Health Impact of Antimicrobial Resistance (AMR) on reducing treatment options

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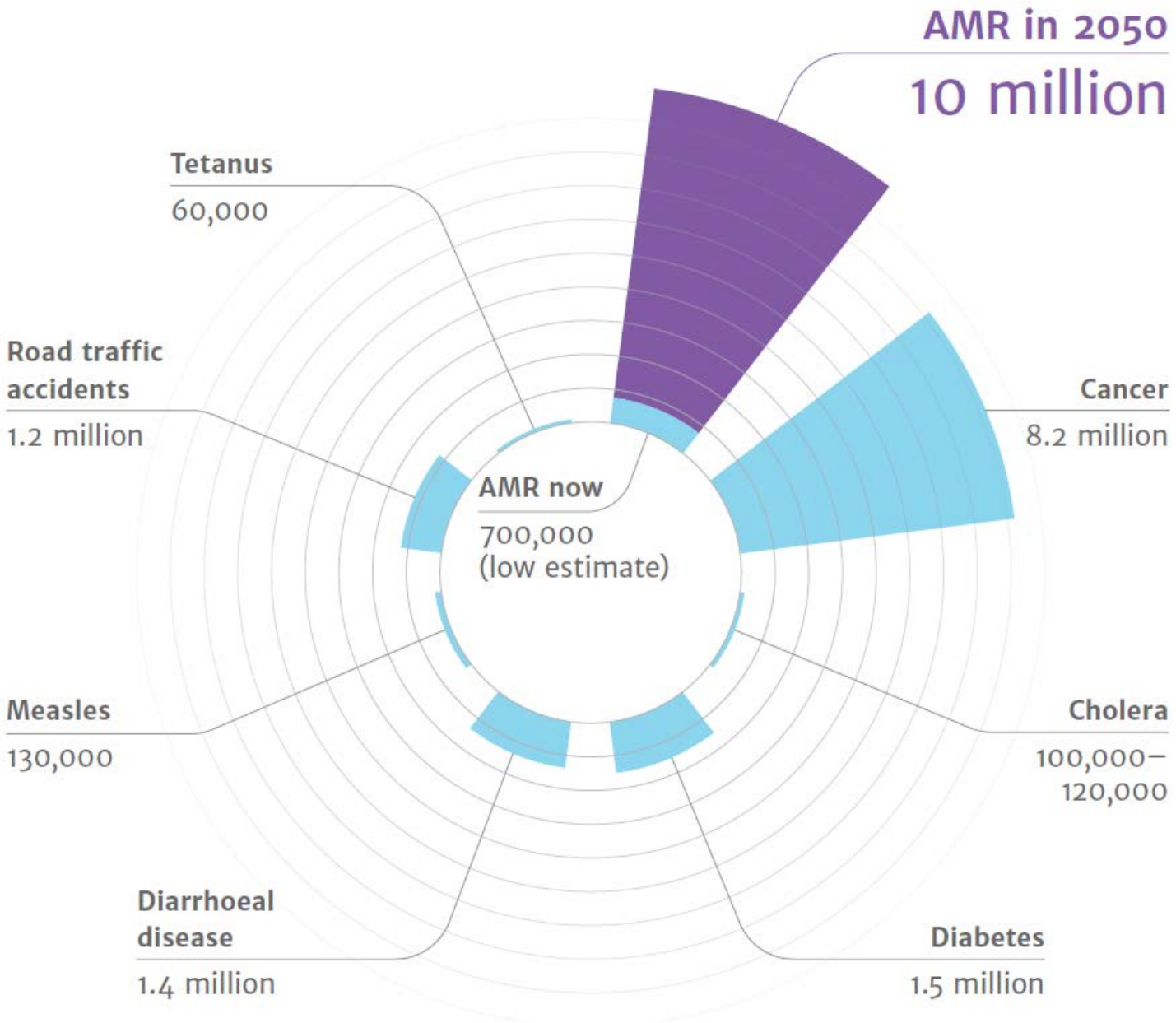
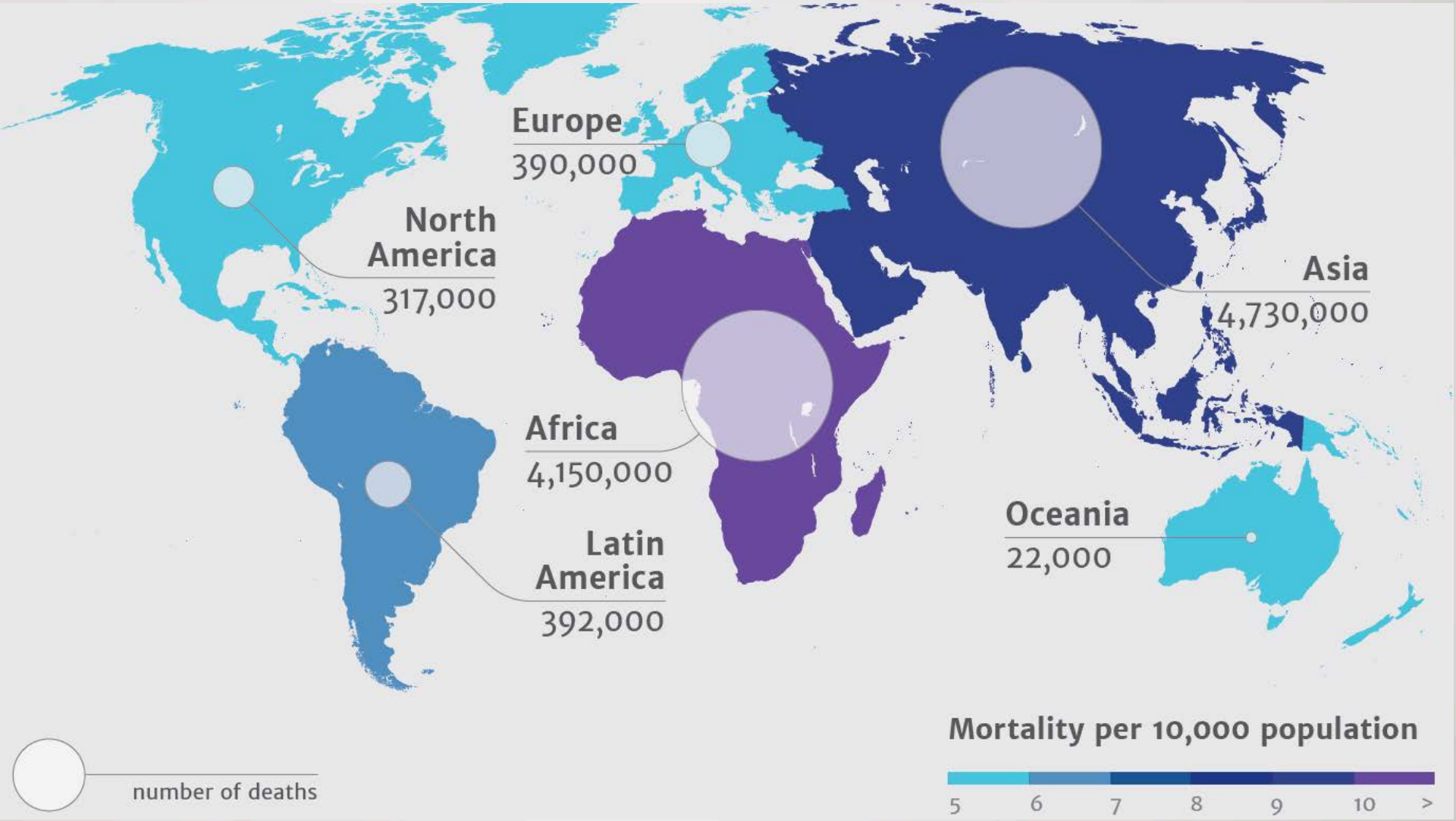


AMR Review: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

Deaths attributable to AMR by 2050



Review on AMR, 2014

Hong Kong Major Health Indicators in 2016 and 2017

Major Health Indicator		2016	2017
Crude birth rate (No. of live births per 1000 population)		8.2	7.7
Crude death rate (No. of deaths per 1000 population)		6.4	6.2
Age-standardised death rate (No. of deaths per 1000 standard population*)		2.9	2.7#
Infant mortality rate (No. of deaths per 1000 live births)		1.7	1.6#
Maternal mortality ratio (No. of deaths per 100000 live births)		0.0	1.8#
Life expectancy at birth (years)	Male	81.3	81.7#
	Female	87.3	87.7#

https://www.chp.gov.hk/en/statistics/data/10/27/110.html

Percentage' change in Leading Cause of Death in Hong Kong, 2001 vs 2017

Cause of Death	2001*	2017*	% change
1. Malignant neoplasms (ICD10: C00-C97)	133.5	97.6	-36.8%
2. Pneumonia (ICD10: J12-J18)	32.4	38.7	19.4%
3. Diseases of heart (ICD10: I00-I09, I11, I13, I20-I51)	52.3	35.0	-33.0%
4. Cerebrovascular diseases (ICD10: I60-I69)	34.4	17.7	-48.5%
5. External causes of morbidity and mortality (ICD10: V01-Y89)	23.5	9.4	-60.0%
6. Nephritis, nephrotic syndrome and nephrosis (ICD10: N00-N07, N17-N19, N25-N27)	11.6	9.1	-21.6%
7. Chronic lower respiratory diseases (ICD10: J40-J47)	22.9	8.3	-63.8%
8. Dementia (ICD10: F01-F03)	2.6	6.0	160.9%
9. Septicaemia (ICD10: A40-A41)	4.7	5.4	14.9%
10. Diabetes mellitus (ICD10: E10-E14)	7.6	2.3	-68.5%
All other causes	55.7	45.8	-17.8%
All causes	381.3	274.9	-27.9%

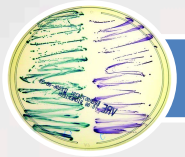
* No./100,000 age-standardized population

https://www.chp.gov.hk/en/statistics/data/10/27/339.html

Antimicrobial Resistance

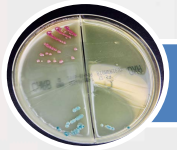
- Makes infections more difficult to treat: Delays appropriate therapy and increases morbidity and mortality
- Increases the length and severity of illness
- Lengthens the period of infectivity
- Increases length of hospital stay
- Increases adverse reactions
- Increases direct and indirect costs

