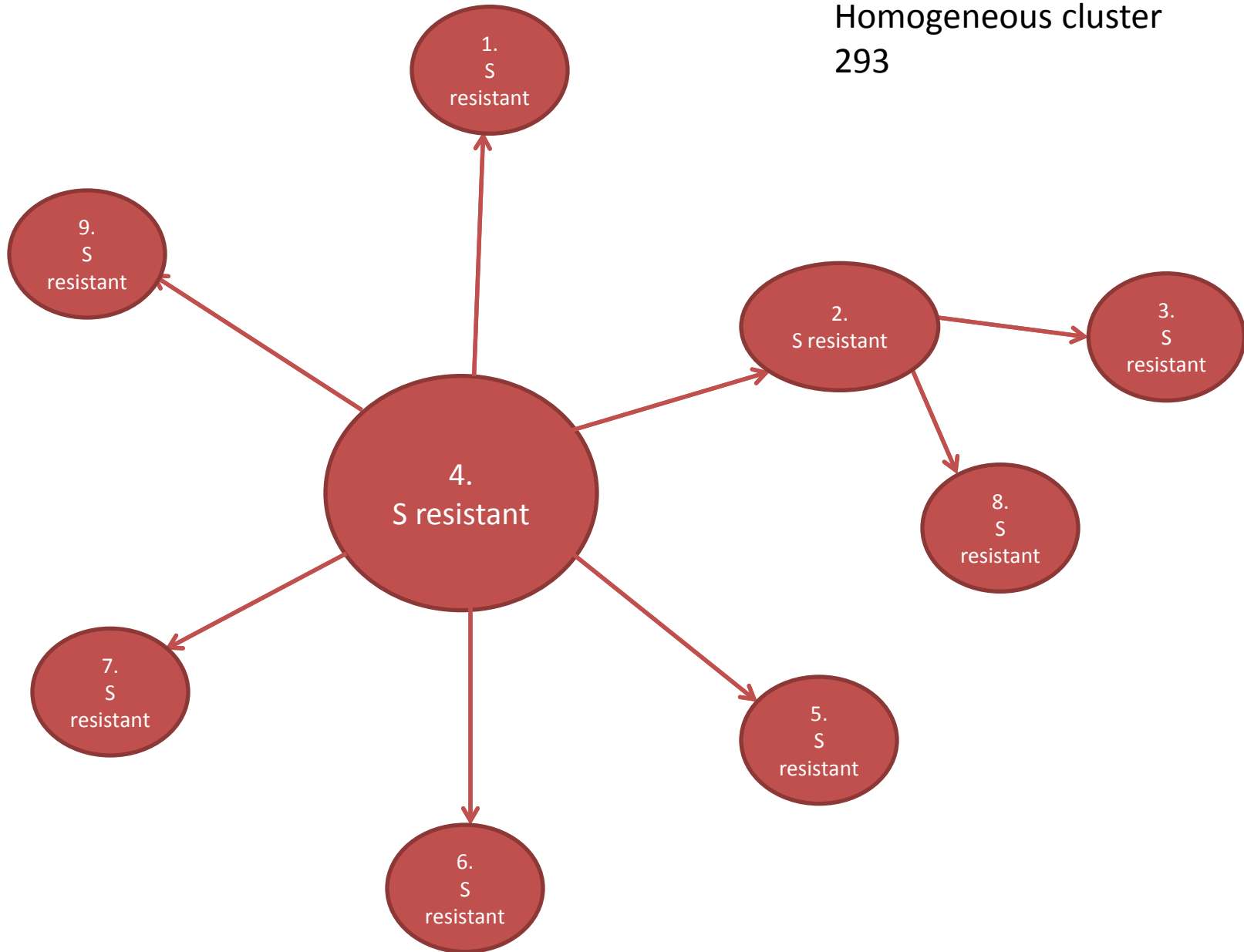


To be continued...

