Supplementary file 3 - additional information relating to the economic evaluation

~~Appendix 12:~~1. Review of existing economic evaluations

~~A12~~1.1 Introduction and objectives

A series of reviews of existing cost-effectiveness evidence and modelling approaches was conducted:

- A review of existing cost-effectiveness evidence for cefiderocol with a focus on studies that include decision-analytic models. The aims were to establish the ~~existance~~existence of potentially policy-relevant models to guide NICE and NHS decisions; and to identify relevant analytical methods and data sources.
- A review of existing approaches for resistance modelling in the target population. The aim of this review was to identify methods that could be adopted for this purpose in EEPRU's modelling.
- A review of existing cost-effectiveness models in HAP/VAP to understand modelling approaches and data sources.
- A review of existing cost-effectiveness models in cUTI. Again, the purpose was to understand modelling approaches and data sources.

~~A12~~1.2 Methods

Each review involved searches of bibliographic databases using standardized search terms, selection of studies using explicit inclusion criteria and data extraction using an agreed template. Details of the bibliographic databases that were searched are provided in Annex~~ 1 to this appendix~~.

~~A12~~1.3 Review 1: existing cost-effectiveness evidence for cefiderocol

The objective of the first review was to identify existing cost-effectiveness modelling studies of cefiderocol. A total of 89 potentially relevant papers or abstracts were identified for the review from the searches. All the publications were screened using their titles and abstracts. Of the 89 publications that were screened, 1 relevant abstract on cefiderocol was included and 88 were excluded. The major reasons for exclusion were that the studies did not include a decision analytic model, did not consider a relevant target population and/or were duplicates of other studies. Table ~~1Table 1~~ ~~Table 63~~ ~~Table 163~~summarises the included study. The only study identified was in the form of a poster and provided limited detail regarding the sources of clinical evidence and how these were used in the modelling.(1) This, together with the study's US focus, means it provides no basis to inform the current ~~evalution~~evaluation of cefidercol.

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Table 1: Summary of included cost-effectiveness studies of cefiderocol

Author, year	Country	Population (Pathogen)	Comparator	Strategies modelled	Did the model incorporate resistance?	Treatment Effect	Primary Evidence Source	Model Structure
Lopes 2020 (1)	United States	cUTI, HAP/VAP (*CR Acinetobacter baumannii, CR Pseudomonas aeruginosa, CR Enterobacterales, and intrinsically CR Stenotrophomonas maltophilia)*	Colistin based therapy; cefiderocol	Microbiology directed treatment	N	Clinical cure rate	Not available	Decision tree

~~A11~~1.4 Review 2: modelling studies considering resistance

A second review was conducted to identify published economic evaluations of AMs that attempted to quantify the effects of resistance, with a focus on resistance modelling. A total of 89 potentially relevant studies or abstracts were identified from the searches. All the publications were screened using their titles and abstracts after which 9 studies were publications were included in the review, which are described in **Table 2~~Table 2~~** ~~in Table 64~~.

Table 2: Summary of included resistance modelling studies

Author, year	Country	Population (Pathogen)	Intervention	Comparator
Chen et al 2019 (2)	Taiwan	cUTI *(E. Coli, K. Pneumoniae, Pseudomonas aeruginosa, P. Mirabilis)*	Ceftolozane/ tazobactam	Piperacillin/ tazobactam
Nelson 2019(3)	US	CRE BSI	Hypothetical	Hypothetical
Mewes 2019 (4)	US	Sepsis and lower respiratory tract infection (*C. Difficile)*	Procalcitonin-algorithm	Standard of care
Gordon 2020 (5)	UK	cUTI, cIAI, HAP (*E.Coli, Pneumoniae, Pseudomonas aeruginosa)*	Peperacillin/Tazobactam	Meropenem/(theoretical) new AM
Tichy et al 2020(6)	Italy	HAP/VAP (*K. pneumonia (37%), Pseudomonas aeruginosa (26%), E. cloacae (14%), E coli (12%), and H. influenzae (9%).)*	ceftazidime/avibactam	Meropenem

Simon et al 2019(7).	United States	CRE Pneumonia, BSI, *(K pneumoniae, Enterobacteriaceae)*		Colistin-based therapy
Kongnakorn et al 2019(8)	Italy	cIAIs *(Escherichia coli, Streptococcus anginosus group, Klebsiella pneumoniae, Bacteroides fragilis, Pseudomonas aeruginosa)*		Ceftolozane/tazobactam plus metronidazole; meropenem
Kongnakorn et al 2019(9)	Italy	cUTI *(Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Enterobacter cloacae)*		Imipenem
Nguyen et al 2019(10)	Netherlands	cUTI, cIAI, BSI *(Extended-spectrum beta-lactamase (ESBL)/AmpC-producing Gram-negative pathogens)*		Meropenem

AM, antimicrobial; BSI, bloodstream infection; cIAI, complicated intraabdominal infection; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia

The 5 studies modelling the cost-effectiveness of ceftazidime/avibactam (cefiderocol) did not assess the implications of changes in resistance over time. Three of these studies (6, 11),(9) made assumptions about the proportion of patients with resistant infection in the relevant population, and the impact of resistance on clinical parameters including cure rates. These studies also tried to reflect the wider set of existing therapies used in clinical practice by drawing on non-RCT evidence in the target population. The two remaining studies considered a broader evidence base than just regulatory trials to relate their analyses more directly to populations with a higher likelihood of pathogens resistant to existing therapies. Simon *et al* focused on the cost-effectiveness of cefiderocol in carbapenem-resistant *Enterobacteriaceae* pneumonia or bacteraemia, drawing on evidence from observational studies on the proportions of patients with different types of infection, mortality rates with the comparator (colistin-based) therapy and the absolute effect of cefiderocol on mortality.(7) Nguyen *et al* considered the cost-effectiveness of cefiderocol (and other carbapenem-sparing beta-lactams) compared to meropenem in cUTI or intra-abdominal infections in extended-spectrum beta-lactamase (ESBL)/AmpC-producing pathogens which have a high risk of carbapenem resistance.(10) Both observational and RCT evidence was used for the analysis, although RCT evidence was used for the cefiderocol analysis which showed no significant difference in clinical cure versus meropenem with limited information about patients' resistance status.

The additional four studies provide some indications of how these effects could be captured. Chen *et al* considered alternative antibiotics for complicated UTI in the empiric setting.(2) They used a cohort study from a Taiwanese hospital to assess the appropriateness of each alternative empiric therapy based on clinical isolates. Specifically, each randomly drawn isolate from the cohort represents a specific patient in the model and their susceptibility to a given antibiotic was used to determine whether a patient remained on their initial therapy or switched to an alternative regimen or required salvage therapy.

In the economic evaluation of Procalcitonin-guided antibiotic stewardship, Mewes *et al* attempted to estimate the reduction in resistant infections resulting from the use of the biomarker.(4) The key parameter was an estimate of the correlation between the percentage reduction in days of antibiotic use resulting from use of the Procalcitonin-guided test and antibiotic resistance. This estimate was taken from secondary sources and the authors emphasised the weakness in the data.

The other two studies in this review attempted to deal with resistance through mechanistic infectious disease modelling. In a conference abstract, Nelson *et al* reported on the use of a compartmental model to show how the use of two hypothetical antibiotics for hospitalised patients with carbapenem-resistant *Enterobacteriaceae* (CRE) could reduce transmission of this pathogen.(3) The ultimate purpose of the analysis was to describe the methods necessary to capture the transmission value of such products and the magnitude of this effect compared to the direct benefits of treatment. Hypothetical data were only used for illustrative purposes.

The study by Gordon et al also used the combination of a dynamic transmission model and a treatment pathway model as a generic framework to evaluate up to three lines of antibiotics in different indications and pathogens.(5) This version of the model was applied to hospitalised patients in the UK with infections from a range of pathogens and in different sites. Transition parameters for the transmission model were derived using calibration from data from the English Surveillance Programme for AM Utilisation and Resistance (ESPAUR) and the Public Health Profiles Fingertips tool on utilisation. In principle, this model could be capable of quantifying not just the direct health effects of a new antibiotic, but also the indirect impacts via any reduction in transmission of relevant pathogens. It could also reflect changes in resistance over time in response to different stewardship strategies and the introduction of new AMs. However, whether the model can achieve this in practice will inevitably depend on the available evidence and the assumptions necessary given the evidence gaps.

~~A12~~1.5 Review 3: modelling studies focused on HAP/VAP

A targeted review was also conducted of models specifically in HAP/VAP to expand our understanding of models relating to this site of infection given its relevance to the HVCSs. A recent systematic literature review of models in HAP/VAP by Wenger et al was identified with searches conducted in 2017.(12) In addition, a targeted search of HAP/VAP models published since 2017 was conducted but no additional relevant studies were identified except for Tichy et al(6) from Review 2. The review by Wagner et al was used to extract information on the target population, modelling assumptions, model structure, clinical evidence, healthcare resource use, costs. This information is summarized in- **Table 3**~~**Table 3**~~~~Table 65~~.

Table 3: Summary of included HAP/VAP modelling studies based on in the review by Wagner et al *(12)*

Author, year	Country	Population (Pathogen)	Intervention	Comparator	Strategies modelled	Resistance considered (Y/N)	Treatment Effectiveness	Evidence Source	Model Structure
Edwards et al 2012(13)	UK	HAP	Meropenem	Piperacillin/ tazobactam	Following failure of 1st line antibiotics	N	Clinical response; Diarrhoea	Literature review and meta-analysis	Markov model
Grau et al 2013(14)	Spain	VAP	Linezolid	Vancomycin	Empiric	N	Clinical Cure, Survival Rates (for life-years and QALYs)	Retrospective analysis of RCTs	Decision Tree
Kongnakorn et al 2010(15)	US	Nosocomial Pneumonia	Doripenem	Imipenem	Empiric	Y	Number of seizures, number of cases of emerging *Pseudomonas aeruginosa* resistance, length of stay at hospital, transmissions	RCT, Published sources	Patient-level simulation model

Edwards *et al* compared meropenem and Piperacillin/ tazobactam for the treatment of pneumonia.(13) The cost-effectiveness modelling involved a standard Markov model with states based on location of care in hospital and mortality. Efficacy data were taken from a synthesis of RCT studies and allowance was made for relapse. Grau *et al* developed a decision tree model to evaluate linezolid compared with vancomycin in patients with VAP in Spain, distinguishing between different pathogens.(14) Efficacy data relating to clinical cure were taken from two RCTs and mortality was conditional on Acute Physiology And Chronic Health Evaluation (APACHE) scores and secondary data on long-term effects of a serious septic condition. Kongnakorn *et al* used discrete event simulation to model the cost-effectiveness of doripenem compared with imipenem in nosocomial pneumonia.(15) The model allowed for differences in baseline characteristics of nosocomial pneumonia type (without VAP, early-onset VAP, late-onset VAP) and PsA presence and PsA resistance to the given drug. Efficacy and risk equations for hospital discharge and mortality were estimated from regulatory RCTs. The number of PsA transmissions was estimated based on the efficacy of treatment.