ESKAPE - Bacteria



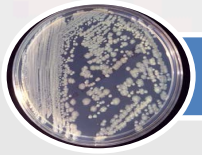
Enterococcus faecium

Staphylococcus aureus



Klebsiella pneumoniae

Pseudomonas aeruginosa



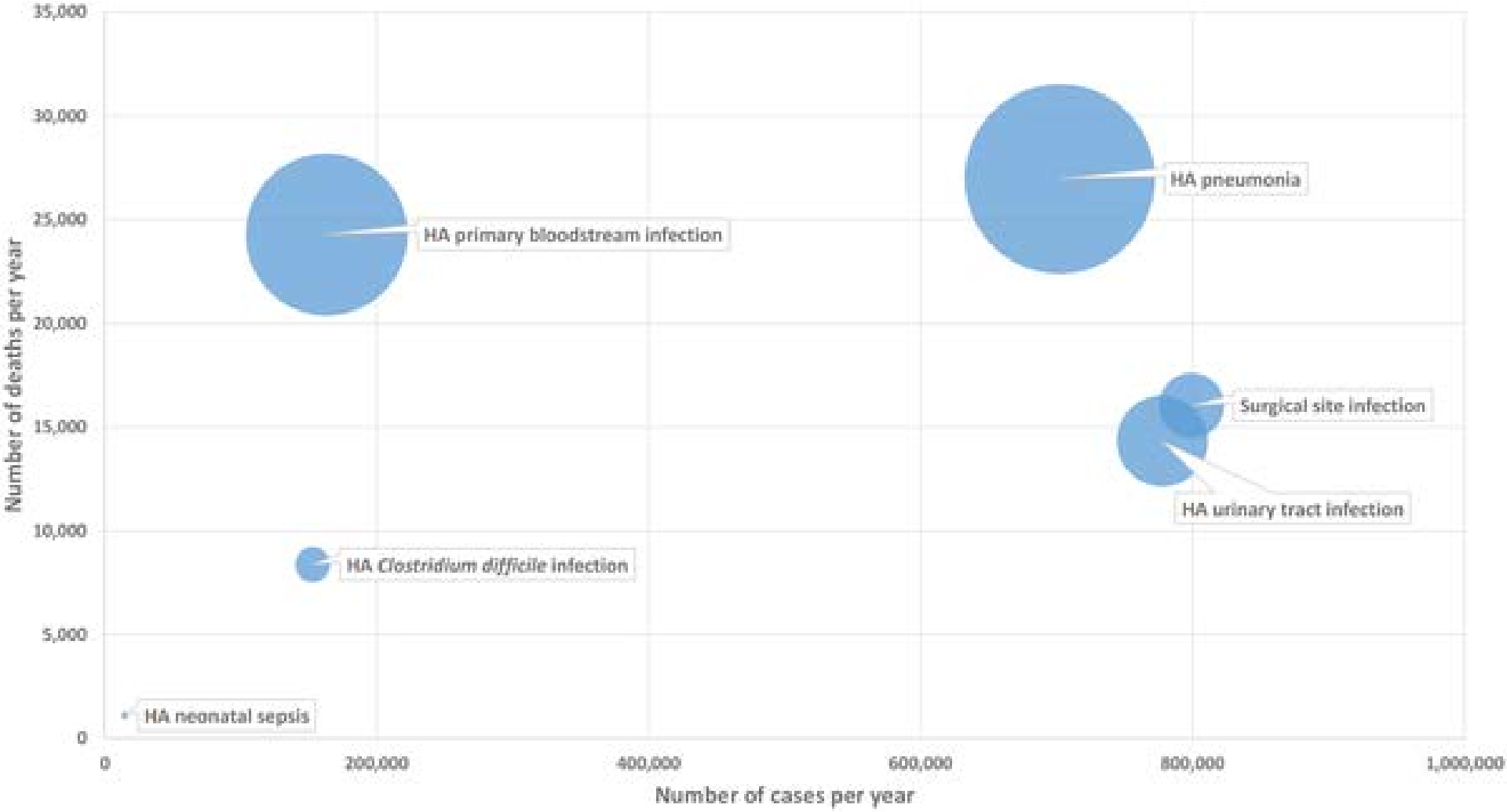
Enterobacter spp

Burden of HAI in European Population: Estimating Incidence-based DALYs through a population prevalence-based model

- Morbidity and mortality of increasingly resistant organisms is difficult to quantify
- Burden of 6 common HAIs was estimated based on European CDC point prevalence survey of HAIs and antimicrobial use
  - HA Pneumonia
  - HA primary Bloodstream infection
  - HA Clostridium difficile infections
  - Surgical site infections
  - HA UTI
  - HA neonatal sepsis
- Reduced life expectancy within hospital population was adjusted for using severity groups based on McCabe score
- Estimated burden of HAIs in DALYs allowing combined estimates of morbidity and mortality to compare with other diseases and inform ranking suitable for prioritization

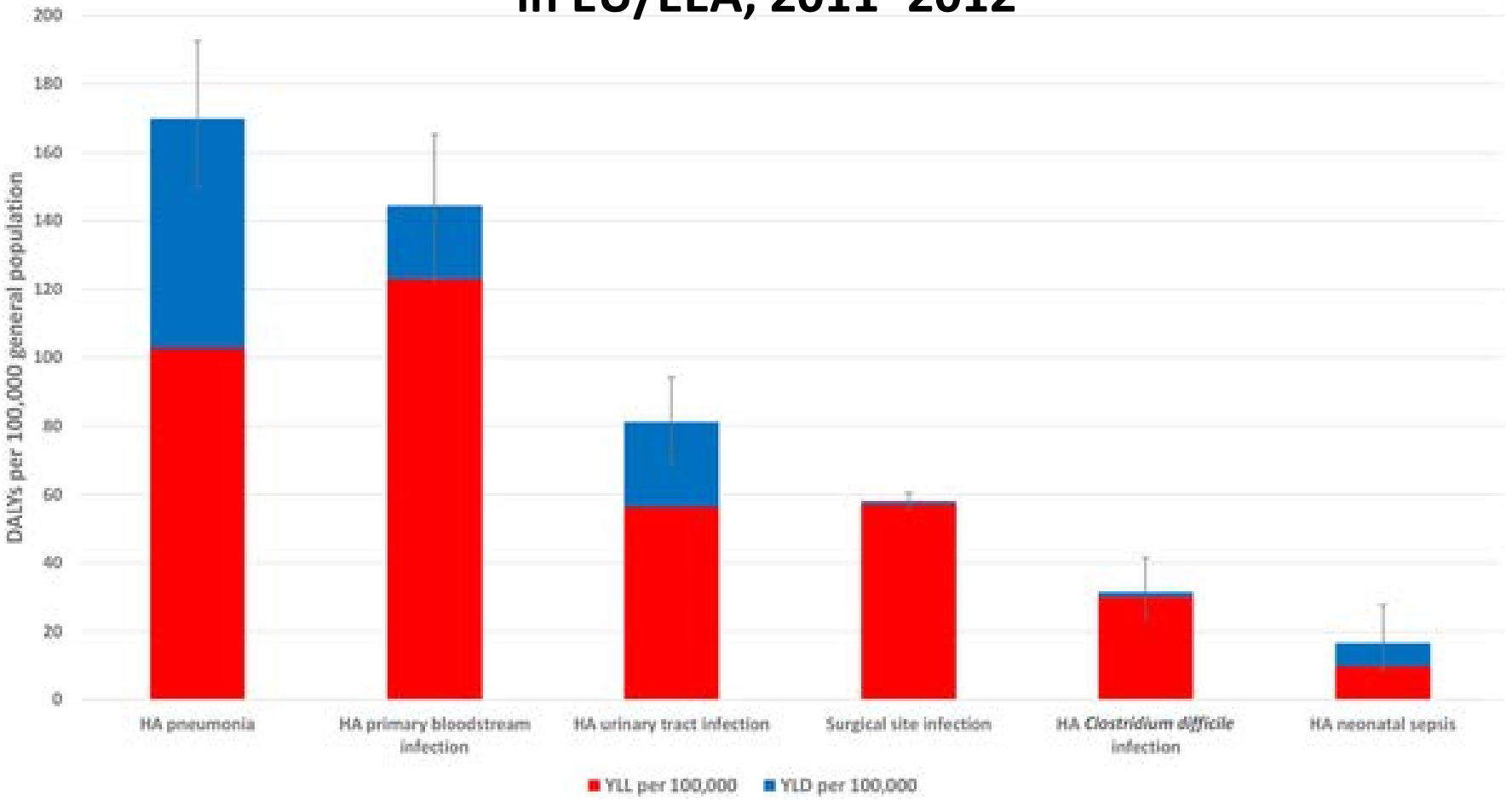
Cassini A, et al. PLOS Medicine 13(10): e1002150. https://doi.org/10.1371/journal.pmed.1002150
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002150

Six healthcare-associated infections according to their number of cases per year (x-axis), number of deaths per year (y-axis), and DALYs per year (width of bubble), EU/EEA, 2011–2012.



Cassini A, et al. PLOS Medicine 13(10): e1002150. https://doi.org/10.1371/journal.pmed.1002150
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002150

Estimated annual burden of six healthcare-associated infections in Disability-adjusted life years (DALYs) per 100,000 population in EU/EEA, 2011–2012



YLL Years of life lost due to premature mortality

YLD Years lived with disabilities following onset of disease

Cassini A, et al. PLOS Medicine 13(10): e1002150. https://doi.org/10.1371/journal.pmed.1002150
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002150

