MDR TB
Multidrug - resistant TB

Definitsions

- **Monoresistant case** – Resistance to one TB drug
- **Polydrug resistance** – Resistance to 2 or more TB drug,
  but not to isoniaszid and rifampcin on the same time

- **Resistance among cases never treated:** indicates primary drug resistance due to infection with resistant bacilli.
- **Resistance among cases previously treated:** usually indicates
  acquired drug resistance emerging during treatment following selection of drug-resistant mutant bacilli.
  It can also result from exogenous re-infection with resistant bacilli

- **Multidrug resistance (MDR):** resistance to at least isoniazid and rifampicin
  Multiresistentsuse alavormid
  Extensive drug resistance (XDR): resistance to isoniazid and rifampicin (i.e. MDR),
  resistance to a fluoroquinolone, and resistance to one or more of the following
  injectable drugs: amikacin, capreomycin, or kanamycin

- **Rifampicin resistance:** resistance to rifampicin detected using phenotypic or genotypic
  methods, with or without resistance to other anti-TB drugs.
  This includes any resistance to rifampicin, whether mono-resistance, multidrug
  resistance, polydrug resistance or extensive drug resistance.

All patients with confirmed rifampicin resistance should be treated with MDR-TB regimen.

Causes of MDR

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY OR QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

Man-made problem.

Mechanisms of drug resistance

- *M. tuberculosis* develops drug resistance through genetic mutations

(there are no reports of resistance developed by the acquisition of new DNA).

- In these genes, the two major mechanisms of drug resistance
  - target modification (for example, a mutant bacterial RNA polymerase that eludes the action of rifampicin) or
  - a defective enzyme that converts a pro-drug into an active drug (for example, a mutant bacterial catalase that fails to activate isoniazid).

- The understanding of resistance mechanisms is hampered by limitations in both the phenotypic and the genotypic drug susceptibility tests

- The result of phenotypic tests is dichotomous (the *M. tuberculosis* strain is either susceptible or resistant to a set drug dose), and these tests are best standardized for only some drugs (for example, isoniazid, rifampicin and ethambutol).

- Furthermore, genotypic drug susceptibility tests could fail to identify a mutation in a phenotypically resistant isolate.

Mechanisms of drug resistance

- Result of human activity - Man-made problem
- The main reason- treatment mistakes

• Random genetic mutations appear in all bacteria populations.
• Random mutations are not linked, they appear separately,

Mutation of 10^6 - 10^8 divisions

Isoniaszid (H)	*1*	*of 10^6*
Rifampicin (R)	*1*	*of 10^8*
Streptomycin (S)	*1*	*of 10^6*
Simultaneously H and R	*1*	*of 10^{14}*

Simultaneous Resistancy to H and R is relatively rare,

1 of 10^{14}

• it is not known how to avoid mutations those mutations
• These mutations are not clinically significant, do not determine the drug resistance

Spontaneus mutationes, localization

Ravim	mutant gene
isoniazid	*kat*G
isoniazid	ahpC
Rifampicin	*rpo*B
Pyrazinamid	*pnc*A
Ethambutol	*emb*B
Streptomycin	*rpsL*
Streptomycin	*rrs*
Quinolones	gyrA

TB cavities in the lungs containing 10^7 -10^9 rapidly dividing, active MBT
TB with cavities- risk for resistant MBT

