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New methodology to assess the excess burden of antibiotic resistance using country-specific parameters: a case study regarding *E. coli* urinary tract infections

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ABSTRACT

Objectives Antimicrobial resistant (AMR) infections are a major public health problem and the burden on population level is not yet clear. We developed a method to calculate the *excess* burden of resistance which uses country-specific parameter estimates and surveillance data to compare the mortality and morbidity due to resistant infection against a counterfactual (the expected burden if infection was antimicrobial susceptible). We illustrate this approach by estimating the excess burden for AMR (defined as having tested positive for extended-spectrum beta-lactamases) urinary tract infections (UTIs) caused by *E. coli* in the Netherlands in 2018, which has a relatively low prevalence of AMR *E. coli*, and in Italy in 2016, which has a relatively high prevalence.

Design Excess burden was estimated using the incidence-based disability-adjusted life-years (DALYs) measure. Incidence of AMR *E. coli* UTI in the Netherlands was derived from ISIS-AR, a national surveillance system that includes tested healthcare and community isolates, and the incidence in Italy was estimated using data reported in the literature. A systematic literature review was conducted to find country-specific parameter estimates for disability duration, risks of progression to bacteraemia and mortality.

Results The annual excess burden of AMR *E. coli* UTI was estimated at 3.89 and 99.27 DALY/100 0000 population and 39 and 2786 excess deaths for the Netherlands and Italy, respectively.

Conclusions For the first time, we use country-specific and pathogen-specific parameters to estimate the excess burden of resistant infections. Given the large difference in excess burden due to resistance estimated for Italy and for the Netherlands, we emphasise the importance of using country-specific parameters describing the incidence and disease progression following AMR and susceptible infections that are pathogen specific, and unfortunately currently difficult to locate.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The strength of this study method is the application of the novel method to estimate the excess burden of an infection in two example countries to demonstrate its use.
⇒ We used country-specific and pathogen-specific parameters to estimate the excess burden of disease (BoD).
⇒ National-level surveillance data of the Netherlands informed the estimation of the incidence of resistant *E. coli* urinary tract infections.
⇒ The main limitation was that assumptions had to be made for some country-specific parameters for which no suitable studies were found; this might have affected the estimated difference in the burden and excess burden between the Netherlands and Italy.
⇒ Most parameter estimates used in the calculation of excess BoD were derived from studies in hospital populations whereas data from studies in the general population could lead to more accurate and better generalisable estimates.

INTRODUCTION

Information on incidence and burden of disease (BoD) of infections with antimicrobial-resistant (AMR) bacteria is valuable for setting public health priorities, designing and evaluating interventions.[1] However, such information is scarce,[2] even though AMR has been identified in the European Union/European Economic Area (EEA) as a major public health problem.[3]

To gain insight into the AMR-associated BoD, composite health measures, such as the disability-adjusted life-years (DALYs) measure, which can be derived from clinical pathway progression models, and suitable data on mortality and morbidity[4 5] are useful. Composite health measures allow diseases and their infectious causes to be ranked in terms of burden,[6] and—particularly if based on incidence data—also facilitate measurement of the impact of public health interventions. In the case of AMR, the DALY approach can also be applied to compare the burden across resistant infectious agents, between countries or regions, and across time.

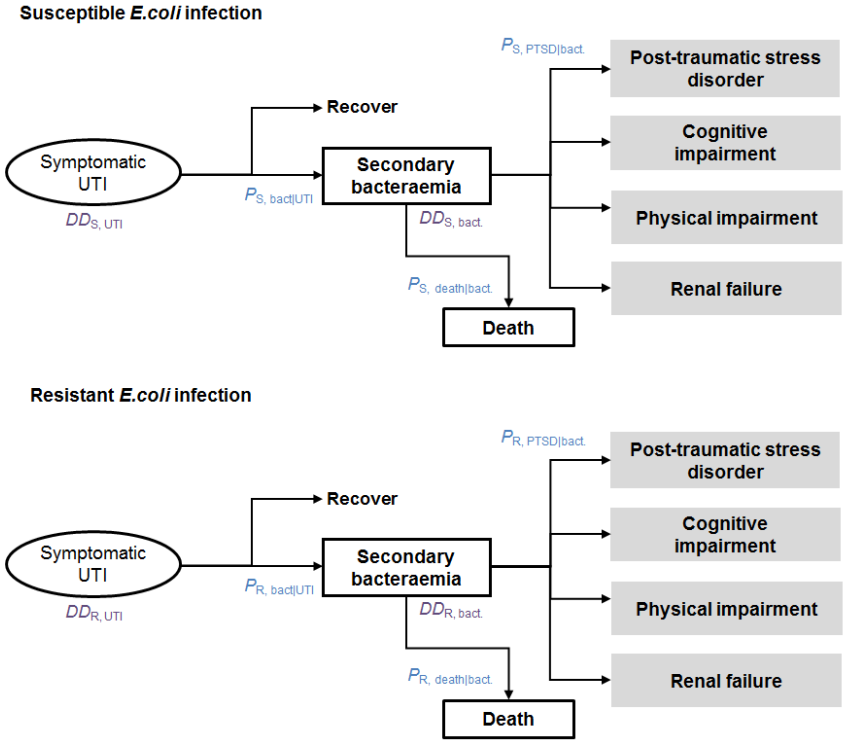

Figure 1 Outcome trees(s) for urinary tract infection (UTI), for antimicrobial-susceptible (upper panel) and antimicrobial-resistant (lower panel) infection. Transition probabilities (P) stratified by type of infection ([S]usceptible or [R]esistant) are indicated for several transitions, as are disability durations (DD).

Attempts to comprehensively estimate the BoD of resistant infection using DALY have only recently been published, and report a large burden of resistance.[2] To calculate BoD, parameters for, among others, the chance of progression from acute infection to severe health outcomes, the risk of mortality and duration in each health outcome are needed. These parameter values are needed for AMR and antimicrobial susceptible (AMS) infections separetely because some previous studies observed worse outcomes for AMR infections. On the other hand, a study on complicated *P. aeruginosa* urinary tract infections (UTIs) and multidrug resistance did not find a difference in 30-day mortality and another study on bacteraemic UTI did also not find an association between 30-day mortality and resistant profiles.[3 7] Parameters to calculate the BoD using the DALY measures should be chosen based on study findings of specific pathogens and infection site to provide more insight on whether resistance increases BoD. Moreover, estimating the BoD brings conceptual challenges, such as determining to what health state resistant infections should be compared, as discussed previously by de Kraker and Lipsitch. For instance, AMR infections can be compared with AMS infections or to the situation in which the infections do not occur and the choice of comparison method influences the calculated excess harm caused by resistance.[8]