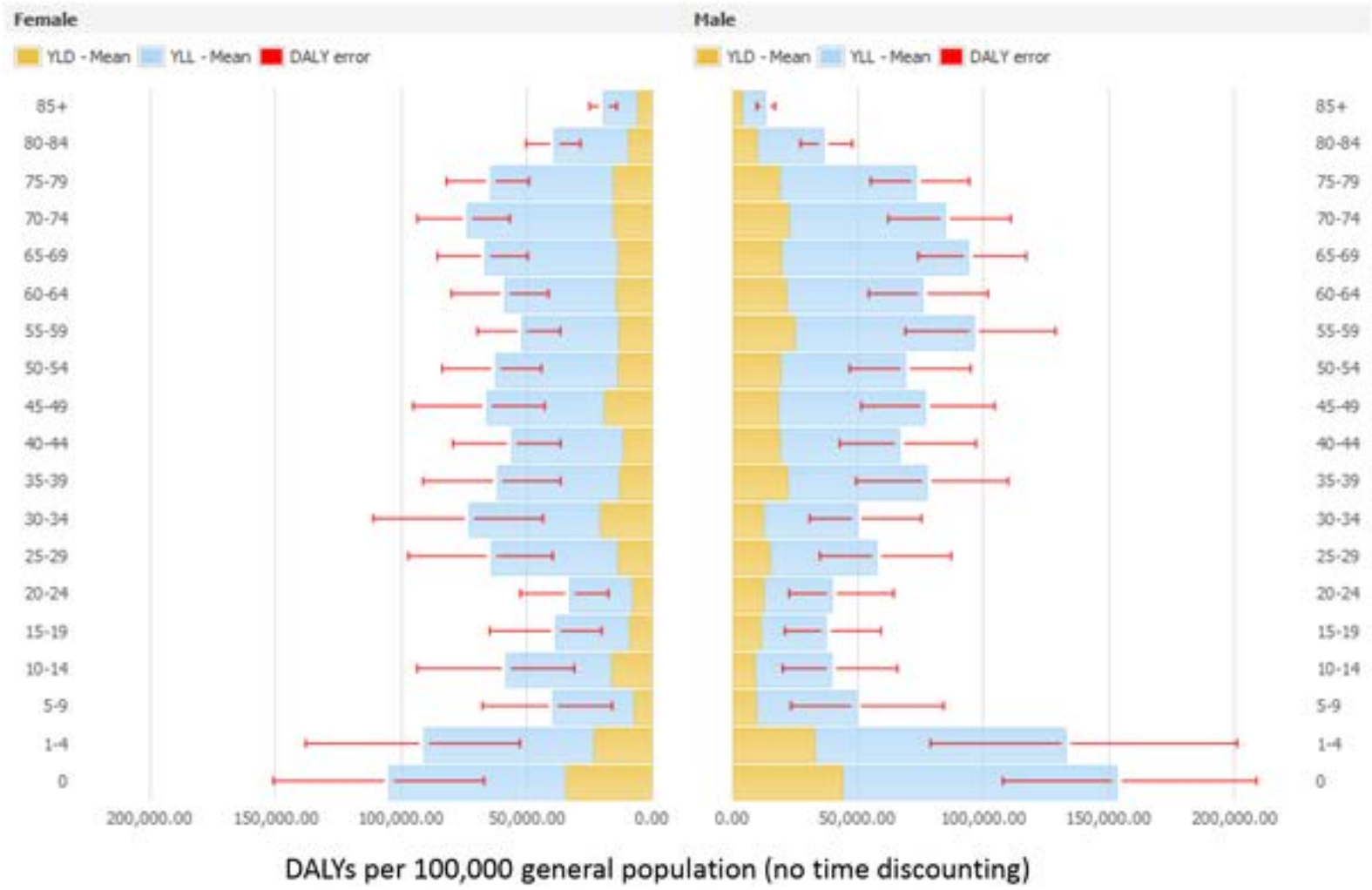
Results and Conclusions

- High burden of HAIs in DALYs in the EU/EEA : >2.5 million cases of HAI in the EU/EEA each year, approx. 2.5M DALYs

  (501 DALYs /100,000 population, 95%UI: 429-582)
- HAI-attributable outcomes and length of stay were based on review of literature.
- Life expectancy was adjusted according to severity of underlying condition.
- HA Pneumonia and HA primary Bloodstream infections were responsible for largest part of total burden of HAIs
- Total burden of 6 HAIs in Europe was higher than that of all other communicable diseases under surveillance at ECDC
- HAIs exceed the burden of other infections like influenza and tuberculosis

Cassini A, et al. PLOS Medicine 13(10): e1002150. https://doi.org/10.1371/journal.pmed.1002150
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002150

Estimated annual burden of six healthcare-associated infections in DALYs per 100,000 general population (median and 95% uncertainty interval) by gender and age group, split between YLLs and YLDs, EU/EEA, 2011–2012.



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https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002150

AR- Impact on Outcome

- Attributable morbidity and mortality of increasingly resistant organisms is difficult to quantify.

- Clinical outcome in bacteraemic infections caused by ESBL-producing K. pneumoniae appears to be worse than that for patients with non-ESBL-producing isolates

- Tumbrels et al, documented the 21-day mortality rate in an ESBL group to be 52% (25/48) whereas that in the non-ESBL group was 29% (29/99) ($P<0.007$, OR 2.62).

- Confirmed in a recent meta-analysis of bacteraemia caused by ESBL-producing Enterobacteriaceae by Schwaber et al which demonstrated an increased risk for delay in effective therapy (pooled RR, 5.36; 95% CI, 2.73 to 10.53)

(Tumbrels et al, AAC 2006; 50: 498 – 504,
Schwaber and Carmeli. JAC 2007;60:913-920)

Predictors and Mortality between ESBL- *E.coli* and *K. pneumoniae* bacteremia in 33 hospitals in 12 countries

Covariate		ESBL-EC (N = 687), No. (%)	ESBL-KP (N = 222), No. (%)	Crude OR	*P* Value	OR Multivariate (95% CI)[b]	*P* Value
Demographics							
Sex	Male	370 (54)	134 (60)	1.305	.09		
	Female	317 (46)	88 (40)				
Age, medan y (IQR)		69 (56–79)	70 (59–79)	1.003	.509		
Site of acquisition							
Nosocomial		284 (42)	139 (63)	2.349	<.001	1.391 (0.929–2.081)	.109
Community		383 (58)	80 (37)				
	Strictly community	128 (36)	21 (27)		.12		
	Community-healthcare- associated	230 (64)	58 (73)				
Epidemiological parameters							
Source	Urinary tract	327 (48)	70 (32)	0.507	<.001	0.596 (0.416–0.854)	.005
	Other	360 (52)	152 (68)				
Ward type	Emergency dept.	219 (32)	21 (15)				
	Medical ward	316 (46)	97 (45)				
	Surgical ward	92 (14)	39 (18)				
	ICU	56 (8)	47 (22)	3.151	<.001	2.303 (1.45–3.65)	<.001
	Unknown	22					
LOS to bacteremia	0–14 days	575 (84)	150 (68)	2.464	<.001	1.703 (1.1–2.639)	.017
	>14 days	112 (16)	72 (32)				
Clinical characteristics and comorbidity							
Cardiovascular disease		137 (20)	81 (36.5)	2.306	<.001	2.187 (1.527–3.13)	<.001
Neurologic disease		83 (12)	41 (18)	1.623	.02	1.618 (1.032–2.537)	.036

Scheurerman et al, ICHE 2018;39:660-667

Risk Factors for 30-day Mortality in patients with ESBL- *E.coli* Bacteremia

Parameter		No Mortality (n = 567), No. (%)	30-Day Mortality (n = 120), No. (%)	Crude OR	*P* Value	OR Multivariate (95% CI)[a]	*P* Value
Male sex		303 (53)	67 (56)	1.101	.633	1.08 (2.309–0.742)	.352
Age, median y (IQR)		68 (55–79)	73 (60–79)	1.016	.012	1.042 (1.020–1.064)	<.001
Site of acquisition	Nosocomial	221 (40)	63 (55)	1.820	.003	1.160 (0.586–2.296)	.671
	Community	332 (60)	52 (45)				
Source	Urine	295 (52)	32 (27)	0.330	<.001	0.316 (0.165–0.608)	<.001
	Other	272 (48)	88 (73)				
Appropriate empirical therapy	No	257 (45)	75 (62)	0.497	<.001	0.841 (0.422–1.677)	.623
	Yes	310 (55)	45 (33)				
Appropriate targeted therapy	No	69 (12)	53 (44)	0.175	<.001	0.202 (0.093–0.439)	<.001
	Yes	498 (88)	67 (56)				
Length of stay to bacteremia	0–14 days	483 (85)	92 (77)	1.75	.022	1.384 (0.609–3.145)	.438
	>14 days	84 (15)	28 (23)				
ICU		37 (7)	19 (16)	2.706	<.001	2.188 (0.923–5.187)	.075
McCabe classification	Nonfatal	305 (56)	32 (28)		<.001		.001
	5 years	182 (33)	44 (38)			1.950 (0.974–3.903)	
	1 year	58 (11)	39 (34)			5.501 (2.185–13.849)	
Global Pitt score	≤4	559 (99)	98 (82)	15.686	<.001	5.214 (1.377–19.740)	.151
	>4	8 (1)	22 (18)				
Severe sepsis/shock		140 (26)	87 (74)	8.431	<.001	6.724	<.001

Scheuerman et al. ICHE 2018;39:660-667

Risk Factors for 30-day Mortality in patients with ESBL- *Klebsiella pneumoniae* Bacteremia

Parameter		No Mortality (n = 147), No. (%)	30-Day Mortality (n = 75), No. (%)	Crude OR	*P* Value	OR Multivariate (95% CI)[a]	*P* Value
Male sex		90 (61)	44 (59%)	0.899	.712	0.731 (0.661–1.615)	.424
Age, median y (IQR)		71 (55–79)	68 (61–76)	1.003	.785	1.010 (0.983–1.037)	.481
McCabe classification	Nonfatal	82 (57)	27 (37)		<.001		.022
	5 years	10 (7)	19 (26)			1.553 (0.640–3.770)	
	1 year	50 (37)	27 (37)			5.567 (1.638–18.927)	
Global Pitt score	≤4	143 (97)	59 (79)	9.69	<.001	3.949 (0.983–15.870)	.053
	>4	4 (3)	16 (21)				
Severe sepsis/shock		42 (30)	54 (72)	6.06	<.001	4.270 (1.952–9.339)	<.001

