Dirençli Bakterilerde Güncel Epidemiyoloji

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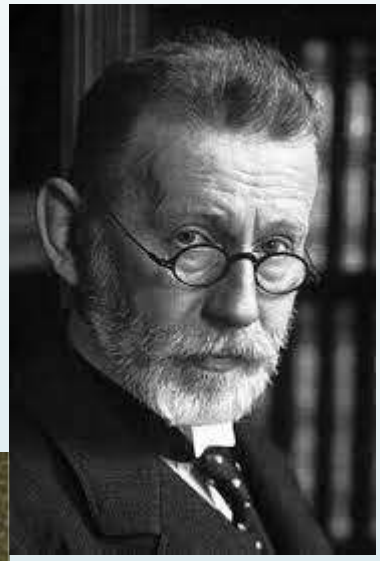
Antibiyotik Öncesi Dönem

- Mikroplar ve bulaşıcı hastalıklar konusunda bilgi yetersiz
- Bulaşı önleme ve tedavi yetersizliği
- Milyonlarca insanın ölümüyle sonuçlanan salgınlar
  - Veba salgını

Antibiyotiklerin erken dönemi

- 1909 Paul Ehrlich
- Treponema pallidum
- İlk sentetik arsenik türevi Salvarsan
- Neosalvarsan

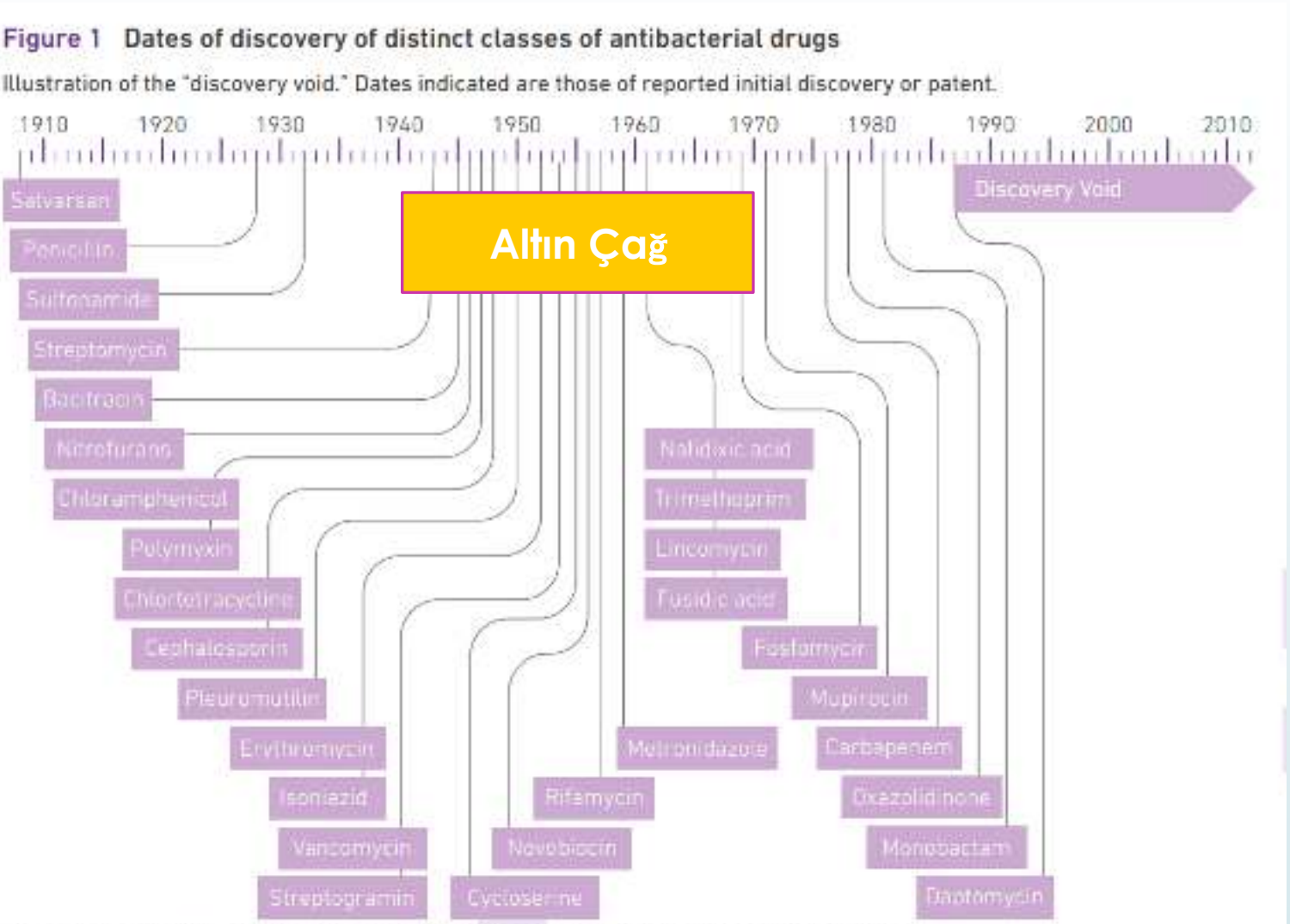


Penisilin Keşfi

- 1928-Alexander Fleming
  - *Penicilium notatum*
- 1939 H. Florey ve E.Chain
  - 1940 II. Dünya Savaşı
  - 1942 menenjit tedavisi

Antibiyotiklerin altın çağı

- 1940-Selman Waksman
  - *Streptomyces spp.*
- Aktinomisin (*Streptomyces spp.*)
- Neomisin (*Streptomyces fradiae*)
- Streptomisin (*Streptomyces griseus*)
- Klavasin (*Aspergillus clavatus*
- Fumigasin (*Aspergillus fumigatus*)



WHO: Antimicrobial Resistance Global Report on Surveillance 2014

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[20, 21]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[8,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015