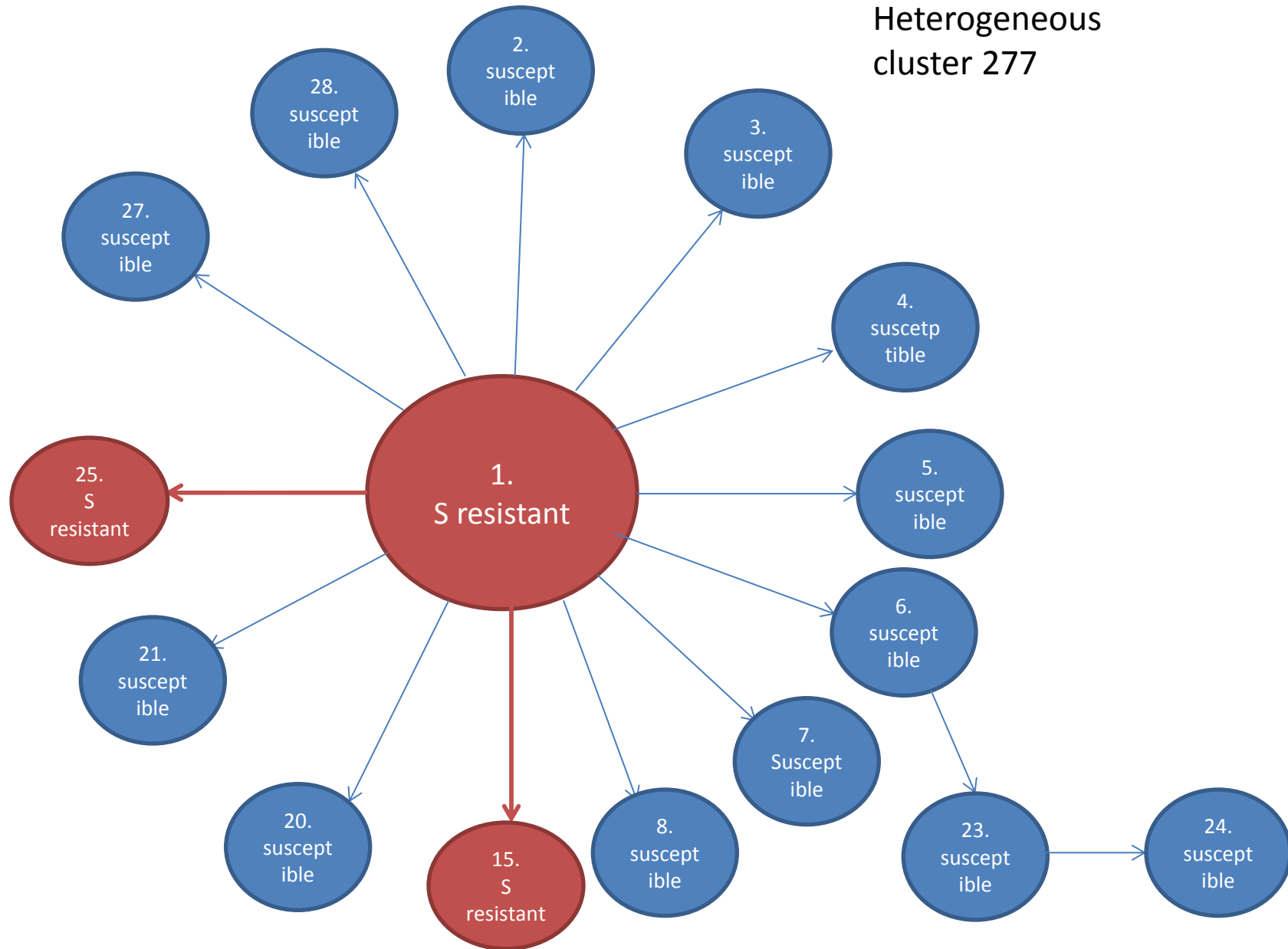
1. 45 Cases of drug resistance acquired in the Netherlands
 - a) Patient files
 - b) Information about previous treatment

2. Heterogeneous clusters (patients with different resistance profiles in one cluster)

Homogeneous cluster
293



Heterogeneous cluster 277





To be continued...

1. 45 Cases of drug resistance acquired in the Netherlands
 - a) Patient files
 - b) Information about previous treatment

2. Heterogeneous clusters (patients with different resistance profiles in one cluster)
 - a) Back to the laboratory and GGD'en:
 - i. Did the resistance profiles really differ?
 - ii. Was there confirmed transmission between cases?