All of these studies include standard cost-effectiveness models that did not consider the impact of alternative therapies on resistance patterns over time. Kongnakorn *et al* attempted to include transmission rates in the modelling but this was not extrapolated to estimate population-level health effects.(15) As a UK study, Edwards *et al* provides some potentially useful evidence sources for the current evaluation.(13)

~~A12~~1.6 Review 4: modelling studies focused on cUTI

A targeted review of models specifically in cUTI was undertaken to better understand the relevance of existing modelling assumptions, model structure, model inputs to the HVCSs. In addition to the models in cUTI identified in Review 2,(1, 2, 5, 9, 10) we identified one additional study which is summarised in- **Table 4~~Table 4~~** ~~Table 66~~.

Kauf et al used a micro-simulation model to evaluate empiric ceftolozane/tazobactam compared with piperacillin/ tazobactam as empiric therapy for hospitalized with cUTI.(16) The model tracked patients over different assessment periods allowing for treatment switching as microbiological information becomes available. A surveillance dataset is used to sample isolates and to determine susceptibility to different treatments. Mortality rates and hospital length of stay were taken from a single study. Although modelling patients included those with resistant pathogens, no attempt was made to model the effects of resistance over time.

Table 4: Summary of included cUTI modelling studies in addition to those in Review 2

Author, year	Country	Population (Pathogen)	Intervention	Comparator	Strategies modelled	Resistance considered (Y/N)	Treatment Effectiveness	Evidence Source	Model Structure
Kauf 2017(16)	US	cUTI *(E. Coli, K. Pneumoniae, Pseudomonas aeruginosa, P. Mirabilis)*	Ceftolozane/ tazobactam	Piperacillin/ tazobactam	Empiric	Y	Clinical cure; appropriate therapy	Susceptibility data from the PACTS dataset - Real-World Evidence	Patient-level simulation

cUTI, complicated urinary tract infection

Annex: ~~to Appendix 12:~~ Search strategies

Search of cost-effectiveness models

Searches for cost-effectiveness studies (either cefiderocol or cefiderocol) were conducted in MEDLINE, Embase, CRD and NHS EED. An additional search for HTA / regulatory agencies / conference proceedings was conducted using WoS. The search terms used are provided below.

Cefiderocol CEA models

Term group(s): Cefiderocol AND filter
Filters: Economic (MEDLINE, Embase), exclusion filter (Embase)
Limits: None

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 26, 2021 (searched via the Ovid SP platform)
1st March 2021

#	Searches	Results
1	cefiderocol.mp.	160
2	fetroja.mp.	4
3	fetcroja.mp.	0
4	rsc-649266.mp.	0
5	or/1-4	160
6	exp "Costs and Cost Analysis"/	242835
7	Economics/	27294
8	exp Economics, Hospital/	24969
9	exp Economics, Medical/	14242
10	Economics, Nursing/	4002
11	exp models, economic/	15443
12	Economics, Pharmaceutical/	2971
13	exp "Fees and Charges"/	30592
14	exp Budgets/	13800
15	budget*.tw.	30546
16	ec.fs.	431631
17	cost*.ti.	125579
18	(cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab.	157179
19	(economic* or pharmacoeconomic* or pharmaco-economic*).ti.	50939
20	(price* or pricing*).tw.	42703
21	(financial or finance or finances or financed).tw.	97358
22	(fee or fees).tw.	18704
23	(value adj2 (money or monetary)).tw.	2515
24	quality-adjusted life years/	12949
25	(qaly or qalys).af.	11325
26	(quality adjusted life year or quality adjusted life years).af.	19387
27	or/6-26	801858

28	5 and 27	0

Embase 1974 to 2021 February 26 (searched via the Ovid SP platform)
1st March 2021

#	Searches	Results
1	cefiderocol.mp.	278
2	fetroja.mp.	9
3	fetcroja.mp.	1
4	rsc-649266.mp.	0
5	or/1-4	278
6	"cost benefit analysis"/	87111
7	"cost effectiveness analysis"/	158540
8	economics/	241957
9	health economics/	33700
10	pharmacoeconomics/	7505
11	fee/	14329
12	budget/	30564
13	budget$.tw.	40639
14	cost$.ti.	168111
15	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.	218259
16	(economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.	64563
17	(price$ or pricing$).tw.	60859
18	(financial or finance or finances or financed).tw.	135326
19	(fee or fees).tw.	25728
20	(value adj2 (money or monetary)).tw.	3455
21	health care quality/	247699
22	quality adjusted life year/	28517
23	(qaly or qalys).tw.	21188
24	(quality adjusted life year or quality adjusted life years).tw.	20472
25	or/6-24	1102354
26	letter.pt.	1185036
27	editorial.pt.	691062
28	historical article.pt.	0
29	or/26-28	1876098
30	25 not 29	1021484
31	animals/	1253461
32	humans/	13458185
33	31 not (31 and 32)	965742
34	30 not 33	1010813
35	5 and 34	3

CRD database (searched via the University of York CRD platform)
1st March 2021

#	Searches	Results
1	(cefiderocol)	0

2	(fetroja)	0
3	(fetcroja)	0
4	(rsc-649266)	0

Web of Science - Conference proceedings index (searched via the Clarivate Analytics platform)
1st March 2021

#	Searches	Results
# 1	TOPIC: (cefiderocol)	8
# 2	TOPIC: (fetroja)	0
# 3	TOPIC: (fetcroja)	0
# 4	TOPIC: (rsc-649266)	0
# 5	#4 OR #3 OR #2 OR #1	8

CAZ/AVI CEA models

Term group(s): CAZ/AVI AND filters
Filters: Economic (MEDLINE, Embase), Exclusion (Embase)
Limits: None

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 26, 2021 (searched via the Ovid SP platform)
1st March 2021

#	Searches	Results
1	ceftazidime.mp.	10210
2	Ceftazidime/	4047
3	1 or 2	10210
4	avibactam.mp.	964
5	3 and 4	789
6	ceftazidime-avibactam.mp.	711
7	zavicefta.mp.	2
8	avycaz.mp.	8
9	(ctz-avi or **cefiderocol**).mp.	65
10	or/5-9	792
11	exp "Costs and Cost Analysis"/	242835
12	Economics/	27294
13	exp Economics, Hospital/	24969
14	exp Economics, Medical/	14242
15	Economics, Nursing/	4002
16	exp models, economic/	15443
17	Economics, Pharmaceutical/	2971
18	exp "Fees and Charges"/	30592
19	exp Budgets/	13800
20	budget*.tw.	30546
21	ec.fs.	431631

22	cost*.ti.	125579
23	(cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab.	157179
24	(economic* or pharmacoeconomic* or pharmaco-economic*).ti.	50939
25	(price* or pricing*).tw.	42703
26	(financial or finance or finances or financed).tw.	97358
27	(fee or fees).tw.	18704
28	(value adj2 (money or monetary)).tw.	2515
29	quality-adjusted life years/	12949
30	(qaly or qalys).af.	11325
31	(quality adjusted life year or quality adjusted life years).af.	19387
32	or/11-31	801858
33	10 and 32	16

Embase 1974 to 2021 February 26 (searched via the Ovid SP platform)
1st March 2021

#	Searches	Results
1	ceftazidime.mp.	45327
2	ceftazidime/	43189
3	1 or 2	45327
4	avibactam.mp.	1893
5	3 and 4	1609
6	ceftazidime-avibactam.mp.	955
7	zavicefta.mp.	18
8	avycaz.mp.	62
9	(ctz-avi or **cefiderocol**).mp.	156
10	or/5-9	1618
11	"cost benefit analysis"/	87111
12	"cost effectiveness analysis"/	158540
13	economics/	241957
14	health economics/	33700
15	pharmacoeconomics/	7505
16	fee/	14329
17	budget/	30564
18	budget$.tw.	40639
19	cost$.ti.	168111
20	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.	218259
21	(economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.	64563
22	(price$ or pricing$).tw.	60859
23	(financial or finance or finances or financed).tw.	135326
24	(fee or fees).tw.	25728
25	(value adj2 (money or monetary)).tw.	3455
26	health care quality/	247699
27	quality adjusted life year/	28517
28	(qaly or qalys).tw.	21188
29	(quality adjusted life year or quality adjusted life years).tw.	20472
30	or/11-29	1102354

31	letter.pt.	1185036
32	editorial.pt.	691062
33	historical article.pt.	0
34	or/31-33	1876098
35	30 not 34	1021484
36	animals/	1253461
37	humans/	13458185
38	36 not (36 and 37)	965742
39	35 not 38	1010813
40	10 and 39	56

CRD database (searched via the University of York CRD platform)
1st March 2021

#	Searches	Results
1	(ceftazidime)	49
2	(avibactam)	0
3	(ceftazidime-avibactam)	0
4	(zavicefta)	0
5	(avycaz)	0
6	((ctz-avi or **cefiderocol**))	0

Web of Science - Conference proceedings index (searched via the Clarivate Analytics platform)
1st March 2021

#	Searches	Results
# 1	TOPIC: (ceftazidime)	9,711
# 2	TOPIC: (avibactam)	1,167
# 3	#2 AND #1	984
# 4	TOPIC: (ceftazidime-avibactam)	919
# 5	TOPIC: (zavicefta)	2
# 6	TOPIC: (avycaz)	6
# 7	TOPIC: ((ctz-avi or **cefiderocol**))	59
# 8	#7 OR #6 OR #5 OR #4 OR #3	14

Search of economic evaluations of AMs that have explicitly modelled resistance

Searches were conducted in Medline, Embase and CRD.