The aim of this paper is to introduce a method to calculate the *excess* BoD. By 'excess BoD' we mean the mortality and morbidity (computed as DALY) associated with resistance, over and above the mortality and morbidity associated with infection by the same—but AMS pathogen. In this approach, AMS infections with incidence identical to that for AMR infections serve as a counterfactual to estimate the additional health burden that is attributable to resistance. Our approach is new in that we combine country-specific incidence numbers from surveillance data with country-specific parameter values to calculate the excess BoD for infection caused by a specific resistant pathogen. Methods in previous studies did not include country-specific and pathogen-specific data to estimate the BoD. Subsequently, the method is demonstrated by calculating the excess BoD for a single infection site (UTI) and a single bacterial agent (*E. coli*) as AMR compared with AMS *E. coli*, where a resistant *E. coli* UTI is defined as a tested urine sample containing *E. coli* which produce extended spectrum beta-lactamases (ESBLs) as confirmed by a laboratory. The excess BoD of these infections was assessed for two countries: Italy, which was previously estimated to have the highest antibiotic-resistant BoD in the EEA, and the Netherlands, which was ranked third from last in the list of highest antibiotic resistant BoD in the EEA.[2] Note that our goal is to illustrate how the methodology can be applied to countries with differing AMR *E. coli* prevalence and with differing surveillance data available, and not to conduct a formal comparison of these countries in terms of excess burden. We selected UTIs because they are among the most frequent infections in both the outpatient and inpatient setting and we choose *E. coli* UTIs specifically because UTIs are frequently caused by *E. coli*.[9 10] Furthermore, UTI is a

Table 1 Disease burden model parameter values, with references, for susceptible and resistant *E. coli* urinary tract infections in the Netherlands and the Italy settings, as derived from systematic review

	Netherlands		Italy	
Parameter	Susceptible	Resistant	Susceptible	Resistant
P(Bact|UTI)	3.6% (95% CI 3.4% to 3.8%)[39]*	3.6% (95% CI 3.4% to 3.8%)[39]*	3.6% (95% CI 3.4% to 3.8%)*	3.6% (95% CI 3.4% to 3.8%)*
P(Death|Bact)	11.3% (24/212)[29]	27.5% (19/69)[29]	5.47%†	26.2%[40]
P(PTSD|Bact)	Uniform(0.13, 0.21)[14]	Uniform(0.13, 0.21)[14]	Uniform(0.13, 0.21)[14]	Uniform(0.13, 0.21)[14]
P(CogImp|Bact)	Uniform(0.11–0.47)[14]	Uniform(0.11–0.47)[14]	Uniform(0.11–0.47)[14]	Uniform(0.11–0.47)[14]
P(PhysImp|Bact)	1.0[14]	1.0[14]	1.0[14]	1.0[14]
P(Renal|Bact)	Uniform(0.009–0.13)[14]	Uniform(0.009–0.13)[14]	Uniform(0.009–0.13)[14]	Uniform(0.009–0.13)[14]
DD(UTI)	5.1d (95% CI 4.3 to 5.9)[41]	8.7d (95%CI 7.0 to 10.8)[41]	10d (IQR (7–17))[42 43]	10d (IQR (7–17)[42 43]
DD(Bact)	2.9d (95% CI 1.7 to 4.0)[44]	7.9d (95% CI 3.5 to 13.0)[44]	13±9[45]	20±17 days[45]
DW(UTI)	Uniform(0.039, 0.152)[14]	Uniform(0.039, 0.152)[14]	Uniform(0.039, 0.152)[14]	Uniform(0.039, 0.152)[14]
DW(Bact)	Pert(0.579,0.655,0.727)[14]	Pert(0.579,0.655,0.727)[14]	Pert(0.579,0.655,0.727)[14]	Pert(0.579,0.655,0.727)[14]
DW(PTSD)	Pert(0.07,0.808,0.108)[14]	Pert(0.07,0.808,0.108)[14]	Pert(0.07,0.808,0.108)[14]	Pert(0.07,0.808,0.108)[14]
DW(CogImp)	Pert(0.026,0.043,0.064)[14]	Pert(0.026,0.043,0.064)[14]	Pert(0.026,0.043,0.064)[14]	Pert(0.026,0.043,0.064)[14]
DW(PhysImp)	Uniform(0.011,0.053)[14]	Uniform(0.011,0.053)[14]	Uniform(0.011,0.053)[14]	Uniform(0.011,0.053)[14]
DW(Renal)	Uniform(0.03,0.487)[14]	Uniform(0.03,0.487)[14]	Uniform(0.03,0.487)[14]	Uniform(0.03,0.487)[14]

*Pooled value from Mangen *et al*.[5]
†Calculated using the mortality rate of resistant *E. coli* bacteraemia given in Palacios-Baena *et al*[40] and the ratio between resistant *E. coli* bacteraemia mortality and *E.coli* bacteraemia mortality in Tumbarello *et al*.[45]
CI, confidence interval.

common cause of sepsis a life-threatening complication with a very high mortality rate for all ages.[11] The excess BoD for AMR *E. coli* has not been estimated previously for the Netherlands and Italy using national-level data and country-specific parameter values.

METHODS

We begin by reviewing the parameter requirements for DALY estimation, then describe the systematic reviews that were carried out to locate country-specific parameter values, and finally detail the calculation of AMR *E. coli* UTI incidence for both target countries.

Outcome trees

We modified an existing outcome tree (OT) developed by the European Centre of Disease Control (ECDC) describing the clinical progression pathway for UTI,[2] shown in figure 1. We describe the separate transition probability parameters, disability durations (DDs), and disability weights (DWs) that are needed to quantify the BoD, in DALYs, due to infection with either the susceptible or resistant strain as shown in figure 1. The method simulates an incidence of AMS *E. coli* that is equal to resistant *E. coli* to estimate what the additional burden would be of resistant *E.coli* compared with the same number of AMS *E. coli* infections. Our excess BoD approach involves subtracting the estimated annual DALY for AMS UTIs, using the 'susceptible' version of the OT, from the annual DALY for AMR *E. coli* UTIs, using the 'resistant' version of the OT, while simulating that incidence is identical. We simulate this identical incidence for calculating the excess burden, because we assume that a person would have had a susceptible infection in case they would not have had a resistant infection. Thus, only the OT parameters for resistant and susceptible *E. coli* UTIs differ.

The starting health outcome of the OT is a symptomatic UTI, after which patients can recover, or progress to secondary bacteraemia, and following bacteraemia progress to several long-term sequelae or death.

DALY parameters and calculation

The principal 'input' to the DALY computation is the number of incident cases, in the current example the number of people experiencing an AMR *E. coli* UTI in 1 year. Transition probabilities between symptomatic UTI and all subsequent health outcomes are required. These estimates are required for AMR and AMS *E. coli* UTI separately because the probability of transitioning from one health state to another is often not the same for AMR and AMS infections. We use the notation $P(Outcome_2|Outcome_1)$ to indicate the progression probability from $Outcome_1$ to $Outcome_2$. For instance, P(Bact|UTI) is the probability of progression to bacteraemia given symptomatic UTI. No mortality risk is assumed following a UTI that does not progress to secondary bacteraemia. The OT specifies mortality risk as the parameter P(Death|Bact).

