BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064335
Article Type:	Original research
Date Submitted by the Author:	03-Jun-2022
Complete List of Authors:	Godijk, Noortje ; UMC Utrecht, Julius Centre of Primary Care and Health Sciences McDonald, Scott; Rijksinstituut voor Volksgezondheid en Milieu, Altorf-van der Kuil, W.; National Institute for Public Health & the Environment Schoffelen, A.F.; National Institute for Public Health & the Environment Franz, Eelco; National Institute for Public Health and the Environment, Centre for Infectious Disease Control Bootsma, M.C.J.; University Medical Center Utrecht; Utrecht University, Department of Mathematics
Keywords:	Epidemiology < INFECTIOUS DISEASES, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, STATISTICS & RESEARCH METHODS, Urinary tract infections < UROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Noortje G. Godijk*[1], Scott A. McDonald[2], Wieke Altorf-van der Kuil[2], Annelot F. Schoffelen[2], Eelco Franz[2], Martin C.J. Bootsma[1,3]

[1] Julius Center for Health Sciences & Primary Care, University Medical Center Utrecht, NL

[2] Centre for Infectious Disease Control, National Institute for Public Health & the Environment, Bilthoven, NL

[3] Department of Mathematics, Faculty of Sciences, Utrecht University, Utrecht, NL

*Corresponding author: N.G. Godijk, Noortje G. Godijk, +31(0)887568147, University Medical Center Utrecht, Postbox 85500, 3508 GA Utrecht, n.g.godijk@gmail.com

Word count: 5175

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 ESBL) urinary tract infections (UTI) 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.

Method. Excess burden was estimated using the incidence-based disability-adjusted life-years (DALY) 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 2,786 excess deaths for the Netherlands and Italy, respectively.

Conclusion

For the first time, we use country- 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 emphasize 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 strengths of this study are the development of a new method to estimate the excess BoD due to antimicrobrial resistance, and the application of this method to two example countries to demonstrate its use.

- We used country- and pathogen-specific parameters to estimate the excess BoD.

- National-level surveillance data of the Netherlands informed the estimation of the incidence of resistant E. coli UTI

- 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 (DALY) 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.

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, amongst 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* UTI 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 & Lipsitch (2021). For instance, AMR infections can be compared to 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- 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 an *E. coli* UTI was labelled antibiotic resistant if the tested urine sample contained *E. coli* which produced 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). 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 UTI are frequently caused by *E. coli* (9,10). Furthermore, UTI is a 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 to 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 one 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 disability (YLD) which is calculated by summing over the YLD for each (non-fatal) health outcome in the OT:

$$DALY = YLL + YLD$$

$$YLD_i = \sum_i N_i * DW_i * DD_i$$

*YLL = No. deaths * life expectancy at age of death*

Ni = the yearly incidence of health outcome i

DWi = the average disability weight of health outcome i

DDi = 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 one 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 one 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 life expectancy (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 version 1.4 (17). In this software, Monte-Carlo simulation with 1,000 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), years lived with disability (YLDs) and years of life lost (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 risk. The systematic reviews, performed separately for the Netherlands and Italy, are described in detail in Appendix 2, Appendix 3, Figure S1 and Figure 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 Figure S3. ISIS-AR contains data of 46 laboratory which represent around 80% of the Dutch hospitals (20).

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 five-year age-group. 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 two weeks in the same patient. If the urinary samples were more than two 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 two 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 version 4.0.2.

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

No Italian source comparable to ISIS-AR was found. Therefore, we took 7 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 GP patients from 1 January 2016 through 31 December 2016 (23). The coverage of this study around 2% (21) 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 (21).

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 (22).

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. (23) which we identified in the systematic review (Appendix 1) (23). From January 2013 to June 2017, Cardone et al. (23) 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 (24) and this percentage was 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 version 1.4 (17) (e.g. 10-14, 15-19), we distributed UTIs within the age-categories used in Serretiello et al. (22) 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 at https://github.com/NoorGo/ExcessBurden.

Patient and public involvement

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

RESULTS

The results of the systematic review are discussed in Appendix 4, and the identified parameter values are described below (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 [4.3-5.9]) and for AMR *E. coli* at 8.7 days (95% CI [7.0-10.8]). DD(Bact) for AMS *E. coli* is 2.9 days (95%CI [1.7-4]) and for AMR *E. coli* 7.9 days (95% CI [3.5-13.0]). 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 to 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

Table 1.

Disease burden model parameter values, with references, for susceptible and resistant E. coli UTIs 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 [3.4-3.8%]) (25) [a]	3.6% (95% CI [3.4-3.8%]) (25) [a]	3.6% (95% CI [3.4-3.8%]) [a]	3.6% (95% CI [3.4-3.8%]) [a]
P(Death|Bact)	11.3% (24/212) (26)	27.5% (19/69) (26)	5.47% [b]	26.2% (27)
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 [4.3-5.9]) (28)	8.7d (95%CI [7.0-10.8]) (28)	10d (IQR [7-17]) (29,30)	10d (IQR [7-17]) (29,30)
DD(Bact)	2.9d (95% CI [1.7-4.0]) (31)	7.9d (95% CI [3.5-13.0]) (31)	13 ± 9 (32)	20 ± 17 days (32)
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)

[a] Pooled value from (5).

[b] Calculated using the mortality rate of resistant *E. coli* bacteraemia given in (27) and the ratio between resistant *E.coli* bacteraemia mortality and *E.coli* bacteraemia mortality in (32)

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- 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 2,786 (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 the 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- 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 to 26,184 DALY). The 5-year age-group contributing the largest estimated excess BoD was 55-59 year old females and 65-69 year old males (5,990 and 6041 DALY, respectively).

Resistant burden

The Netherlands

In the Netherlands a total of 9,623 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 7,586 unique patients, resulting in an annual incidence of 0.44 AMR *E. coli* UTIs/1000 inhabitants, excluding recurrent UTIs. 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. 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 three 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. 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: 8.5-9.9). The YLL component accounted for 71.0% of the resistant BoD and 66 deaths were estimated. The sex- and age-aggregated BoD for AMR *E. coli* UTI in the Dutch population in 2018 was estimated at 1,581 DALY (95% UI: 1,467-1,701), or per 100 cases 20.8 DALY (95% UI: 19.3-22.3) 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 (1,127 DALY, 95% UI: 1,020-1,238).

Table 2.

Sex- and age-aggregated YLD, YLL and DALY estimates for antimicrobial resistant and the

counterfactual susceptible E. coli UTI 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 (424-497)	1223 (1016-1234)	1,581 (1467-1701)	20.84 (19.34-22.42)	9.20 (8.58-9.90)
Counterfactual susceptible	445 (409-482)	467 (424-513)	913 (854-934)	12.03 (11.26-12.84)	5.31 (4.97-5.67)
Excess burden	*13*	*655*	*669*	*8.81*	*3.89*

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 Table 3 and Table 4.

In Italy, we estimated 192 DALY/100,000 (95% UI: 181-203). The YLL component accounted for 66.9% of the resistant UTI BoD. For the AMR model 3,617 (95% UI: 3,352-3,884) deaths were estimated. The sex- and age-aggregated BoD for resistant AMR *E. coli* UTI in the Italian population in 2016 was estimated at 166,488 (95% UI: 109,744-123,106) 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: 72,736-84,493), 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 to 51,610 DALY). The 55-59 year old females (9,688 DALY) and 65-69 year old males contributed the most (9,765 DALY).

Table 3. *Incidence of resistant E. coli UTI 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	82565	10	0.00012	12.1	232955	6185	0.02655	2655.2
1 tot 4	340514	110	0.00032	32.3	1017487	8155	0.00801	801.5
5 tot 9	452563	130	0.00029	28.7	1385255	1544	0.00111	111.5
10 tot 14	471948	58	0.00012	12.3	1384866	1159	0.00084	83.7
15-19	511180	54	0.00011	10.6	1391122	2626	0.00189	188.8
20-24	525964	121	0.00023	23.0	1472791	6411	0.00435	435.3
25-29	545838	155	0.00028	28.4	1607399	6619	0.00412	411.8
30-34	522235	131	0.00025	25.1	1761403	7940	0.00451	450.8
35-39	512431	105	0.00020	20.5	2037299	10088	0.00495	495.2
40-44	521589	100	0.00019	19.2	2399975	13999	0.00583	583.3

45-49	634635	173	0.00027	27.3	2490023	14392	0.00578	578.0
50-54	635623	227	0.00036	35.7	2420239	24738	0.01022	1022.1
55-59	605380	362	0.00060	59.8	2110923	25965	0.01230	1230.0
60-64	542198	364	0.00067	67.1	1891237	26513	0.01402	1401.9
65-69	503662	388	0.00077	77.0	1927499	29486	0.01530	1529.8
70-74	447439	499	0.00112	111.5	1533451	22993	0.01499	1499.4
75-79	314838	540	0.00172	171.5	1552174	24926	0.01606	1605.9
80-84	235430	525	0.00223	223.0	1227709	18861	0.01536	1536.2
85+	248011	820	0.00331	330.6	1365423	21841	0.01600	1599.6

Table 4. *Incidence of resistant E. coli UTI including recurrent UTI in 2018 in the Netherlands and 2016 in Italy in males stratified per 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**
Males								
0	87001	12	0.00014	13.8	246656	10516	0.04263	4263.2
1 tot 4	358019	21	0.00006	5.9	1075850	12419	0.01154	1154.3
5 tot 9	475503	10	0.00002	2.1	1469465	4714	0.00321	320.8
10 tot 14	494511	8	0.00002	1.6	1469325	850	0.00058	57.8
15-19	536852	15	0.00003	2.8	1490426	1712	0.00115	114.9
20-24	542817	15	0.00003	2.8	1563396	4037	0.00258	258.2
25-29	560319	31	0.00006	5.5	1653304	3049	0.00184	184.4
30-34	530554	35	0.00007	6.6	1776419	3479	0.00196	195.8
35-39	512925	19	0.00004	3.7	2043171	9548	0.00467	467.3
40-44	516723	35	0.00007	6.8	2380558	4098	0.00172	172.2

45-49	634188	69	0.00011	10.9	2441662	10417	0.00427	426.6
50-54	644223	114	0.00018	17.7	2337449	11304	0.00484	483.6
55-59	606130	163	0.00027	26.9	1990139	10322	0.00519	518.6
60-64	537540	216	0.00040	40.2	1755003	30703	0.01749	1749.5
65-69	495875	349	0.00070	70.4	1757419	37111	0.02112	2111.7
70-74	424486	440	0.00104	103.7	1322775	21430	0.01620	1620.1
75-79	273902	437	0.00160	159.5	1227379	17312	0.01411	1410.5
80-84	172825	357	0.00207	206.6	826785	13985	0.01691	1691.5
85+	122648	368	0.00300	300.0	629140	8887	0.01413	1412.6

Table 5.

Sex- and age-aggregated YLD, YLL and DALY estimates for resistant and counterfactual susceptible E. coli UTI 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	38499.48 (35,387-41,684)	77,989 (72,056-83,785)	116,488 (109,744-123,106)	23.76 (22.38–25.11)	192.02 (180.90-202.92)
Counterfactual susceptible	38,349 (35,212-41,359)	17,920 (15,134-21,105)	56,268 (52,069-60,696)	11.48 (10.62-12.43)	92.75 (85.83-100.49)
Excess burden	*151*	*60,069*	*60,220*	*12.28*	*99.27*

DISCUSSION

We developed a method for estimating the *excess* BoD due to antimicrobial resistance, and applied the method to AMR *E. coli* UTI infection for two countries using country-specific parameters and incidence data. Using country-specific parameters for BoD estimates is crucial, as outcome measures (e.g. mortality) are not only influenced by 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 (33). 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. For example, 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 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%) (34). 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 (34) 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 8 hospitals was published suggesting a different mortality when comparing highly resistant to non-highly resistant bacteraemia, namely an RR of 1.08 (95% CI 0.48-2.41) (35). 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. (35) is smaller than that of van Hout et al. (26). However, the confidence interval of Rotter et al. (35) 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 the paper of de Kraker & 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. (36). 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 (37).

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. Firstly, 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 upon 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. Secondly, 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 UTI infections, 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 (38), 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. 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, for example when the drug is necessary in order not to interrupt the treatment of a chronic disease(39)); thus prescriptions are required (39,40), 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 these 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 (26), 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 (41). 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.

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 grousps (42), 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 (33). 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 generalizable 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- 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 emphasize 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.

Funding:

This study was supported by the research project RADAR (Risk Assessment and Disease burden of Antimicrobial Resistance) funded through the One Health European Joint Programme by the EU's Horizon-2020 Research and Innovation Programme (grant 773830).

Competing interests:

The authors declare that no competing interests exist.

Contributors:

NGG, SAM and MCJB conceptualized 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. WAK and AFS had access to the ISIS-AR data and subtracted the needed data for the incidence calculations. WAK created figure S3. Moreover, SAM, MCJB, WAK, AFS and EF reviewed the manuscript and performed a critical revision of the manuscript text which aided substantially in clarifying the used methodology.

Data sharing statement

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.

Ethics Approval Statement

This study does not involve human participants.

REFERENCES

1. Wernli D, Jørgensen PS, Harbarth S, Carroll SP, Laxminarayan R, Levrat N, et al. Antimicrobial resistance: The complex challenge of measurement to inform policy and the public. PLoS Med [Internet]. 2017 Aug 17;14(8):e1002378–e1002378. Available from: https://pubmed.ncbi.nlm.nih.gov/28817562

2. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis [Internet]. 2019 Jan 1;19(1):56–66. Available from: https://doi.org/10.1016/S1473-3099(18)30605-4

3. Eliakim-Raz N, Babitch T, Shaw E, Addy I, Wiegand I, Vank C, et al. Risk Factors for Treatment Failure and Mortality Among Hospitalized Patients With Complicated Urinary Tract Infection: A Multicenter Retrospective Cohort Study (RESCUING Study Group). Clin Infect Dis [Internet]. 2018 May 17;68(1):29–36. Available from: https://doi.org/10.1093/cid/ciy418

4. Kretzschmar M, Mangen M-JJ, Pinheiro P, Jahn B, Fèvre EM, Longhi S, et al. New Methodology for Estimating the Burden of Infectious Diseases in Europe. PLOS Med [Internet]. 2012 Apr 17;9(4):e1001205. Available from: https://doi.org/10.1371/journal.pmed.1001205

5. Mangen M-JJ, Plass D, Havelaar AH, Gibbons CL, Cassini A, Mühlberger N, et al. The Pathogen- and Incidence-Based DALY Approach: An Appropriated Methodology for Estimating the Burden of Infectious Diseases. PLoS One [Internet]. 2013 Nov

20;8(11):e79740. Available from: https://doi.org/10.1371/journal.pone.0079740

6. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England). 2016 Oct;388(10053):1545–602.

7. Horcajada JP, Shaw E, Padilla B, Pintado V, Calbo E, Benito N, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. Clin Microbiol Infect [Internet]. 2013 Oct 1;19(10):962–8. Available from: https://doi.org/10.1111/1469-0691.12089

8. de Kraker MEA, Lipsitch M. Burden of Antimicrobial Resistance: Compared to What? Epidemiol Rev. 2021 Mar;

9. Gomila A, Carratalà J, Eliakim-Raz N, Shaw E, Wiegand I, Vallejo-Torres L, et al. Risk factors and prognosis of complicated urinary tract infections caused by Pseudomonas aeruginosa in hospitalized patients: a retrospective multicenter cohort study. Infect Drug Resist. 2018;11:2571–81.

10. Zorginstituut Nederland. Screeningsrapport Systematische analyse Infectieziekten [Internet]. 2019. Available from: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2019/05/14/zinnige-zorg---rapport-screeningsfase-infectieziekten/Zinnige+Zorg+-+Rapport+screeningsfase+Systematische+analyse+Infectieziekten.pdf

11. Bonkat G, Cai T, Veeratterapillay R, Bruyère F, Bartoletti R, Pilatz A, et al.

Management of Urosepsis in 2018. Eur Urol Focus [Internet]. 2019 Jan 1;5(1):5–9. Available from: https://doi.org/10.1016/j.euf.2018.11.003

12. World Health Organization. WHO methods and data sources for global burden of disease estimates 2000–2011. Global Health Estimates Technical Paper. [Internet]. 2013. Available from: http://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf. Accessed 6 Dec 2018.

13. Haagsma JA, van Beeck EF, Polinder S, Toet H, Panneman M, Bonsel GJ. The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. Popul Health Metr [Internet]. 2011 Apr 24;9:10. Available from: https://pubmed.ncbi.nlm.nih.gov/21513572

14. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank H-P, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016 Oct;13(10):e1002150.

15. van Lier A, de Gier B, McDonald SA, Mangen M-JJ, van Wijhe M, Sanders EAM, et al. Disease burden of varicella versus other vaccine-preventable diseases before introduction of vaccination into the national immunisation programme in the Netherlands. Euro Surveill [Internet]. 2019 May;24(18):1800363. Available from: https://pubmed.ncbi.nlm.nih.gov/31064637

16. Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010:

design, definitions, and metrics. Lancet (London, England) [Internet]. 2012 Dec;380(9859):2063—2066. Available from: https://doi.org/10.1016/S0140-6736(12)61899-6

17. Colzani E, Cassini A, Lewandowski D, Mangen M-JJ, Plass D, McDonald SA, et al. A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years. PLoS One [Internet]. 2017;12(1):1–14. Available from: https://doi.org/10.1371/journal.pone.0170662

18. Altorf-van der Kuil W, Schoffelen AF, de Greeff SC, Thijsen SF, Alblas HJ, Notermans DW, et al. National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the Netherlands. Euro Surveill Bull Eur sur les Mal Transm = Eur Commun Dis Bull. 2017 Nov;22(46).