Term group(s): Focused AM resistance AND modelling AND filter
Filters: Pragmatic economic filter (MEDLINE, Embase)
Limits: 2011-present, English language

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to March 31, 2021 (searched via the Ovid SP platform)
1st April 2021

#	Searches	Results

1	((AM or antibiotic or antibacterial) and resistan*).mp.	148175
2	(model* or "population dynamic*" or simulat*).ti.	718508
3	1 and 2	2671
4	limit 3 to yr="2011 -Current"	1901
5	limit 4 to english language	1884
6	Cost-benefit analysis/	83842
7	Economic value of life/	5741
8	Quality-adjusted life years/	13042
9	exp models, economic/	15508
10	cost utilit$.tw.	4939
11	cost benefit$.tw.	11329
12	cost minim$.tw.	1563
13	cost effect$.tw.	143618
14	economic evaluation$.tw.	12455
15	or/6-14	213673
16	5 and 15	26

Embase 1974 to 2021 March 31 (searched via the Ovid SP platform)
1st April 2021

#	Searches	Results
1	((AM or antibiotic or antibacterial) and resistan*).mp.	298764
2	(model* or "population dynamic*" or simulat*).ti.	863662
3	1 and 2	4531
4	limit 3 to yr="2011 -Current"	3042
5	"cost benefit analysis"/	86983
6	Economic value of life/	145299
7	quality adjusted life year/	28664
8	exp economic model/	2513
9	cost utilit$.tw.	7843
10	cost benefit$.tw.	15750
11	cost minim$.tw.	2664
12	cost effect$.tw.	198907
13	economic evaluation$.tw.	17713
14	("quality adjusted life year*" or qaly or qalys).tw.	26170
15	or/5-14	433603
16	4 and 15	67

CRD database (searched via the University of York CRD platform)
1st April 2021

#	Searches	Results
1	(((AM or antibiotic or antibacterial) and resistan*))	459
2	((model* or "population dynamic*" or simulat*)):TI	1554
3	#1 AND #2	8
5	(#3) FROM 2011 TO 2021	2

~~Appendix 17:~~2. Transmission model linking usage to resistance

~~A17~~2.1 Methods

Population

The target population was people in hospital who would be eligible for susceptibility testing. We assumed that at the start of the model these people are either exposed to or colonised with the bacteria of interest, and at the end of the model have clearance of their colonisation, death, or discharge from hospital.

Mathematical model

We developed a statistical model to quantify the parameters driven the dynamics of the gain and loss of bacteria that are resistant to AMs. We aimed to apply the model when there is insufficient evidence in the literature to directly identify drivers of resistance and estimate their impact. In particular, this model focused on the impact of AM use on AM resistance

Key assumptions and components.

- The proportional resistant for both incidence and prevalence are identical.
- The effects of demographic dynamics can be ignored.
- Resistance gained from transmission is considered with natural mutation (no transmission modelcomponent)

Equations

$$\frac{dX}{dt} = qX - \vartheta X - \delta TX + \sigma Y - \gamma_x X$$
$$= -\delta TX + (q - \vartheta - \gamma_x)X + \sigma Y$$
$$\frac{dY}{dt} = qY + \vartheta X + \delta TX - \sigma Y - \gamma_y Y$$
$$= \delta TX + \vartheta X + (q - \sigma - \gamma_y)Y$$
$$X = \pi_t \times (1 - P(Res))$$
$$Y = \pi_t \times P(Res)$$

where X and Y indicate the prevalence of infected people bacteria without and with drug resistancerespectively and T denote the use of AM; $P(Res)$ is proportional resistant sourcing from data.

Parameters

π_t prevalence of the eligible population at
time tq ratio of incidence over prevalence
ϑ rate of resistance development due to natural mutation
δ rate of resistance amplification due to respective AM treatment
σ rate of resistance loss
γ_x outflow rate of the drug susceptible, including self-clearance, death, treatment successful.
γ_y outflow rate of the drug resistant, including self-clearance, death, treatment successful.

Empirical model

We discretised the above differential equations with a central difference approach. That is, we cananalogue a differential equation model with a difference equation:

$$\frac{du}{dt} = f(t)$$

$$\Rightarrow \frac{u_{t+\Delta t} - u_t}{\Delta t} = f(t + \frac{\Delta t}{2}) \sim \frac{f(t + \Delta t) + f(t)}{2}$$

Therefore, our model can be reformatted as

$$\frac{X_{t+\Delta t} - X_t}{\Delta t} = -\delta \overline{TX_t} + (q - \theta - \gamma_x)\overline{X_t} + \sigma \overline{Y_t}$$
$$\frac{Y_{t+\Delta t} - Y_t}{\Delta t} = \delta \overline{TX_t} + \theta \overline{X_t} + (q - \sigma - \gamma_y)\overline{Y_t}$$

where = $(X_{t+\Delta t} + X_t)/2$, = $(Y_{t+\Delta t} + Y_t)/2$, and = $(X_{t+\Delta t}T_{t+\Delta t} + X_tT_t)/2$; $\Delta t = 1$ for annually data and $\Delta t = 0.25$ for quarterly data. The model was programmed in R.(17)

~~A17.~~2.1.1 The Bayesian approach

We proposed the following Bayesian model with the time-series data of onset rates (Λ), proportionalresistant $P(Res)$, ~~and .~~and.

Priors for the parameters with the log-Normal distribution

$\pi \sim Uniform(0, 1)$

$\delta \sim LogNormal(0, 1)$

$\sigma \sim LogNormal(0, 1)$

$\gamma_x \sim LogNormal(0, 1)$

$\gamma_y \sim LogNormal(0, 1)$

Priors for random errors with the inverse-Gamma distribution

$E_x \sim InvGamma(1, 1)$

$E_y \sim InvGamma(1, 1)$

$\omega \sim InvGamma(1, 1)$

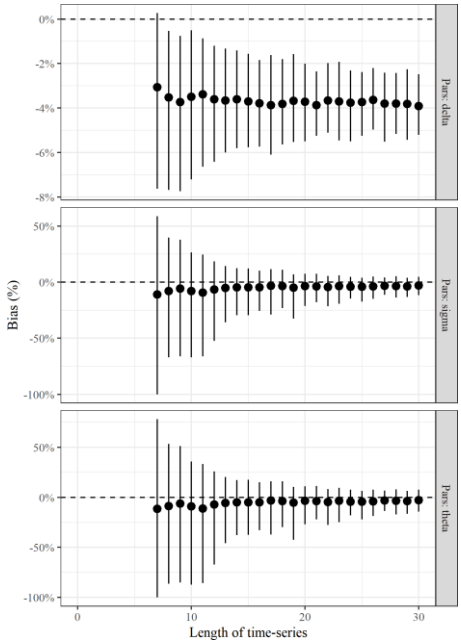
Main model fitting to data We fixed q at 1 (or any other value with exogenous data source) for ensuring the identifiability of the other parameters. The main model links the parameters to data.

$$\mu_{x,t} = -\delta \overline{TX_t} + (q - \theta - \gamma_x)\overline{X_t} + \sigma \overline{Y_t}$$
$$\mu_{y,t} = \delta \overline{TX_t} + \theta \overline{X_t} + (q - \sigma - \gamma_y)\overline{Y_t}$$
$$\frac{X_{t+\Delta t} - X_t}{\Delta t} \sim Normal(\mu_{x,t}, \epsilon_x)$$
$$\frac{Y_{t+\Delta t} - Y_t}{\Delta t} \sim Normal(\mu_{y,t}, \epsilon_y)$$
$$\Lambda \sim Normal(q\pi_t, omega)$$

~~A17~~2.2 Results: simulation study

We started with a simulation study for checking (1) sample size needed for this model and (2) potentialbias of the parameter estimators. Firstly, we started with a parameter set of (*theta* = 0.02, *delta* = 0.02, *sigma* = 0.05) and tested the bias in percentage. Figure 1~~Figure 150~~~~Figure 50~~ shows that the model estimators start to converge when the lengths of time-series larger than 15.

Figure 1~~150~~: Length of time-series and convergence



Then, we expanded the parameter space with $\vartheta \in (0.01, 0.05)$, $\delta \in (0.01, 0.05)$, and $\sigma \in (0.01, 0.1)$ to check if the model can provide unbiased estimators. Figure 2~~Figure 251~~~~Figure 51~~ and Figure 4~~Figure 453~~~~Figure 53~~ demonstrate that ϑ and σ are unbiased while Figure 3~~Figure 352~~~~Figure 52~~ suggests that there is a system bias of δ causing underestimation.

Figure 2~~251~~: Resistance development, natural mutation (θ)

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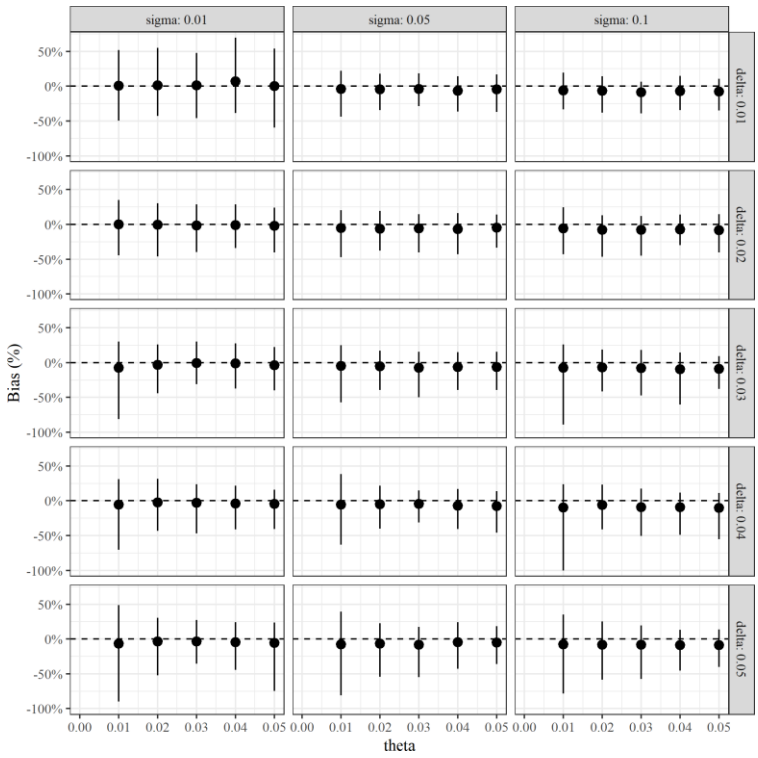