In general, DALYs are calculated as follows: the years of life lost (YLL) are added to the total years lost due to

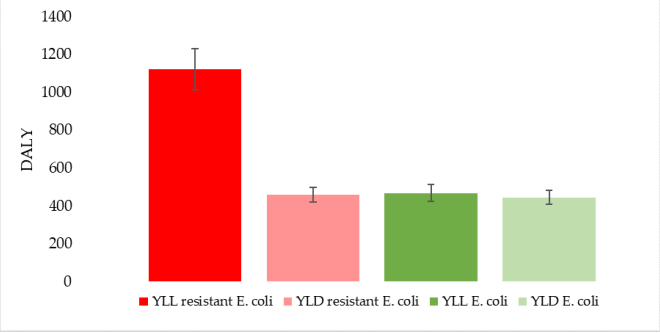

Figure 2 YLD and YLL due to resistant and counterfactual susceptible *E. coli* urinary tract infections in the Netherlands in 2018. Lines indicate 95% uncertainty intervals. DALY, disability-adjusted life-year; YLD, years lost due to disability; YLL, years of life lost.

disability (YLD) which is calculated by summing over the YLD for each (non-fatal) health outcome in the OT:

$$\text{DALY} = \text{YLL} + \text{YLD}$$

$$\text{YLD}_i = \sum_i N_i \times \text{DW}_i \times \text{DD}_i$$

YLL=No. deaths×life expectancy (LE) at age of death.
N_i=the yearly incidence of health outcome *i*.
DW_i=the average disability weight of health outcome *i*.
DD_i=Average duration of disability *i*.

DALY combines the YLL due to premature mortality and YLD, which captures time lived by an individual in less than full health. A loss of 1 year of full health is equivalent to one DALY.[12] For the computation of YLDs, DWs and DDs for each health outcome are required. Given availability of hospital length of stay (LOS) data in the literature, LOS data can serve as a measure of DD if the health state can involve hospital stay. When a patient can transition to more than one, simultaneously experienced, health outcome (so-called 'internal comorbidity'), such as the long-term sequelae following secondary bacteraemia (figure 1), DWs of the overlapping health outcomes can be adjusted to take this into account.[13] We decided a priori to adopt the same DWs as used by ECDC.[2 14]

The risk of recurrent UTI episodes per patient was incorporated using a simple multiplier approach. Dealing with recurrence is necessary as the incidence data consist of the number of patients with at least one UTI episode in 1 year, and the transition probability from UTI to bacteraemia is defined per patient, but the annual BoD will depend on the total number of episodes in a year. Therefore, given an average annual number of episodes per patient, *j*, the total duration of time spent in the health outcome symptomatic UTI in a year is defined as *j*×DD[UTI].

For the computation of YLL, normative LE values by age-group at death are needed. Consistent with previous BoD exercises,[2 15] we chose to use the Global Burden of Disease project (GBD-2010)[16] values.

All BoD measures were estimated using pre-existing software, the BCoDE toolkit V.1.4.[17] In this software, Monte-Carlo simulation with 1000 iterations is employed to compute 95% uncertainty intervals around the BoD. We present the excess BoD and resistant BoD as DALY per 100 000 population (to allow comparison between countries), DALY per 100 cases (for assessing the patient-level burden; also useful for between-country comparison), YLDs and YLL.

Systematic reviews

We performed systematic literature reviews to locate parameter estimates for the risk of progression to bacteraemia, risk of progression to health states following bacteraemia, LOS, other indicators of DDs and mortality

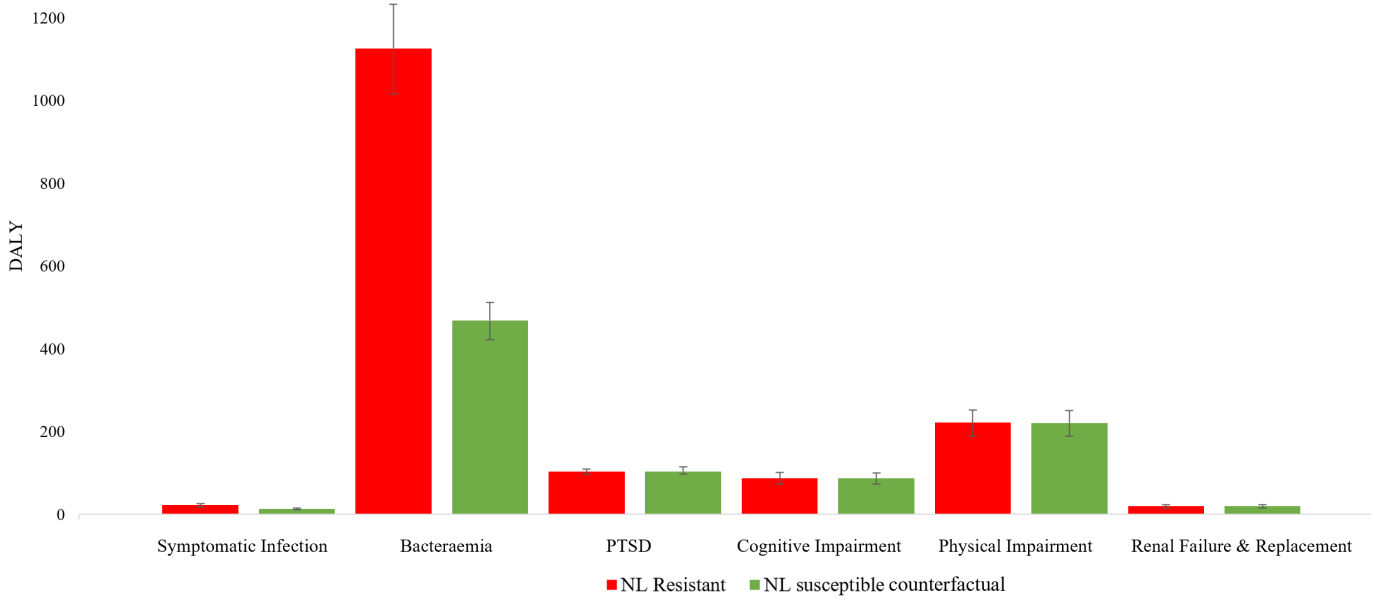

Figure 3 DALYs attributable to six sequelae of resistant and counterfactual susceptible *E. coli* urinary tract infections in the Netherlands in 2018. DALY, disability-adjusted life-year; PTSD, post-traumatic stress disorder.

