Global Trends in Antimicrobial Resistance in Animals in Low- and Middle-Income Countries

One Sentence Summary: Global analysis of point prevalence surveys show a rapid increase of antimicrobial resistance in animals in emerging countries

Authors: Thomas P. Van Boeckel[1,2,6 †,*], Joao Pires[1,6,†], Reshma Silvester[2], Cheng Zhao[1], Julia Song[3,4], Nicola Criscuolo[1], Marius Gilbert[5], Sebastian Bonhoeffer[6,§], and Ramanan Laxminarayan[1,2,4,§].

Affiliations:
1. Institute for Environmental Decisions, ETH Zurich, Zurich, Switzerland.
2. Center for Disease Dynamics, Economics & Policy, New Delhi, India.
3. Department of Ecology and Evolutionary Biology, Princeton University, NJ, USA.
4. Princeton Environmental Institute, Princeton University, NJ, USA.
5. Université Libre de Bruxelles (ULB), Brussels, Belgium.
6. Institute for Integrative Biology, ETH Zurich, Zurich, Switzerland.

*Correspondence to: thomas.vanboeckel@env.ethz.ch

[†]these authors contributed equally.

[§] these authors supervised the work equally.

Abstract (125 words max): The global scaleup in demand for animal protein represents among the most notable dietary trends of our time. Antimicrobial consumption in animals, which outweighs human consumption, has enabled large-scale production of animal protein, but its consequences on the development of antimicrobial resistance has received comparatively less attention than in humans. We analyzed 901 point prevalence surveys of pathogens from developing countries to map resistance in animals. China and India represented the largest hotspots of resistance. From 2000 to 2018, the proportion of antimicrobials with resistance higher than 50% increased from 0.15 to 0.41 in chickens, and from 0.13 to 0.34 in pigs with important consequences for animal health, and eventually for human health. Global maps of resistance provide a baseline for targeting urgently needed interventions.

Words (~ **4,500**) = 4,774 = 3,273 (main text) + 1,364 (references) + 137 (acknowledgment).

Ref: 37 (max 40)

Antimicrobials have saved millions of human lives, yet the majority (73%) of antimicrobials are used in animals raised for food (*1*). The large and increasing use of antimicrobials in animals is both an enabler and a consequence of the global scaleup in demand for animal protein. Since 2000, meat production has plateaued in high-income countries but has grown by 64%, 53% and 66% in Asia, Africa and South America, respectively (FAOSTAT 2016). The transition to high-protein diets in low- and middle-income countries (LIMCs) was facilitated by the global expansion of intensive animal production systems, in which antimicrobials are used routinely to maintain health and productivity (*2*). A growing body of evidence has linked this practice with antimicrobial resistant infections not just in animals but also in some cases, in humans (*3–5*). Although a majority of emerging infectious disease events have been associated with drug-resistant pathogens of zoonotic origins (*6*), antimicrobial resistance (AMR) in animals has received comparatively less attention than resistance in humans.

In LMICs, trends in AMR in animals are poorly documented. Colombia's is currently the only country that has made publicly available surveillance data on AMR in animals (*7*). As in high-income countries, antimicrobials are used in LMICs to treat animals and as surrogates for poor hygiene on farms. However, in LMICs, AMR levels could be exacerbated by lower biosecurity, less nutritious feed, and looser regulations on veterinary drugs (*8*). Conversely, in LMICs, AMR levels may also be reduced by lower meat consumption and limited access to veterinary drugs in rural areas. Few works have attempted to disentangle the effect of those factors, and thus far, expert opinion has prevailed over an evidence-based assessment AMR in LMICs (*9*).

In 2017, The World Health Organization (WHO) called on its member states to reduce veterinary antimicrobial use (*10*, *11*). Coordinating the global response to AMR requires epidemiological

data to assess trends in AMR across regions. In human medicine, the WHO's Global Antimicrobial Resistance Surveillance System (GLASS) (*12*) has encouraged adoption of a harmonized reporting framework, but there is no comparable framework for AMR in animals. Scandinavian countries have been at the forefront of monitoring AMR in animals, and Europe and the United States have adopted similar systems (*13*). However, in LMICs, similar surveillance systems are nascent, at best, and building a globally harmonized surveillance systems could take a long time. The challenge posed by AMR requires immediate action, and thus alternatives to systematic surveillance are needed to guide intervention based on the best evidence currently available.

In LMICs, point prevalence surveys are a largely untapped source of information to map trends in AMR in animals. Generating resistance maps from these surveys presents several challenges. First, surveys often differ in protocol, sample size and breakpoints used for antimicrobial susceptibility testing. Harmonizing those variations is a first step towards improving comparability. Second, because AMR affects many organisms, indicator organisms should be identified; the foodborne pathogens listed by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) are an ideal starting point (*14*). Third, since the problem of AMR affects many drug-pathogen combinations, it is difficult to communicate with policy makers. Introducing composite metrics of resistance may help summarize its global trends. Finally, the interpolation of epidemiological observations from data-rich regions to data-poor regions is inherently uncertain, and could be improved using factors associated with AMR. The field of species distribution modelling has proposed approaches to use such associations for predictive mapping, and the development of ensemble geospatial modelling (*15*) has help improve their accuracy.

In this study, we address these challenges to map AMR in animals in LMICs at 10-km resolution using point prevalence surveys of common foodborne pathogens. The maps summarize current knowledge, and give policymakers—or a future international panel (*16*)—a baseline to monitor AMR levels in animals, and target interventions across regions.

Results

We identified 901 point prevalence surveys reporting AMR rates in animals and food products in low- and middle-income countries. Our analysis focused on resistance in *E. coli*, *Campylobacter* spp., non-typhoidal *Salmonella* and *S. aureus*. The number of published surveys on resistance to those pathogens in LMICs increased from 3 in 2000 to 121 in 2018, and peaked at 156 per year in 2017. However, the number of surveys conducted during that period was uneven across regions (Fig. 1A): surveys from Asia (n = 509) exceeded the total for Africa and the Americas (n = 415). The number of surveys per country was not correlated with gross domestic product (GDP) per capita (Fig. 1B).

Fig. 1. Number of surveys conducted on AMR in animals. Publications by continent (A). Publications per capita *vs* gross domestic product per capita; each country is designated by ISO3 country code (B).

In LMICs, from 2000 to 2018, the proportion of antimicrobial compounds with resistance higher than 50% (P50) increased from 0.15 to 0.41 in chickens, from 0.13 to 0.34 in pigs, and plateaued between 0.12 to 0.23 in cattle (Fig. 2). Those trends were inferred from average yearly increase in P50, (1.5%/year for chickens, and 1.3%/year for pigs), weighted by the number of studies published each year (Supplementary Material).

Fig. 2. Increase in antimicrobial resistance in low- and middle-income countries. Proportion of antimicrobial compounds with resistance higher than 50% (P50). Solid lines indicate

statistically significant (5% level) increases of P50 over time, shades indicate the number of surveys per year relative to total number of surveys per species.

In LMICs, resistance levels show considerable geographic variations (Fig. 3A, and Fig. S11 for country level indexes). Regional hotspots (P50 > 0.4) of multidrug resistance were predicted in south and Northeast India, north-eastern China, northern Pakistan, Iran, Turkey, the south coast of Brazil, the Nile River delta, the Red River delta in Vietnam and the areas surrounding Mexico City and Johannesburg. Low P50 values were predicted in the rest of Africa, Mongolia and western China. Based on maps of animal densities (Fig. S7), we estimate that across LMICs, 9% [95% confidence interval (CI) (5-12%)] of cattle, 18% [95% CI (11-23%)] of pigs and 21% [95% CI (11%-28%)] of chickens were raised in hotspots of AMR in 2013. For chickens, the percentage of birds raised in hotspots of resistance in each country exceeded global average in China (38% [95% CI (24-46%)]), Egypt (38% [95% CI (22-55%)]) and Turkey (72% [95% CI (41-81%)]). We also identified regions where AMR is starting to emerge by subtracting, P50 from P10, the proportion of antimicrobial compounds with resistance higher than 10% (Fig. 3C). In Kenya, Morocco, Uruguay, southern Brazil, central India and southern China, the proportion of drugs with 10% resistance was 2 to 3 times higher than the proportion of drugs with 50% resistance, indicating that those regions are emerging AMR hotspots. Established hotspots of AMR, where the difference between P10 and P50 was low (~ 10%), included north-eastern China, West Bengal and Turkey.

The accuracy of the P50 maps (Fig. 3B) reflects the density of surveys for a region as well as the ability to associate the geographic distribution of P50 with environmental covariates using geospatial models (Supplementary Material). All geospatial model had limited accuracies (AUCs [0.674-0.68]), but all identified the travel time to cities of 50,000 people as the leading factor

associated with the geographic distribution of P50. Minimum annual temperature, and percentage of irrigated land were also positively associated with P50, but had smaller influence (Table S5).

Fig. 3. Geographic distribution of antimicrobial resistance in low- and middle-income countries. (A) P50, the proportion of antimicrobials compounds with resistance higher than 50%. (B) 95% confidence intervals on P50 (supplementary material). (C) Difference in the proportion of antimicrobials with 10% resistance and 50% resistance. Red areas indicate new hotspots of resistance to multiple drugs; blue areas established hotspots. Maps at resistancebank.org.

Uncertainty in the mapped predictions was greatest in the Andes, the Amazon region, West and Central Africa, the Tibetan plateau, Myanmar and Indonesia. Good geographic coverage of surveys enabled more accurate predictions in India, the Rift region in Africa, and the south coast of Brazil. Dense geographical coverage of surveys (> 4 PPS / 100,000 km2) did not systematically correlate with high P50 values, (Ethiopia, Thailand, Chhattisgarh; India and Rio Grande do Sul; Brazil).

The highest resistance rates were observed in the most commonly used classes of antimicrobials in animal production (Fig 4): tetracyclines, sulfonamides and penicillins (*1*). Among antimicrobials considered critical to human medicine (*17*), the highest resistance rates were for ciprofloxacin and erythromycin (20–60%) and moderate rates for $3^{rd}/4^{th}$ generation cephalosporins (10–40%). Other critically important antimicrobials, such as linezolid and gentamicin, were associated with lower resistance rates (< 20%). AMR trends in LMICs were in agreement with the trends reported in Europe and the United States (*13*, *18*) for tetracyclines, sulfonamides, and $3^{rd}/4^{th}$ generation cephalosporins, but differences also exist for quinolones and aminoglycosides.

In *E. coli* and *Salmonella* spp., quinolones resistance in LMICs (20-60%) was comparable with European levels (59.8-64% (*13*)), but gentamycin resistance was higher in LMICs (5-38%) than in Europe (2.4-8.9%). The reverse situation was observed when comparing LMICs and the US where quinolone resistance is low (2.4-4.6%) and gentamycin resistance higher (22.1% and 41.3% for *Salmonella* and *E. coli,* respectively (*18*)). In LMICs, high resistance in 3rd and 4th generation cephalosporins in E. coli was high (~40%). Resistance to carbapenems was low in all host species in LMICs, as previously reported in animals (*19*). Asia, and the Americas currently have the highest rate of colistin resistance (~18-40%).

In *Campylobacter* spp., in LMICs, the highest resistance rates were found for tetracycline (60%) and quinolones (60%). Tetracycline resistance was also the highest among all animals in the US (49.1–100% (*18*)), but lower for quinolones in chickens (20%). Resistance to erythromycin was moderate (< 30%) in LMICs, but higher than in high-income countries (0.3%-22% in US and 0-21.6% in Europe), indicating that erythromycin resistance genes (e.g., *erm*(B)) could be spreading more commonly on mobile genetic elements in LMICs.

