Predictive Mapping of Antimicrobial Resistance for *Escherichia coli*, *Salmonella*, and *Campylobacter* in Food-Producing Animals, Europe, 2000–2021

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In Europe, systematic national surveillance of antimicrobial resistance (AMR) in food-producing animals has been conducted for decades; however, geographic distribution within countries remains unknown. To determine distribution within Europe, we combined 33,802 country-level AMR prevalence estimates with 2,849 local AMR prevalence estimates from 209 point prevalence surveys across 31 countries. We produced geospatial models of AMR prevalence in *Escherichia coli,* nontyphoidal *Salmonella*, and *Campylobacter* for cattle, pigs, and poultry. We summarized AMR trends by using the proportion of tested antimicrobial compounds with resistance >50% and generated predictive maps at 10 × 10 km resolution that disaggregated AMR prevalence. For *E. coli,* predicted prevalence rates were highest in southern Romania and southern/eastern Italy; for *Salmonella,* southern Hungary and central Poland; and for *Campylobacter*, throughout Spain. Our findings suggest that AMR distribution is heterogeneous within countries and that surveillance data from below the country level could help with prioritizing resources to reduce AMR.

Antimicrobial resistance (AMR) is a substantial threat to the health of humans and animals. Among humans, in 2019 an estimated 1.27 million deaths were associated with bacterial AMR (*1*). Among food-producing animals (i.e., animals that are used for or produce food items for human consumption), estimates of global AMR burden are still lacking. However, recent work has suggested that among common indicator bacteria of food-producing animals in low- and middle-income countries, the proportion of antimicrobials with resistance >50% increased from 12%–15% in 2000 to 34%–41% in 2018 (*2*), an increase that may have harmful consequences for humans (*3*). Moreover, the loss of treatment effectiveness in animals is a long-term threat for animal production and the millions of persons who rely on raising animals for subsistence (*4*,*5*). Therefore, monitoring AMR in food-producing animals has become a global priority for effective prevention strategies.

Since 2009, the European Food Safety Authority (EFSA) has led a harmonized surveillance system for AMR in food-producing animals and products (*6*). The system includes AMR prevalence estimates for *Escherichia coli*, nontyphoidal *Salmonella*, and *Campylobacter* among cattle and pigs (odd years) and chickens and turkeys (even years) (*7*). Data collected by EFSA have been instrumental for monitoring AMR and for guiding policy decisions in the European Union (e.g., the 2018 ban on prophylactic use of antimicrobials in animals [*8*]). The efforts to document AMR have also enabled comparison between countries in Europe by estimating prevalence of AMR at the national level. However, recent works have shown that resistance levels in humans and animals can vary at a fine spatial scale, and accumulation of resistance genes in those areas may create geographic hotspots for AMR (*2*,*9*). Identifying geographic hotspots of AMR within countries could help with targeting interventions against AMR, such as improved farm biosecurity and targeted surveillance, where they might have the greatest benefits (*10*–*12*).

In that context, point prevalence surveys (PPSs) of AMR among food-producing animals, with data points collected at individual geographic locations,

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provide an opportunity to supplement the national estimates of AMR assembled by EFSA (*2*). The resulting mapped predictions could be used to help design regional antibiotic stewardship campaigns or target local investment in farm biosecurity (*12*). However, generating robust predictions of AMR pose at least 3 challenges. First, comparisons need to be made between the resistance trends inferred from PPSs and EFSA; second, subnational predictions should reflect resistance levels reported by EFSA at the national level; and third, an appropriate geospatial modeling approach must be developed to combine data collected at different spatial scales.

In this study, we disaggregated trends in AMR prevalence of *E. coli,* nontyphoidal *Salmonella*, and *Campylobacter* among cattle, pigs, and poultry. We used stacked geospatial models that supplement data from EFSA with individual PPSs to map predictions of AMR prevalence at a resolution of 10 × 10 km for 31 countries in Europe.

Materials and Methods

EFSA Data Collection

We reviewed annual EFSA reports published during 2011–2022 (*13*). We extracted country-level data on AMR prevalence (2009–2020), focusing on the percentage resistance to antimicrobials against *E. coli*, *Salmonella*, *Campylobacter coli*, and *Campylobacter jejuni*. We extracted information on country, year of isolation, animal type (cattle, pigs, chickens, turkeys), sample origin (slaughtered animal, living animal, or meat), bacteria, species, number of samples, antimicrobial tested, and resistance prevalence. We followed European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines to assess microbiological resistance and used microdilution methods and epidemiologic cutoff (ECOFF) values (*14*). We retained only antimicrobial/bacteria combinations recommended by the World Health Organization Advisory Group on Integrated Surveillance of Antimicrobial Resistance (*15*) for antimicrobial susceptibility testing (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/30/1/22-1450-App1.pdf).

PPS Data Collection

We systematically reviewed PPSs (Appendix) reporting AMR prevalence at individual locations in Europe (Appendix Figure 1). We searched PubMed, Web of Science, and Scopus for PPSs reporting AMR prevalence for *E. coli*, nontyphoidal *Salmonella*, and *Campylobacter* in healthy cattle, pigs, and poultry (combined data for chickens, turkeys, or other poultry), as well as their products (meat and dairy) in Europe during 2000–2021. Environmental samples (e.g., water, soil) were not included. We also extracted information on the geographic location of the PPS (Appendix), the year the PPS was conducted, the year the bacteria was isolated (but not species identification methods used), sample types collected (cecal, cloacal, lymph, or fecal samples taken from living animals, slaughtered animals, dairy products, or meat), animal species, number of samples collected and tested, susceptibility testing guidelines used, and susceptibility guidelines used for resistance interpretation.

We assessed microbiological resistance across PPSs by using different methods (disk diffusion vs. broth dilution), guidelines (Clinical and Laboratory Standards Institute [https://www.clsi.org] 52%, EUCAST 29%, other 14.6%) and cutoffs (clinical break points vs. ECOFFs [*15*]). We attempted to account for these differences by using a harmonization approach developed by Van Boeckel et al. (*2*) (Appendix). We calibrated data from PPSs by using antimicrobial susceptibility testing, guidelines, and breakpoints reported in each study to match those of EUCAST guidelines each year, to enable comparison between those data and data reported by EFSA. As with EFSA data, we retained only antimicrobial/bacteria combinations recommended by the World Health Organization Advisory Group on Integrated Surveillance of Antimicrobial Resistance (*15*). In addition, for our analysis we retained only countries that reported to EFSA and that had reported >50 samples during the study period. All prevalence estimates extracted from PPS are available at resistancebank.org (https://resistancebank.org) (*16*).

Comparative Analysis of Data Sources

We used the proportion of antimicrobials with >50% resistance (P50s) to summarize trends in resistance across each drug/bacteria combination, as in previous works (*2*,*12*,*17*); all P50s can be recalculated by using the data available at resistancebank.org. To assess the difference in AMR prevalence between PPS and EFSA data, as well as the implications that that could have for geospatial modeling, we compared the average P50 in countries reporting at >1 PPS and to EFSA during 2018–2020 (Appendix Table 3). A ratio <1 indicated a lower 3-year mean P50 using PPS data, and a ratio >2 meant a more than double 3-year mean P50 from PPS data compared with EFSA data.

Geospatial Modeling of P50

We mapped predicted subnational antimicrobial resistance in food-producing animals at a resolution of

0.08333 decimal degrees, corresponding to ≈10 km at the equator. To create the map, we used a 3-step procedure (Appendix Figure 2).

In the first step, we trained 3 child models (one of the individual models that are combined to form the final model) to quantify the relationship between P50 and a set of 9 environmental and anthropogenic covariates (Appendix Table 2). We selected those covariates because of their suspected association with AMR in animals (*2*,*12*,*17*–*19*). The models used for the first step were boosted regression trees (*20*); LASSO (least absolute shrinkage and selection operator) applied to logistic regression (*21*); and overlapped grouped LASSO penalties for General Additive Models selection (A. Chouldechova, unpub. data, https://arxiv.org/abs/1506.03850). We calculated the importance of each covariate by comparing the areas under the receiver operator curve (AUCs) between a full model that contained all covariates and a model without each covariate. To evaluate the relative importance of each covariate to the full model, we repeated the procedure sequentially (Appendix Table 5).

We weighted all models by the number of isolates tested in each survey and conducted 10 Monto Carlo simulations on the models to account for the variation introduced by transformation of prevalence estimates into binary variables. The models were trained by using 4-fold spatial cross-validation to prevent overfitting and ensure generalization in geographic regions poorly represented in the training dataset. We defined the 4 spatial folds by using a k-means clustering algorithm (*22*). The algorithm clustered the surveys according to their spatial distances and partitioned them into 4 spatially disjointed sets with equal sizes (Appendix). No predictions were made in urban settlements; there were areas defined as artificial surfaces in GlobCover 2009 (*23*). We conducted sensitivity analyses by restricting PPSs to 2009–2020 only (to match EFSA reporting period), to 6 or 7 of the most common antimicrobial/bacteria combinations only, and to P50 calculated by class (rather than compound) (Appendix).