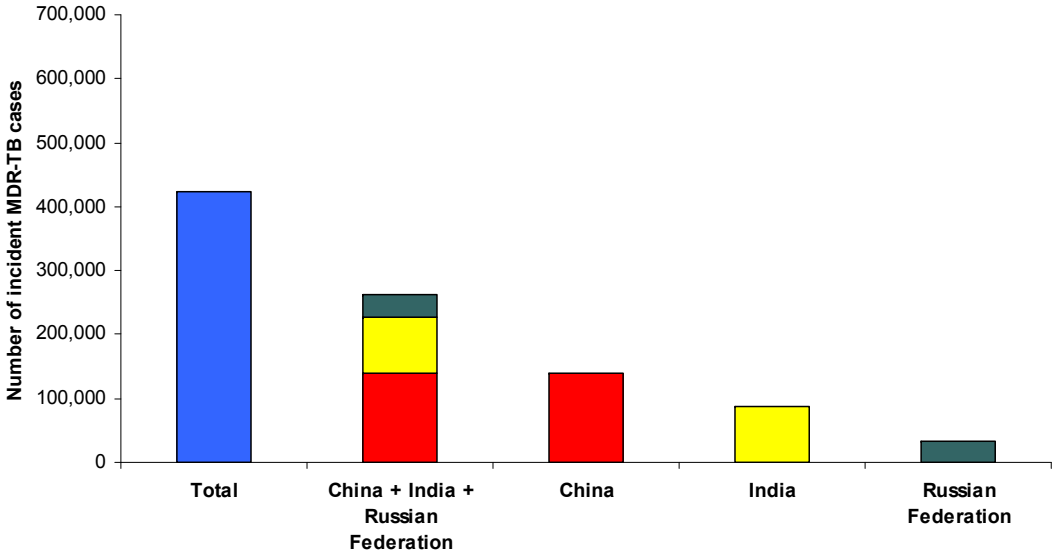
MDRTB

- Globally, the prevalence of MDR-TB is estimated at 5%
  3.5% in new cases of active TB disease
  20.5% in previously treated cases

- This prevalence varies

from 1% in many countries in sub-Saharan Africa, western Europe and North America
to >20% in areas of the former Soviet Union;Azerbaijan, Belarus, Kyrgyzstan Moldova

- Most cases of MDR-TB are estimated to reflect transmission rather than initial acquisition. Thus, a high priority for the response to drug-resistant TB is to identify and target 'hotspots' of MDR-TB transmission

