The AMR threat, drivers and solutions in human medicine

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THREAT

Review on Antimicrobial Resistance, First report, December 2014


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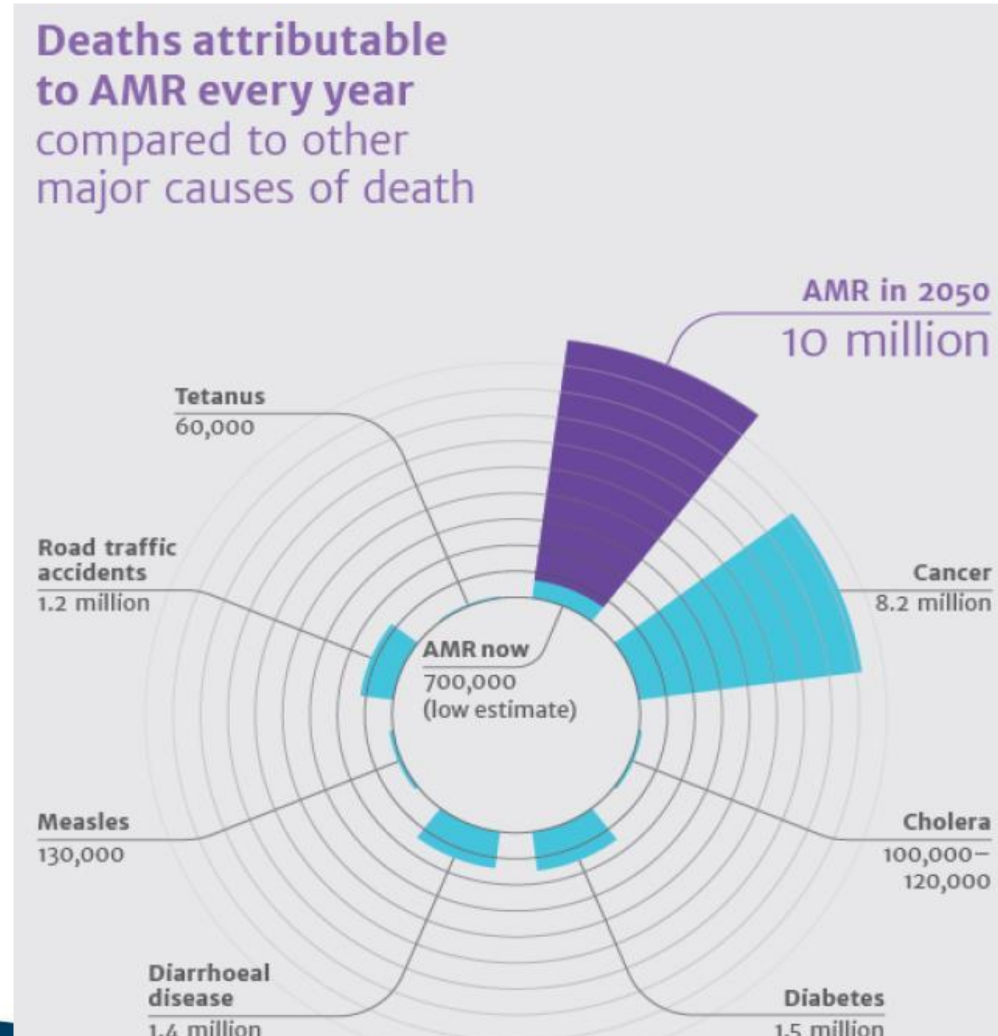
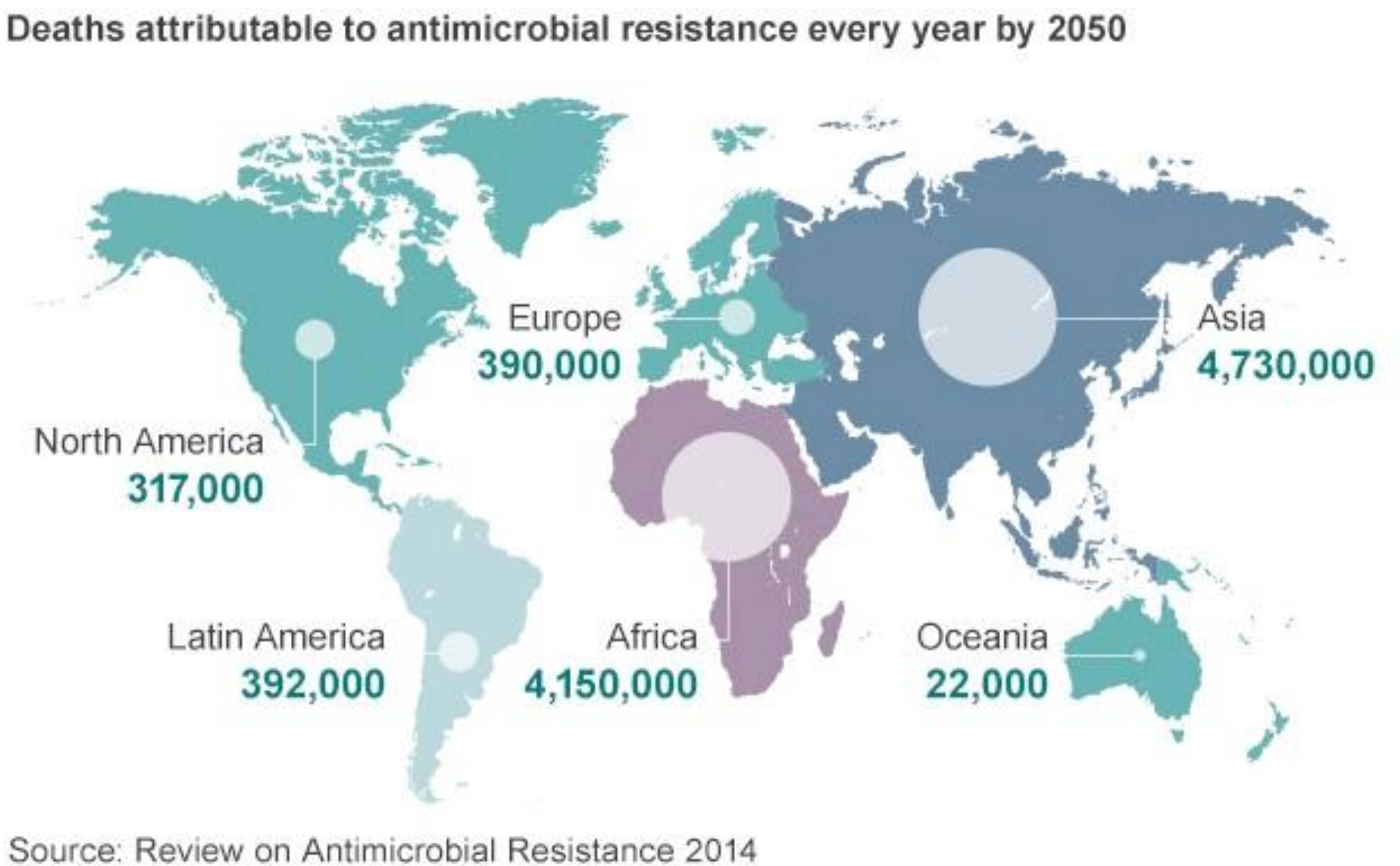
Antimicrobial resistance a 'greater threat than cancer by 2050'

UK chancellor George Osborne to tell IMF that 10m people a year could die without radical action

