Estimating the number of infections caused by antibiotic-resistant *Escherichia coli* and *Klebsiella pneumoniae* in 2014: a modelling study

Elizabeth Temkin, Noga Fallach, Jonatan Almagor, Beryl Primrose Gladstone, Evelina Tacconelli, Yehuda Carmeli, on behalf of the DRIVE-AB Consortium

Summary

Background The number of infections caused by resistant organisms is largely unknown. We estimated the number of infections worldwide that are caused by the WHO priority pathogens third-generation cephalosporin-resistant and carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae*.

Methods We calculated a uniform weighted mean incidence of serious infections caused by antibiotic-susceptible *E coli* and *K pneumoniae* using data from 17 countries. Using this uniform incidence, as well as population sizes and country-specific resistance levels, we estimated the number of infections caused by third-generation cephalosporin-resistant and carbapenem-resistant *E coli* and *K pneumoniae* in 193 countries in 2014. We also calculated interval estimates derived from changing the fixed incidence of susceptible infections to 1 SD below and above the weighted mean. We compared an additive model with combination models in which resistant infections were replaced by susceptible infections. We distinguished between higher-certainty regions (those with good-quality data sources for resistance levels and resistance ≤30%), moderate-certainty regions (those with good-quality data sources for resistance levels and including some countries with resistance >30%), and low-certainty regions (those in which good-quality data sources for resistance levels were unavailable for countries comprising at least 20% of the region's population, regardless of resistance level).

Findings Using the additive model, we estimated that third-generation cephalosporin-resistant *E coli* and *K pneumoniae* caused 6·4 million (interval estimate 3·5–9·2) bloodstream infections and 50·1 million (27·5–72·8) serious infections in 2014; estimates were 5·5 million (3·0–7·9) bloodstream infections and 43·1 million (23·6–62·2) serious infections in the 25% replacement model, 4·6 million (2·5–6·6) bloodstream infections and 36·0 million (19·7–52·2) serious infections in the 50% replacement model, and 3·7 million (2·0–5·3) bloodstream infections and 28·9 million (15·8–41·9) serious infections in the 75% replacement model. Carbapenem-resistant strains caused 0·5 million (0·3–0·7) bloodstream infections and 3·1 million (1·8–4·5) serious infections based on the additive model, 0·5 million (0·3–0·7) bloodstream infections and 3·0 million (1·7–4·3) serious infections based on the 25% replacement model, 0·4 million (0·2–0·6) bloodstream infections and 2·8 million (1·6–4·1) serious infections based on the 50% replacement model, and 0·4 million (0·2–0·6) bloodstream infections and 2·7 million (1·5–3·8) serious infections based on the 75% replacement model.

Interpretation To our knowledge, this study is the first to report estimates of the global number of infections caused by antibiotic-resistant priority pathogens. Uncertainty stems from scant data on resistance levels from low-income and middle-income countries and insufficient knowledge regarding resistance dynamics when resistance is high.

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Department of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (E Temkin DrPH, N Fallach MA, J Almagor PhD, Prof Y Carmeli MD); **Division of Infectious Diseases, Department of Internal Medicine 1, German Center for Infection Research, University Hospital Tuebingen, Tuebingen, Germany** (B P Gladstone PhD, Prof E Tacconelli MD); **and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel** (Prof Y Carmeli)

Correspondence to:
Dr Elizabeth Temkin, Department of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
lizt@tlvmc.gov.il

Introduction

Antimicrobial resistance has been recognised as a global public health crisis by organisations such as the UN and WHO.[1,2] WHO's Global Action Plan on Antimicrobial Resistance calls for research to fill the knowledge gaps regarding the incidence of infections caused by antimicrobial-resistant pathogens.[2] Data on the number and incidence of infections caused by these organisms are scarce. Multicountry antimicrobial resistance surveillance systems, such as the European Antimicrobial Resistance Surveillance Network (EARS-Net)[3] and the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR),[4] track the proportion of isolates within a given species that are resistant to an antibiotic, and not the number of infections caused by antimicrobial-resistant organisms, which are much harder data to collect. Likewise, in its 2014 global report on surveillance of antimicrobial resistance, WHO presented country-level data only on the proportion of resistant isolates.[5] This proportion is

Research in context

Evidence before this study

We searched PubMed between Jan 1, 2000, and May 31, 2017, to identify studies that estimated the number of infections caused by antimicrobial-resistant organisms in a country, a region, or worldwide. A search using the terms ("antibiotic-resistant bacteria" OR "multidrug-resistant bacteria" OR "multidrug-resistant organisms") AND ("estimates" OR "estimating") yielded three relevant studies. These studies estimated the number of bloodstream infections caused by third-generation cephalosporin-resistant *Escherichia coli* and meticillin-resistant *Staphylococcus aureus* in 31 European countries in 2007, the number of inpatient infections caused by seven antimicrobial-resistant bacteria in France in 2012, or the number of health-care-associated resistant infections in Finland in 2010. We also knew of three relevant reports that are not indexed in PubMed. The first, by the European Centre for Disease Prevention and Control, used data from the European Antimicrobial Resistance Surveillance Network to estimate the number of infections caused by six resistant species in 29 European countries in 2007. A 2013 report by the US Centers for Disease Control and Prevention presented estimates of the annual number of hospital-acquired infections in the USA caused by antimicrobial-resistant organisms, which included 26 000 infections caused by third-generation cephalosporin-resistant, and 9300 infections caused by carbapenem-resistant, *E coli* and *Klebsiella pneumoniae*. The 2014 O'Neill Report commissioned by the UK Government estimated that 700 000 deaths per year worldwide are attributable to infections caused by six antimicrobial-resistant species, including *E coli* and *K pneumoniae*; estimating the number of infections was a step in the analysis, but those results were not published.

Added value of this study

To our knowledge, this study is the first to report worldwide, pathogen-specific estimates of the number of infections caused by antimicrobial-resistant organisms in 1 year (2014). We estimated the number of infections caused by third-generation cephalosporin-resistant and carbapenem-resistant *E coli* and *K pneumoniae* in 193 countries. We presented methods to convert the proportion of resistance (a value that is often known through laboratory-based surveillance) into the number of resistant infections (data that are difficult to obtain and collected infrequently). When possible, our calculations were based on country-specific data on the level of resistance, and we graded the quality of these data. Because of the lack of empirical evidence describing resistance dynamics when the level of resistance is high, we compared the results of four models: an additive model in which resistant infections supplement antibiotic-susceptible infections, and 25%, 50%, and 75% replacement models in which resistant infections supplant susceptible infections once resistance rises above 30%. We validated our results for eight countries or states that collect incidence data based on mandatory reporting of resistant infections.

