# Estimating future antimicrobial resistance in Europe with structured expert judgement

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Aalto University COST Meeting

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Health

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

By James Gallagher
Health editor, BBC News website

19 November 2015 | Health

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nature International weekly journal of science



NATURE | NEWS

# WHO warns against 'post-antibiotic' era

**Agency recommends global system to monitor spread of resistant microbes.**

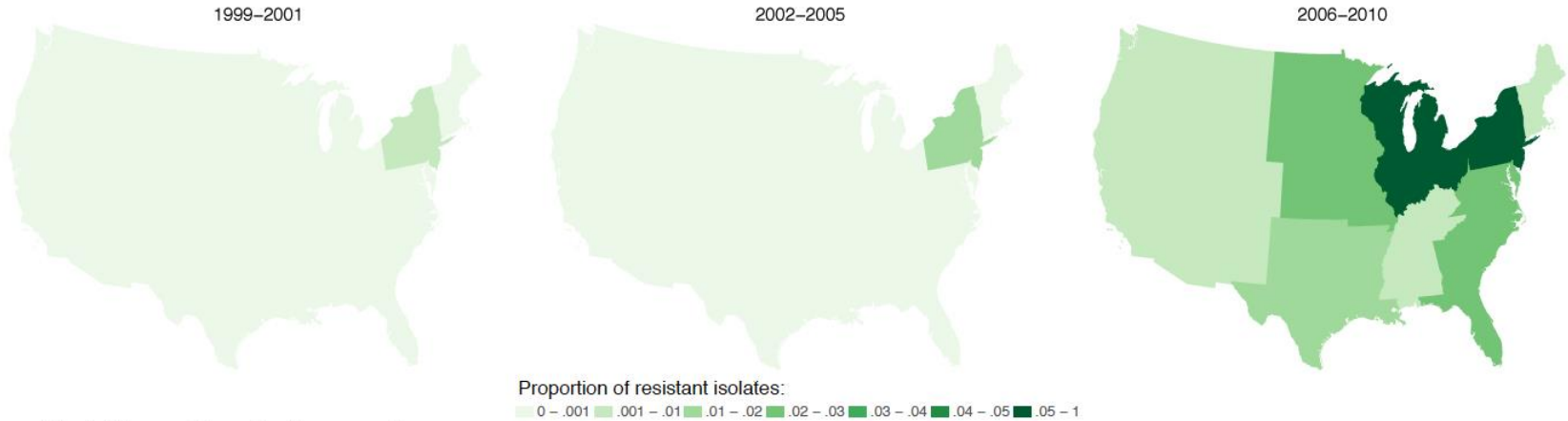
Sara Reardon

30 April 2014

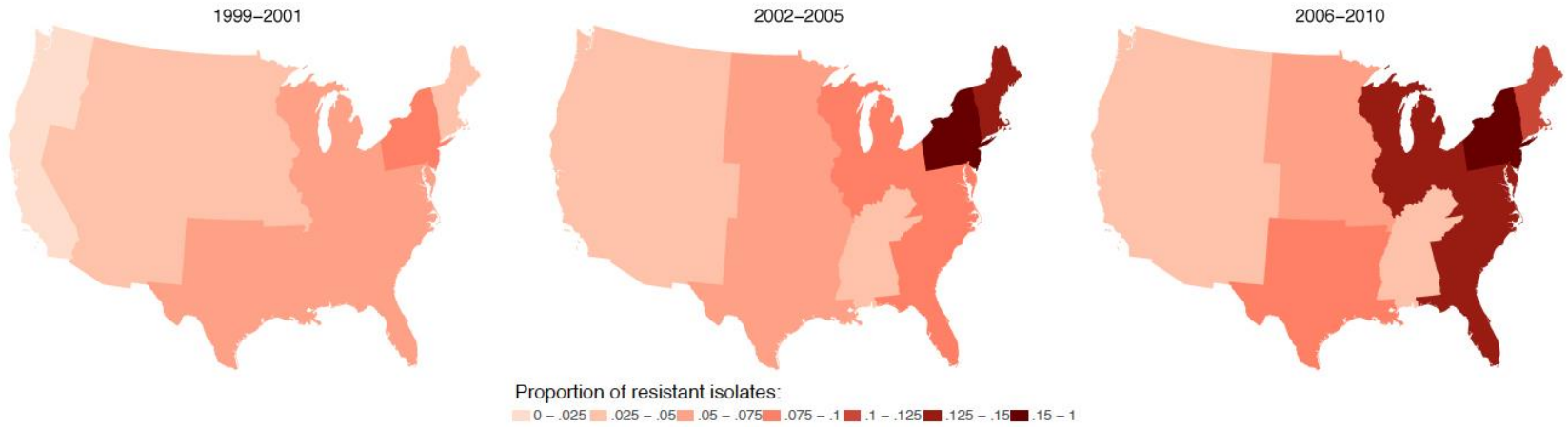


# Carbapenem and 3rd. gen. cephalosporin resistance among *K. pneumoniae* highest along the East Coast, but present in all regions of the country

## Carbapenem




## 3rd Gen. Cephalosporins




Note: Data for 2010 available through July.