Figure 3~~3~~~~52~~: Resistance loss (σ)

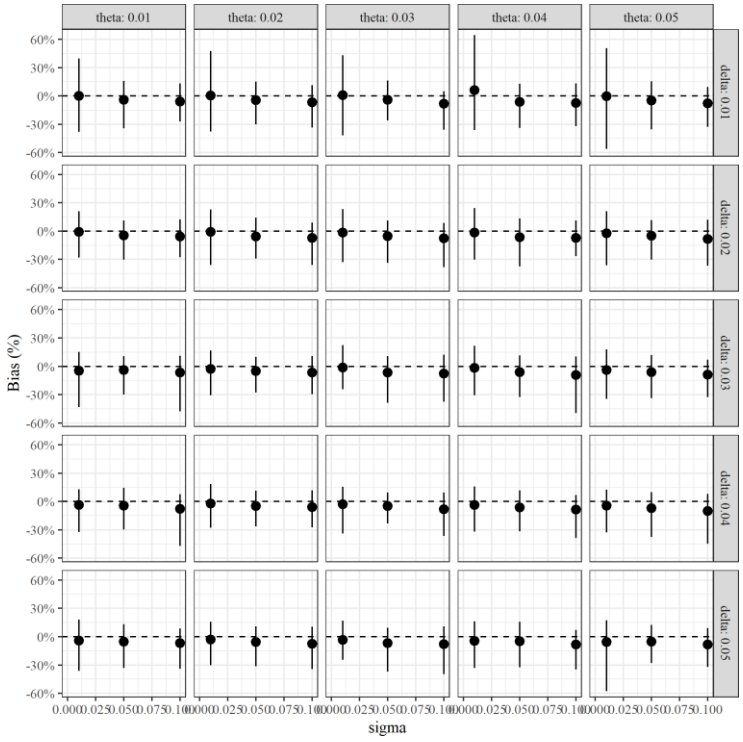
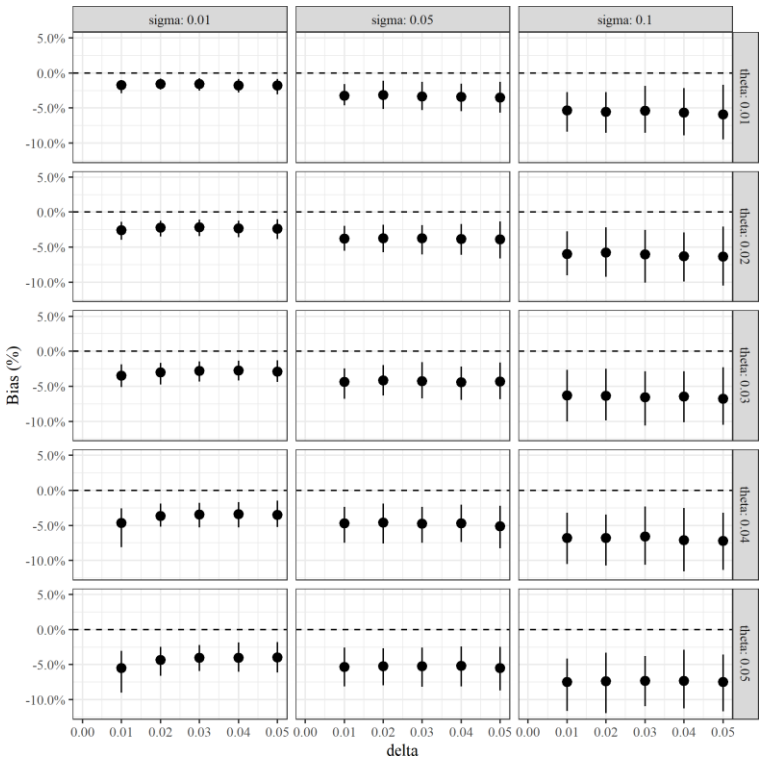


Figure 4453: Resistance development, amplification (δ)



~~Appendix 18:~~3. Implementing the relationship between drug use and resistance~~.~~

For illustration, this will use the estimated strong association value from the Escherichia coli analyses (coefficient of 10.11). The following steps were implemented:

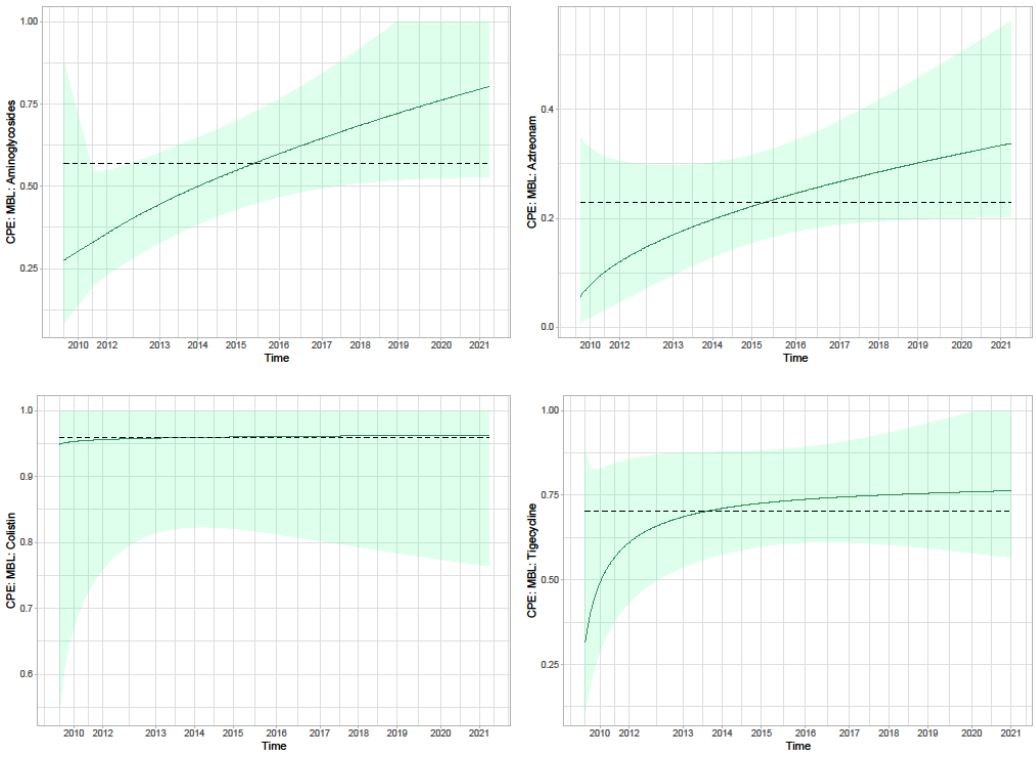
- Obtain estimates of the numbers treated per year with cefiderocol. The derivation of these estimates is described in the main text. This was done separately for the two clinical sites of cUTI and HAP/VAP. To obtain an extreme estimate of the impact of AM use on resistance, it was assumed that these sites also included:
    - For cUTI, IAI was also included.
    - For HAP/VAP, BSI was also included.
    - For the MBL *Enterobacterales* population, stenotrophomonas were also included.
- The impact of these assumptions ~~were~~was to concentrate all of the increase in resistance (due to use amongst a broad patient population) in the HVCS.
- Evidence on duration of treatment was taken from Section 8.2.3.6, with no difference by pathogen (CPE or psuedomona).
- It was assumed that multiplying the number of people treated by their duration of treatment and dividing by 365.25 would provide the defined daily doses per day. To support this assumption, the recommended indications for each AM in the British National Formulary (BNF) were compared with defined daily doses (DDDs) provided by the World Health Organization (WHO). The two were deemed to be sufficiently similar. For example, for colistin (colistimethate sodium) the BNF provides an indication of 9 million units daily by intravenous infusion for adults with “serious infections due to selected aerobic Gram-negative bacteria in patients with limited treatment options”. This is the same as the DDD for colistin provided by the WHO. Similarly, the BNF indication for tigecycline is 0.1g per day by intravenous infusion for “complicated intra-abdominal infections (when other antibiotics are not suitable)”. This is again the same as the WHO DDD.
- This value was then multiplied by 1,000 and divided by the Office for National Statistics' Mid-Year Population Estimate for the United Kingdom (June 2020). The value for the entire population was used (67,081,234) for consistency with the definition of AM use provided by ESAC-Net.
- The year-on-year increase in resistance was calculated by ~~mutliplying~~multiplying the year-on-year increase in AM use (DDD per 1,000 inhabitants) by the coefficient of 10.11. This provided the absolute increase in resistance. It was assumed that to begin with there was no use of cefiderocol. This will be a slight under-estimate and hence the subsequent increase in

resistance will be a slight over-estimate.

This approach led to estimated very small increases in resistance: over 20 years the resistance to cefiderocol increased by 0.12% 1.38%. Hence alternative scenarios were considered to explore more extreme increases in resistance over time. An exploratory analysis used the same surveillance data (used to estimate the relationship between AM use and resistance) to inform absolute rates of change in susceptibility over time. This was motivated by noting that there are several potential drivers for AM resistance beyond AM use. For each country a linear regression was fit with resistance level as the outcome (range 0 to 100) and time in years as the independent variable. The statistical significance of the trend coefficient was used to identify countries for which there was a significant increase in resistance over time during the period for which data was available. Statistical significance was originally taken to be a p-value of less than 0.05. Of these significant associations, the most extreme (largest trend coefficient) was used to represent an extreme scenario of growth in susceptibility. For the Escherichia coli cephalosporins, all of the regressions were statistically significant, with trend coefficients ranging ~~form~~from 0.41 (Malta) to 1.65 (Bulgaria). The only significant positive association for the Escherichia coli carbapenems was for Greece (0.04). Hence, for the CPE analyses an increase in resistance of 1.65% per year was used.
For the *pseudomonas* the only significant positive association was for the Netherlands (0.17). However, the value for Slovenia (0.83) was almost five times larger, with a p-value of 0.07. Hence for *pseudomonas* an increase in resistance of 0.83% per year was used. Employing these absolute increases led to an absolute twenty-year increase in resistance of 33.07% (for the CPE population) and 16.57% for the *pseudomonas* population. The second largest increase over 20 years was 19% for Greece. As a result, a twenty-year increase of 30% was viewed to represent the most extreme possible increase in resistance. ~~Hence~~Hence, we considered scenarios in which the twenty-year increase in resistance to cefiderocol was 1%, 5%, 10%, and 30%.