Implications of all the available evidence

According to our estimates, the number of infections caused by antibiotic-resistant *E coli* and *K pneumoniae* in 2014 was high: 50·1 million serious third-generation cephalosporin-resistant infections and 3·1 million serious carbapenem-resistant infections by the additive model, decreasing to 36·0 million and 2·8 million, respectively, in the 50% replacement model. Accurate global estimates depend on strengthening surveillance of antimicrobial resistance in low-income and middle-income countries. Laboratory-based antimicrobial resistance surveillance systems must incorporate epidemiological data to improve estimates of the incidence of resistant infections.

important to clinicians choosing empirical therapy but does not provide the necessary information for policy makers and antibiotic developers to act on the number and incidence of infections (ie, market size and, when combined with associated morbidity and mortality, the burden of disease).[6]

See Online for appendix 1

Third-generation cephalosporin-resistant and carbapenem-resistant Enterobacteriaceae appear in the highest category on WHO's list of priority pathogens for research and development of new antibiotics.[7] The US Centers for Disease Control and Prevention (CDC) classify third-generation cephalosporin-resistant Entero-bacteriaceae as a serious threat and carbapenem-resistant Entero-bacteriaceae as an urgent threat.[8] We aimed to estimate the annual number and incidence per million population of infections caused by third-generation cephalosporin-resistant and carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* worldwide.

Methods

Study overview

We followed the Guidelines for Accurate and Transparent Health Estimates Reporting.[9] A list of the guidelines' elements and where they can be found in this manuscript is in appendix 1. A detailed description of our methods is also presented in appendix 1.

We hypothesised that the incidence per 1000 population of serious infections caused by third-generation cephalosporin-susceptible or carbapenem-susceptible *E coli* and *K pneumoniae* is similar across countries. This hypothesis is biologically plausible because most infections caused by antibiotic-susceptible Enterobacteriaceae result from translocation of indigenous gut flora to extraintestinal sites;[10] we would not expect such events to vary greatly by country. We tested our hypothesis using country-level data. We then used this uniform incidence of susceptible infections, as well as population sizes and

country-specific resistance levels (ie, proportion of isolates resistant to a given antibiotic class), to calculate the number and incidence of infections caused by third-generation cephalosporin-resistant and carbapenem-resistant *E coli* and *K pneumoniae*.

Whether antimicrobial resistance follows an additive model, a replacement model, or a combination of both is uncertain. In an additive model, resistant infections occur in addition to susceptible infections, whereas in a replacement model, resistant infections supplant susceptible infections. Previous studies[11–13] have provided evidence in support of the additive model but were limited to countries with resistance levels lower than 30%; thus, it is possible that replacement occurs in settings with higher levels of resistance. We compared four models: a fully additive model and models of 25%, 50%, and 75% replacement, beginning once resistance surpasses 30%. Figure 1 presents a conceptual overview of the analysis using the example of third-generation cephalosporin-resistant *E coli*.

We estimated the number and incidence of bloodstream infections and serious infections (which include bloodstream infections) caused by third-generation cephalosporin-resistant and carbapenem-resistant *E coli* and *K pneumoniae*. We defined serious infections as those that ideally should be treated in a hospital, while recognising that not all patients with infections live in an area with access to inpatient care. For third-generation cephalosporin-resistant *E coli* and *K pneumoniae*, we also estimated the number of outpatient infections; we assumed that all infections caused by carbapenem-resistant *E coli* and *K pneumoniae*, for which oral therapy is rarely available, are serious and would require inpatient treatment. Our estimates encompassed all patients, regardless of age and sex.

We produced country-level estimates for the 193 member states in the UN,[14] which we grouped into 18 regions according to the UN's classification system.[15] The period for our estimates was 2014: whenever available, we used