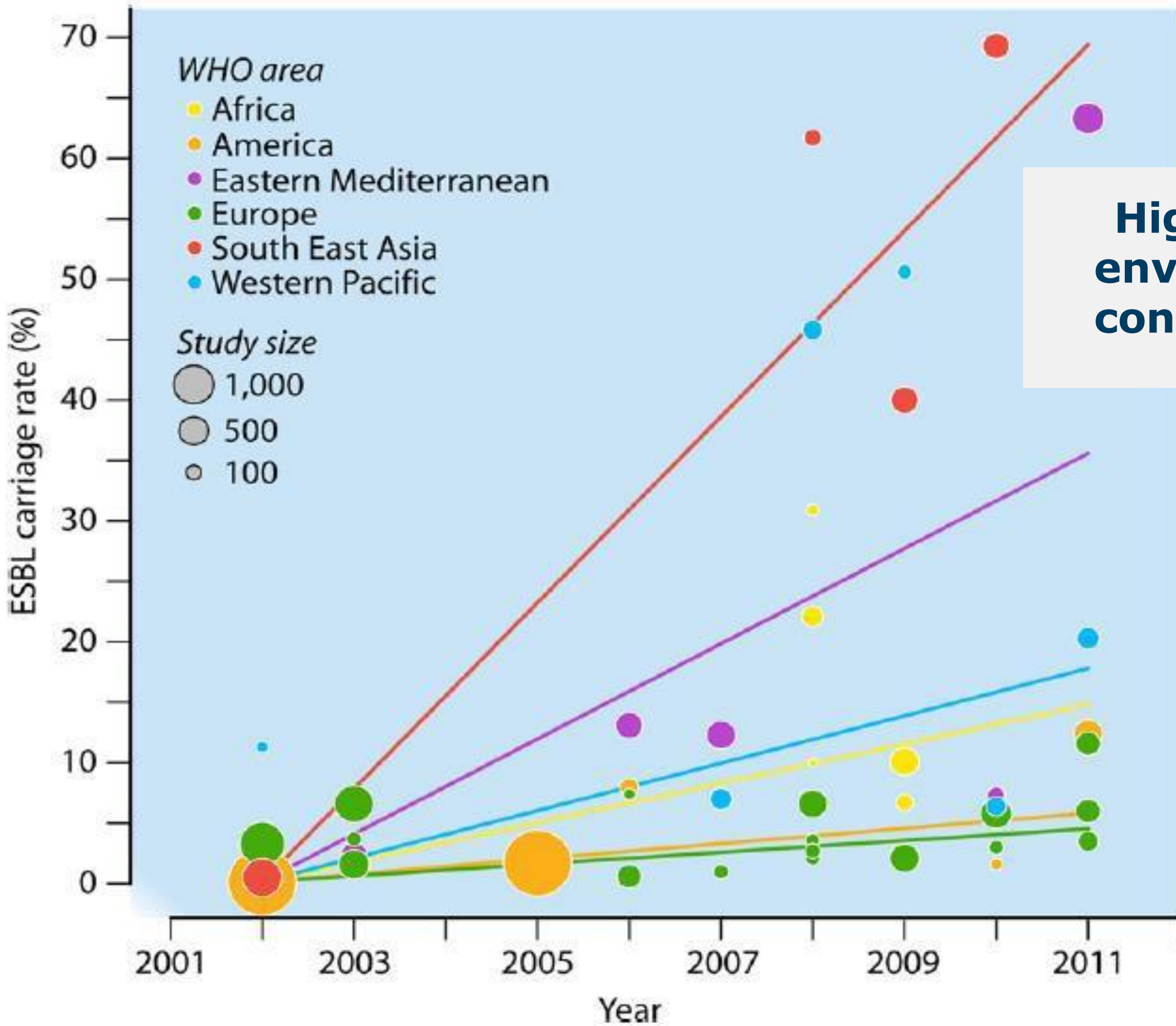
The chancellor will call for incentives for pharmaceutical companies to develop new antibiotics. Photograph:



Antimicrobial resistance is a major public health threat in LMIC

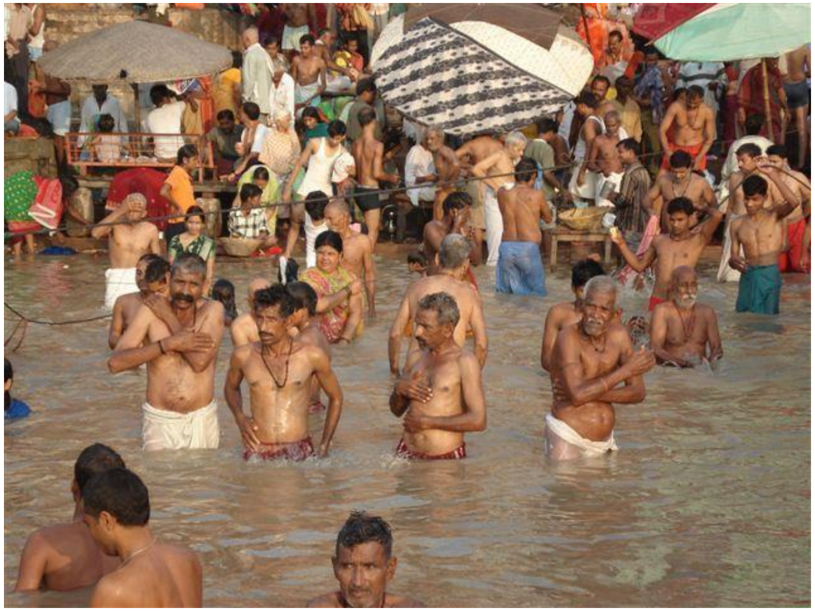


ESBL Carriage Rates in the Community



High-level of environmental contamination

Woerther et al, Clin Microbiol Rev 2013; 26: 744-58

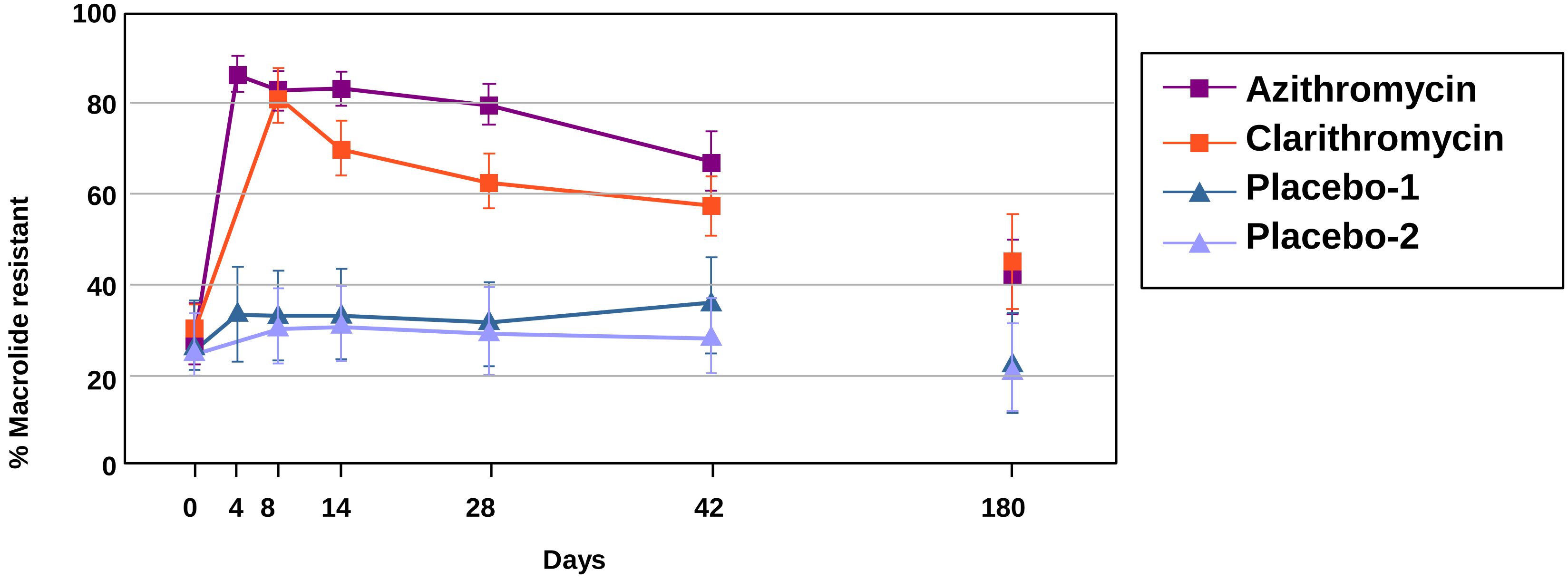



AP

Carbapenemases in animals and the environment

DRIVERS

Antibiotic Use:
Macrolide use is the single most important driver for the emergence of macrolide resistance



MAIN FINDINGS

- **Mean pre-antibiotic (Day 0) carriage of macrolide-resistant streptococci was 28%**
- **Use of both macrolides resulted in a huge increase in resistant streptococci, which persisted for at least 6 months (*P*≤0.01)**

Malhotra-Kumar S, et al. Lancet. 2007;369:482-490.