Scheurerman et al, ICHE 2018;39:660-667

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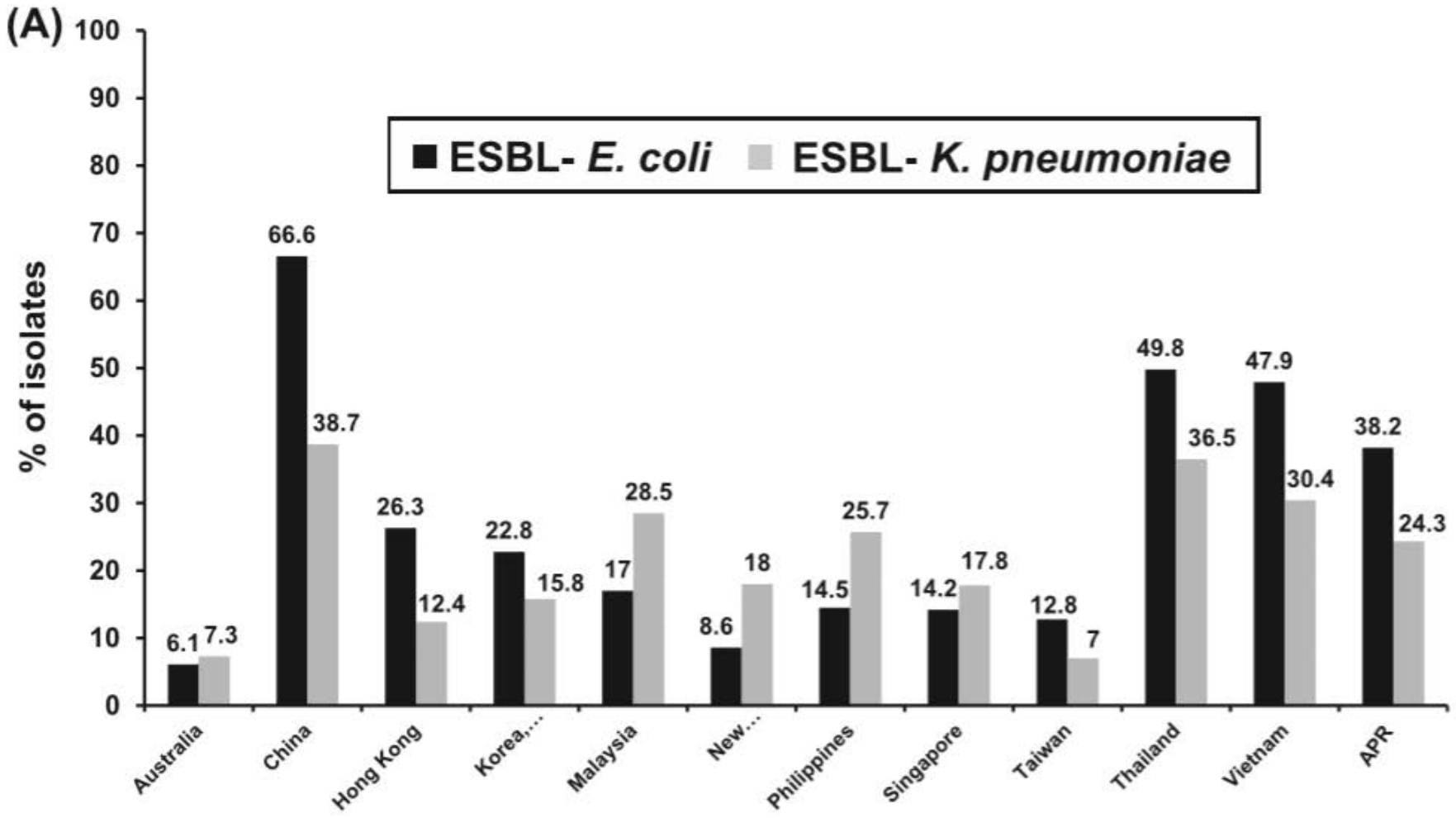
Rates of ESBL-producing *E.coli* and *K. pneumoniae* causing intra-abdominal infections in Asia Pacific region (2002-2013)



Chang et al, IJAA 2017;734-739

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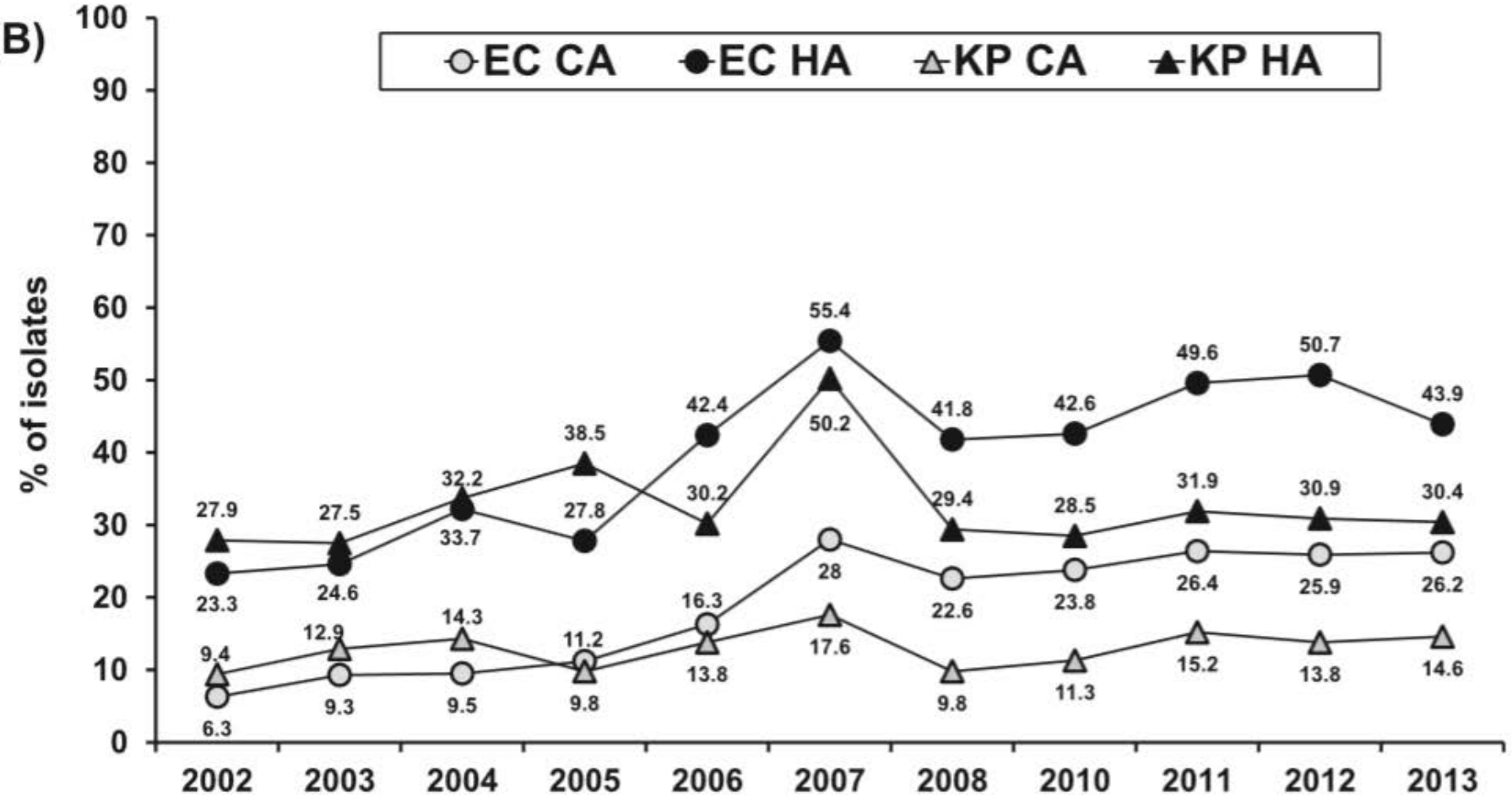


Chang et al, IJAA 2017;734-739

Vancomycin Trough Concentrations and Poor Outcomes in MRSA infections

Characteristic *N* = 308[a]	Vancomycin failure *n* (%)	*P* (vs reference category)	Nephrotoxicity[b] *n* (%)	*P* (vs reference category)
Trough <10 mg/L (*n*=70)	46 (65.7%)	0.001	10/65 (15.4%)	.682
Trough 10–14.9 mg/L(*n*=90)	52 (57.8%)	0.016	13/76 (17.1%)	.476
Trough 15–20 mg/L(n=86)	34 (39.5%)	REF	10/77 (13.0%)	REF
Trough >20 mg/L(n=62)	31 (50.0%)	0.206	17/62 (27.4%)	.032

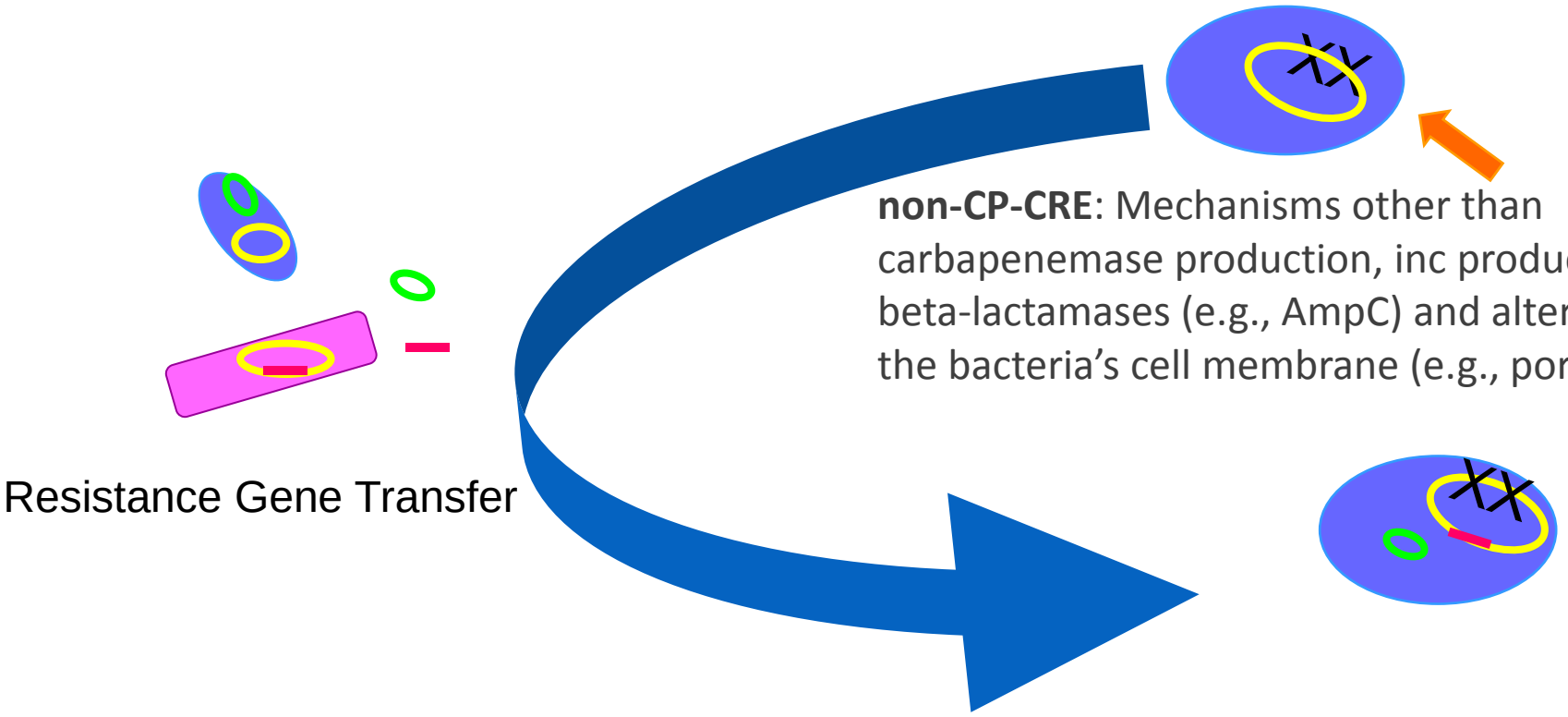
aTwelve patients without trough concentrations drawn at steady state were excluded from analysis.
bDenominators reflect exclusion of patients with end-stage renal disease from analysis of nephrotoxicity.