19. Rijksinstituut voor Volksgezondheid en Milieu. Handleiding ISIS-AR [Internet]. Bilthoven; 2017. Available from: https://www.rivm.nl/sites/default/files/2018-11/Handleiding ISIS-AR 2017 %28februari 2017%29.pdf

20. Rijksinstituut voor Volksgezondheid en Milieu. ISIS AR - Populatie en representativiteit [Internet]. 2021 [cited 2021 Nov 29]. Available from: https://www.rivm.nl/isis-ar/populatie-en-representativiteit

21. ISTAT. Resident population by age, sex and marital status on 1st January 2016 Italy [Internet]. [cited 2020 Jul 30]. Available from: http://demo.istat.it/pop2016/index_e.html

22. Serretiello E, Folliero V, Santella B, Giordano G, Santoro E, De Caro F, et al. Trend of Bacterial Uropathogens and Their Susceptibility Pattern: Study of Single Academic

High-Volume Center in Italy (2015–2019). Falkinham J, editor. Int J Microbiol [Internet]. 2021;2021:5541706. Available from: https://doi.org/10.1155/2021/5541706

23. Cardone S, Petruzziello C, Migneco A, Fiori B, Spanu T, D'Inzeo T, et al. Age-related Trends in Adults with Urinary Tract Infections Presenting to the Emergency Department: A 5-Year Experience. Rev Recent Clin Trials. 2019;14(2):147–56.

24. Luzzaro F, Ortisi G, Larosa M, Drago M, Brigante G, Gesu G. Prevalence and epidemiology of microbial pathogens causing bloodstream infections: results of the OASIS multicenter study. Diagn Microbiol Infect Dis. 2011 Apr;69(4):363–9.

25. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. Am J Infect Control. 2000 Feb;28(1):68–75.

26. van Hout D, Verschuuren TD, Bruijning-Verhagen PCJ, Bosch T, Schürch AC, Willems RJL, et al. Extended-spectrum beta-lactamase (ESBL)-producing and non-ESBL-producing Escherichia coli isolates causing bacteremia in the Netherlands (2014 – 2016) differ in clonal distribution, antimicrobial resistance gene and virulence gene content. PLoS One [Internet]. 2020 Jan 14;15(1):e0227604. Available from: https://doi.org/10.1371/journal.pone.0227604

27. Palacios-Baena ZR, Gutiérrez-Gutiérrez B, De Cueto M, Viale P, Venditti M, Hernández-Torres A, et al. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother. 2017 Mar;72(3):906–13.

28. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant

infections in primary care are symptomatic for longer and increase workload: outcomes for patients with E. coli UTIs. Br J Gen Pract J R Coll Gen Pract. 2006 Sep;56(530):686–92.

29. Vallejo-Torres L, Pujol M, Shaw E, Wiegand I, Vigo JM, Stoddart M, et al. Cost of hospitalised patients due to complicated urinary tract infections: a retrospective observational study in countries with high prevalence of multidrug-resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study. BMJ Open [Internet]. 2018 Apr 1;8(4):e020251. Available from: http://bmjopen.bmj.com/content/8/4/e020251.abstract

30. Covino M, Manno A, Merra G, Simeoni B, Piccioni A, Carbone L, et al. Reduced utility of early procalcitonin and blood culture determination in patients with febrile urinary tract infections in the emergency department. Intern Emerg Med. 2020 Jan;15(1):119–25.

31. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother. 2011 Feb;66(2):398–407.

32. Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother [Internet]. 2010/07/26. 2010 Oct;54(10):4085–91. Available from: https://pubmed.ncbi.nlm.nih.gov/20660675

33. Tacconelli E, Pezzani MD. Public health burden of antimicrobial resistance in Europe. Lancet Infect Dis [Internet]. 2019 Jan 1;19(1):4–6. Available from: https://doi.org/10.1016/S1473-3099(18)30648-0

34. Bordino V, Vicentini C, D'Ambrosio A, Quattrocolo F, Zotti CM. Burden of healthcare-associated infections in Italy: incidence, attributable mortality and disability-adjusted life years (DALYs) from a nationwide study, 2016. J Hosp Infect. 2021 Jul;113:164–71.

35. Rottier WC, Deelen JWT, Caruana G, Buiting AGM, Dorigo-Zetsma JW, Kluytmans JAJW, et al. Attributable mortality of antibiotic resistance in gram-negative infections in the Netherlands: a parallel matched cohort study. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2020 Jul;

36. Godijk NG, Bootsma MCJ, van Werkhoven HC, Schweitzer VA, de Greeff SC, Schoffelen AF, et al. Modelling addition and replacement mechanisms of plasmid-based beta-lactam resistant E. coli infections. medRxiv [Internet]. 2021 Jan 1;2021.03.17.21253797. Available from: http://medrxiv.org/content/early/2021/03/20/2021.03.17.21253797.abstract

37. Temkin E, Carmeli Y, Consortium for the DR in R and D and RAU (DRIVE-A. Zero or More: Methodological Challenges of Counting and Estimating Deaths Related to Antibiotic-resistant Infections. Clin Infect Dis [Internet]. 2019 Nov 13;69(11):2029–34. Available from: https://doi.org/10.1093/cid/ciz414

38. Pezzani MD, Tornimbene B, Pessoa-Silva C, de Kraker M, Rizzardo S, Salerno ND, et al. Methodological quality of studies evaluating the burden of drug-resistant

infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2021 Jan;27(5):687–96.

39. Lombardia F per i servizi degli O dei farmacisti della. Dispensazione senza ricetta: quando si può e come si fa [Internet]. [cited 2021 Dec 1]. Available from: https://www.ordinifarmacistilombardia.it/farmacista/per_la_farmacia/dispensazione_senza_ricetta.html?fbclid=IwAR2Hzk07wRFnygmyG5Z1m4d5OkBnUbvFXqYMIfurvRbROzSms4XzU450PWM

40. Italian Medicines Agency. Antibiotics [Internet]. [cited 2021 Dec 1]. Available from: https://www.aifa.gov.it/en/farmaci-antibiotici?fbclid=IwAR2jIo2UTMVnOcHP80us5MOjk9OpLwg21rYWWWi2Yvx7LdkKdusaVzqdKqs

41. MacKinnon MC, McEwen SA, Pearl DL, Lyytikäinen O, Jacobsson G, Collignon P, et al. Mortality in Escherichia coli bloodstream infections: a multinational population-based cohort study. BMC Infect Dis [Internet]. 2021 Jun 25;21(1):606. Available from: https://pubmed.ncbi.nlm.nih.gov/34172003

42. ECDC. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017 [Internet]. Stockholm; 2018. Available from: https://www.ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-EARS-Net-2017.pdf

Figure 1

Outcome trees(s) for 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).

Figure 2

YLD and YLL due to resistant and counterfactual susceptible *E. coli* UTIs in the Netherlands in 2018

Notes: Lines indicate 95% uncertainty intervals.

Figure 3

DALYs attributable to six sequelae of resistant and counterfactual susceptible *E. coli* UTIs in the Netherlands in 2018

Figure 4

DALYs of resistant and counterfactual susceptible *E. coli* UTIs in the Netherlands in 2018 per age and sex-stratified group

Figure 5

YLD and YLL due to resistant and counterfactual susceptible *E. coli* UTIs in Italy in 2016

Notes: Lines indicate 95% uncertainty intervals.

Figure 6

DALYs attributable to six sequelae of resistant and counterfactual susceptible *E. coli* UTIs in Italy in 2016

Figure 7

DALYs of resistant and counterfactual susceptible *E. coli* UTIs in Italy in 2016 per age and sex-stratified group

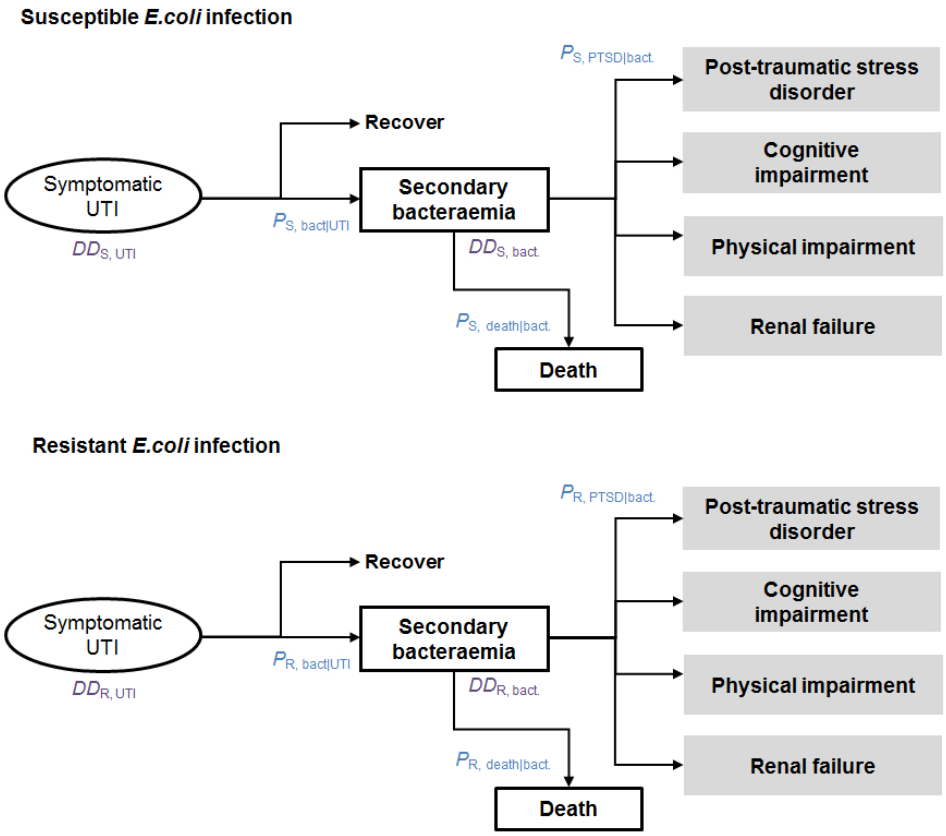

Figure 1
Outcome trees(s) for UTI, for antimicrobial-susceptible (upper panel) and antimicrobial-resistant (lower panel) infection. Transition probabilities (P) stratified by type of infection ([S]usceptible or [R]esistant) are indicated for several transitions, as are disability durations (DD).

613x515mm (38 x 38 DPI)

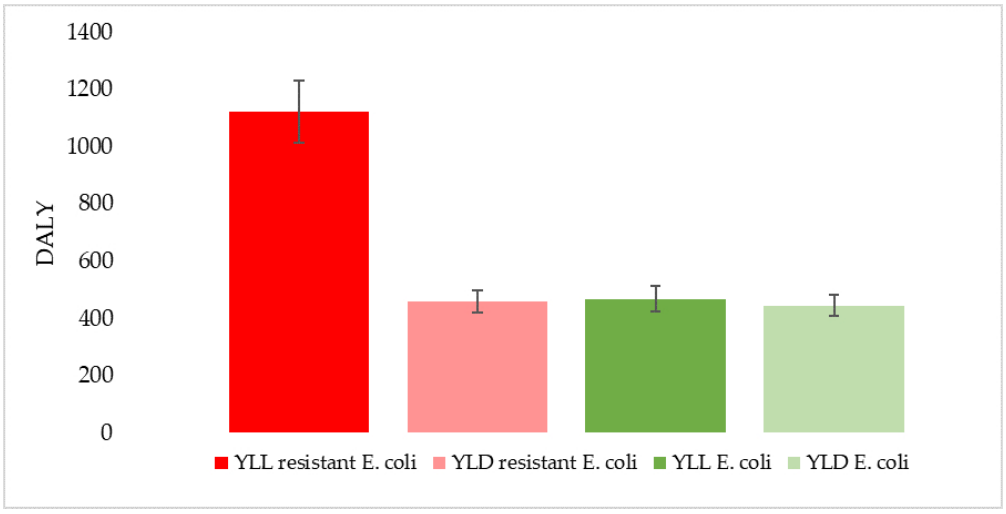

Figure 2
YLD and YLL due to resistant and counterfactual susceptible E. coli UTIs in the Netherlands in 2018
Notes: Lines indicate 95% uncertainty intervals

388x195mm (59 x 59 DPI)

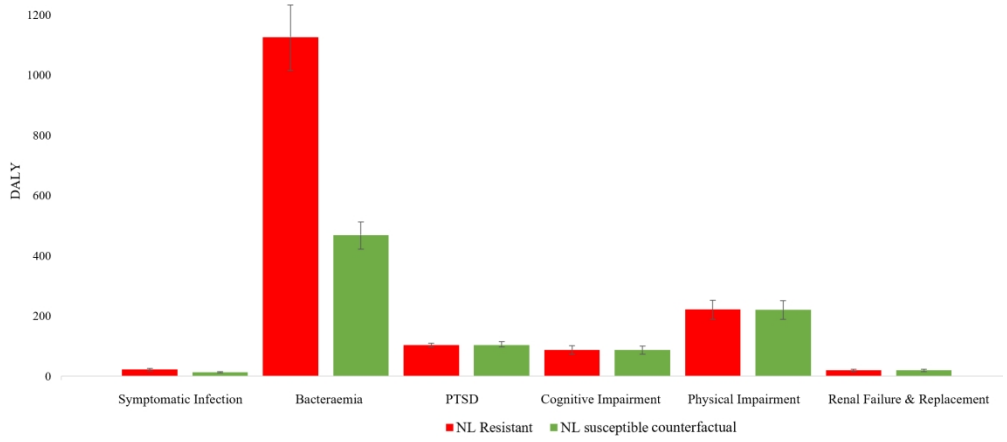

Figure 3
DALYs attributable to six sequelae of resistant and counterfactual susceptible E. coli UTIs in the Netherlands in 2018

1646x739mm (38 x 38 DPI)

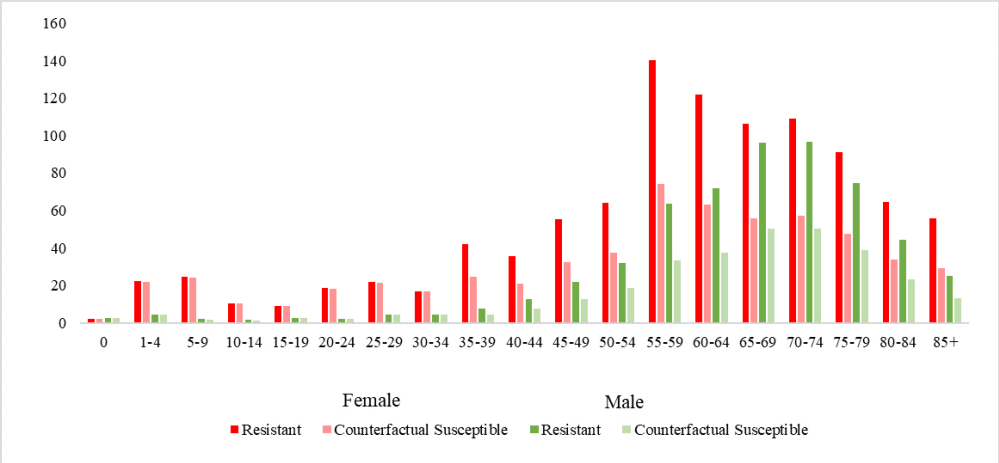

Figure 4
DALYs of resistant and counterfactual susceptible E. coli UTIs in the Netherlands in 2018 per age and sex-stratified group

500x232mm (59 x 59 DPI)

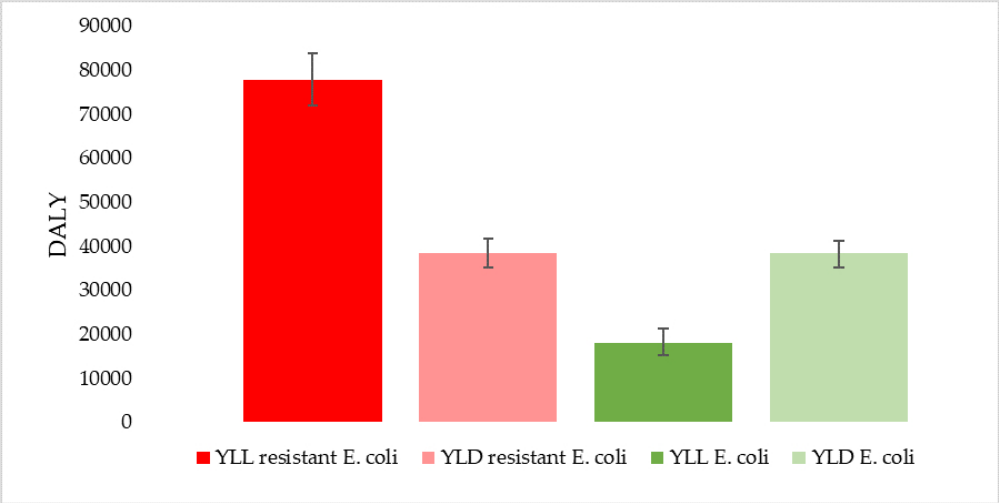

Figure 5
YLD and YLL due to resistant and counterfactual susceptible E. coli UTIs in Italy in 2016
Notes: Lines indicate 95% uncertainty intervals.