Pandemic Spread:

CTX-M-15 producing *E. coli* ST131

- CTX-M-15 producing ST131 *E. coli* emerged simultaneously in three continents in 2008 as ExPEC in community (and hospital settings)
- High spread capacity due to combination of:
  - Spread of an **epidemic clone** (ST131) with selective advantages (multiple antibacterial resistance, mainly fluoroquinolones, and enhanced virulence factors); mainly found with CTX-M-15 but also CTX-M-3 (UK), CTX-M-14 (Canada, China, Japan, Spain) and CTX-M-27 (France, Switzerland, Japan)
  - Horizontal transfer of **plasmids (IncF) or genes** carrying the blaCTX-M-15 alleles

Global dissemination of ESBL-positive *Escherichia coli* ST131 clone

Clin Microbiol Rev. 2014; 27(3): 543–574.

Pandemic Spread:

KPC Producing *K. pneumoniae* ST258

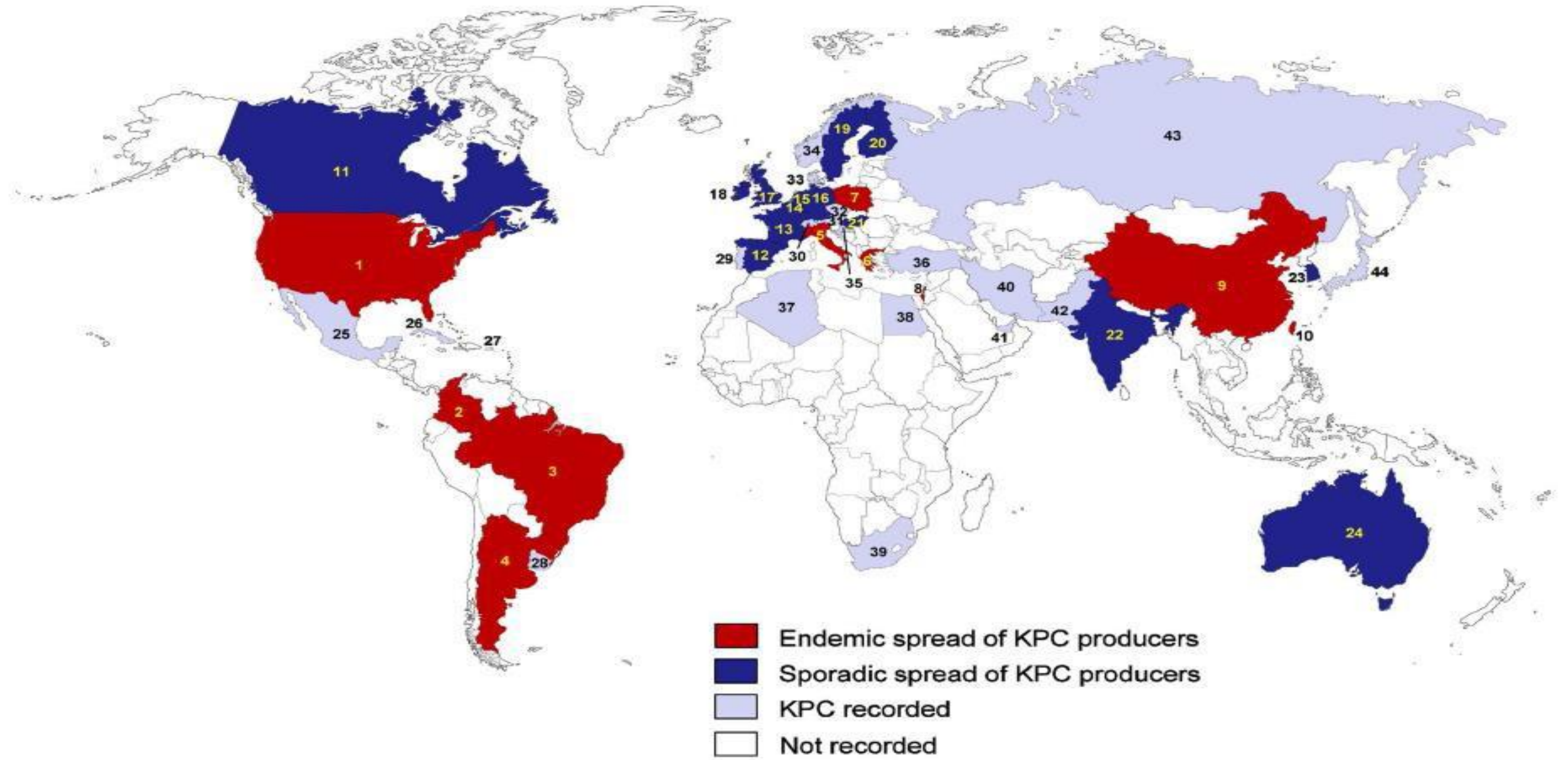


FIGURE 1 | Epidemiological features of KPC-producing *Klebsiella pneumoniae*. (1) USA; (2) Colombia; (3) Brazil; (4) Argentina; (5) Italy; (6) Greece; (7) Poland; (8) Israel; (9) China; (10) Taiwan; (11) Canada; (12) Spain; (13) France; (14) Belgium; (15) Netherlands; (16) Germany; (17) UK; (18) Ireland; (19) Sweden; (20) Finland; (21) Hungary; (22) India; (23) South Korea; (24) Australia; (25) Mexico; (26) Cuba; (27) Puerto Rico; (28) Uruguay; (29) Portugal; (30) Switzerland; (31) Austria; (32) Czech Republic; (33) Denmark; (34) Norway; (35) Croatia; (36) Turkey; (37) Algeria; (38) Egypt; (39) South Africa; (40) Iran; (41) United Arab Emirates; (42) Pakistan; (43) Russia; (44) Japan.

Lee et al. Front Microbiol. 2016; 7: 895.