Kullar et al, CID2011;52:975-981

CRE vs CPEs(non-CP-CRE)

- **CRE** : *Enterobacteriaceae* nonsusceptible to carbapenems.
  - phenotypic definition i.e., based on the antibiotic susceptibility pattern
  - inc bacteria that are not susceptible to carbapenems via more than one type of mechanism.

Carbapenemase (CP-CRE) enzymes that hydrolyze carbapenems and related b-lactams



non-CP-CRE: Mechanisms other than carbapenemase production, inc production of beta-lactamases (e.g., AmpC) and alterations in the bacteria's cell membrane (e.g., porins loss).

Resistance Gene Transfer

U.S. phenotypic CRE definitions attempts to target **CP-CRE** for both surveillance and prevention, as these enzymes are carried in plasmids or MGEs and have ability to spread rapidly

Association Between Carbapenem Resistance and Mortality Among Adult with Infections Due to *Enterobacteriaceae*

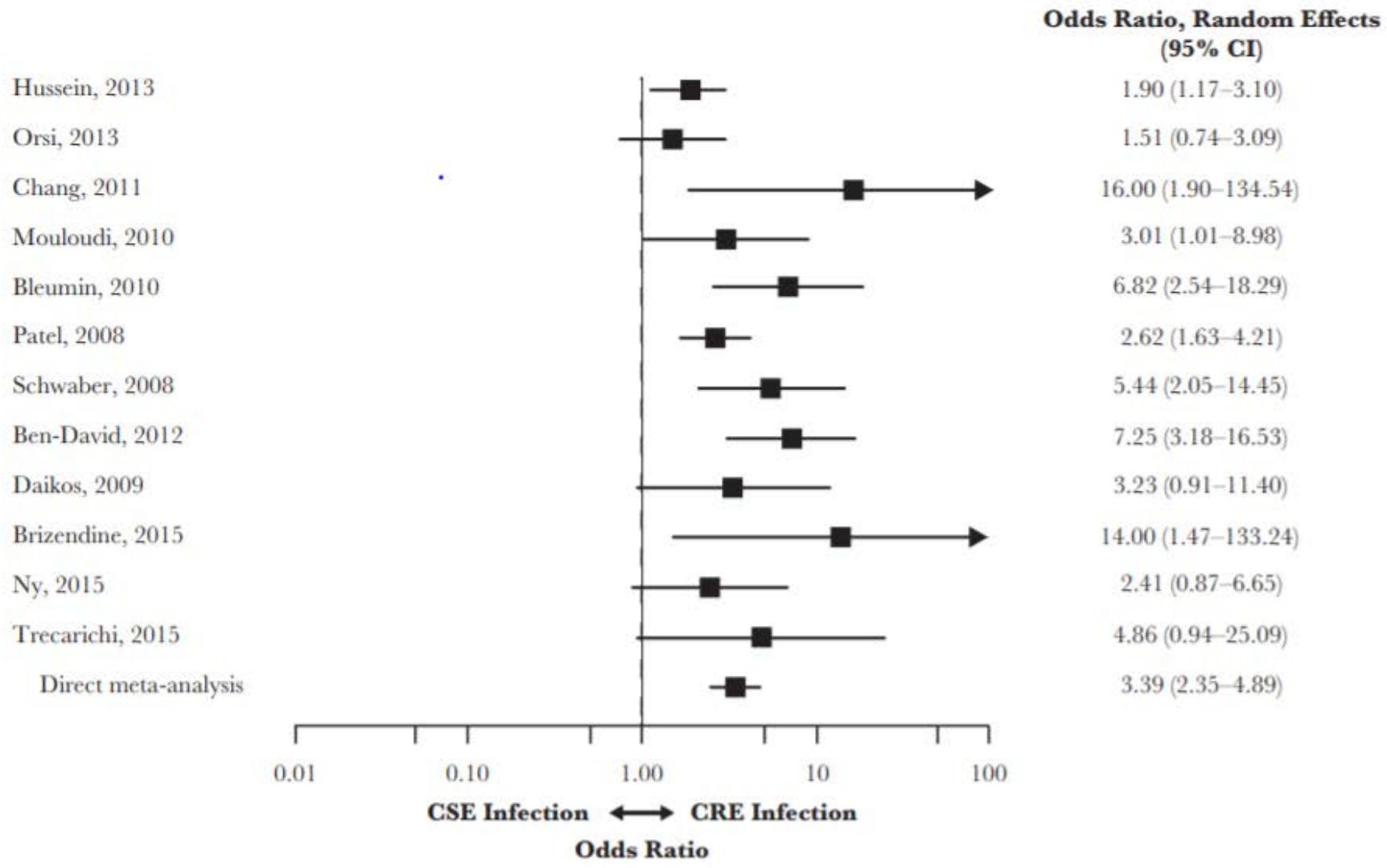


Figure 2. Mortality in patients with CRE vs CSE infections. Abbreviations: CI, confidence interval; CRE, carbapenem-resistant *Enterobacteriaceae*; CSE, carbapenem-susceptible *Enterobacteriaceae*.

Martin et al, OpenForum ID 2018

Association Between Carbapenem Resistance and Mortality Among Adults with *E. coli* Bacteremia

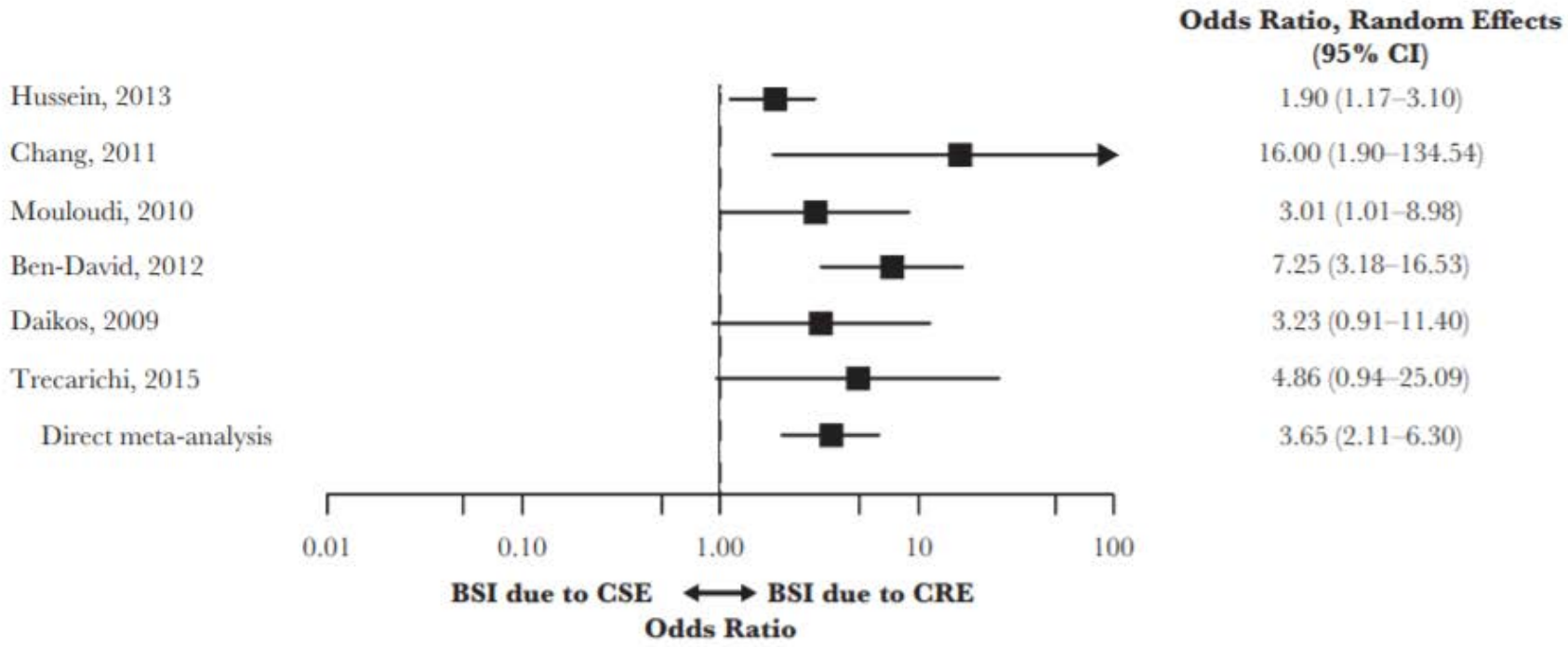
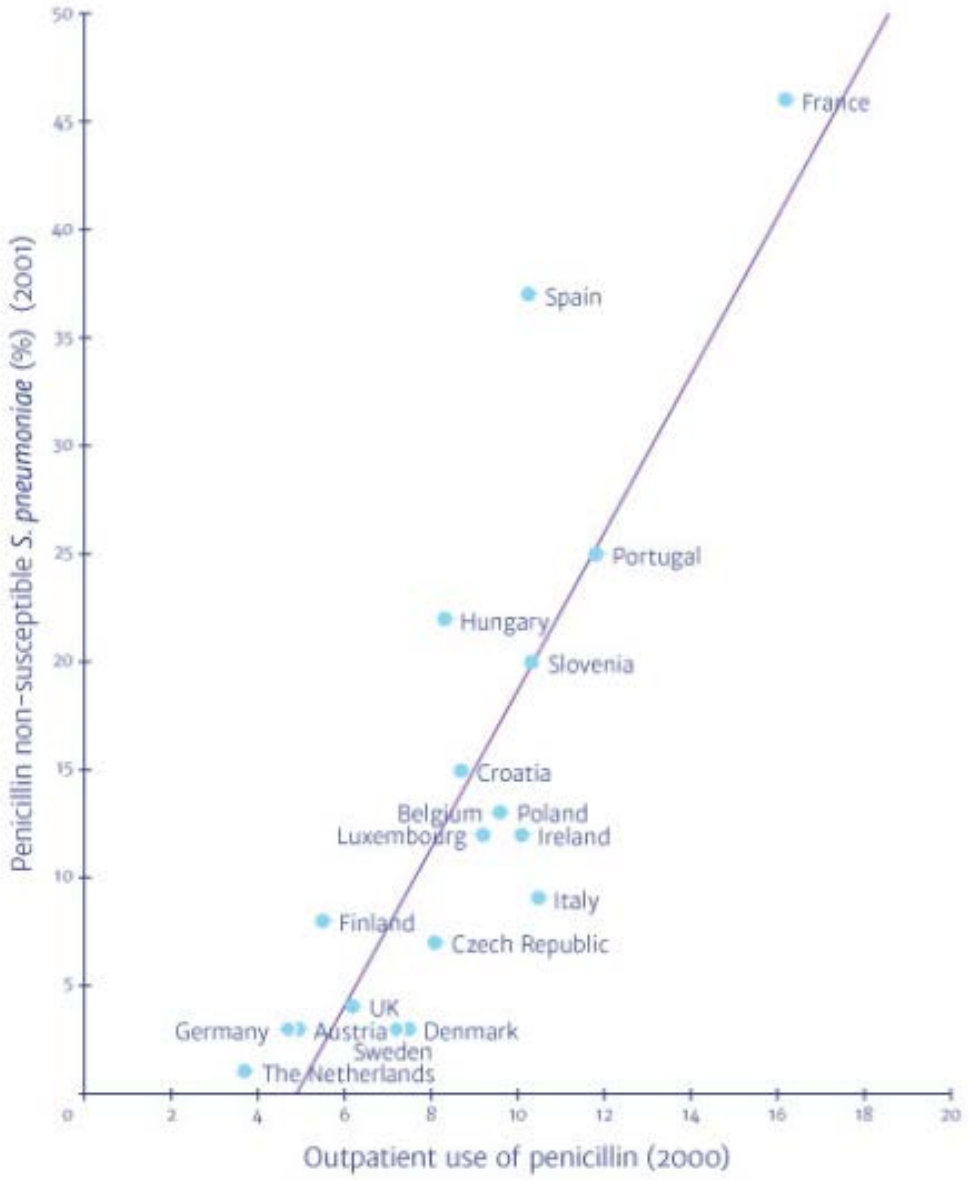