Data source: Braykov NB, Eber MR, Klein EY, Morgan DJ, Laxminarayan R. Trends in Resistance to Carbapenems and Third- Generation Cephalosporins among Clinical Isolates of Klebsiella pneumoniae in the United States, 1999-2010. Infect Control and Hospital Epidemiology. 2013; 34(3)



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WASHINGTON DC • NEW DELHI

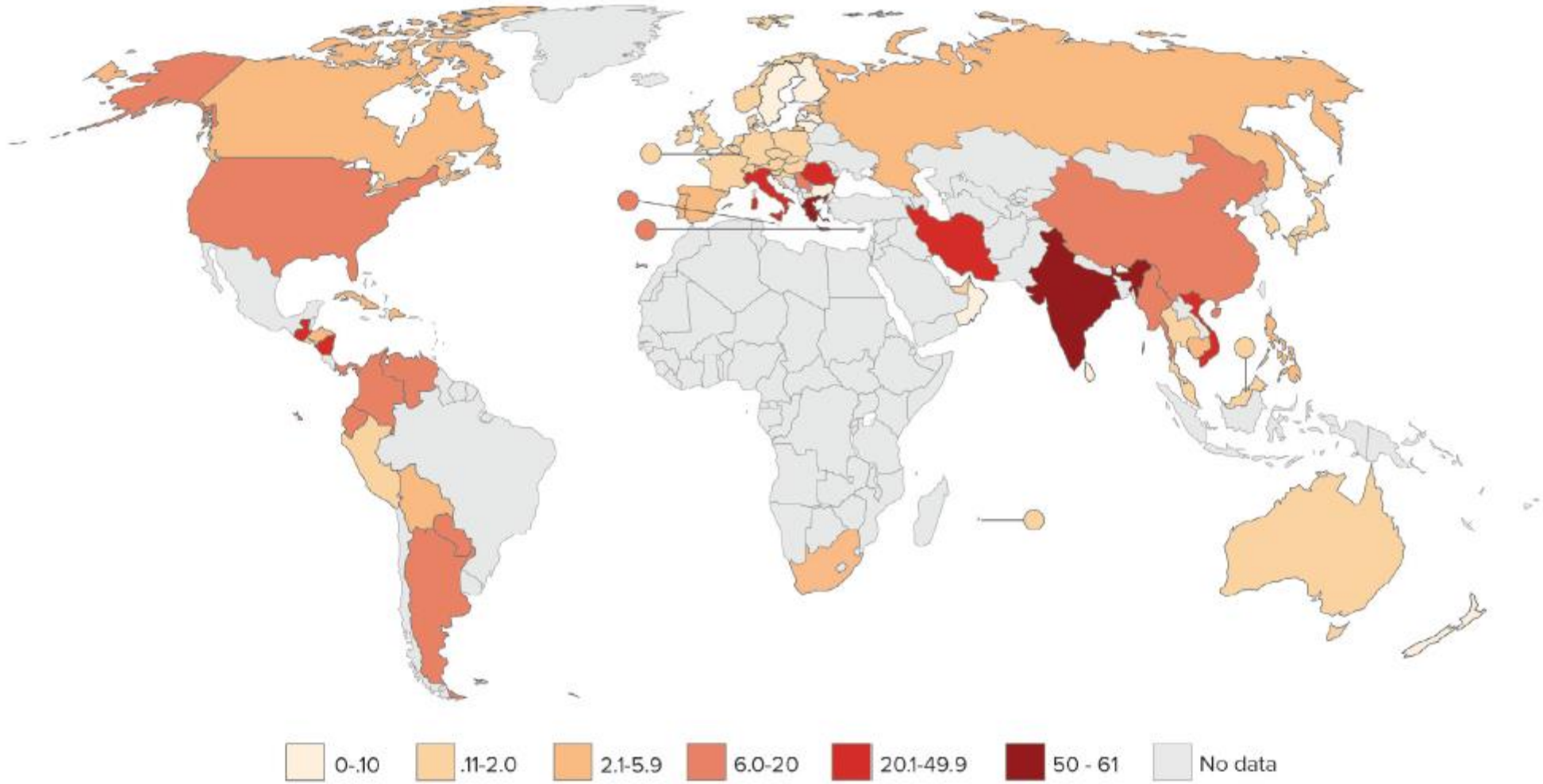
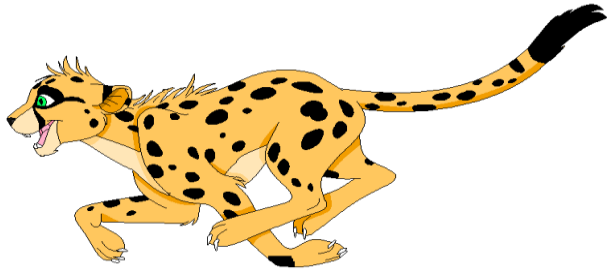



FIGURE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011–2014)

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

# Antibiotic resistance is a coevolution problem.



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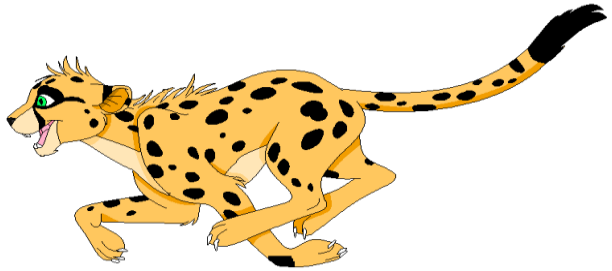

…and an innovation problem.