K. pneumoniae ST258

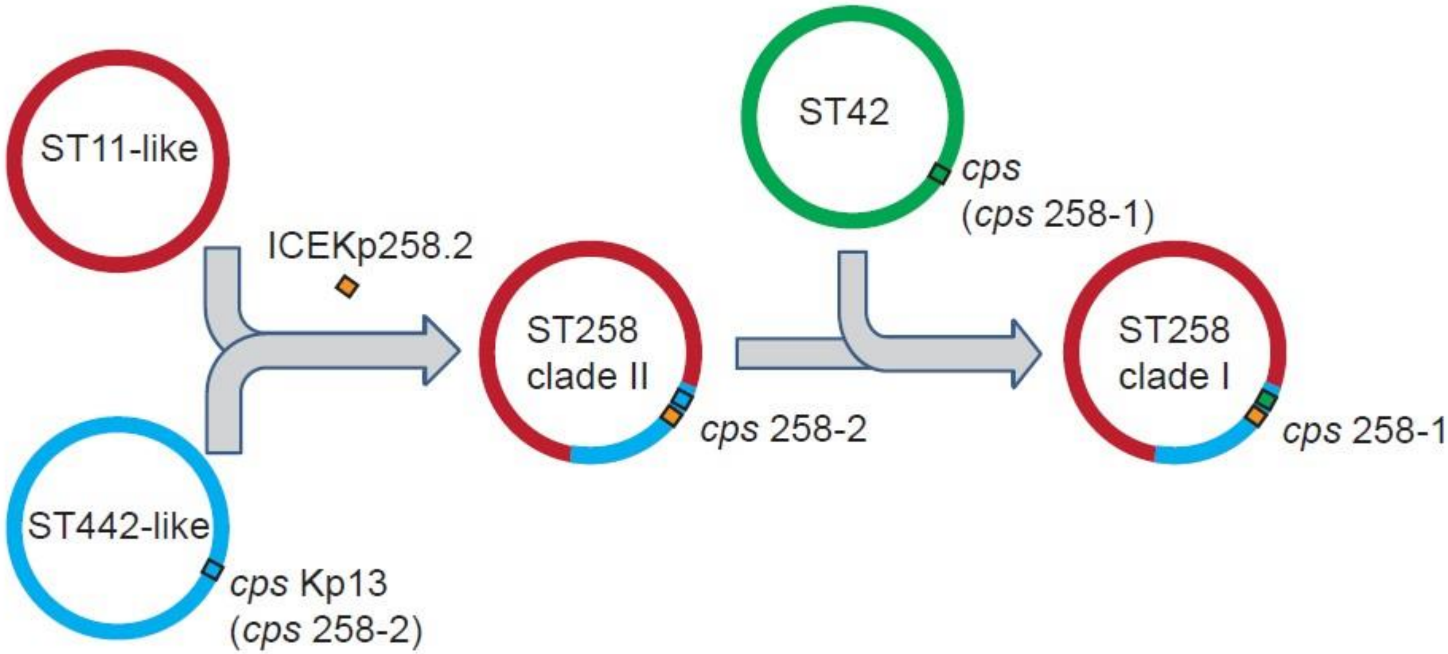


FIG 4 Hypothesized evolutionary history in *K. pneumoniae* ST258 strains.

Chen et al. mBio 5, e1355; 2014

Pandemic Spread

NDM gene on broad range plasmids

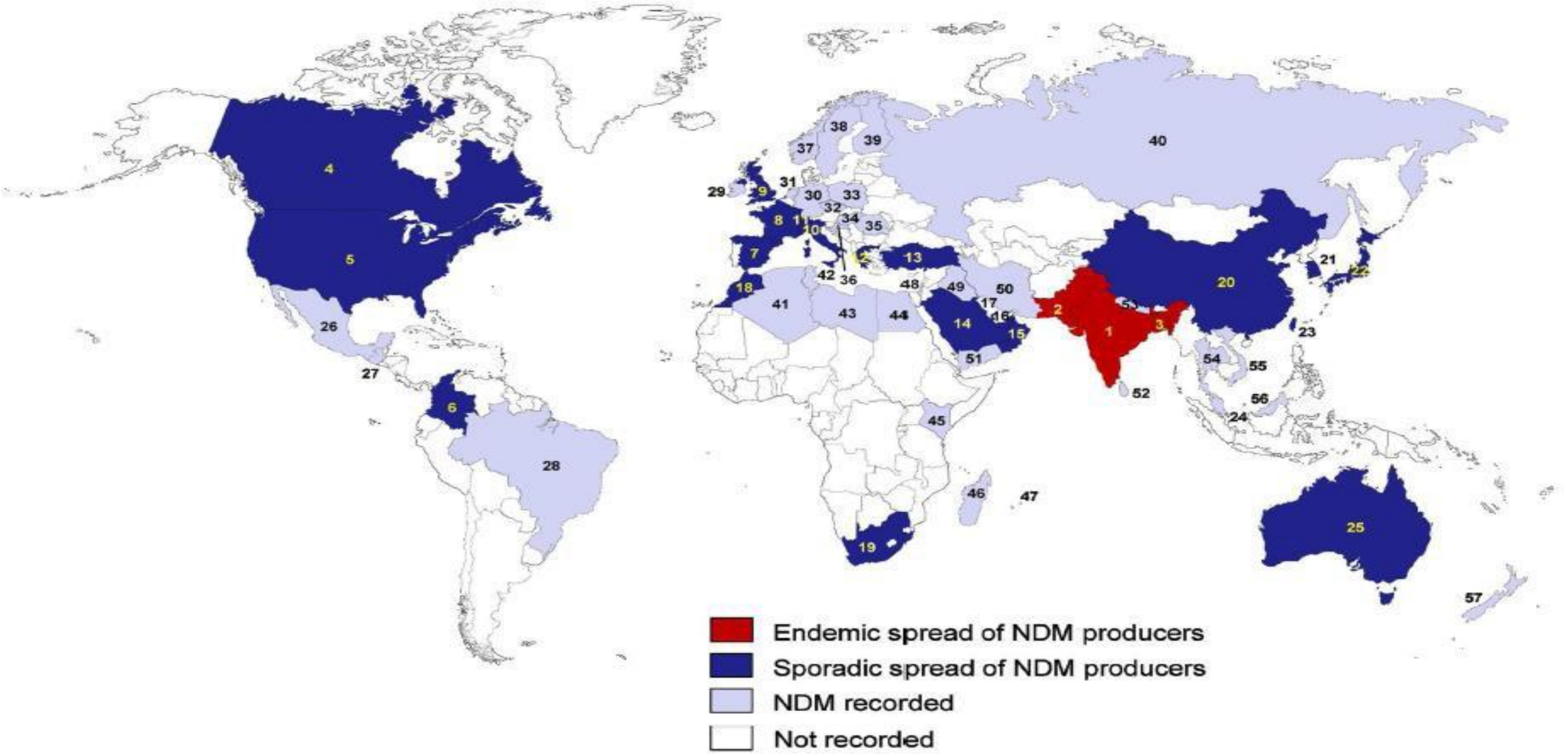


FIGURE 3 | Epidemiological features of NDM-producing *K. pneumoniae*. (1) India; (2) Pakistan; (3) Bangladesh; (4) Canada; (5) USA; (6) Colombia; (7) Spain; (8) France; (9) UK; (10) Italy; (11) Switzerland; (12) Greece; (13) Turkey; (14) Saudi Arabia; (15) Oman; (16) United Arab Emirates; (17) Kuwait; (18) Morocco; (19) South Africa; (20) China; (21) South Korea; (22) Japan; (23) Taiwan; (24) Singapore; (25) Australia; (26) Mexico; (27) Guatemala; (28) Brazil; (29) Ireland; (30) Germany; (31) Netherlands; (32) Czech Republic; (33) Poland; (34) Hungary; (35) Romania; (36) Croatia; (37) Norway; (38) Sweden; (39) Finland; (40) Russia; (41) Algeria; (42) Tunisia; (43) Libya; (44) Egypt; (45) Kenya; (46) Madagascar; (47) Mauritius; (48) Israel; (49) Iraq; (50) Iran; (51) Yemen; (52) Sri Lanka; (53) Nepal; (54) Thailand; (55) Vietnam; (56) Malaysia, (57) New Zealand.

Lee et al. Front Microbiol. 2016; 7: 895.