Finally, for *S. aureus*, resistance rates across all antimicrobials were higher in Asia than in other regions. The highest rates were found for penicillin (40–80%), erythromycin (20–60%), tetracycline (20–60%) and oxacillin (20–60%). For *S. aureus*, unlike other pathogens, resistance rates across drugs (except for penicillin) varied greatly by region. Comparisons with high-income countries are limited, as few European countries reported resistance in *S. aureus* in 2016, and

178 susceptibility testing was typically restricted to MRSA, which have considerable variation in
179 prevalence (0% in Irish cattle and chickens to 40-87% in Danish pigs (*13*)).
180
181 **Fig. 4. Resistance in foodborne pathogens recommended for susceptibility testing by the**
182 **World Health Organization.** Resistance rates and number of surveys (n) by region. Transparency
183 levels reflect sample sizes for each animal-pathogen combination. (Drug acronyms, see Protocol
184 S1).
185

Discussion

In most high-income countries, AMR has been monitored in animals for over 10 years (*13*). Here, we used point prevalence surveys to conduct a global assessment of trends in AMR in animals in LMICs. A singular challenge in the epidemiology of AMR is to synthesize a problem involving multiple pathogens and compounds across different regions. We therefore introduced two summary metrics of resistance –P50 and P10– , that reflect the ability of veterinarians to provide effective treatment. Based on the evidence assembled, P50 increased in LMICs from 0.15 to 0.41 (+ 173%) in chickens, from 0.13 to 0.34 (+161%) in pigs, and plateau between 0.12 and 0.23 in cattle. Rapid increases in AMR in chicken and pigs are consistent with the intensification of livestock operations for these species compared with cattle (*20*). The main consequence of those trends is a depletion of the portfolio of treatment solutions available to treat pathogens in animals raised for food. This loss has economic consequences for farmers because affordable antimicrobials are becoming ineffective as first-line treatment (*21*) and this could eventually be reflected in higher food prices.

The number of surveys supporting this first assessment is limited (n = 901) and heterogeneous across countries (Fig. S6A). However, it enables us to draw inferences on large-scale trends in AMR (Fig. 3A). Globally, the percentage of animals raised in hotspots of AMR was limited (< 20%), with the notable exception of chicken production in upper-middle-income countries, such as Turkey (72%) and Egypt (38%). These countries are also the first- and third-largest per-capita consumers of antimicrobials in human medicine amongst LMICs (*22*).

209 The largest hotspots of AMR in animals were in Asia, which is home to 56% of the world's pigs
210 and 54% of chickens (FAOSTAT 2016). In Asia, targeted interventions such as legislative action,
211 subsidies to improve farm hygiene could reduce the need for antimicrobials in animal production
212 (*1*), thereby preserving important drugs for human medicine, and the treatment of sick animals.
213 We identified hotspots for the emergence of AMR including central India and Kenya, where
214 resistance to multiple drugs has appeared but not yet reached 50% (Fig. 3C). In these regions, meat
215 consumption is still low and animal production is gradually intensifying: there may be a window
216 of opportunity to contain AMR by imposing strict hygiene standards in newly built farms. This
217 approach could reduce the risk of spread of resistant pathogens such as *mcr-1*-carrying *E. coli* (*23*)
218 that have emerged in regions where intensive meat production has been facilitated by enormous
219 quantities of veterinary antimicrobials (*1*).
220
221 In Africa, resistance maps reveal the absence of major AMR hotspots, with the exception of the
222 Johannesburg metropolitan area. This suggests –based on the regions surveyed– that Africa
223 probably bears proportionately less of the current global burden of AMR than high- and upper-
224 middle-income countries. Policymakers coordinating an international response to AMR might
225 therefore spare Africa from the most aggressive measures, which may be perceived as unfair and
226 undermine livestock-based economic development.
227
228 In the Americas, where the number of surveys was limited (Fig. 3B), the observed low AMR levels
229 could reflect either good farming practices (low antimicrobial use) or the absence of surveys
230 conducted in areas most affected by AMR. Considering that Uruguay, Paraguay, Argentina and
231 Brazil are net meat exporters (FAOSTAT 2016), it is of particular concern that little

epidemiological surveillance of AMR is publicly available for these countries. Many low-income African countries have more point prevalence surveys per capita than middle-income countries in South America. Globally, our findings show that the number of surveys per capita was not correlated with GDP per capita, suggesting that surveillance capacities are not solely driven by financial resources.

In this study, we stacked prediction from geospatial models to map P50 and P10 in LMICs. The moderate accuracy of the these models reflect the challenge of associating the spatial distribution of AMR with environmental and socio-economic factors (*24*). AMR in animals may be driven by factors known to influence antimicrobial use in humans—such as cultural norms, presence of drug manufacturers on national market, or the density of health professionals (*25*)—that could not be easily mapped from publicly available sources of information. The leading factor associated with the spatial distribution of P50 was the travel time to cities (*26*). Ease of access to providers of veterinary drugs may drive AMR, and hotspots appear to correspond to peri-urban environments where large farms supply city dwellers, whose meat consumption typically exceeds national averages (*27*). We also found a positive association between P50 and temperature. Evidence for a link with temperature in animals is less established than in humans (*28*) but it has been suggested that high temperatures cause stress in animals, thus increasing the risk of wounds that require preventive antimicrobial treatment (*29*). Finally, in Asia, 74% of P50 hotspots corresponded to areas previously identified for their projected increase in antimicrobial use (Fig. S12). The relative influence of antimicrobial use on the spatial distribution of P50 was only of 3.8% (Table S5) but this association should be treated with caution given the scarcity of original data on antimicrobial use from LMICs (*30*).

We identified diverging patterns of resistance across combinations of pathogens and drugs. For *S. aureus*, geographic differences in AMR levels could be explained by sub-lineages carrying different SCC*mec* cassettes that are specific to certain regions (*31*). Of greater concern for public health is the presence of resistance to $3^{rd}/4^{th}$ generation cephalosporins—critically important antimicrobials for human medicine—on all continents. In addition, the high levels of colistin resistance found in Asia suggest that regional spread may have been driven by plasmid-mediated resistance (*23*), as well as the widespread use of this cheap antimicrobial. The recent Chinese ban on colistin (*32*), if enforced, may improve the situation. However, globally, progress may be undermined by the large quantities of colistin still used, including in some high-income countries. For quinolones, patterns fo resistance differed greatly between regions. For *E. coli* and *Campylobacter*, LMICs had resistance levels comparable with European levels but considerably higher than in the United States, where quinolones were banned in poultry in 2005. Conversely, for *Salmonella* and *E. coli,* LMICs had substantially higher resistance to gentamycin than Europe, where this compound is not authorized for use in poultry and cattle (*33*). These findings suggest that regional restrictions on the use of specific compounds are associated with lower AMR rates.

As with any modelling study, our analysis has limitations. The uncertainty associated with interpolation of resistance rates is captured with confidence interval maps (Fig. 3B). However, there are additional sources of uncertainty. First, insufficient geographic coverage may lead to inaccurate spatial predictions, and local variations in AMR may not reflect 'ground truth'. In this study, we attenuate the risk of overfitting geospatial models to local outliers by using spatial cross-validation. Future research efforts should increase the geographic coverage of surveys by engaging

with local partners (e.g., in India for this analysis, supplementary information). Second, temporal variation in AMR over the period 2000–2018 was not accounted for. As more surveys become available, spatio-temporal, model-based geostatistics approaches could help overcome this limitation. However, the limited number of surveys (n = 901) identified in this first assessment did not allow for the use of those methods. Third, in slaughterhouse surveys, most did do not perform molecular typing longitudinally throughout the different processing stages that would enable to assess potential cross-contamination. While it may generally affect AMR rates, it is -in the absence of international benchmarking- unknown if it could systematically bias our result in any single country. Fourth, our dataset of surveys may include observational bias at sampling sites although we attempted to account for this by distributing pseudo-absence according to rural human population density (Table S4). Finally, whilst our analysis raises renewed concerns about the pace of increase of AMR in animals it is not an attempt to draw definitive conclusions on the intensity and directionality of transfer of AMR between animals and humans which should be further investigated with robust genomics methods (*34*).

Conclusions

Point prevalence surveys are imperfect surrogates for surveillance networks. However, in the absence of systematic surveillance, maps have been useful to guide interventions against other disease of global importance such as malaria (*35*). In human medicine, point prevalence surveys of AMR in hospitals have generated snapshots of AMR across regions (*36*). This initial assessment helps outline three global priorities for action. First, our maps show regions poorly surveyed where intensified sampling efforts could be most valuable. Second, our findings clearly indicate that the

highest levels of AMR in animals are currently found in China and India where immediate actions could be taken to preserve antimicrobials that are essential in human medicine by restricting their use in animal production. Third, high-income countries, where antimicrobials have been used on farms since the 1950s, should support transition to sustainable animal production in LMICs—for example, through a global fund to subsidize improvement in farm-level biosafety and biosecurity (*37*).

References and Notes:

1. T. P. Van Boeckel *et al.*, Reducing antimicrobial use in food animals. *Science*. **357**, 1350–1352 (2017).

2. E. K. Silbergeld, J. Graham, L. B. Price, Industrial food animal production, antimicrobial resistance, and human health. *Annu Rev Public Health*. **29**, 151–169 (2008).

3. M. J. Ward *et al.*, Time-Scaled Evolutionary Analysis of the Transmission and Antibiotic Resistance Dynamics of Staphylococcus aureus Clonal Complex 398. *Appl. Environ. Microbiol.* **80**, 7275–7282 (2014).

4. S. P. W. de Vries *et al.*, Phylogenetic analyses and antimicrobial resistance profiles of Campylobacter spp. from diarrhoeal patients and chickens in Botswana. *PLOS ONE*. **13**, e0194481 (2018).

5. Y.-Y. Liu *et al.*, Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases*. **16**, 161–168 (2016).

6. K. E. Jones *et al.*, Global trends in emerging infectious diseases. *Nature*. **451**, 990–993 (2008).

7. The Establishment of the Colombian Integrated Program for Antimicrobial Resistance Surveillance (COIPARS): A Pilot Project on Poultry Farms, Slaughterhouses and Retail Market - Donado- Godoy - 2015 - Zoonoses and Public Health - Wiley Online Library, (available at https://onlinelibrary.wiley.com/doi/abs/10.1111/zph.12192).

8. D. F. Maron, T. J. Smith, K. E. Nachman, Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. *Globalization and Health*. **9**, 48 (2013).

9. D. Grace, Review of evidence on antimicrobial resistance and animal agriculture in developing countries (2015) (available at https://cgspace.cgiar.org/handle/10568/67092).

10. K. L. Tang *et al.*, Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *The Lancet Planetary Health*. **1**, e316–e327 (2017).

11. WHO guidelines on use of medically important antimicrobials in food-producing animals (2017), (available at http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia_guidelines/en/).

12. Global Antimicrobial Resistance Surveillance System: Manual for Early Implementation, (available at http://apps.who.int/medicinedocs/en/m/abstract/Js22228en/).

13. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. *EFSA Journal*. **16**, e05182 (2018).

14. Integrated surveillance of antimicrobial resistance in foodborne bacteria: application of a one health approach: guidance from the WHO Advisory Group on Integrated Surveillanec of Antimicrobial Resistance (AGISAR) (2017).

15. N. Golding *et al.*, Mapping under-5 and neonatal mortality in Africa, 2000–15: a baseline analysis for the Sustainable Development Goals. *The Lancet*. **390**, 2171–2182 (2017).

16. M. Woolhouse, J. Farrar, Policy: An intergovernmental panel on antimicrobial resistance. *Nature*. **509**, 555–557 (2014).

17. WHO | Critically important antimicrobials for human medicine, 5th revision. *WHO*, (available at http://www.who.int/foodsafety/publications/antimicrobials-fifth/en/).

18. C. for V. Medicine, National Antimicrobial Resistance Monitoring System - NARMS Now: Integrated Data, (available at https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm416741.htm).

19. Extended-spectrum β-lactamase/AmpC- and carbapenemase-producing Enterobacteriaceae in animals: a threat for humans? *Clinical Microbiology and Infection*. **23**, 826–833 (2017).

20. H. Steinfeld *et al.*, *Livestock's long shadow* (FAO Rome, 2006; http://www.globalmethane.org/expo-docs/china07/postexpo/ag_gerber.pdf).

21. B. Bengtsson, C. Greko, Antibiotic resistance--consequences for animal health, welfare, and food production. *Ups. J. Med. Sci.* **119**, 96–102 (2014).

22. E. Y. Klein *et al.*, Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *PNAS*, 201717295 (2018).

23. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases*. **16**, 161–168 (2016).

24. P. Collignon, J. J. Beggs, T. R. Walsh, S. Gandra, R. Laxminarayan, Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *The Lancet Planetary Health*. **2**, e398–e405 (2018).

25. E. Y. Klein *et al.*, Influence of provider and urgent care density across different socioeconomic strata on outpatient antibiotic prescribing in the USA. *J Antimicrob Chemother*. **70**, 1580–1587 (2015).

26. D. J. Weiss *et al.*, A global map of travel time to cities to assess inequalities in accessibility in 2015. *Nature*. **553**, 333 (2018).