# 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

- 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

- Important data gaps exist for these questions, though more work is currently underway addressing them (including work by WP1B).

- 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.

# What is "The Classical Model"?

- A method to combine and validate experts' quantifications of uncertainty
- It's NOT a method to coerce agreement between the experts
- The method has been used by WHO, EU, EPA, NOAA, NASA, etc.

- In the classical model, experts answer 2 types of questions:
  - Calibration (aka "seed") questions
  - Variables of interest
- With calibration variables, any expert (or combination of experts) can be treated like a statistical hypothesis.
- Experts' assessments are weighted according to performance and combined.

# Principles

- ✓Reproducibility
- ✓Accountability
- ✓Empirical control
- ✓Neutrality
- ✓Fairness

# An example question

| **In the United States in 2012, how many of the 4,104 tested *E. coli* isolates included in data from The Surveillance Network (TSN) were resistant to fluoroquinolones?** | | | | |
|---|---|---|---|---|
| _____ | _____ | _____ | _____ | _____ |
| 5% | 25% | 50% | 75% | 95% |

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True value: 1,230

# Measuring expert performance

## Statistical accuracy:

- Do the expert's assessments capture the true values at the expected frequency?
- P-value of a statistical test of the expert's hypotheses

## Informativeness:

- How concentrated is the assessment, relative to a background measure?
- The background measure normally uniform with a 10% overshoot range.

# Variables of interest

**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. Germany
2. France
3. UK
4. Spain
5. Italy

# Why use expert judgment?

**Existing relevant data are an imperfect picture of the past.**

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**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: United Kingdom

| Expert | SA | Info | Combined | 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 |
| PW | 0.50 | 0.61 | 0.30 | |
| EW | 0.13 | 0.33 | 0.04 | |

# Expert scores: Spain

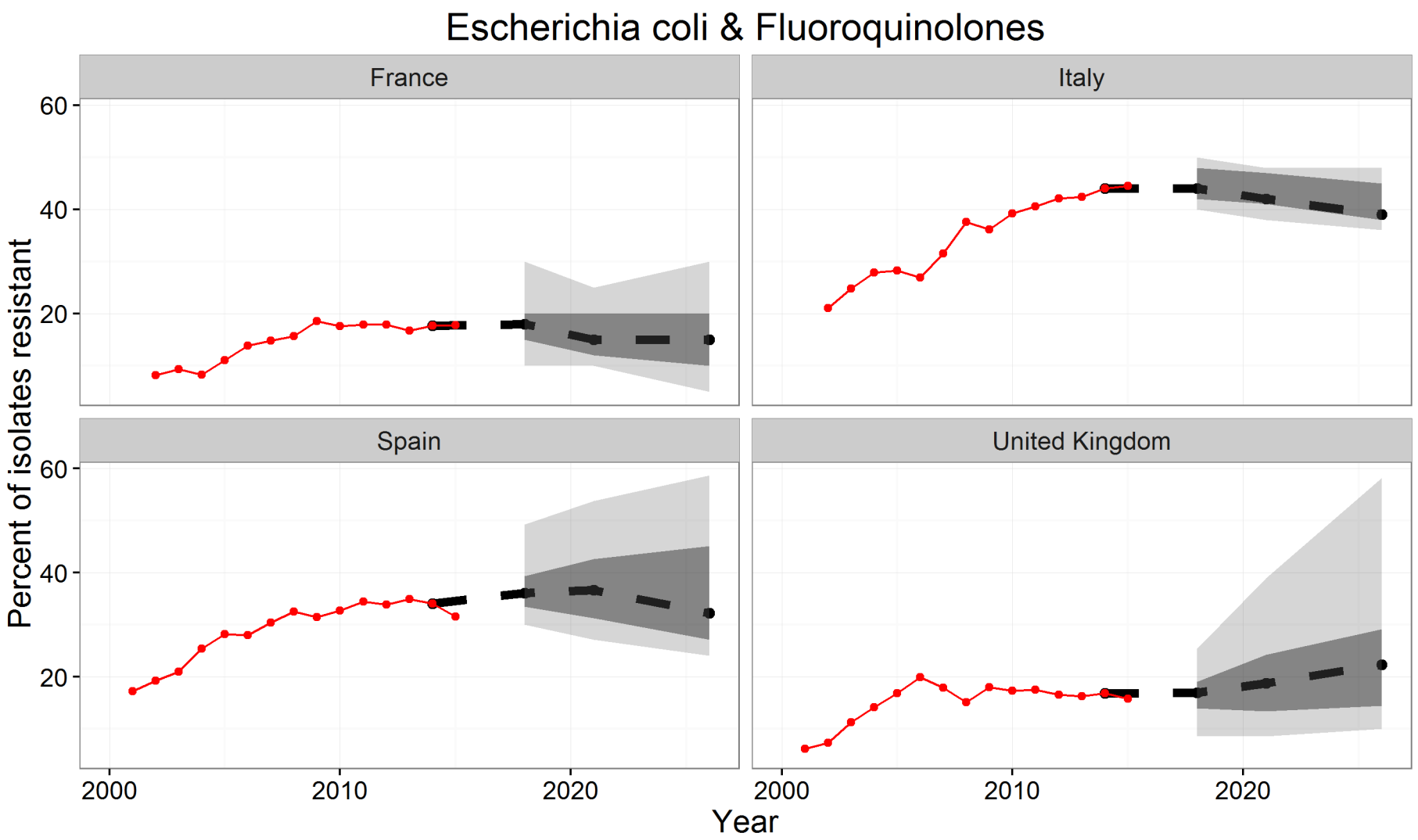
| Expert | SA | Info | Combined | Weight (PW) |
|---|---|---|---|---|
| 1 | 1.22E-05 | 0.57 | 6.98E-06 | 0.23 |
| 2 | 1.03E-09 | 1.45 | 1.49E-09 | 0 |
| 3 | 1.99E-07 | 0.42 | 8.43E-08 | 0 |
| 4 | 3.23E-07 | 1.64 | 5.31E-07 | 0 |
| 5 | 2.24E-05 | 1.04 | 2.33E-05 | 0.77 |
| PW | 3.59E-05 | 0.67 | 2.39E-05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

