Quantifying uncertainty about future antimicrobial resistance with structured expert judgment

Abigail Colson, Department of Management Science
5 July, 2017
TU Delft COST Meeting

Collaborators: Itamar Megiddo, Gerardo Alvarez-Uria, Sumanth Gandra, Tim Bedford, Alec Morton, and Ramanan Laxminarayan

Antibiotic resistance is a global problem.

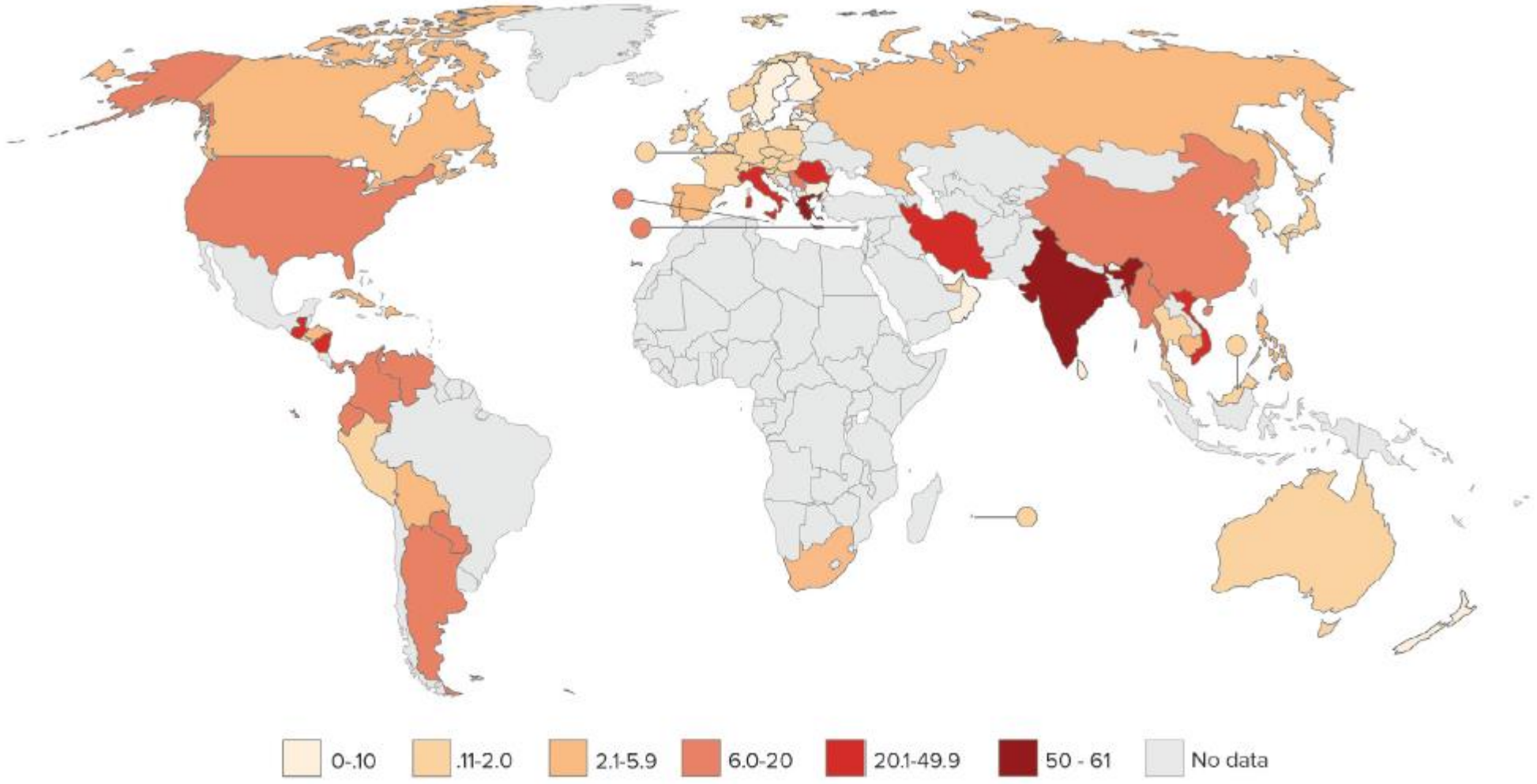
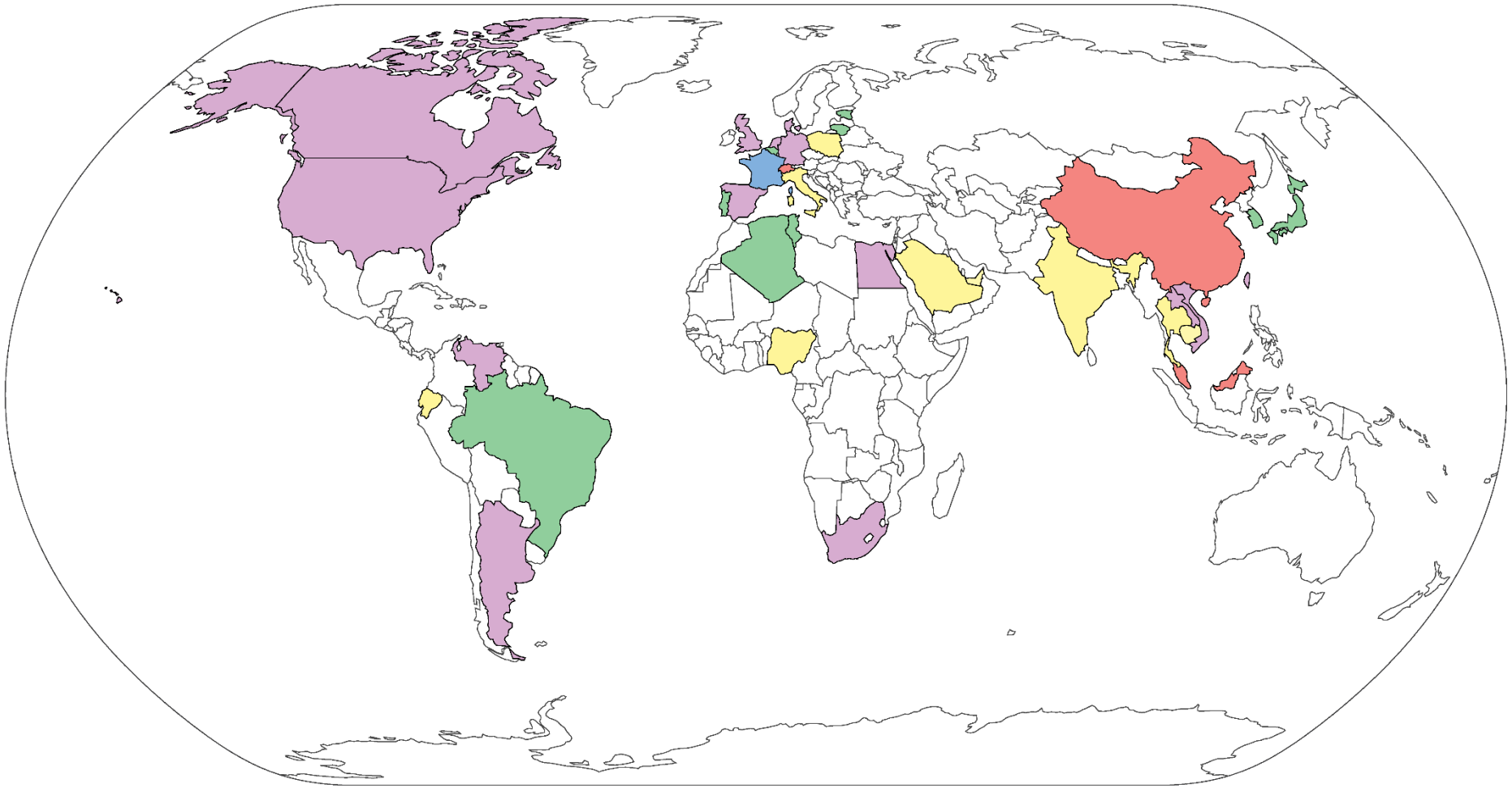