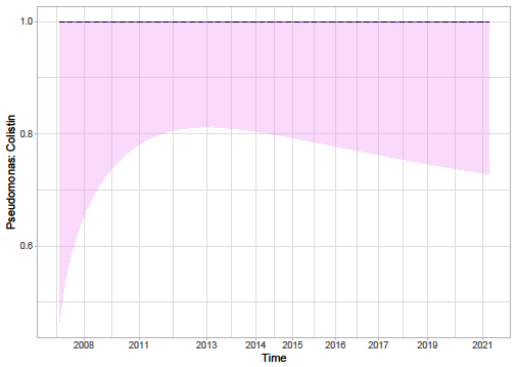
~~Appendix 19:~~4. Plots of AM resistance over time: Public Health England data~~.~~

Figure ~~55~~54: Resistance over time in CPE-MBL



CPE, carbapenemase-producing Enterobacterales ;MBL, metallo-beta-lactamase

Figure ~~66~~55: Resistance over time in *Pseudomonas*



~~Appendix 20:~~5. Plots of AM resistance over time: surveillance data.

Figure ~~77~~56: *E. coli* resistance to carbapenems in France

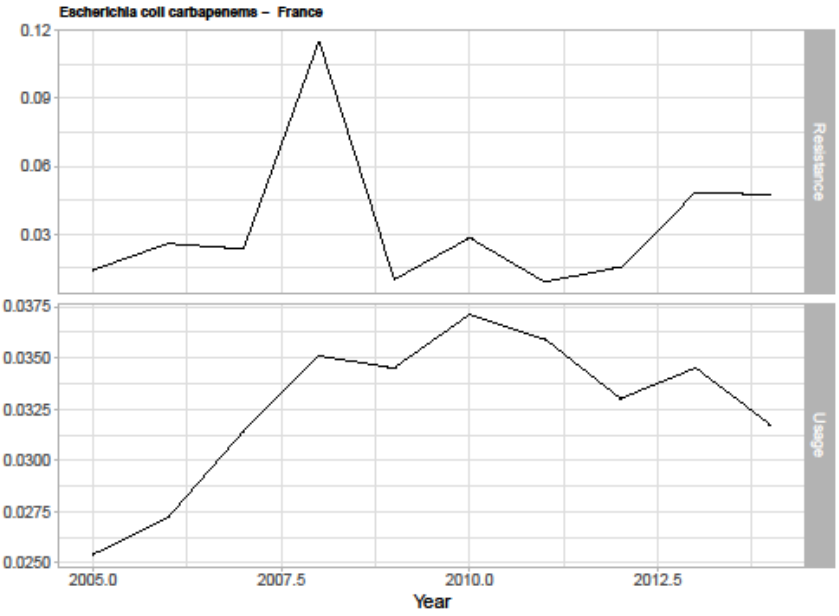


Figure ~~88~~57: *E. coli* resistance to carbapenems in Greece

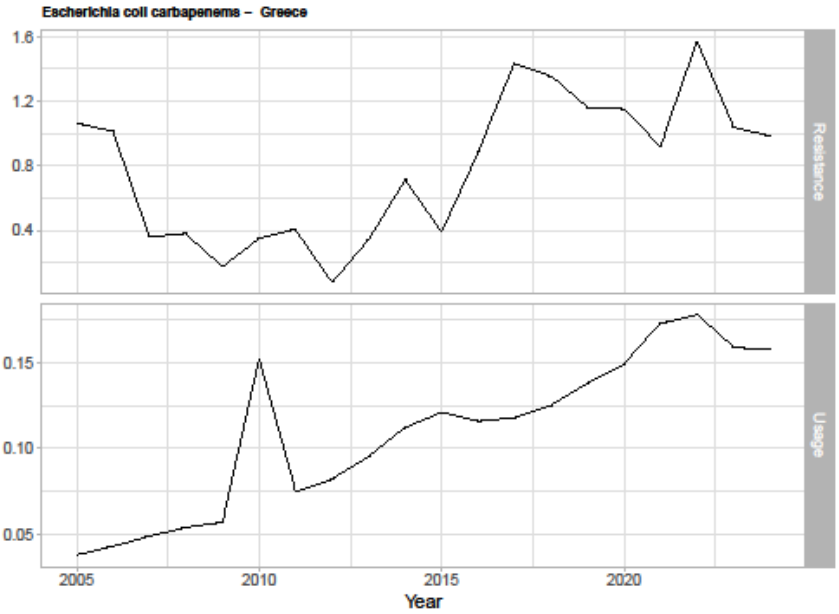


Figure 9958: *E. coli* resistance to carbapenems in the Netherlands

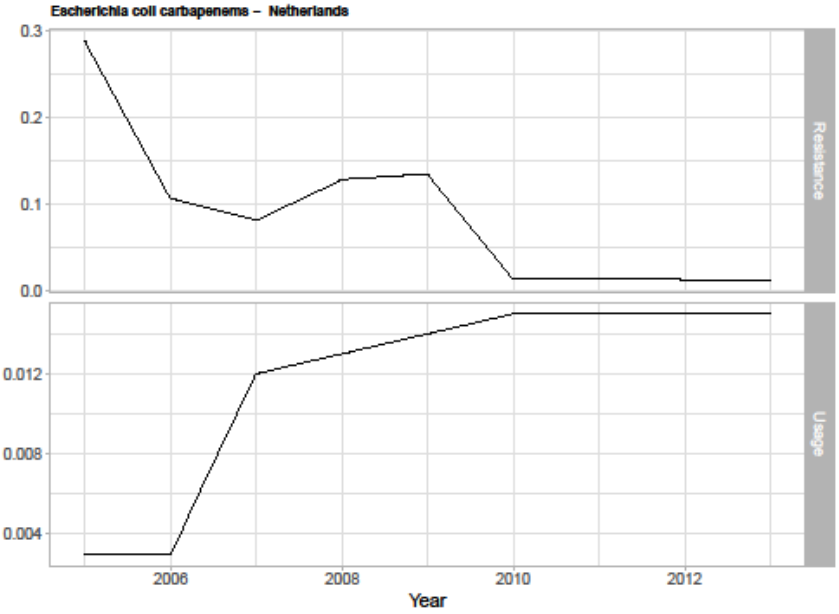