Pandemic Spread:

pOXA-48a plasmid

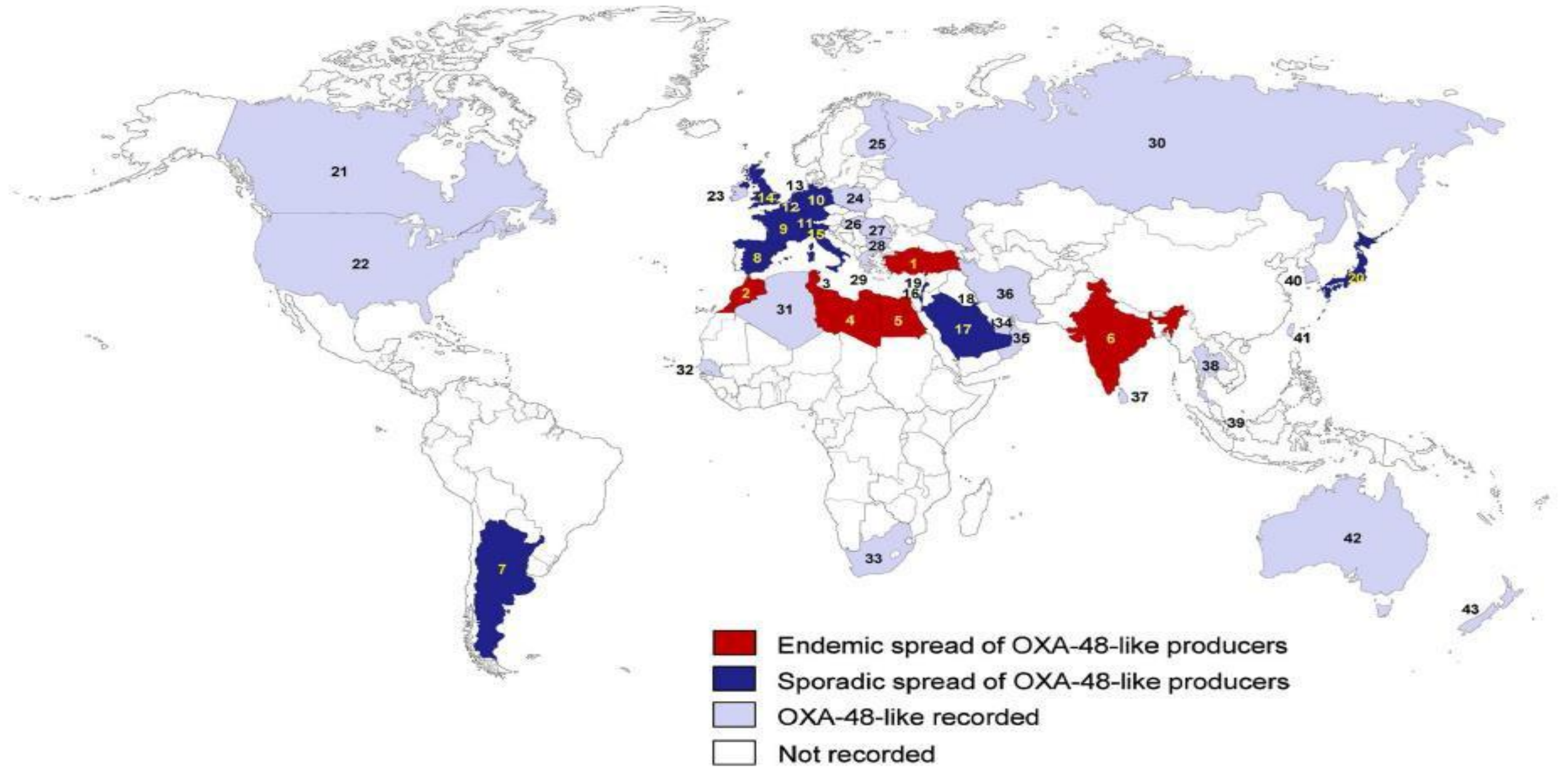
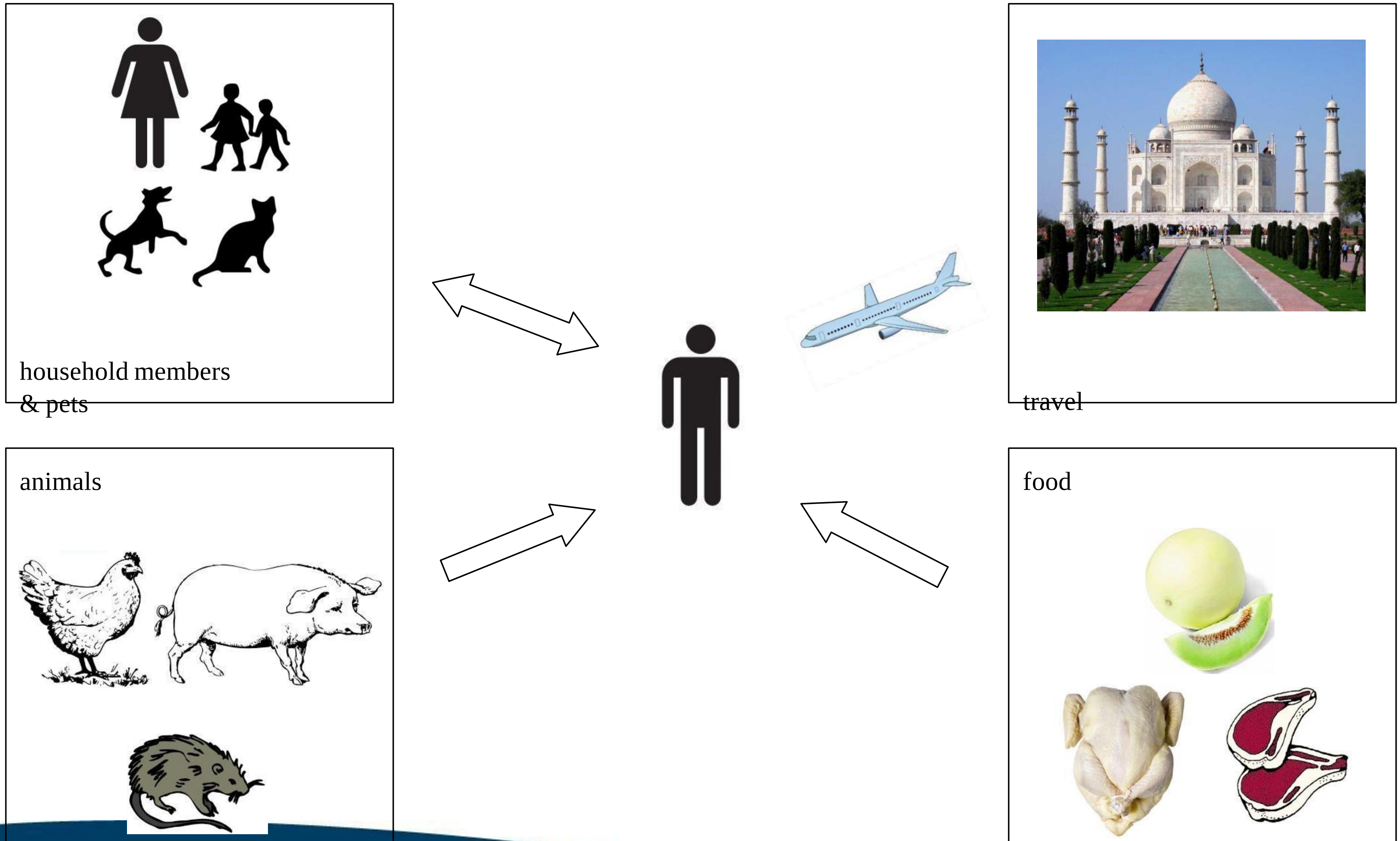


FIGURE 4 | Epidemiological features of OXA-48-like-producing *K. pneumoniae*. (1) Turkey; (2) Morocco; (3) Tunisia; (4) Libya; (5) Egypt; (6) India; (7) Argentina; (8) Spain; (9) France; (10) Germany; (11) Switzerland; (12) Belgium; (13) Netherlands; (14) UK; (15) Italy; (16) Israel; (17) Saudi Arabia; (18) Kuwait; (19) Lebanon; (20) Japan; (21) Canada; (22) USA; (23) Ireland; (24) Poland; (25) Finland; (26) Hungary; (27) Romania; (28) Bulgaria; (29) Greece; (30) Russia; (31) Algeria; (32) Senegal; (33) South Africa; (34) United Arab Emirates; (35) Oman; (36) Iran; (37) Sri Lanka; (38) Thailand; (39) Singapore; (40) South Korea; (41) Taiwan; (42) Australia; (43) New Zealand.