In the second step, we ensembled predictions from the 3 models according to the models' predictive ability, assessed by using the AUC. We calculated the resulting map of P50 as the mean of the 3 model predictions weighted by their AUC values. We calculated the associated map of prediction uncertainty as the SD of predicted P50 values from the 10 Monte Carlo simulations (Appendix Figure 4, panel A).

In the third step, we adjusted the P50 predictions in each country, using P50 values calculated from EFSA reports. Concretely, we multiplied P50 values in each pixel by the ratio of country-level P50 as reported by EFSA and the mean P50 of all pixels across each country as predicted by the geospatial model. That step ensured that the country-level mean of P50 values corresponded to reports from EFSA while preserving geographic variations in AMR levels within each country. To assess the variations in P50 values within each country, we calculated country-level SDs of P50s (Appendix Figure 4, panel C).

Last, we created the predictive maps of AMR hotspots for each pathogen. The threshold value for a pixel to be classified as a hotspot corresponded to the 95th percentile of all P50 values across the map and varied for each pathogen (Appendix Figure 4, panel B). We obtained estimated animal densities associated with those areas from Gilbert et al. (*24*). Using those estimates, for each country we calculated the percentage of each animal species living in the hotspot areas.

Results

EFSA Surveillance

At the country level, EFSA data for 2009–2020 provided 33,802 AMR prevalence estimates (resulting in 2,996 P50s). The data were for *E. coli*, nontyphoidal *Salmonella*, *C. coli*, and *C. jejuni* in cattle, pigs, and poultry across 31 countries in Europe.

PPSs

At the local level, for 2000–2021 we identified 209 PPSs, which provided 2,849 AMR prevalence estimates (resulting in 368 P50s). The data were for *E. coli*, nontyphoidal *Salmonella*, and *Campylobacter* in food-producing animals and derived products from 21 countries in Europe. In terms of AMR prevalence, *E. coli* accounted for 44.4%, *Salmonella* for 34.2%, and *Campylobacter* for 21.4%. Poultry accounted for approximately half of the AMR prevalence (n = 1,429, 50.2%), followed by pigs (28.1%) and cattle (21.8%). One third of the sample types tested were meat (34.7%, n = 988), followed by fecal samples (23.4%). Across the countries included in the analysis, geographic coverage was on average 4.21 PPSs (interquartile range 0–11.7)/100,000 km^2. Half of the PPSs identified were from the combination of Spain (20.5%), Italy (18.7%), and Germany (10.5%) (Figure 1). The average number of PPSs published by year increased from 3 during 2000–2005 to 14 during 2015–2021 (Figure 1, panel B).

Comparison of PPS and EFSA

AMR prevalence estimates varied considerably between data sources and country. For 2018–2020, Greece, Poland, and Germany accounted for more

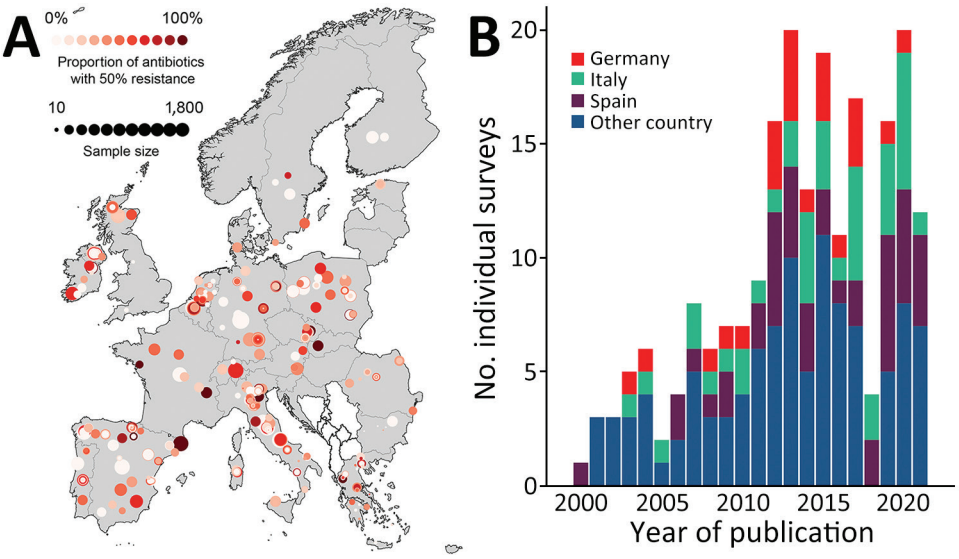

Figure 1. Data from study of predictive mapping for antimicrobial resistance of *Escherichia coli*, *Salmonella*, and *Campylobacter* in food-producing animals, Europe, 2000–2021. A) Geographic distribution of point prevalence surveys (PPSs). B) Number of PPSs published per year. Additional information is provided in the Appendix (https://wwwnc.cdc.gov/EID/article/30/1/22-1450-App1.pdf).

than double the national average P50 calculated from PPS data compared with P50s calculated from EFSA (Table 1). Conversely, the national average P50 calculated from PPS data from Portugal and Switzerland was ≤30% lower than that calculated from EFSA.

The highest resistance prevalence estimates were for tetracycline (57.9%–36.4%), ampicillin (58.6%–34.9%), ciprofloxacin (64.6%–13.1%), and nalidixic acid (60.9%–25.5%). The difference in mean P50 between PPSs and EFSA data ranged from 15.2% to −17.4% for *Salmonella* and from 19.1% to −7.96% for *E. coli*. For *Campylobacter*, systematically higher prevalence estimates were obtained from PPSs; differences ranged from 12.1% to 0.78% (Figure 2).

Geospatial Modeling

We mapped predicted P50s at 10 × 10 km resolution for each of the 3 bacteria across Europe (Figure 3). In the final models, the predicted P50 values ranged from 0 to 79% for *E. coli*, 0 to 40% for *Salmonella*, and 0 to 100% for *Campylobacter* (Figure 3, panel A; prediction uncertainty, Appendix Figure 3, panel A). P50 cutoffs for hotspots of AMR (calculated as the top 95% of the values on the map) were 0.43 for *E. coli*, 0.23 for *Salmonella*, and 0.60 for *Campylobacter*. AMR hotspots for *E. coli* were predicted to be located in southern Romania (Muntenia, Dobrogea) and southern and eastern Italy (Sicily, Emilia-Romagna, Apulia); and for *Salmonella*, predicted hotspots were in southern Hungary, northern Italy, and central Poland. More than 90% of hotspot areas for *Campylobacter* were predicted to be throughout mainland Spain (Figure 3, panel B).

For *E. coli*, the highest geographic variations in predicted P50 levels were in Romania (13% pixel-level SDs), Bulgaria (11%), Greece 1(2%), and Italy (11%). For *Campylobacter*, the highest geographic variations in P50 were in France (10%) and Germany (10%; Appendix Figure 4, panel C). No countries had high spatial variations in predicted P50s for *Salmonella*. Cold spots for all 3 bacteria were identified in Sweden, Norway, Finland, and Iceland (data not shown). Spatial variations of P50 for countries containing coldspots were small, with pixel-level standard deviations of 3.2% (*E. coli*), 0.9% (*Salmonella*), and 1.0% (*Campylobacter*). Restricting PPS by year and antimicrobial bacteria combinations resulted in little difference (mean Pearson correlation coefficient 0.992; mean absolute error 0.932%) to the overall model predictions (Appendix Table 4). In addition, we found little difference when P50 was calculated by antimicrobial class rather than individual compound (Pearson correlation coefficient 0.995, mean absolute error 0.66%) (Appendix Table 4, Figure 4). Importance of environmental covariates to the models varied by pathogen (Appendix Table 5). For *E. coli* and *Salmonella*, the covariate with highest importance was the percentage of tree coverage

Table 1. Three-year mean of proportion of antimicrobial drugs with >50% resistance from PPS and EFSA data and ratios of P50 for countries reporting to both data sources, Europe, 2018–2020*

Country	Mean P50 from PPSs	Mean P50 from EFSA	PPS and EFSA P50 ratio
Poland	0.64	0.26	2.47
Germany	0.60	0.25	2.42
Greece	0.39	0.19	2.02
Spain	0.39	0.24	1.67
Belgium	0.29	0.21	1.34
Romania	0.31	0.28	1.10
Italy	0.23	0.25	0.92
Switzerland	0.17	0.22	0.77
Portugal	0.18	0.32	0.57

*EFSA, European Food Safety Authority; PPS, point prevalence surveys; P50, >50% antimicrobial resistance.