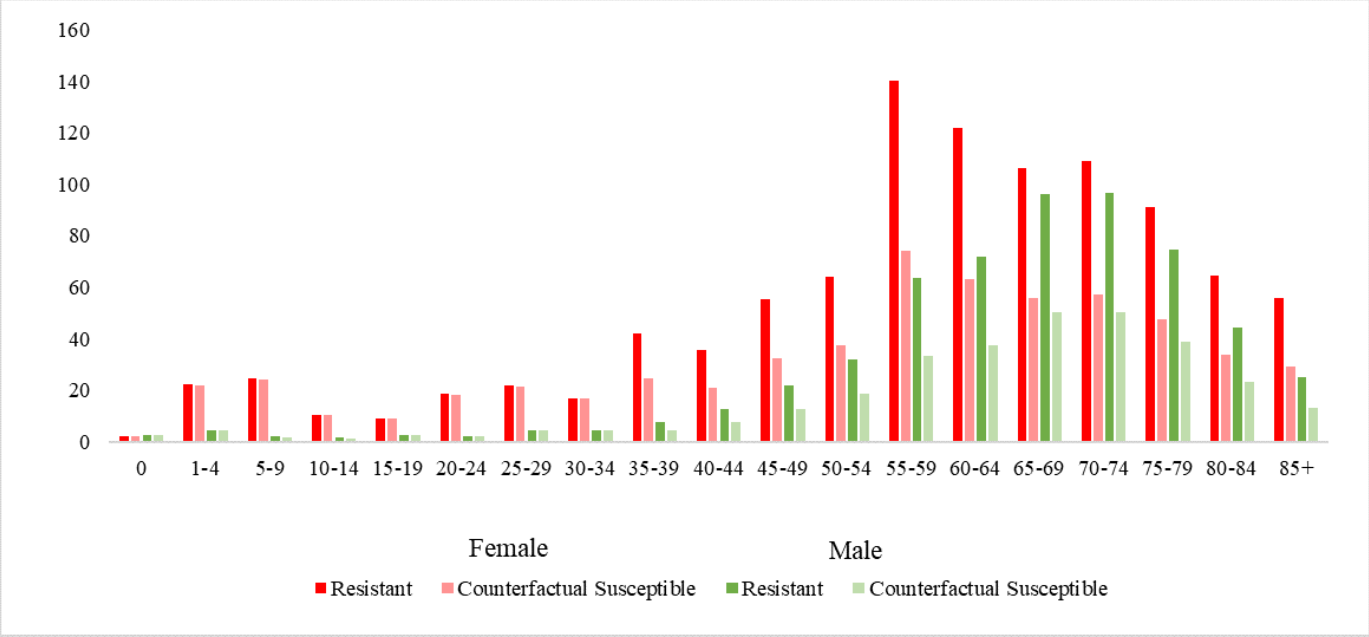

Figure 4 Disability-adjusted life-years of resistant and counterfactual susceptible *E. coli* urinary tract infections in the Netherlands in 2018 per age- and sex-stratified group.

risk. The systematic reviews, performed separately for the Netherlands and Italy, are described in detail in online supplemental appendices 1–3, figures S1 and S2.

AMR *E. coli* UTI incidence in the Netherlands

Data of 2018 from ISIS-AR, a laboratory based AMR surveillance system in the Netherlands[18] were used to estimate AMR *E. coli* UTI incidence. ISIS-AR contains results of antimicrobial susceptibility testing of bacterial isolates routinely tested in medical microbiology laboratories in the Netherlands. ISIS-AR contains data on all consecutive samples of patients, sampled in hospitals (inpatient and outpatient), general practices and long-term care facilities.[19] The coverage of the surveillance system is shown in online supplemental figure S3. ISIS-AR contains data of 46 laboratory which represent around 80% of the Dutch hospitals.[20]

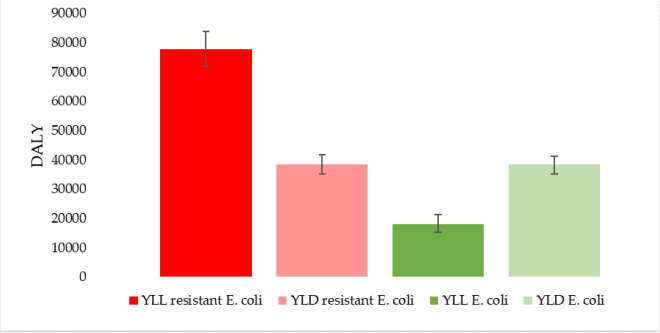

Figure 5 YLD and YLL due to resistant and counterfactual susceptible *E. coli* urinary tract infections in Italy in 2016. Lines indicate 95% uncertainty intervals. DALY, disability-adjusted life-year; YLD, years lost due to disability; YLL, years of life lost.

AMR *E. coli* UTI incidence was defined as the number of persons having at least one urinary AMR *E. coli* isolate in 2018 per 1000 population. The incidence was stratified by sex and 5-year age-group. Online supplemental table S1) shows the data used per sex and age-group to calculate the incidence and recurrence rate. Incidence is thus calculated as the total number of resistant *E. coli* UTI in 2018 per sex and age group divided by the number of inhabitants of the Netherlands per sex and age group in 2018, and subsequently multiplied by 1000. An algorithm was created which calculated the days in between two urinary test samples of the same patient to determine if two consecutive tests had been conducted within 2 weeks in the same patient. If the urinary samples were more than 2 weeks apart, the UTI was labelled as recurrent and then only one isolate was counted. If two tests conducted for the same individual were more than 2 weeks apart, the UTI was defined as recurrent. As a sensitivity analyses, we also show the incidence if we would have defined a recurrent UTI as being longer than 3 months apart. We estimated the average number of recurrent episodes per patient per year. Moreover, we estimate the total incidence of *E. coli* UTIs regardless of resistance to indicate the percentage of resistant *E. coli* UTIs in 2018. The analysis to estimate the incidence were performed in R V.4.0.2.

Estimation of AMR *E. coli* UTI incidence in Italy

No Italian source comparable to ISIS-AR was found. Therefore, we took seven steps to calculate the incidence.

Step 1. We took the number of UTIs (n=57 271) reported in a study that retrospectively used primary care electronic medical records of around 1.1 million Italian general practitioner (GP) patients from 1 January 2016 through 31 December 2016.[21] The coverage of this study

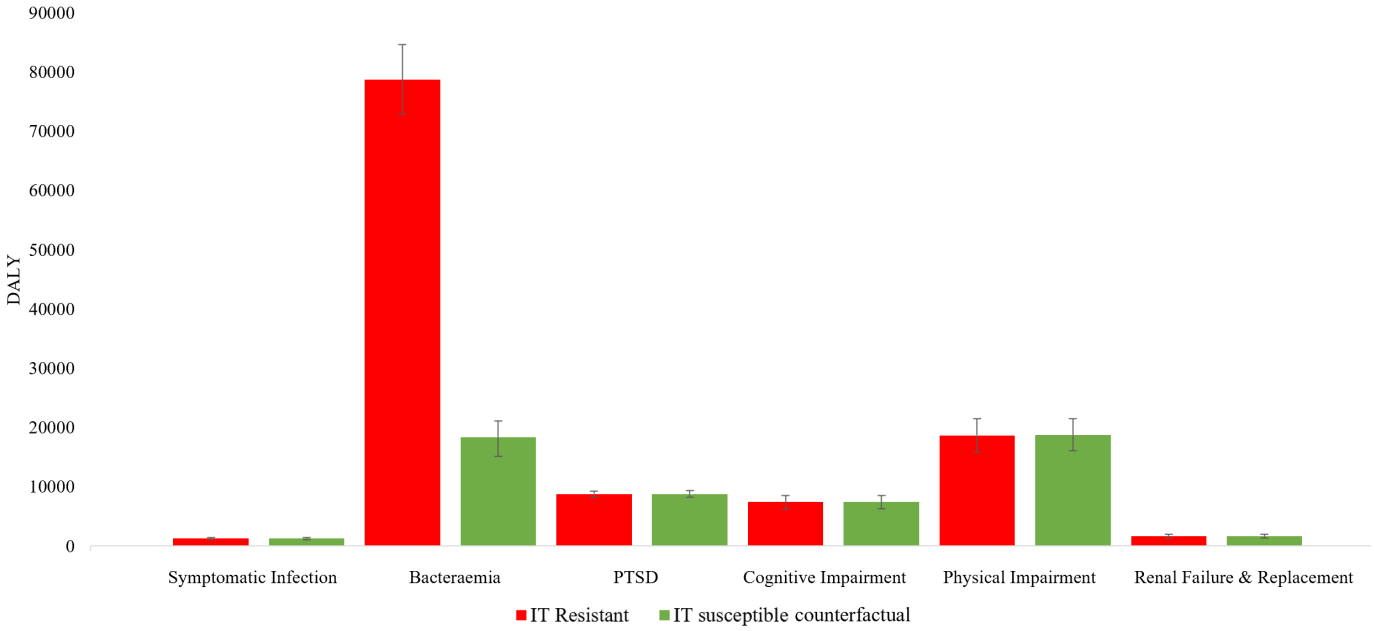

Figure 6 DALYs attributable to six sequelae of resistant and counterfactual susceptible *E. coli* urinary tract infections in Italy in 2016. DALY, disability-adjusted life-year; PTSD, post-traumatic stress disorder.