Lee et al. Front Microbiol. 2016; 7: 895.

What makes Gram-negatives unique?
Horizontal Gene Transfer

Spread

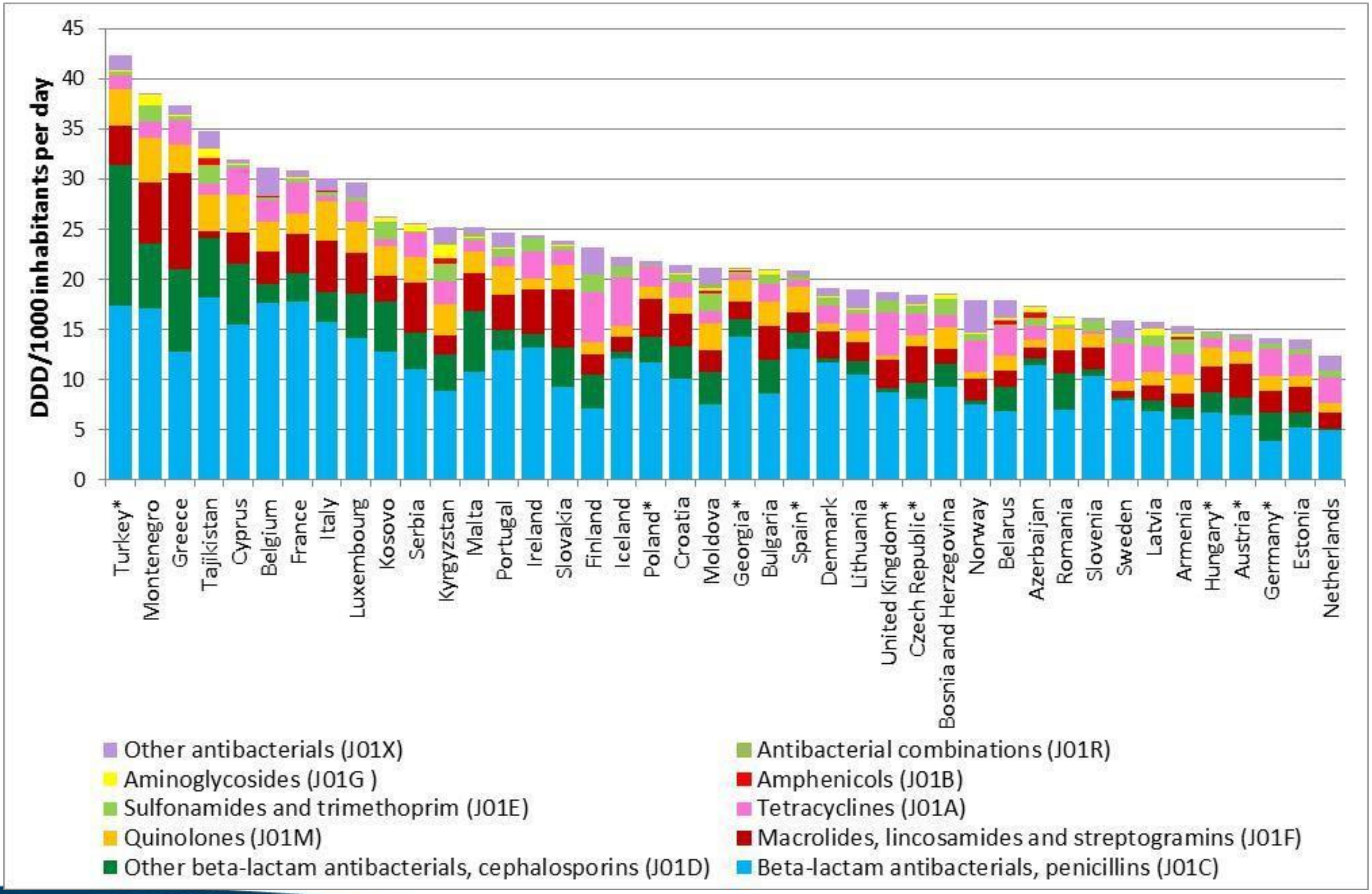


SOLUTIONS

"If you cannot measure it, you cannot improve it"

Lord Kelvin
1824-1907

Total antibiotic use in 2011 in number of DDD per 1000 Inhabitants per Day in 12 European countries and Kosovo as compared to 29 ESAC-Net countries