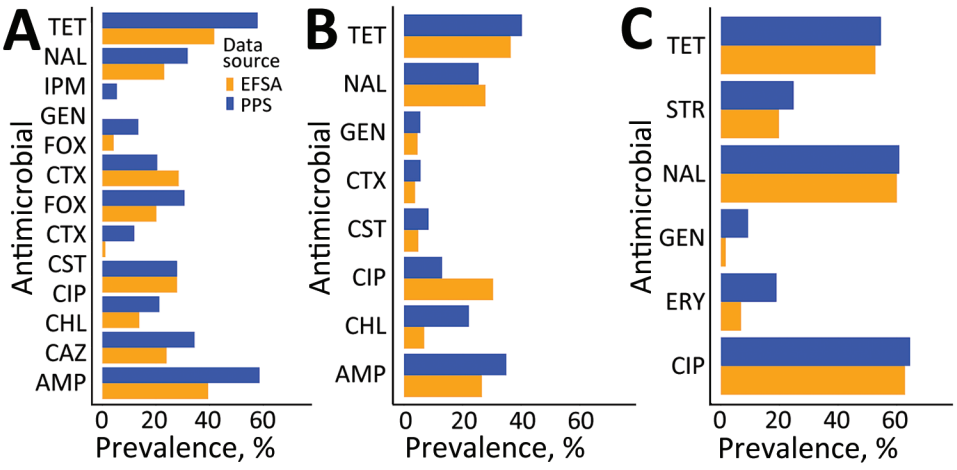

Figure 2. Mean prevalence for antimicrobial class and bacteria combinations, split by data source, Europe, 2009–2020. A) *Escherichia coli*; B) *Salmonella*; C) *Campylobacter*. AMP, ampicillin; CAZ, ceftazidime; CHL, chloramphenicol; CIP, ciprofloxacin; CST, colistin; CTX, clavulanic acid; EFAS, European Food Safety Authority; FOX, cefoxitin; GEN, gentamicin; IPM, imipenem; NAL, nalidixic acid; PPS, point prevalence survey; STR, streptomycin; TET, tetracycline.

(ΔAUC 0.106 for *E. coli* and 0.078 for *Salmonella*). For *Campylobacter*, the covariate with highest importance was antimicrobial use in animals (ΔAUC 0.037), closely followed by yearly average of minimum monthly temperature (ΔAUC 0.034).

In 9 of the 31 countries in Europe, >50% of cattle, pigs, or poultry are estimated to be raised in the predicted AMR hotspot areas (Table 2). For instance, 93% of poultry in Spain, 90% of poultry in Greece, and 97% of poultry and 92% of pigs in Cyprus are raised in AMR hotspots.

Discussion

In this study, we geographically disaggregated AMR prevalence for *E. coli*, nontyphoidal *Salmonella*, and *Campylobacter* reported among food-producing animals across Europe by supplementing national EFSA data with subnational PPS data to produce maps of estimated AMR prevalence. For multiple countries, such as Italy, Romania, and Poland, rather than consistently high countrywide AMR levels, in our final model we predicted specific geographic hotspots of high AMR prevalence that may coexist within regions

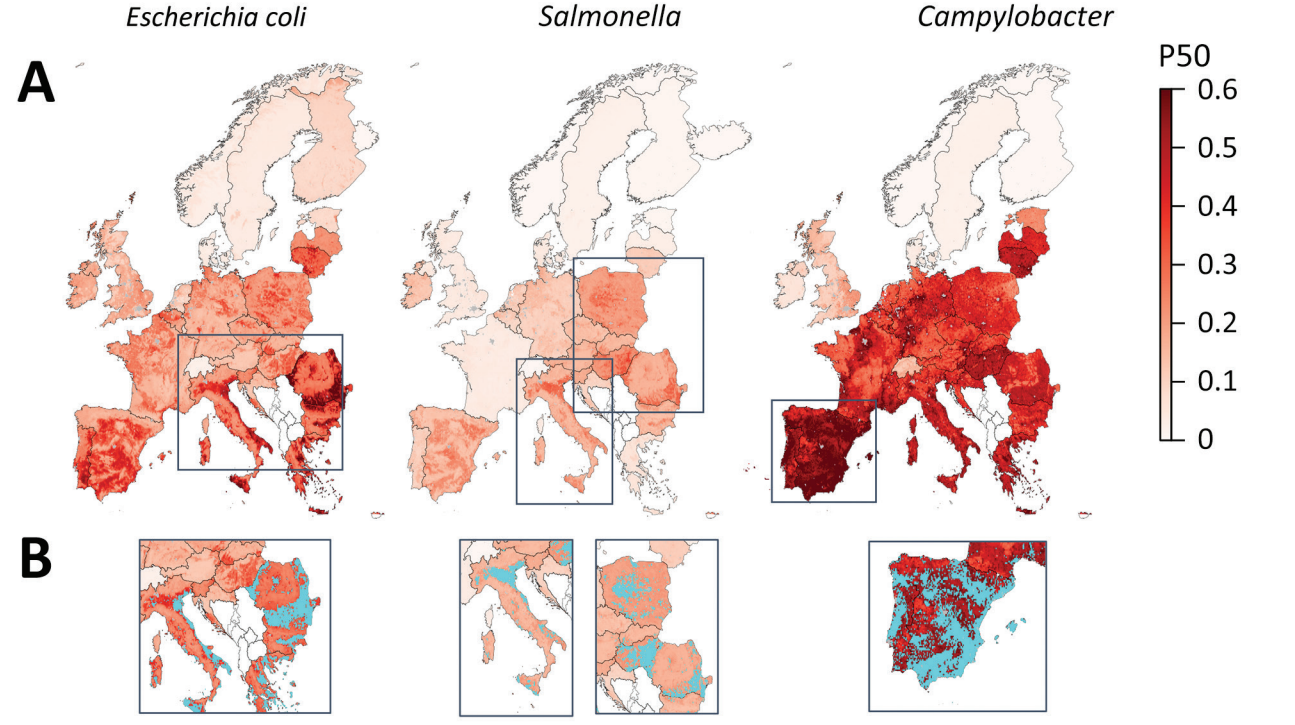

Figure 3. Mapping of predicted P50s and hotspot areas for antimicrobial resistance of *Escherichia coli*, *Salmonella*, and *Campylobacter*, Europe. A) Predicted proportions of antimicrobials with P50 at 10 × 10 km resolution per bacteria. B) Antimicrobial resistance hotspots (light blue) in eastern Europe, Italy, and Spain. Cutoffs: *E. coli*, 0.43; *Salmonella*, 0.23; *Campylobacter*, 0.6 (95% percentile). P50, >50% antimicrobial resistance.

of lower AMR prevalence in the same countries. In specific regions, countries in which AMR seems to be consistently high may have made more progress against AMR than previously thought (with only some, rather than all, areas containing high levels) by interpretation of EFSA data or nationally published reports. Further improvements could be made in those countries by targeting interventions (e.g., improved farm biosecurity and targeted surveillance in hotspots where AMR levels remain high). In contrast, largely diffuse and geographically uniform (low) countrywide AMR prevalence was found in countries with low AMR levels (e.g., Sweden, Norway, and Iceland); uncertainty in these predictions were higher for *Campylobacter* than for *E. coli* and *Salmonella*.

For all 3 bacteria studied, AMR prevalence was substantially lower in Norway, Sweden, Denmark, and Switzerland than the average for Europe. Those countries were among the first to establish animal AMR surveillance (i.e., DANMAP in Denmark in 1995 [*25*]) and have now integrated surveillance of zoonotic bacteria in humans and animals. For several decades, they have been guiding national and international control strategies. For instance, in the 1990s, increased prevalence of vancomycin-resistant enterococci reported by DANMAP was instrumental to banning use of antimicrobial drugs for growth promotion in livestock (*25*).

In contrast, countries in which a high proportion of food-producing animals are raised in areas predicted as hotspots of resistance by our study are Cyprus, Portugal, and Spain. In 2018, one fifth (20.8%) of the pigs in the European Union were reared in Spain (*26*), where 88% of its pigs were predicted to be raised in geographic hotspots of *Campylobacter* resistance, primarily in Aragon and Catalonia. However, that finding was not the case for other high-density pig regions such as Brittany (France), northwest Germany (Lower Saxony and North Rhine-Westphalia), and Denmark (*27*). Those findings suggest that high AMR is not necessarily associated with high animal densities but possibly with other drivers such as farming practices, biosecurity measures, and antimicrobial use (*28*).