Figure 3. Mortality in patients with BSIs due to CRE vs CSE. Abbreviations: BSI, blood stream infection; CI, confidence interval; CRE, carbapenem-resistant *Enterobacteriaceae*; CSE, carbapenem-susceptible *Enterobacteriaceae*.

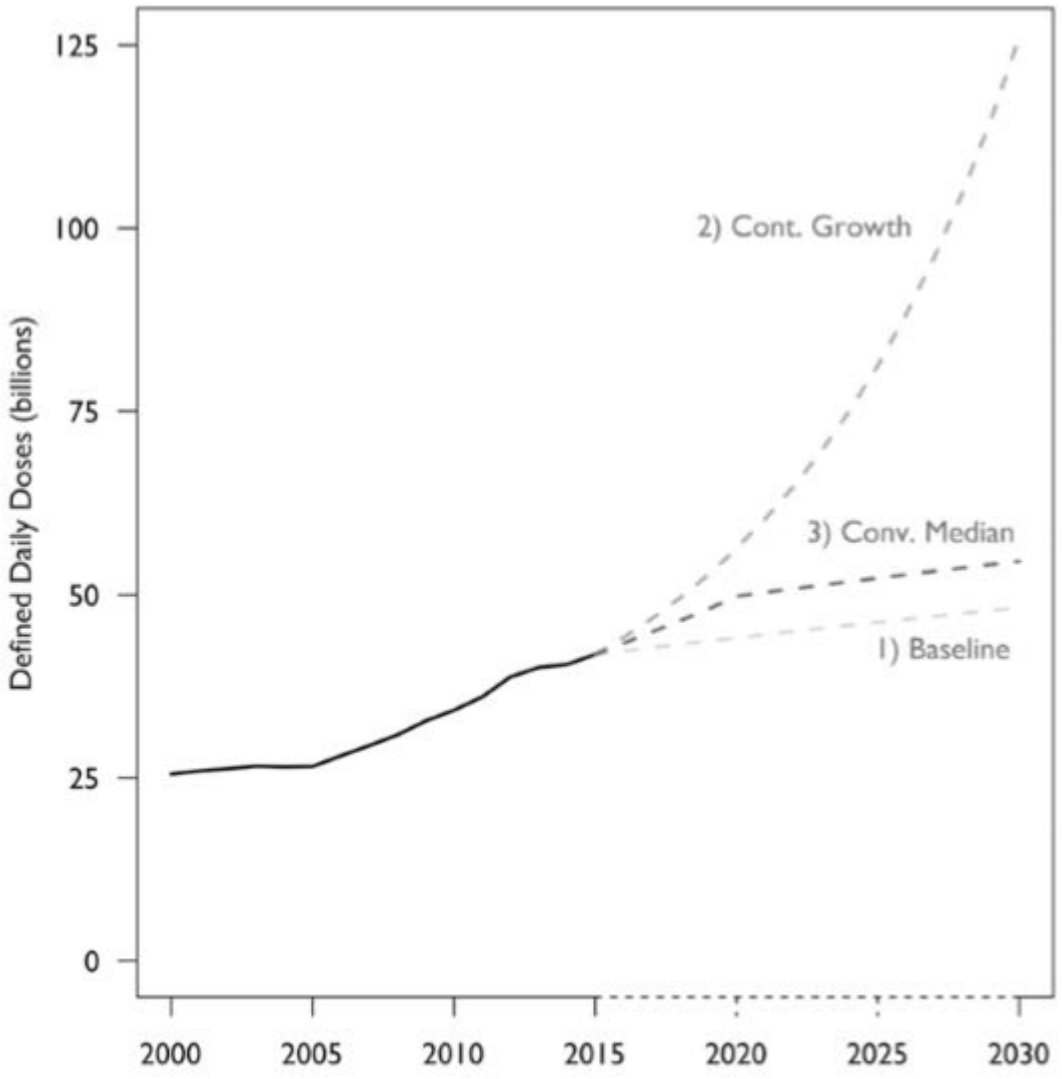
Martin et al, OpenForum ID 2018

There is a high correlation between Antibiotic Use and Resistance



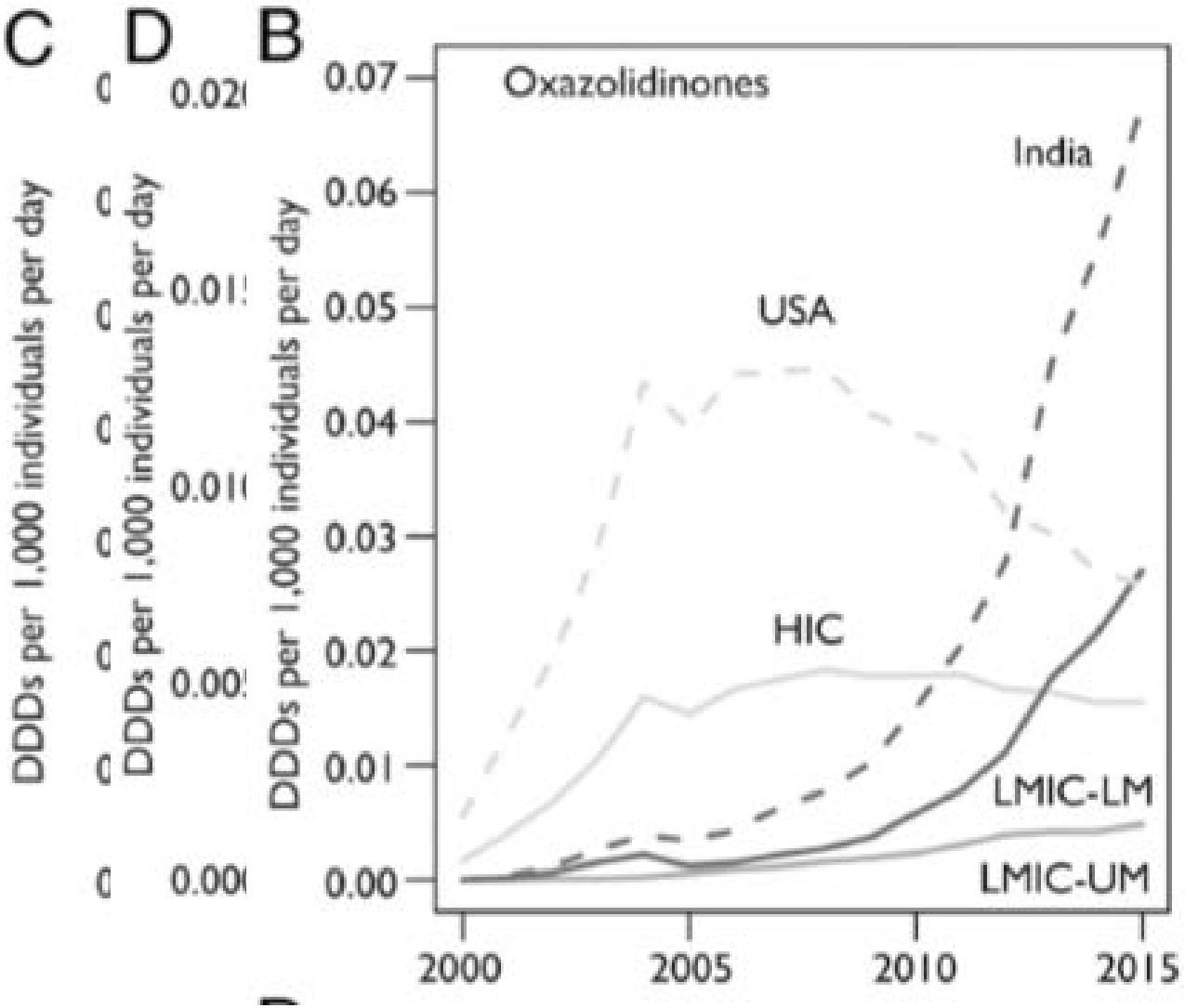
Goossens et al. Lancet 2005; 365(9459):579-87