around 2%[22] and the Italian population size in 2016 reported on ISTAT was used to estimate the total number of patients with a UTI in the entire population in 2016.[22]

Step 2. The sex and age-group distribution from a study on UTIs in 2015–2019 in an academic Italian high-volume centre, namely the University Hospital 'San Giovann di Dio e Ruggi d'Aragona' in Salerno, was used to distribute the total estimated UTIs among women (62.33%), men (37.77%) and age-groups.[23]

Step 3. The number of *E. coli* UTIs was calculated assuming that 59.9% of UTIs were caused by *E. coli* as reported in Cardone *et al*[24] which we identified in the systematic review (online supplemental appendix 1).[24] From January 2013 to June 2017, Cardone *et al*[24] included urine samples collected in the emergency department and used two inclusion criteria. The urine samples had to be collected in (1) patients with UTI symptoms and (2) it had to be their first positive culture urine culture in a given year.

Step 4. A large study from April 2007 to April 2008 in 20 microbiology laboratories found that 15.1% of *E. coli* bacteraemia produced ESBL[25] and this percentage was

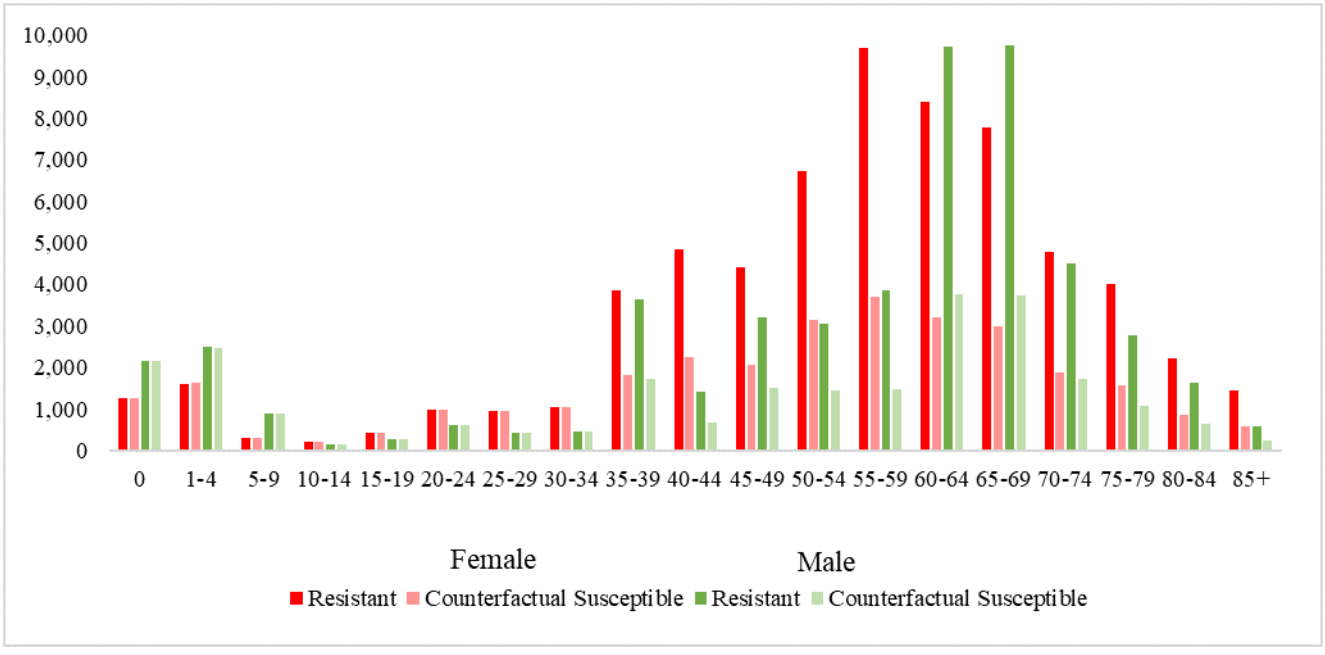

Figure 7 Disability-adjusted life-years of resistant and counterfactual susceptible *E. coli* urinary tract infections in Italy in 2016 per age- and sex-stratified group.

Table 2 Sex-aggregated and age-aggregated YLD, YLL and DALY estimates for antimicrobial resistant and the counterfactual susceptible *E. coli* urinary tract infection, and estimated excess burden attributable to resistance (in DALY), for the Netherlands in 2018

	YLD (95% UI)	YLL (95% UI)	DALY (95% UI)	DALY/100 cases (95% UI)	DALY/100 000 pop (95% UI)
Resistant	458	1223	1581	20.84	9.20
	(424 to 497)	(1016 to 1234)	(1467 to 1701)	(19.34 to 22.42)	(8.58 to 9.90)
Counterfactual susceptible	445	467	913	12.03	5.31
	(409 to 482)	(424 to 513)	(854 to 934)	(11.26 to 12.84)	(4.97 to 5.67)
Excess burden	*13*	*655*	*669*	*8.81*	*3.89*

DALY, disability-adjusted life-year; pop, population; UI, uncertainty interval; YLD, years lost due to disability; YLL, years of life lost.

then applied to the results of Step 3 to estimate the AMR *E. coli* UTI incidence.

Step 5. To estimate the incident number of AMR *E. coli* UTIs per 5-year age category as needed for the BCoDE toolkit V.1.4[17] (eg, 10–14, 15–19), we distributed UTIs within the age-categories used in Serretiello *et al*[23] proportionally according to the age-category and sex-specific population size.

Step 6. To calculate the incident number of AMR *E. coli* UTIs including clinical and outpatient cases, we used the same ratio of hospital to GP cases and outpatient to GP cases, sex and age-stratified, as in the Netherlands. We used the same recurrence rate as we found in the Netherlands, as we were unable to identify a better estimate.

All calculations for the Italian incidence can be found online (https://github.com/NoorGo/ExcessBurden).

Patient and public involvement

There was no direct patient or public involvement in the design of this study.