27. L. Jiang, J. Bai, K. C. Seto, Urban economic development, changes in food consumption patterns and land requirements for food production in China. *China Ag Economic Review*. **7**, 240–261 (2015).

28. C. García-Rey, A. Fenoll, L. Aguilar, J. Casal, Effect of social and climatological factors on antimicrobial use and Streptococcus pneumoniae resistance in different provinces in Spain. *Journal of Antimicrobial Chemotherapy*. **54**, 465–471 (2004).

29. A. Diana, E. G. Manzanilla, J. A. Calderón Díaz, F. C. Leonard, L. A. Boyle, Do weaner pigs need in-feed antibiotics to ensure good health and welfare? *PLoS One*. **12** (2017), doi:10.1371/journal.pone.0185622.

30. N. T. Nhung, N. Chansiripornchai, J. J. Carrique-Mas, Antimicrobial Resistance in Bacterial Poultry Pathogens: A Review. *Front. Vet. Sci.* **4** (2017), doi:10.3389/fvets.2017.00126.

31. P. Asadollahi *et al.*, Distribution of the Most Prevalent Spa Types among Clinical Isolates of Methicillin-Resistant and -Susceptible Staphylococcus aureus around the World: A Review. *Front. Microbiol.* **9** (2018), doi:10.3389/fmicb.2018.00163.

32. T. R. Walsh, Y. Wu, China bans colistin as a feed additive for animals. *The Lancet Infectious Diseases*. **16**, 1102–1103 (2016).

33. European Public MRL assessment report (EPMAR) Gentamicin (all mammalian food producing species and fin fish).

34. D. Muloi *et al.*, Are Food Animals Responsible for Transfer of Antimicrobial-Resistant Escherichia coli or Their Resistance Determinants to Human Populations? A Systematic Review. *Foodborne Pathogens and Disease* (2018), doi:10.1089/fpd.2017.2411.

35. S. I. Hay *et al.*, A world malaria map: Plasmodium falciparum endemicity in 2007. *PLoS Medicine*. **6**, e1000048 (2009).

36. A. Versporten *et al.*, Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *The Lancet Global Health*. **6**, e619–e629 (2018).

37. M. Mendelson *et al.*, A Global Antimicrobial Conservation Fund for Low- and Middle-Income Countries. *International Journal of Infectious Diseases*. **51**, 70–72 (2016).

38. S. Bengtsson, C. Bjelkenbrant, G. Kahlmeter, Validation of EUCAST zone diameter breakpoints against reference broth microdilution. *Clin. Microbiol. Infect.* **20**, O353-360 (2014).

39. S. Bhatt *et al.*, Improved prediction accuracy for disease risk mapping using Gaussian process stacked generalization. *J R Soc Interface*. **14** (2017), doi:10.1098/rsif.2017.0520.

40. J. Elith, J. R. Leathwick, T. Hastie, A working guide to boosted regression trees. *Journal of Animal Ecology*. **77**, 802–813 (2008).

41. R. Tibshirani, Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society. Series B (Methodological)*, 267–288 (1996).

42. A. Chouldechova, T. Hastie, Generalized Additive Model Selection. *arXiv:1506.03850 [stat]* (2015) (available at http://arxiv.org/abs/1506.03850).

43. M. Barbet- Massin, F. Jiguet, C. H. Albert, W. Thuiller, Selecting pseudo-absences for species distribution models: how, where and how many? *Methods in Ecology and Evolution*. **3**, 327–338 (2012).

44. R. J. Hijmans, Cross-validation of species distribution models: removing spatial sorting bias and calibration with a null model. *Ecology*. **93**, 679–688 (2012).

45. J. Elith, J. R. Leathwick, T. Hastie, A working guide to boosted regression trees. *J Anim Ecol*. **77**, 802–813 (2008).

46. A. Getis, J. K. Ord, in *Perspectives on Spatial Data Analysis* (Springer, 2010), pp. 127–145.

47. The External Quality Assurance System (EQAS) of the WHO Global Foodborne Infections Network 2015 (2015), (available at http://antimicrobialresistance.dk/CustomerData/Files/Folders/2-newsletter-pdf/34_21-who-eqas-2015-report-final.pdf).

48. G. Zuo, Z. Xu, B. Hao, Shigella Strains Are Not Clones of Escherichia coli but Sister Species in the Genus Escherichia. *Genomics, Proteomics & Bioinformatics*. **11**, 61–65 (2013).

49. T. P. Van Boeckel *et al.*, Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences*. **112**, 5649–5654 (2015).

50. WorldClim 2: new 1- km spatial resolution climate surfaces for global land areas - Fick - 2017 - International Journal of Climatology - Wiley Online Library, (available at https://rmets.onlinelibrary.wiley.com/doi/abs/10.1002/joc.5086).

51. S. Siebert *et al.*, Development and validation of the global map of irrigation areas. *Hydrology and Earth System Sciences Discussions*. **2**, 1299–1327 (2005).

52. M. Gilbert *et al.*, Income Disparities and the Global Distribution of Intensively Farmed Chicken and Pigs. *PLOS ONE*. **10**, e0133381 (2015).

53. G. Nicolas *et al.*, Using Random Forest to Improve the Downscaling of Global Livestock Census Data. *PLOS ONE*. **11**, e0150424 (2016).

54. M. C. Hansen, R. S. DeFries, J. R. Townshend, R. Sohlberg, Global land cover classification at 1 km spatial resolution using a classification tree approach. *International journal of remote sensing*. **21**, 1331–1364 (2000).

55. S. Bontemps *et al.*, "{GLOBCOVER 2009 - Products description and validation report}" (2011), (available at http://mfkp.org/INRMM/article/12770349).

Acknowledgments: We thank Jief Bastin for providing vegetation layers, Sara Droz and Vincent Perreten for providing CLSI guidelines, and Souria Nussbaumer for research assistance. **Funding:** TPVB, CZ, and NC were supported by The Branco Weiss Fellowship, and the Swiss National Science Foundation. JP was supported by the ETH Zurich Seed Grant. RS was supported by the Bill & Melinda Gates Foundation. JS was supported by a Health Grand Challenges Grant from Princeton University; **Author contributions:** TPVB, SB, and RL designed the study. TPVB performed the analysis and wrote the first version of the manuscript. JP, JS, RS and CZ conducted literature reviews. JP and NC developed resistancebank.org. All authors contributed to the final version of the manuscript; **Competing interests:** Authors declare no competing interests; and **Data and materials availability:** resistancebank.org.

Supplementary Materials:

Materials and Methods

Supplementary Text: Protocol S1, S2, and S3.

Figures S1-S12

Tables S1-S6

Science
AAAS

Supplementary Materials for

Global Trends in Antimicrobial Resistance in Animals in Low- and Middle-Income Countries

Thomas P. Van Boeckel, Joao Pires, Reshma Silvester, Cheng Zhao, Julia Song, Nicola Criscuolo, Marius Gilbert, Sebastian Bonhoeffer, and Ramanan Laxminarayan.

Correspondence to: thomas.vanboeckel@env.ethz.ch

This PDF file includes:

Materials and Methods

Literature Review

Three bibliographic databases were screened for point prevalence surveys of AMR in *Escherichia coli*, *Campylobacter* spp., non-typhoidal *Salmonella* and *Staphylococcus aureus* in LMICs (Fig. S1, Protocol S1). As recommended by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance for surveillance in their manual for integrated surveillance of antimicrobial resistance in foodborne bacteria, we search for epidemiological studies in which antimicrobial susceptibility testing was used to determine the resistance phenotypes of bacteria sampled from animals on farms, slaughterhouse, and retail markets (but not diseased and sick animals. The literature review resulted in 32,030 search results. The titles an abstract of these publications were used for initial screening. We removed duplicates records (between search engines) and excluded book-chapters, reviews and meta-analysis. We also excluded publication that did not report antimicrobial resistance rates such as studies on the activity of new compounds in strains of animal origin, or on farming practices. Following the initial screening, 1,992 PPS were identified as having potentially relevant information to be extracted and were read in full. We extracted data from a total of 1,252 point prevalence surveys reporting a total of 25,929 resistance rates". In addition, in India, field visits were conducted in five veterinary schools to collect data from 178 surveys from paper journals, PhD and MSc theses and conference proceedings (Protocol S1).

All records are publicly available at resistancebank.org. The information extracted from each survey included type of pathogen, anatomical therapeutic chemical classification codes of the drugs tested, year of publication, latitude and longitude of sampling sites, sample size and host animals. A description of each variable extracted from the publications is available in the RESBANK legend file (Protocol S2). From this initial database, 667 records were excluded because they lacked sufficient information to assign geographic coordinates, and 412 point prevalence surveys were excluded because resistance rates were pooled across two or more animal species and could not be disaggregated. Of the 443 emailed requests for clarification, 162 (36.9%) were positively answered. The 67 records associated with *Enterococcus* spp. in *resistancebank* were not used for the present analysis because only a very small proportion (3.4%) of surveys from LMICs reported Enterococcus spp. A further eight records were excluded because their breakpoints were not within the range of values recommended by antimicrobial susceptibility testing guidelines. The geospatial analysis was conducted for records of drugs recommended for antimicrobial susceptibility testing by the WHO AGISAR (*14*) consortium. The final data set had 12,933 resistance rates, extracted from 901 surveys distributed across 822 locations, totaling 285,496 samples from across LMICs.

Harmonization of Antimicrobial Resistance Rates

Various experimental methods can be used for antimicrobial susceptibility testing. The literature search showed two main families of approaches: diffusion methods (disc diffusion and gradient diffusion such as E-test) and dilution methods (broth dilution and automated devices such as VITEK2). Surveys reporting AMR in LMICs predominantly used diffusion methods, which are less expensive. A notable exception was China (Fig. S2) where the percentage of studies that reported using dilution methods (45%) was significantly higher (Chi-squared = 1,441) than in other LMICs (11%). For those countries, we used two-sided Wilcoxon rank-sum test to evaluate potential differences in mean antimicrobial resistance rates associated with each antimicrobial susceptibility testing method. We considered all drug-pathogen combinations represented by at least 10 records for each susceptibility testing method. For nearly all drug-pathogen combinations (25 of 28), mean AMR levels did not differ based on the method used (Fig. S3). This is consistent with works (*38*) showing good agreement between diffusion and dilution methods for foodborne pathogens. In this analysis, the potential overestimation of resistance rates by 'method bias' was limited to 87 records (0.67% of all records) where dilutions methods were used for cefoxitin, oxacillin in *S. aureus*, and nalidixic acid in *E. coli.* For those 87 records, we modulated the rates reported in the surveys by the ratio of the mean of rates identified by dilution methods to the mean of rates identified by diffusion methods for the corresponding drug-pathogen combination.

Breakpoints, used to identify resistant phenotypes, can differ depending on laboratory guidelines and are revised annually (Fig. S4). Accounting for breakpoint variations over time is thus essential. In *resistancebank*, only 6.2% of records reported the breakpoint values, but 96% of records were associated with referenced guidelines, and 68% of records could be associated with the guidelines' year. For surveys that did not report the guidelines used, we assumed that the guidelines came from the Clinical & Laboratory Standards Institute (CLSI), which were the most commonly used guidelines across all the surveys. For surveys that did not report the guidelines' year, we assumed a date of four years before publication (the median lag between publication date of the survey and year of the guidelines, inferred from the 68% of records that did report the year of the guidelines).

We assembled guidelines published by CLSI, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the French Society of Microbiology (SFM). We then developed a harmonization procedure for breakpoint variations, based on EUCAST minimum inhibitory concentration distributions and zone diameter distributions (Fig. S5), as follows.

Step 1. Each record was assigned an 'observed breakpoint (BP_{obs})', which was either the reported breakpoint from the publication or the breakpoint value from the EUCAST, CLSI or SFM guidelines corresponding to the year of the guidelines.

Step 2. Each record was also assigned a 'reference breakpoint (BP_{ref})', which was the lowest inhibition concentration (for studies using dilution methods) or the highest inhibition diameters (for studies using diffusion methods) recorded in the EUCAST guidelines for each drug-pathogen combination. This reference breakpoint was specific for each drug-pathogen combination such that studies using different BP_{obs} could be compared. For the harmonization of resistance rates, the use of a human breakpoints was preferred over animal breakpoints or epidemiological cutoffs because the overwhelming majority

the studies reporting AMR in animals used human clinical breakpoints (97% of surveys in *resistancebank*)."

Step 3. For each record with BP_{obs} values that differed from the BP_{ref} values, the following correction was applied to modulate the resistance rates extracted from publications (R_{obs}) and take into account variations in breakpoints across years and guidelines (CLSI, EUCAST or SFM).