FIGURE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011–2014)

Source: CDDEP. 2015. "The State of the World's Antibiotics, 2015." Washington, D.C.: Center for Disease Dynamics, Economics & Policy.

Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*



Isolate source(s):

- Animals
- Humans
- Animals and humans
- Animals and environment
- Animals, humans and environment

Data source: Al-Tawfiq, J. A., Laxminarayan, R. & Mendelson, M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? Int. J. Infect. Dis. (2016). doi:10.1016/j.ijid.2016.11.415

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

Health

Antibiotic resistance: World on cusp of 'post-antibiotic era'

By James Gallagher
Health editor, BBC News website

19 November 2015 | Health

Share

nature International weekly journal of science

NATURE | NEWS

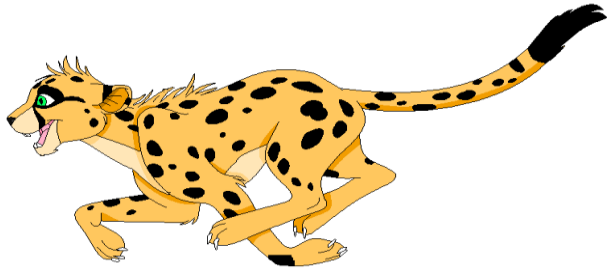
WHO warns against 'post-antibiotic' era

Agency recommends global system to monitor spread of resistant microbes.

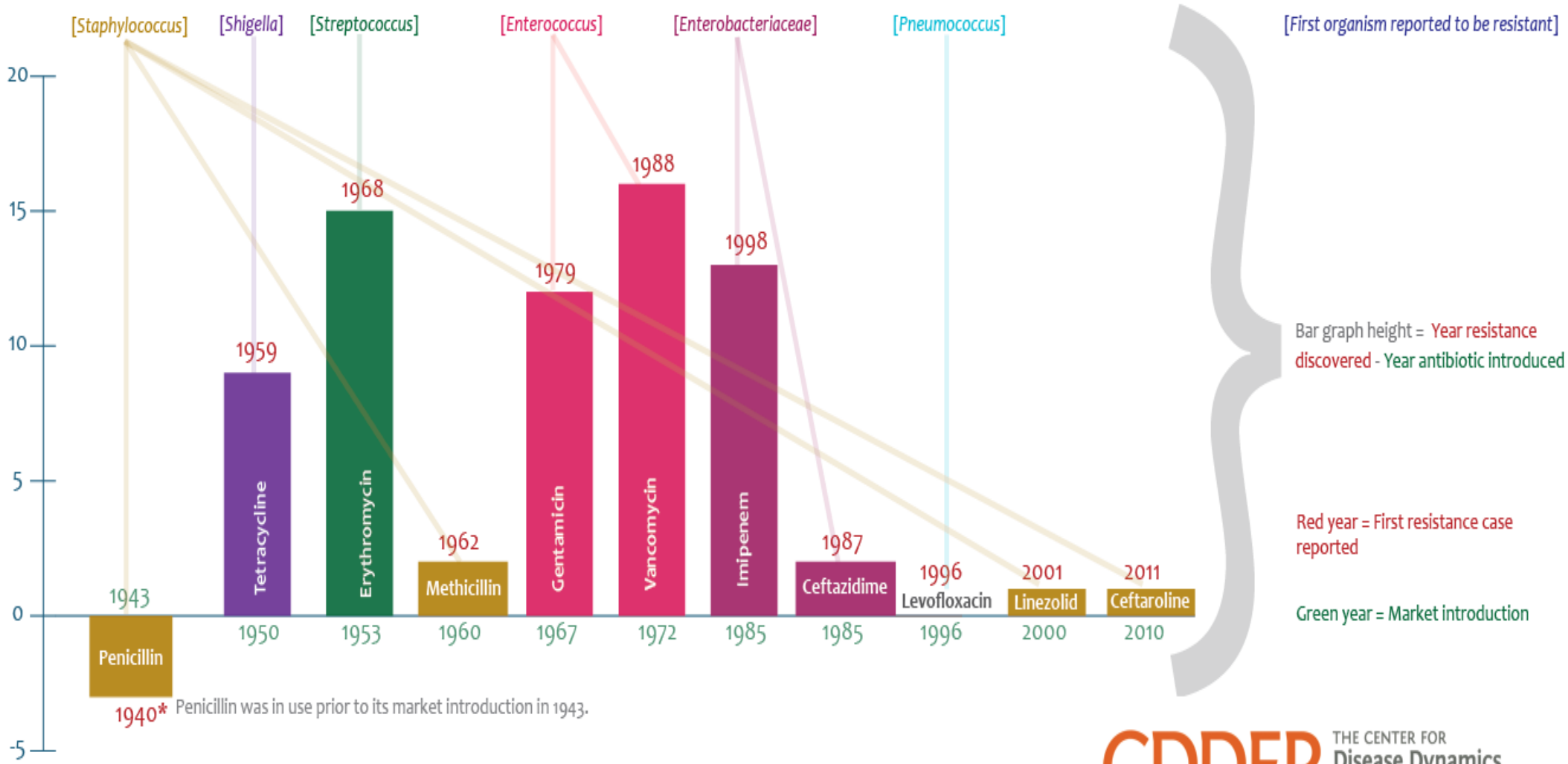
Sara Reardon

30 April 2014

Antibiotic resistance is a coevolution problem.