Antibiotic Resistance Threats In The United States 2019

Günümüz

- İlaç firmalarının çoğu artık antibiyotik keşfi alanını terk etmiş durumda
- Temel neden antibiyotiklere karşı direnç
- Finansal güçlükler
- Üniversiteler ve ilaç firmaları arasındaki işbirlikler
  - New Drugs 4 Bad Bugs: ENABLE
  - CARB-X
- Bakteriyofajlar
- Antimikrobiyal peptitler

doi:10.1038/nrd.2016.155

Antibiyotik Direnci

Doğal Direnç

- Mikroorganizmanın genetik özellikleri nedeniyle ilacın hedefi olan yapıyı taşımaması
- Yapısal özellikleri nedeniyle ilacın hedefe ulaşamaması
  - Gram negatif bakterilerde glikopeptit direnci

Kazanılmış Direnç

- Bakterinin genetik yapısındaki değişimlere bağlı olarak, önceden duyarlı olduğu bir antimikrobiyal ajana genetiğinde meydana gelen değişmelere bağlı olarak duyarlılığını yitirmesi

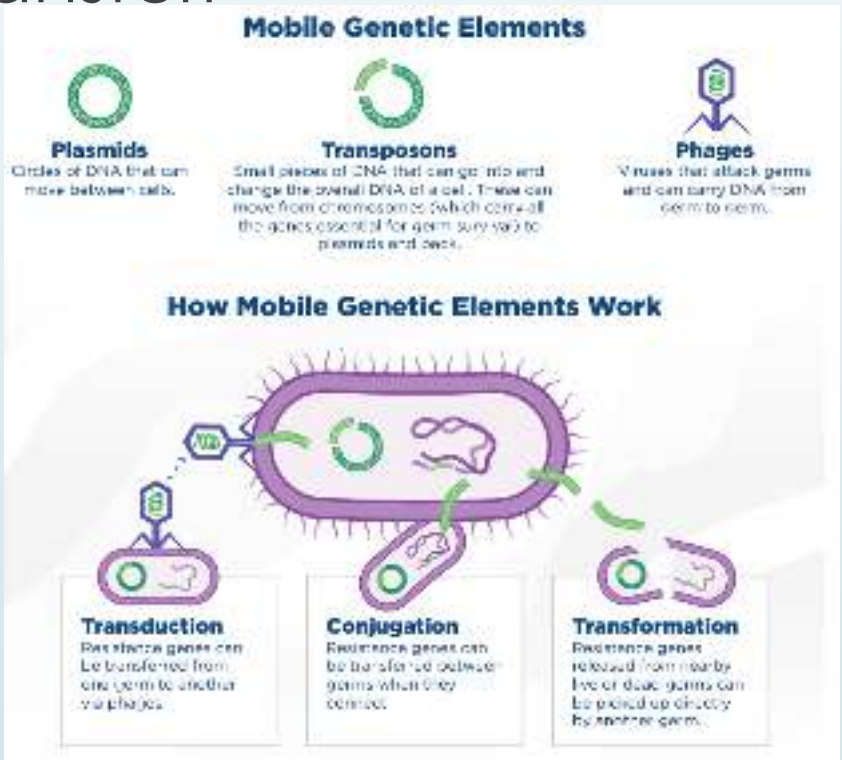
Çevre ve Koşullara Bağlı Direnç

- Oksijen basıncı değişiklikleri, dokudaki pH değişiklikleri ve antmikrobiyal ilacin infeksiyon bölgesine ulaşamaması gibi nedenlerle in vitro testlere yanıt veren antimikrobiyal ilaçlar in-vivo ortamda yanıt vermeyebilir

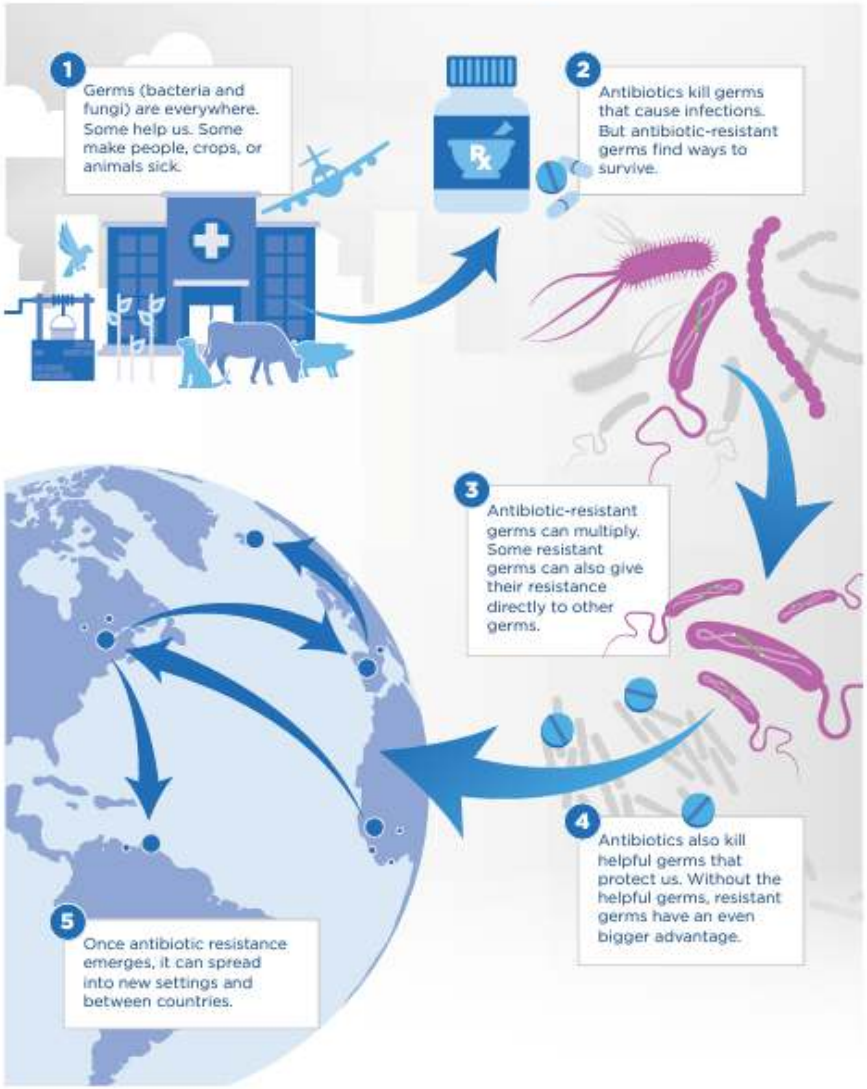
Kayiş U. Antimikrobiyal Direnç Mekanizmalari. Aydın Sağlık Dergisi - Yıl 5 Sayı 1 - Nisan -