Acknowledgements

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- Hanna Guimaraes

Thank you





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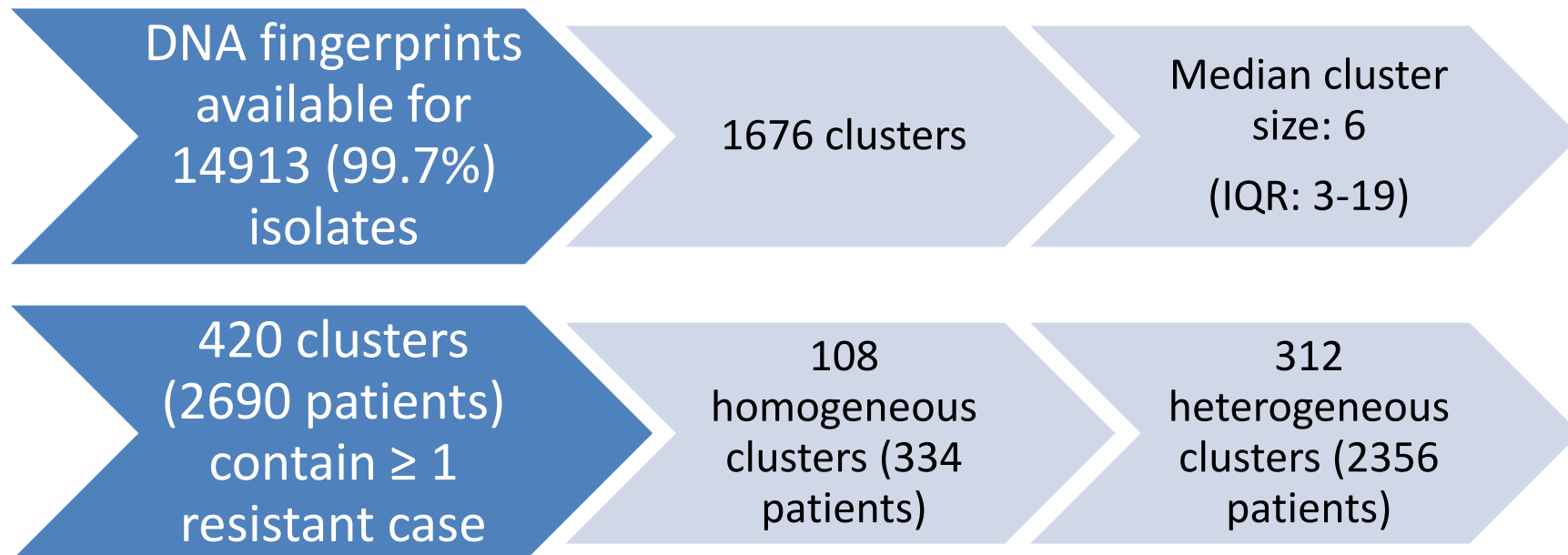
Determinants of resistance

	All isolates (n=14959)	Resistant isolates (n=1890)	Susceptible isolates (n=12930)	Adjusted OR* (95% CI)
Male gender (%)	60	58	60	1.02 (0.88-1.18)
→ Age (years) - mean (SD)	41 (20)	33 (15)	42 (20)	0.98 (0.97-0.98)
From urban area (%)	35	35	35	1.09 (0.94-1.28)
→ Non-native (%)	69	84	66	1.92 (1.55-2.38)
BCG vaccination (%)	50	67	48	1.06 (0.87-1.28)
Belonging to risk group (%)	62	74	61	1.15 (0.96-1.37)
→ Previous TB-treatment (%)	4	8	4	2.31 (1.71-3.13)
Pulmonary TB (incl. PTB&ETB) (%)	68	65	68	0.92 (0.79-1.07)

* Adjusted for gender, age, urban area, foreign-born, BCG-vaccination, belonging to risk group, previous treatment, and pulmonary TB



Clustering 1993-2011





Clustering 1993-2011

DNA fingerprints available for 14913 (99.7%) isolates

8330 (58%) cases
with unique
fingerprint

- Of which 1676 (20%) first case in a cluster

6129 (42%)
cases in clusters

- 2690 cases in clusters with ≥ 1 resistant case
- 984 cases with resistance to ≥ 1 drug
- 1685 susceptible cases



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RESULTS – RESISTANCE WITHIN CLUSTERS

Direction of resistance transmission in heteroresistant clusters

Direction of 76 epi link confirmed transmissions of resistance*	
<u>Source and secondary case resistant – n (%)</u>	<u>43 (57)</u>
Resistance profiles:	
• Same resistance profile – n (%)	35 (81)
• Secondary case developed extra resistance – n (%)	5 (12)
• + Isoniazid mono – n (%)	1 (20)
• + Ethambutol mono – n (%)	3 (60)
• + Streptomycin mono – n (%)	1 (20)
• Secondary case less resistant [#] – n (%)	1 (2)
• - Streptomycin mono – n (%)	1 (100)
• Secondary case resistant to other drug(s) – n (%)	2 (5)
<u>Source susceptible, secondary case resistant – n (%)</u>	<u>25 (33)</u>
Resistance profile secondary case:	
• Streptomycin mono – n (%)	17 (68)
• Isoniazid mono – n (%)	6 (24)
• Pyrazinamide mono – n (%)	1 (4)
• Isoniazid & streptomycin – n (%)	1 (4)
<u>Source resistant, secondary case susceptible – n (%)</u>	<u>8 (11)</u>
Resistance profile secondary case:	
• Streptomycin mono – n (%)	4 (50)
• Isoniazid mono – n (%)	3 (38)
• Pyrazinamide mono – n (%)	1 (12)

* Resistance profile unknown for 17 cases with an epidemiological link with one of the 116 resistant cases, 23 resistant source cases were source of a resistant secondary case and were excluded to prevent double counting of the same transmission.