387x195mm (59 x 59 DPI)

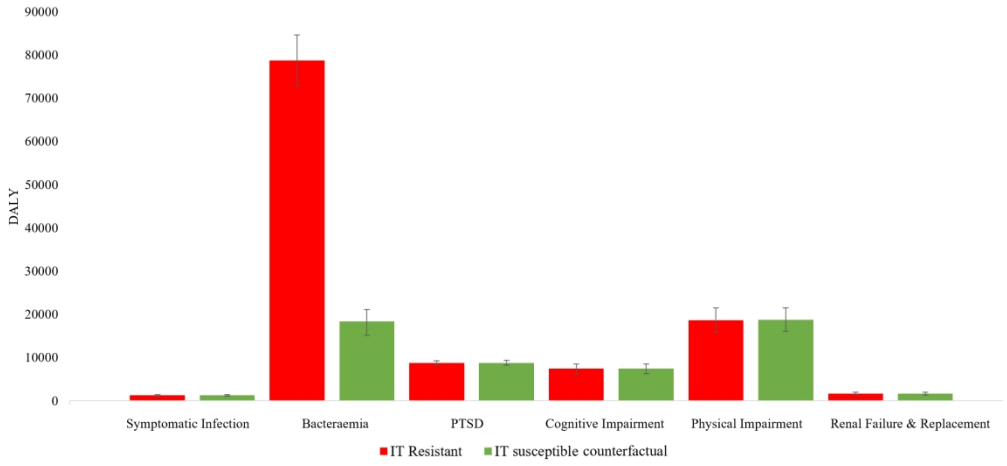

Figure 6
DALYs attributable to six sequelae of resistant and counterfactual susceptible E. coli UTIs in Italy in 2016

1660x774mm (38 x 38 DPI)

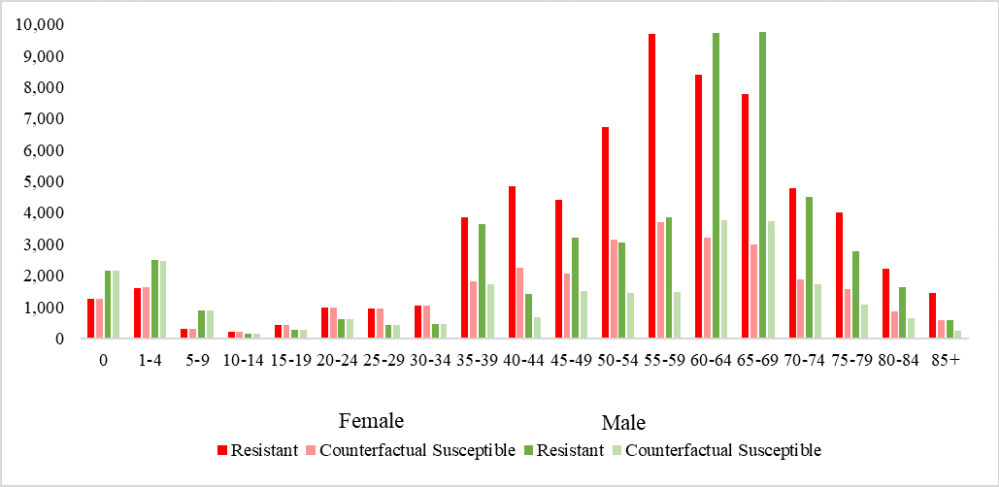

Figure 7
DALYs of resistant and counterfactual susceptible E. coli UTIs in Italy in 2016 per age and sex-stratified group

443x216mm (59 x 59 DPI)

Appendix 1. Systematic Review Methods

The Netherlands

PubMed and Embase were searched using the search terms shown in Appendix 3, resulting in 242 and 136 articles respectively. The removing of duplicates in Endnote and Rayyan resulted in a final set of 296 articles for title/abstract screening. In this stage, articles were included that reported Dutch studies on UTI or bacteraemia, that potentially contained data for both susceptible and resistant UTIs, but had not necessarily reported these data or did not mention the specific pathogen. In the case where, for example, testing for resistance had been mentioned but specific data were not separately reported for AMR and AMS *E. coli,* the authors were emailed. After full-text screening of 43 articles, a total of 18 were retained, and the authors were requested more data. If there was no response after a month, a follow-up email was sent.

We excluded case studies and studies that were carried out in a specific vulnerable population (elderly persons, children), or in highly-specific clinical patient populations. Inclusion criteria applied to the final set of articles were : a Dutch study, published in 2017 or later, UTI caused by resistant and/or susceptible *E. coli*, and estimates for of one or more of parameters needed for the OTs. Following this systematic literature search, further relevant articles were possibly identified during correspondence with authors.

Given the almost null yield of the first search, a second literature search was undertaken to locate relevant studies specifically informing the model parameters involving bacteraemia (i.e., $P(\text{Bact}|\text{UTI})$, $DD(\text{Bact})$, $P(\text{Death}|\text{Bact})$) (Appendix 3). This produced 24 hits, due to the limited number of hits, we performed full-text screening for all. Inclusion criteria were only that the study reported suitable data on cases of bacteraemia in which *E. coli* had been isolated.

Following this search, further relevant articles were possibly identified in correspondence with authors of retained articles. We then applied the following algorithm to the set of identified articles: (i) if no eligible Dutch population studies were found reporting parameter values involving bacteraemia due to susceptible/resistant *E. coli* UTI, then (ii) Dutch studies reporting parameter values involving bacteraemia with susceptible/resistant *E. coli from any infection site* were used. (iii) If still no eligible studies found, then *EU* studies reporting parameter values due to bacteraemia with AMR/AMS *E. coli* from any infection site were considered eligible.

A third systematic literature search was conducted to attempt to find relevant studies specifically to inform $P(\text{Bact}|\text{UTI})$, with restriction to studies of resistant *E. coli* UTIs (Appendix 1). This produced 13 hits; 10 articles were eliminated based on abstract screening and the remaining three after full-text screening. A PRISMA diagram for all three searches together is shown in Figure S1.

Italy

PubMed and Embase were searched using the search term in Appendix 4, and yielded 231 and 176 results respectively. After removing duplicates in EndNote and Rayan, 290 articles remained. After title/abstract screening 56 articles were screened full text and 32 articles potentially contained parameter estimates relevant for the Italian population.

Given the almost null yield of the first search, we performed new separate searches for the incidence, progression from UTI to bacteraemia, DD(UTI) and LOS due to bacteraemia. For LOS(UTI) a third search was conducted (Appendix 4). Eventually, three articles from the search and one article recommended to the authors which fell outside the initial search criteria

of articles published from 2017 or later were used to estimate the parameters. A PRISMA diagram for all searches on Italian parameters together is shown in Figure S2.

Appendix 2 – Systematic review to identity Dutch parameter estimates

Search 1

4th of February 2019

PubMed: (("2017/01/01"[Date - Publication] : "3000"[Date - Publication])) AND (((((urinary[Title/Abstract] AND tract[Title/Abstract]) AND (infection[Title/Abstract] OR infections[Title/Abstract])) OR urinary tract infection[MeSH] OR UTI[Title/Abstract]) AND (Netherlands OR Netherlands[MeSH] OR Dutch) AND (english[Language] OR dutch[Language])) AND ("2017/01/01"[PDat] : "3000/12/31"[PDat]))

242 results

4th of February 2019

Embase: ('urinary':ab,ti AND 'tract':ab,ti AND ('infection':ab,ti OR 'infections':ab,ti) OR 'uti':ab,ti) AND ('netherlands' OR 'dutch') AND [article]/lim AND ([dutch]/lim OR [english]/lim) AND [humans]/lim AND [embase]/lim AND [2017-2019]/py

136 results

Search 2

10th of February, 2020

PubMed: *((bacteraemia[Title/Abstract]) OR (bacteremia[Title/Abstract])) AND ((Netherlands[Text Word]) AND Dutch[Text Word]).*

24 results

13th of February, 2020

PubMed:((((((urinary tract[Title/Abstract]) AND infection[Title/Abstract])) OR

UTI[Title/Abstract])) AND ((Netherlands[Text Word]) OR Dutch [Text Word])) AND ((lenght of stay[Text Word]) OR LOS[Text Word])

3 results

Search 3 –

13th of February, 2020

PubMed: (((bacteraemia[Text Word]) OR (bacteremia[Text Word])) AND resist*[Text Word] AND (E coli[MeSH] OR E coli[Text Word]) AND ((urinary tract infection[MeSH]) OR (UTI[Text Word])) AND (("probability of"[Text Word]) OR (progress*[Text Word]) OR ("risk of "[Text Word]))).

13 results

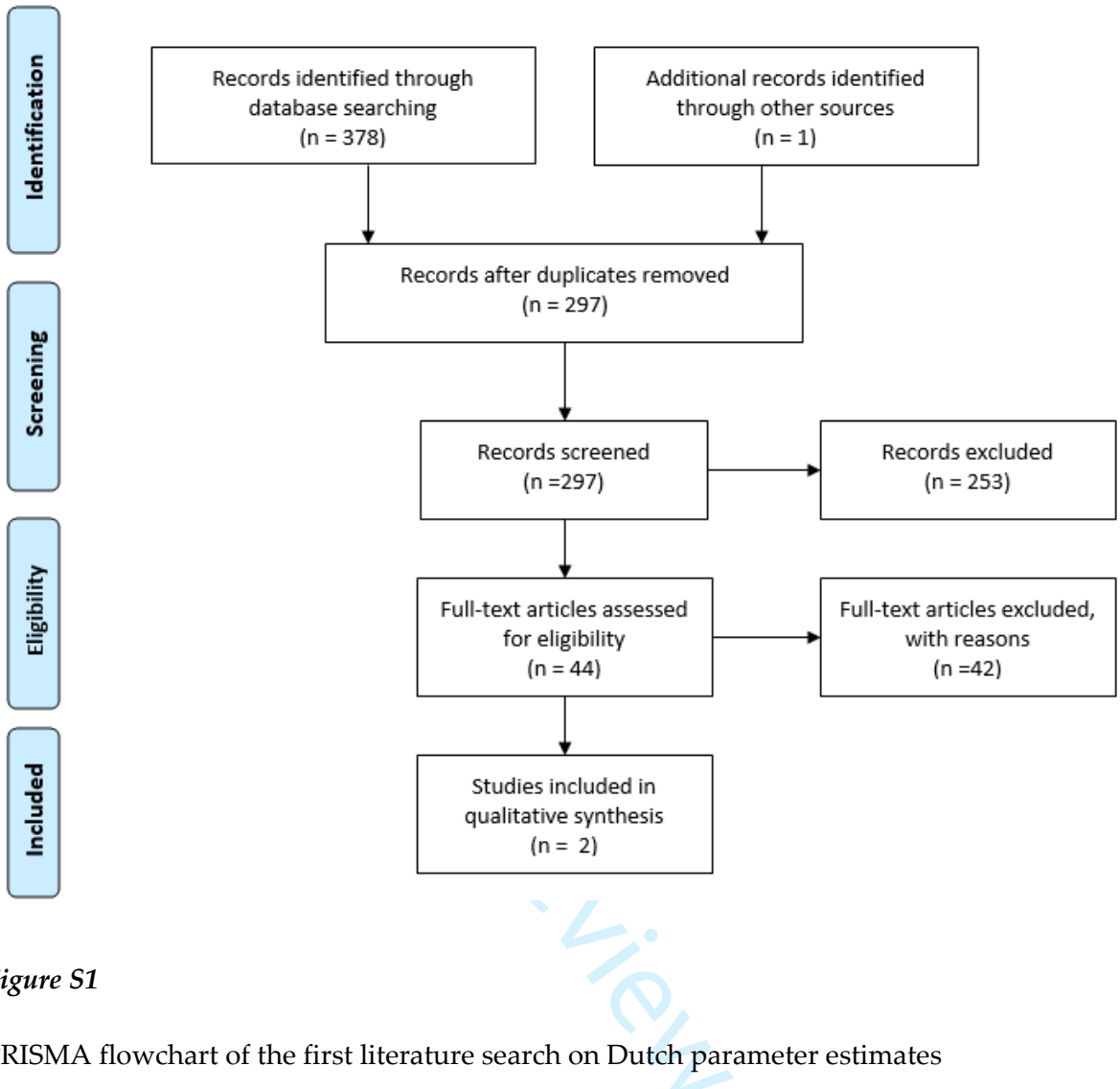

Figure S1

PRISMA flowchart of the first literature search on Dutch parameter estimates

Appendix 3 – Systematic review to identify Italian parameter estimates

Search 1

4th of February, 2019

Pubmed: ((("2017/01/01"[Date - Publication] : "3000"[Date - Publication])) AND (((((urinary[Title/Abstract] AND tract[Title/Abstract]) AND (infection[Title/Abstract] OR infections[Title/Abstract])) OR urinary tract infection[MeSH] OR UTI[Title/Abstract]) AND (Italy OR Italy[MeSH] OR Italian) AND (english[Language] OR dutch[Language])) AND ("2017/01/01"[PDat] : "3000/12/31"[PDat])))

231 results

('urinary':ab,ti AND 'tract':ab,ti AND ('infection':ab,ti OR 'infections':ab,ti) OR 'uti':ab,ti) AND ('italy' OR 'italian') AND [article]/lim AND ([dutch]/lim OR [english]/lim) AND [humans]/lim AND [embase]/lim AND [2017-2019]/py

176 results

Search 2

3th of June, 2020

Incidence - PubMed: ("2019/01/01"[Date - Publication] : "3000"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR UTI [Title/Abstract]) AND incidence.

35 results

3th of June, 2020

LOS UTI - PubMed ("2019/01/01"[Date - Publication] : "3000"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR

UTI [Title/Abstract]) AND (LOS [Title/Abstract] OR (length [Title/Abstract] AND stay [Title/Abstract])).

5 results

18th of June, 2020

UTI to bacteraemia – PubMed: (("2019/01/01"[Date - Publication] : "2020/06/18"[Date - Publication])) AND ((Italy[Text Word]) AND ((UTI[Title/Abstract]) OR (((urinary[Title/Abstract]) AND (tract[Title/Abstract])) AND (infection[Title/Abstract])))).

21 results

31st of August, 2020

LOS Bacteraemia – PubMed: (("2005/01/01"[Date - Publication] : "3000"[Date - Publication])) AND ((Italy[Text Word]) AND (((((bacteraemia[Title/Abstract]) OR (bacteraemias[Title/Abstract])) OR (bacteremia[Title/Abstract])) OR (bacteremias[Title/Abstract])) AND (((days[Title/Abstract]) OR (((length[Title/Abstract]) AND (of[Title/Abstract])) AND (stay[Title/Abstract]))) OR (LOS[Title/Abstract]))))

24 results

Search 3

16th of June, 2020

LOS UTI– Pubmed (("2015/01/01"[Date - Publication] : "3000"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR UTI [Title/Abstract]) AND (LOS [Title/Abstract] OR disability duration [Title/Abstract] OR (length [Title/Abstract] AND stay [Title/Abstract]))) NOT (("2019/01/01"[Date - Publication] : "2020/06/02"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR UTI [Title/Abstract]) AND (LOS

[Title/Abstract] OR (length [Title/Abstract] AND stay [Title/Abstract]))).