Figure 101059: *E. coli* resistance to carbapenems in Norway

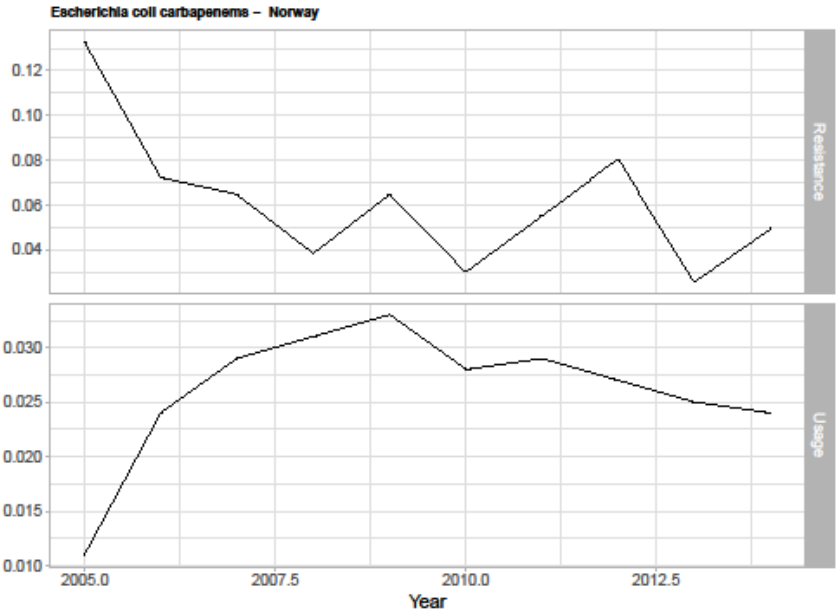


Figure 11~~160~~: *E. coli* resistance to cephalosporins in Bulgaria

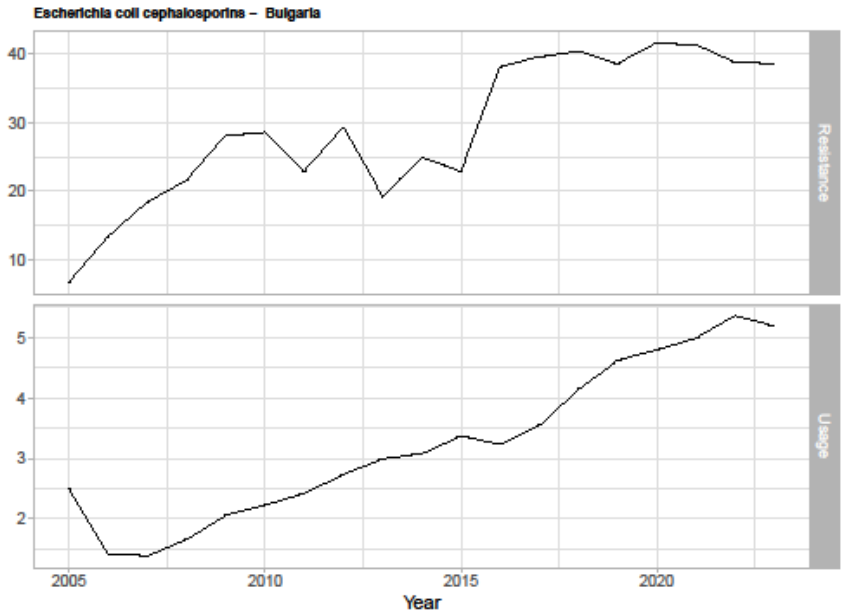


Figure 12~~261~~: *E. coli* resistance to cephalosporins in Croatia

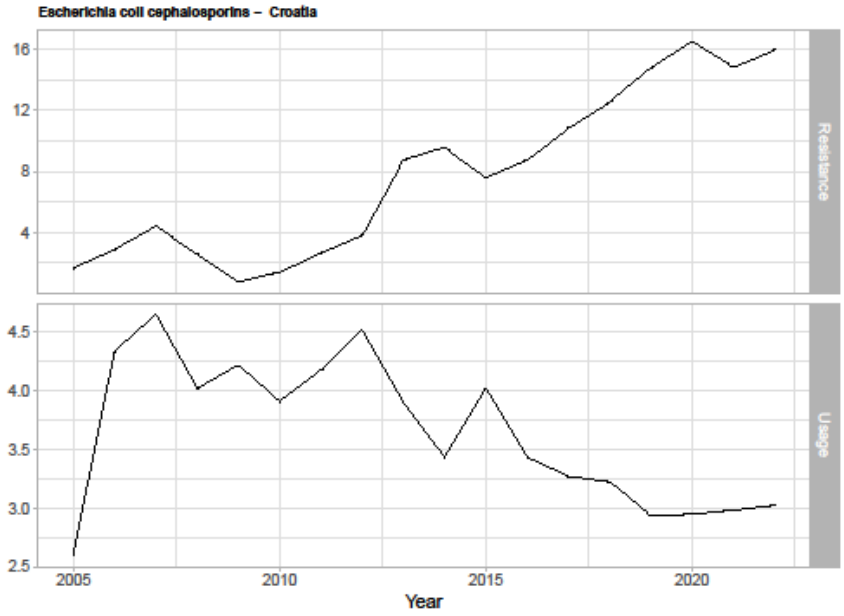


Figure 13~~1362~~: *E. coli* resistance to cephalosporins in Estonia

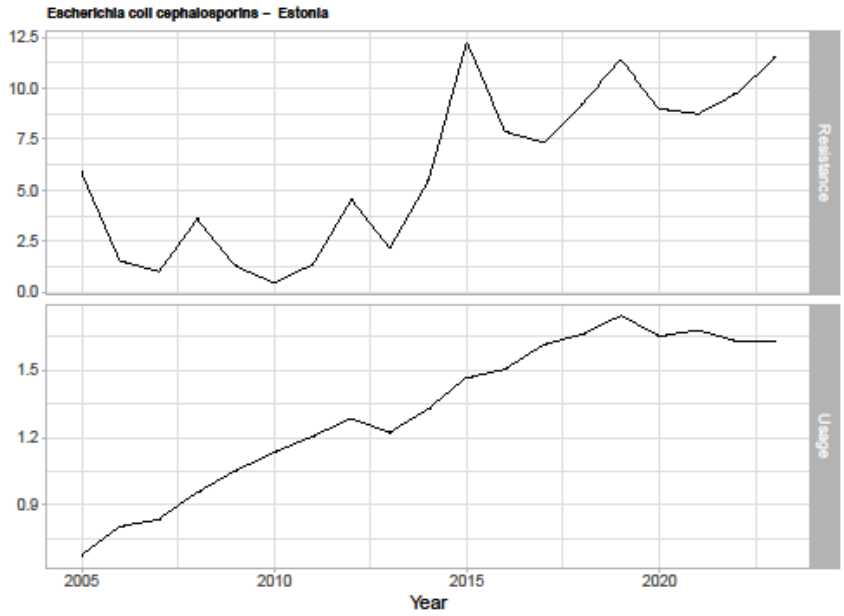


Figure 14~~1463~~: *E. coli* resistance to cephalosporins in Finland

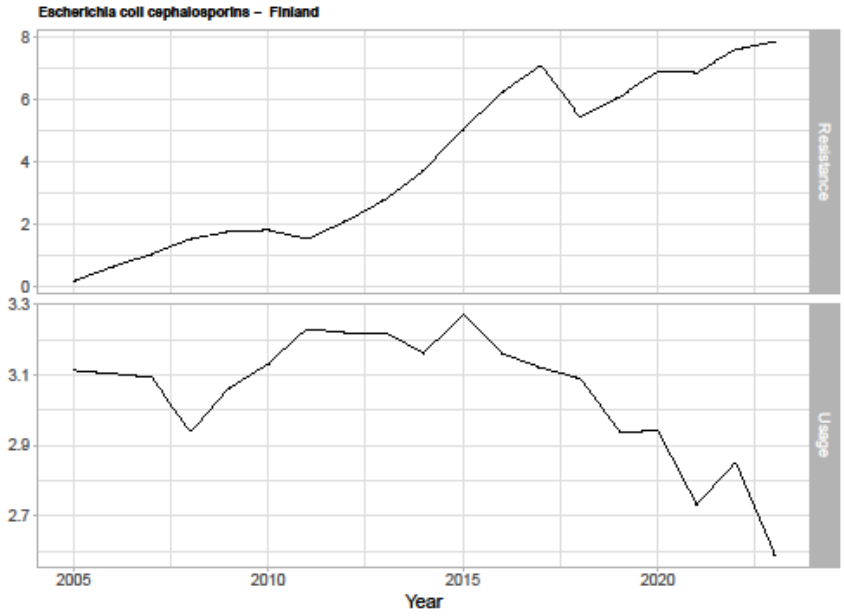


Figure 151~~564~~: *E. coli* resistance to cephalosporins in France

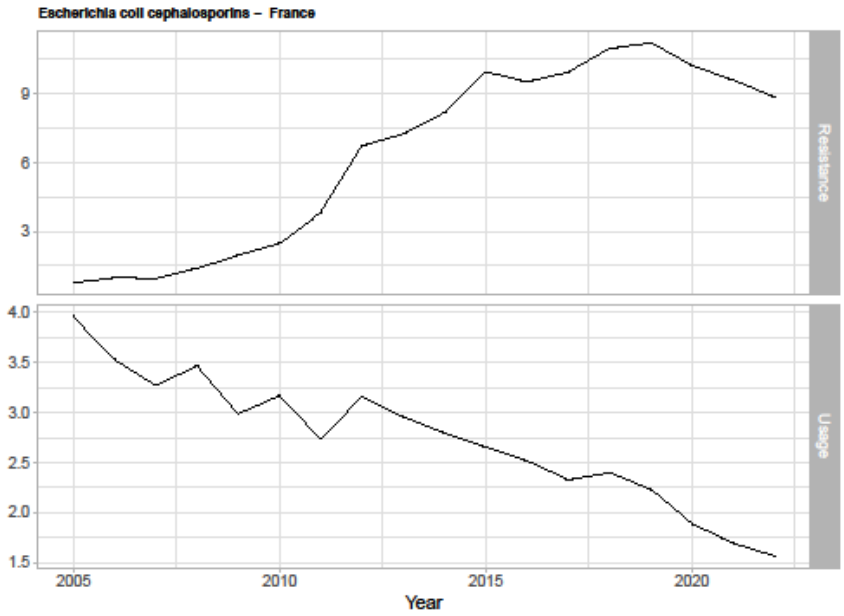


Figure 161~~665~~: *E. coli* resistance to cephalosporins in Greece