Table 3 Incidence of resistant *E. coli* urinary tract infection including recurrent UTI in 2018 in the Netherlands and 2016 in Italy of females stratified by age

	Netherlands				Italy			
Age and sex category	Population (N)	Number of infections	Incidence rate	Incidence/ 100 000 inhabitants	Population (N)	Number of infections	Incidence rate	Incidence/ 100 000 inhabitants
Females								
0	82 565	10	0.00012	12.1	232 955	6185	0.02655	2655.2
1–4	340 514	110	0.00032	32.3	1 017 487	8155	0.00801	801.5
5–9	452 563	130	0.00029	28.7	1 385 255	1544	0.00111	111.5
10–14	471 948	58	0.00012	12.3	1 384 866	1159	0.00084	83.7
15–19	511 180	54	0.00011	10.6	1 391 122	2626	0.00189	188.8
20–24	525 964	121	0.00023	23.0	1 472 791	6411	0.00435	435.3
25–29	545 838	155	0.00028	28.4	1 607 399	6619	0.00412	411.8
30–34	522 235	131	0.00025	25.1	1 761 403	7940	0.00451	450.8
35–39	512 431	105	0.00020	20.5	2 037 299	10 088	0.00495	495.2
40–44	521 589	100	0.00019	19.2	2 399 975	13 999	0.00583	583.3
45–49	634 635	173	0.00027	27.3	2 490 023	14 392	0.00578	578.0
50–54	635 623	227	0.00036	35.7	2 420 239	24 738	0.01022	1022.1
55–59	605 380	362	0.00060	59.8	2 110 923	25 965	0.01230	1230.0
60–64	542 198	364	0.00067	67.1	1 891 237	26 513	0.01402	1401.9
65–69	503 662	388	0.00077	77.0	1 927 499	29 486	0.01530	1529.8
70–74	447 439	499	0.00112	111.5	1 533 451	22 993	0.01499	1499.4
75–79	314 838	540	0.00172	171.5	1 552 174	24 926	0.01606	1605.9
80–84	235 430	525	0.00223	223.0	1 227 709	18 861	0.01536	1536.2
85+	248 011	820	0.00331	330.6	1 365 423	21 841	0.01600	1599.6

Table 4 Incidence of resistant *E. coli* urinary tract infection (UTI) including recurrent UTI in 2018 in the Netherlands and 2016 in Italy in males stratified per age

Age and sex category	Netherlands				Italy			
	Population (N)	Number of infections	Incidence rate	Incidence/ 100 000 inhabitants	Population (N)	Number of infections	Incidence rate	Incidence/ 100 000 inhabitants
Males								
0	87 001	12	0.00014	13.8	246 656	10 516	0.04263	4263.2
1–4	358 019	21	0.00006	5.9	1 075 850	12 419	0.01154	1154.3
5–9	475 503	10	0.00002	2.1	1 469 465	4714	0.00321	320.8
10–14	494 511	8	0.00002	1.6	1 469 325	850	0.00058	57.8
15–19	536 852	15	0.00003	2.8	1 490 426	1712	0.00115	114.9
20–24	542 817	15	0.00003	2.8	1 563 396	4037	0.00258	258.2
25–29	560 319	31	0.00006	5.5	1 653 304	3049	0.00184	184.4
30–34	530 554	35	0.00007	6.6	1 776 419	3479	0.00196	195.8
35–39	512 925	19	0.00004	3.7	2 043 171	9548	0.00467	467.3
40–44	516 723	35	0.00007	6.8	2 380 558	4098	0.00172	172.2
45–49	634 188	69	0.00011	10.9	2 441 662	10 417	0.00427	426.6
50–54	644 223	114	0.00018	17.7	2 337 449	11 304	0.00484	483.6
55–59	606 130	163	0.00027	26.9	1 990 139	10 322	0.00519	518.6
60–64	537 540	216	0.00040	40.2	1 755 003	30 703	0.01749	1749.5
65–69	495 875	349	0.00070	70.4	1 757 419	37 111	0.02112	2111.7
70–74	424 486	440	0.00104	103.7	1 322 775	21 430	0.01620	1620.1
75–79	273 902	437	0.00160	159.5	1 227 379	17 312	0.01411	1410.5
80–84	172 825	357	0.00207	206.6	826 785	13 985	0.01691	1691.5
85+	122 648	368	0.00300	300.0	629 140	8887	0.01413	1412.6

RESULTS

The results of the systematic review are discussed in online supplemental appendix 4, and the identified parameter values are described in table 1.

Parameters

The Netherlands

P(Death|Bact) for AMS *E. coli* was 11.3% and for AMR *E. coli* 27.5%. We estimated the DD(UTI) for AMS *E. coli* at 5.1 days (95% CI 4.3 to 5.9) and for AMR *E. coli* at 8.7 days (95% CI 7.0 to 10.8). DD(Bact) for AMS *E. coli* is 2.9 days (95% CI 1.7 to 4) and for AMR *E. coli* 7.9 days (95% CI 3.5 to 13.0). All parameters and their sources can be found in table 1.

Italy

P(Death|Bact) for AMS *E. coli* was 5.47% and for AMR *E. coli* this was estimated to be 26.5%.[5] We were only able to find a single Italian parameter value for DD(UTI), which did not distinguish between AMS *E. coli* and AMR *E. coli* (10.7 days, IQR (7–17)). DD(Bact) for AMS *E. coli* was estimated at 13 days (SD=9) and for AMR *E. coli* at 20 days (SD=17).

Excess burden

The Netherlands

Per 100 0000 inhabitants we found an excess burden of 3.9 DALY/100 000. The YLL component accounted for 98% of the excess BoD. We found 39 (59%) excess deaths compared with the AMS model. Figure 2 shows the YLL and YLD for the Netherlands, while assuming equal incidence of susceptible and AMR *E. coli*. Per 100 cases the excess burden was estimated at 8.8 DALY/100 cases. The greatest excess burden was observed for bacteraemia (658 DALY) as can be seen in figure 3 which shows the excess burden for each of the six specified health outcomes in the clinical pathway progression model for UTI. Sex-group and age-group differences in both BoD and excess burden were apparent (figure 4); the latter was two times greater for females (527 compared with 257 DALY per year in the population of males).

Italy

Per 100 000 inhabitants In Italy, we estimated an excess burden of 99 DALY/100 000. The YLL component accounted for 99.7% of the excess burden and 2786 (77.0%) excess deaths were estimated. Per 100 cases the excess BoD was estimated at 12.3 DALY/100 cases. Figure 5 shows the YLL and YLD for Italy for AMR *E. coli* UTI and when simulating equal incidence of the counterfactual

AMS *E. coli* UTI. Figure 6 which shows the excess burden for each of the six specified health outcomes in the clinical pathway progression model for UTI. Sex-group and age-group differences in both BoD and excess burden were apparent (figure 7); the excess burden was 1.3 times greater for females (34 036 compared with 26 184 DALY). The 5-year age-group contributing the largest estimated excess BoD was 55 to 59-year-old women and 65 to 69-year-old men (5990 and 6041 DALY, respectively).