Across Europe, the highest prevalence of resistance in our models was reported for antimicrobial drugs commonly used in animal production: tetracyclines, quinolones, penicillins, and aminoglycosides (gentamicin and streptomycin). Of particular concern were the compounds considered critically important antimicrobials for human medicine (*29*) and for which AMR prevalence was predicted to be >50% (ampicillin in *E. coli* [58.6%] and ciprofloxacin in *Campylobacter* [64.6%]).

Table 2. Percentages of food-producing animals raised in each country that fall within an antimicrobial resistance hotspot area (95th percentile per pathogen) for France, Germany, Spain, and countries in which pathogen percentage >50% for ≥1 animal species*

Pathogen, country	Cattle, %	Pigs, %	Poultry, %
Escherichia coli			
France	0	0	0
Germany	0	0	0
Spain	2.1	2.3	1.8
Bulgaria	34.4	51.5	57.8
Cyprus	33.8	68.9	68.5
Greece	39.4	57.9	35.5
Romania	34.8	77.5	57.8
Salmonella			
France	0	0	0
Germany	0	0	0
Spain	8.8	28.2	24.8
Cyprus	51.8	91.6	96.6
Hungary	63.5	64.7	80.6
Italy	52.0	70.2	64.0
Poland	21.6	66.0	74.3
Romania	17.0	65.2	45.0
Campylobacter			
France	0.5	4.6	6.2
Germany	1.8	14.9	23.2
Spain	32.3	87.9	93.0
Cyprus	26.0	44.9	66.3
Greece	10.9	58.4	90.3
Portugal	22.1	74.9	88.0

*Antimicrobial resistance for *Escherichia coli*, nontyphoidal *Salmonella*, and *Campylobacter*.

In our study, estimates of P50 for *Salmonella* were much lower than those for *E. coli* and *Campylobacter*, which could potentially be attributed to the success of targets imposed by the European Union (e.g., reducing *Salmonella* prevalence in poultry over the past decade [*30*]). In addition, several countries had already implemented *Salmonella* control strategies before European Union–wide initiatives. For instance, in the 1970s, the United Kingdom set up national AMR surveillance for *Salmonella*, and in 1969, France had similar initiatives for *Salmonella* and *E. coli* (*25*). Switzerland also implemented a stringent control program for *Salmonella* Enteritidis in 1993 (*31*), more than a decade earlier than the first European Union–wide initiative (*30*).

When we compared estimates of resistance (P50) derived from PPS and EFSA data, the average P50 from PPSs seemed to more closely match national EFSA prevalence values in some countries more than in others. For instance, in Spain and Italy, the ratios of P50 inferred from PPS and EFSA data were close to 1 over the past 3 years. One reason may be the higher number of PPSs from these countries (17 in Spain and 13 in Italy), which average out closer to the EFSA values. In contrast, in countries with P50 ratios >2 or <0.8 (Poland, Germany, Greece, Portugal) inferred from PPS and EFSA data, only 1–4 studies have been conducted in the past 3 years. Therefore, although

smaller sample sizes may be insufficient for comparing national averages (PPS vs. EFSA) they may still represent subnational heterogeneity in AMR not observed in the national average from EFSA. A higher coverage of PPSs may further improve the confidence in subnational model predictions.

Among the limitations of our modeling study, the first is that our literature search for PPSs published in Europe during 2000–2021 resulted in a mere 209 PPSs that were associated with geographic information. In contrast, for the same period, 446 PPSs with geographic information were published in China (*12*). Torres et al. also assembled AMR studies of food-producing animals during 1957–2018; however, of the 510 papers from Europe identified, the breakdown of their surveys corresponding to our search criteria was not available in open access (*32*). Thus, the limited number of surveys that satisfied our inclusion criteria, particularly the reporting of geographic information, precluded mapping AMR prevalence for individual drug/bacteria combinations or animal species.

Second, with regard to using PPSs for regional estimations, differences in sampling strategy and sample sizes may affect the comparability of surveys and potentially explain why prevalence calculated from PPSs was in some instances higher than the prevalence estimates reported by EFSA. In particular, targeted sampling for bacteria that probably have high-resistance profiles, such as extended-spectrum beta lactamase–producing *E. coli* (*33*), could lead to comparatively higher AMR in PPS data than in the general population, which are more likely to be observed with the EFSA sampling scheme. In terms of microbiology, the set of tested antimicrobials differed between PPSs, which necessitated use of a composite metric. In addition, there were some transparency issues in terms of which methods or breakpoints were used (i.e., assumptions had to be made in the case of missing data [such as guideline year] and in the harmonization approach used for PPSs that used different guidelines, which may have led to some unintended bias), as well as a diversity of breakpoints used. Despite attempts to reduce variability between surveys, some variability may still exist and therefore efforts should be made to develop standardized protocols in the future, such as for all PPSs to shift to using ECOFF values and to release raw data. The creation of a consensus breakpoint table that could be used by all would also greatly assist with the comparability of those data and reduce the need for such adjustments. Because most studies reported only sampling location or region by name rather than specific coordinates, coordinates and size of region were estimated (and may not always represent the location of the farms where the animals were raised), which may have led to further uncertainty in our models.

Third, because of the limited number of PPSs, as well as their heterogenous distribution across the study period, incorporating the temporal dimension into the modeling framework remains challenging at this stage. Therefore, countries that have had considerably reduced AMR levels since 2009, such as the Netherlands (*34*), may be associated with higher AMR prevalence in our maps than that in the latest reports. However, as the number of surveys grows in the future, other spatio-temporal approaches, such as the Integrated Nested Laplace Approximation (*35*), could be used to account for not only spatial but also temporal variations in AMR prevalence extracted from PPSs.

Last, because of the static framework of geospatial modeling, it was not possible to incorporate all relevant data. That limitation may have a dynamic effect on AMR prevalence estimates, notably animal movement.

In conclusion, high-resolution maps that predict subnational hotspots can help support targeted resource allocation and control strategies for reducing AMR burden. Such strategies could include improving farm biosecurity and targeted surveillance. The accuracy of these maps could be gradually improved in the future should countries routinely report geographic location data along with microbiological sampling results.

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review and data extraction; J.P. contributed to interpretation and revision of the manuscript; T.V.B. contributed to study conception and design, data interpretation, supervision, revision of the manuscript, and final approval.

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Ms. Mulchandani is a research assistant at ETH Zurich, where she is researching AMR in animals. Her main research interests are zoonotic diseases and outbreak responses.

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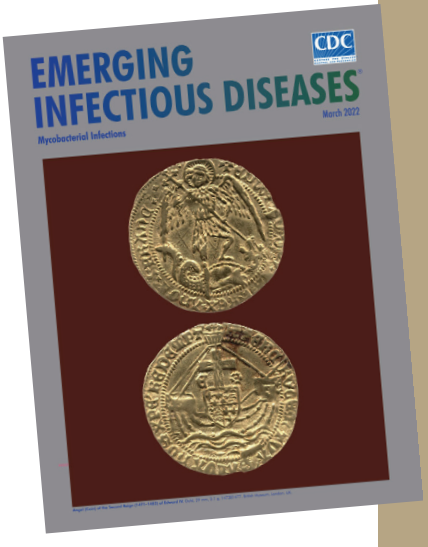
etymologia revisited

Schizophyllum commune

[skiz-of′-ĭ-ləm kom′-yoon]

Schizophyllum commune, or split-gill mushroom, is an environmental, wood-rotting basidiomycetous fungus. *Schizophyllum* is derived from "*Schíza*" meaning split because of the appearance of radial, centrally split, gill like folds; "*commune*" means common or shared ownership or ubiquitous. Swedish mycologist, Elias Magnus Fries (1794–1878), the Linnaeus of Mycology, assigned the scientific name in 1815. German mycologist Hans Kniep in 1930 discovered its sexual reproduction by consorting and recombining genomes with any one of numerous compatible mates (currently >2,800).



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Article DOI: https://doi.org/10.3201/eid3001.221450

Predictive Mapping of Antimicrobial Resistance for *Escherichia coli*, *Salmonella,* and *Campylobacter* in Food-Producing Animals, Europe, 2000–2021

Appendix

Methods

Literature Review

We conducted a systematic literature review on antimicrobial resistance (AMR) prevalence in livestock and livestock products in Europe (Appendix Figure 1). We used three databases: PubMed, ISI Web of Science, and Scopus. Our original search focused on four pathogens commonly found in animals and their products*: Escherichia coli*, *Staphylococcus aureus, Campylobacter* spp., and non-typhoidal *Salmonella* spp. The searches were conducted at different time periods between May 2019 and January 2022, and included studies published between 2000 and 2021.

The general format for our literature queries was: (Resistance) AND (Bacterial Species) AND (Animal/Sample Type) AND (Country).