First reported cases of bacterial resistance against key antibiotics



Data source: Antibiotic Resistance Threats in the United States, 2013.
US Centers for Disease Control and Prevention (CDC).

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

DRIVE-AB

Developing new economic models to incentivise antibiotic discovery and development activities while safeguarding the efficacy of antibiotics by researching and advocating their appropriate use.

October 2014 – September 2017

DRIVE-AB Work Packages

- WP 1A: Define “responsible” use of antibiotics
- WP 1B: Set, communicate and revise public health priorities
- WP 1C: Develop antibiotic valuation models
- WP 2: Create, test and validate new economic models
- WP 3A: Coordinate and manage the project
- WP 3B: Stakeholder platform and external communication

Determining the economic value of antibiotics

- Antibiotics have unique sources of value
  - Direct treatment, transmission, enabling, diversity, option

- In order to estimate the value of new antibiotics, we need to know:
  - The levels of resistance to current treatment options, now and in the future
  - The clinical impact of resistance

- To supplement the growing evidence base, we are using structured expert judgment (specifically, the classical model) to get estimates and uncertainty bounds related to the future trajectory of resistance.

Elicitation structure

Bug/drug pairs

1. *E. coli* and fluoroquinolones
2. *E. coli* and cephalosporins
3. *E. coli* and carbapenems
4. *K. pneumoniae* and cephalosporins
5. *K. pneumoniae* and carbapenems
6. *S. aureus* and methicillin
7. *S. pneumoniae* and penicillins
8. *N. gonorrhoeae* and cephalosporins
9. *P. aeruginosa* and any treatment

Countries

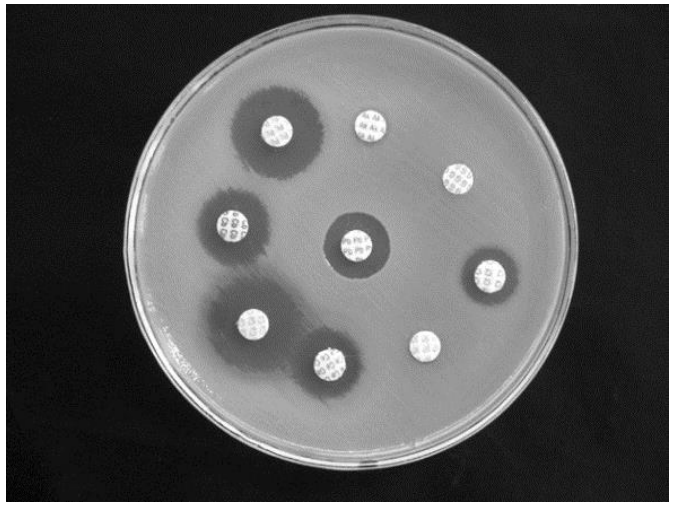
1. France
2. ~~Germany~~
3. Italy
4. Spain
5. UK

Seed questions

Why use expert judgment?

Existing relevant data are an imperfect picture of the past.

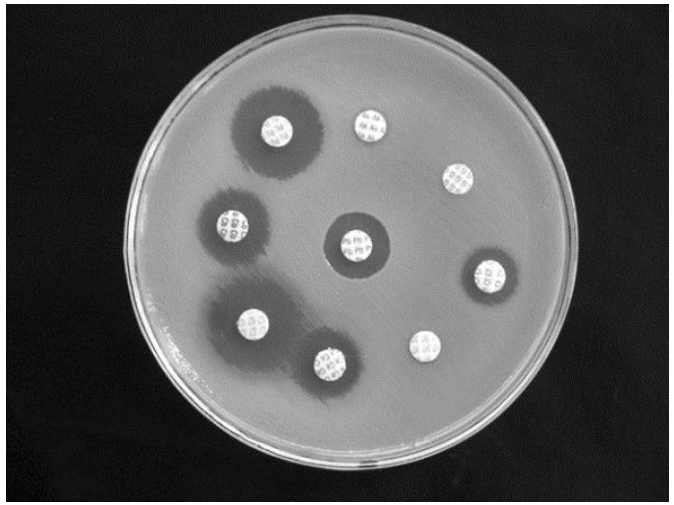
- Short history of observations.
- Data not representative.
- Definition of “resistant” not consistent over time.



Why use expert judgment?

Existing relevant data are an imperfect picture of the past.

- Short history of observations.
- Data not representative.
- Definition of “resistant” not consistent over time.



Experts have a lot of additional information about the future.

- Changes in antibiotic prescribing.
- Changes in hospital infection control.
- Changes in available treatment options.
- …

Expert scores: France

Expert	Statistical accuracy	Information	Combined score	Weight (PW)
1	2.20E-04	1.47	3.24E-04	0
2	0.03	1.38	0.04	0
3	1.99E-07	0.72	1.43E-07	0
4	2.16E-03	0.67	1.45E-03	0
5	0.65	1.96	1.28	1
Perf Weight	0.65	1.96	1.28	
Equal Weight	0.08	0.43	0.03	

Expert scores: France

Perf. Weights more accurate and more informative than Equal Weights

Expert	Statistical accuracy	Information	Combined score	Weight (PW)
1	2.20E-04	1.47	3.24E-04	0
2	0.03	1.38	0.04	0
3	1.99E-07	0.72	1.43E-07	0
4	2.16E-03	0.67	1.45E-03	0
5	0.65	1.96	1.28	1
Perf Weight	0.65	1.96	1.28	
Equal Weight	0.08	0.43	0.03	

Expert scores: France

Only 1 expert receives weight
(happens in about 1/3 of studies)

Expert	Statistical accuracy	Information	Combined score	Weight (PW)
1	2.20E-04	1.47	3.24E-04	0
2	0.03	1.38	0.04	0
3	1.99E-07	0.72	1.43E-07	0
4	2.16E-03	0.67	1.45E-03	0
5	0.65	1.96	1.28	1
Perf Weight	0.65	1.96	1.28	
Equal Weight	0.08	0.43	0.03	

Expert scores: Italy

Again, Perf Weights do better than EW and only 1 expert is weighted

Expert	Statistical accuracy	Information	Combined score	Weight (PW)
1	0.03	0.63	0.02	0
2	0.02	0.46	0.01	0
3	0.45	0.47	0.21	1
4	5.56E-06	0.99	5.50E-06	0
Perf Weight	0.45	0.47	0.21	
Equal Weight	0.22	0.20	0.04	