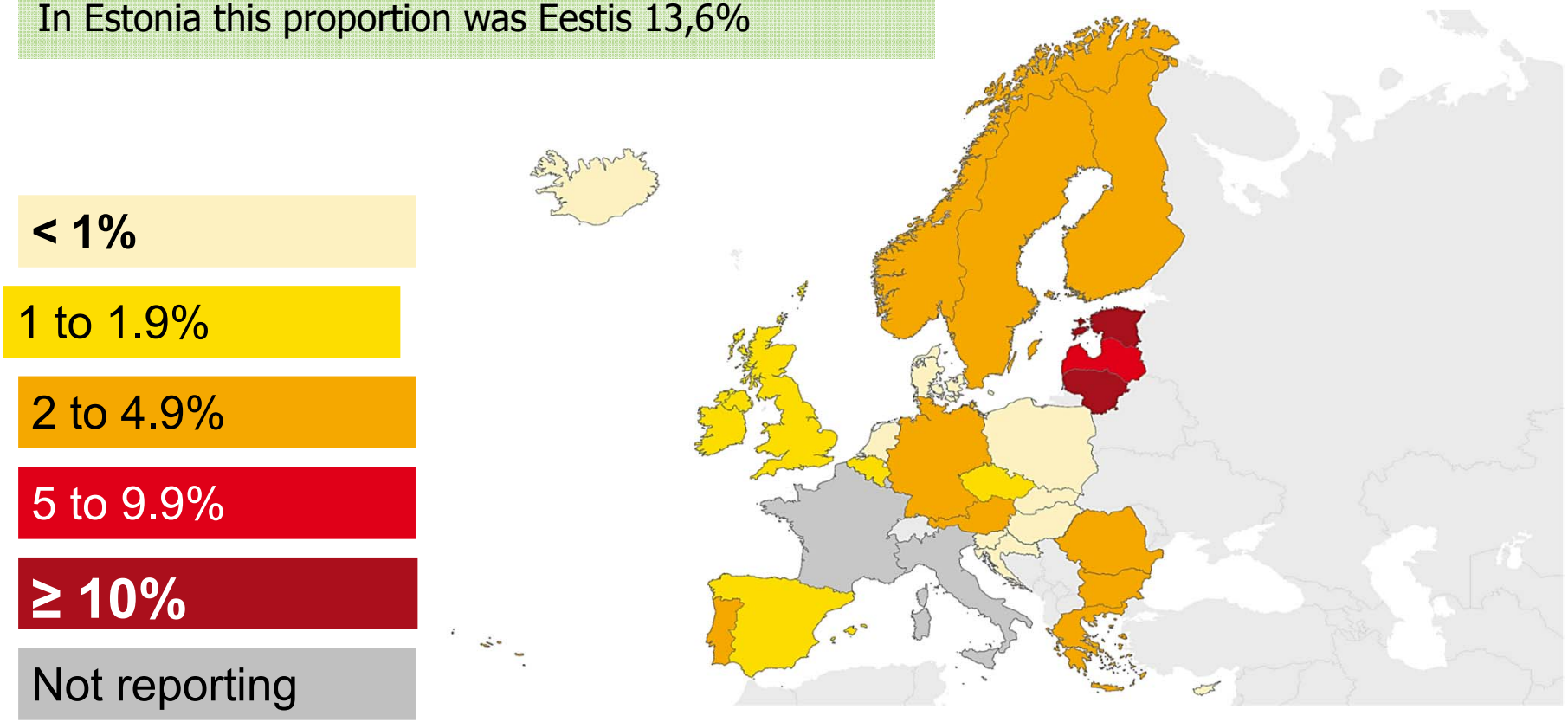


WHO estimated, that globally 62% of all MDR-TB cases located in China, India and Russia.

Proportion of notified **new TB** cases with multidrug resistance in EU/EEA, 2014

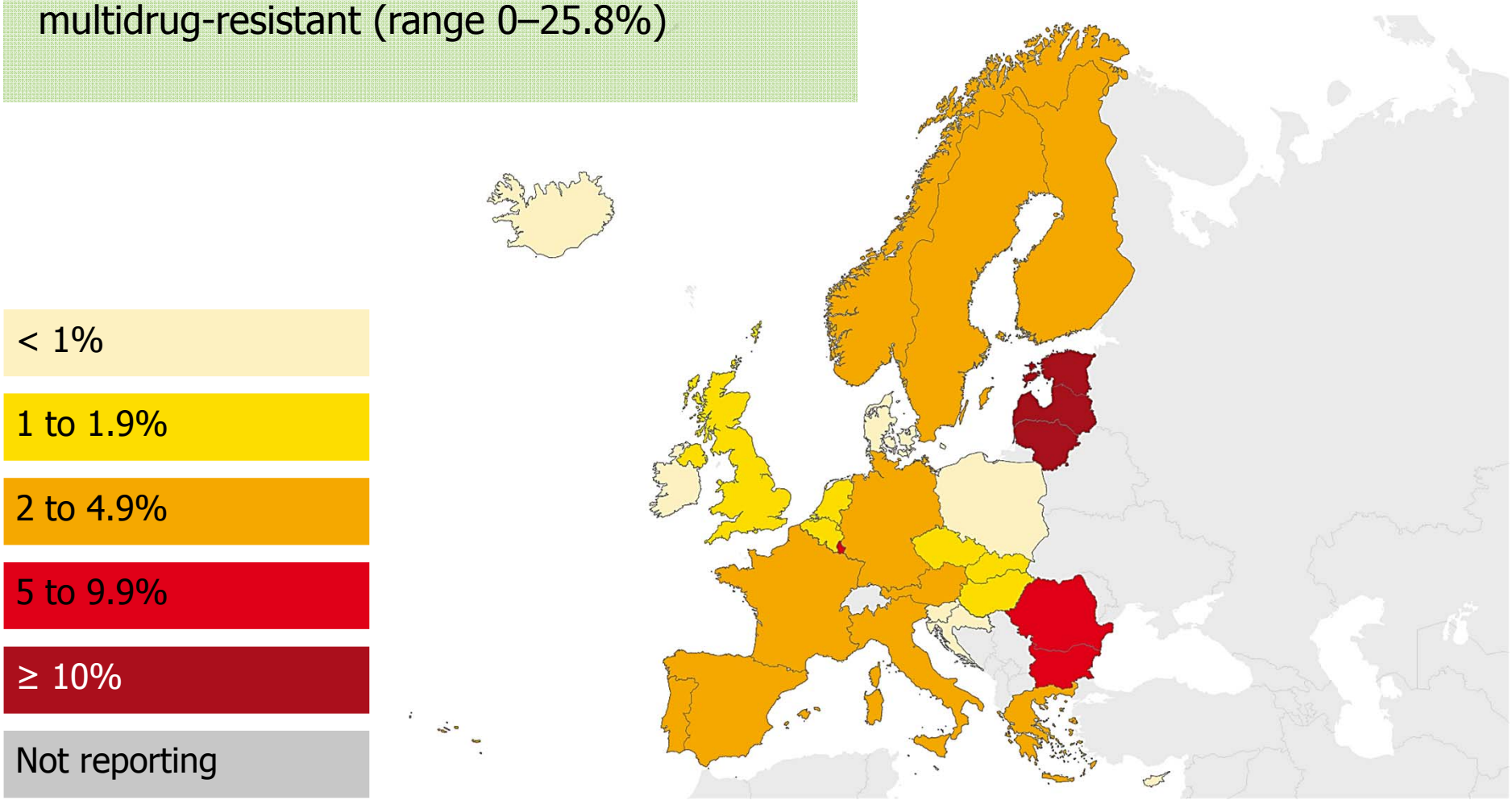
In 2014, the overall proportion of new TB cases with multidrug resistance **in EU/EEA** was 2,4% (range 0–19,5%)