Projected total global antibiotic consumption, 2000 - 2030
(billions of DDDs)



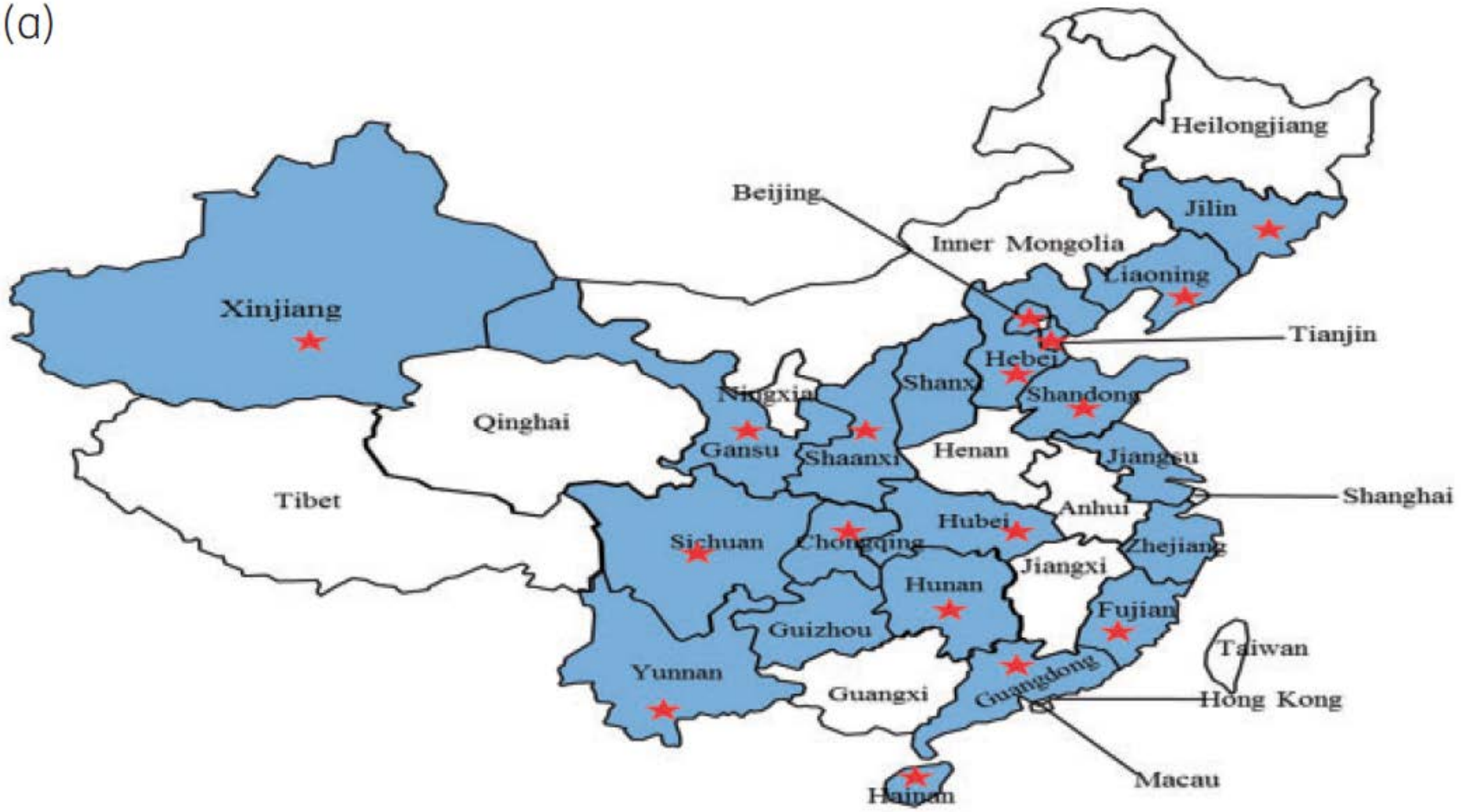
(Klein et al, PNAS 2018; doi.org/10.1073/pnas.1717295115)

Consumption of ‘last resort’ antibiotics



(Klein et al, PNAS 2018; doi.org/10.1073/pnas.1717295115)

Rates of mcr1- *E.coli* and *K. pneumoniae* in China (2007-2016)



Liu et al, JAC 2018;1786-1790

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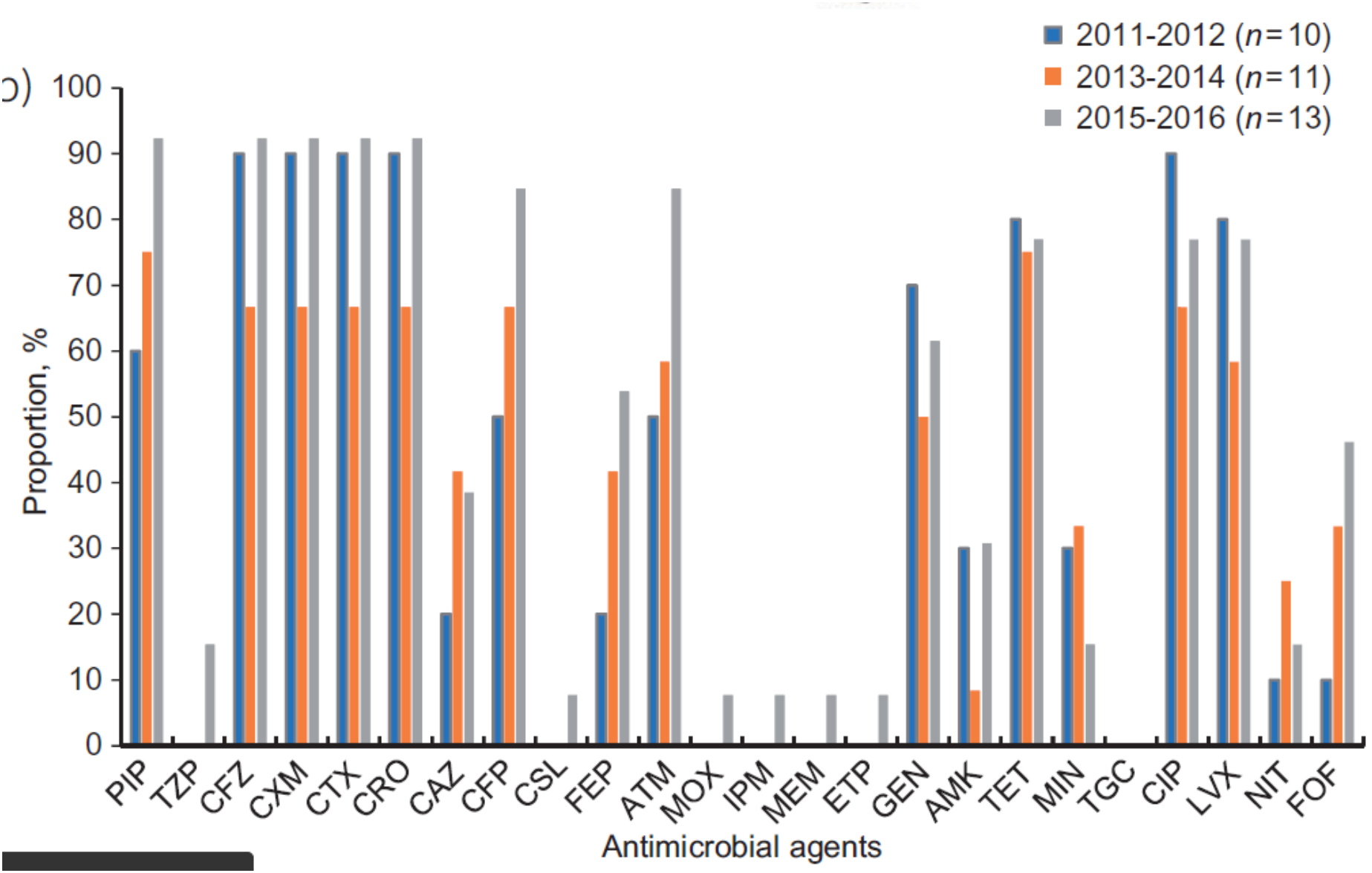
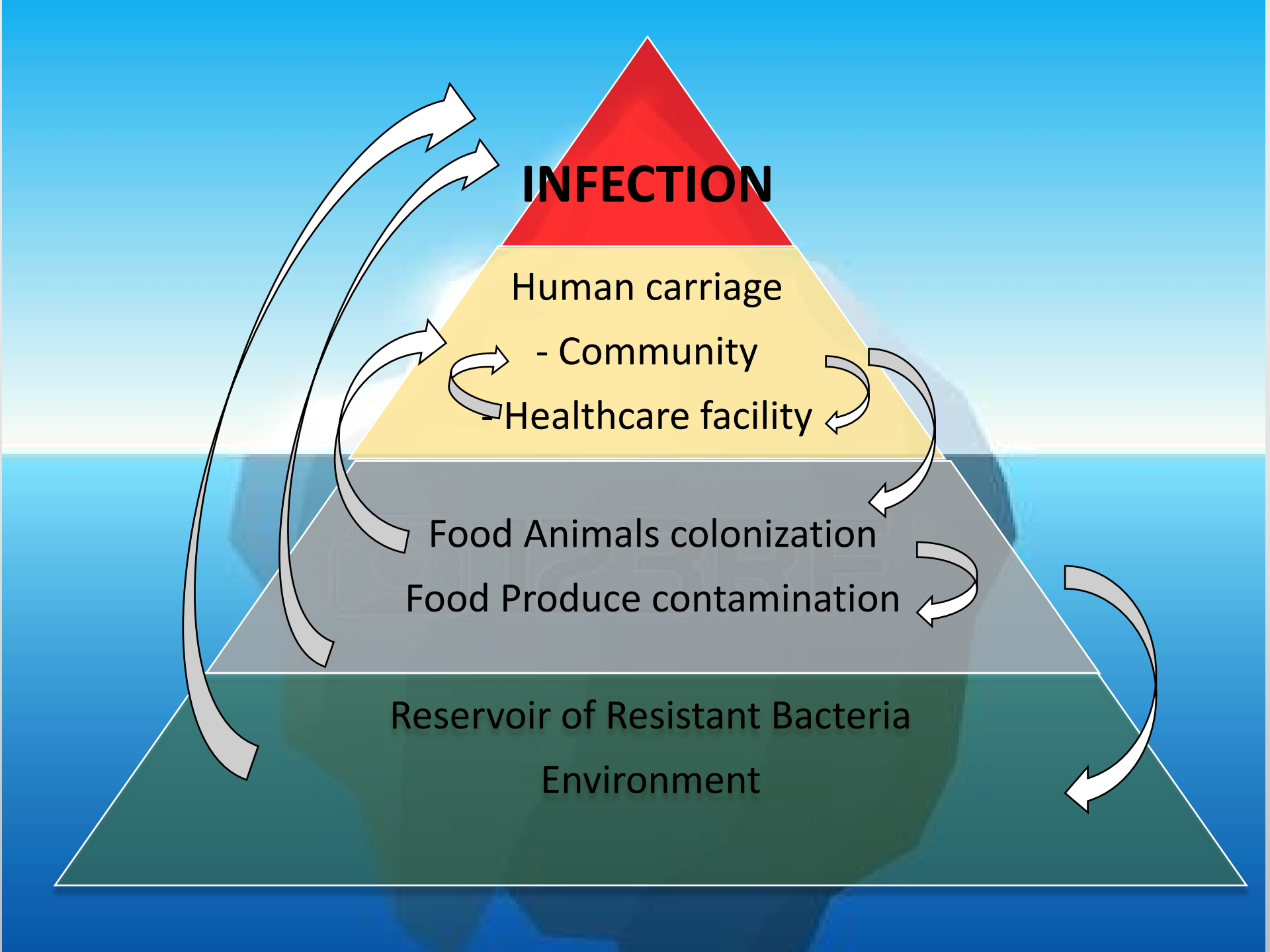
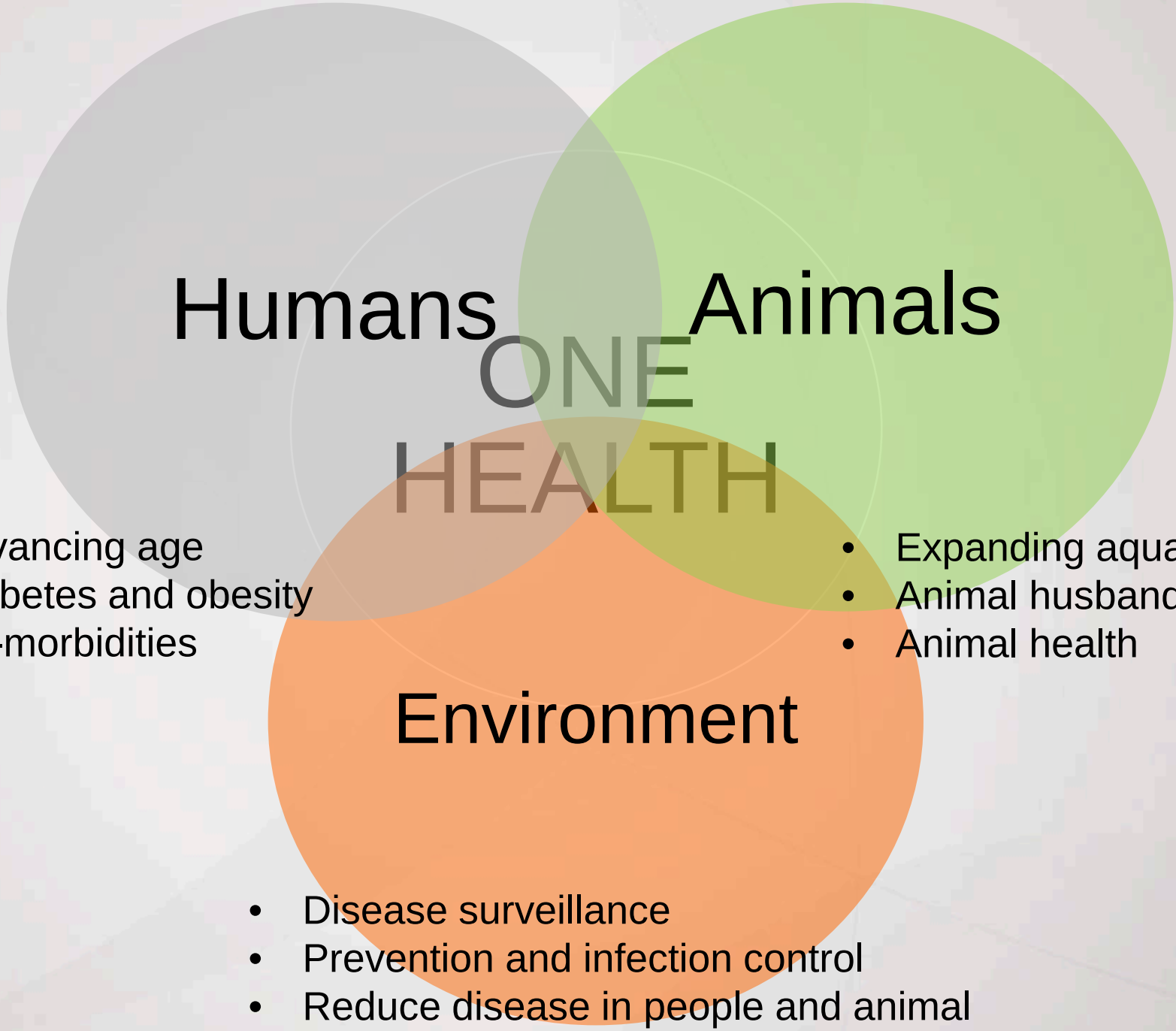