Expert scores: Spain

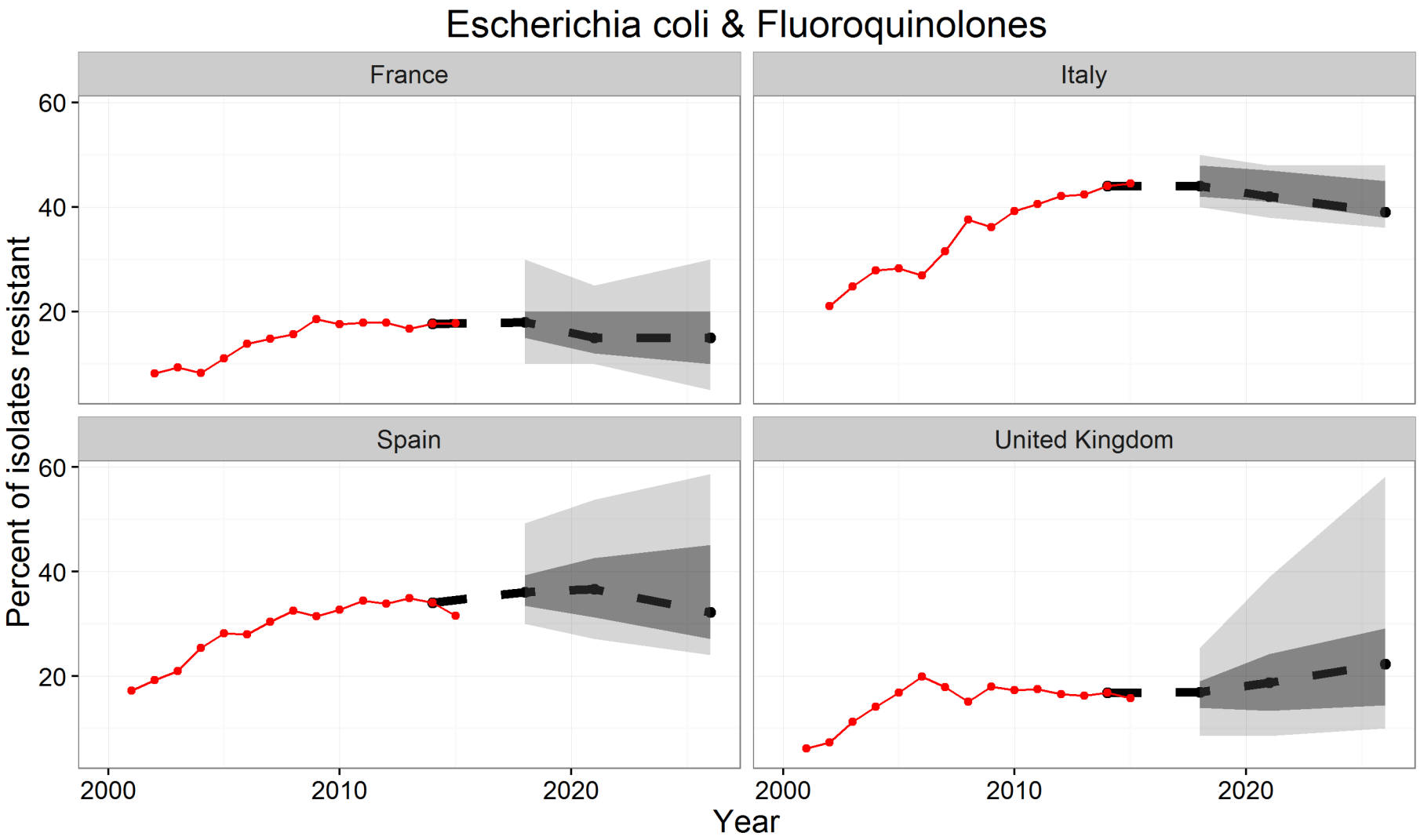
Perf Weights do better than EW, but neither combination has good statistical accuracy

Expert	Statistical accuracy	Information	Combined score	Weight (PW)
1	1.22E-05	0.57	6.98E-06	0.23
2	1.03E-09	1.45	1.49E-09	0
3	1.99E-07	0.42	8.43E-08	0
4	3.23E-07	1.64	5.31E-07	0
5	2.24E-05	1.04	2.33E-05	0.77
Perf Weight	3.59E-05	0.67	2.39E-05	
Equal Weight	1.22E-05	0.23	2.82E-06	

Expert scores: United Kingdom

Perf Weights do better than EW; 4 of 6 experts are weighted

Expert	Statistical accuracy	Information	Combined score	Weight (PW)
1	1.55E-03	0.47	7.33E-04	0
2	0.02	1.83	0.03	0.09
3	0.18	1.13	0.20	0.66
4	0.18	0.39	0.07	0.23
5	2.61E-03	1.99	0.01	0.02
6	1.96E-08	0.79	1.54E-08	0
Perf Weight	0.50	0.61	0.30	
Equal Weight	0.13	0.33	0.04	