Resistant burden

The Netherlands

In the Netherlands a total of 9623 AMR *E. coli* UTIs occurred in 2018 based on the tested isolates in ISIS-AR, corresponding to an annual incidence of 0.56 AMR *E. coli* UTIs/1000 inhabitants. This incidence includes recurrent UTIs. These UTIs occurred in 7586 unique patients, resulting in an annual incidence of 0.44 AMR *E. coli* UTIs/1000 inhabitants, excluding recurrent UTIs. Online supplemental table S1 was used to calculate the AMR *E. coli* UTI incidence and recurrence rate per age and sex group. Of the unique AMR *E. coli* UTIs, 64.2% occurred in women and 62.3% in people aged 65 years or older. The total number of *E. coli* UTI in 2018 was 199 441 and excluding recurrent UTI 165 258. The incidence including recurrent UTIs was 11.61/1000 inhabitants and 9.62/1000 inhabitants excluding recurrent *E. coli* UTI. The percentage resistant *E. coli* UTIs was 4.8% including recurrent UTIs and 4.6% excluding recurrent UTIs of the total number of *E. coli* UTIs in 2018. Online supplemental table S2 was used to calculate the *E. coli* UTI incidence and recurrence rate per age and sex group. In the sensitivity analysis in which we assumed a recurrent UTI to be more than 3 months apart we found an overall incidence of 0.47 AMR *E. coli* UTIs/1000 inhabitants and an incidence of 0.44 AMR *E. coli* UTI/1000 inhabitants excluding recurrent UTIs. Online supplemental table S3 shows the data of the incidence calculation for the sensitivity analysis.

Per 100 000 inhabitants in the Netherlands, we estimated an AMR *E. coli* UTI incidence of 9.2 DALY/100 000 inhabitants (95% UI 8.5 to 9.9). The YLL component accounted for 71.0% of the resistant BoD and 66 deaths were estimated. The sex-aggregated and age-aggregated BoD for AMR *E. coli* UTI in the Dutch population in 2018 was estimated at 1581 DALY (95% UI 1467 to 1701), or per 100 cases 20.8 DALY (95% UI 19.3 to 22.3) DALY (table 2). The resistant BoD for females was approximately two times that for males (1011 compared with 570 DALY) as shown in figure 4. Figure 3 shows the BoD for the specified health outcomes in the UTI clinical pathway progression model. The health outcome with the highest BoD for UTIs caused by AMR *E. coli* was bacteraemia (1127 DALY, 95% UI 1020 to 1238).

Italy

In Italy in 2016, we estimated 490 332 AMR *E. coli* UTI and an incidence of 8.1 UTIs/1000 inhabitants excluding recurrent UTI. In women, 56% of infections occurred and 44% occurred in people aged ≥65 years. Incidences per age and sex group can be found in tables 3 and 4.

In Italy, we estimated 192 DALY/100 000 (95% UI 181 to 203). The YLL component accounted for 66.9% of the resistant UTI BoD. For the AMR model 3617 (95% UI 3352 to 3884) deaths were estimated. The sex-aggregated and age-aggregated BoD for resistant AMR *E. coli* UTI in the Italian population in 2016 was estimated at 166 488 (95% UI 109 744 to 123 106) DALY, or 23.8 DALY per 100 cases (table 5). Just as for the Netherlands, the health outcome with the highest BoD for UTIs caused by AMR *E. coli* was bacteraemia (78 686 DALY, 95% UI 72 736 to 84 493), which also caused the larger excess burden (69 885 DALY) as can be seen in figures 3 and 6). The resistant BoD for females was approximately 1.3 times that for males (64 878 compared with 51 610 DALY). The 55 to 59-year-old women (9688 DALY) and 65 to 69-year-old men contributed the most (9765 DALY).

DISCUSSION

We developed a method for estimating the *excess* BoD due to antimicrobial resistance, and applied the method to AMR *E. coli* UTI for two countries using country-specific parameters and incidence data. Using country-specific parameters for BoD estimates is crucial, as outcome measures (eg, mortality) are not only influenced by

Table 5 Sex-aggregated and age-aggregated YLD, YLL and DALY estimates for resistant and counterfactual susceptible *E. coli* urinary tract infection, and estimated excess burden attributable to resistance (in DALY), for Italy in 2016

	YLD (95% UI)	YLL (95% UI)	DALY (95% UI)	DALY/ 100 cases (95% UI)	DALY/ 100 000 pop (95% UI)
Resistant	38 499.48	77 989	116 488	23.76	192.02
	(35 387 to 41 684)	(72 056 to 83 785)	(109 744 to 123 106)	(22.38 to 25.11)	(180.90 to 202.92)
Counterfactual susceptible	38 349	17 920	56 268	11.48	92.75
	(35 212 to 41 359)	(15 134 to 21 105)	(52 069 to 60 696)	(10.62 to 12.43)	(85.83 to 100.49)
Excess burden	*151*	60 069	60 220	*12.28*	*99.27*

DALY, disability-adjusted life-year; pop, population; UI, uncertainty interval; YLD, years lost due to disability; YLL, years of life lost.

resistance itself, but can also be influenced by inappropriate treatment,[8] and BoD depends on the prevalence of comorbidities, as well as country-specific differences in hospital and prevention policies.[26] Previous large BoD studies such as Cassini *et al*[2] did not use country-specific parameter estimates,[2] whereas our results indicate that this is important. Two examples, among others that we found in our study, of why the use of country-specific parameters is important are that parameters such as the risk of death following bacteraemia and the disease duration of bacteraemia we found in the literature differed between Italy and the Netherlands. Subsequently these parameter differences between Italy and the Netherlands contribute to the differences in the excess burden between Italy and the Netherlands.

YLL accounted for most of the estimated AMR BoD in the Netherlands and in Italy (71% and 66.3%, respectively). A previous study on healthcare-associated (HA) infections, including bloodstream infections and UTI, based on data of Italy in 2016, also found that the majority of the BoD of AMR was attributable to YLL (79.7%).[27] Regarding the burden of AMR in DALYs per 100 000 population, HA UTIs were estimated at 81.2 (69.0–94.4) DALYs/100 000 population. Both studies noted that UTIs were the second[14] or most frequent[27] HA in terms of incidence. The difference in excess BoD and in the AMR disease burden between the Netherlands and Italy that we found might be partly due to differences in treatment and resistance testing policies. Since our literature search, a Dutch study in eight hospitals was published suggesting a different mortality when comparing highly resistant to non-highly resistant bacteraemia, namely an RR of 1.08 (95% CI 0.48 to 2.41).[28] This estimated mortality would imply that our estimates of the excess burden for NL may be over-estimated as the mortality risk difference of Rottier *et al*[28] is smaller than that of van Hout *et al*.[29] However, the CI of Rottier *et al*[28] is relatively large and of the bacteraemia that were included, only 52% (n=1001) had the urinary tract as source and 62% (n=1190) was caused by *E. coli*.

Previous incidence estimates of resistant *E. coli* UTI based on data from 2015 indicate a third generation cephalosporin resistant *E. coli* UTI incidence in Italy that is 7.3 times higher than in the Netherlands, and a carbapenem resistant *E. coli* UTI incidence that is 12.3 times higher.[2] In the current study, we estimated AMR *E. coli* incidence to be 18.3 times higher in Italy in 2016 than in the Netherlands in 2018. However, these previous estimates from Cassini *et al*[2] were derived using a different approach[2]; namely, the incidence of blood-stream infection served as primary data, which was then extrapolated to specific infection sites and to each EU/EAA country. Also, in contrast to the study of Cassini *et al*,[2] we use country-specific parameters which might be more suitable to indicate differences between countries in contributors to BoD. In a recent burden study DALYs attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019 are provided. The authors mention the difficulty of understanding the burden of AMR when data are sparse and mention that because of data sparsity, they assumed the relative risk of death was the same for every syndrome, location and age group.[30] We also found it difficult to locate country-specific mortality risks and other parameter values, and have argued that such data is important for accurate excess burden estimation at country level because country-specific parameters of for example mortality differ between Italy and the Netherlands.