In Estonia this proportion was Eestis 13,6%



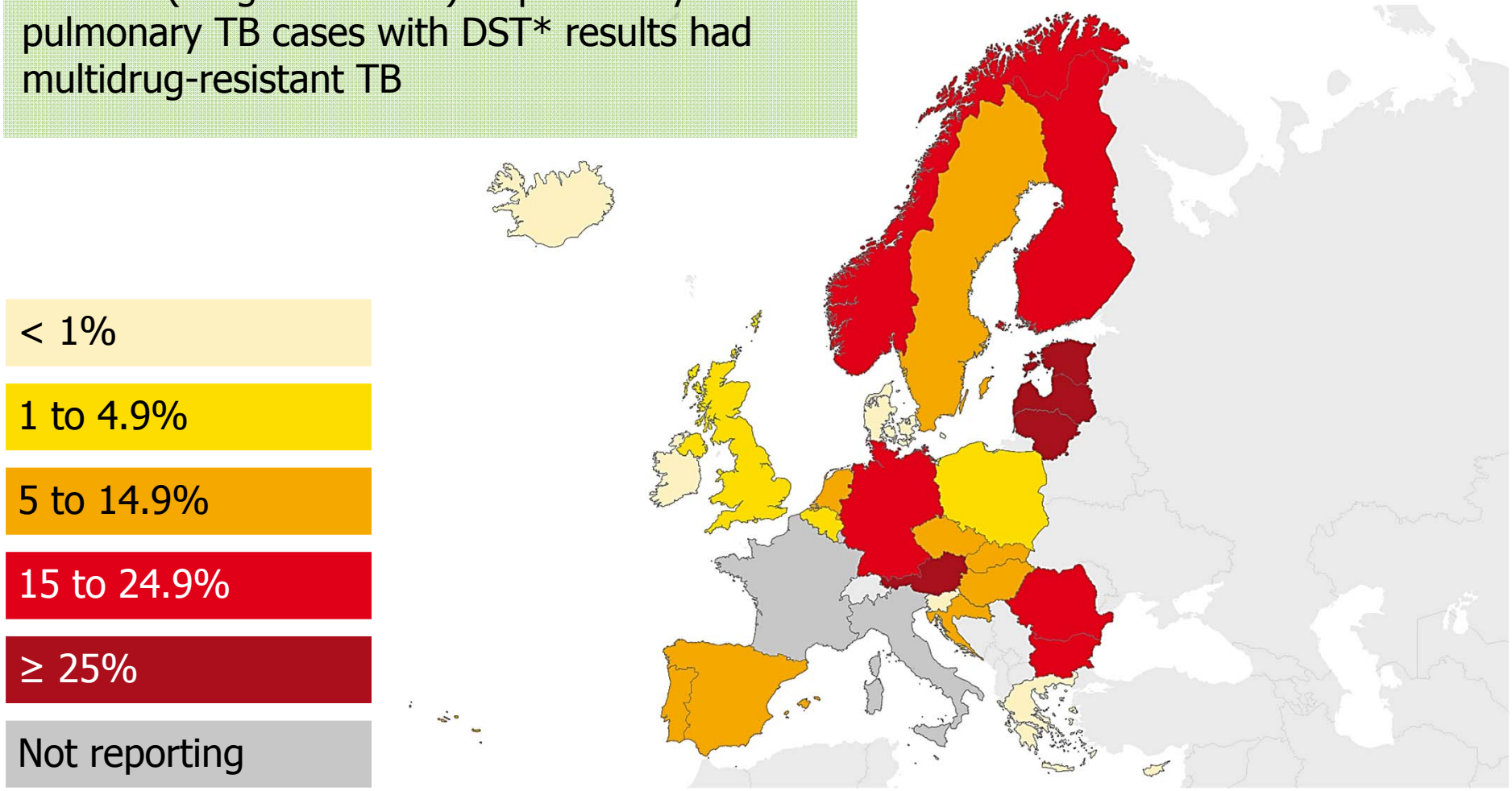
Multidrug-resistant TB, EU/EEA, 2014, all cases