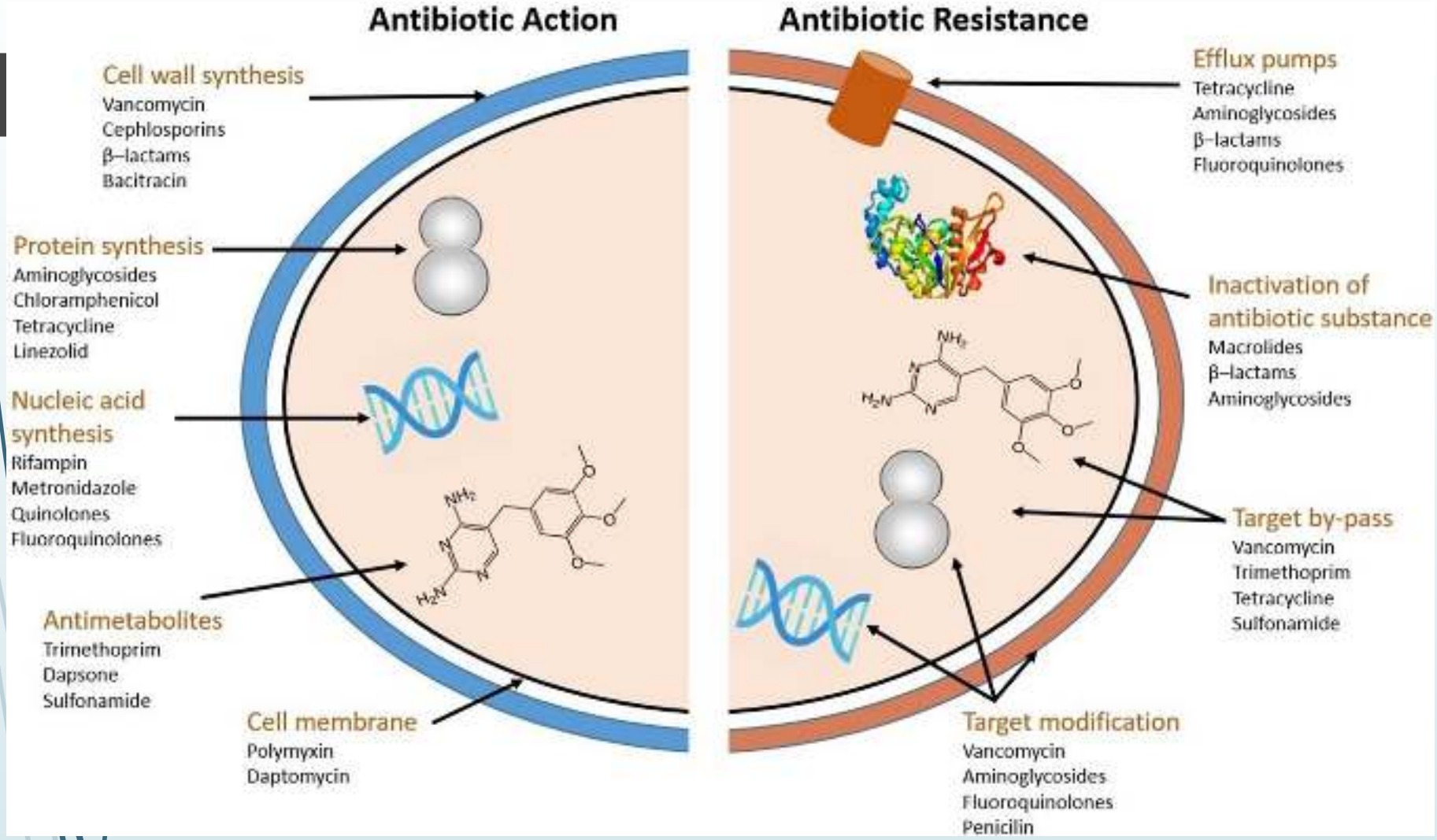
Kazanılmış Direnç

- Kromozomal nokta mutasyonlar
- Genetik materyal transferi
  - Transformasyon
  - Transdüksiyon
  - Konjugasyon



How Antibiotic Resistance Spreads





Uluseker C, Kaster KM, Thorsen K, Basiry D, Shobana S, Jain M, Kumar G, Kommedal R and Pala-Ozkok I (2021) A Review on Occurrence and Spread of Antibiotic Resistance in Wastewaters and in Wastewater Treatment Plants: Mechanisms and Perspectives. Front. Microbiol. 12:717809

- Dünya Sağlık Örgütü(DSÖ) 2019 raporuda
  - Her yıl 700.000 kişi çoklu ilaca dirençli enfeksiyon nedeniyle ölüyor
  - 2050 yılına kadar bu rakamın 20 milyona çıkacağı ve 2,9 trilyon doların üzerinde bir maliyete yol açacağı tahmin ediliyor

https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis

DSÖ öncelikli patojenler listesi

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

- Avrupa Antimikrobiyal Direnç Sürveyans Ağı (EARS Net)
- Orta Asya ve Avrupa Antimikrobiyal Direnç Sürveyans Ağı (CAESAR)
- Kan ve Beyin omurilik sıvısı
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Acinetobacter türleri*
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
  - *Enterococcus faecalis Enterococcus faecium*

Fig. 1 *Escherichia coli.* Percentage of invasive isolates resistant to fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin), by country, WHO European Region, 2021