Red line: historical data from EARS-Net

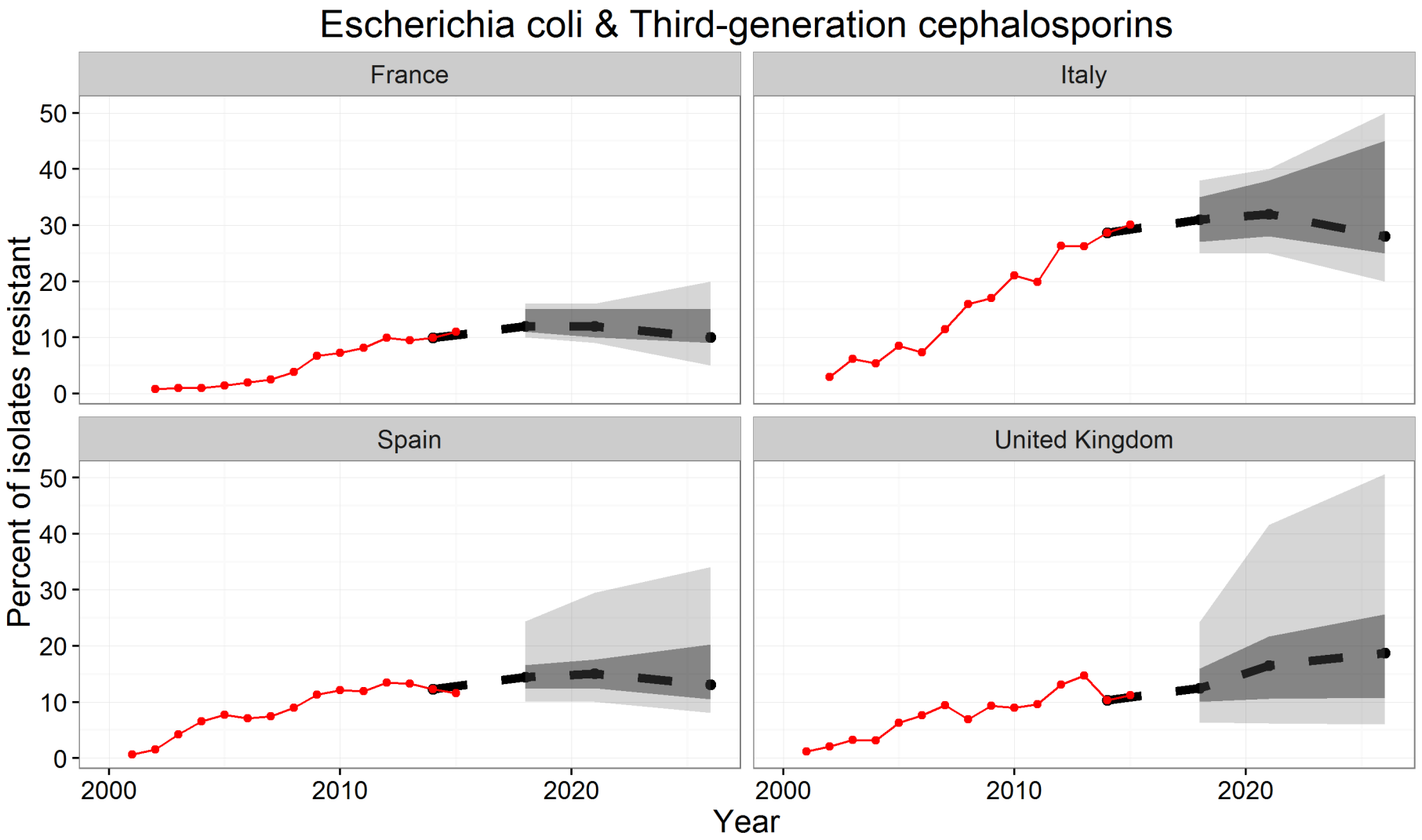
Dashed line: median assessments

Light grey: 90% credible range

Dark grey: 50% credible range

Experts provided assessments for 2018, 2021, and 2026.

Medians in all countries fairly stable.
Distributions all right-skewed: rates could be much worse than the median, but not much better.



Red line: historical data from EARS-Net

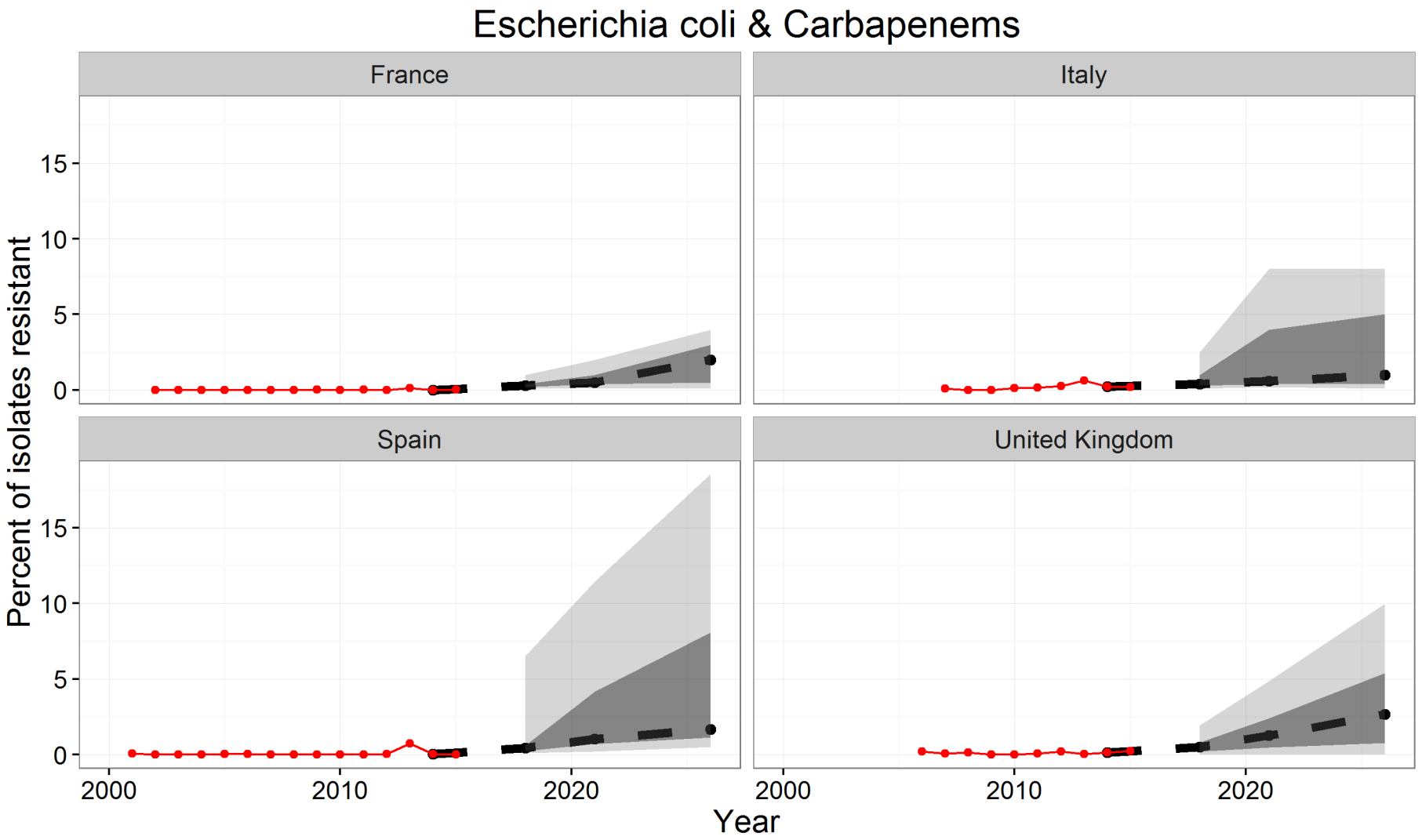
Dashed line: median assessments

Light grey: 90% credible range

Dark grey: 50% credible range

Experts provided assessments for 2018, 2021, and 2026.

Similar story to fluoroquinolones, just different magnitude.