4.0 % of TB cases with DST* results were multidrug-resistant (range 0–25.8%)



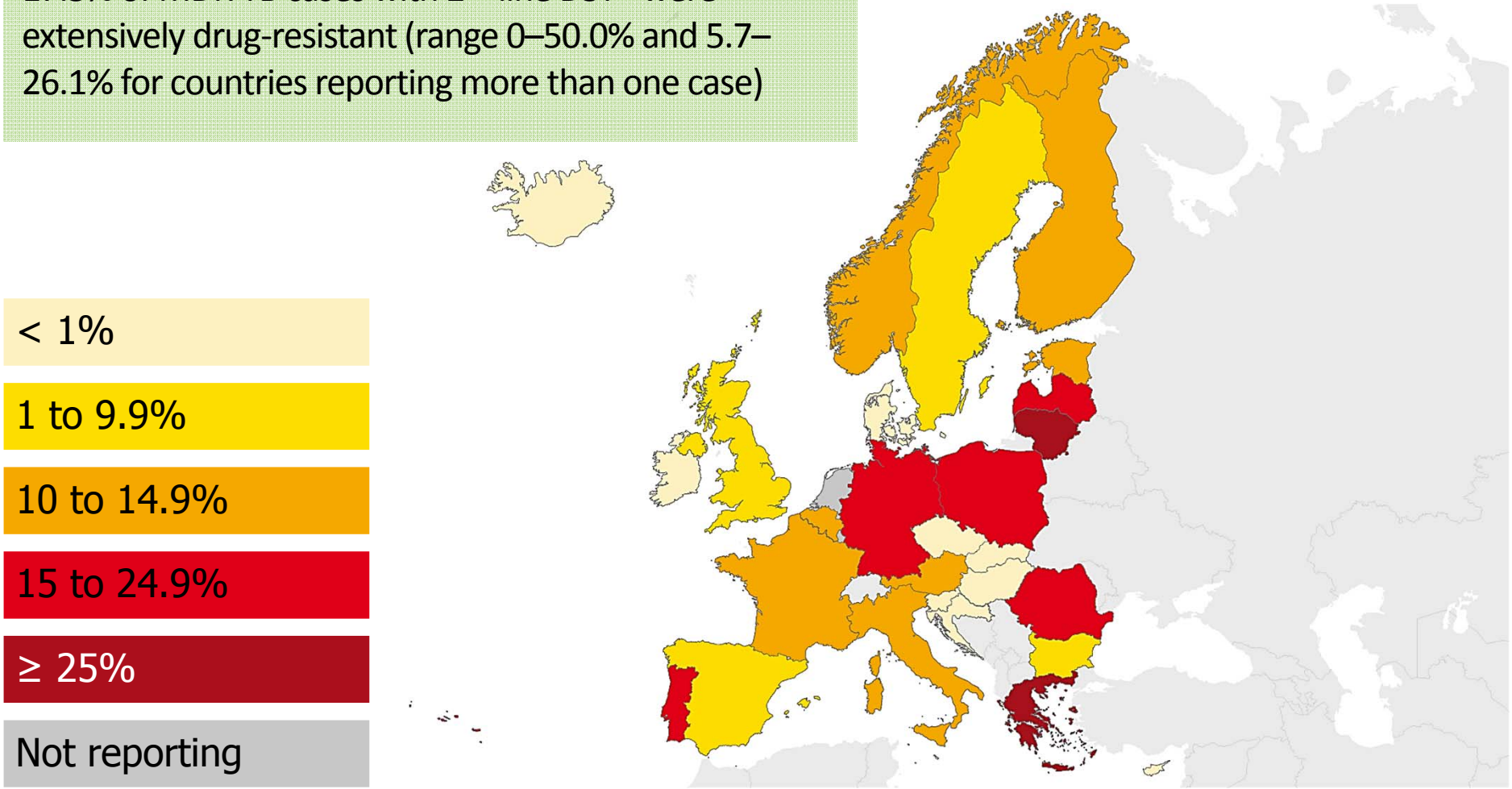
Multidrug resistance among previously treated pulmonary TB cases, EU/EEA, 2014