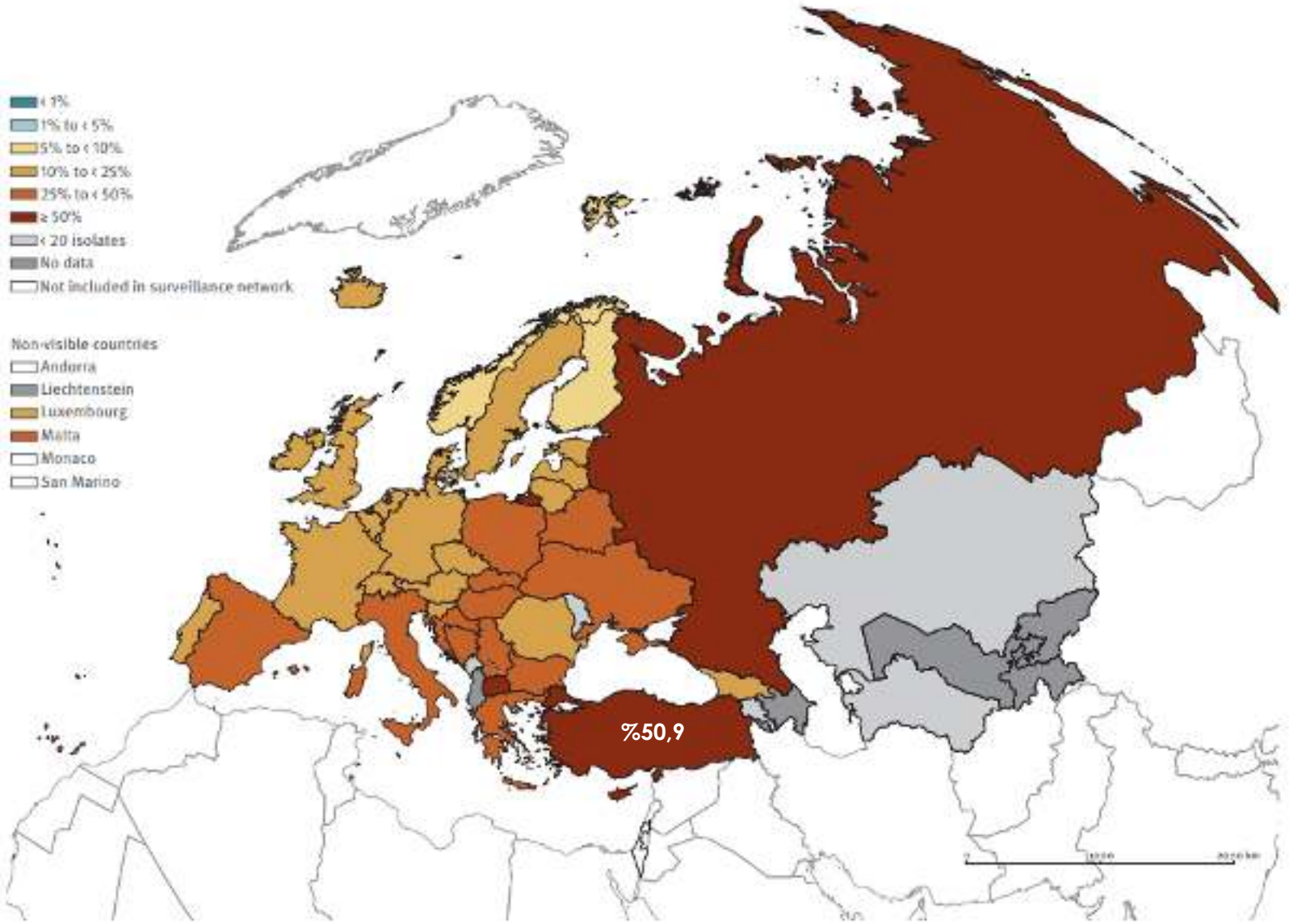


Fig. 2 *Escherichia coli*. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021