Red line: historical data from EARS-Net

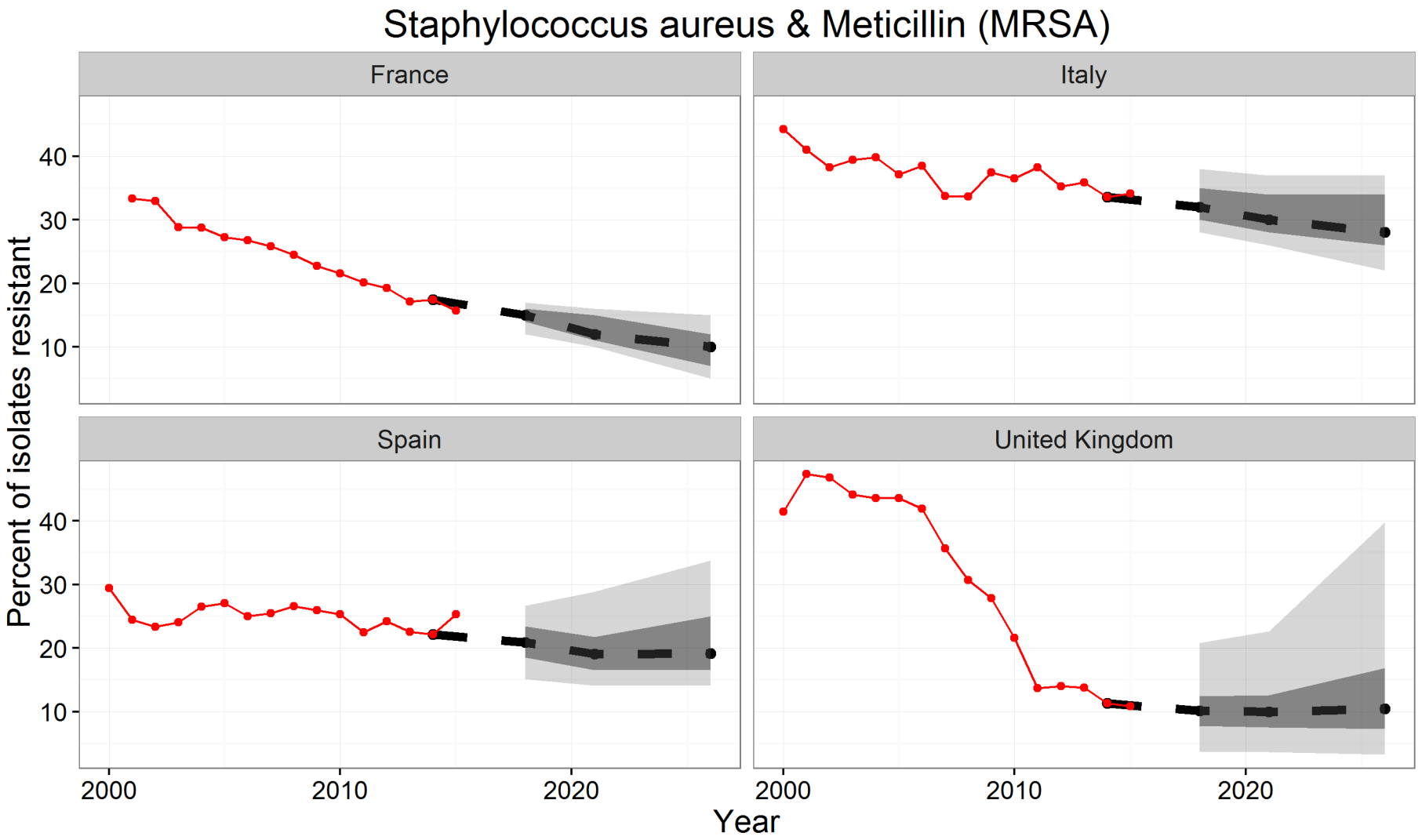
Dashed line: median assessments

Light grey: 90% credible range

Dark grey: 50% credible range

Experts provided assessments for 2018, 2021, and 2026.

Experts thought carbapenem-resistant E. coli was coming, but slowly.
Medians reflect a steady increase, not an exponential jump.