The keywords used for the literature review on PubMed, ISI Web of Science, and Scopus were: ("antibiotic resistance" OR "antimicrobial resistance" OR resistance OR resistencia OR "resistencia aos antibioticos" OR resistencia OR "resistencia a antibioticos" OR susceptibility OR susceptibilidade OR suscetibilidade OR antibiogram OR "antibiotic susceptibility testing" OR antibacteriano OR antibiotic OR antimicrobial OR antibiotic OR antibacterial OR antimicrobiano OR antibiograma OR antibiotic) AND (Escherichia OR "E. coli" OR coliform OR salmonella OR "salmonella spp." OR "S. aureus" OR staphylococcus OR "Staphylococcus spp." OR "MRSA" OR "MSSA" OR campylobacter OR "campylobacter spp." OR "C. jejuni" OR "C.

coli") AND (animal OR food OR "food producing" OR meat OR cow OR cattle OR beef OR bovine OR buffalo OR pig OR piggeries OR pork OR "chicken" OR "flock" OR "broiler" OR "layer" OR "egg" OR "poultry" OR "avian" OR milk OR dairy OR cheese) AND (France OR Spain OR Netherlands OR Denmark OR Sweden OR Italy OR Greece OR Germany OR French OR Spanish OR Dutch OR Danish OR Swedish OR Italian OR Greek OR German OR Norway OR Norwegian OR Finland OR Finnish OR Poland OR Polish OR "United Kingdom" OR England OR English OR Romania OR Romanian OR Bulgaria OR Bulgarian OR Iceland OR Icelandic OR Hungary or Hungarian OR Portugal OR Portuguese OR Austria OR Austrian OR Czechia OR "Czech Republic" OR Czechian OR Ireland OR Irish OR Lithuania OR Lithuanian OR Latvia OR Latvian OR Croatia OR Croatian OR Slovakia OR Slovakian OR Estonia OR Estonian OR Switzerland OR Swiss OR Moldova OR Moldovan OR Belgium OR Belgian OR "North Macedonia" OR Macedonia OR Macedonian OR Slovenia OR Slovenian OR Cyprus OR Luxembourg OR Malta OR Maltese). In PubMed, this query was put directly into the search bar. On Scopus, this search was conducted using TS = (keywords given above), where TS stands for our search topic. In the ISI Web of Science, the search was conducted using TITLE-ABS-KEY = (keywords given above). Here, TITLE-ABS-KEY stands for title, abstract, and keywords.

In PubMed, Scopus, and ISI Web of Science, an initial search on eight European countries (Italy, Germany, the Netherlands, Spain, France, Greece, Denmark, and Sweden) was conducted on January 7, 2020, for Point Prevalence Survey (PPS) published between 2000 and 2019. These searches yielded 14,445 results. Titles and abstracts were screened manually. After removing duplications, reviews, meta-analyses, book chapters, and papers irrelevant to our topic of interest, we had 1,265 potentially relevant manuscripts. At this point, papers were read and removed if geographic data was unavailable, no antimicrobial susceptibility testing was performed, the study focused on sick animals, the survey focused on animals at the country-wide level, results were pooled between different animal species or sample types, or resistance prevalences were pooled between different pathogen types. From these, 191 papers were extracted, yielding 4853 resistance estimates.

Next, in PubMed, Scopus, and ISI Web of Science, a search for the remaining European countries was conducted on April 23, 2020, for PPS published between 2000 and 2019. This search yielded 54,591 results. Titles and abstracts were screened in the same manner as the first

search, and the same non-relevant results were removed. After this step, we had 745 potentially relevant manuscripts. From these, 98 were extracted, yielding 1567 resistance prevalences.

In PubMed, Scopus, and ISI Web of Science, a search for all European countries was conducted on January 7, 2021, for PPS published in 2020. This search yielded 6,005 results. Titles and abstracts were reviewed in the same manner as the previous two searches, and the same non-relevant results were removed. After this step, we had 253 potentially relevant manuscripts. From these, 34 were extracted, yielding 783 resistance prevalences.

A final literature search (identical to that of January 7, 2021) was run on January 10, 2022, to identify all PPS published in 2021. This search yielded an additional 6,598 results. As outlined previously, all the same steps for title and abstract screening were followed, leaving 110 potentially relevant manuscripts. Of these, 22 were extracted, yielding 606 resistance prevalences. Overall, this gave 345 papers with 7,809 resistance estimates of any antibiotic-pathogen combination.

As there was no mandated or routine reporting of *Staphylococcus aureus* to EFSA (there was only limited voluntary reporting of MRSA from 5 countries in 2018 and 6 countries in 2019) AMR estimates for *S. aureus* were subsequently excluded. Additionally, only countries reporting to EFSA were retained. The final number of manuscripts was 209.

Geographic localization of point prevalence surveys

Only PPS that reported geographic information were included in the study. The extracted information was recorded in "name_of_location" and "level_of_uncertainty" variables.

- "Name_of_location" contains the name(s) of the most precise location information available in the article. Where more than one location was reported, both names were recorded.
- "Level_of_uncertainty" contains the administrative level at which the sampling was performed (see Legend on resistancebank.org for full details). These data were then used to determine "Ycoord" and "Xcoord" variables.
- These data were then used to determine "Ycoord" and "Xcoord" variables. There were two ways in which these were generated:

1. **Samples taken from across an area/province** – the centroid of the province was obtained.

2. **Several sampling points across an area/region** – the middle point of all the sampling points was taken. This can be identified using variable "name_of_location" where more than one name is recorded.

Example:

DOI: 10.1155/2009/456573

Extract 1 from paper: "C. jejuni isolates were selected from a prevalence study of thermophilic campylobacters in livestock carried out in the Basque Country (Northern Spain)"

Extract 2 from paper: "…isolates were selected on the basis of isolation source (host, farm, and flock). Hence, the 72 isolates analysed by broth microdilution included 19 isolates from 12 poultry farms (18 flocks), 25 from dairy sheep (21 farms), and 28 isolates from cattle (14 beef cattle and 11 dairy cattle farms)"

Interpretation: Tested a specific subset of isolates from across Basque.

Level of uncertainty: Province

Name of location: Basque County

X/Y Coordinates: taken from the centroid of the Basque province.

Harmonization of antimicrobial resistance rates

The two most frequently used systems for antimicrobial susceptibility testing (AST) are Clinical and Laboratory Standards Institute (CLSI) and European Committee for Antimicrobial Susceptibility Testing (EUCAST). Each system uses breakpoints to classify susceptible and resistant phenotypes; these values are updated annually. Therefore, adjustment for breakpoint variation over time is essential.

In this study, we found 96% of records reported the guidelines used, while 72% of these records also reported the year of the guidelines used. The majority of records reported CLSI (52%), followed by EUCAST (29%), despite all studies originating from the European region. 4.4% of records did not report a guideline, and these records were excluded from subsequent analysis. The remaining records reported a mix of guidelines used in mentioned surveillance

systems (e.g., DANMAP, NARMS, BSAC etc). For records where the guideline was reported, but no specific year, a date 4 years prior was assumed as this was the median lag between publication date of the survey and year of the guidelines. These assumptions were applied to maximise the amount of data retained for subsequent analyses.

The same harmonization procedure was then applied to all records as outlined in reference (*1*). This harmonization procedure resulted in 9% of records (262 out of 2888) being revised.

To assess the impact of using CBPs rather than ECOFFs, we changed the breakpoints used to ECOFFs rather than CBP, which resulted in 11% of the calculated P50s changing. Of these 38 P50s, the average absolute change was 18.9%. For these P50s, the majority (n = 35) became larger, while five became smaller. Therefore, ≈90% of the calculated P50s would remain the same if the breakpoints were changed, and the absolute change would be relatively small.

Desk review of national reports

We conducted a desk review of European countries to identify national reports that contain information on AMR in food-producing animals (Appendix Table 6). The contents of the reports were compared with EFSA, to determine if there was any further relevant data contained within these reports. Due to the limited additional data, with low comparability, these data were not extracted for this study.

Geospatial modeling of P50

During the first step, the P50 values (proportions) were transformed into presence and absence of resistance using a random binarization procedure. Concretely, each P50 value was duplicated 5 times, and compared with a random number between 0 and 1. P50 values higher than the random number were classified as presence of resistance, otherwise the values were classified as absence of resistance.

Sensitivity analyses and covariate importance

Sensitivity analyses were conducted by (a) restricting PPS to the same period as EFSA (2009–2020), (b) restricting to the six/seven most common drug-bug combinations and (c) by calculating P50 by class of drug rather than individual compound. For analysis (b), for *E. coli* and *Salmonella* the seven drugs included were: TET, AMP, SXT, CHL, CIP, GEN, CTX. The six most common drugs for *Campylobacter* were AMP, STR, GEN, CIP, TET, ERY.