7 results

2nd of September, 2020

(((general practitioner) OR (general practice)) AND (((urinary tract infection) OR (UTI)) AND (Italy))) AND ((out-patient) OR (outpatient))

10 results, 1 included

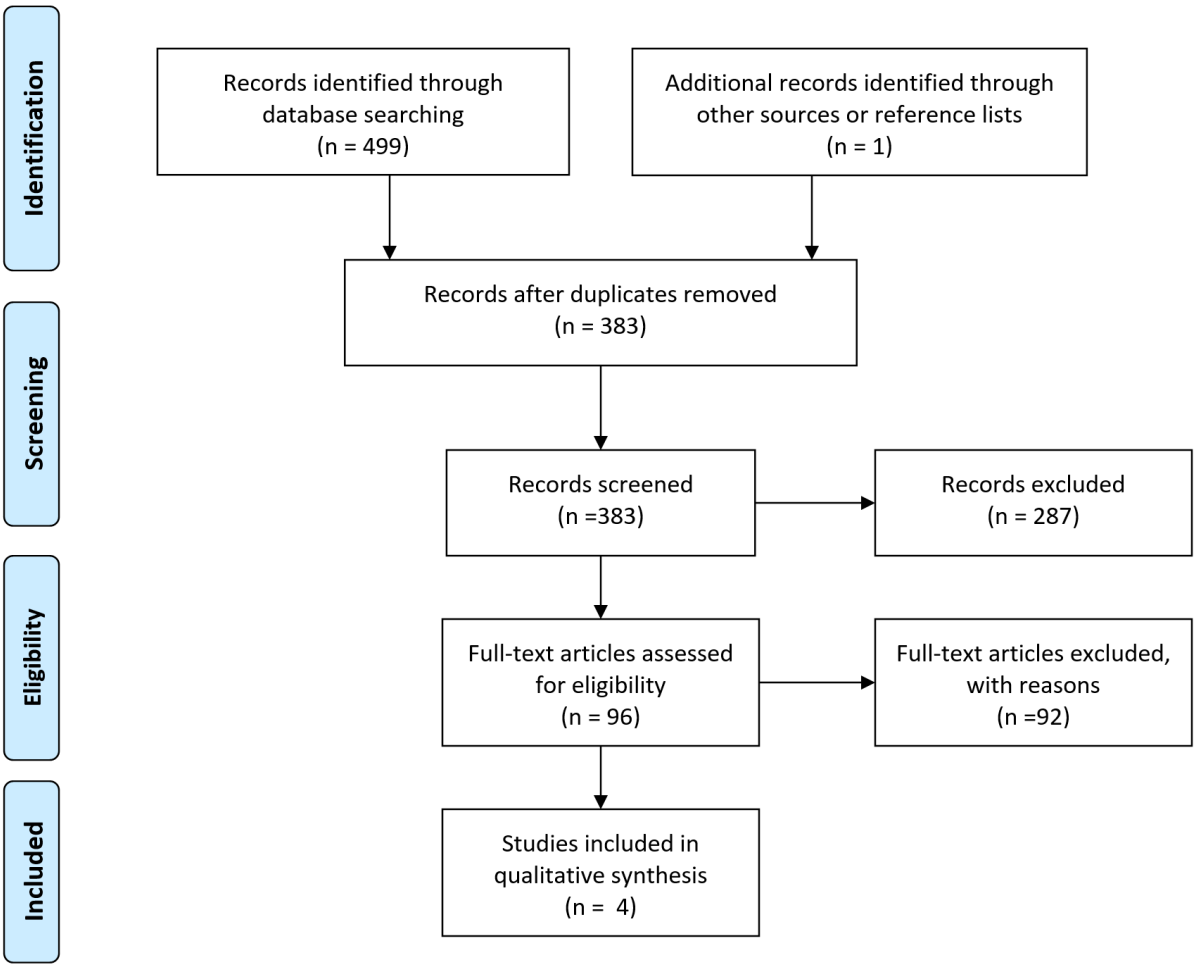

Figure S2

PRISMA flowchart of the literature search on Italian parameter estimates

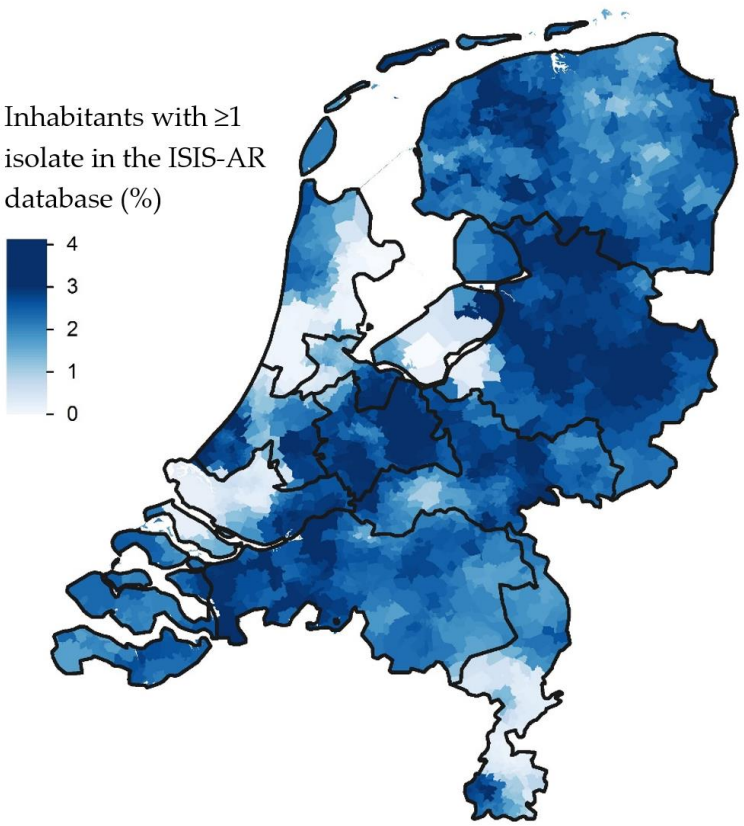

Figure S3

smoothed geographical distribution of the percentage of inhabitants for whom at least 1 urinary isolate was found in the ISIS-AR database in 2018, by 4-digit postal code area and with regional cooperative network borders

Appendix 4.

Systematic review results

The Netherlands

The first systematic literature review yielded only two articles, both providing an estimate of DD(UTI). In the first study the Netherlands was one of four countries on which analysis was based, and bacteria species and AMS vs. AMR infections were not distinguished. Correspondence with the authors yielded a more appropriate citation (1), which was carried out in England and Wales in 2002-2004 and reported DD(UTI) for *E. coli* UTIs separately for AMS and AMR infection. (In Figure S1 this article is indicated as an additional record identified through other sources). We justified this choice as the analysis in (2) did not find any between-country difference in DD(UTI).

The second review resulted in one suitable study for P(Death|Bact), which was a Dutch study that reported 30-day mortality in bacteraemia patients with either resistant *E. coli* or susceptible *E. coli* in 2014–2016 (3). The study population had a median age of 69 years (*IQR* 57 to 77); it is plausible that a lower mortality rate would be observed for younger age-groups. We could only locate a single study reporting age-group specific values for 30-day mortality due to bacteraemia (4). This study was conducted in Iceland among patients with bacteraemia caused by *S. aureus.* We took the simple approach of setting the parameter values for P(Death|Bact) for the age-groups 55 years and older to the value from study (3), and then scaling the parameter values for the younger age-groups according to the ratio of 30-day mortality risks between the 'reference' age-group, 55-74 years, and the <35 years and 35-54 years age-groups from the Icelandic study (4). This meant P(Death|Bact) was zero for <35

years (since mortality risk was 0% for <35 years (4)), and a scaling factor of 0.54 (from 3.8%/7.1%) was applied to 35-54 years.

For the parameter DD(Bact), the literature reviews did not yield any eligible studies. We decided to adopt values from (5), which is a large well-conducted multi-country study that was carried out in 2007/8, and that reported patient characteristic-adjusted LOS values for both AMS and 3rd generation cephalosporin-resistant *E. coli* bloodstream infections (BSIs). All selected parameter values are provided in Table 1.

As the third systematic literature review, which was specifically aimed at P(Bact|UTI), did not yield any studies. We relied on a previous pooled analysis [24] which we identified through citation search. This study did not distinguish between AMR and AMS infections, and the contributing studies were all carried out in the USA in the 1980s.

Italy

We found one article providing estimates on P(Death|Bact). The study of Palacios-Baena et al. (6) found a 30-day mortality of 26.2% of ESBL blood stream infections (BSI), 34 of the 130 Italian BSI patients died. We calculated the mortality for susceptible BSI using the ratio of susceptible vs. resistant mortality reported in another, less recent, Italian study by Tumbarello et al. (7) and estimated a 30-day mortality of 5.47% for susceptible BSI.

Furthermore, for DD(UTI) and DD(BACT) we only found an Italian study amongst elderly (*Mdn* = 77, *IQR* = 65–83) with UTIs or urosepsis which reported a mean LOS of 10 [7-17] days (8) and a median LOS of 9.5 days for Italian patients with complicated UTIs in Italy (9). Of the UTIs 58% was caused by *E. coli.* Unfortunately, no studies were identified which specified LOS for ESBL *E. coli* and *E. coli* UTIs. Because the lack of better studies on DD(UTI) and

DD(BACT) amongst adults, we used the estimate of Covino et al. (8) in elderly and Vallejo-Torres et al. (9) on complicated UTIs.

Moreover, we searched the citations of Cassini et al. (10) for relevant Italian studies and found that Tumbarello et al. (7) reported LOS for resistant BSI of 20 ± 17 days and 13 ± 9 days for non-AMR BSI.

For P(Bact|UTI) we were unable to locate a parameter and, therefore, we used the same value as the Dutch parameter. For the health outcomes following bacteremia, other than death, we used the same values as Cassini et al. (10).

Regarding the incidence of resistant *E. coli,* we did not locate any direct estimates; therefore, we estimated incidence (see Methods).

References Appendix 4.

1. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with E. coli UTIs. Br J Gen Pract J R Coll Gen Pract. 2006 Sep;56(530):686–92.

2. Altorf-van der Kuil W, Schoffelen AF, de Greeff SC, Thijsen SF, Alblas HJ, Notermans DW, et al. National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the Netherlands. Euro Surveill Bull Eur sur les Mal Transm = Eur Commun Dis Bull. 2017 Nov;22(46).

3. van Hout D, Verschuuren TD, Bruijning-Verhagen PCJ, Bosch T, Schürch AC, Willems RJL, et al. Extended-spectrum beta-lactamase (ESBL)-producing and non-ESBL-producing Escherichia coli isolates causing bacteremia in the Netherlands (2014 – 2016) differ in clonal distribution, antimicrobial resistance gene and virulence gene content. PLoS One [Internet]. 2020 Jan 14;15(1):e0227604. Available from: https://doi.org/10.1371/journal.pone.0227604

4. Asgeirsson H, Gudlaugsson O, Kristinsson KG, Heiddal S, Kristjansson M. Staphylococcus aureus bacteraemia in Iceland, 1995-2008: changing incidence and mortality. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2011 Apr;17(4):513–8.

5. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant

to third-generation cephalosporins. J Antimicrob Chemother. 2011 Feb;66(2):398–407.

6. Palacios-Baena ZR, Gutiérrez-Gutiérrez B, De Cueto M, Viale P, Venditti M, Hernández-Torres A, et al. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother. 2017 Mar;72(3):906–13.

7. Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother [Internet]. 2010/07/26. 2010 Oct;54(10):4085–91. Available from: https://pubmed.ncbi.nlm.nih.gov/20660675

8. Covino M, Manno A, Merra G, Simeoni B, Piccioni A, Carbone L, et al. Reduced utility of early procalcitonin and blood culture determination in patients with febrile urinary tract infections in the emergency department. Intern Emerg Med. 2020 Jan;15(1):119–25.

9. Vallejo-Torres L, Pujol M, Shaw E, Wiegand I, Vigo JM, Stoddart M, et al. Cost of hospitalised patients due to complicated urinary tract infections: a retrospective observational study in countries with high prevalence of multidrug-resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study. BMJ Open [Internet]. 2018 Apr 1;8(4):e020251. Available from: http://bmjopen.bmj.com/content/8/4/e020251.abstract

10. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al.

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis [Internet]. 2019 Jan 1;19(1):56–66. Available from: https://doi.org/10.1016/S1473-3099(18)30605-4

Table S1. *Number and incidence of resistant E. coli UTI per age- and sex category in the Netherlands in 2018*

	Males					Females				
Age category	**Male inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *E.coli* UTIs incidence**	**Recurrent* resistant *E. Coli* UTIs**	**Average resistant *E. coli* UTIs per patient**	**Female inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *coli* UTIs incidence**	**Recurrent* resistant *E. coli* UTIs**	**Average resistant *E. coli* UTIs per patient**
0	87001	12	0.000137929	0	1.00	82565	10	0.000121117	0	1.00
1-4	358019	25	5.86561E-05	4	1.19	340514	111	0.000323041	7	1.06
5-9	475503	19	2.10304E-05	9	1.90	452563	148	0.000287253	18	1.14
10-14	494511	11	1.61776E-05	3	1.38	471948	62	0.000122895	4	1.07
15-19	536852	20	2.79407E-05	5	1.33	511180	66	0.000105638	6	1.11
20-24	542817	19	2.76336E-05	4	1.27	525964	142	0.000230054	19	1.16
25-29	560319	36	5.53256E-05	5	1.16	545838	155	0.000283967	0	1.00
30-34	530554	38	6.59688E-05	3	1.09	522235	136	0.000250845	5	1.04
35-39	512925	26	3.70425E-05	7	1.37	512431	114	0.000204906	9	1.09

40-44	516723	53	6.77346E-05	18	1.51	521589	12[illegible]	0.000191722	25	1.25
45-49	634188	92	0.000108801	23	1.33	634635	19[illegible]	0.000272598	25	1.14
50-54	644223	143	0.000176957	29	1.25	635623	27[illegible]	0.00035713	43	1.19
55-59	606130	211	0.000268919	48	1.29	605380	44[illegible]	0.000597972	79	1.22
60-64	537540	287	0.000401831	71	1.33	542198	44[illegible]	0.000671341	81	1.22
65-69	495875	460	0.000703806	111	1.32	503662	47[illegible]	0.000770358	85	1.22
70-74	424486	633	0.001036548	193	1.44	447439	61[illegible]	0.001115236	114	1.23
75-79	273902	621	0.001595461	184	1.42	314838	68[illegible]	0.001715168	149	1.28
80-84	172825	487	0.002065673	130	1.36	235430	68[illegible]	0.002229962	158	1.30
≥ 85	122648	495	0.003000457	127	1.35	248011	105[illegible]	0.00033063	236	1.29
Total	8527041	3688	0.000432506	974	1.36	8654043	593[illegible]	0.000685807	1063	1.22

**Defined as a UTI occurring more than 14 days after another UTI*

Table S2. *Number and incidence of E. coli UTI per age- and sex category in the Netherlands in 2018*

	Males					Females				
Age category	**Male inhabitants**	**Number of *E. coli* UTIs**	***E.coli* UTIs incidence**	**Recurrent * *E. Coli* UTIs**	**Average *E. coli* UTIs per patient**	**Female inhabitants**	**Number of *E. coli* UTIs**	***E. coli* UTIs incidence**	**Recurrent * *E. coli* UTIs**	**Average *E. coli* UTIs per patient**
0	87001	453	0.0052	0	1.00	82565	413	0.0044	52	1.14
1-4	358019	598	0.0015	74	1.14	340514	4079	0.0105	518	1.15
5-9	475503	351	0.0006	45	1.15	452563	6336	0.0115	1111	1.21
10-14	494511	260	0.0005	34	1.15	471948	2766	0.0049	473	1.21
15-19	536852	315	0.0005	41	1.15	511180	2651	0.0047	260	1.11
20-24	542817	318	0.0005	30	1.10	525964	3499	0.0061	316	1.10
25-29	560319	492	0.0008	60	1.14	545838	3745	0.0069	0	1.00
30-34	530554	500	0.0009	25	1.05	522235	3714	0.0069	102	1.03
35-39	512925	731	0.0012	106	1.17	512431	3638	0.0063	432	1.13
40-44	516723	968	0.0016	147	1.18	521589	3608	0.0060	497	1.16

45-49	634188	1630	0.0022	242	1.17	634635	5053	0.0068	742	1.17
50-54	644223	2224	0.0029	331	1.17	635623	6648	0.0089	1022	1.18
55-59	606130	3154	0.0044	498	1.19	605380	8686	0.0120	1418	1.20
60-64	537540	4166	0.0065	672	1.19	542198	10635	0.0161	1880	1.21
65-69	495875	6022	0.0099	1113	1.23	503662	12863	0.0210	2296	1.22
70-74	424486	7930	0.0149	1598	1.25	447439	16474	0.0297	3201	1.24
75-79	273902	7017	0.0203	1465	1.26	314838	15964	0.0407	3162	1.25
80-84	172825	6148	0.0280	1312	1.27	235430	16251	0.0548	3340	1.26
≥ 85	122648	6251	0.0411	1213	1.24	248011	22890	0.0747	4355	1.23
Total	**8527041**	**49528**	**0.0058**	**9006**	**1.22**	**8654043**	**149913**	**0.0173**	**25177**	**1.20**

**Defined as a UTI occurring more than 14 days after another UTI*

Table S3. *Sensitivity analysis of the number and incidence of resistant E. coli UTI per age- and sex category in the Netherlands in 2018*

	Males					Females				
Age category	**Male inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *E.coli* UTIs incidence**	**Recurrent* resistant *E. Coli* UTIs**	**Average resistant *E. coli* UTIs per patient**	**Female inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *coli* UTIs incidence**	**Recurrent* resistant *E. coli* UTIs**	**Average resistant *E. coli* UTIs per patient**
0	87001	12	0.000137929	0	1.00	82565	10	0.000121117	0	1.00
1-4	358019	21	5.86561E-05	0	1.00	340514	111	0.000323041	1	1.01
5-9	475503	10	2.10304E-05	0	1.00	452563	130	0.000287253	7	1.05
10-14	494511	8	1.61776E-05	0	1.00	471948	58	0.000122895	0	1.00
15-19	536852	16	2.79407E-05	1	1.07	511180	54	0.000105638	0	1.00
20-24	542817	16	2.76336E-05	1	1.07	525964	121	0.000230054	0	1.00
25-29	560319	32	5.53256E-05	1	1.03	545838	155	0.000283967	0	1.00
30-34	530554	35	6.59688E-05	0	1.00	522235	132	0.000250845	1	1.01
35-39	512925	19	3.70425E-05	0	1.00	512431	107	0.000204906	2	1.02

40-44	516723	38	6.77346E-05	3	1.09	521589	100	0.000191722	0	1.00
45-49	634188	75	0.000108801	6	1.09	634635	174	0.000272598	5	1.03
50-54	644223	118	0.000176957	4	1.04	635623	233	0.00035713	4	1.02
55-59	606130	169	0.000268919	6	1.04	605380	371	0.000597972	15	1.04
60-64	537540	227	0.000401831	11	1.05	542198	381	0.000671341	18	1.05
65-69	495875	368	0.000703806	19	1.05	503662	402	0.000770358	21	1.05
70-74	424486	488	0.001036548	48	1.11	447439	528	0.001115236	27	1.05
75-79	273902	477	0.001595461	40	1.09	314838	588	0.001715168	41	1.08
80-84	172825	379	0.002065673	22	1.06	235430	567	0.002229962	38	1.07
≥ 85	122648	400	0.003000457	32	1.09	248011	879	0.003306305	59	1.07
Total	**8527041**	**2908**	**0.000341**	**194**	**1.07**	**8654043**	**5113**	**0.000591**	**239**	**1.05**

**Defined as a UTI occurring more than 3 months after another UTI*

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064335.R1
Article Type:	Original research
Date Submitted by the Author:	18-Nov-2022
Complete List of Authors:	Godijk , Noortje; University Medical Centre Utrecht McDonald, Scott; Rijksinstituut voor Volksgezondheid en Milieu, Altorf-van der Kuil, W.; National Institute for Public Health & the Environment Schoffelen, A.F.; National Institute for Public Health & the Environment Franz, Eelco; National Institute for Public Health and the Environment, Centre for Infectious Disease Control Bootsma, M.C.J.; University Medical Center Utrecht; Utrecht University, Department of Mathematics
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, STATISTICS & RESEARCH METHODS, Urinary tract infections < UROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Noortje G. Godijk*[1], Scott A. McDonald[2], Wieke Altorf-van der Kuil[2], Annelot F. Schoffelen[2], Eelco Franz[2], Martin C.J. Bootsma[1,3]

[1] Julius Center for Health Sciences & Primary Care, University Medical Center Utrecht, NL

[2] Centre for Infectious Disease Control, National Institute for Public Health & the Environment, Bilthoven, NL

[3] Department of Mathematics, Faculty of Sciences, Utrecht University, Utrecht, NL

*Corresponding author: N.G. Godijk, Noortje G. Godijk, +31(0)887568147, University Medical Center Utrecht, Postbox 85500, 3508 GA Utrecht, n.g.godijk@gmail.com

Word count: 5175

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 (ESBL)) urinary tract infections (UTI) caused by *Escherichia 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 (DALY) 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 2,786 excess deaths for the Netherlands and Italy, respectively.