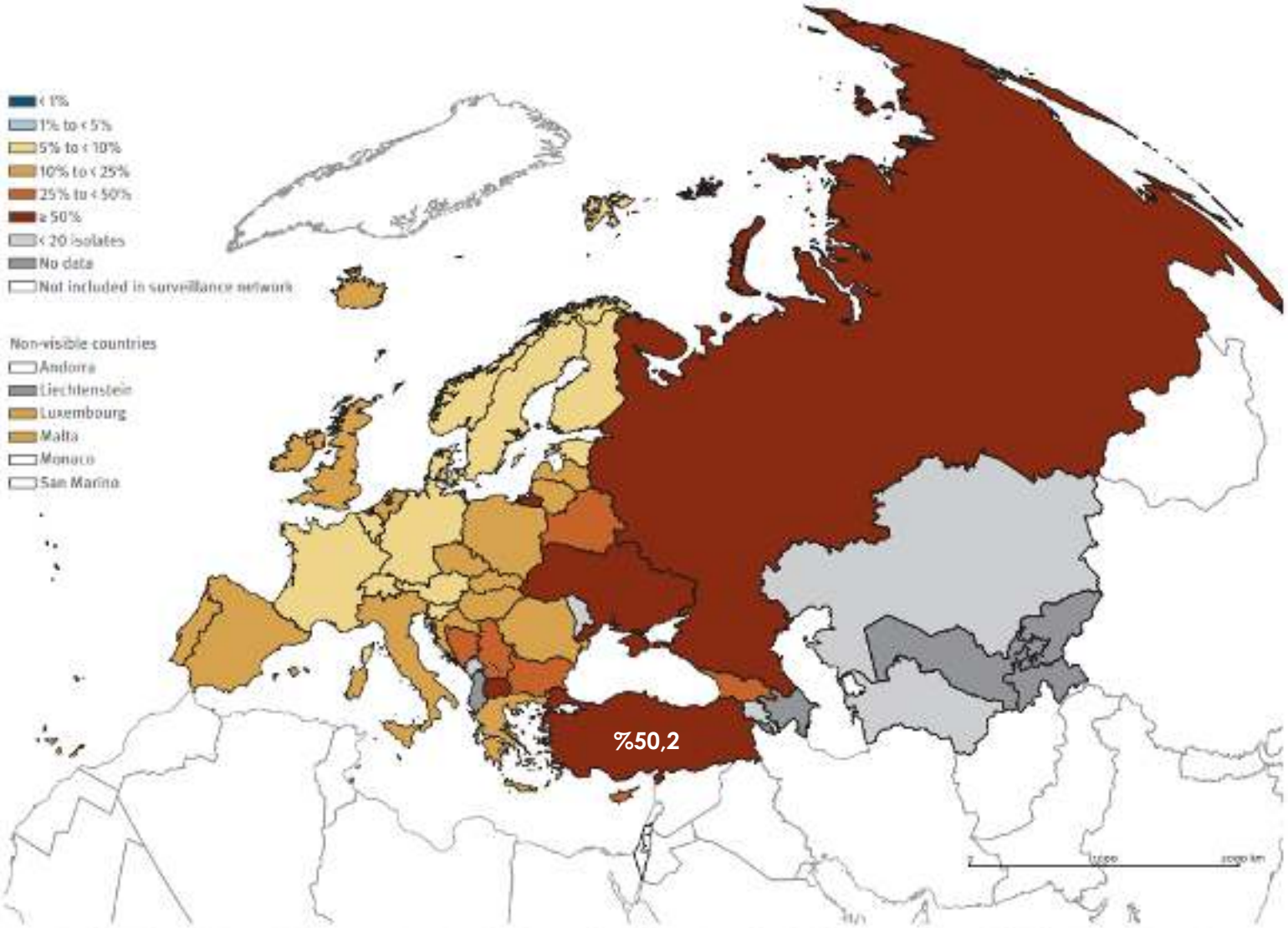


Fig. 3 *Escherichia coli*. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

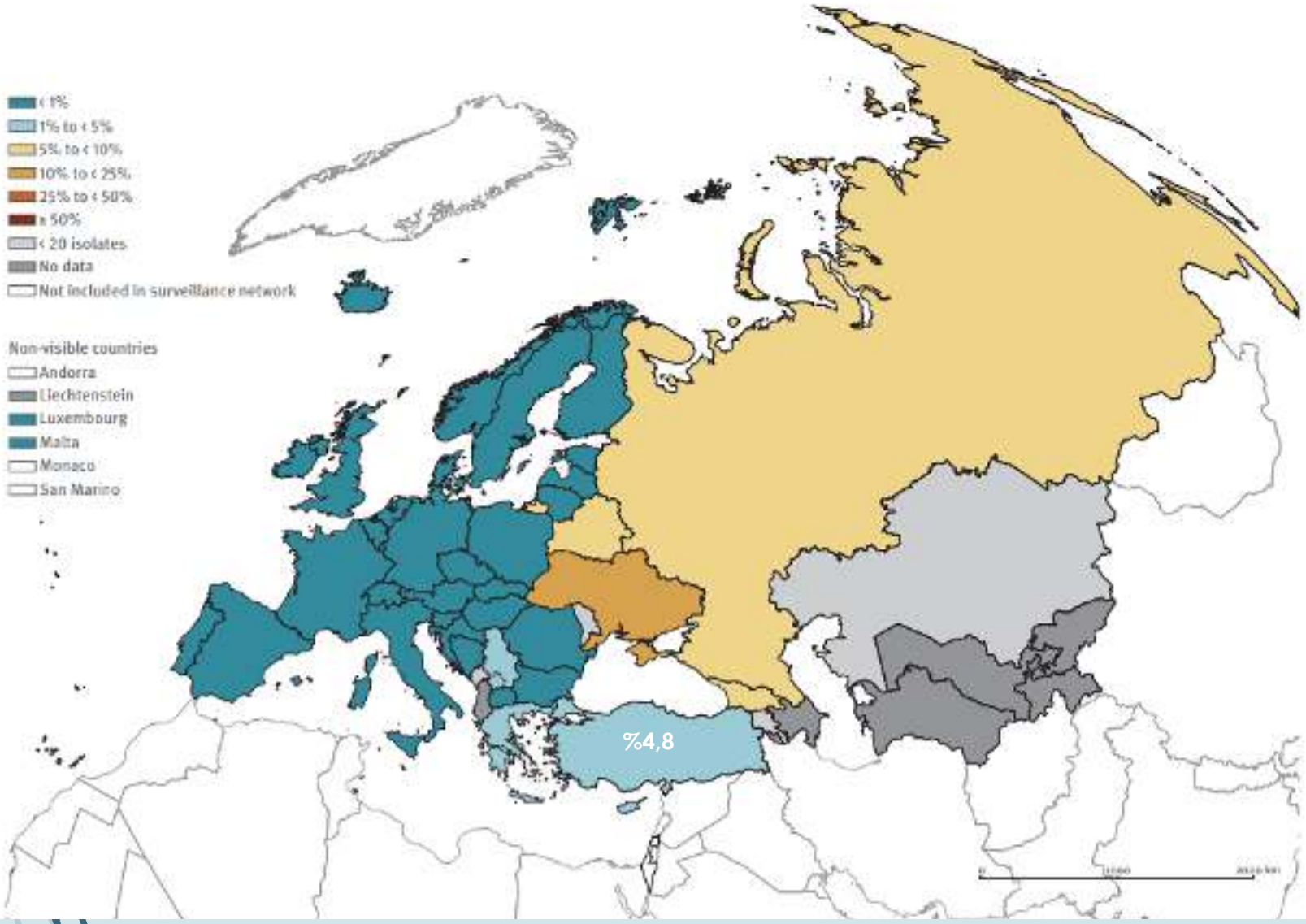


Fig. 4 *Klebsiella pneumoniae.* Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021