Red line: historical data from EARS-Net

Dashed line: median assessments

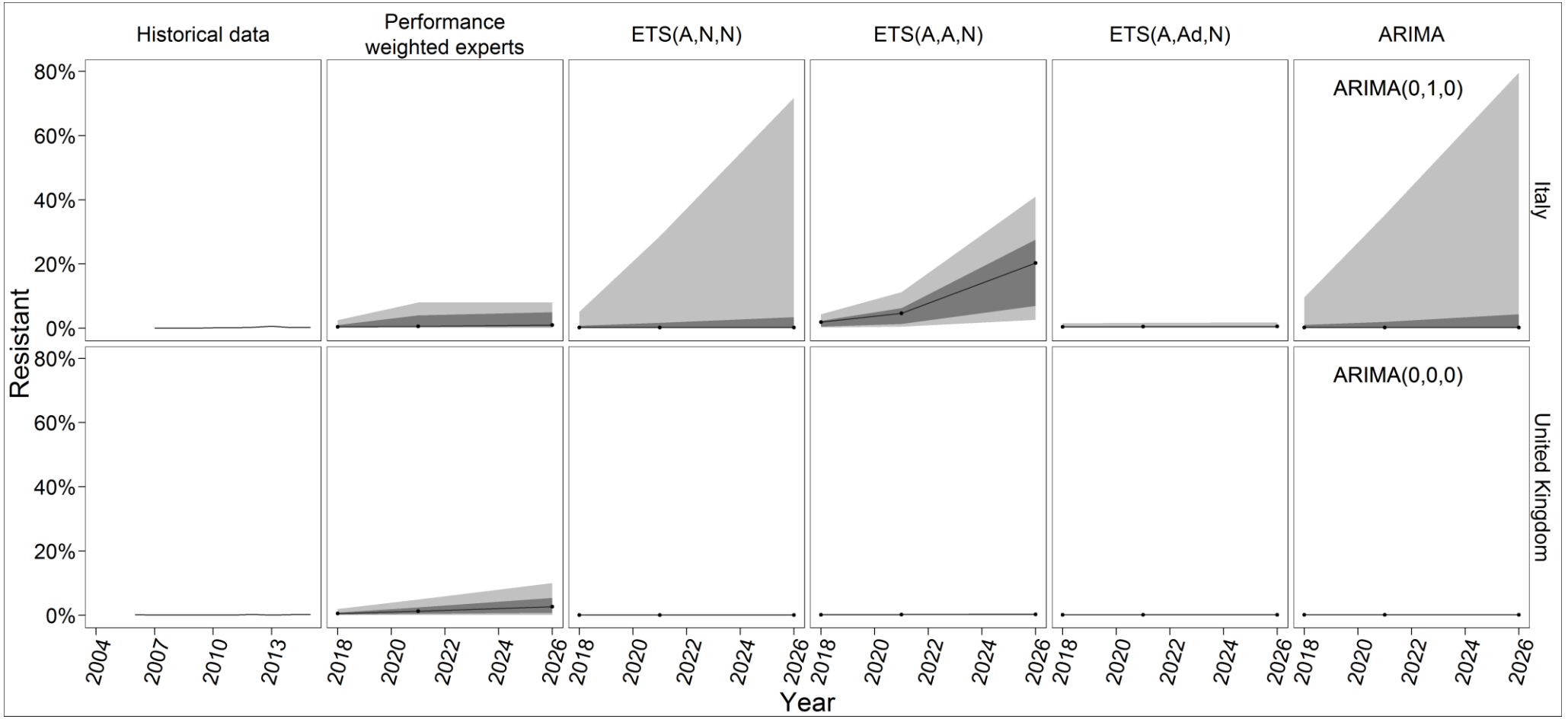
Light grey: 90% credible range

Dark grey: 50% credible range

Experts provided assessments for 2018, 2021, and 2026.

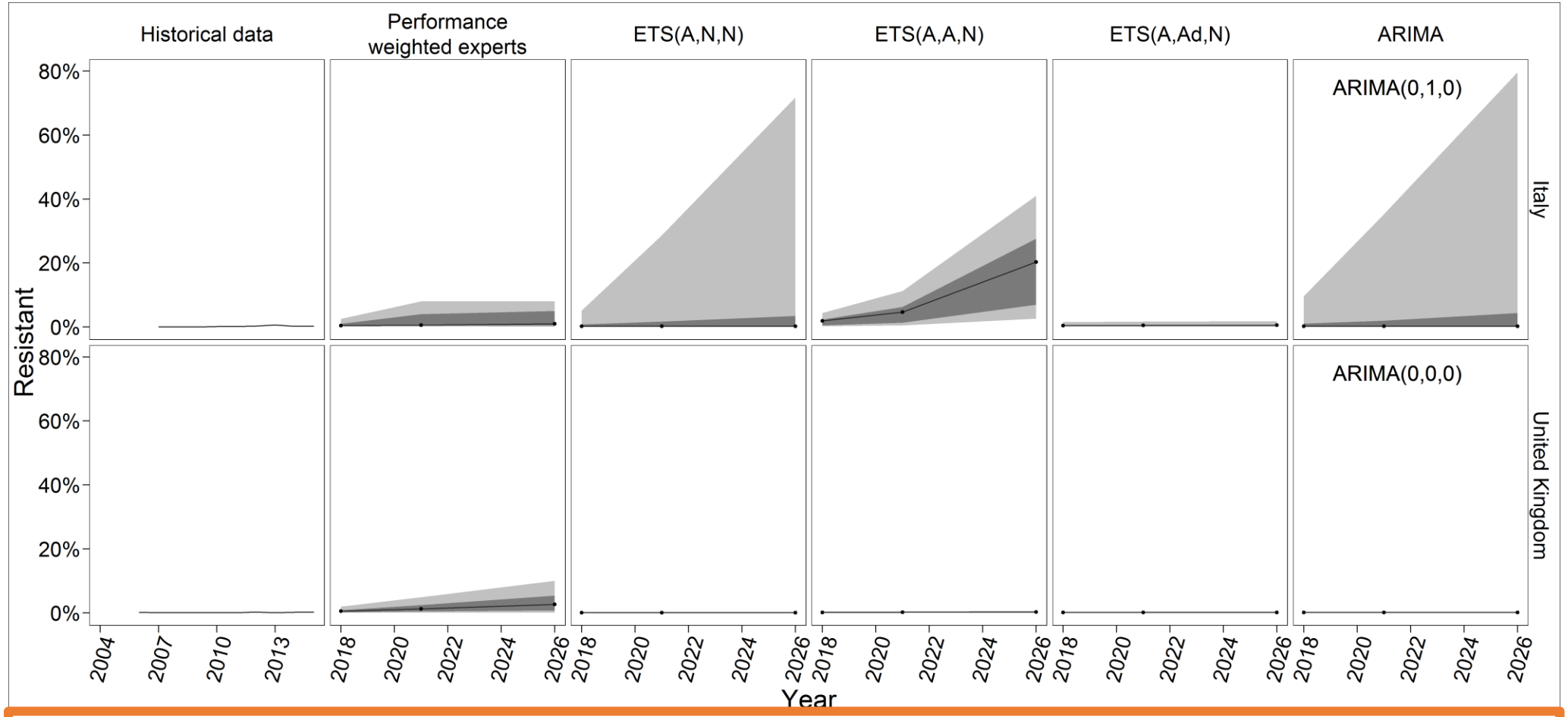
Rates will continue to decline, until they hit a floor.

Comparing experts and statistical forecasting: E. coli and carbapenems



ETS(A,N,N): exponential smoothing with additive error, no trend, no seasonality
ETS(A,A,N): exponential smoothing with additive error and trend, no seasonality
ETS(A,Ad,N): exponential smoothing with additive error, damped trend, no seasonality