The importance of covariates was calculated by sequentially removing each covariate from the modeling procedure and comparing the changes in the mean AUC across 10 Monte Carlo simulations.

Results

Descriptive analysis

A total of 81,639 records were identified from the literature search (Appendix Figure 1). Following de-duplication, title, abstract and subsequent full paper screen, a total of 209 studies with geographic information had data extracted. From 209 PPS where geographic information was reported, 2,849 AMR estimates were extracted, providing 368 P50s.

From the EFSA reports, 2,996 P50s at country-level (33,802 AMR estimates) were calculated from data collected between 2009 and 2020. The numbers of countries reporting to EFSA each year ranged from 23 in 2009, 20 in 2011, to 31 countries reporting annually from 2015 onwards.

Appendix Table 1. Suggested antimicrobials, by bacteria, for inclusion for antimicrobial susceptibility testing (AST) for surveillance of AMR in foodborne bacteria (*2*)

Antimicrobial classes	*Salmonella, E. coli*	*Campylobacter*
Aminoglycosides	Gentamicin	Gentamicin
		Streptomycin
Amphenicols	Chloramphenicol	
Carbapenems	Imipenem	
	Meropenem	
Cephalosporins II	Cefoxitin	
Cephalosporins III	Cefatoxime (or Ceftriaxone)	
	Ceftazidime	
Cephalosporins IV	Cefepime	
Glycopeptides		
Glycylcyclines	*Tigecycline*	
Lincosamides		*Clindamycin*
Lipopeptides		
Macrolides	Azithromycin	Erythromycin*
Nitrofurans	*Nitrofurantoin*	
Oxaxolidinones		
Penicillins	Ampicillin	Ampicillin
	Amoxicillin	
	Temocillin	
Polymyxins	Colistin	
Quinolones	Ciprofloxacin	Ciprofloxacin
	Nalidixic acid	*Nalidixic acid*
	Pefloxacin^	
Rifamycins		
Streptogramins		
Sulfonamides	Sulfisoxazole[#]	
Tetracyclines	Tetracycline	Tetracycline[~]
Trimethoprim	Trimethoprim	

Antimicrobials italicized are second priority
* Resistance toward erythromycin reflects azithromycin resistance
^ To screen for ciprofloxacin resistance in *Salmonella* spp. when disk diffusion is used.
[#] Trimethoprim-sulfamethoxazole can be used instead of using sulfisoxazole or trimethoprim alone
[~] Doxycycline may be used instead of tetracycline

Appendix Table 2. Environmental and anthropogenic covariates use to train child models

Name	Acronym	Year	Original Resolution	Source	Unit
Travel time to cities	acc	2015	30-arcsec resolution	(*3*) https://www.map.ox.ac.uk/accessibility_to_cities/.	minute
Antimicrobial use in animals	use	2013	0.083333 decimal degrees	(*4*) http://science.sciencemag.org/content/357/6358/1350.full	Log10[(mg/pixel)+1]
Yearly average of minimum monthly temperature	tmp	1970–2000	2.5 min	(*5*) http://worldclim.org/version2	°C * 10
Percentage irrigated areas	irg	2015	0.083333 decimal degrees	Global Map of Irrigation Areas (GMIA) (6) https://zenodo.org/record/6886564#.YuZ1HS8RpN0	%
Population density of cattle, chickens, pigs, and sheep (GLW version 4)	ca_v4 ch_v4 pg_v4 sh_v4	2015	0.083333 decimal degrees	(*7*) (https://www.nature.com/articles/sdata2018227)	Log10[(Heads/pixel) +1]
Percentage of tree coverage	veg	2013	0.008333 decimal degrees	(*8*) https://earthenginepartners.appspot.com/science-2013-global-forest/download_v1.2.html	%

Appendix Table 3. Absolute difference between resistance prevalence for antimicrobials by data source (point prevalence survey (PPS) vs European Food Safety Authority (EFSA)) between 2018 and 2020, and their WHO designation of antimicrobial importance*.

Variable	*E. coli*	*Salmonella*	*Campylobacter*	WHO Grouping
AMP	19.11	8.27	-	Critically important
CAZ	10.41	-	-	Critically important
CHL	7.51	15.2	-	Highly important
CIP	−0.02	−17.4	1.71	Critically important
CST	10.66	3.41	-	Critically important
CTX	10.41	1.87	-	Critically important
ERY	-	-	12.1	Critically important
FOX	−7.96	-	-	Highly important
GEN	9.09	0.96	7.66	Critically important
IPM	5.53	-	-	Critically important
NAL	8.7	−2.35	0.78	Critically important
STR	-	-	4.99	Critically important
TET	16.07	3.81	1.87	Highly important

*A ratio <1 indicated a lower 3-y mean P50 using PPS data, and a ratio >2 meant a more than double 3-y mean P50 from PPS data compared to EFSA.

Appendix Table 4. Comparison between maps produced using all extracted data, maps produced using restricted number of drugs, maps produced when P50 is calculated by class of drug (rather than individual compound), and maps produced using only surveys published between 2009 and 2020. Mae: mean absolute error; Cor: Pearson correlation coefficient.

Variable	*E. coli*	*Salmonella*	*Campylobacter*
(a) Restricted by year (2009–2020)			
No. of surveys	123	66	74
Mae	0.85%	0.75%	1.4%
Cor	0.994	0.986	0.995
(b) Restricted pathogen-antimicrobial combinations			
No. of surveys	153	97	111
Mae	1.5%	0.46%	0.63%
Cor	0.984	0.994	0.999
(c) P50 calculated at class level			
No. of surveys	156	99	113
Mae	1.0%	0.5%	0.49%
Cor	0.992	0.993	0.999

Appendix Table 5. Importance of covariates for mapping the distribution of AMR, indicating mean AUC of the full model, and the decrease in mean AUC after each covariate was removed from the modeling procedure.

Variable	*E. coli*	*Salmonella*	*Campylobacter*
Full model	0.635	0.606	0.536
Travel time to cities	0.03	0.001	0.02
Antimicrobial use in animals	0.019	0.037	0.037
Yearly average of minimum monthly temperature	0.033	0.042	0.034
Percentage irrigated areas	0.016	0.034	0.027
Population density of cattle	0.024	0.036	0.023
Population density of chicken	0.025	0.041	0.023
Population density of pigs	0.017	0.03	0.032
Population density of sheep	0.03	0.029	0.032
Percentage of tree coverage	0.106	0.078	0.024

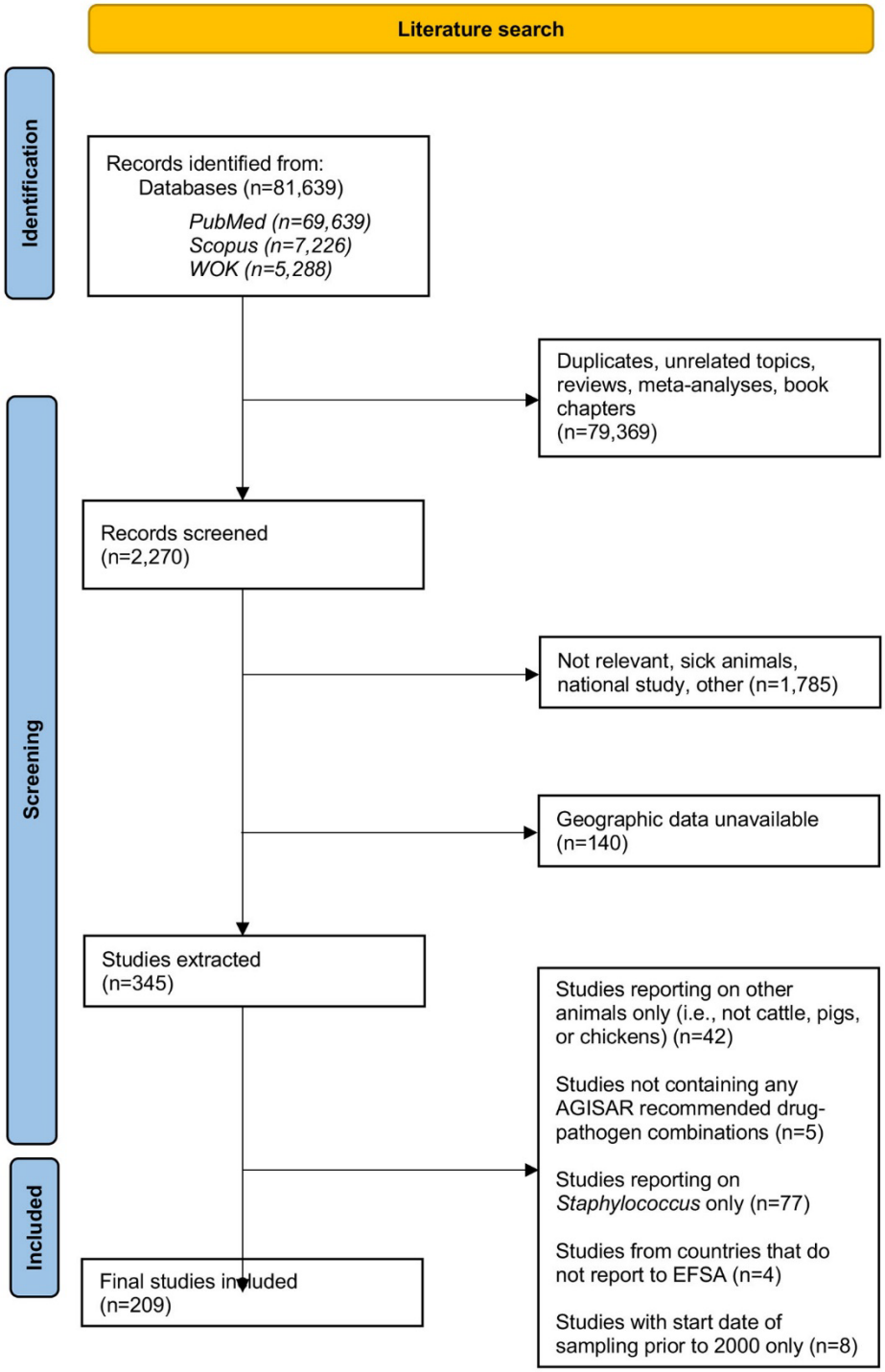
Appendix Table 6. Desk review of European countries reporting AMR in zoonotic and foodborne bacteria (2007–2020)