Conclusions. For the first time, we use country- 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 emphasize 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 strengths 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- and pathogen-specific parameters to estimate the excess BoD.
- National-level surveillance data of the Netherlands informed the estimation of the incidence of resistant E. coli UTI
- 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 (DALY) 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.

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, amongst 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* UTI 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 & Lipsitch (2021). For instance, AMR infections can be compared to 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- 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 asa 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 UTI are frequently caused by *E. coli* [9,10]. Furthermore, UTI is a 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 to 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 one 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 disability (YLD) which is calculated by summing over the YLD for each (non-fatal) health outcome in the OT:

$$DALY = YLL + YLD$$

$$YLD_i = \sum_i N_i * DW_i * DD_i$$

*YLL = No. deaths * life expectancy at age of death*

Ni = the yearly incidence of health outcome i

DWi = the average disability weight of health outcome i

DDi = 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 one 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 one 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 life expectancy (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 version 1.4 [17]. In this software, Monte-Carlo simulation with 1,000 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), years lived with disability (YLDs) and years of life lost (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 risk. The systematic reviews, performed separately for the Netherlands and Italy, are described in detail in Appendix 1, Appendix 2, Appendix 3, Figure S1 and Figure 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 Figure S3. ISIS-AR contains data of 46 laboratory which represent around 80% of the Dutch hospitals [20].

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 five-year age-group. 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 two weeks in the same patient. If the urinary samples were more than two 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 two 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 version 4.0.2.

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

No Italian source comparable to ISIS-AR was found. Therefore, we took 7 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 GP patients from 1 January 2016 through 31 December 2016 [21]. The coverage of this study 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 (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 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 version 1.4 [17] (e.g. 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 at https://github.com/NoorGo/ExcessBurden.

Patient and public involvement

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

RESULTS

The results of the systematic review are discussed in Appendix 4, and the identified parameter values are described below (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 [4.3-5.9]) and for AMR *E. coli* at 8.7 days (95% CI [7.0-10.8]). DD(Bact) for AMS *E. coli* is 2.9 days (95%CI [1.7-4]) and for AMR *E. coli* 7.9 days (95% CI [3.5-13.0]). 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 to 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

Table 1.

Disease burden model parameter values, with references, for susceptible and resistant E. coli UTIs 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 [3.4-3.8%]) [26] [a]	3.6% (95% CI [3.4-3.8%]) [26] [a]	3.6% (95% CI [3.4-3.8%]) [a]	3.6% (95% CI [3.4-3.8%]) [a]
P(Death|Bact)	11.3% (24/212) [27]	27.5% (19/69) [27]	5.47% [b]	26.2% [28]
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 [4.3-5.9]) [29]	8.7d (95%CI [7.0-10.8]) [29]	10d (IQR [7-17]) [30,31]	10d (IQR [7-17]) [30,31]
DD(Bact)	2.9d (95% CI [1.7-4.0]) [32]	7.9d (95% CI [3.5-13.0]) [32]	13 ± 9 [33]	20 ± 17 days [33]
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]

[a] Pooled value from [5].

[b] Calculated using the mortality rate of resistant *E. coli* bacteraemia given in [28] and the ratio between resistant *E.coli* bacteraemia mortality and *E.coli* bacteraemia mortality in [33]

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- 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 2,786 (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 the 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- 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 to 26,184 DALY). The 5-year age-group contributing the largest estimated excess BoD was 55-59 year old females and 65-69 year old males (5,990 and 6041 DALY, respectively).

Resistant burden

The Netherlands

In the Netherlands a total of 9,623 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 7,586 unique patients, resulting in an annual incidence of 0.44 AMR *E. coli* UTIs/1000 inhabitants, excluding recurrent UTIs. 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. 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 three 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. 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: 8.5-9.9). The YLL component accounted for 71.0% of the resistant BoD and 66 deaths were estimated. The sex- and age-aggregated BoD for AMR *E. coli* UTI in the Dutch population in 2018 was estimated at 1,581 DALY (95% UI: 1,467-1,701), or per 100 cases 20.8 DALY (95% UI: 19.3-22.3) 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 (1,127 DALY, 95% UI: 1,020-1,238).

Table 2.

Sex- and age-aggregated YLD, YLL and DALY estimates for antimicrobial resistant and the

counterfactual susceptible E. coli UTI 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 (424-497)	1223 (1016-1234)	1,581 (1467-1701)	20.84 (19.34-22.42)	9.20 (8.58-9.90)
Counterfactual susceptible	445 (409-482)	467 (424-513)	913 (854-934)	12.03 (11.26-12.84)	5.31 (4.97-5.67)
Excess burden	*13*	*655*	*669*	*8.81*	*3.89*

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 Table 3 and Table 4.

In Italy, we estimated 192 DALY/100,000 (95% UI: 181-203). The YLL component accounted for 66.9% of the resistant UTI BoD. For the AMR model 3,617 (95% UI: 3,352-3,884) deaths were estimated. The sex- and age-aggregated BoD for resistant AMR *E. coli* UTI in the Italian population in 2016 was estimated at 166,488 (95% UI: 109,744-123,106) 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: 72,736-84,493), 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 to 51,610 DALY). The 55-59 year old females (9,688 DALY) and 65-69 year old males contributed the most (9,765 DALY).

Table 3. *Incidence of resistant E. coli UTI 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	82565	10	0.00012	12.1	232955	6185	0.02655	2655.2
1 tot 4	340514	110	0.00032	32.3	1017487	8155	0.00801	801.5
5 tot 9	452563	130	0.00029	28.7	1385255	1544	0.00111	111.5
10 tot 14	471948	58	0.00012	12.3	1384866	1159	0.00084	83.7
15-19	511180	54	0.00011	10.6	1391122	2626	0.00189	188.8
20-24	525964	121	0.00023	23.0	1472791	6411	0.00435	435.3
25-29	545838	155	0.00028	28.4	1607399	6619	0.00412	411.8
30-34	522235	131	0.00025	25.1	1761403	7940	0.00451	450.8
35-39	512431	105	0.00020	20.5	2037299	10088	0.00495	495.2
40-44	521589	100	0.00019	19.2	2399975	13999	0.00583	583.3

45-49	634635	173	0.00027	27.3	2490023	14392	0.00578	578.0
50-54	635623	227	0.00036	35.7	2420239	24738	0.01022	1022.1
55-59	605380	362	0.00060	59.8	2110923	25965	0.01230	1230.0
60-64	542198	364	0.00067	67.1	1891237	26513	0.01402	1401.9
65-69	503662	388	0.00077	77.0	1927499	29486	0.01530	1529.8
70-74	447439	499	0.00112	111.5	1533451	22993	0.01499	1499.4
75-79	314838	540	0.00172	171.5	1552174	24926	0.01606	1605.9
80-84	235430	525	0.00223	223.0	1227709	18861	0.01536	1536.2
85+	248011	820	0.00331	330.6	1365423	21841	0.01600	1599.6

342 **Table 4.** *Incidence of resistant E. coli UTI including recurrent UTI in 2018 in the Netherlands and 2016 in Italy in males stratified per 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**
Males								
0	87001	12	0.00014	13.8	246656	10516	0.04263	4263.2
1 tot 4	358019	21	0.00006	5.9	1075850	12419	0.01154	1154.3
5 tot 9	475503	10	0.00002	2.1	1469465	4714	0.00321	320.8
10 tot 14	494511	8	0.00002	1.6	1469325	850	0.00058	57.8
15-19	536852	15	0.00003	2.8	1490426	1712	0.00115	114.9
20-24	542817	15	0.00003	2.8	1563396	4037	0.00258	258.2
25-29	560319	31	0.00006	5.5	1653304	3049	0.00184	184.4
30-34	530554	35	0.00007	6.6	1776419	3479	0.00196	195.8
35-39	512925	19	0.00004	3.7	2043171	9548	0.00467	467.3
40-44	516723	35	0.00007	6.8	2380558	4098	0.00172	172.2

45-49	634188	69	0.00011	10.9	2441662	10417	0.00427	426.6
50-54	644223	114	0.00018	17.7	2337449	11304	0.00484	483.6
55-59	606130	163	0.00027	26.9	1990139	10322	0.00519	518.6
60-64	537540	216	0.00040	40.2	1755003	30703	0.01749	1749.5
65-69	495875	349	0.00070	70.4	1757419	37111	0.02112	2111.7
70-74	424486	440	0.00104	103.7	1322775	21430	0.01620	1620.1
75-79	273902	437	0.00160	159.5	1227379	17312	0.01411	1410.5
80-84	172825	357	0.00207	206.6	826785	13985	0.01691	1691.5
85+	122648	368	0.00300	300.0	629140	8887	0.01413	1412.6

Table 5.

Sex- and age-aggregated YLD, YLL and DALY estimates for resistant and counterfactual susceptible E. coli UTI 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	38499.48 (35,387-41,684)	77,989 (72,056-83,785)	116,488 (109,744-123,106)	23.76 (22.38–25.11)	192.02 (180.90-202.92)
Counterfactual susceptible	38,349 (35,212-41,359)	17,920 (15,134-21,105)	56,268 (52,069-60,696)	11.48 (10.62-12.43)	92.75 (85.83-100.49)
Excess burden	*151*	*60,069*	*60,220*	*12.28*	*99.27*

DISCUSSION

We developed a method for estimating the *excess* BoD due to antimicrobial resistance, and applied the method to AMR *E. coli* UTI infection for two countries using country-specific parameters and incidence data. Using country-specific parameters for BoD estimates is crucial, as outcome measures (e.g. mortality) are not only influenced by 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 [34]. 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, amongst 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%) [35]. 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 [35] 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 8 hospitals was published suggesting a different mortality when comparing highly resistant to non-highly resistant bacteraemia, namely an RR of 1.08 (95% CI 0.48-2.41) [36]. 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. [36] is smaller than that of van Hout et al. [27]. However, the confidence interval of Rotter et al. [36] 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 [37]. 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 & 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. [38]. 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 [39].

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. Firstly, 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 upon 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. Secondly, 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 UTI infections, 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 [40], 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 developing 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, for example when the drug is necessary in order not to interrupt the treatment of a chronic disease [41]); thus prescriptions are required [41,42], 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 these 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 [27], 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 [43]. 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 [44].

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 grousps [45], 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 [34]. 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 generalizable 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- 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 emphasize 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.

Funding:

This study was supported by the research project RADAR (Risk Assessment and Disease burden of Antimicrobial Resistance) funded through the One Health European Joint Programme by the EU's Horizon-2020 Research and Innovation Programme (grant 773830).

Competing interests:

The authors declare that no competing interests exist.

Contributors:

NGG, SAM and MCJB conceptualized 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. WAK and AFS had access to the ISIS-AR data and subtracted the needed data for the incidence calculations. WAK created figure S3. Moreover, SAM, MCJB, WAK, AFS and EF reviewed the manuscript and performed a critical revision of the manuscript text which aided substantially in clarifying the used methodology.

Data sharing statement

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 [44].

Ethics Approval Statement

This study does not involve human participants.

REFERENCES

1. Wernli D, Jørgensen PS, Harbarth S, Carroll SP, Laxminarayan R, Levrat N, et al. Antimicrobial resistance: The complex challenge of measurement to inform policy and the public. PLoS Med [Internet]. 2017 Aug 17;14(8):e1002378–e1002378. Available from: https://pubmed.ncbi.nlm.nih.gov/28817562

2. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis [Internet]. 2019 Jan 1;19(1):56–66. Available from: https://doi.org/10.1016/S1473-3099(18)30605-4

3. Eliakim-Raz N, Babitch T, Shaw E, Addy I, Wiegand I, Vank C, et al. Risk Factors for Treatment Failure and Mortality Among Hospitalized Patients With Complicated Urinary Tract Infection: A Multicenter Retrospective Cohort Study (RESCUING Study Group). Clin Infect Dis [Internet]. 2018 May 17;68(1):29–36. Available from: https://doi.org/10.1093/cid/ciy418

4. Kretzschmar M, Mangen M-JJ, Pinheiro P, Jahn B, Fèvre EM, Longhi S, et al. New Methodology for Estimating the Burden of Infectious Diseases in Europe. PLOS Med [Internet]. 2012 Apr 17;9(4):e1001205. Available from: https://doi.org/10.1371/journal.pmed.1001205

5. Mangen M-JJ, Plass D, Havelaar AH, Gibbons CL, Cassini A, Mühlberger N, et al. The Pathogen- and Incidence-Based DALY Approach: An Appropriated Methodology for Estimating the Burden of Infectious Diseases. PLoS One [Internet]. 2013 Nov

20;8(11):e79740. Available from: https://doi.org/10.1371/journal.pone.0079740

6. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England). 2016 Oct;388(10053):1545–602.

7. Horcajada JP, Shaw E, Padilla B, Pintado V, Calbo E, Benito N, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. Clin Microbiol Infect [Internet]. 2013 Oct 1;19(10):962–8. Available from: https://doi.org/10.1111/1469-0691.12089

8. de Kraker MEA, Lipsitch M. Burden of Antimicrobial Resistance: Compared to What? Epidemiol Rev. 2021 Mar;

9. Gomila A, Carratalà J, Eliakim-Raz N, Shaw E, Wiegand I, Vallejo-Torres L, et al. Risk factors and prognosis of complicated urinary tract infections caused by Pseudomonas aeruginosa in hospitalized patients: a retrospective multicenter cohort study. Infect Drug Resist. 2018;11:2571–81.

10. Zorginstituut Nederland. Screeningsrapport Systematische analyse Infectieziekten [Internet]. 2019. Available from: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2019/05/14/zinnige-zorg---rapport-screeningsfase-infectieziekten/Zinnige+Zorg+-+Rapport+screeningsfase+Systematische+analyse+Infectieziekten.pdf

11. Bonkat G, Cai T, Veeratterapillay R, Bruyère F, Bartoletti R, Pilatz A, et al.

Management of Urosepsis in 2018. Eur Urol Focus [Internet]. 2019 Jan 1;5(1):5–9. Available from: https://doi.org/10.1016/j.euf.2018.11.003

12. World Health Organization. WHO methods and data sources for global burden of disease estimates 2000–2011. Global Health Estimates Technical Paper. [Internet]. 2013. Available from: http://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf. Accessed 6 Dec 2018.

13. Haagsma JA, van Beeck EF, Polinder S, Toet H, Panneman M, Bonsel GJ. The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. Popul Health Metr [Internet]. 2011 Apr 24;9:10. Available from: https://pubmed.ncbi.nlm.nih.gov/21513572

14. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank H-P, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016 Oct;13(10):e1002150.

15. van Lier A, de Gier B, McDonald SA, Mangen M-JJ, van Wijhe M, Sanders EAM, et al. Disease burden of varicella versus other vaccine-preventable diseases before introduction of vaccination into the national immunisation programme in the Netherlands. Euro Surveill [Internet]. 2019 May;24(18):1800363. Available from: https://pubmed.ncbi.nlm.nih.gov/31064637

16. Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010:

design, definitions, and metrics. Lancet (London, England) [Internet]. 2012 Dec;380(9859):2063—2066. Available from: https://doi.org/10.1016/S0140-6736(12)61899-6

17. Colzani E, Cassini A, Lewandowski D, Mangen M-JJ, Plass D, McDonald SA, et al. A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years. PLoS One [Internet]. 2017;12(1):1–14. Available from: https://doi.org/10.1371/journal.pone.0170662

18. Altorf-van der Kuil W, Schoffelen AF, de Greeff SC, Thijsen SF, Alblas HJ, Notermans DW, et al. National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the Netherlands. Euro Surveill Bull Eur sur les Mal Transm = Eur Commun Dis Bull. 2017 Nov;22(46).