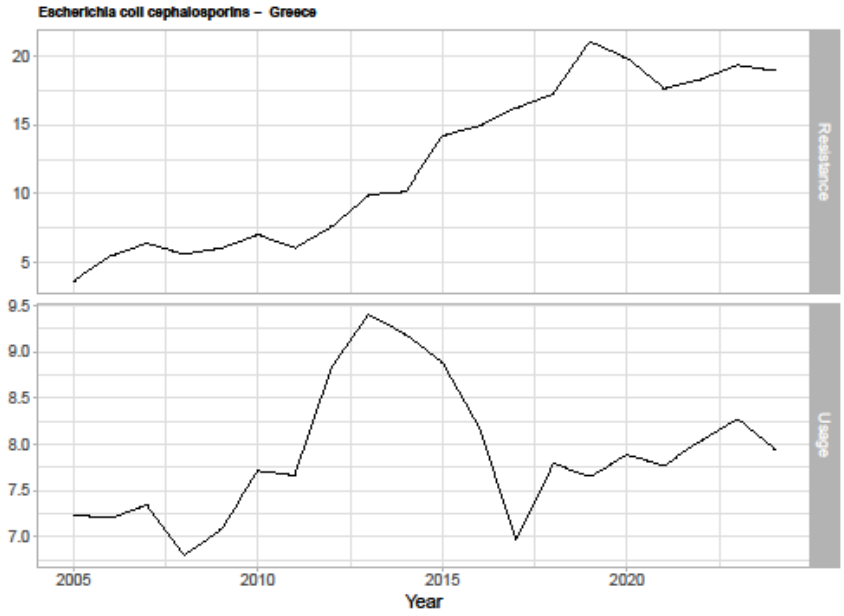


Figure 171~~766~~: *E. coli* resistance to cephalosporins in Ireland

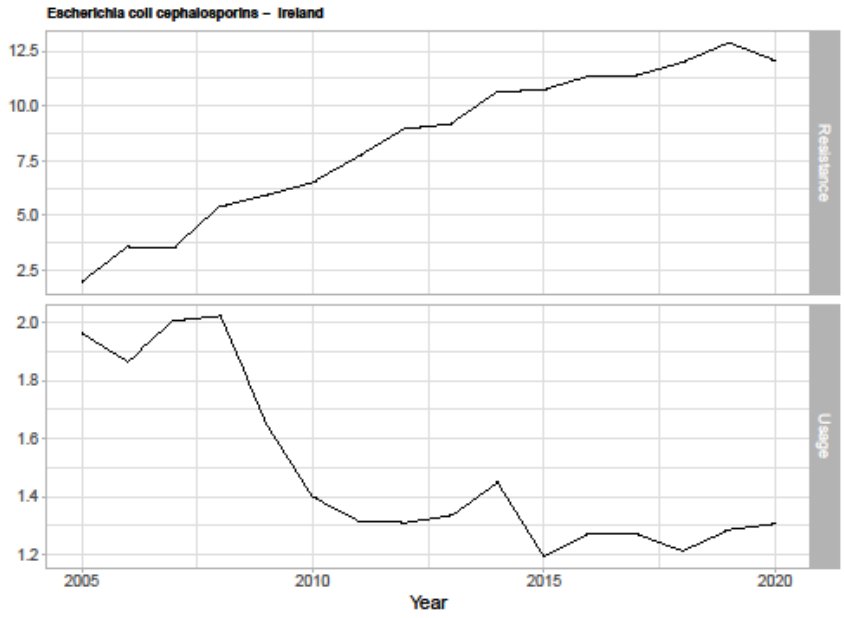


Figure 181~~867~~: *E. coli* resistance to cephalosporins in Luxembourg

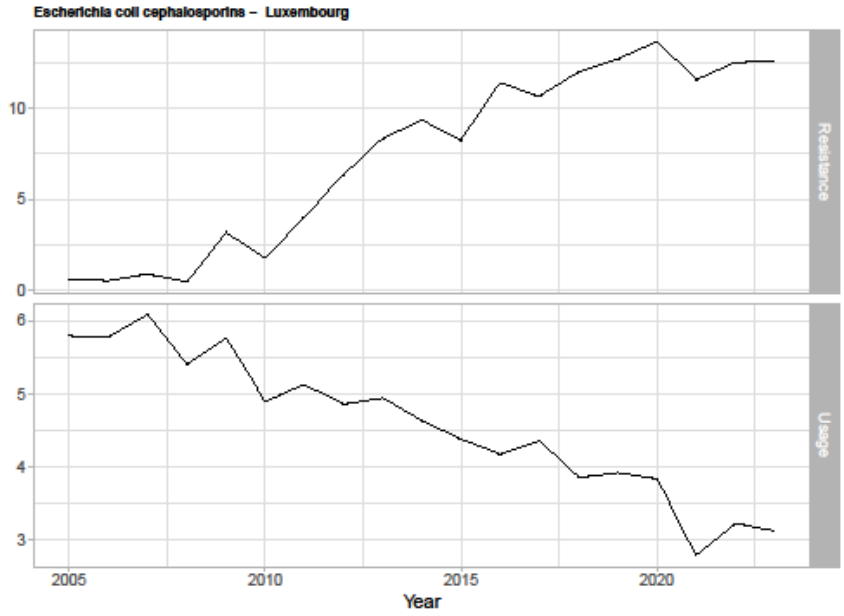


Figure 191~~968~~: *E. coli* resistance to cephalosporins in Malta

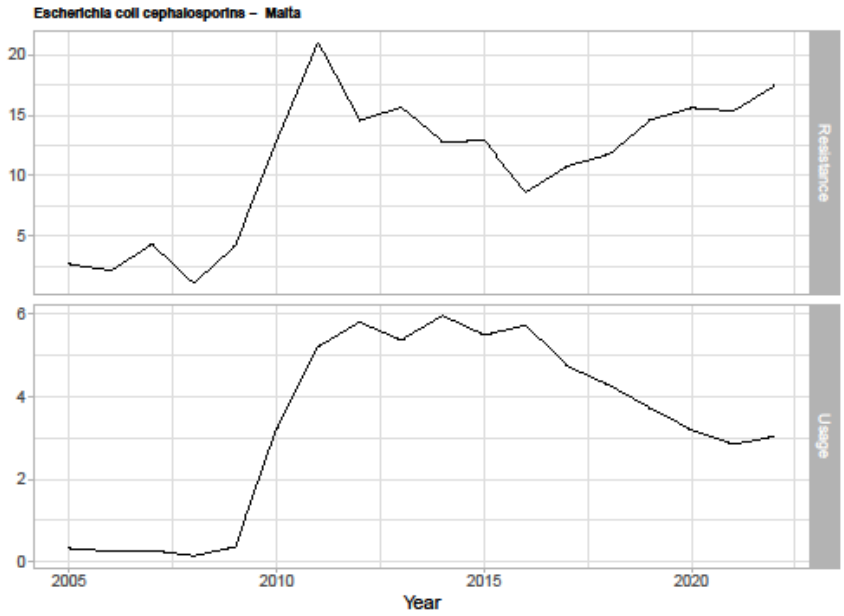


Figure 202~~069~~: *E. coli* resistance to cephalosporins in Norway

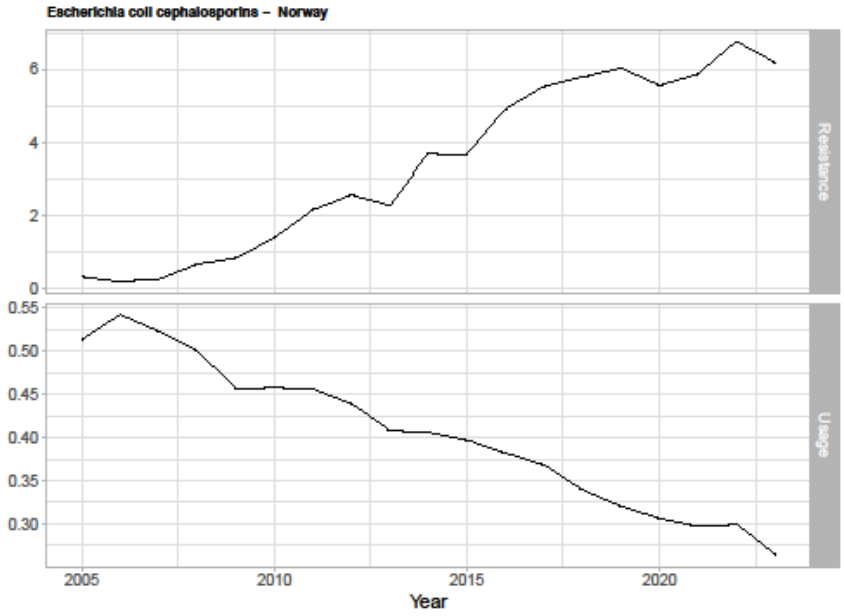


Figure 21~~21~~~~70~~: *E. coli* resistance to cephalosporins in Slovenia

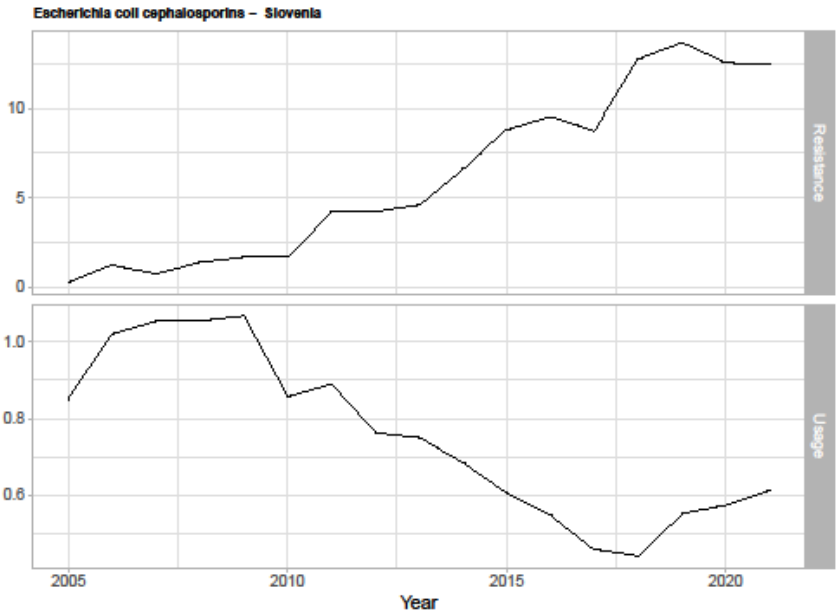


Figure 22~~22~~~~71~~: *E. coli* resistance to cephalosporins in Sweden

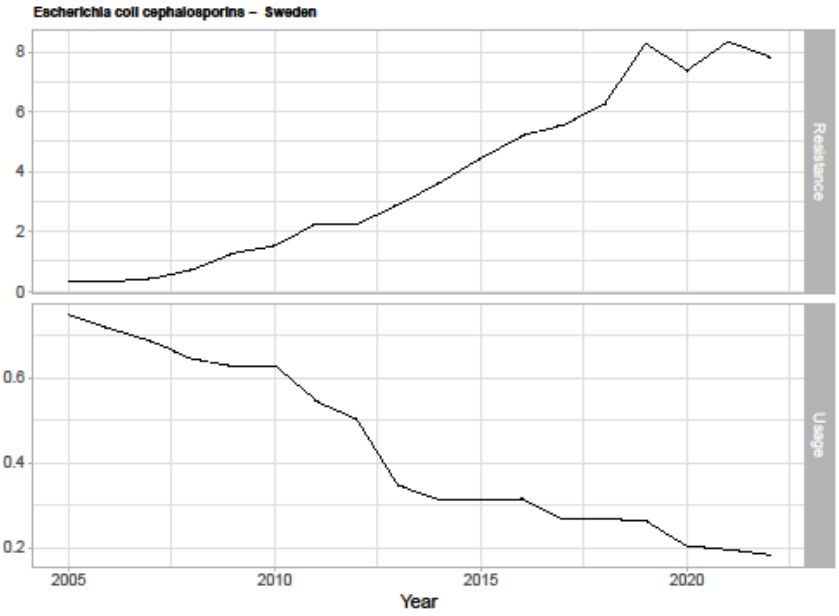