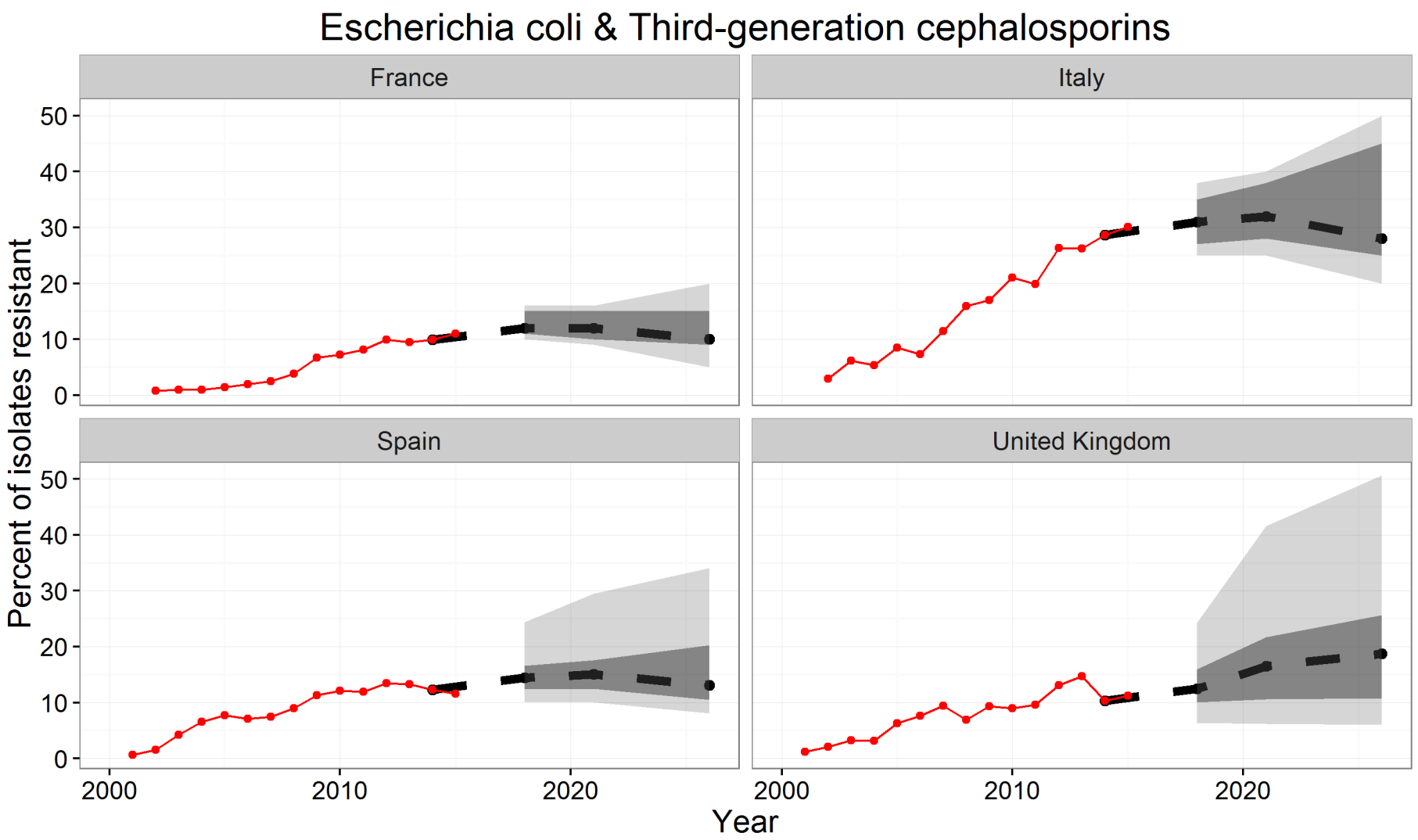
# Expert scores: France

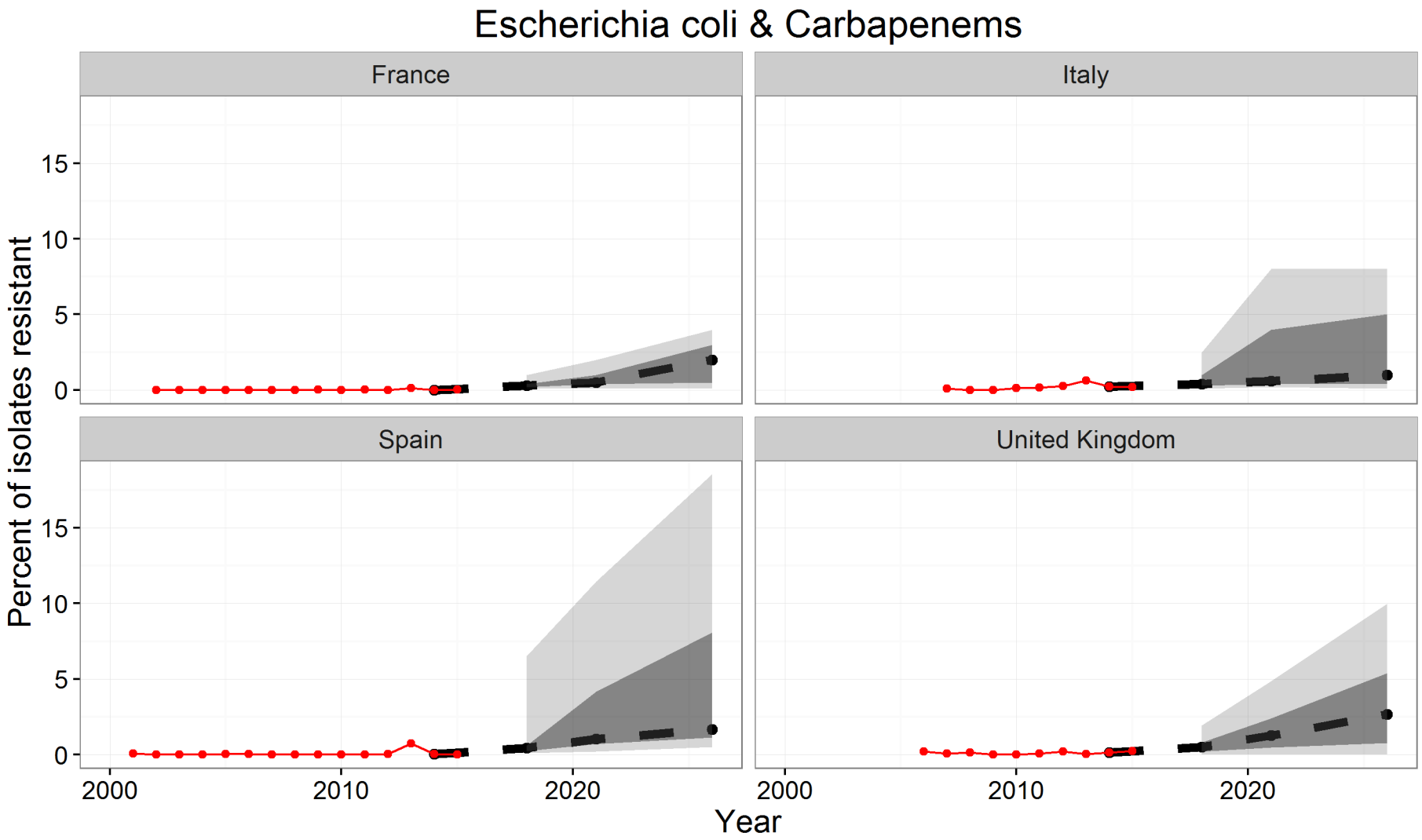
| Expert | SA | Info | Combined | Weight (PW) |
|---|---|---|---|---|
| 1 | 2.20E-04 | 1.47 | 3.24E-04 | 0 |
| 2 | 0.03 | 1.38 | 0.04 | 0 |
| 3 | 1.99E-07 | 0.72 | 1.43E-07 | 0 |
| 4 | 2.16E-03 | 0.67 | 1.45E-03 | 0 |
| 5 | 0.65 | 1.96 | 1.28 | 1 |
| PW | 0.65 | 1.96 | 1.28 | |
| EW | 0.08 | 0.43 | 0.03 | |