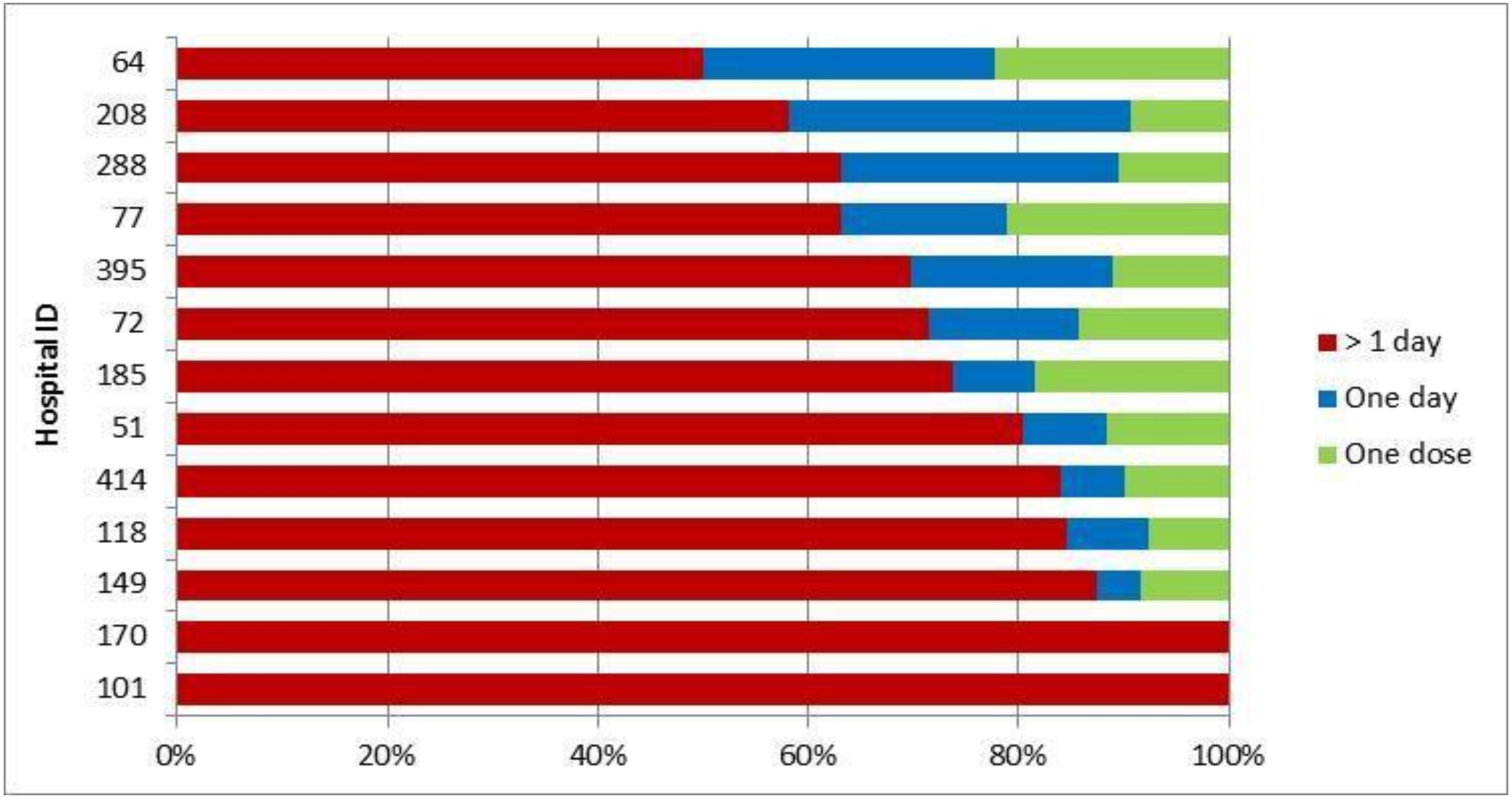
Versporten et al, LID, 20 March 2014

National Quantity Targets to Improve Outpatient Antibiotic Prescribing

Country	Quantity metric for antibiotic consumption	Level of target
Belgium	Packages per 1000 inhabitants per year (PID)	600 PID by 2020 400 PID by 2025
Sweden	Prescriptions per 1000 inhabitants per year (PrID)	250 PrID by 2014
Norway	Defined Daily Doses per 1000 inhabitants per day (DID)	30% reduction in DID by 2020 compared to 2012
England	Prescriptions per 100 patients per year (PrID)	≥4% reduction in PrID in 2016/17 on 2013/2014 performance
Turkey	Defined Daily Doses per 1000 inhabitants per day (DID)	35 DID by 2017

Point Prevalence Survey in Japan

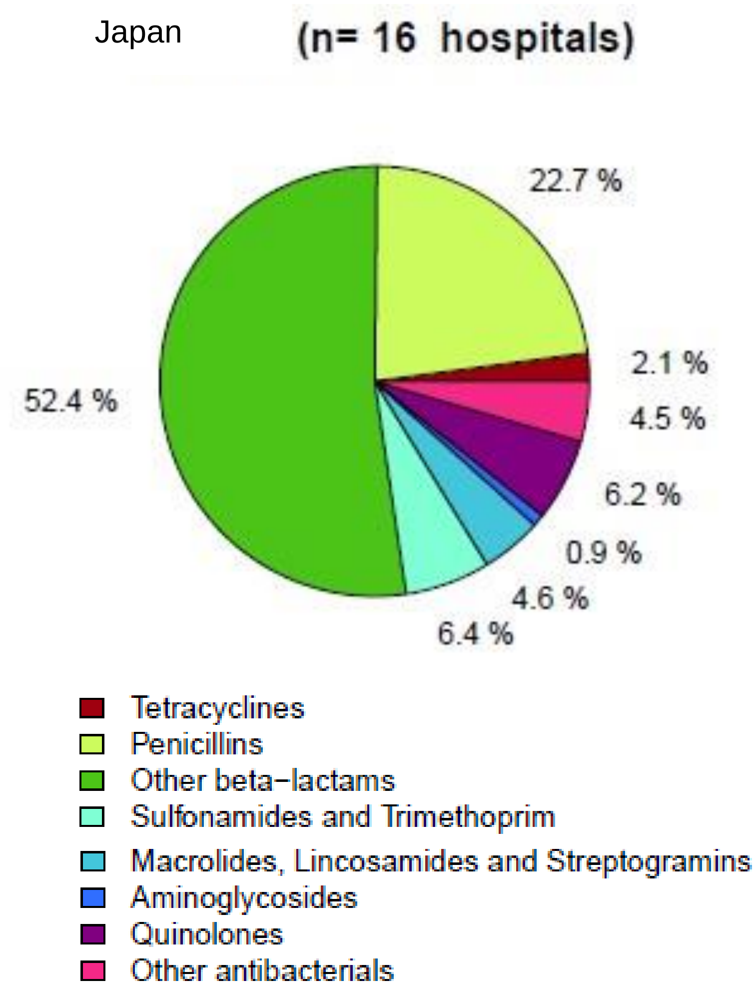
Duration of surgical prophylaxis in 13 Japanese hospitals



Selection hospitals with ≥ 10 patients receiving surgical prophylaxis (n=13 hospitals)

Antibiotic choice for surgical prophylaxis in Japanese hospitals

	Japan (%)	Europe (%)
Cefazolin	38.2	28.5
Cefcapene	10.9	/
Cefmetazole	8.9	/
Cefditoren	6.3	/
Cefotiam	5.3	/
Cefdinir	3.8	/
Ampicillin/ enz.inh.	3.6	0.3
Flomoxef	3.4	/
Cefaclor	3.1	0.1
Levofloxacin	2.5	0.6
Ceftriaxone	1.4	16.7
Ciprofloxacin	0.5	4.8
Clindamycin	0.5	1.8
Amoxicillin/enz.inh.	0.4	7.8
Cefuroxime	/	9.4
Metronidazole	/	7.9
Gentamicin	/	6.1



National Quantity Targets to Improve Inpatient Antibiotic Prescribing

Scotland: duration of surgical prophylaxis <24 hours ≥95% compliance

England: total antibiotic consumption to be reduced by 1% per year 2015-2019 as measured by DDD per 1000 Admissions per Year

USA: inappropriate antibiotic use will be reduced by 20% from 2014 levels by 2020.

China: antibiotic utilization in general hospitals should be less than 40 DDD/ per 100 Patient Days