19. Rijksinstituut voor Volksgezondheid en Milieu. Handleiding ISIS-AR [Internet]. Bilthoven; 2017. Available from: https://www.rivm.nl/sites/default/files/2018-11/Handleiding ISIS-AR 2017 %28februari 2017%29.pdf

20. Rijksinstituut voor Volksgezondheid en Milieu. ISIS AR - Populatie en representativiteit [Internet]. 2021 [cited 2021 Nov 29]. Available from: https://www.rivm.nl/isis-ar/populatie-en-representativiteit

21. Cai T, Palagin I, Brunelli R, Cipelli R, Pellini E, Truzzi JC, et al. Office-based approach to urinary tract infections in 50 000 patients: results from the REWIND study. Int J Antimicrob Agents [Internet]. 2020;56(1):105966. Available from: http://www.sciencedirect.com/science/article/pii/S0924857920301230

22. ISTAT. Resident population by age, sex and marital status on 1st January 2016 Italy

[Internet]. [cited 2020 Jul 30]. Available from: http://demo.istat.it/pop2016/index_e.html

23. Serretiello E, Folliero V, Santella B, Giordano G, Santoro E, De Caro F, et al. Trend of Bacterial Uropathogens and Their Susceptibility Pattern: Study of Single Academic High-Volume Center in Italy (2015–2019). Falkinham J, editor. Int J Microbiol [Internet]. 2021;2021:5541706. Available from: https://doi.org/10.1155/2021/5541706

24. Cardone S, Petruzziello C, Migneco A, Fiori B, Spanu T, D'Inzeo T, et al. Age-related Trends in Adults with Urinary Tract Infections Presenting to the Emergency Department: A 5-Year Experience. Rev Recent Clin Trials. 2019;14(2):147–56.

25. Luzzaro F, Ortisi G, Larosa M, Drago M, Brigante G, Gesu G. Prevalence and epidemiology of microbial pathogens causing bloodstream infections: results of the OASIS multicenter study. Diagn Microbiol Infect Dis. 2011 Apr;69(4):363–9.

26. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. Am J Infect Control. 2000 Feb;28(1):68–75.

27. van Hout D, Verschuuren TD, Bruijning-Verhagen PCJ, Bosch T, Schürch AC, Willems RJL, et al. Extended-spectrum beta-lactamase (ESBL)-producing and non-ESBL-producing Escherichia coli isolates causing bacteremia in the Netherlands (2014 – 2016) differ in clonal distribution, antimicrobial resistance gene and virulence gene content. PLoS One [Internet]. 2020 Jan 14;15(1):e0227604. Available from: https://doi.org/10.1371/journal.pone.0227604

28. Palacios-Baena ZR, Gutiérrez-Gutiérrez B, De Cueto M, Viale P, Venditti M, Hernández-Torres A, et al. Development and validation of the INCREMENT-ESBL

predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother. 2017 Mar;72(3):906–13.

29. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with E. coli UTIs. Br J Gen Pract J R Coll Gen Pract. 2006 Sep;56(530):686–92.

30. Vallejo-Torres L, Pujol M, Shaw E, Wiegand I, Vigo JM, Stoddart M, et al. Cost of hospitalised patients due to complicated urinary tract infections: a retrospective observational study in countries with high prevalence of multidrug-resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study. BMJ Open [Internet]. 2018 Apr 1;8(4):e020251. Available from: http://bmjopen.bmj.com/content/8/4/e020251.abstract

31. Covino M, Manno A, Merra G, Simeoni B, Piccioni A, Carbone L, et al. Reduced utility of early procalcitonin and blood culture determination in patients with febrile urinary tract infections in the emergency department. Intern Emerg Med. 2020 Jan;15(1):119–25.

32. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother. 2011 Feb;66(2):398–407.

33. Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, et al.

Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother [Internet]. 2010/07/26. 2010 Oct;54(10):4085–91. Available from: https://pubmed.ncbi.nlm.nih.gov/20660675

34. Tacconelli E, Pezzani MD. Public health burden of antimicrobial resistance in Europe. Lancet Infect Dis [Internet]. 2019 Jan 1;19(1):4–6. Available from: https://doi.org/10.1016/S1473-3099(18)30648-0

35. Bordino V, Vicentini C, D'Ambrosio A, Quattrocolo F, Zotti CM. Burden of healthcare-associated infections in Italy: incidence, attributable mortality and disability-adjusted life years (DALYs) from a nationwide study, 2016. J Hosp Infect. 2021 Jul;113:164–71.

36. Rottier WC, Deelen JWT, Caruana G, Buiting AGM, Dorigo-Zetsma JW, Kluytmans JAJW, et al. Attributable mortality of antibiotic resistance in gram-negative infections in the Netherlands: a parallel matched cohort study. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2020 Jul;

37. Collaborators AR. Articles Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis Antimicrobial Resistance Collaborators*. Lancet. 2022 Jan 20;399.

38. Godijk NG, Bootsma MCJ, van Werkhoven HC, Schweitzer VA, de Greeff SC, Schoffelen AF, et al. Modelling addition and replacement mechanisms of plasmid-based beta-lactam resistant E. coli infections. medRxiv [Internet]. 2021 Jan 1;2021.03.17.21253797. Available from: http://medrxiv.org/content/early/2021/03/20/2021.03.17.21253797.abstract

39. Temkin E, Carmeli Y, Consortium for the DR in R and D and RAU (DRIVE-A. Zero or More: Methodological Challenges of Counting and Estimating Deaths Related to Antibiotic-resistant Infections. Clin Infect Dis [Internet]. 2019 Nov 13;69(11):2029–34. Available from: https://doi.org/10.1093/cid/ciz414

40. Pezzani MD, Tornimbene B, Pessoa-Silva C, de Kraker M, Rizzardo S, Salerno ND, et al. Methodological quality of studies evaluating the burden of drug-resistant infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2021 Jan;27(5):687–96.

41. Lombardia F per i servizi degli O dei farmacisti della. Dispensazione senza ricetta: quando si può e come si fa [Internet]. [cited 2021 Dec 1]. Available from: https://www.ordinifarmacistilombardia.it/farmacista/per_la_farmacia/dispensazione_senza_ricetta.html?fbclid=IwAR2Hzk07wRFnygmyG5Z1m4d5OkBnUbvFXqYMIfurvRbROzSms4XzU450PWM

42. Italian Medicines Agency. Antibiotics [Internet]. [cited 2021 Dec 1]. Available from: https://www.aifa.gov.it/en/farmaci-antibiotici?fbclid=IwAR2jIo2UTMVnOcHP80us5MOjk9OpLwg21rYWWWi2Yvx7LdkKdusaVzqdKqs

43. MacKinnon MC, McEwen SA, Pearl DL, Lyytikäinen O, Jacobsson G, Collignon P, et al. Mortality in Escherichia coli bloodstream infections: a multinational population-based cohort study. BMC Infect Dis [Internet]. 2021 Jun 25;21(1):606. Available from: https://pubmed.ncbi.nlm.nih.gov/34172003

44. [dataset] Godijk NG, McDonald SA, Altorf-van der Kuil W, Schoffelen AF, Franz E, Bootsma MCJ. GitHub, January 5, 2022. Available from: https://github.com/NoorGo/ExcessBurden.

45. ECDC. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017 [Internet]. Stockholm; 2018. Available from: https://www.ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-EARS-Net-2017.pdf

Figure 1

Outcome trees(s) for 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).

Figure 2

YLD and YLL due to resistant and counterfactual susceptible *E. coli* UTIs in the Netherlands in 2018

Notes: Lines indicate 95% uncertainty intervals.

Figure 3

DALYs attributable to six sequelae of resistant and counterfactual susceptible *E. coli* UTIs in the Netherlands in 2018

Figure 4

DALYs of resistant and counterfactual susceptible *E. coli* UTIs in the Netherlands in 2018 per age and sex-stratified group

Figure 5

YLD and YLL due to resistant and counterfactual susceptible *E. coli* UTIs in Italy in 2016

Notes: Lines indicate 95% uncertainty intervals.

Figure 6

DALYs attributable to six sequelae of resistant and counterfactual susceptible *E. coli* UTIs in Italy in 2016

Figure 7

DALYs of resistant and counterfactual susceptible *E. coli* UTIs in Italy in 2016 per age and sex-stratified group

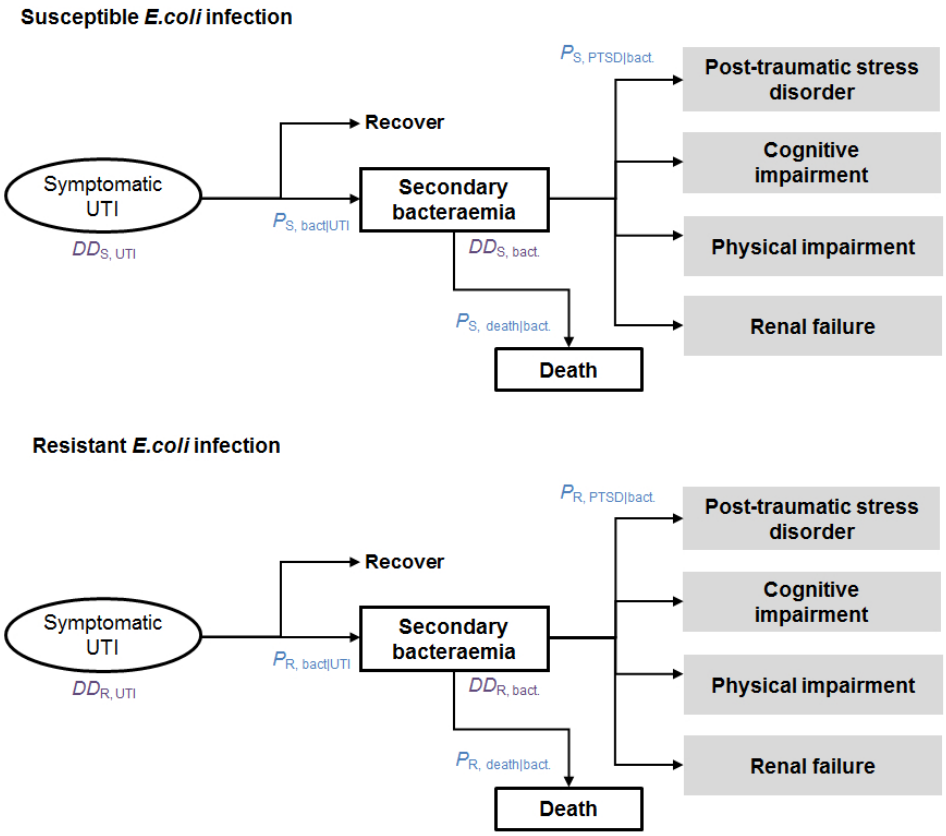

Figure 1
Outcome trees(s) for UTI, for antimicrobial-susceptible (upper panel) and antimicrobial-resistant (lower panel) infection. Transition probabilities (P) stratified by type of infection ([S]usceptible or [R]esistant) are indicated for several transitions, as are disability durations (DD).

613x515mm (38 x 38 DPI)

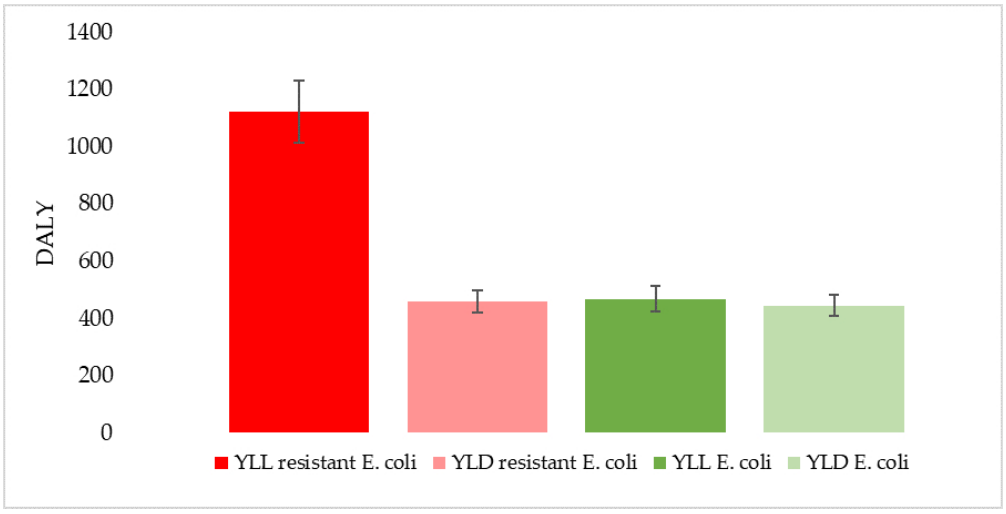

Figure 2
YLD and YLL due to resistant and counterfactual susceptible E. coli UTIs in the Netherlands in 2018
Notes: Lines indicate 95% uncertainty intervals

388x195mm (59 x 59 DPI)

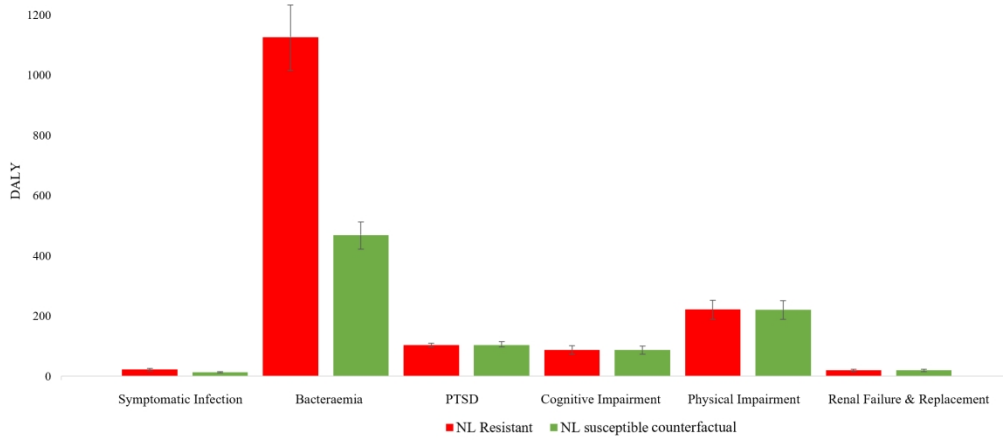

Figure 3
DALYs attributable to six sequelae of resistant and counterfactual susceptible E. coli UTIs in the Netherlands in 2018

1646x739mm (38 x 38 DPI)

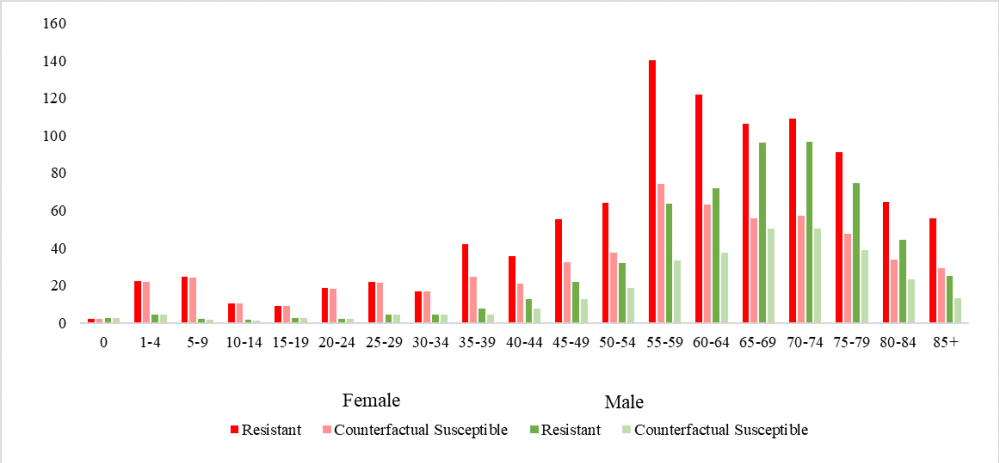

Figure 4
DALYs of resistant and counterfactual susceptible E. coli UTIs in the Netherlands in 2018 per age and sex-stratified group

500x232mm (59 x 59 DPI)

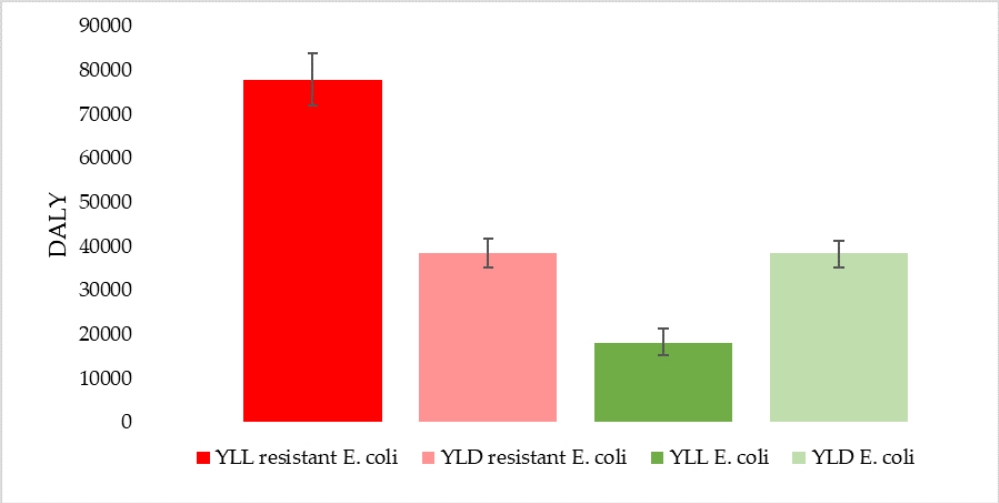

Figure 5
YLD and YLL due to resistant and counterfactual susceptible E. coli UTIs in Italy in 2016
Notes: Lines indicate 95% uncertainty intervals.