For dilution-based methods

$$R_c^{ad} = R_{obs} \cdot \frac{AUC_{BP_{obs}}}{AUC_{BP_{ref}}}$$

For diffusion-based method

$$R_c^{dd} = R_{obs} \cdot \frac{AUC_{BP_{ref}}}{AUC_{BP_{obs}}}$$

Where R_{obs} is the resistance rate reported in a point prevalence survey, R_c^{ad} is the modulated resistance rates for survey using dilution methods, and R_c^{dd} is the modulated resistance rate for surveys using diffusion methods. AUCs are the areas under the curve of the minimum inhibitory concentration distribution (dilution methods) or the inhibition zone diameter distribution (diffusion methods) obtained from *eucast.org* (Fig. S5). For dilution methods, the AUC is the integral of the distribution from the highest inhibition concentration to the reference concentration and observed concentrations. For diffusion methods, the AUC is the integral from the smallest possible inhibition radius to values of inhibition diameters corresponding to the observed and reference breakpoints, respectively. Of the 12,933 records, 1,487 had identical breakpoint (BP_{obs} = BP_{ref}) values and did not require modulation of the resistance rates; 8,139 records were modulated to account for changes in guidelines; and 3,307 records were not suitable for modulation because breakpoint values were not provided in the survey or in the guidelines documentation.

After harmonizing resistance rates, we defined a summary metric to compare resistance rates across pathogens and host species. We define 'P50' as the proportion of drugs tested with resistance higher than 50% across all samples tested in a point prevalence surveys (Fig. S6). P50 was chosen because drugs that have a failure rate exceeding 50% in a given region are unlikely to be used for first-line treatment. P50 is thus a reflection of the challenge faced by veterinarians in providing treatment. We assessed the trends in P50 between 2000 and 2018 for each livestock species. We use linear regression models, weighted by the number of surveys per year, to assess the statistical significance at the 5% level of the temporal trends between P50 and year of publication. The average yearly increase in P50 for chicken and pigs were respectively 1.5%, and 1.3% per year.

Geospatial Modelling

We interpolated P50 values from point prevalence surveys to map AMR in LMICs at a resolution of 0.0833 decimal degrees, or approximately 10 km at the equator. We used a two-step procedure inspired by Golding and colleagues (*15*). First, multiple 'child models' were trained to quantify the association between the geographic distribution of P50 and environmental covariates (Fig. S7).

Second, universal kriging was used to stack predictions from child models. The approach enables us to capture the potential spatial autocorrelation in the geographic distribution of P50 as well as the associations between P50 and environmental covariates. Stacking predictions from different statistical methods produces more accurate disease risk maps (*39*) than predictions from individual models. The set of environmental covariates was restricted to biologically relevant factors that may be associated with antimicrobial resistance, such as antimicrobial use, minimum monthly temperature and animal densities (Table S3). All covariates were log-transformed and resampled from their original resolution of 0.0833 decimal degrees.

Three classes of child models were used: boosted regression trees (*40*) (BRT); least absolute shrinkage and selection operator applied to logistic regression (*41*) (LASSO-GLM); and overlapped grouped LASSO penalties for General Additive Models selection (*42*) (LASSO-GAM). For the BRT model, we used a tree complexity of three, a learning rate of 0.0025, and a step size of 50. These three meta-parameters control the level of interactions between variables, the weights of each individual tree in the final model and the number of trees added at each cycle, respectively. For all child models, P50 values were transformed into presence/absence using a random binarization procedure: all records in the data set were replicated five times, and P50 values in this expanded data set were then compared with a random number between zero and one. P50 values larger than the random number were classified as presence; lower values were classified as absences. In addition, pseudo-absence points were distributed across LMICs to provide the child models with additional covariate values that were not associated with presences (P50 = 0). Pseudo-absence points were sampled within a radius of 10 to 2,000 km from presence points using stratified random sampling proportional to the log10 of the population density outside urban areas. The child models contained equal numbers of true presence versus absences (true absence + pseudo absences), since balanced data sets have been shown to improve spatial predictions (*43*).

Child models were fitted using fourfold spatial cross validation to prevent local overfitting and to ensure that predictions reflected extrapolation capacities outside training regions. Four validation regions were defined (Fig. S8): Africa, South America, western Asia (longitude < 90 degrees), and eastern Asia (longitude > 90 degrees). In addition, we calculated the spatial sorting bias (SSB) index (*44*) to ensure that it was negligible (mean SSB = 0.90). The model fitting procedure was bootstrapped 10 times to account for variations attributable to the stratified sampling of pseudo-absence points and the random binarization of P50 values. The predictive ability of each child model was evaluated by averaging the value of the area under the received-operator curve for all runs. The influence of each variable in each child was also evaluated across 10 bootstraps: for the BRT models we used mean relative influences (*40*), for the LASSO regression we used the fraction of bootstraps where covariate had a non-null coefficient after regularization, and for the GAM-LASSO we used the fraction of bootstraps where covariates had a non-null linear or non-linear coefficient after regularization.

All child models had moderate accuracies ($AUC_{BRT} = 0.674$, $AUC_{LASSO\text{-}GLM} = 0.683$, $AUC_{LASSO\text{-}GAM} = 0.680$). For the BRT model, the travel time to cities of 50,000 or more people accounted for 68% of the relative influence (*45*) and was negatively associated with P50 (Table S5). Other variables were positively associated with P50 but had smaller influence in the final model: minimum annual temperature (7%), density of intensively raised chickens (6%) and percentage of irrigated land (5%). For the LASSO-GLM, the most influential covariates were travel times to

cities (100% of bootstraps, and negative coefficient), percentage of irrigated land (100% of bootstraps, and positive coefficient) and density of extensively raised chickens (90% of bootstraps, positive coefficient). For the LASSO-GAM model, the main coefficients included linear terms from density of extensively raised chickens (100% of bootstraps), the minimum annual temperature (80% of bootstraps), as well as a non-linear term for antimicrobial use (90% of bootstraps).

In the second step of the geospatial procedure, we combined predictions of child models (Fig. S9). The predictions of each child model were used as covariate for universal kriging of the P50 values between survey locations. The kriging procedure was weighted by the number of samples reported at each location, adjusted for regional variations. Concretely, the number of samples at each location was multiplied by an accuracy factor ranging between 0 and 1 that reflects regional variations in performing antimicrobial susceptibility testing, as estimated by the *WHO External Quality Assurance System of the Global Foodborne Infections Network* (Protocol S3). We fitted a Matern semi-variogram model with a maximum range of 1,000 km. Duplicated coordinates, those that corresponded to P50 for different pathogens in the same location, were randomly redistributed within a radius of 1 km of the survey sites multiplied by the log10 of the number of samples in the survey to reflect greater spatial range of large surveys. Following the kriging procedure, all negative values of P50 were reclassified as zeros.

We quantified the spatial uncertainty associated with the maps of P50 in a two-step procedure. First, we calculated the standard deviation in the predictions in each pixel for each child model. Second, we calculated a standardized kriging variance after stacking such that variance was equal to zero at the location of the observations. We produced a 95% confidence interval (CI) on the final prediction as follows:

$$95\%\ CI = 1.96 \times \left(sd(P_{BRT}, P_{LASSO-GLM}, P_{LASSO-GAM}) + \sqrt{Var_K} \right)$$

where $P_{BRT}, P_{LASSO-GLM}, P_{LASSO-GAM}$, are the predicted P50 values resulting from each child models, and Var_K is the standardized kriging variance after stacking. The upper bound of the 95% confidence interval is limited to the maximum value of the pixels where all child models predicted non-null results.

Finally, we also mapped regions where multidrug-resistance was starting to emerge. We repeated the geospatial procedure to map P10 (the proportion of drugs tested with resistance higher than 10%) and subtracted P50 from P10 values in each pixel. The resulting 'map of differences' shows regions where multidrug-resistance phenotypes are emerging (10% resistance) but have not yet reached alarming levels (50% resistance). All geospatial analyses were conducted using the statistical language R. A map of P50 is available in Google Earth format for detailed visualization (https://www.dropbox.com/s/bi3jp5mb3zfozh5/P50.kmz?dl=0).

Metrics of exposure to AMR

We used the global maps of P50 to derive two metrics of exposure of resistance. First, we calculated the proportion of animals raised in these hotspots of resistance. Two approaches were

compared to define hotspots. The first approach simply assumes a cutoff value of 0.4 on P50 values, whilst the second used the Getis-Ord method (*46*). Both approaches led to comparable results (Fig. S10), but the first was preferred because it has a straightforward biological interpretation: in a hotspot pixel, 40% of drugs have resistance levels above 50%. The 95% confidence interval on the minimum and maximum extent of the hotspots of P50 was calculate as follow

$$95\%\ CI = 1.96 \times \left(sd(P_{BRT}, P_{LASSO-GLM}, P_{LASSO-GAM}) + \sqrt{Var_{K,HS}} \right)$$

where $P_{BRT}, P_{LASSO-GLM}, P_{LASSO-GAM}$ are the predicted P50 values resulting from each child models, and $Var_{K,HS}$ is the average kriging variance in the hotspots pixels.

The second metric of exposure to resistance was calculated at the country level for chicken and pigs (Fig. S11). In each pixel, we multiplied the number of animals raised by the P50 value in the same location. This product was aggregated in each country then normalized by the total number of animals in the country. This metric quantifies the level of exposure of the animal population of a country relative to its stock. The analysis was restricted to countries with at least 10 million birds, and 250,000 pigs, and 500,00 cattle heads in order to establish a ranking of countries that is not bias by a density effect due to small islands and microstates.

Supplementary Text

Protocol S1. Literature Review

We identified point prevalence surveys (PPS), and extracted information on antimicrobial resistance rates in animals in low- and middle-income countries. The resulting database – *resistancebank* – is available in open access (https://www.dropbox.com/s/qf5nrmqjieds6th/resbank_all.csv?dl=0). The literature search was conducted in three databases (PubMed, Scopus and ISI Web of Science) in English, Spanish, Portuguese and French by 4 independent researchers (2 per geographic region of interest). All studies published between 2000 and March 2019 were included (Table S1). PPS were screened using the generic formula:

(Resistance) AND (Bacterial Species) AND (Animals and Sample types) AND (Geographic Regions)

Different key words were used to maximize number of hits identified, the full search query used in PubMed was: (antibiotic resistance OR antimicrobial resistance OR resistance OR susceptibility OR antibiogram OR antibiotic susceptibility testing OR antibiotic OR antimicrobial OR antibacterial) AND (Escherichia OR E. coli OR coliform OR salmonella OR salmonella spp. OR enterococcus OR enterococcus spp. OR enterococci OR VRE OR E. faecalis OR E. faecium 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 farm OR farm animal 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 (Country*).

In addition, keywords for resistance, animals, sample types and geographic regions were translated into Spanish, Portuguese and French. The list of countries included in the search was: Afghanistan, Angola, Anguilla, United Arab Emirates, Argentina, Armenia, Antigua and Barb., Azerbaijan, Burundi, Benin, Burkina Faso, Bangladesh, Bahrain, Belize, Bermuda, Bolivia, Brazil, Barbados, Brunei, Bhutan, Botswana, Central African Rep., Chile, China, Cote d'Ivoire, Cameroon, Dem. Rep. Congo, Congo, Colombia, Comoros, Cape Verde, Costa Rica, Cuba, Curacao, Djibouti, Dominica, Dominican Rep., Algeria, Ecuador, Egypt, Eritrea, Ethiopia, Gabon, Georgia, Ghana, Guinea, Gambia, Guinea-Bissau, Equatorial Guinea, Grenada, Guatemala, Guyana, Hong Kong, Honduras, Haiti, Indonesia, India, Iran, Iraq, Israel, Jamaica, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Cambodia, Kuwait, Lao PDR, Lebanon, Liberia, Libya, Sri Lanka, Lesotho, Morocco, Madagascar, Mexico, Mali, Myanmar, Mongolia, Mozambique, Mauritania, Montserrat, Malawi, Malaysia, Namibia, Niger, Nigeria, Nicaragua, Nepal, Oman, Pakistan, Panama, Peru, Philippines, Dem. Rep. Korea, Paraguay, Palestine, Qatar, Rwanda, W. Sahara, Saudi Arabia, Sudan, Senegal, Singapore, Sierra Leone, El Salvador, Somaliland, Somalia, St. Pierre and Miquelon, Sao Tome and Principe, Suriname, Swaziland, Syria, Chad, Togo, Thailand, Tajikistan, Turkmenistan, Timor-Leste, Trinidad and Tobago, Tunisia, Turkey, Taiwan, Tanzania, Uganda, Uruguay, Uzbekistan, Venezuela, Vietnam, Yemen, South Africa, Zambia, and Zimbabwe.