Figure 23~~22~~~~72~~: *Pseudomonas* resistance in France

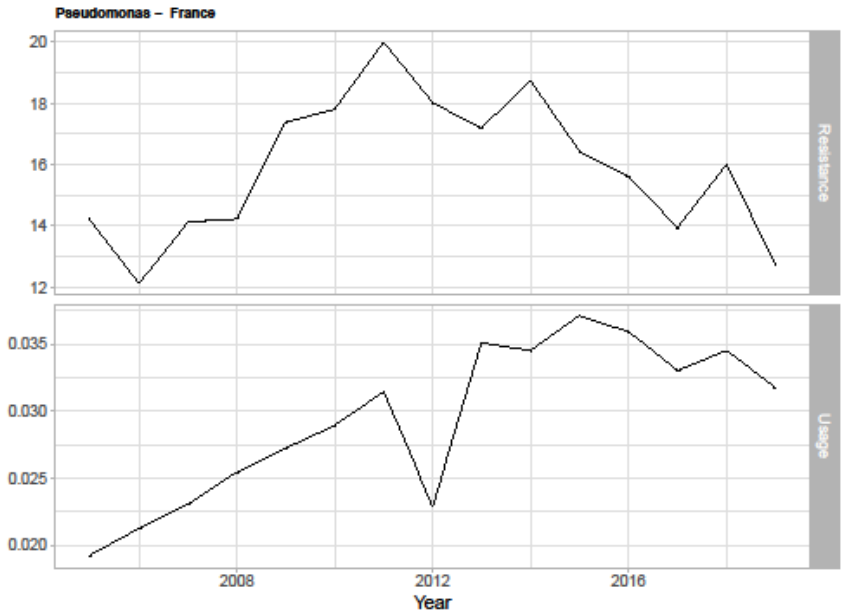


Figure 24~~22~~~~73~~: *Pseudomonas* resistance in Finland

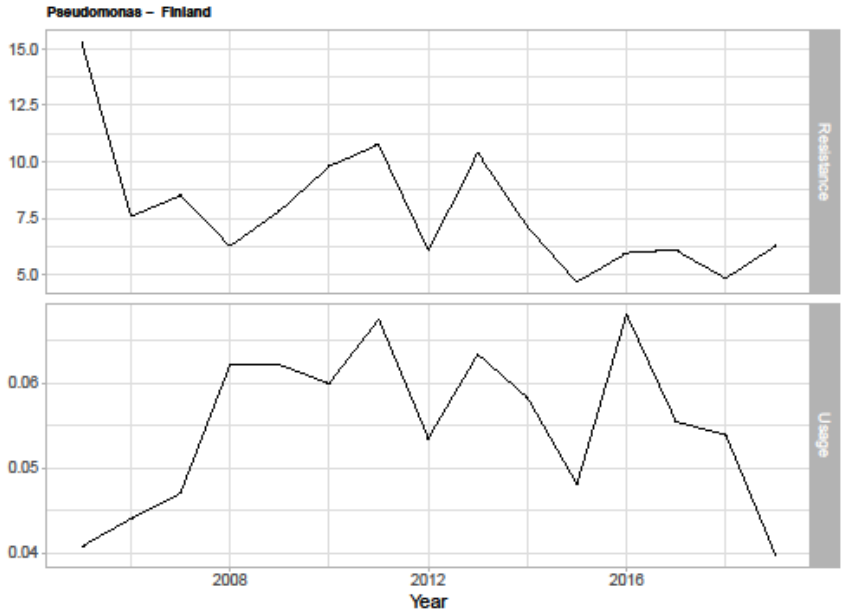


Figure 25~~25~~74: *Pseudomonas* resistance in Ireland

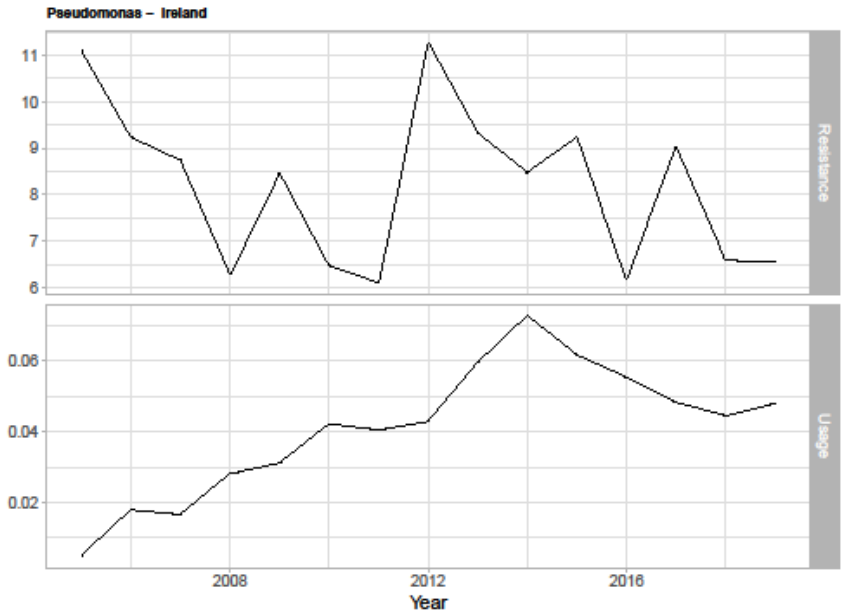


Figure 26~~26~~75: *Pseudomonas* resistance in The Netherlands

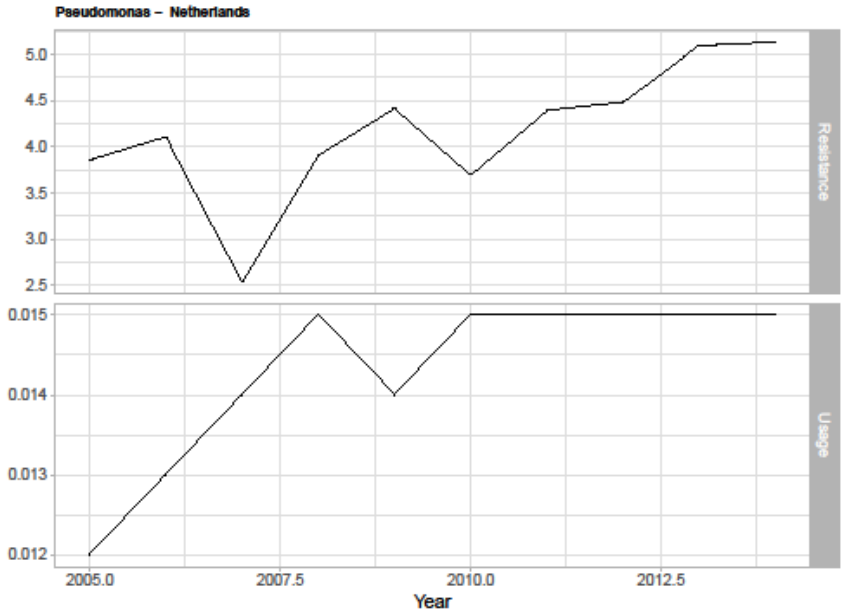


Figure 272~~776~~: *Pseudomonas* resistance in Norway.

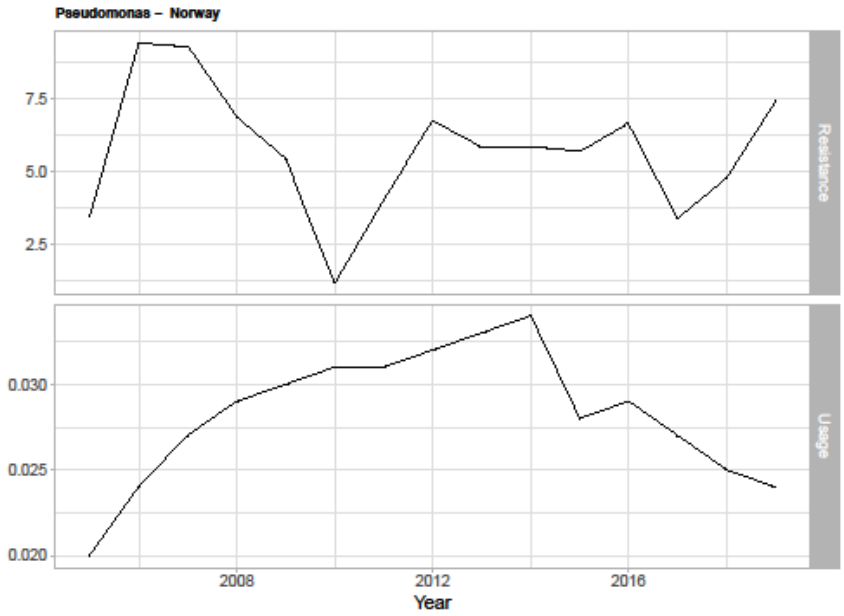


Figure 282~~877~~: *Pseudomonas* resistance in Slovenia

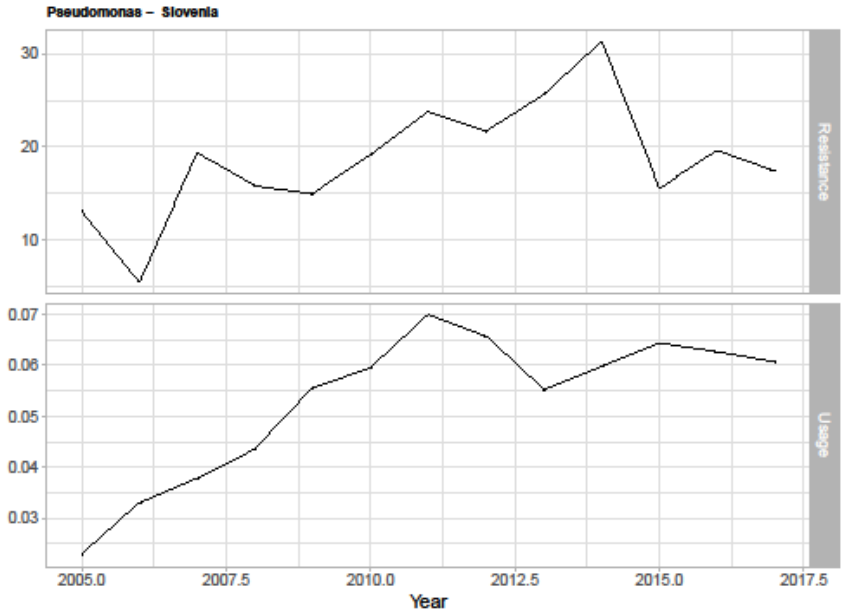
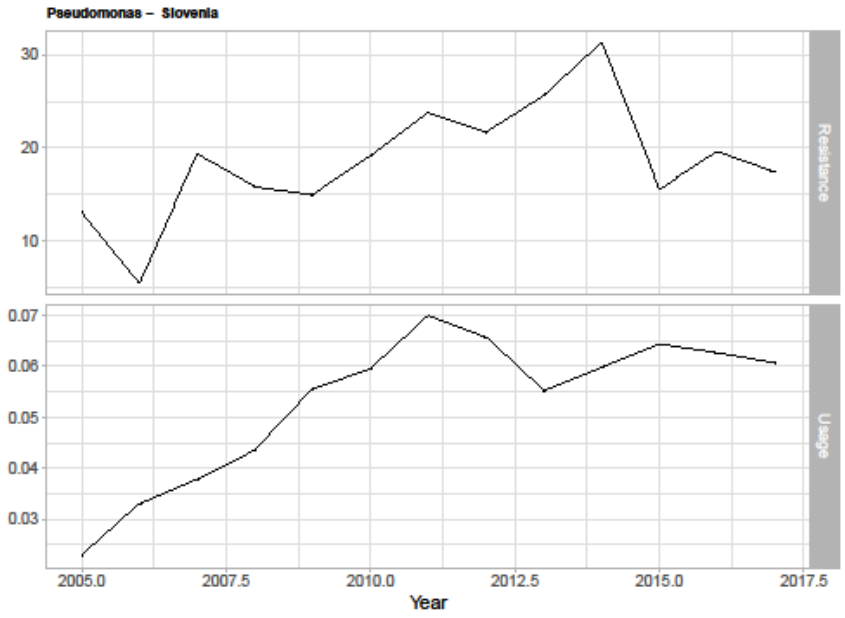


Figure 292978: *Pseudomonas* resistance in Slovenia



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