387x195mm (59 x 59 DPI)

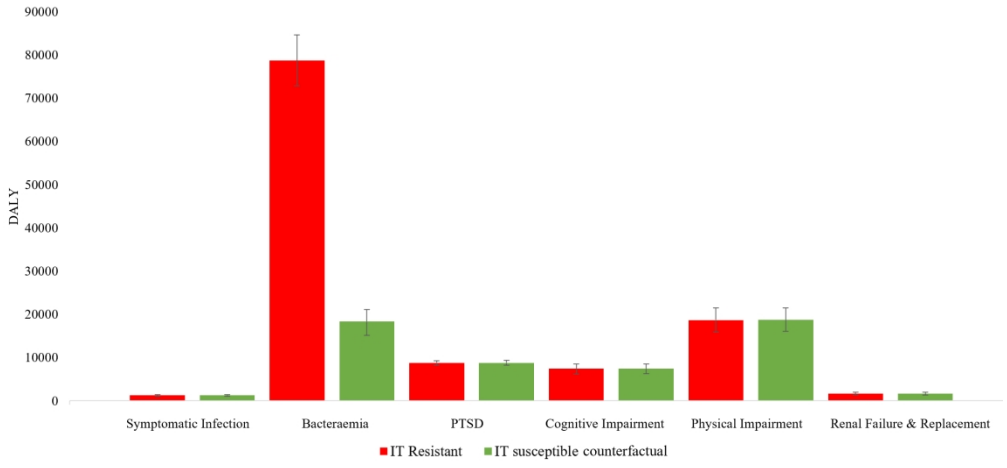

Figure 6
DALYs attributable to six sequelae of resistant and counterfactual susceptible E. coli UTIs in Italy in 2016

1660x774mm (38 x 38 DPI)

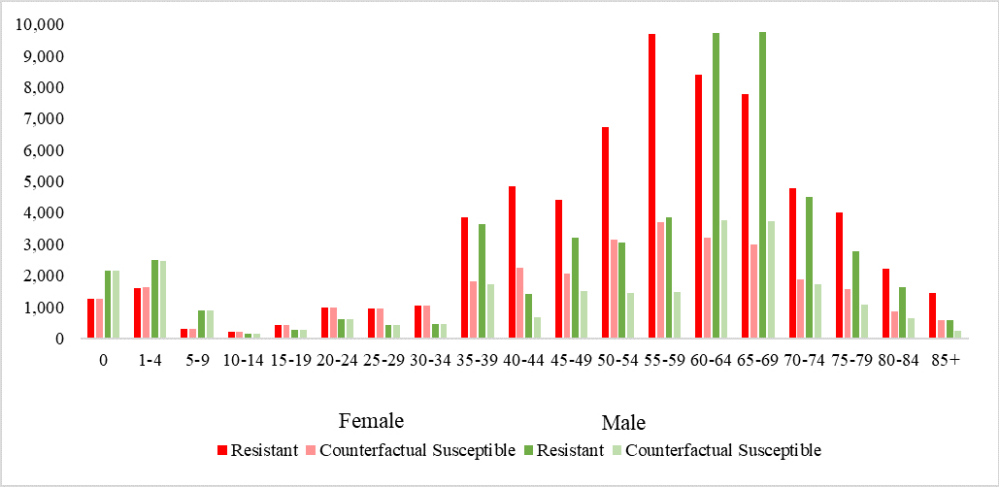

Figure 7
DALYs of resistant and counterfactual susceptible E. coli UTIs in Italy in 2016 per age and sex-stratified group

443x216mm (59 x 59 DPI)

Appendix 1. Systematic Review Methods

The Netherlands

PubMed and Embase were searched using the search terms shown in Appendix 3, resulting in 242 and 136 articles respectively. The removing of duplicates in Endnote and Rayyan resulted in a final set of 296 articles for title/abstract screening. In this stage, articles were included that reported Dutch studies on UTI or bacteraemia, that potentially contained data for both susceptible and resistant UTIs, but had not necessarily reported these data or did not mention the specific pathogen. In the case where, for example, testing for resistance had been mentioned but specific data were not separately reported for AMR and AMS *E. coli,* the authors were emailed. After full-text screening of 43 articles, a total of 18 were retained, and the authors were requested more data. If there was no response after a month, a follow-up email was sent.

We excluded case studies and studies that were carried out in a specific vulnerable population (elderly persons, children), or in highly-specific clinical patient populations. Inclusion criteria applied to the final set of articles were : a Dutch study, published in 2017 or later, UTI caused by resistant and/or susceptible *E. coli*, and estimates for of one or more of parameters needed for the OTs. Following this systematic literature search, further relevant articles were possibly identified during correspondence with authors.

Given the almost null yield of the first search, a second literature search was undertaken to locate relevant studies specifically informing the model parameters involving bacteraemia (i.e., $P(\text{Bact}|\text{UTI})$, $DD(\text{Bact})$, $P(\text{Death}|\text{Bact})$) (Appendix 3). This produced 24 hits, due to the limited number of hits, we performed full-text screening for all. Inclusion criteria were only that the study reported suitable data on cases of bacteraemia in which *E. coli* had been isolated.

Following this search, further relevant articles were possibly identified in correspondence with authors of retained articles. We then applied the following algorithm to the set of identified articles: (i) if no eligible Dutch population studies were found reporting parameter values involving bacteraemia due to susceptible/resistant *E. coli* UTI, then (ii) Dutch studies reporting parameter values involving bacteraemia with susceptible/resistant *E. coli from any infection site* were used. (iii) If still no eligible studies found, then *EU* studies reporting parameter values due to bacteraemia with AMR/AMS *E. coli* from any infection site were considered eligible.

A third systematic literature search was conducted to attempt to find relevant studies specifically to inform $P(\text{Bact}|\text{UTI})$, with restriction to studies of resistant *E. coli* UTIs (Appendix 1). This produced 13 hits; 10 articles were eliminated based on abstract screening and the remaining three after full-text screening. A PRISMA diagram for all three searches together is shown in Figure S1.

Italy

PubMed and Embase were searched using the search term in Appendix 4, and yielded 231 and 176 results respectively. After removing duplicates in EndNote and Rayan, 290 articles remained. After title/abstract screening 56 articles were screened full text and 32 articles potentially contained parameter estimates relevant for the Italian population.

Given the almost null yield of the first search, we performed new separate searches for the incidence, progression from UTI to bacteraemia, DD(UTI) and LOS due to bacteraemia. For LOS(UTI) a third search was conducted (Appendix 4). Eventually, three articles from the search and one article recommended to the authors which fell outside the initial search criteria

of articles published from 2017 or later were used to estimate the parameters. A PRISMA diagram for all searches on Italian parameters together is shown in Figure S2.

Appendix 2 – Systematic review to identity Dutch parameter estimates

Search 1

4th of February 2019

PubMed: (("2017/01/01"[Date - Publication] : "3000"[Date - Publication])) AND (((((urinary[Title/Abstract] AND tract[Title/Abstract]) AND (infection[Title/Abstract] OR infections[Title/Abstract])) OR urinary tract infection[MeSH] OR UTI[Title/Abstract]) AND (Netherlands OR Netherlands[MeSH] OR Dutch) AND (english[Language] OR dutch[Language])) AND ("2017/01/01"[PDat] : "3000/12/31"[PDat]))

242 results

4th of February 2019

Embase: ('urinary':ab,ti AND 'tract':ab,ti AND ('infection':ab,ti OR 'infections':ab,ti) OR 'uti':ab,ti) AND ('netherlands' OR 'dutch') AND [article]/lim AND ([dutch]/lim OR [english]/lim) AND [humans]/lim AND [embase]/lim AND [2017-2019]/py

136 results

Search 2

10th of February, 2020

PubMed: *((bacteraemia[Title/Abstract]) OR (bacteremia[Title/Abstract])) AND ((Netherlands[Text Word]) AND Dutch[Text Word]).*

24 results

13th of February, 2020

PubMed:((((((urinary tract[Title/Abstract]) AND infection[Title/Abstract])) OR

UTI[Title/Abstract])) AND ((Netherlands[Text Word]) OR Dutch [Text Word])) AND ((lenght of stay[Text Word]) OR LOS[Text Word])

3 results

Search 3 –

13th of February, 2020

PubMed: (((bacteraemia[Text Word]) OR (bacteremia[Text Word])) AND resist*[Text Word] AND (E coli[MeSH] OR E coli[Text Word]) AND ((urinary tract infection[MeSH]) OR (UTI[Text Word])) AND (("probability of"[Text Word]) OR (progress*[Text Word]) OR ("risk of "[Text Word]))).

13 results

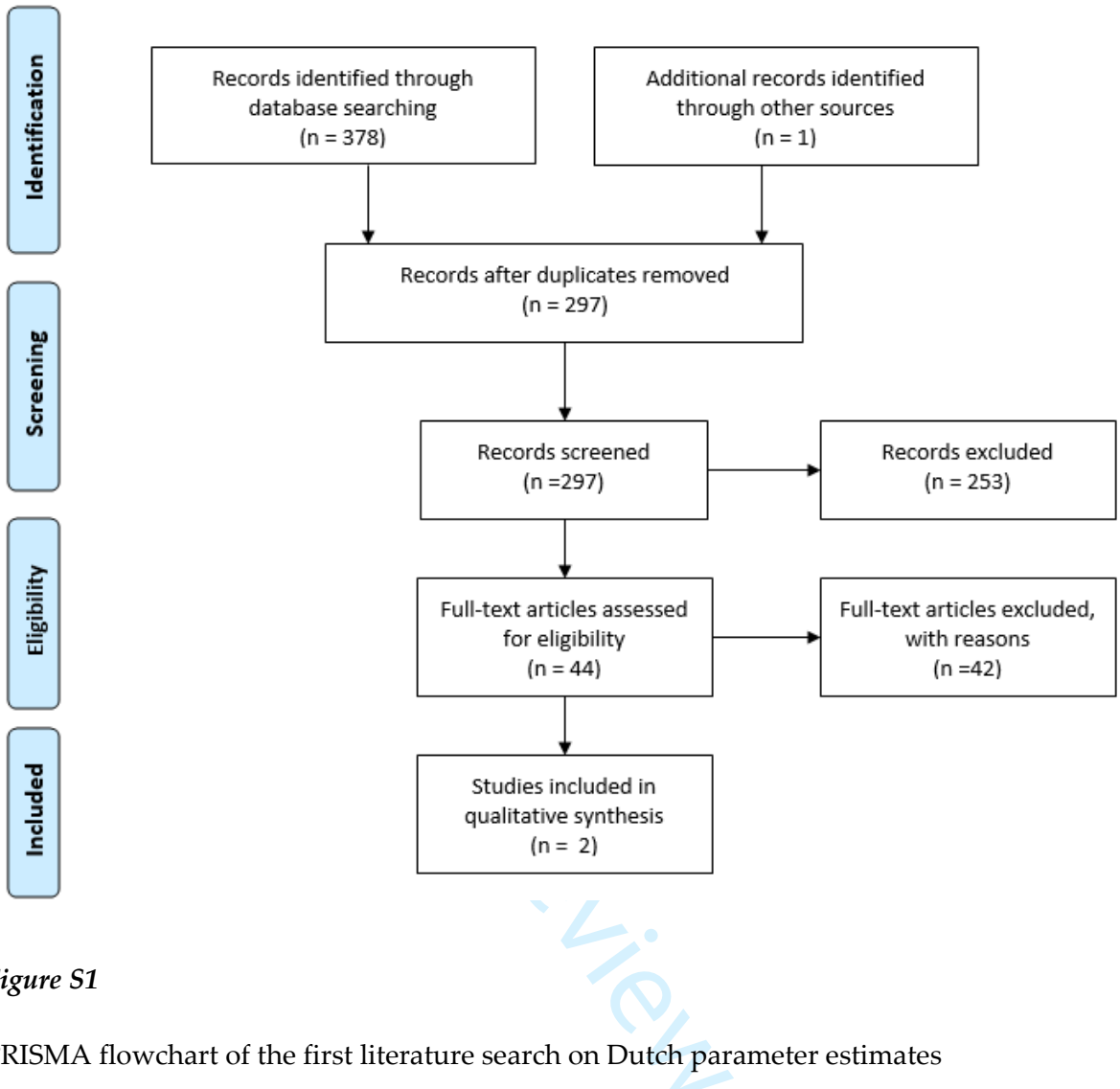

Figure S1

PRISMA flowchart of the first literature search on Dutch parameter estimates

Appendix 3 – Systematic review to identify Italian parameter estimates

Search 1

4th of February, 2019

Pubmed: ((("2017/01/01"[Date - Publication] : "3000"[Date - Publication])) AND (((((urinary[Title/Abstract] AND tract[Title/Abstract]) AND (infection[Title/Abstract] OR infections[Title/Abstract])) OR urinary tract infection[MeSH] OR UTI[Title/Abstract]) AND (Italy OR Italy[MeSH] OR Italian) AND (english[Language] OR dutch[Language])) AND ("2017/01/01"[PDat] : "3000/12/31"[PDat])))

231 results

('urinary':ab,ti AND 'tract':ab,ti AND ('infection':ab,ti OR 'infections':ab,ti) OR 'uti':ab,ti) AND ('italy' OR 'italian') AND [article]/lim AND ([dutch]/lim OR [english]/lim) AND [humans]/lim AND [embase]/lim AND [2017-2019]/py

176 results

Search 2

3th of June, 2020

Incidence - PubMed: ("2019/01/01"[Date - Publication] : "3000"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR UTI [Title/Abstract]) AND incidence.

35 results

3th of June, 2020

LOS UTI - PubMed ("2019/01/01"[Date - Publication] : "3000"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR

UTI [Title/Abstract]) AND (LOS [Title/Abstract] OR (length [Title/Abstract] AND stay [Title/Abstract])).

5 results

18th of June, 2020

UTI to bacteraemia – PubMed: (("2019/01/01"[Date - Publication] : "2020/06/18"[Date - Publication])) AND ((Italy[Text Word]) AND ((UTI[Title/Abstract]) OR (((urinary[Title/Abstract]) AND (tract[Title/Abstract])) AND (infection[Title/Abstract])))).

21 results

31st of August, 2020

LOS Bacteraemia – PubMed: (("2005/01/01"[Date - Publication] : "3000"[Date - Publication])) AND ((Italy[Text Word]) AND (((((bacteraemia[Title/Abstract]) OR (bacteraemias[Title/Abstract])) OR (bacteremia[Title/Abstract])) OR (bacteremias[Title/Abstract])) AND (((days[Title/Abstract]) OR (((length[Title/Abstract]) AND (of[Title/Abstract])) AND (stay[Title/Abstract]))) OR (LOS[Title/Abstract]))))

24 results

Search 3

16th of June, 2020

LOS UTI– Pubmed (("2015/01/01"[Date - Publication] : "3000"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR UTI [Title/Abstract]) AND (LOS [Title/Abstract] OR disability duration [Title/Abstract] OR (length [Title/Abstract] AND stay [Title/Abstract]))) NOT (("2019/01/01"[Date - Publication] : "2020/06/02"[Date - Publication]) AND Italy AND ((urinary[Title/Abstract] AND tract [Title/Abstract] AND infection [Title/Abstract]) OR UTI [Title/Abstract]) AND (LOS

[Title/Abstract] OR (length [Title/Abstract] AND stay [Title/Abstract]))).