No.	Country	EU Member State	Reporting to EFSA*	PPS extracted^	National level integrated surveillance (*9*) Comparison of report content and frequency of data reporting compared to EFSA reports
1	Albania		✓		
2	Austria	✓	✓	✓	
3	Belgium	✓	✓	✓	
4	Bulgaria	✓	✓	✓	
5	Cyprus	✓	✓		
6	Czech Republic	✓	✓	✓	
7	Denmark	✓	✓	✓	✓ DANMAP (Last accessed 21 Feb 2022). Established 1995. Pathogen & animal types: • *Salmonella Typhimurium* (pig) • *Salmonella Derby* (pig) • *Campylobacter jejuni* (chicken, cow) • *E. coli* (chicken, cattle) Reporting content: Same pathogens and animal types are reported to EFSA each year, with the same sample sizes. Additional data available: Last published report contains 2020 data.
8	Estonia	✓	✓	✓	
9	Finland	✓	✓	✓	✓ FINRES-VET (Last accessed 21 Feb 2022) Pathogen & animal types: • *Campylobacter jejuni* (chicken, cow) • *Salmonella* spp. (pooled animal types) Reporting content: Report less in report than to EFSA. Additional data available: Last published report contains 2020 data.

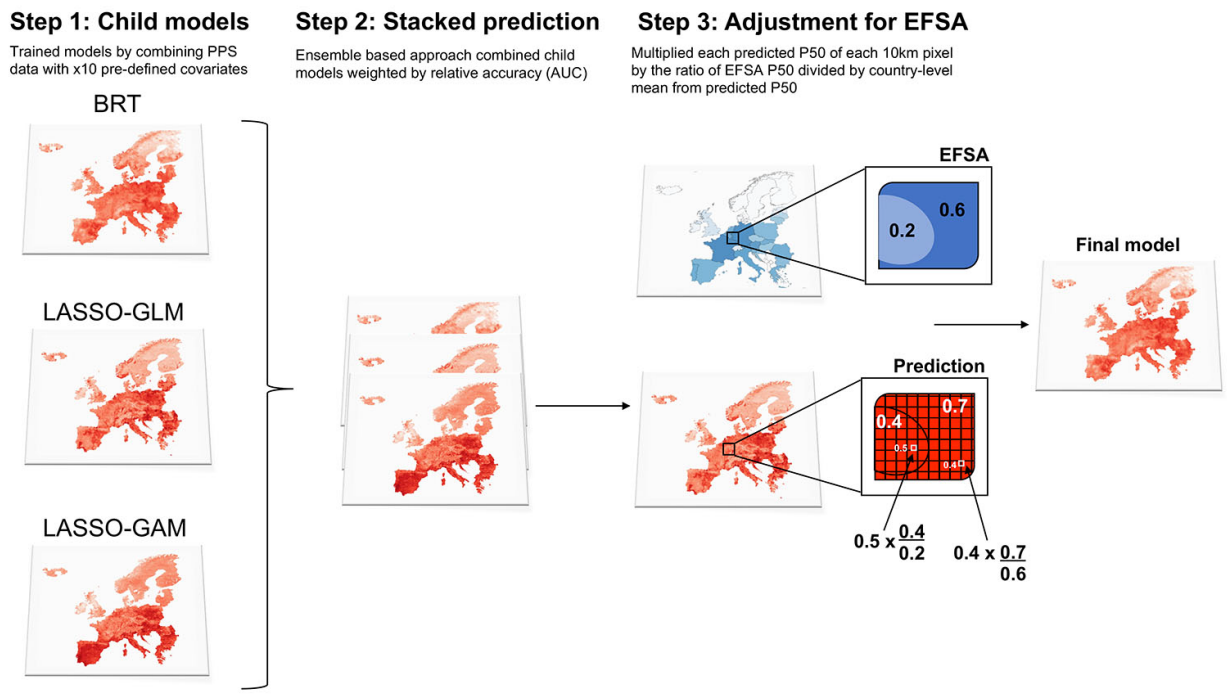
No.	Country	EU Member State	Reporting to EFSA*	PPS extracted^	National level integrated surveillance (*9*) Comparison of report content and frequency of data reporting compared to EFSA reports
10	France	✓	✓	✓	✓ ONERBA (Last accessed 21 Feb 2022) Pathogen & animal types • *E. coli* (cattle, turkeys, pig) Reporting content: Only report mandatory data (e.g., in 2018 only reported on turkeys and chickens, and for the requested sample size). The ONERBA published report in 2018 contains larger samples sizes and contain additional data on pigs. Additional data available: Last published report only contains 2018 data, however historical reports contain additional animal types and larger sample sizes compared to EFSA.
11	Greece	✓	✓	✓	
12	Germany	✓	✓	✓	? GERMAP (no report publicly available since 2015)
13	Croatia	✓	✓		
14	Hungary	✓	✓	✓	
15	Iceland		✓		
16	Ireland	✓	✓	✓	
17	Italy	✓	✓	✓	
18	Lithuania	✓	✓		
19	Luxembourg	✓	✓		
20	Latvia	✓	✓		
21	Malta	✓	✓		
22	The Netherlands	✓	✓	✓	✓ MARAN (NETHMAP) (Last accessed 21 Feb 2022) Pathogen & animal types: • *Salmonella* spp. (pooled animal types) • *E. coli* (pigs, chicken, cow, turkey) Reporting content: Only trends reported in prose. Data not in an extractable format. Additional data available: N/A – no extractable data available.
23	Norway		✓		✓NORM-VET (Last accessed 21 Feb 2022) Pathogen & animal types • *Salmonella* spp., but animals are pooled • *Campylobacter jejuni* and *Campylobacter coli* (chicken, turkey, pigs) • *E. coli* (chicken, turkey, cattle, pigs, goats) Reporting content: Animal types differ year-on-year, in-line with EFSA requirements; report same sample sizes. E.g., in 2020, reported *E. coli* in chicken and turkeys while in 2019, reported *E.coli* in cattle and pig. Additional data available: Last published report contains 2020 data.
24	Poland	✓	✓	✓	
25	Portugal	✓	✓	✓	
-	Republic of North Macedonia		✓		*Excluded from geospatial analysis due to small numbers in EFSA data.*
26	Spain	✓	✓	✓	
27	Sweden	✓	✓	✓	✓ SVARM (Report - SWEDRES) (Last accessed 21 Feb 2022) Pathogen & animal types: • ESBL-producing *E.coli* (chicken) (no AST) • *Salmonella* spp. (pooled animals) • *Campylobacter jejuni* (chicken) and *coli* (pig) Reporting content: Report *Campylobacter* in-line with EFSA requirements. Additional data available: Last published report contains 2020 data.
28	Switzerland		✓	✓	ARC-Vet (Last accessed 21 April 2022) Pathogen & animal types • *E. coli* (pig, cattle) • Campylobacter coli (pig) Reporting content

No.	Country	EU Member State	Reporting to EFSA*	PPS extracted^	National level integrated surveillance (*9*) Comparison of report content and frequency of data reporting compared to EFSA reports
					- Additional data available Last published report contains 2019 data.
29	Slovenia	✓	✓		
30	Slovakia	✓	✓	✓	
31	The United Kingdom	✓	✓	✓	✓ VARSS Pathogen & animal types: • *E. coli* (chicken, turkey, pigs) • *Salmonella* (chicken, turkey) • *Campylobacter jejuni* (chicken, turkey) Reporting content: Animal types and pathogen in-line with EFSA requirements, with same sample size. Additional data available: Last published report contains 2020 data.