In Scopus and ISI Web of Science, the same key words were used in the advanced search functionality. For Scopus, the search was specified as TS=(key words) where TS stands for search topic; whereas for ISI Web of Science the search was specified as TITLE-ABS-KEY=(key words), where TITLE-ABS-KEY stands for title, abstract and key words.

All titles and abstracts were screened for PPS. Full text manuscripts that could not be accessed were included in *resistancebank* when the information in the abstract was considered sufficient for the *resistancebank* format (see Protocol S2).

Exclusion criteria included: reviews, meta-analysis, PPS dealing with diseased animals (except for bovine clinical and sub-clinical mastitis), manuscripts characterizing a defined set of strains not derived from PPS (strain surveys), nation-wide PPS without geographically defined sampling and PPS written in languages not used in the systematic search.

In India, in addition to publication available online we also included PPS from alternative sources. We conducted field visits in 5 of the main veterinary school of the country to access 'grey literature' such as paper-publications, PhD/MSc thesis and conference proceedings. Although the grey literature may in some cases not have been peer-reviewed, it constitutes in many places the sole source of information on AMR given the absence of systematic surveillance in animals. A research assistant visited: Maharashtra Animal and Fishery Science University & Madras Veterinary, Nagpur (104 studies, visited on April 19th 2018); National Library for Veterinary sciences in Bareilly (14 studies, visited on February 22th 2018); Tamil Nadu Veterinary and Animal Sciences University & Madras Veterinary college (34 studies, visited on May 10th 2018); and Kerala Animal and Veterinary Science University (25 studies, visited on May 7th 2018). Altogether, 1,515 studies from systematic online searches and 178 studies from Indian grey literature were screened for content, of which 1,148 PPS were included in *resistancebank*.

Protocol S2. Legend of *resistancebank*

Foreword

resistancebank is a database of antimicrobial resistance (AMR) data extracted from point prevalence surveys (PPS) in food animals and food products. The primary goal of *resistancebank* is to support the production of maps of AMR across different geographic regions, animals and antibiotic classes for further development of applications (e.g., modelling). Currently, data originates from online scientific journals, reports from governmental agencies. In addition, in India, the database is complemented by records from paper journals, MSc/PhD thesis obtained directly from veterinary schools, as well as unpublished data resulting from local surveillance.

Multiple lines in *resistancebank* can correspond to the same publication: different combinations of the studied animals, sample types, coordinates and antibiotics studied. When the information corresponding to a field was not available NA is used. In these cases, a request to the corresponding author was sent by e-mail and when appropriate a comment was added in the remark field based on the author's response.

Fields in the resistancebank database

DOI: *Digital Object Identifier.*

When not available, the PubMed identification number (PMID) was used.

Author: *Author's last name.*

PubDate: *Year the article was published.*

First published date.

ISO3: *Three-letters country codes.*

For full list available at: https://en.wikipedia.org/wiki/ISO_3166-1_alpha-3

Ycoord/Xcoord: *Latitude/Longitude in decimal degree.*

The X/Y-coordinates define the position of the area where the field sampling was performed. We distinguished four different situations:

i) If the location was provided in decimal degrees this format was used as such,
ii) If the location was provided in a degree/minute/second format was converted in decimal degrees.
iii) If the samples were converted across an administrative unit, and specific coordinates were not provided for each sampling site the coordinates of the centroid of the administrative unit was used.

iv) If several locations were mentioned in the manuscript and that resistance rates could not be disaggregated by location based on the information provided in the manuscript the center of mass between the locations was designated as the geographic coordinates of the study.

StartDate/EndDate: *Start date of study, specified in the article.*

This refers to the sampling dates. Following format was used: day/month/year (e.g., 29/09/1985). Sampling might span several time periods. When exact days of sampling were not mentioned, the 15th of each month was assumed. When only sampling year(s) were given, the first and the last day of the referred period will be used (e.g., 2012-2013, 01/01/2012 for StartDate and 31/12/2013 for EndDate).

Species: *Animal species included in the study.*

All animal species were pooled in the following categories of animals Cattle (including buffaloes and yak), Chickens (including duck and geese), Pigs, Sheep (including all small ruminants), Rabbits, Horses, Camel or a mixture of these.

For studies providing aggregated data for different animal species and/or sample types, an entry was included in *resistancebank* with DOI, country and author but no values were entered in the Rescom% column (see below).

SampleType: *Samples recovered from the animals.*

All sample types were pooled in four categories: Living Animals (animal swabs), Killed Animals (cecal samples and lymph nodes), Products (dairy and eggs) and fecal samples. Any PPS with mixed sample type containing meat was categorized as meat, except mixes including killed animals which were categorized as killed animals

Method: *Methodology used for antibiotic susceptibility testing (AST)*

Methods were recorded as either disk diffusion (DD), agar dilution (AD), broth dilution (BD), Etest or the name of the automatic system (e.g., VITEK). Disk diffusion method was assumed when PPS reported the potency of disks used for the AST. When more than one methodology was used, the acronyms of the methods are separated by a _. When non-standard medium was used to perform AST, the name of medium was recorded in the remark section.

For further applications of *resistancebank*, PPS performing molecular typing or population structure analysis were also recorded. For simplicity, _PCR (Polymerase Chain Reaction) was added to all studies performing molecular typing (e.g., detection of antibiotic resistance genes, virulence determinants, mobile genetic elements and MLST) or fingerprinting methods (e.g., PFGE). For PPS reporting whole genome sequencing data, a _WGS was added.

There are several AST possibilities but they can be grouped into Diffusion or Dilution methods. Guidelines for performing these tests are given by different societies and/or organizations (CLSI, EUCAST, French Society for Microbiology – SFM). Note: antibiotic concentrations are normally expressed in μg/mL and in μg for the disk content alone.

Pathogens: *Bacterial species targeted for the study*

Currently *resistancebank* includes the following organisms: non-typhoidal *Salmonella* spp., *Escherichia coli*, *Enterococcus* spp, *Staphylococcus aureus*, *Campylobacter* spp..

Strain: *Bacterial subtype (not used in this study)*

Some studies focus on the epidemiology of restricted strains within a species. If no specification, NA is introduced.

- For PPS reporting exclusively on strains resistant to a specific antimicrobials, a 3-letter code (see below) was used to indicate their resistance phenotype (e.g., nalidixic acid-resistant – NAL-R). For *S. aureus* and *Enterococcus* spp., the common designations for certain resistant types are used instead (e.g., MRSA and MSSA - methicillin resistant and susceptible *S. aureus*, respectively; VISA and VRSA – vancomycin intermediate and resistant *S. aureus*; and VRE – vancomycin resistant enterococci)
- For PPS reporting on single-species, the designation is included in the strain column (e.g., a study focusing only on *Enterococcus faecium*).
- For PPS reporting on *Salmonella* spp., the serotype was reported in the strain column.
- For PPS reporting on *E. coli* pathotypes and/or serotypes characterized, they are inputted into the strain column (e.g., STEC, O157, ExPEC, etc).
- For studies on the characterization of bacteria carrying specific genetic traits such as antibiotic resistance genes or virulence determinants, these are specified in the strain column.

Nsamples: *Number of samples collected.*

The total number of recovered samples per type at the different sampling sites (butchers, markets, farms or retail/supermarkets).

Note: In many studies the number of samples which were referred to KilledAnimal does not entirely represent the number of animals sampled as different organs may have been used for susceptibility testing. When that was the case, an inquiry to the corresponding author was made for a breakdown of the data collected.

Prev%: *Number of samples positive for a pathogen divided by the total number of samples collected.*

In the absence of bacteria, Prev%=0. The value is expressed in percentage and rounded to one decimal.

Nisolates: *Number of isolates*

The total number of isolates used for AST. Normally this is equal to the number of positive samples (prevalence). Increased numbers in comparison to the samples can be due to recovery of more than one bacterium per sample, whereas lower numbers can be attributed to the use of a representative subset or loss of bacterial viability.

Drug: *Antibiotic Class.*

The following broad antibiotic classes were included in *resistancebank*: PEN (Penicillins), CEP (Cephalosporins), MON (Monobactams), CAR (Carbapenems), AMI (Aminoglycosides), QUI (Quinolones), AMP (Amphenicols), TET (Tetracyclines), SUL (Sulfonamides), MAC (Macrolides), Glycopeptides (GLY), POL (Polymixins), OTH (Others).

Compound and ATC-Code: *Antimicrobial compounds used for susceptibility testing designated by a 3-letter code and its designation in the Anatomical Therapeutic Chemical (ATC) Classification.*

ATC-Code starting with J0 stand for antibiotics for human systemic use while QJ01for veterinary use. For additional information and ATC-Code searching, please refer to https://www.whocc.no/atc_ddd_index/ or https://www.whocc.no/atcvet/atcvet_index/.

For antibiotics without attributed ATC codes, a pseudo code was constructed by using the ATC code of the molecular classification (5 or 6 characters for human and veterinary antibiotics, respectively) and adding the first character of the compound's name separated by a - (e.g., Sarafloxacin – J01MA-S; and Mequindox – QJ01MQ-M). Some ATC codes are provided for mixture of compounds (e.g., J01RA01 for penicillins in combination with other antibacterials). Active ingredients' name were reported in *resistancebank* when commercial drugs were used. The antibiotics found across all studies are the following (3 letter code, ATC-code): Amoxicillin-Clavulanic Acid (AMC, J01CR02); Ticarcillin-Clavulanic acid (TIM, J01CR03); Piperacillin-Tazobactam (PIT, J01CR05); Ampicillin-Sulbactam (SAM, J01CR01); Ampicillin (AMP, J01CA01); Amoxicillin (AMX, J01CA04); Ticarcillin (TIC, J01CA13); Cloxacillin (CLO, J01CF02); Oxacillin (OXA, J01CF04); Penicillin & Streptomycin (PES, J01RA01); Mecillinam (MEC, J01CA11); Piperacillin (PIP, J01CA12); Flucloxacillin (FLU, J01CF05); Carbenicillin (CAR, J01CA03); Methicillin (MET, J01CF03); Penicillin (PEN, J01CE01); Temocillin (TEM, J01CA17); Dicloxacillin (DIC, QJ51CF01); Nafcillin (NAF, J01CF06); Mezocillin (MEZ, J01CA10); Ceftriaxone (CRO, J01DD04); Ceftazidime (CAZ, J01DD02); Cefalexin (CLX, J01DB01); Cefotaxime (CTX, J01DD01); Cefepime (FEP, J01DE01); Cefoxitin (FOX, J01DC01); Cefalotin (CFL, J01DB03); Ceftiofur (CFU, QJ01DD90); Cefuroxime (CXM, J01DC02); Cefpodoxime (CPD, J01DD13); Cefazolin (CFZ, J01DB04); Cefixime (CFM, J01DD08); Cefamandole (CMD, J01DC03); Cefoperazone (CFP, J01DD12); Moxalactam (MOX, J01DD06); Cefpirome (CPO, J01DE02); Cefotetan (CTT, J01DC05); Cefradine (CFR, J01DB09); Ceftaroline (CPT, J01DI02); Ceftobiprole (CBP, J01DI01); Cefquinome (CFQ, QJ01DE90); Sulbactam-CFP (SFP, J01DD62); Ceftizoxime (CZM, J01DD07); Cephaloridine (CLD, J01DB02); Cefalonium (CLM, QJ51DB90); CTX-Clavulanic acid (CTC, J01DD51); CAZ-Clavulanic Acid (CAC, J01DD52); Cefmetazole (CEM, J01DC09); Cefaclor (CFC, J01DC04);