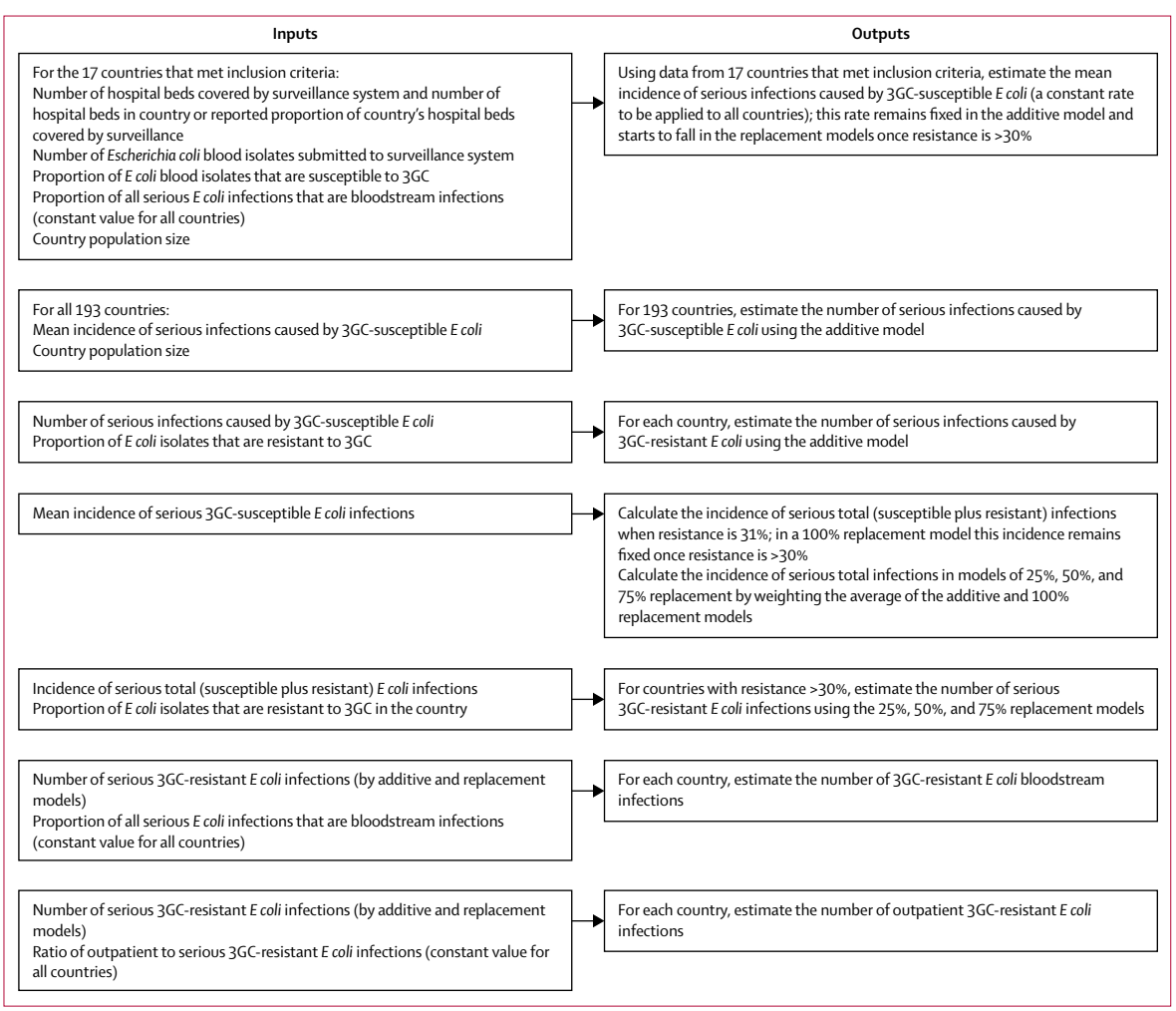

Figure 1: **Conceptual overview of the data analysis method**
3GC=third-generation cephalosporin.

Panel: **Classification scheme to grade data sources for countries' levels of resistance**

Grade 1
Multicountry surveillance systems (eg, European Antimicrobial Resistance Surveillance Network, Central Asian and Eastern European Surveillance of Antimicrobial Resistance, Pan-American Health Organization antimicrobial resistance report) or national surveillance systems

Grade 2
National data obtained for the 2014 WHO antimicrobial resistance report or privately sponsored multicountry surveillance systems (eg, Tigecycline Evaluation and Surveillance Trial) with more than three sites in the country, or data from the Center for Disease Dynamics, Economics and Policy if more than three sites

Grade 3
Published articles with data collected from more than three sites in the country

Grade 4
Published articles with data collected from three sites or fewer in the country or privately sponsored multicountry surveillance systems with three sites or fewer in the country

Grade 5
Any data source with sample size of less than 100 isolates or sample size not reported, or all data collected before 2011

Grade 6
No data available, value imputed

2014 data on levels of resistance and World Bank population estimates for 2014.[16]

Data inputs

Descriptions of the process for identifying and accessing all data inputs, of inclusion and exclusion criteria, and of the methods used to imput missing values are in appendix 1. The first data inputs were those required to estimate, for each of the four species–resistance pairs, the mean incidence of serious infections caused by susceptible organisms, to be applied to all countries. We identified countries with surveillance data, mainly from EARS-Net, that allowed estimation of the proportion of the country's hospital beds covered by surveillance. We excluded countries in which surveillance covered less than 30% of the country's hospital beds. EARS-Net is based on blood isolates, which was advantageous for the purpose of this study because such isolates represent serious infections rather than colonisation or outpatient infections. For each of the 17 countries that met inclusion criteria, we estimated the incidence of serious infections caused by third-generation cephalosporin-susceptible and carbapenem-susceptible *E coli* and *K pneumoniae* using five inputs: the number of isolates submitted to surveillance and the proportion that were susceptible, the proportion of the country covered by surveillance, the population size, and a constant value for the proportion of serious infections that are bloodstream infections (derived with data from our hospital).

The second major input was resistance levels in each country, which were gathered from various sources, including EARS-Net and CAESAR, national antimicrobial resistance surveillance systems, WHO's global report on antimicrobial resistance surveillance,[5] and scientific articles. For countries with no such data, we used the median for the region. The process for identifying sources is shown in appendix 1. We graded the quality of the sources using the scheme shown in the panel and then classified regions as higher certainty, moderate certainty, and low certainty. Higher-certainty regions had grade 1–2 data on level of resistance for countries comprising at least 80% of the region's population, and no country within the region had resistance higher than 30%; for these regions, the additive and replacement models were identical. We classified moderate-certainty regions as those in which grade 1–2 data on resistance levels were available for countries comprising at least 80% of the region's population and in which some countries had resistance higher than 30%. Low-certainty regions were those in which grade 1–2 data were unavailable for countries comprising at least 20% of the region's population, regardless of resistance level.

Data analysis

We estimated the mean incidence of serious infections caused by third-generation cephalosporin-susceptible and carbapenem-susceptible *E coli* and *K pneumoniae*. We first estimated the annual number of antibiotic-susceptible bloodstream infections in each of the 17 countries by dividing the number of susceptible isolates reported to surveillance systems by the proportion of the country that was represented in surveillance. Next, we divided the number of susceptible bloodstream infections by the constant value for the proportion of serious infections that are bloodstream infections (0·12 for *E coli* and 0·17 for *K pneumoniae*) to estimate the annual number of serious infections caused by susceptible strains. We expressed this value as incidence per 1000 population. We then calculated the weighted mean of the incidence of serious susceptible infections in the 17 countries to generate the value to be applied to all countries. Weighting was done according to the proportion of the country that was covered by surveillance. We displayed each country's incidence and weighted mean incidence in funnel plots to see if values clustered around the mean, which would support our primary hypothesis that the incidence of serious susceptible infections is similar in all countries. We displayed upper and lower control limits that were one or two SEs from the mean. For all subsequent calculations, we used one SD below and above the weighted mean incidence as our interval estimate (ie, we