Liu et al, JAC 2018;1786-1790

Summary

- High burden of HAIs in disability adjusted life years (DALYs) in the EU/EEA
- (HA) Pneumonia and (HA) primary Bloodstream infections were responsible for largest part of total burden of HAIs
- Total burden of 6 HAIs in Europe was higher than that of all other communicable diseases under surveillance at ECDC, exceeding the burden of other infections like influenza and tuberculosis
- Examples of continual increasing trend for ESBL- and carbapemase-producing *Enterobacteriaceae* infections in Asian countries with high mortality
- Stewardship and strict use of antimicrobials to minimize resistance development
- Concerted efforts and resources to prevent and control such infections


INFECTION
Human carriage
- Community
- Healthcare facility
Food Animals colonization
Food Produce contamination
Reservoir of Resistant Bacteria
Environment



- Advancing age
- Diabetes and obesity
- Co-morbidities

- Expanding aquaculture
- Animal husbandry
- Animal health

- Disease surveillance
- Prevention and infection control
- Reduce disease in people and animal

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RFCID Commissioned Project Fund 2009-2014

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RGC/ProCore Grant 2017-2018

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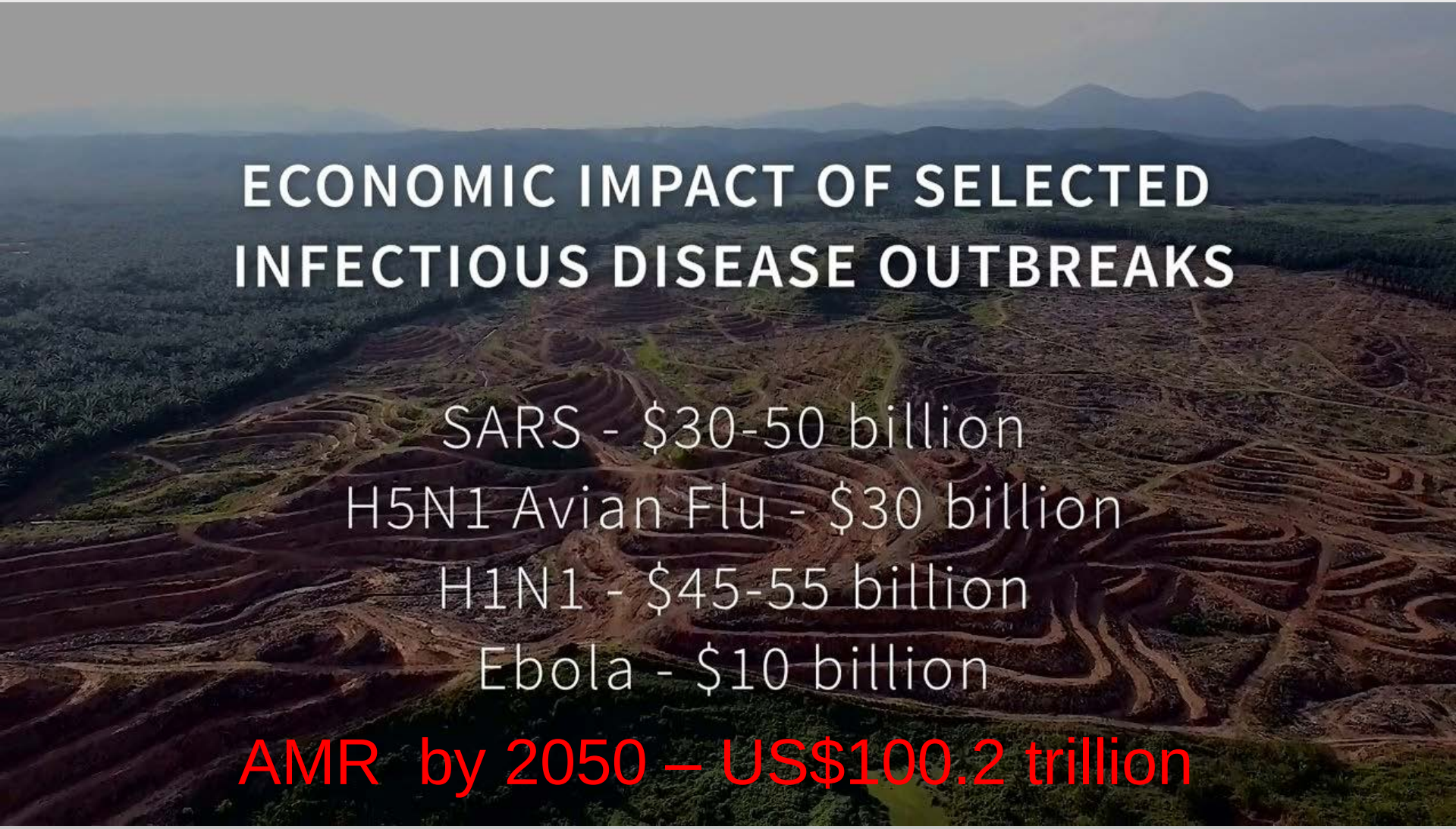
Preserve our Antibiotics



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Team members