Global Trends of MRSA

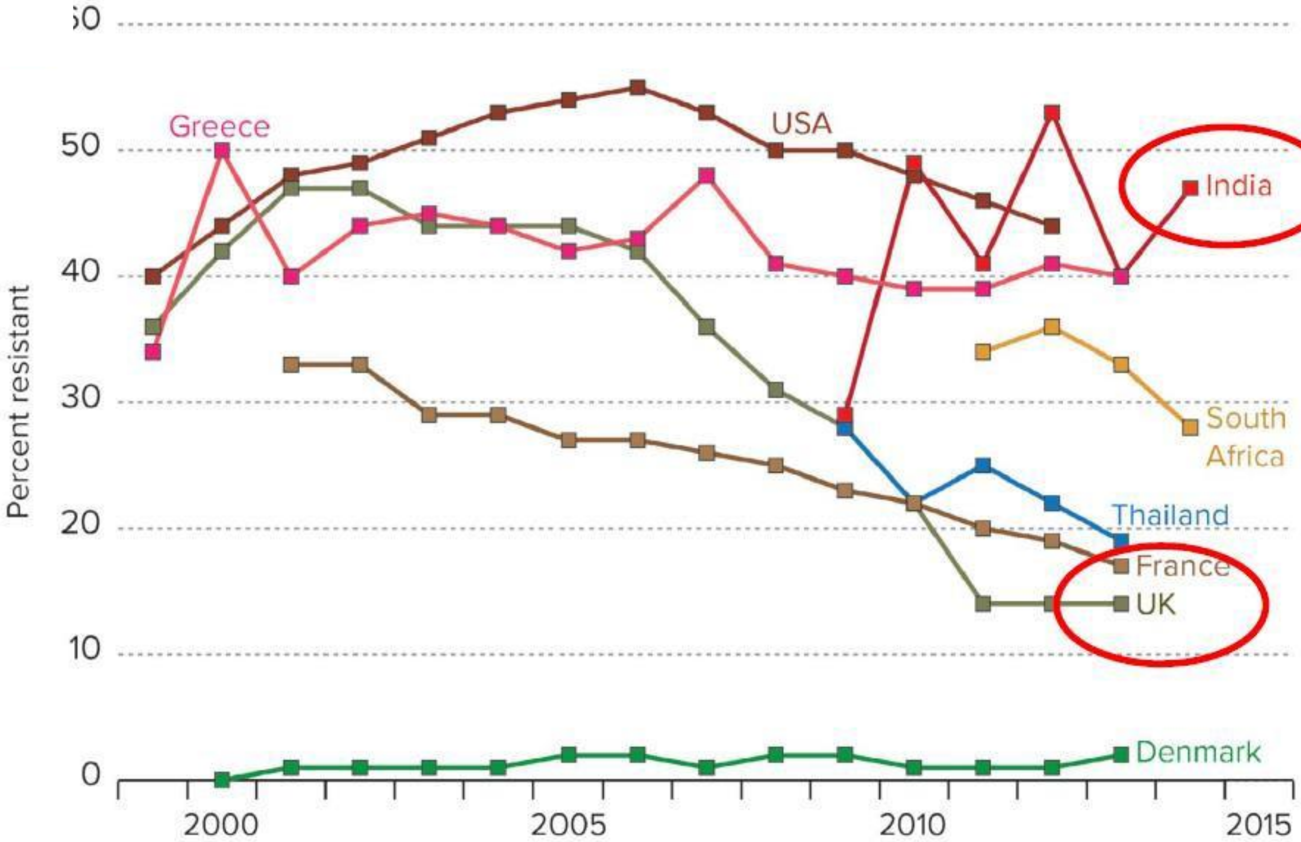


FIGURE ES-1[1]: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014

Source: CDDEP 2015

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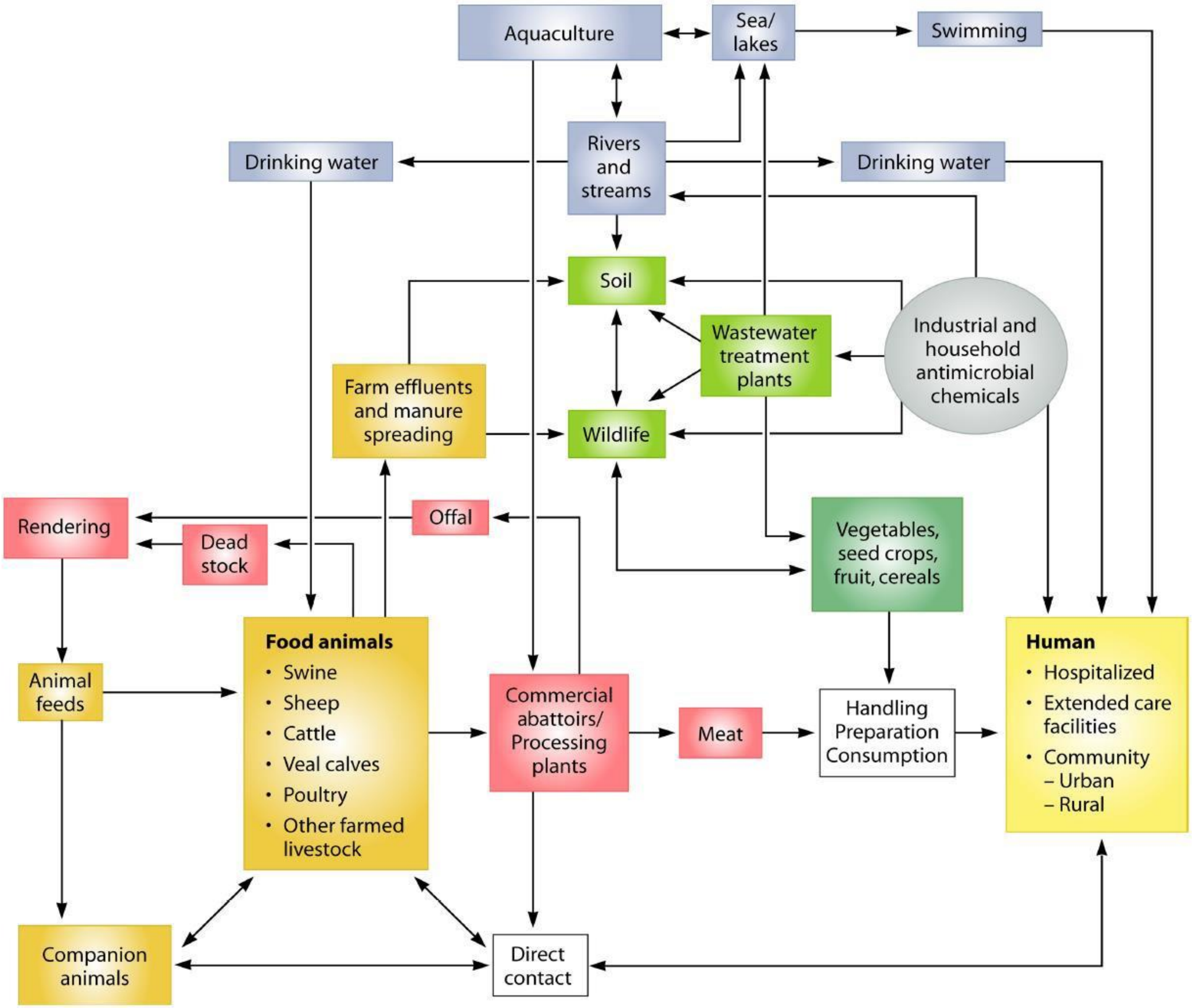
http://cddep.org/publications/state_worlds_antibiotics_2015

Reasons for Success with HA-MRSA in Europe

- **In many of these countries:**
  - Nation-wide implementation of **Infection Control** programs
  - Improvements of contact isolation, environmental control, hand hygiene with reduced cross transmissions
  - Dedicated and coordinated IC networks providing training, surveillance & evaluation
  - Screening for MRSA carriage
- **Other factors:**
  - "Ecosystem-specific" clonal spread of MRSA and absence of Horizontal Gene Transmission?
  - Antibiotic policies with reduced antibiotic selective pressure?
  - Transmissibility, natural fluctuation of certain clones, virulence, change in practise or case mix or LOS,...?
  - Regression to the mean?

The solutions are daunting!!



Davies et al , Microbio Mol Biology Rev 2010; 74-417-33

G20 Leaders' Communique Hangzhou Summit 4-5 September 2016

“We affirm the need to explore in an inclusive manner to fight antimicrobial resistance by developing evidence-based ways to prevent and mitigate resistance, and unlock research and development into new and existing antimicrobials from a G20 value-added perspective, ….”

General Assembly of the UN
21 September 2016

General Assembly of the United Nations

PRESIDENT OF THE 70TH SESSION—A NEW COMMITMENT TO ACTION

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Home › Events › High-level Meeting on Antimicrobial Resistance

High-level Meeting on Antimicrobial Resistance

21 September 2016

On 21 September 2016, the President of the UN General Assembly convenes an one-day high-level meeting at the UN Headquarters in New York on "Antimicrobial Resistance", with the participation of Member States, non-governmental organizations, civil society, the private sector and academic institutions, in order to provide input.

The primary objective of the meeting is to summon and maintain strong national, regional and international political commitment in addressing antimicrobial resistance comprehensively and multi-sectorally, and to increase and improve awareness of antimicrobial resistance.

The meeting emphasizes the important role and the responsibilities of governments, as well as the role of relevant inter-governmental organizations, particularly the World Health Organization within its mandate and in coordination with FAO and o IE, as appropriate, in responding to the challenges of antimicrobial resistance, and the essential need for multi-sectorial and cross-sectorial efforts and engagement of all relevant sectors of society, -such as human and veterinary medicine, agriculture, finance, environment and consumers- to generate an effective response, including towards a one-health approach.

Most significant attention ***ever*** from senior global political leadership in **2016**

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