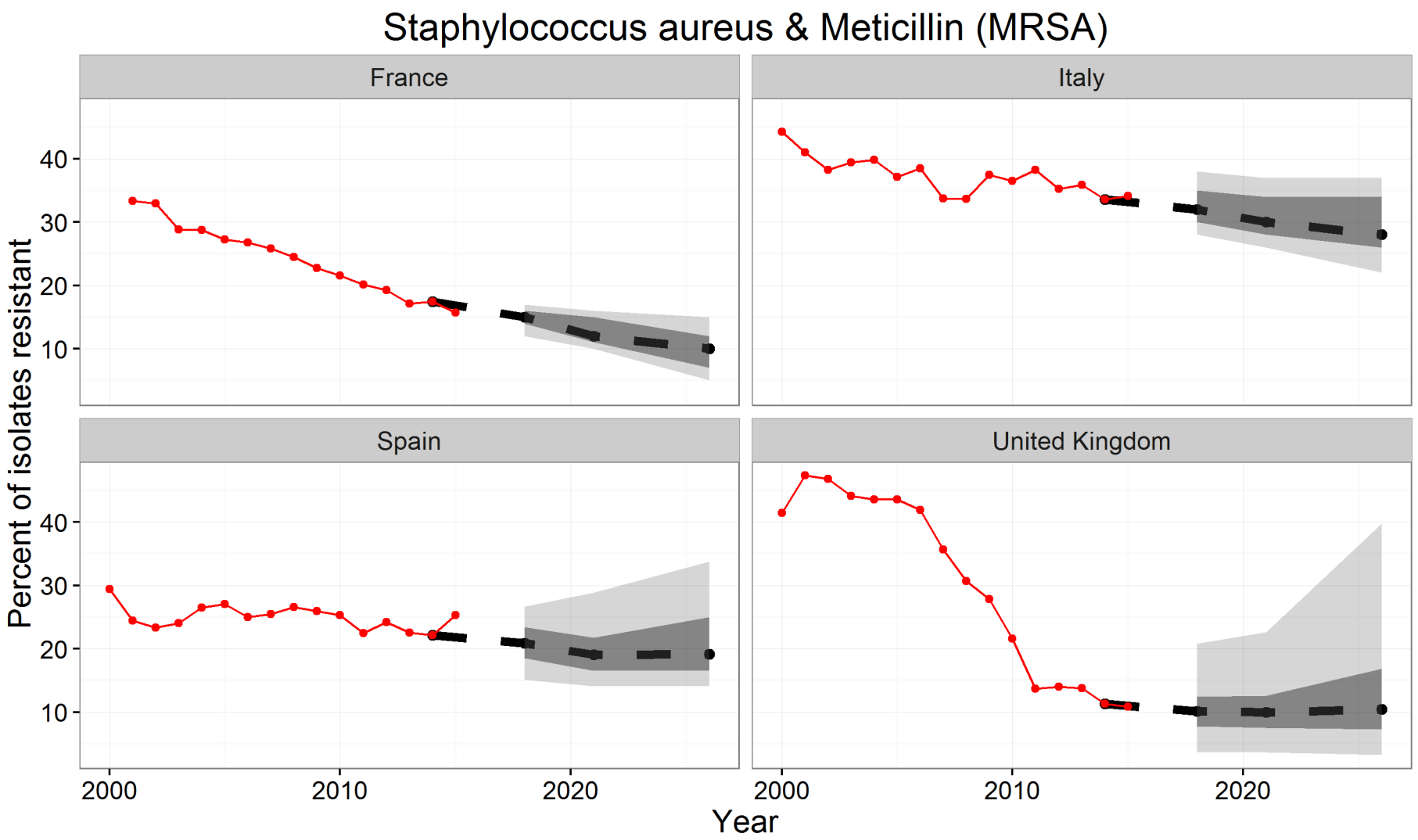
# Expert scores: Italy

| Expert | SA | Info | Combined | 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 |
| PW | 0.45 | 0.47 | 0.21 | |
| EW | 0.22 | 0.20 | 0.04 | |