Cefadroxil (CFR, J01DB05); Aztreonam (ATM, J01DF01); Imipenem (IPM, J01DH51); Ertapenem (ERT, J01DH03); Meropenem (MEM, J01DH02); Doripenem (DOR, J01DH04); Kanamycin (KAN, J01GB04); Gentamicin (GEN, J01GB03); Neomycin (NEO, J01GB05); Streptomycin (STR, J01GA01); Amikacin (AMK, J01GB06); Tobramycin (TOB, J01GB01); Apramycin (APR, QA07AA92); Netilmicin (NET, J01GB07); Spectinomycin (SPT, J01XX04); Isepamicin (ISP, J01GB11); Ciprofloxacin (CIP, J01MA02); Nalidixic acid (NAL, J01MB02); Enrofloxacin (ENR, QJ01MA90); Norfloxacin (NOR, J01MA06); Ofloxacin (OFX, J01MA01); Oxolinic Acid (OXO, J01MB05); Flumequine (FLQ, J01MB07); Moxifloxacin (MXF, J01MA14); Levofloxacin (LVX, J01MA12); Pefloxacin (PEF, J01MA03); Olaquindox (OLA, QJ01MQ01); Mequindox (MEQ, QJ01MQ-M); Marbofloxacin (MRB, QJ01MA93); Gatifloxacin (GAT, S01AE0E); Lomefloxacin (LOM, J01MA07); Danofloxacin (DAN, QJ01MA92); Carbadox (CRB, QJ01MQ-C); Sarafloxacin (SAR, J01MA-S); Chloramphenicol (CHL, J01BA01); Florfenicol (FFC, QJ01BA90); Thiamphenicol (TFC, J01BA02); Tetracycline (TET, J01AA07); Oxytetracycline (OXT, J01AA06); Doxycycline (DOX, J01AA02); Minocycline (MIN, J01AA08); Tigecycline (TIG, J01AA12); Chlortetracycline (CTE, J01AA03); Sulfamethoxazole-Trimethoprim (SXT, J01EE01); Sulfamethoxazole (SMZ, J01EC01); Sulfafurazole or Sulfisoxazole (SOX, J01EB05); Sulfonamides-Trimethoprim (SUT, J01EE); Sulfonamides (SSS, J01E); Trimethoprim-Sulfadiazine (TDZ, QJ01EW10); Trimethoprim (TMP, J01EA01); Sulfamonomethoxine (SMN, QJ01EQ18); Erythromycin (ERY, J01FA01); Lincomycin (LIN, J01FF02); Clindamycin (CLI, J01FF01); Clarithromycin (CLR, J01FA09); Tylosin (TYL, QJ01FA90); Azithromycin (AZM, J01FA10); Spiramycin (SPI, J01FA02); Tilmicosin (TIL, QJ01FA91); Roxithromycin (ROX, J01FA06); Midecamycin (MID, J01FA03); Vancomycin (VAN, J01XA01); Teicoplanin (TEC, J01XA02); Avoparcin (AVO, J01XA-A); Polymixin B (PMB, J01XB02); Colistin (CST, J01XB01); Linezolid (LIZ, J01XX08); Nitrofurantoin (NIT, J01XE01); Rifampicin (RIF, J04AB02); Quinupristin-Dalfopristin (Q-D, J01FG02); Bacitracin (BAC, J01XX10); Furazidin (FUR, J01XE03); Daptomycin (DAP, J01XX09); Mupirocin (MUP, D06AX09); Fosfomycin (FOF, J01XX01); Fusidic acid (FUS, J01XC01); Metronidazole (MTD, J01XD01); Pristinamycin (PRI, J01FG01); Furazolidone (FRZ, QJ01XE90); Tiamulin (TIA, QJ01XQ01); Novobiocin (NOV, QJ01XX95); Valnemulin (VAL, QJ01XQ02).

For data analysis, only compounds within the WHO Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria were used (Table S2):

Rescom%: *Percentage of isolates resistant to the relevant antimicrobial compound*

Intermediate-resistant isolates were considered susceptible. All values are rounded to one decimal place. Any value over 0% was rounded to 1%.

When inconsistencies were noted between the resistance rates reported in the main text of a manuscript and the tables, then values reported in the latter were used in *resistancebank*. Attempts to resolve uncertainties on the number of samples used for calculating resistance rates, or to disaggregate resistance rates between species were made by contacting the corresponding author. Overall 443 emails were sent, and 162 (36.7%) emails were ere answered by April 1st 2019.

Concg: *Concentration of antimicrobial used for susceptibility test susceptibility.*

For dilutions methods, this is the concentration expressed in μg/mL. For diffusion methods, this is the potency of the drug expressed in μg. In the case of antimicrobial mixtures, the sum of both concentrations was taken.

Guidelines: *Category of Guideline document used for performing AST in each PPS*

Refers to the document used to compare AST results against clinical breakpoints to classify a pathogen as phenotypically resistant or susceptible to an antibiotic. Values correspond to the committee that developed the guidelines, including the EUCAST, and the SFM. Since NCCLS was renamed to CLSI in 2005, all NCCLS documents will be recorded as CLSI.

When the year of the guidelines used was not reported in the PPS the acronym of the committee was reported. In the case of CLSI animal-specific documents (M31), if the document identification was not stated, the term animal was used instead (e.g., CLSI 2004 Animal).

Breakpoint: *Breakpoint used for assessing antimicrobial susceptibility testing.*

For diffusion methods, the breakpoint is expressed as <= the diameter value in mm of the growth inhibition zone. For dilution methods, the breakpoint is expressed as >= the value of the concentration μg/mL of bacterial growth inhibition. When breakpoints were not yet established for certain antimicrobials, the breakpoint specified by the authors were recorded. These are typically derived from breakpoints of similar molecules or from the literature. As of the June 2019, this concerns 11 surveys associated with AGISAR pathogens in *resistancebank*.

Remark: *Comments relative to the publication (first row) or for specific compounds (additional rows).*

E-mail contact: *Contact information of authors, and reason for contacting the authors.*

Protocol S3. Regional variations in accuracy of antimicrobial susceptibility testing

We used the 2015 report from the *External Quality Assurance System (EQAS) of the World Health Organization Global Foodborne Infections Network* (*47*) to account for regional differences in the accuracy of antimicrobial susceptibility testing. The EQAS reports aim to estimate performance for antimicrobial susceptibility testing as the percentage of phenotypically resistant isolates correctly identified across 10 sub-regions.

In this study, those estimates were used to calculate an adjusted sample size for of each survey by multiplying the sample size reported by the accuracy published in the EQAS report for each year and region. For example for a surveys on *Salmonella* spp. conducted in Southeast Asia in 2015 with original sample size of 200, the adjusted sample size was: 180 = round(200 x 0.899). In comparison, a survey conducted with the same number of samples conducted on the same year on *Campylobacter* spp. in Africa where the accuracy of susceptibility testing is lower (0.719) would have its sample size further reduce: 144 = round (200 x 0.719). The contribution of the African studies to the global interpolation used to produce the maps of P50 maps would be relatively lower than the Asian studies. Since *E. coli* is not part of the panel used within EQAS, the *Shigella* spp. values were used as a proxy for the accuracy on *E. coli* testing given the close relatedness (*48*) of this genus with *Escherichia* spp..

Accuracies were not reported in the EQAS report before to 2001 for *Salmonella* spp., and before 2009 for *Campylobacter* spp. and *Shigella* spp.. Therefore, the accuracies reported on the first year were used to adjust sample size for all years before EQAS reporting started. For all years after 2015, the accuracies reported in 2015 were used, and for any year missing accuracy reports, the last accuracy estimate reported was used. For MRSA, no metrics of accuracy were provided in the EQAS report from 2015. The average accuracies reported for *Shigella* spp., *Salmonella* spp. and *Campylobacter* spp. each year were used as proxy for each year.

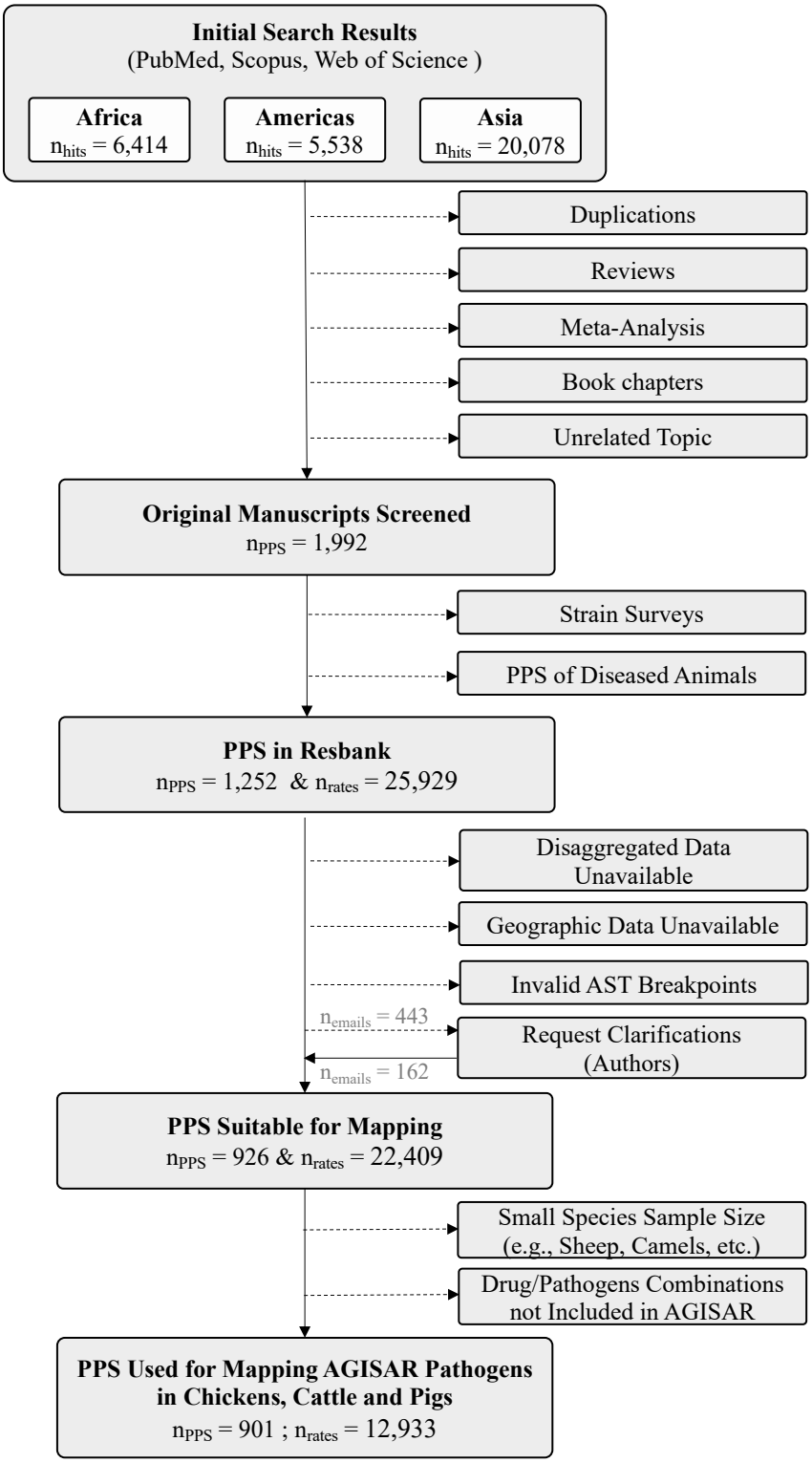

Fig. S1. Literature Review. Number of resistance rates (n_{rates}), and point-prevalence surveys (n_{PPS}) identified, exclusion criteria and records used for mapping antimicrobial resistance. AGISAR = Advisory Group on Integrated Surveillance of Antimicrobial Resistance**.**

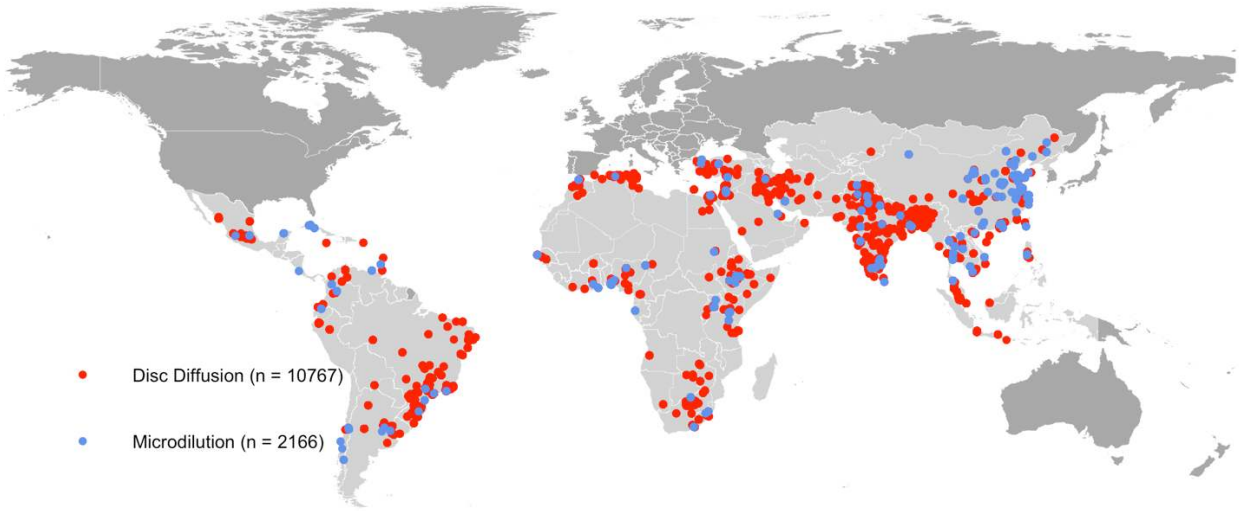

Fig. S2. Geographic distribution of antimicrobial susceptibility testing methods.