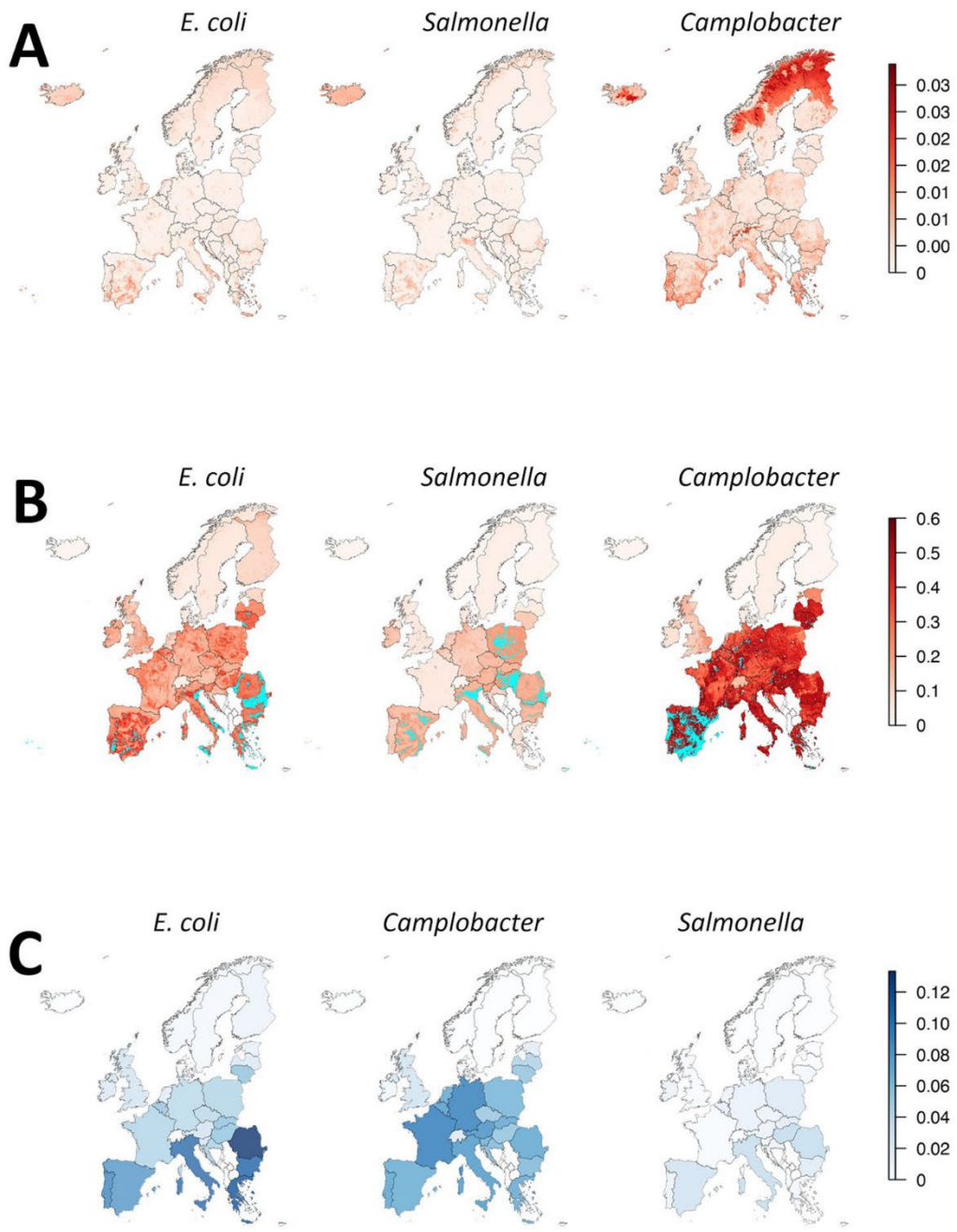
*Last published report in April 2022 contains data from 2019/2020
^Where at least one PPS extracted per country, either published or data collected between 2000 and 2021



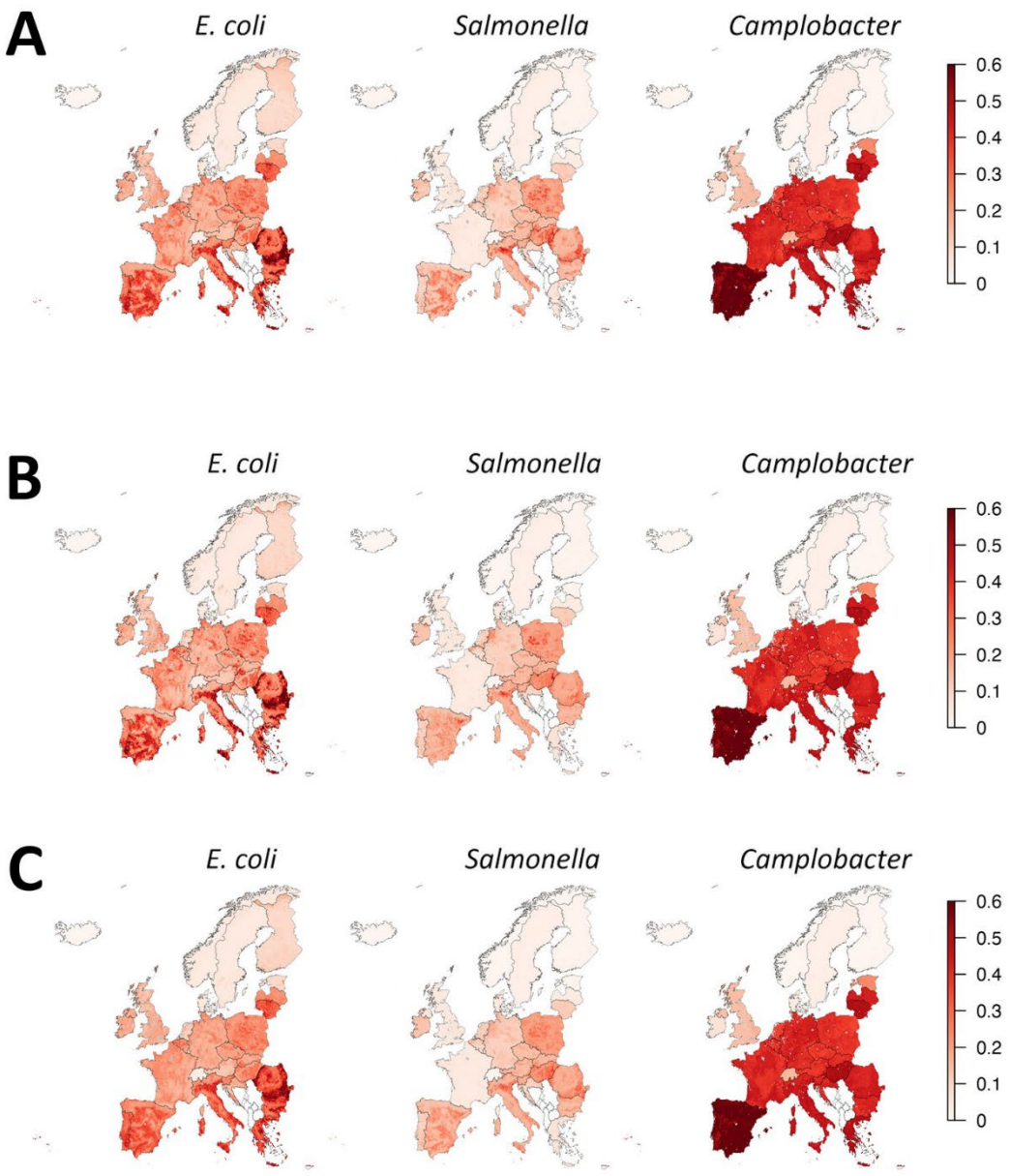
Appendix Figure 1. PRISMA Flow Diagram



Appendix Figure 2. Geospatial modelling framework



Appendix Figure 3. (a) Prediction uncertainty calculated from the variation of predicted P50 values across the ten bootstraps **(b)** Hotspot map for 31 countries (light blue indicates hotspot areas, the top 95% percentile) **(c)** Standard deviation in P50 estimates per country



Appendix Figure 4. Sensitivity analyses of geospatial modelling for (a) date restriction to 2009-2020 only (b) 6-7 most common drug-bug combinations and (c) P50 by class of drug rather than individual compound.

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