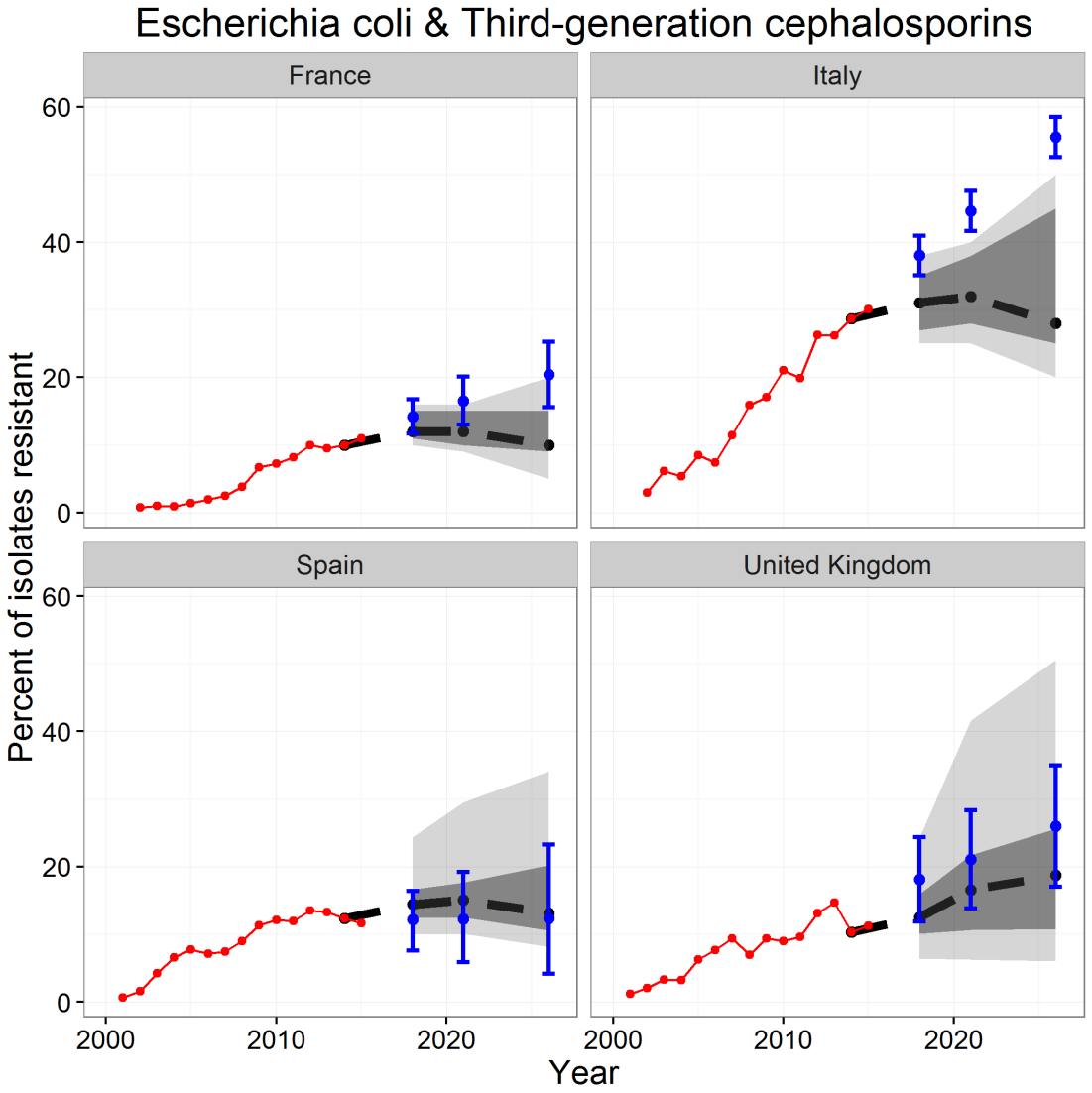

Escherichia coli & Fluoroquinolones
France
Italy
Spain
United Kingdom
Percent of isolates resistant
60
40
20
2000
2010
2020
Year


Escherichia coli & Third-generation cephalosporins
France
Italy
Spain
United Kingdom
Percent of isolates resistant
0
10
20
30
40
50
2000
2010
2020
Year


Escherichia coli & Carbapenems
France
Italy
Spain
United Kingdom
Percent of isolates resistant
0
5
10
15
2000
2010
2020
Year


Staphylococcus aureus & Meticillin (MRSA)
France
Italy
Spain
United Kingdom
Percent of isolates resistant
40
30
20
10
2000
2010
2020
Year