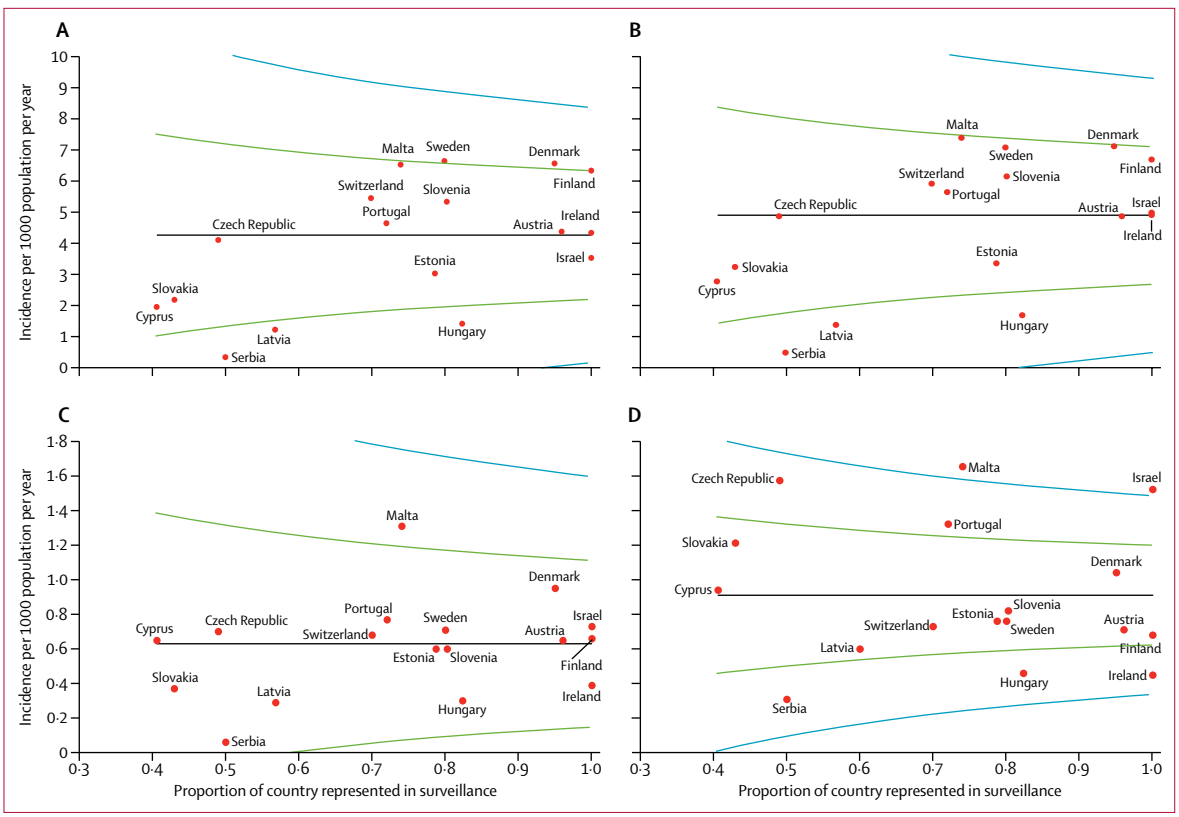

Figure 2: **Annual incidence of serious infections caused by antibiotic-susceptible *Escherichia coli* and *Klebsiella pneumoniae* in 17 countries**
Black solid lines are the weighted means; green lines are 1 SE and blue lines are 2 SEs from the weighted means. (A) Third-generation cephalosporin-susceptible *E coli*. (B) Carbapenem-susceptible *E coli*. (C) Third-generation cephalosporin-susceptible *K pneumoniae*. (D) Carbapenem-susceptible *K pneumoniae*.

set a middle, low, and high value for the incidence of serious susceptible infections).

The major steps to calculate the number of infections caused by resistant strains were as follows. First, for the additive model, we calculated the number of serious resistant infections in each country using the fixed incidence of serious susceptible infections, the population size, and the country-specific resistance level. Second, we modelled 100% replacement, in which every resistant infection replaces a susceptible infection once resistance is above 30%. At that point, the incidence of all serious infections (resistant plus susceptible) remains fixed at a value set slightly above that reached by the additive model at 30% resistance. To calculate the incidence of all serious infections for the 25%, 50%, and 75% replacement models, we weighted the average of the additive and 100% replacement models accordingly. Using the incidence of all serious infections, the population size, and the country-specific resistance level, we calculated the number of serious resistant infections for each country. To calculate the number of bloodstream infections caused by resistant strains, we multiplied the number of serious resistant infections by the constant value for the proportion of serious infections that are bloodstream infections. To calculate the number of outpatient infections, we used a constant ratio of outpatient to serious infections derived from Swiss surveillance data (4·0 for third-generation cephalosporin-resistant and 2·1 for carbapenem-resistant infections).[17]

For all indicators, interval estimates were based on changing only the incidence of serious susceptible infections. We did not vary three other important parameters: the proportion of isolates that were resistant in each country, the proportion of serious infections that were bloodstream infections, or the ratio of outpatient to serious infections.

Role of the funding source
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all of the data in the study and the final responsibility for the decision to submit for publication.

Results
The annual incidence of serious infections caused by third-generation cephalosporin-susceptible and carbapenem-susceptible *E coli* and *K pneumoniae* in the 17 countries that met inclusion criteria are shown in figure 2 and appendix 2. For all four species–resistance pairs, most countries fell

See Online for appendix 2

	Additive model			100% replacement model		
	Incidence of susceptible infections	Incidence of resistant infections	Incidence of all infections	Incidence of susceptible infections	Incidence of resistant infections	Incidence of all infections
10%	4·26	0·47	4·73	4·26	0·47	4·73
20%	4·26	1·07	5·33	4·26	1·07	5·33
30%	4·26	1·83	6·09	4·26	1·83	6·09
40%	4·26	2·84	7·10	3·67	2·45	6·12
50%	4·26	4·26	8·52	3·06	3·06	6·12
60%	4·26	6·39	10·65	2·45	3·67	6·12

Data are incidence per 1000 population. In the additive model, the incidence of serious susceptible infections remains fixed and resistant infections occur in addition to susceptible infections. In the 100% replacement model, once the level of resistance is greater than 30%, the incidence of total serious infections remains fixed as resistant infections replace susceptible infections. The incidence of resistant infections is higher in the additive model than in the 100% replacement model after 30% resistance, and the gap widens as resistance rises.