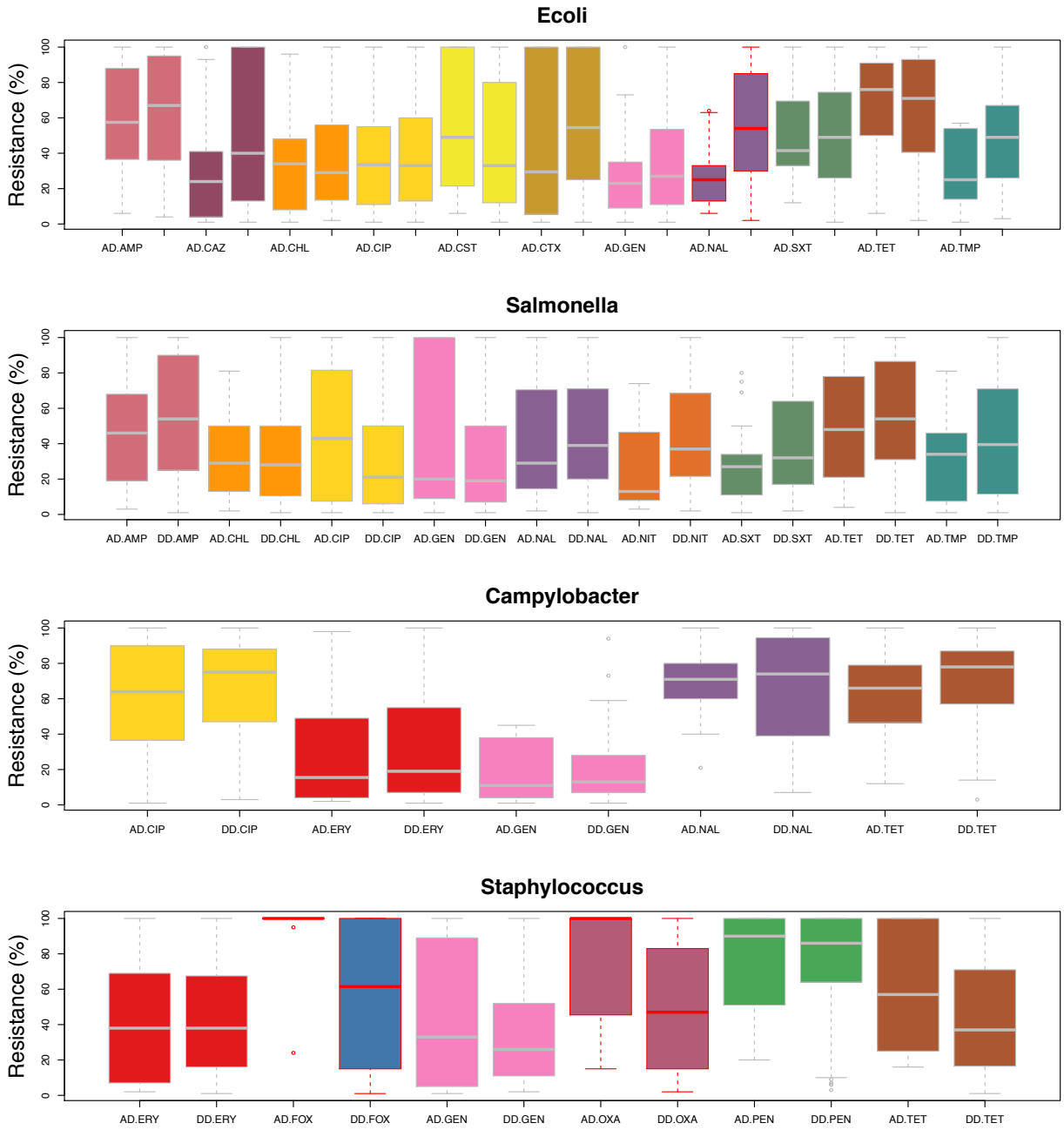

Fig. S3. Average resistance levels and susceptibility testing methods. Variations (or absence thereof) in levels of antimicrobial resistance associated with each susceptibility testing method: antimicrobial dilution (AD) and disc diffusion (DD). Statistically significant differences are highlighted with red borders on the boxplots (Mann–Whitney U test).

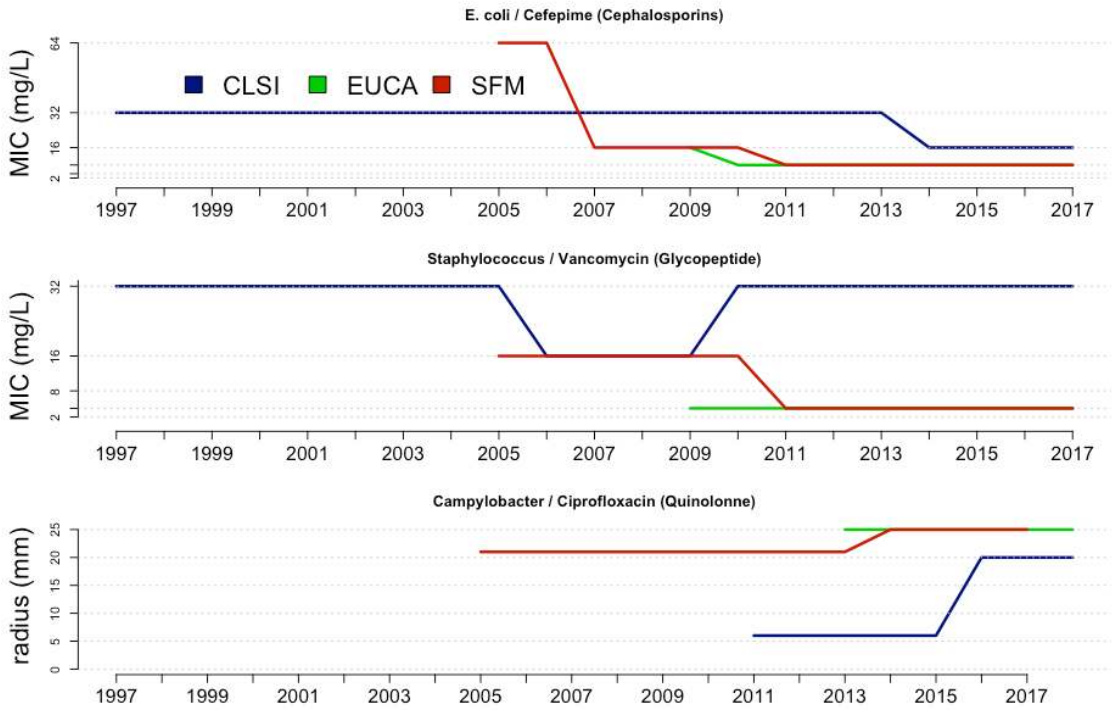

Fig. S4. Guidelines variation for Susceptibility testing. Variations in breakpoints between guidelines from (CLSI, EUCAST, and SFM) over time for *E. coli*/Cefepime (top), *Staphylococcus*/ Vancomycin (middle), and *Campylobacter*/ Ciprofloxacin (bottom).

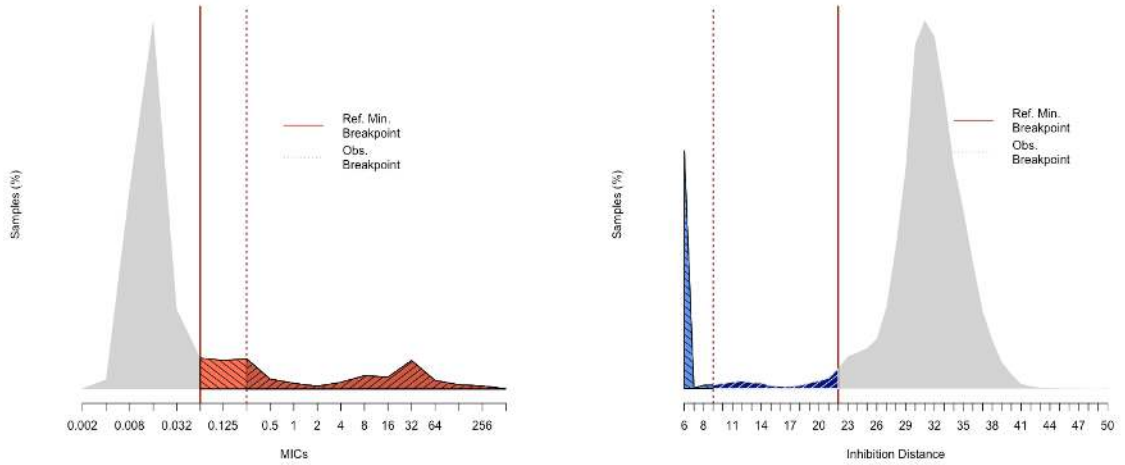

Fig. S5. Modulation of resistance rates. Illustration of the calculation of Areas Under the Curve for the correction applied to observed resistance rates reported in PPS for an hypothetical drug-pathogen combination where reference breakpoints differ from the observed breakpoints by two dilutions or 13 mm. MIC/inhibition zone distribution were obtained from the EUCAST online database (grey polygon, http://www.eucast.org/mic_distributions_and_ecoffs/).

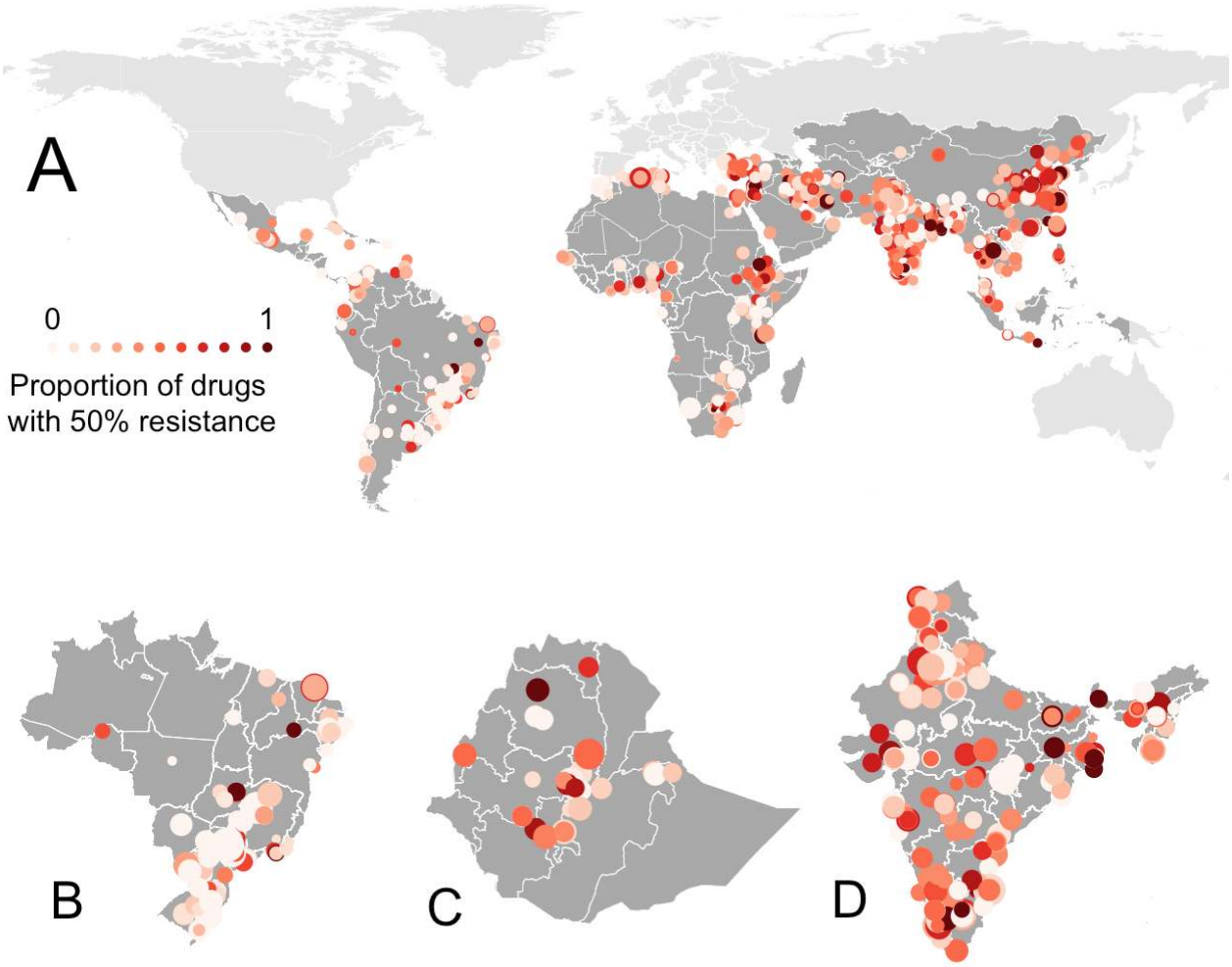

Fig S6. Global distribution of multi-resistance. Proportion of drugs with resistance 50% of higher (P50) in 901 points prevalence surveys on Amr in animals (A). P50 in countries with rapid intensification of the animal production such as Brazil (B), Ethiopia (C) and India (D).