In the paper of de Kraker and Lipsitch[8] it is proposed to let the counterfactual in the BoD calculation depend on the type of intervention.[8] The excess BoD method proposed in the current study defines the susceptible counterfactual to have identical incidence as resistant infection. This method could accordingly be useful for estimating the effect of reduction of broad spectrum antimicrobial use, vaccination against pathogens that are associated with antimicrobial use, introduction of new antibiotics, reduction of environmental or agricultural antibiotic use, and a combination of interventions targeted at the resistant strain. For these estimations, the model parameters could for example be adjusted and made specific for another pathogen and for a new intervention. The susceptible counterfactual is relevant under the assumption that resistant and susceptible strain compete as previously indicated to be the case by Godijk *et al*.[31] Under the assumption that the replacement scenario is (mostly) occurring, the comparison group should be the same group of patients with infections caused by AMS pathogens to calculate excess mortality and BoD.[32]

A strength of this study is that we used national-level surveillance data of the Netherlands to calculate the incidence of resistant *E. coli* UTI. The use of these data enabled us to estimate the incidence of AMR *E. coli* as a basis for the BoD estimate. However, the use of these data harbour some limitations. First, the national coverage is less than 100%; therefore AMR *E. coli* UTI incidence is underestimated. Also, in Italy the study on which we based our estimation of the proportion of resistant *E. coli* is dependent on samples being taken, which is also sensitive to testing practice and does not have a complete national coverage. However, the BoD experienced by these 'missed' patients is expected to be small because their UTI resolved on first line treatment and therefore, they experienced little BoD. Their chance of progressing to bacteraemia would be minimal. Our DALY estimate is mostly determined by those patients that develop bacteraemia, which has an accompanying high risk of mortality. Second, the surveillance date are routine data from medical microbiological laboratories. The ISIS-AR data only contains UTIs that have been sampled and tested for resistance. In general practices in the Netherlands, UTIs are often sampled only when infection is not eliminated after initial treatment. A part of the UTIs, therefore, may have been missed in our study. However, since we based our calculations on AMR infections only, we do not expect that this has largely influenced our estimates.

Another strength of this study is that we not only propose a new method to calculate the excess BoD, but that we also apply our method to two countries to demonstrate its use and explore the methods drawbacks. A drawback of this method, as mentioned previously,[33] is that it often is difficult to locate high-quality AMR surveillance data and country-specific AMR attributable mortality and morbidity parameters, as we experienced in the current study. Even though we performed a systematic review, we were not able to locate relevant studies and/or recent estimates for all parameters. In low-income and middle-income countries data scarcity is an even larger problem, which makes using country-specific parameter estimates and incidence data as we advise for out method harder, even though the use of country-specific parameters is probably even more important when comparing developing to developed countries. Apart from the higher percentage of resistance in Italy, the difference in parameter estimates between Italy and the Netherlands explain the larger BoD and excess BoD for Italy. For the Netherlands, available studies showed a smaller difference in the bacteraemia mortality rate for AMR *E. coli* and AMS *E. coli* (27.5% vs 11.3%, respectively) than for Italy (26.2% vs 5.5%, respectively). Moreover, for the Netherlands DDs for the UTI and bacteraemia health outcomes were shorter. However, we had to make multiple assumptions of the model parameters, especially for Italy, as country-specific data were not available for all estimates. These assumptions may also affect the estimated difference in the burden and excess burden between the Netherlands and Italy. For example, we used the same ratio of hospital to GP cases and outpatient to GP cases for Italy as for the Netherlands because we could not find specific data for Italy. However, in both the Netherlands and Italy antibiotics are not sold over the counter (in Italy there are some exceptions, eg, when the drug is necessary in order not to interrupt the treatment of a chronic disease[34]); thus prescriptions are required,[34 35] and it is most common in both countries to first visit the GP, get treatment if necessary, and thereafter get additional care if needed. For this reason, we choose to use the same ratio of hospital to GP cases and outpatient to GP cases, even though there are some antibiotic prescription and treatment differences between the two countries. Furthermore, the estimated mortality following bacteraemia as a consequence of UTI was estimated to be 11.3% for AMS *E. coli* and for AMR *E. coli* 27.5% in the Netherlands,[29] whereas a previous study in Finland, Sweden and Canada found a mortality rate of 9.2% of *E. coli* BSI with third-generation cephalosporin susceptibility and a mortality of 14.1% of *E. coli* BSIs with third-generation cephalosporin resistance.[36] As we found few parameter estimates that were country-specific, we were unable to, for example, do a small meta-analysis, and get more valid estimates. Thus, our results should be interpreted with caution. The codes used to calculate the incidence in Italy, the excel in which the figures were created and the excel sheets used to calculated the excess burden are available on the Github repository (https://github.com/NoorGo/ExcessBurden).[37]

Moreover, the assumed 15.1% resistance prevalence *E. coli* UTIs in Italy is likely to be an underestimate, as other data from 2017 suggested around 75% of the *E. coli* isolates in Italy to be resistant to at least one antibiotic group and around 45% to be resistant to three or more antibiotic groups,[38] however the 2017 prevalence was not specific for UTIs and we preferred to use UTI-specific AMR *E. coli* estimates. Future research would benefit from using more recent country-specific surveillance data, when it becomes available, to more accurately estimate AMR *E. coli* incidence.

In addition, parameter estimates were limited by restricted analysis of confounders.[26] We did, however, stratify our results for age and sex. Moreover, we adjusted the risk of mortality following bacteraemia for age. Future research could use parameter estimates derived from the general population. Most estimates used in this study were derived from studies in hospital populations. Parameter estimates based on studies in the general population could lead to more accurate estimates that are better generalisable to the Dutch and Italian populations. For example, hospital patients presenting with a UTI may more likely progress to bacteraemia, due to an already weakened immune system, than individuals who present with a UTI at the GP. As we were unable to locate parameter estimates in the general population, we also recommend future research to focus on estimating these parameters. An example of such a study could be following GP patients who have a confirmed AMR or AMS *E. coli* UTI to estimate the probability of progression to bacteraemia and subsequent mortality.

To conclude, for the first time, we use country-specific and pathogen-specific parameters to estimate the excess burden of resistant infections. Given the large excess burden difference between AMR *E. coli* and AMS *E. coli* UTI, we emphasise the importance of using country-specific parameters describing the incidence and disease progression following resistant and susceptible infections that are pathogen-specific. Unfortunately, these parameters are currently difficult to locate.

Contributors NGG, SAM and MCJB conceptualised the study. NGG conducted the literature review and performed the data analyses with the help of SAM. NGG generated the figures and drafted the manuscript. WA-vdK and AFS had access to the ISIS-AR data and supplied the required data for the incidence calculations. WA-vdK created online supplemental figure S3. SAM, MCJB, WA-vdK, AFS and EF reviewed the manuscript and performed a critical revision of the manuscript text to clarify the methodology. NGG is guarantor and is responsible for the overall content.

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Data availability statement Data are available in a public, open access repository. The code used to calculate the incidence in Italy, the spreadsheet in which the figures were created and the spreadsheets used to calculated the excess burden are available in the Github repository https://github.com/NoorGo/ExcessBurden.

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