17.7% (range 0–62.1%) of previously treated pulmonary TB cases with DST* results had multidrug-resistant TB



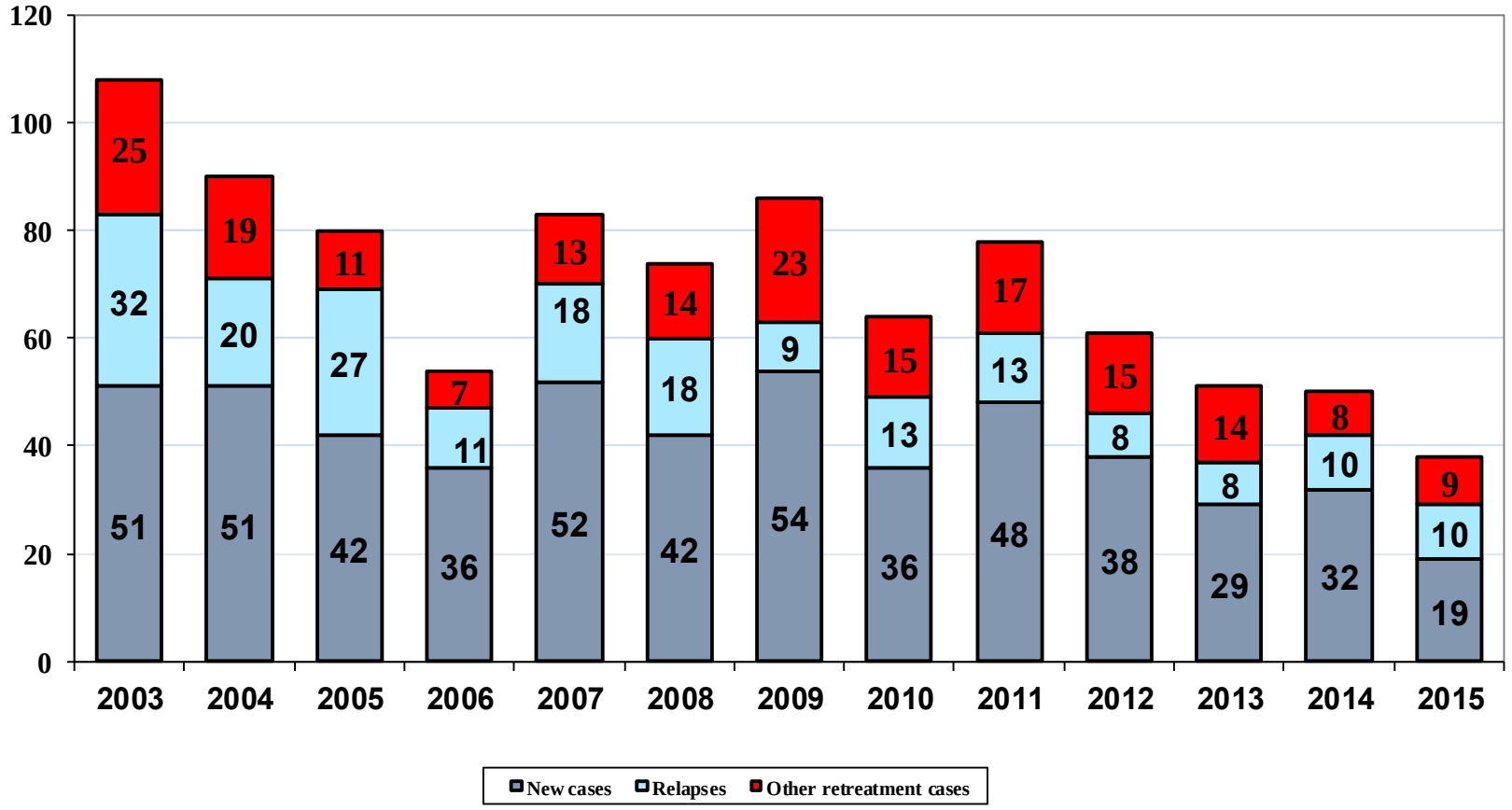
Extensively drug-resistant TB (XDR TB), EU/EEA, 2014

17.5% of MDR TB cases with 2nd line DST* were extensively drug-resistant (range 0–50.0% and 5.7–26.1% for countries reporting more than one case)



MDR-TB cases in Estonia, 2003 - 2015

(New cases, relapses ja other retreatment cases)



TB registry, 2016