Table 1: **Comparison of the additive and 100% replacement models by percentage of *Escherichia coli* isolates that are resistant to third-generation cephalosporins**

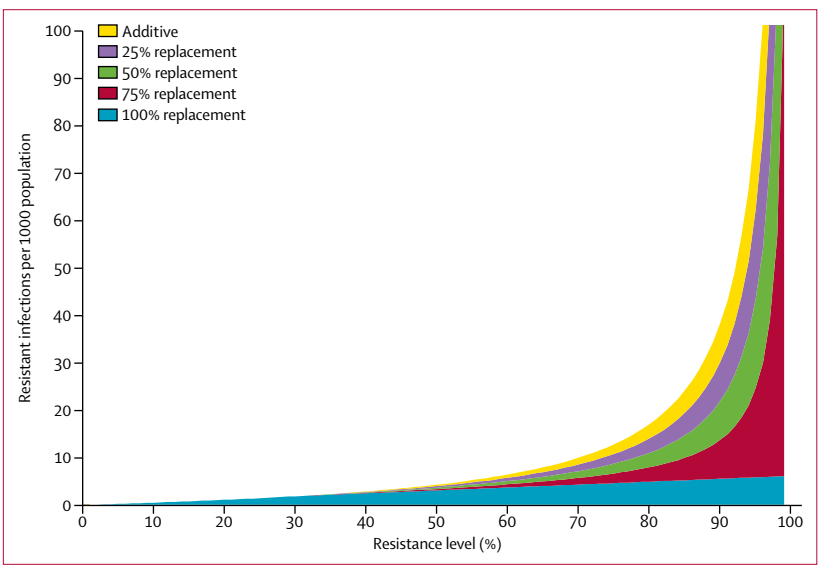

Figure 3: **Estimated incidence of serious infections caused by third-generation cephalosporin-resistant *Escherichia coli* with the various models**

In the combination models, replacement begins once the level of resistance is greater than 30%.

within 1 SE of the weighted mean and all fell within 2 SEs of the weighted mean, except for Malta and Israel where the annual incidence of infections caused by carbapenem-susceptible *K pneumoniae* was more than 2 SEs higher than the weighted mean. The plots confirmed our hypothesis of a similar incidence of serious susceptible infections in these countries, allowing use of the weighted mean incidence in subsequent calculations.

Our grading of sources reporting levels of resistance in individual countries is presented, by region, in appendix 1. Grade 1–2 data were available for about half of the world's population, and were rare or absent for countries in the Caribbean, all regions of Asia except for east Asia, and all regions of Africa except for southern Africa.

The effect of the additive, replacement, and combination models on the estimated incidence of resistant infections are presented in table 1 and figure 3, using third-generation cephalosporin-resistant *E coli* as an example. As resistance levels increase, differences between the models in estimates of the number of resistant infections become more pronounced. When resistance is 40%, estimates from the additive model are 12% higher than those from the 75% replacement model; when resistance reaches 77%, estimates from the additive model are twice those from the 75% replacement model. Thus, uncertainty in estimating the number of resistant infections is much greater in countries with very high resistance.

Table 2 presents estimates of the number of bloodstream and serious infections from the additive and combination models, by region for carbapenem-resistant *K pneumoniae* and by certainty level for third-generation cephalosporin-resistant *E coli* and *K pneumoniae* and carbapenem-resistant *E coli*. Estimates by region for third-generation cephalosporin-resistant *E coli* and *K pneumoniae* and carbapenem-resistant *E coli* are presented in appendix 1. Estimates by country for cephalosporin-resistant *E coli* and *K pneumoniae* and carbapenem-resistant *E coli* and *K pneumoniae* are presented in appendix 2.

For carbapenem-resistant *K pneumoniae* (for which few countries had resistance >30%), the worldwide point estimate of serious infections was 2·1 million (interval estimate 1·1–3·0) with the additive model versus 1·6 million (0·9–2·3) with the 75% replacement model (table 2); the difference was driven by high levels of resistance in India. For third-generation cephalosporin-resistant *E coli* (for which high resistance was more common), the difference between models was wider than for carbapenem-resistant *K pneumoniae*: from 43·1 million (23·5–62·7) in the additive model to 24·9 million (13·5–36·2) in the 75% replacement model. Country-level estimates of outpatient infections are shown in appendix 3.

We identified six countries and two US states with mandatory reporting systems for third-generation cephalosporin-resistant or carbapenem-resistant Enterobacteriaceae (table 3). Those systems differ from laboratory-based systems such as EARS-Net in that they count all cases (defined by different systems as bloodstream infections only, inpatient infections only, or all infections) throughout the country (or US state), and not only the proportion of resistant isolates in a sample. We compared our estimates with the observed number of infections in 2014 (table 3). In 21 of 32 instances, the observed value definitely or probably fell within our estimated range and, in six other instances, we underestimated or overestimated by fewer than 30 cases per year. Only one datapoint involved a resistance level of greater than 30% (third-generation cephalosporin-resistant *K pneumoniae* in Israel, with 54% resistance). The observed number of bloodstream infections caused