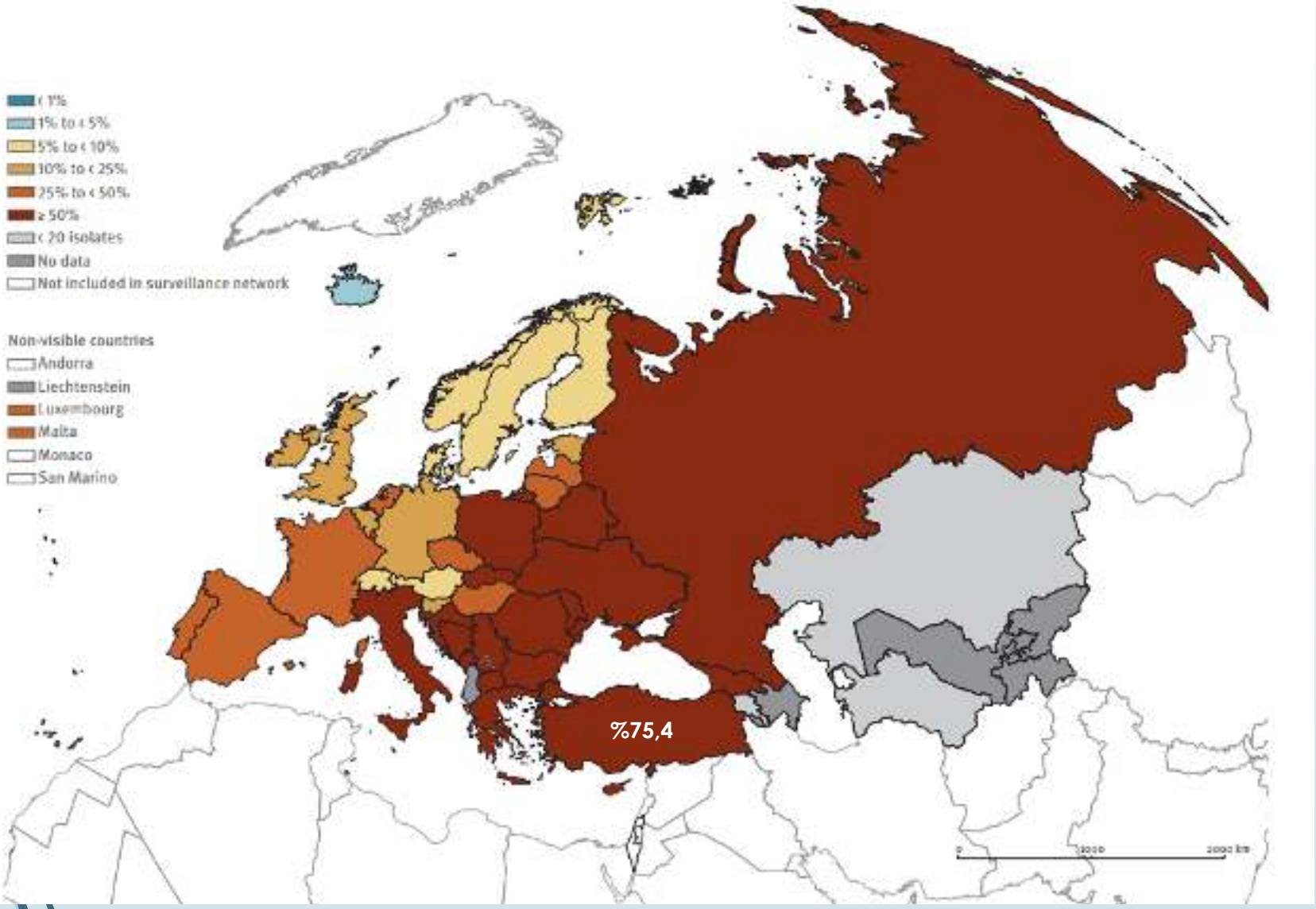


Fig. 5 *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

Fig. 6 *Pseudomonas aeruginosa*. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

Fig. 7 *Acinetobacter* species. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

Fig. 8 *Staphylococcus aureus*. Percentage of invasive isolates resistant to meticillin (MRSA),* by country, WHO European Region, 2021

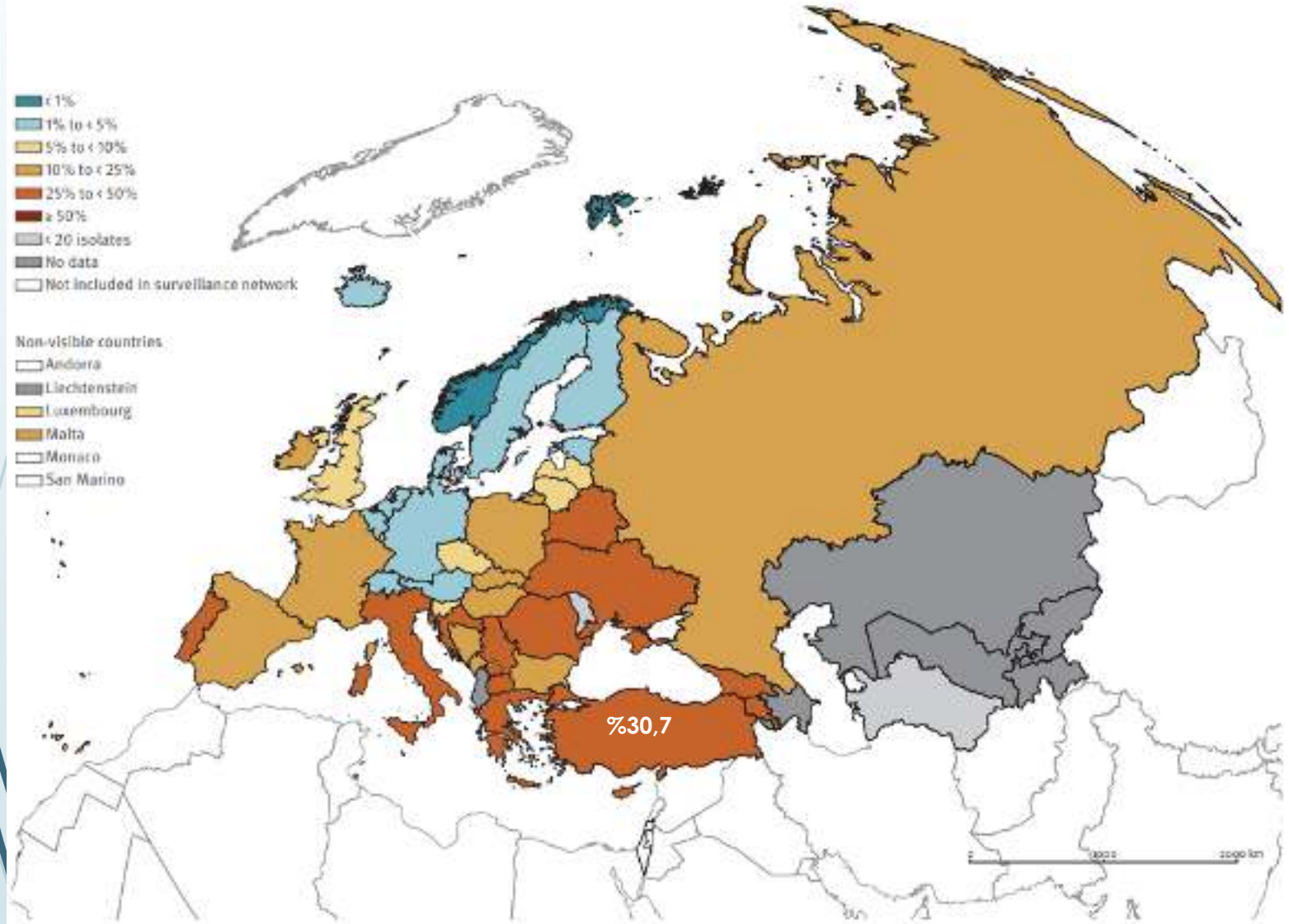


Fig. 9 *Streptococcus pneumoniae*. Percentage of penicillin[a] non-wild-type[b] invasive isolates, by country, WHO European Region, 2021