# Comparing SEJ to mathematical forecasting



# 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!

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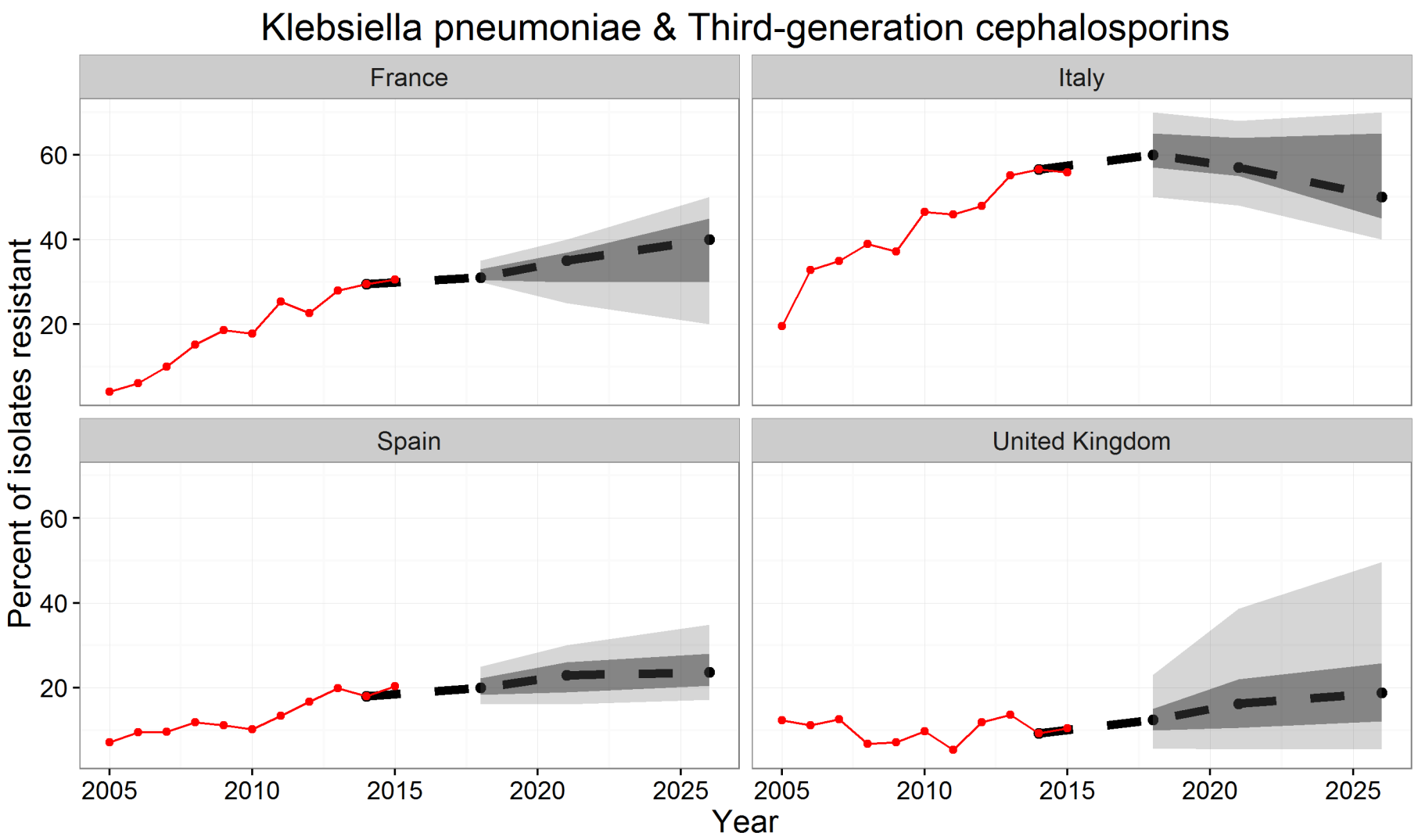
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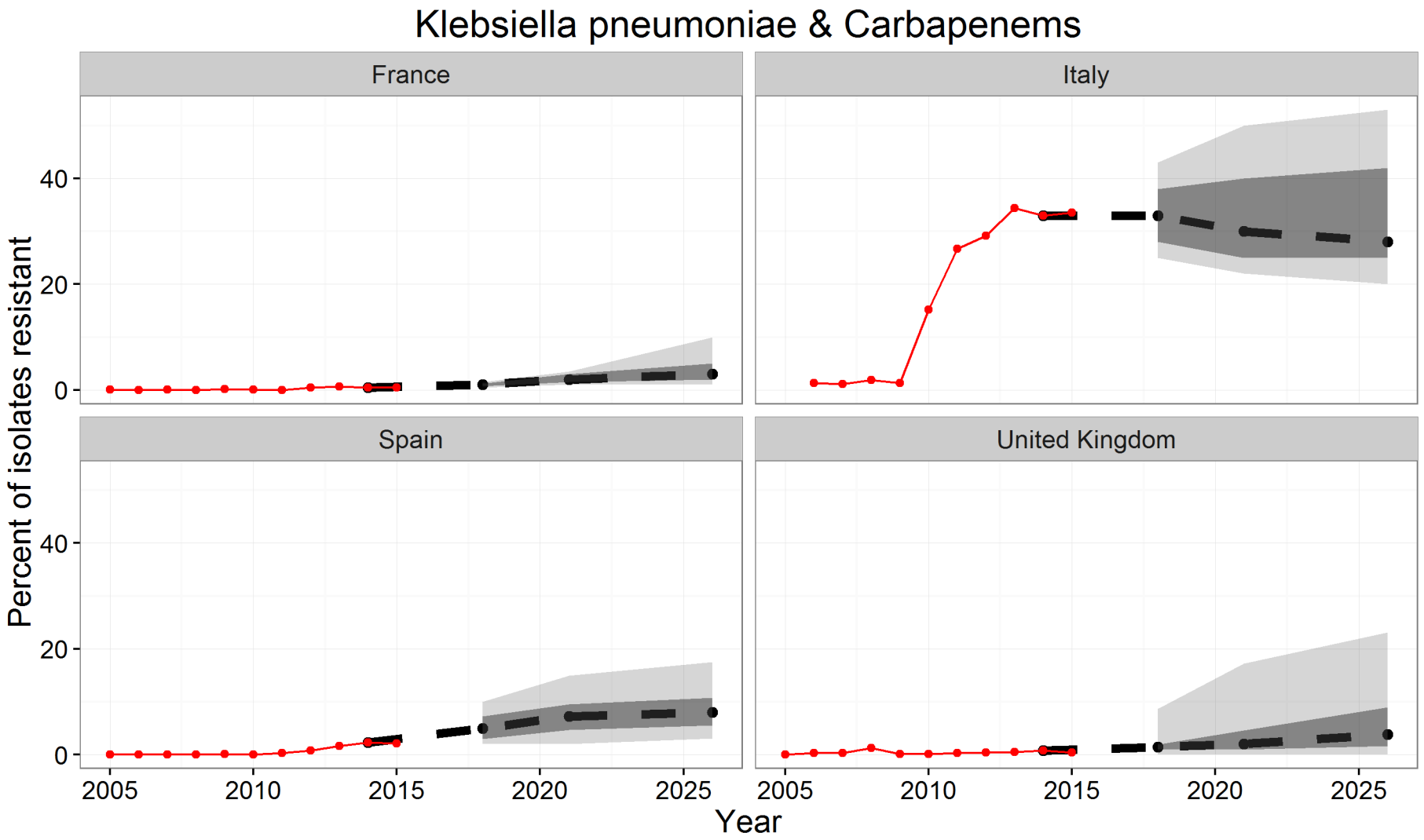
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