	Bloodstream infections (in thousands)				Serious infections (in thousands)			
	Additive	25% replacement	50% replacement	75% replacement	Additive	25% replacement	50% replacement	75% replacement
Carbapenem-resistant *Klebsiella pneumoniae**								
World total	351 (195–506)	324 (180–468)	297 (165–430)	270 (150–392)	2062 (1146–2978)	1905 (1058–2753)	1747 (971–2529)	1590 (884–2305)
Higher certainty	24 (13–34)	24 (13–34)	24 (13–34)	24 (13–34)	138 (77–200)	138 (77–200)	138 (77–200)	138 (77–200)
Western Europe	0·3 (0·2–0·4)	0·3 (0·2–0·4)	0·3 (0·2–0·4)	0·3 (0·2–0·4)	2 (1–2)	2 (1–2)	2 (1–2)	2 (1–2)
Northern Europe	0·1 (0·1–0·2)	0·1 (0·1–0·2)	0·1 (0·1–0·2)	0·1 (0·1–0·2)	0·8 (0·5–1·2)	0·8 (0·5–1·2)	0·8 (0·5–1·2)	0·8 (0·5–1·2)
Northern America	4 (2–6)	4 (2–6)	4 (2–6)	4 (2–6)	25 (14–36)	25 (14–36)	25 (14–36)	25 (14–36)
Central America	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	14 (8–20)	14 (8–20)	14 (8–20)	14 (8–20)
Southern Africa	0·3 (0·2–0·5)	0·3 (0·2–0·5)	0·3 (0·2–0·5)	0·3 (0·2–0·5)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Eastern Asia	16 (9–23)	16 (9–23)	16 (9–23)	16 (9–23)	95 (53–138)	95 (53–138)	95 (53–138)	95 (53–138)
Moderate certainty	38 (21–55)	37 (21–54)	36 (20–52)	34 (19–50)	226 (125–326)	218 (121–315)	210 (117–304)	202 (112–293)
Southern Europe	9 (5–13)	9 (5–13)	8 (5–12)	8 (4–11)	54 (30–78)	51 (28–74)	48 (27–70)	45 (25–66)
Eastern Europe	8 (4–11)	7 (4–11)	7 (4–10)	6 (4–9)	45 (25–66)	43 (24–62)	41 (23–59)	38 (21–55)
South America	22 (12–31)	21 (12–30)	21 (11–30)	20 (11–29)	127 (70–183)	124 (69–179)	121 (67–175)	118 (66–172)
Low certainty	289 (160–417)	263 (146–381)	238 (132–344)	212 (118–308)	1698 (944–2452)	1549 (861–2239)	1399 (778–2025)	1250 (695–1812)
Southeastern Asia	6 (3–8)	6 (3–8)	6 (3–8)	6 (3–8)	33 (19–48)	33 (19–48)	33 (19–48)	33 (19–48)
South-central Asia	266 (148–385)	241 (134–348)	216 (120–312)	190 (106–276)	1567 (871–2263)	1418 (788–2050)	1269 (705–1837)	1120 (623–1624)
Western Asia	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	17 (10–25)	17 (10–25)	17 (10–25)	17 (10–25)
Eastern Africa	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	17 (10–25)	17 (10–25)	17 (10–25)	17 (10–25)
Middle Africa	0·4 (0·2–0·5)	0·4 (0·2–0·5)	0·4 (0·2–0·5)	0·4 (0·2–0·5)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Northern Africa	8 (4–11)	8 (4–11)	8 (4–11)	8 (4–11)	45 (25–66)	45 (25–66)	45 (25–66)	44 (25–64)
Western Africa	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)	15 (8–21)	15 (8–21)	15 (8–21)	15 (8–21)
Caribbean	0·05 (0·03–0·8)	0·05 (0·03–0·8)	0·05 (0·03–0·8)	0·05 (0·03–0·8)	0·3 (0·2–0·5)	0·3 (0·2–0·5)	0·3 (0·2–0·5)	0·3 (0·2–0·5)
Oceania	0·05 (0·03–0·7)	0·05 (0·03–0·7)	0·05 (0·03–0·7)	0·05 (0·03–0·7)	0·3 (0·2–0·4)	0·3 (0·2–0·4)	0·3 (0·2–0·4)	0·3 (0·2–0·4)
Third-generation cephalosporin-resistant *Escherichia coli*								
World total	5173 (2817–7529)	4447 (2423–6476)	3718 (2024–5410)	2986 (1626–4345)	43 107 (23 476–62 737)	37 060 (20 194–53 966)	30 985 (16 871–45 087)	24 887 (13 548–36 207)
Higher certainty	56 (31–82)	56 (31–82)	56 (31–82)	56 (31–82)	469 (255–682)	469 (255–682)	469 (255–682)	469 (255–682)
Moderate certainty	1220 (664–1776)	1124 (613–1639)	1025 (558–1491)	923 (503–1343)	10 167 (5537–14 797)	9364 (5112–13 661)	8542 (4650–12 428)	7696 (4189–11 195)
Low certainty	3896 (2122–5671)	3267 (1779–4755)	2637 (1436–3837)	2007 (1092–2920)	31 784 (17 309–46 258)	27 227 (14 826–39 623)	21 975 (11 965–31 976)	16 723 (9104–24 329)
Third-generation cephalosporin-resistant *K pneumoniae*								
World total	1197 (684–1710)	1024 (585–1462)	851 (486–1214)	677 (387–966)	7042 (4024–10 061)	6023 (3442–8601)	5003 (2859–7141)	3985 (2277–5680)
Higher certainty	8 (5–12)	8 (5–12)	8 (5–12)	8 (5–12)	48 (28–69)	48 (28–69)	48 (28–69)	48 (28–69)
Moderate certainty	291 (166–415)	260 (148–371)	227 (130–325)	196 (112–279)	1709 (977–2442)	1527 (872–2180)	1338 (765–1910)	1151 (658–1640)
Low certainty	898 (513–1283)	756 (432–1080)	615 (351–878)	474 (271–675)	5285 (3020–7550)	4448 (2542–6353)	3617 (2067–5162)	2785 (1591–3971)
Carbapenem-resistant *E coli*								
World total	130 (76–184)	130 (76–184)	130 (76–184)	130 (76–184)	1084 (634–1533)	1084 (634–1533)	1084 (634–1533)	1084 (634–1533)
Higher certainty	13 (7–18)	13 (7–18)	13 (7–18)	13 (7–18)	106 (62–150)	106 (62–150)	106 (62–150)	106 (62–150)
Low certainty	117 (69–166)	117 (69–166)	117 (69–166)	117 (69–166)	978 (572–1383)	978 (572–1383)	978 (572–1383)	978 (572–1383)

Data in parentheses are interval estimates derived from changing the fixed incidence of susceptible infections to 1 SD below and above the weighted mean. Estimates were the same for all models when resistance was ≤30%. *Data are also shown by UN region.

Table 2: **Estimates of resistant bloodstream infections and serious infections in 2014, by model, WHO priority pathogen, and certainty level**