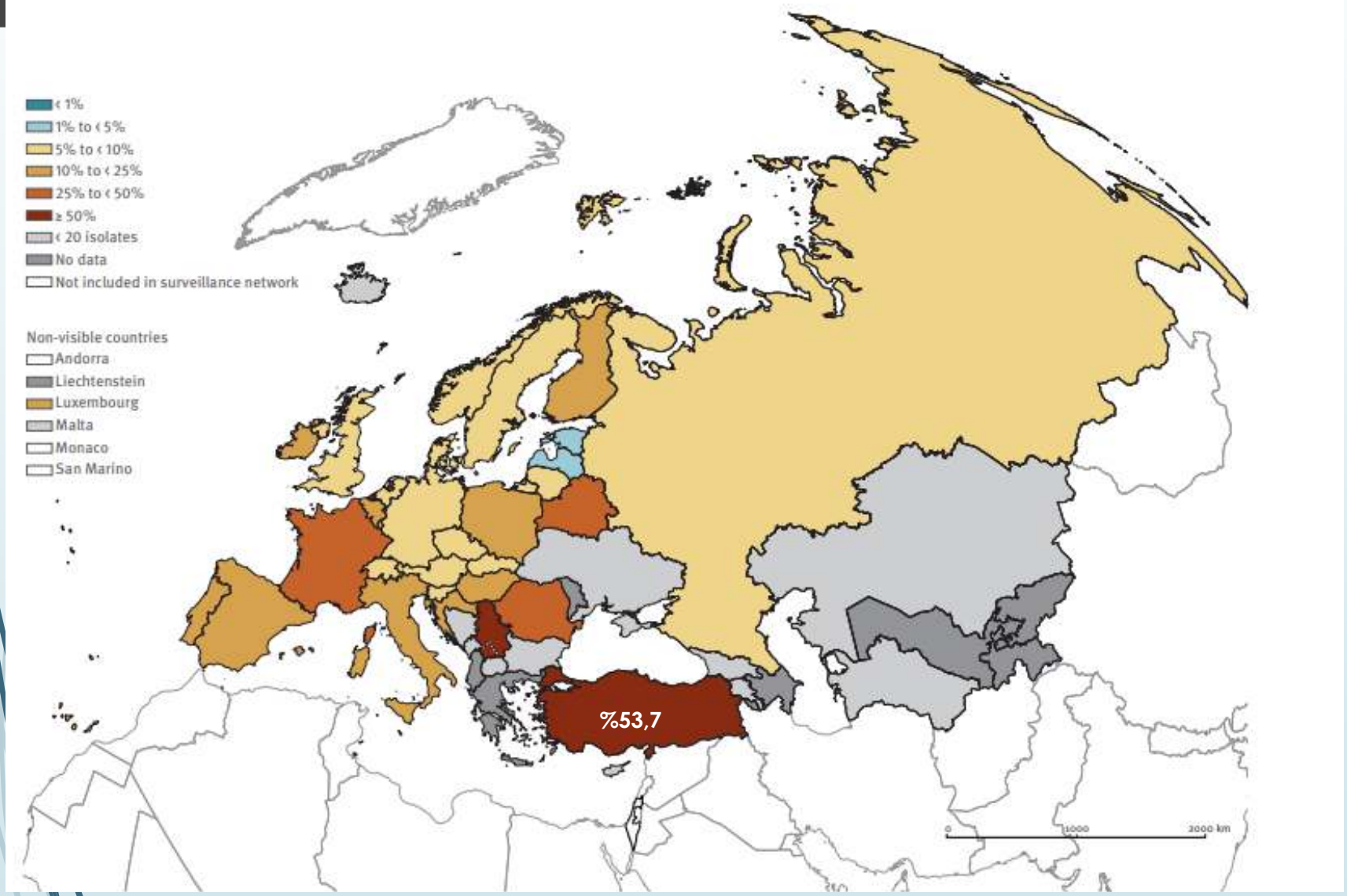
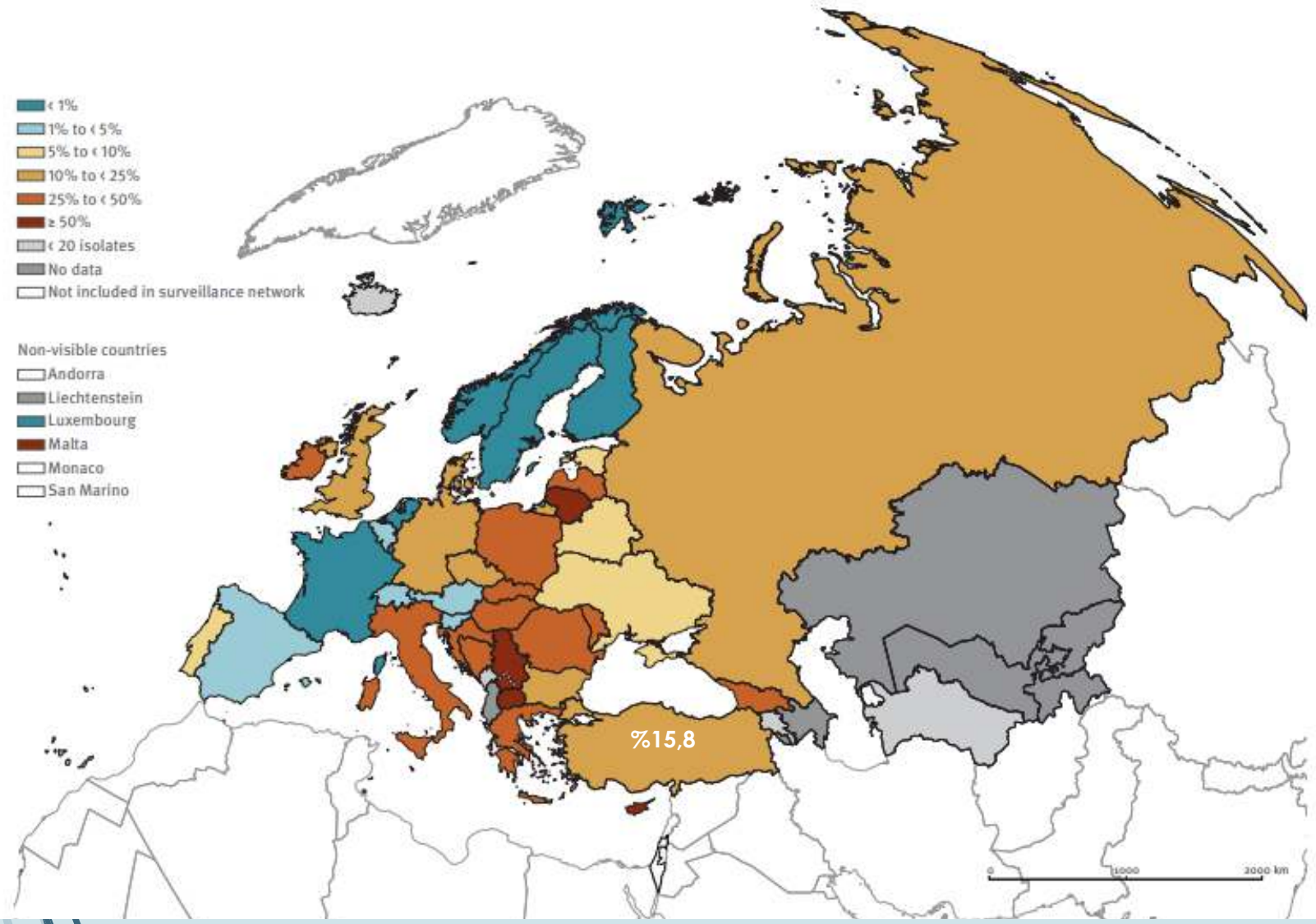
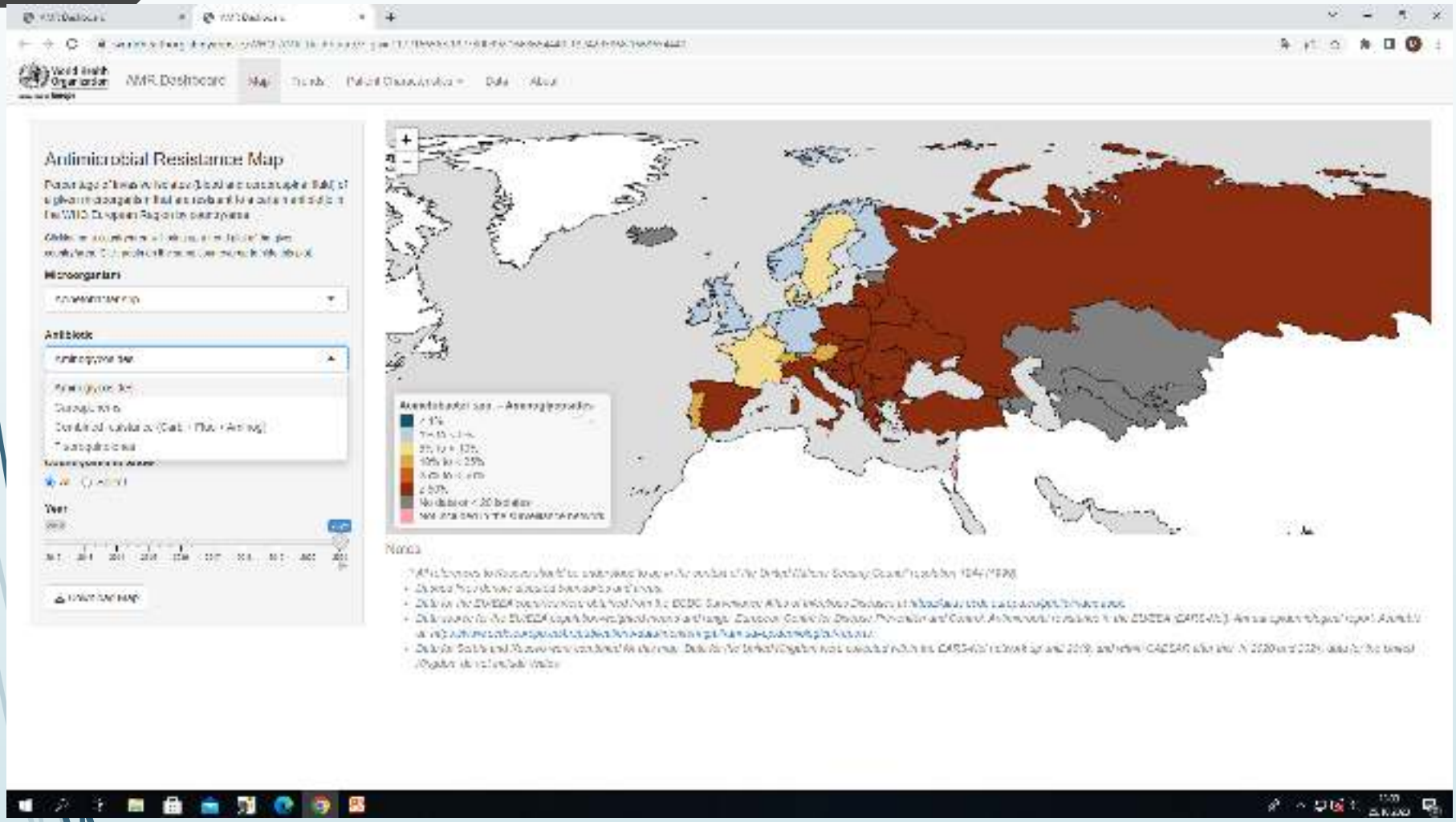


Fig. 10 *Enterococcus faecium*. Percentage of invasive isolates resistant to vancomycin, by country, WHO European Region, 2021





https://worldhealthorg.shinyapps.io/WHO-AMR-Dashboard/?_ga=2.172166563.1827800992.1668654440-1324205868.1668654440

Teşekkürler