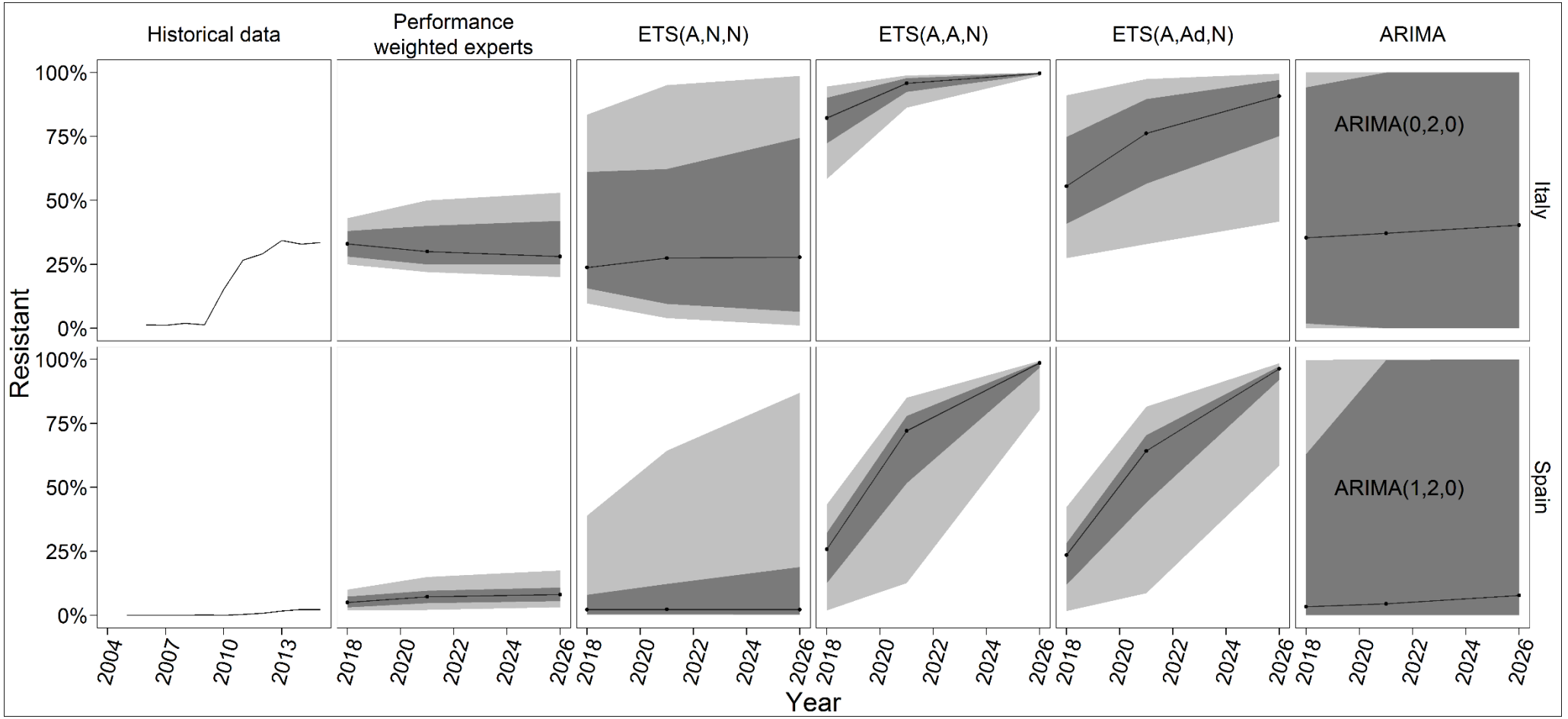
E. coli and carbapenems



Italy: Some models give similar results; experts disagree with models.

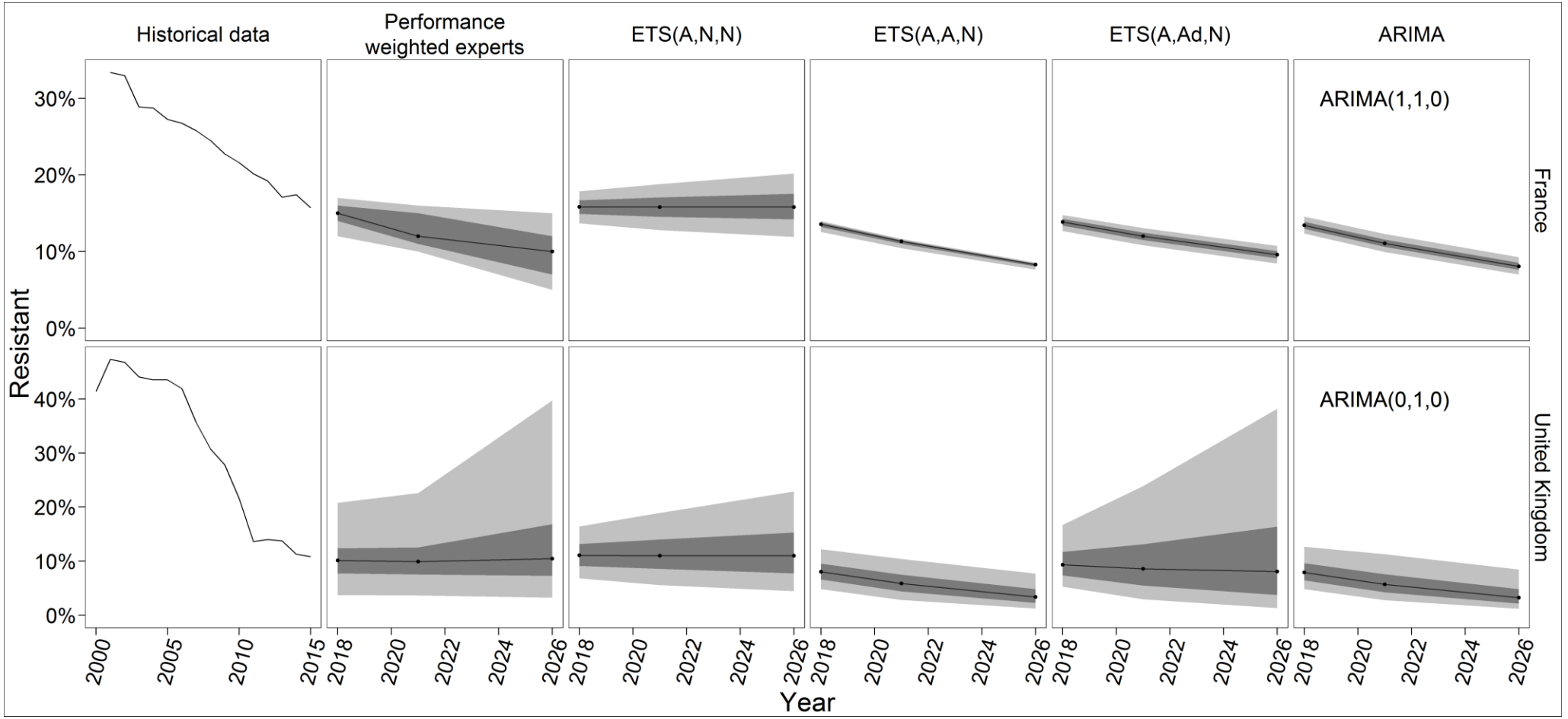
UK: All models similar; experts disagree with models.

K. pneumo and carbapenems



Models and experts quite different.

MRSA



Models and experts quite similar.

Conclusions

- Experts do not think we'll be in a post-antibiotic world in 10 years *given that they think antibiotic stewardship and infection control programs will both have an impact and continue.*

- Experts have knowledge about future resistance rates that is not captured in statistical forecasting.
- The classical model is a technique to elicit that information.

Next steps

- Results of this work will feed into antibiotic valuation models.

- There are a lot of interesting dependencies to explore!
  - The same bug/drug combination in different years.
  - Different drugs treating the same bug.
  - The same drug treating different bugs.

Thank you!

This research has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115618 [Driving re-investment in R&D and responsible antibiotic use – DRIVE-AB – www.drive-ab.eu], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.