	Observed values, 2014		Estimated values, 2014 (additive model)		Summary
	Data type	Infections	Data type	Estimate*	
Ireland[3,18]					
3GC-resistant *Escherichia coli*	Invasive isolates (blood or CSF)	357	Bloodstream infections	313 (170–455)	In range
3GC-resistant *Klebsiella pneumoniae*	Invasive isolates (blood or CSF)	46	Bloodstream infections	74 (42–106)	In range
Carbapenem-resistant *K pneumoniae*	Invasive isolates (blood or CSF)	4	Bloodstream infections	4 (2–6)	In range
Finland[19]					
3GC-resistant *E coli*	Bloodstream infections	232	Bloodstream infections	156 (85–227)	Underestimate
3GC-resistant *K pneumoniae*	Bloodstream infections	20	Bloodstream infections	19 (11–28)	In range
3GC-resistant *E coli*	All infection types; inpatients and outpatients; includes unknown percentage of screening cultures†	4190	All infection types; inpatients and outpatients	6511 (3546–9475)	Probably in range
3GC-resistant *K pneumoniae*	All infection types; inpatients and outpatients; includes unknown percentage of screening cultures†	312	All infection types; inpatients and outpatients	353 (201–504)	Probably in range
Denmark[3,20]					
3GC-resistant *E coli*	Bloodstream infections (first infection per patient per year)	314	Bloodstream infections	244 (133–355)	In range
3GC-resistant *K pneumoniae*	Bloodstream infections (first infection per patient per year)	75	Bloodstream infections	59 (34–84)	In range
3GC-resistant *E coli*	Inpatient blood and urine (first infection per patient per year)	2953	All infection types; inpatients only	2034 (1108–2960)	Probable underestimate
3GC-resistant *K pneumoniae*	Inpatient blood and urine (first infection per patient per year)	520	All infection types; inpatients only	347 (198–496)	Underestimate
Carbapenem-resistant *E coli*	Bloodstream infections	3	Bloodstream infections	1 (0–1)	Underestimate
Carbapenem-resistant *K pneumoniae*	Bloodstream infections	4	Bloodstream infections	3 (2–5)	In range
Sweden[3,21]					
3GC-resistant *E coli*	All infection types; inpatients and outpatients; includes about 28% screening cultures†	8161	All infection types; inpatients and outpatients	13 417 (7307–19 526)	Overestimate
3GC-resistant *K pneumoniae*	All infection types; inpatients and outpatients; includes about 28% screening cultures†	668	All infection types; inpatients and outpatients	1166 (666–1666)	Overestimate
ESBL-producing Enterobacteriaceae	Bloodstream infections	520	Bloodstream infections; *E coli* and *K pneumoniae* only	396 (212–560)	Probably in range
Carbapenem-resistant Enterobacteriaceae	All infection types	19	All infection types; *E coli* and *K pneumoniae* only	32 (19–46)	Probably in range
Norway[3,22]					
3GC-resistant *E coli*	Bloodstream infections (6 months only)	95	Bloodstream infections (12 months)	174 (95–253)	Probably in range
3GC-resistant *K pneumoniae*	Bloodstream infections (9 months only)	26	Bloodstream infections (12 months)	43 (24–61)	Probably in range
Carbapenem-resistant *E coli*	All infection types	4	All infection types	7 (4–10)	In range
Carbapenem-resistant *K pneumoniae*	All infection types	6	All infection types	5 (3–7)	In range
Israel‡					
3GC-resistant *E coli*	Bloodstream infections	1526	Bloodstream infections	1757 (957–2558)	In range
3GC-resistant *K pneumoniae*	Bloodstream infections	1213	Bloodstream infections	1033 (590–1476)	In range
Carbapenem-resistant *E coli*	Bloodstream infections	11	Bloodstream infections	14 (8–20)	In range
Carbapenem-resistant *K pneumoniae*	Bloodstream infections	113	Bloodstream infections	61 (34–88)	Underestimate
New York, USA[23,24]					
Carbapenem-resistant *E coli*	All infection types	249	All infection types	386 (226–546)	In range
Carbapenem-resistant *K pneumoniae*	All infection types	2470	All infection types	2941 (1634–4248)	In range
Carbapenem-resistant *E coli* and *K pneumoniae*	Bloodstream infections	372	Bloodstream infections	546 (305–788)	In range
Maryland, USA[25]§					
Carbapenem-resistant *E coli*	All infection types	69	All infection types	0	Underestimate
Carbapenem-resistant *K pneumoniae*	All infection types	242	All infection types	166 (92–240)	Underestimate
Carbapenem-resistant *E coli*	Bloodstream infections (first infection per patient per year)	2	Bloodstream infections	0	Underestimate
Carbapenem-resistant *K pneumoniae*	Bloodstream infections (first infection per patient per year)	14	Bloodstream infections (first infection per patient per year)	28 (16–41)	Overestimate

3GC=third-generation cephalosporin. ESBL=extended-spectrum β-lactamase. *Data in parentheses are interval estimates derived from changing the fixed incidence of susceptible infections to 1 SD below and above the weighted mean.†Screening cultures detect colonisation, not infection. ‡Data for Israel were obtained from the National Center for Infection Control, Israel, and are unpublished. §The observed data came from personal communication with David Blythe and Elisabeth Vaeth at Maryland Department of Health and Mental Hygiene.

Table 3: **Comparison of estimated number of infections and number observed by surveillance systems based on mandatory reporting**

by third-generation cephalosporin-resistant *K pneumoniae* in Israel (1213) fell within the ranges estimated by the additive (1033 [interval estimate 590–1476]) and 25% (946 [541–1351]) and 50% (860 [491–1226]) replacement models; the estimate from the 75% replacement model was lower than the observed value (773 [442–1101]).

Discussion

In 2014, the O'Neill report estimated that 700 000 deaths per year are attributable to antimicrobial-resistant infections (including malaria, HIV, and tuberculosis).[26] Although estimation of the number of resistant infections was a step in this calculation, those methods and results were not published.[26,27] We aimed to estimate the global number of infections caused by third-generation cephalosporin-resistant and carbapenem-resistant *E coli* and *K pneumoniae*, and to provide an explicit assessment of the assumptions and the quality of data on which the estimates were based.

The first report to present a multicountry estimate of the incidence of antibiotic-resistant infections was The Bacterial Challenge: Time to React, issued by the European Centre for Disease Prevention and Control (ECDC) in 2009.[28] Using data from EARS-Net, the report estimated the number of inpatient infections caused by resistant organisms in 29 European countries in 2007, including 32 500 by third-generation cephalosporin-resistant *E coli* and 18 900 by third-generation cephalosporin-resistant *K pneumoniae*. The methods differed from ours in that the ECDC calculated the number of resistant bloodstream infections in each country using the number of resistant isolates submitted to EARS-Net and the proportion of the country that was covered by surveillance. By contrast, we defined a constant mean incidence of susceptible infections that enabled generation of estimates for all countries, based solely on the level of resistance.