7 results

2nd of September, 2020

(((general practitioner) OR (general practice)) AND (((urinary tract infection) OR (UTI)) AND (Italy))) AND ((out-patient) OR (outpatient))

10 results, 1 included

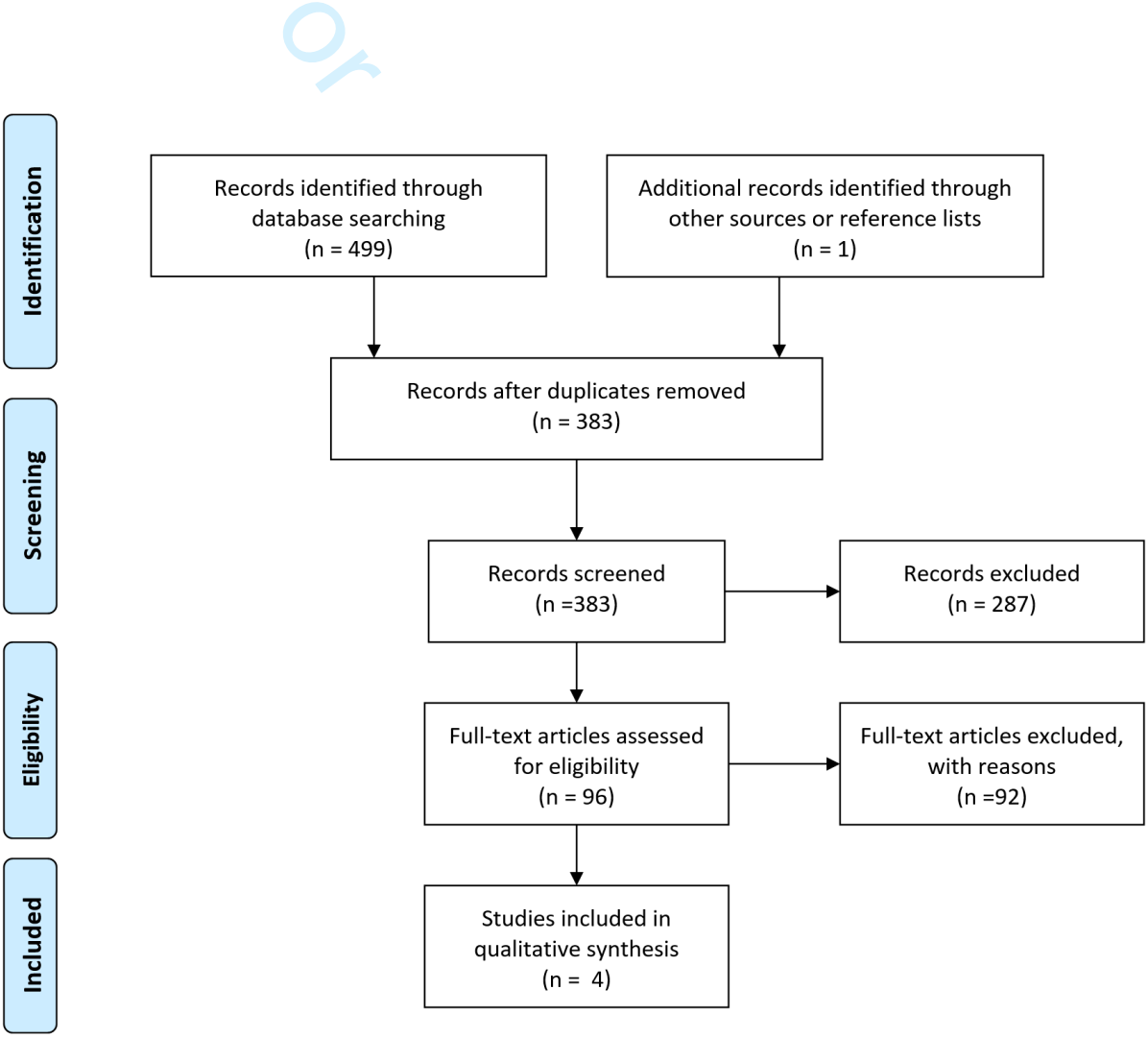

Figure S2

PRISMA flowchart of the literature search on Italian parameter estimates

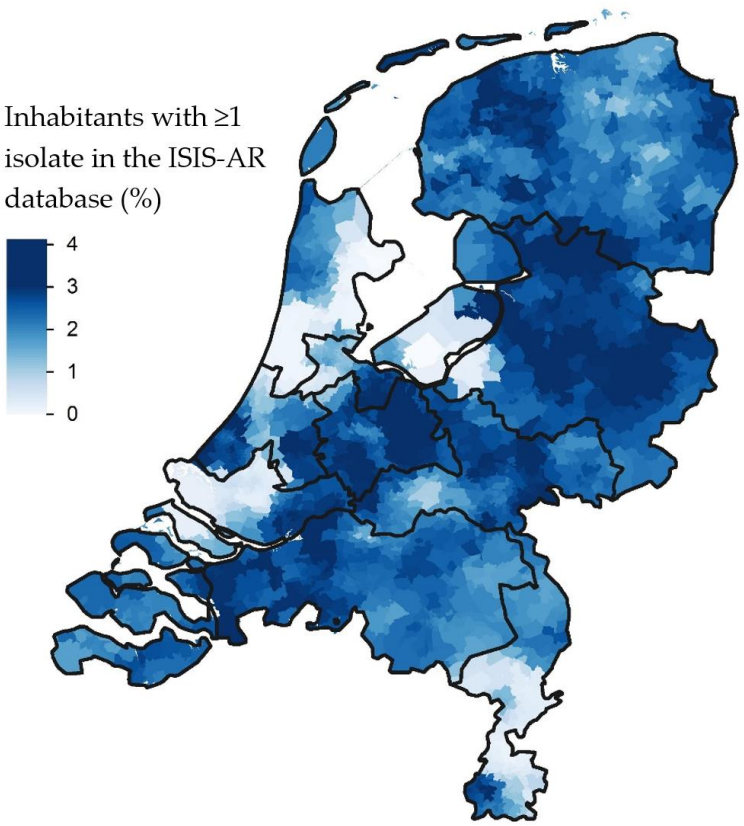

Figure S3

smoothed geographical distribution of the percentage of inhabitants for whom at least 1 urinary isolate was found in the ISIS-AR database in 2018, by 4-digit postal code area and with regional cooperative network borders

Appendix 4.

Systematic review results

The Netherlands

The first systematic literature review yielded only two articles, both providing an estimate of DD(UTI). In the first study the Netherlands was one of four countries on which analysis was based, and bacteria species and AMS vs. AMR infections were not distinguished. Correspondence with the authors yielded a more appropriate citation (1), which was carried out in England and Wales in 2002-2004 and reported DD(UTI) for *E. coli* UTIs separately for AMS and AMR infection. (In Figure S1 this article is indicated as an additional record identified through other sources). We justified this choice as the analysis in (2) did not find any between-country difference in DD(UTI).

The second review resulted in one suitable study for P(Death|Bact), which was a Dutch study that reported 30-day mortality in bacteraemia patients with either resistant *E. coli* or susceptible *E. coli* in 2014–2016 (3). The study population had a median age of 69 years (*IQR* 57 to 77); it is plausible that a lower mortality rate would be observed for younger age-groups. We could only locate a single study reporting age-group specific values for 30-day mortality due to bacteraemia (4). This study was conducted in Iceland among patients with bacteraemia caused by *S. aureus.* We took the simple approach of setting the parameter values for P(Death|Bact) for the age-groups 55 years and older to the value from study (3), and then scaling the parameter values for the younger age-groups according to the ratio of 30-day mortality risks between the 'reference' age-group, 55-74 years, and the <35 years and 35-54 years age-groups from the Icelandic study (4). This meant P(Death|Bact) was zero for <35

years (since mortality risk was 0% for <35 years (4)), and a scaling factor of 0.54 (from 3.8%/7.1%) was applied to 35-54 years.

For the parameter DD(Bact), the literature reviews did not yield any eligible studies. We decided to adopt values from (5), which is a large well-conducted multi-country study that was carried out in 2007/8, and that reported patient characteristic-adjusted LOS values for both AMS and 3rd generation cephalosporin-resistant *E. coli* bloodstream infections (BSIs). All selected parameter values are provided in Table 1.

As the third systematic literature review, which was specifically aimed at P(Bact|UTI), did not yield any studies. We relied on a previous pooled analysis [24] which we identified through citation search. This study did not distinguish between AMR and AMS infections, and the contributing studies were all carried out in the USA in the 1980s.

Italy

We found one article providing estimates on P(Death|Bact). The study of Palacios-Baena et al. (6) found a 30-day mortality of 26.2% of ESBL blood stream infections (BSI), 34 of the 130 Italian BSI patients died. We calculated the mortality for susceptible BSI using the ratio of susceptible vs. resistant mortality reported in another, less recent, Italian study by Tumbarello et al. (7) and estimated a 30-day mortality of 5.47% for susceptible BSI.

Furthermore, for DD(UTI) and DD(BACT) we only found an Italian study amongst elderly (*Mdn* = 77, *IQR* = 65–83) with UTIs or urosepsis which reported a mean LOS of 10 [7-17] days (8) and a median LOS of 9.5 days for Italian patients with complicated UTIs in Italy (9). Of the UTIs 58% was caused by *E. coli.* Unfortunately, no studies were identified which specified LOS for ESBL *E. coli* and *E. coli* UTIs. Because the lack of better studies on DD(UTI) and

DD(BACT) amongst adults, we used the estimate of Covino et al. (8) in elderly and Vallejo-Torres et al. (9) on complicated UTIs.

Moreover, we searched the citations of Cassini et al. (10) for relevant Italian studies and found that Tumbarello et al. (7) reported LOS for resistant BSI of 20 ± 17 days and 13 ± 9 days for non-AMR BSI.

For P(Bact|UTI) we were unable to locate a parameter and, therefore, we used the same value as the Dutch parameter. For the health outcomes following bacteremia, other than death, we used the same values as Cassini et al. (10).

Regarding the incidence of resistant *E. coli*, we did not locate any direct estimates; therefore, we estimated incidence (see Methods).

References Appendix 4.

1. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with E. coli UTIs. Br J Gen Pract J R Coll Gen Pract. 2006 Sep;56(530):686–92.

2. Altorf-van der Kuil W, Schoffelen AF, de Greeff SC, Thijsen SF, Alblas HJ, Notermans DW, et al. National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the Netherlands. Euro Surveill Bull Eur sur les Mal Transm = Eur Commun Dis Bull. 2017 Nov;22(46).

3. van Hout D, Verschuuren TD, Bruijning-Verhagen PCJ, Bosch T, Schürch AC, Willems RJL, et al. Extended-spectrum beta-lactamase (ESBL)-producing and non-ESBL-producing Escherichia coli isolates causing bacteremia in the Netherlands (2014 – 2016) differ in clonal distribution, antimicrobial resistance gene and virulence gene content. PLoS One [Internet]. 2020 Jan 14;15(1):e0227604. Available from: https://doi.org/10.1371/journal.pone.0227604

4. Asgeirsson H, Gudlaugsson O, Kristinsson KG, Heiddal S, Kristjansson M. Staphylococcus aureus bacteraemia in Iceland, 1995-2008: changing incidence and mortality. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2011 Apr;17(4):513–8.

5. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant

to third-generation cephalosporins. J Antimicrob Chemother. 2011 Feb;66(2):398–407.

6. Palacios-Baena ZR, Gutiérrez-Gutiérrez B, De Cueto M, Viale P, Venditti M, Hernández-Torres A, et al. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother. 2017 Mar;72(3):906–13.

7. Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother [Internet]. 2010/07/26. 2010 Oct;54(10):4085–91. Available from: https://pubmed.ncbi.nlm.nih.gov/20660675

8. Covino M, Manno A, Merra G, Simeoni B, Piccioni A, Carbone L, et al. Reduced utility of early procalcitonin and blood culture determination in patients with febrile urinary tract infections in the emergency department. Intern Emerg Med. 2020 Jan;15(1):119–25.

9. Vallejo-Torres L, Pujol M, Shaw E, Wiegand I, Vigo JM, Stoddart M, et al. Cost of hospitalised patients due to complicated urinary tract infections: a retrospective observational study in countries with high prevalence of multidrug-resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study. BMJ Open [Internet]. 2018 Apr 1;8(4):e020251. Available from: http://bmjopen.bmj.com/content/8/4/e020251.abstract

10. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al.

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis [Internet]. 2019 Jan 1;19(1):56–66. Available from: https://doi.org/10.1016/S1473-3099(18)30605-4

Table S1. *Number and incidence of resistant E. coli UTI per age- and sex category in the Netherlands in 2018*

	Males					Females				
Age category	**Male inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *E.coli* UTIs incidence**	**Recurrent* resistant *E. Coli* UTIs**	**Average resistant *E. coli* UTIs per patient**	**Female inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *coli* UTIs incidence**	**Recurrent* resistant *E. coli* UTIs**	**Average resistant *E. coli* UTIs per patient**
0	87001	12	0.000137929	0	1.00	82565	10	0.000121117	0	1.00
1-4	358019	25	5.86561E-05	4	1.19	340514	111	0.000323041	7	1.06
5-9	475503	19	2.10304E-05	9	1.90	452563	148	0.000287253	18	1.14
10-14	494511	11	1.61776E-05	3	1.38	471948	62	0.000122895	4	1.07
15-19	536852	20	2.79407E-05	5	1.33	511180	66	0.000105638	6	1.11
20-24	542817	19	2.76336E-05	4	1.27	525964	142	0.000230054	19	1.16
25-29	560319	36	5.53256E-05	5	1.16	545838	155	0.000283967	0	1.00
30-34	530554	38	6.59688E-05	3	1.09	522235	136	0.000250845	5	1.04
35-39	512925	26	3.70425E-05	7	1.37	512431	114	0.000204906	9	1.09

40-44	516723	53	6.77346E-05	18	1.51	521589	12[illegible]	0.000191722	25	1.25
45-49	634188	92	0.000108801	23	1.33	634635	19[illegible]	0.000272598	25	1.14
50-54	644223	143	0.000176957	29	1.25	635623	27[illegible]	0.00035713	43	1.19
55-59	606130	211	0.000268919	48	1.29	605380	44[illegible]	0.000597972	79	1.22
60-64	537540	287	0.000401831	71	1.33	542198	44[illegible]	0.000671341	81	1.22
65-69	495875	460	0.000703806	111	1.32	503662	47[illegible]	0.000770358	85	1.22
70-74	424486	633	0.001036548	193	1.44	447439	61[illegible]	0.001115236	114	1.23
75-79	273902	621	0.001595461	184	1.42	314838	68[illegible]	0.001715168	149	1.28
80-84	172825	487	0.002065673	130	1.36	235430	68[illegible]	0.002229962	158	1.30
≥ 85	122648	495	0.003000457	127	1.35	248011	105[illegible]	0.00033063	236	1.29
Total	8527041	3688	0.000432506	974	1.36	8654043	593[illegible]	0.000685807	1063	1.22

**Defined as a UTI occurring more than 14 days after another UTI*

Table S2. *Number and incidence of E. coli UTI per age- and sex category in the Netherlands in 2018*

	Males					Females				
Age category	**Male inhabitants**	**Number of *E. coli* UTIs**	***E.coli* UTIs incidence**	**Recurrent * *E. Coli* UTIs**	**Average *E. coli* UTIs per patient**	**Female inhabitants**	**Number of *E. coli* UTIs**	***E. coli* UTIs incidence**	**Recurrent * *E. coli* UTIs**	**Average *E. coli* UTIs per patient**
0	87001	453	0.0052	0	1.00	82565	413	0.0044	52	1.14
1-4	358019	598	0.0015	74	1.14	340514	4079	0.0105	518	1.15
5-9	475503	351	0.0006	45	1.15	452563	6336	0.0115	1111	1.21
10-14	494511	260	0.0005	34	1.15	471948	2766	0.0049	473	1.21
15-19	536852	315	0.0005	41	1.15	511180	2651	0.0047	260	1.11
20-24	542817	318	0.0005	30	1.10	525964	3499	0.0061	316	1.10
25-29	560319	492	0.0008	60	1.14	545838	3745	0.0069	0	1.00
30-34	530554	500	0.0009	25	1.05	522235	3714	0.0069	102	1.03
35-39	512925	731	0.0012	106	1.17	512431	3638	0.0063	432	1.13
40-44	516723	968	0.0016	147	1.18	521589	3608	0.0060	497	1.16

45-49	634188	1630	0.0022	242	1.17	634635	5053	0.0068	742	1.17
50-54	644223	2224	0.0029	331	1.17	635623	6648	0.0089	1022	1.18
55-59	606130	3154	0.0044	498	1.19	605380	8686	0.0120	1418	1.20
60-64	537540	4166	0.0065	672	1.19	542198	10635	0.0161	1880	1.21
65-69	495875	6022	0.0099	1113	1.23	503662	12863	0.0210	2296	1.22
70-74	424486	7930	0.0149	1598	1.25	447439	16474	0.0297	3201	1.24
75-79	273902	7017	0.0203	1465	1.26	314838	15964	0.0407	3162	1.25
80-84	172825	6148	0.0280	1312	1.27	235430	16251	0.0548	3340	1.26
≥ 85	122648	6251	0.0411	1213	1.24	248011	22890	0.0747	4355	1.23
Total	**8527041**	**49528**	**0.0058**	**9006**	**1.22**	**8654043**	**149913**	**0.0173**	**25177**	**1.20**

**Defined as a UTI occurring more than 14 days after another UTI*

Table S3. *Sensitivity analysis of the number and incidence of resistant E. coli UTI per age- and sex category in the Netherlands in 2018*

	Males					Females				
Age category	**Male inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *E.coli* UTIs incidence**	**Recurrent* resistant *E. Coli* UTIs**	**Average resistant *E. coli* UTIs per patient**	**Female inhabitants**	**Number of resistant *E. coli* UTIs**	**Resistant *coli* UTIs incidence**	**Recurrent* resistant *E. coli* UTIs**	**Average resistant *E. coli* UTIs per patient**
0	87001	12	0.000137929	0	1.00	82565	10	0.000121117	0	1.00
1-4	358019	21	5.86561E-05	0	1.00	340514	111	0.000323041	1	1.01
5-9	475503	10	2.10304E-05	0	1.00	452563	130	0.000287253	7	1.05
10-14	494511	8	1.61776E-05	0	1.00	471948	58	0.000122895	0	1.00
15-19	536852	16	2.79407E-05	1	1.07	511180	54	0.000105638	0	1.00
20-24	542817	16	2.76336E-05	1	1.07	525964	121	0.000230054	0	1.00
25-29	560319	32	5.53256E-05	1	1.03	545838	155	0.000283967	0	1.00
30-34	530554	35	6.59688E-05	0	1.00	522235	132	0.000250845	1	1.01
35-39	512925	19	3.70425E-05	0	1.00	512431	107	0.000204906	2	1.02

40-44	516723	38	6.77346E-05	3	1.09	521589	100	0.000191722	0	1.00
45-49	634188	75	0.000108801	6	1.09	634635	174	0.000272598	5	1.03
50-54	644223	118	0.000176957	4	1.04	635623	235	0.00035713	4	1.02
55-59	606130	169	0.000268919	6	1.04	605380	374	0.000597972	15	1.04
60-64	537540	227	0.000401831	11	1.05	542198	387	0.000671341	18	1.05
65-69	495875	368	0.000703806	19	1.05	503662	402	0.000770358	21	1.05
70-74	424486	488	0.001036548	48	1.11	447439	528	0.001115236	27	1.05
75-79	273902	477	0.001595461	40	1.09	314838	588	0.001715168	41	1.08
80-84	172825	379	0.002065673	22	1.06	235430	567	0.002229962	38	1.07
≥ 85	122648	400	0.003000457	32	1.09	248011	879	0.003306305	59	1.07
Total	**8527041**	**2908**	**0.000341**	**194**	**1.07**	**8654043**	**5114**	**0.000591**	**239**	**1.05**

**Defined as a UTI occurring more than 3 months after another UTI*