On a national scale, in 2013, the US CDC issued estimates of the number of hospital-acquired infections caused by antibiotic-resistant bacteria based on data from a point-prevalence study done in acute-care hospitals in ten US states.[29] The US CDC's estimates were lower than the estimates in this study—for example, the US CDC estimated that 9300 hospital-acquired infections were caused by carbapenem-resistant *E coli* and *K pneumoniae*, whereas we estimated that 33 994 (interval estimate 19 163–48 824) inpatient infections were caused by these microorganisms. In New York, USA, half of all infections caused by carbapenem-resistant *E coli* and *K pneumoniae* in 2014 were hospital acquired.[23] If the same is true throughout the USA, then our point estimate of nosocomial carbapenem-resistant infections (16 997) is almost twice as high as the US CDC's. Another study[30] based on data from electronic medical records from 192 US hospitals reported an estimate for carbapenem-resistant *E coli* and *K pneumoniae* that was slightly higher than our point estimate but within our range: 42 852 infections in the USA in 2014. The difference might be due to their inclusion of all species of carbapenem-resistant Enterobacteriaceae. Colomb-Cotinat and colleagues[31] estimated the number of inpatient infections caused by multidrug-resistant bacteria in France in 2012, and reported estimates for infections caused by third-generation cephalosporin-resistant *K pneumoniae* (16 314 infections) and carbapenem-resistant *K pneumoniae* (602 infections) that overlap with ours (estimates for France from this study are in appendix 2). By contrast, our estimate for infections caused by third-generation cephalosporin-resistant *E coli* was slightly lower than Colomb-Cotinat and colleagues' estimate (50 916 infections).

We recognise the many potential sources of bias or uncertainty in our estimations. First, use of a single incidence of serious infections caused by susceptible *E coli* and *K pneumoniae* for all countries might have been an oversimplification. Although the funnel plots supported our hypothesis of a uniform incidence, data were available only from high-income and upper-middle-income countries. We confirmed that estimates based on this fixed incidence were generally accurate for sites with incidence data from mandatory reporting, but no such comparisons were available for low-income or lower-middle-income countries. The incidence of susceptible infections in these countries might be higher (eg, because of poorer sanitation) or lower (eg, because of differences in population age structure) than our fixed incidence.

Second, we based the calculation of the incidence of serious susceptible infections in each country on the number of isolates submitted for surveillance by 17 countries. This number is subject to ascertainment bias stemming from differences in countries' practices regarding the frequency of taking blood cultures. Indeed, when we used EARS-Net data[32] to estimate the number of blood-culture sets processed in participating laboratories per 1000 population covered by surveillance, the ratio was two times lower for Latvia and Hungary (which were consistently near the bottom of our funnel plots) than for other countries. Notably, most countries with a high surveillance coverage are wealthy countries where we would expect high ascertainment of infections. The incidence of serious susceptible infections in these countries was often higher than the mean, suggesting that the mean incidence of susceptible infections in our study (and thus the calculated number of resistant infections) might be an underestimate.

Third, there were potential sources of bias regarding our estimates for each country. Grade 1–2 quality data on levels of resistance were available for only 31% (for carbapenem-resistant *E coli*) to 43% (for third-generation cephalosporin-resistant *E coli*) of countries. We imputed resistance levels for 31–41% of countries. Additionally, samples might not have been representative of the whole country because resistance can vary by region, and tertiary care hospitals, which are the source of most academic reports, might have higher levels of resistance than would community hospitals (although a

US study[33] found no such difference). The possibility of sampling bias is particularly relevant to India, whose resistance estimates (82% in the case of third-generation cephalosporin-resistant *E coli*) were obtained from small samples of isolates. Because India comprises 18% of the world's population, overestimation of resistance in India would substantially inflate the world totals; for this reason, we distinguished between higher-certainty, moderate-certainty, and low-certainty regions when presenting global estimates. Moreover, some data on resistance levels were collected before 2014, which might have led to underestimation of the number of resistant infections in countries where levels of resistance are rapidly increasing. Furthermore, anatomical sources of isolates varied, although the bias that this variation introduces might be minor given that antimicrobial resistance monitors in Sweden reported that resistance among *E coli* isolates from outpatient urine and inpatient blood cultures was quite similar.[34]

Finally, we note that our 25%, 50%, and 75% replacement models are, indeed, models. No empirical evidence exists to validate which, if any, of these models approximates resistance dynamics in countries where resistance levels are high. High resistance in the most populated countries, particularly China (for third-generation cephalosporin-resistant *E coli*) and India (for all but carbapenem-resistant *E coli*), drives the wide variation in our global estimates. Although we acknowledge these limitations, we believe that we have generated the best possible estimates with the available data.

In their article, de Kraker and colleagues[27] were critical of the methods used to estimate antimicrobial-resistant infections in the O'Neill and ECDC reports.[26,28] Some of these weaknesses, such as the use of data that might not be representative or possible error in estimating infections in all anatomical sites from surveillance based on blood cultures, might also apply to our study. However, we have overcome other limitations cited by de Kraker and colleagues. First, O'Neill[26] estimated the number of resistant infections in countries not in EARS-Net by applying the EARS-Net mean incidence, whereas we searched other sources to identify country-specific estimates of resistance. For highly populated countries such as China, Russia, and Brazil, we cited grade 1 data sources that reported resistance levels higher than those in most EARS-Net countries, suggesting that O'Neill's methods produced underestimates. Second, de Kraker and colleagues observed that the reports by the ECDC and O'Neill did not clearly state the uncertainties inherent in each step of their calculations. We have stated uncertainties and potential sources of bias, and have supplied our calculations for scrutiny and revision.

Our approach of using a uniform incidence of serious susceptible infections to estimate the number of resistant infections is probably not suitable for other resistant pathogens such as carbapenem-resistant *Acinetobacter* and *Pseudomonas* and vancomycin-resistant enterococci; the incidence of infections caused by the susceptible form of these pathogens differs substantially between locations.[35,36] To generate estimates of the incidence and number of infections caused by these organisms, and to improve our estimates for *E coli* and *K pneumoniae*, surveillance systems must gather both numerator data on the number of resistant infections per time period and population-level denominator data. Two new WHO initiatives to strengthen and standardise antimicrobial resistance surveillance worldwide, the Global Antimicrobial Resistance Surveillance System[37] and ESBL Ec Tricycle,[38] might help to provide the necessary additional data. Improving the accuracy of global estimates of the number of antibiotic-resistant infections will enhance efforts to prioritise infection prevention activities, limit the spread of antibiotic resistance, and develop new antibiotics.

Contributors

YC and ETe conceived the study and developed the models. ETe and NF prepared the first draft. All other authors collected data and reviewed results. All authors reviewed the final manuscript.

Declaration of interests

YC reports grants or personal fees from MSD, AstraZeneca, DaVoltera, Intercell AG, Allecra Therapeutics, BioMerieux SA, Rempex Pharmaceuticals, Nariva, Achoagen, Roche, Pfizer, and Shionogi. All other authors declare no competing interests.

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