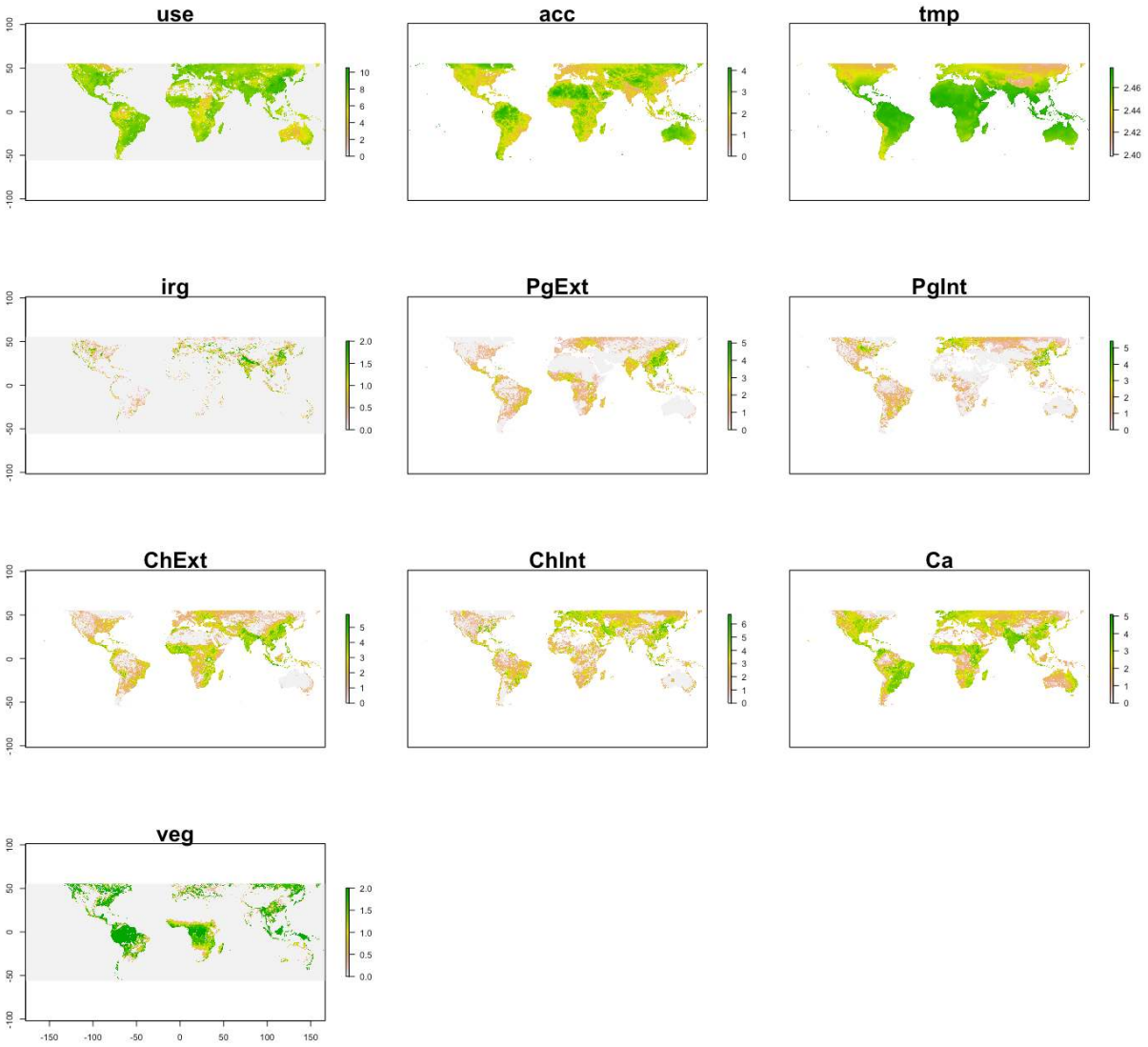

Fig. S7. Environmental and anthropogenic covariates used for training the child models (log10 scaled). Predicted antimicrobial use in animals (use), travel time to cities of more than 50,000 people (acc), yearly average of minimum monthly temperature (tmp), percentage of pixel area irrigated (irg), population densities of extensively raised pigs (PgExt), intensively raised pigs (PgInt), extensively raised chicken (ChExt), intensively raised chicken (ChInt), Cattle (Ca), and percentage are covered in vegetation (veg).

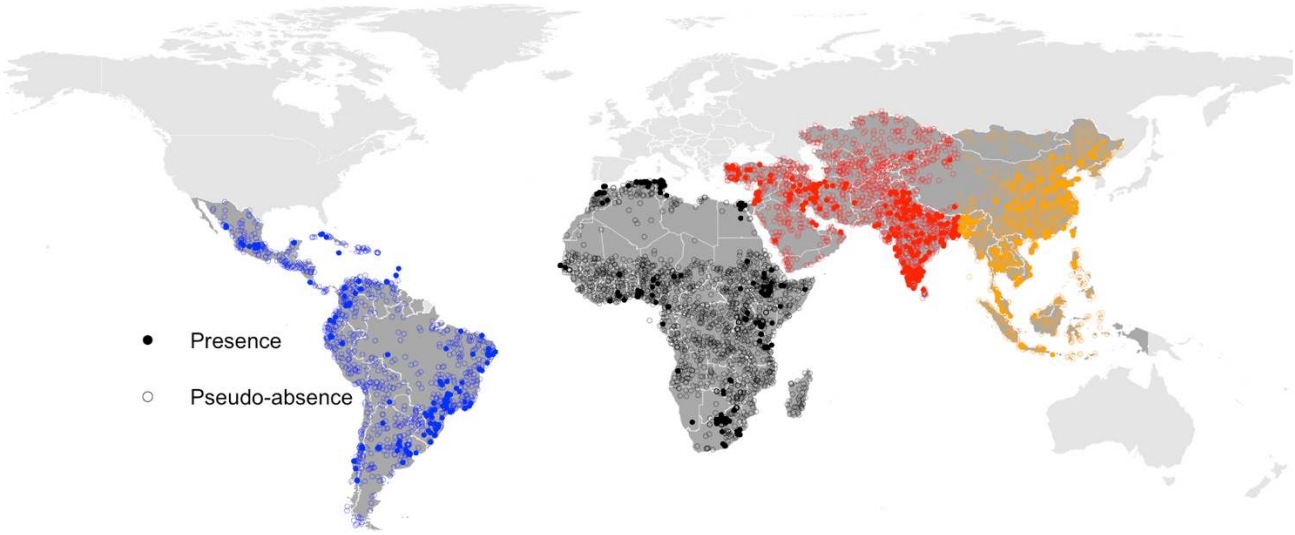

Fig. S8. Geographic distribution or presence and pseudo-absence. Points in four regions were used for the K-fold spatial cross-validation procedure of the child models.

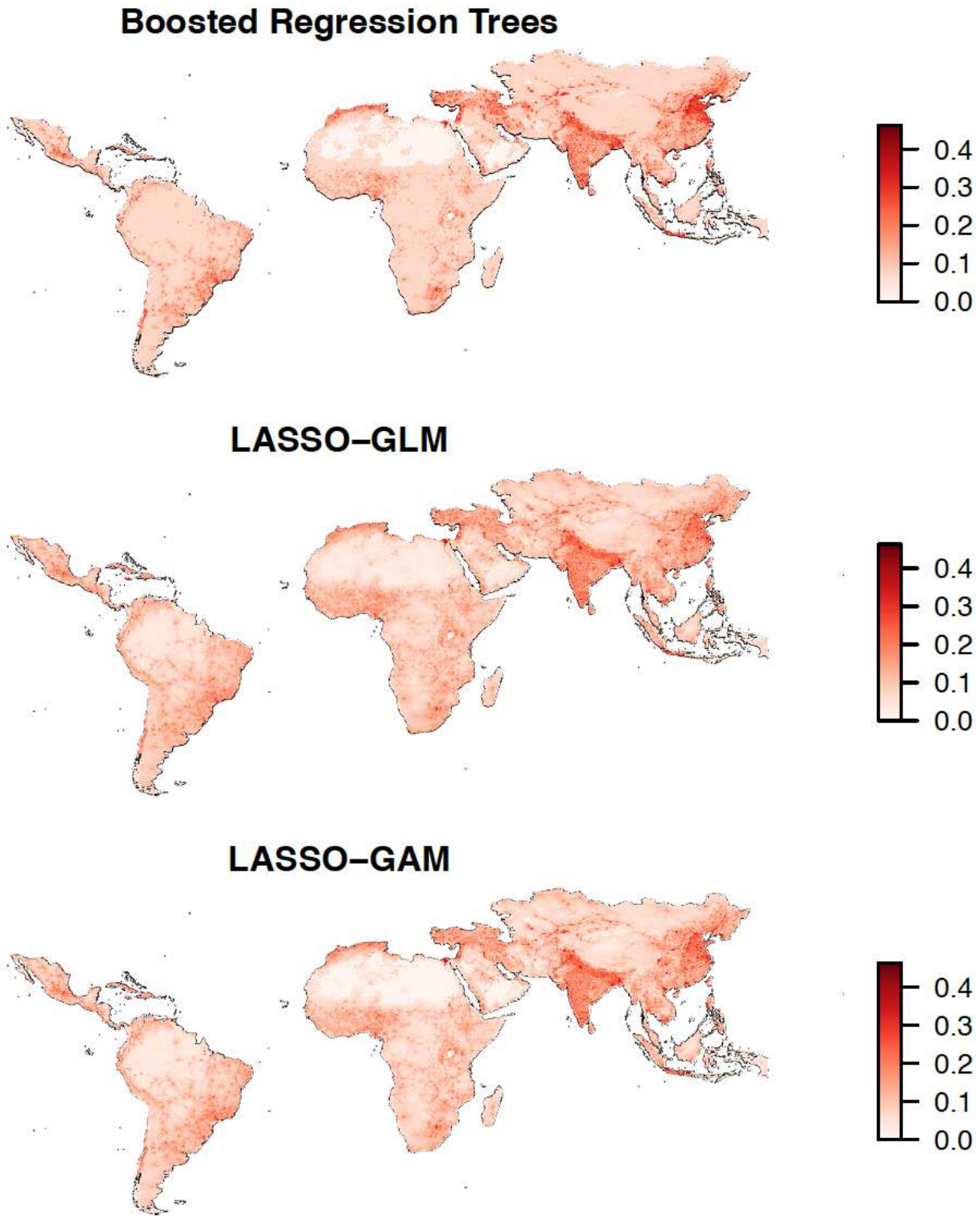

Fig. S9. Global maps of P50 obtained from child models using environmental covariates. Boosted Regression Trees (top), least absolute shrinkage and selection operator (LASSO) applied to logistic regression (middle), and Generalized Additive Model (GAM) (bottom).

1144

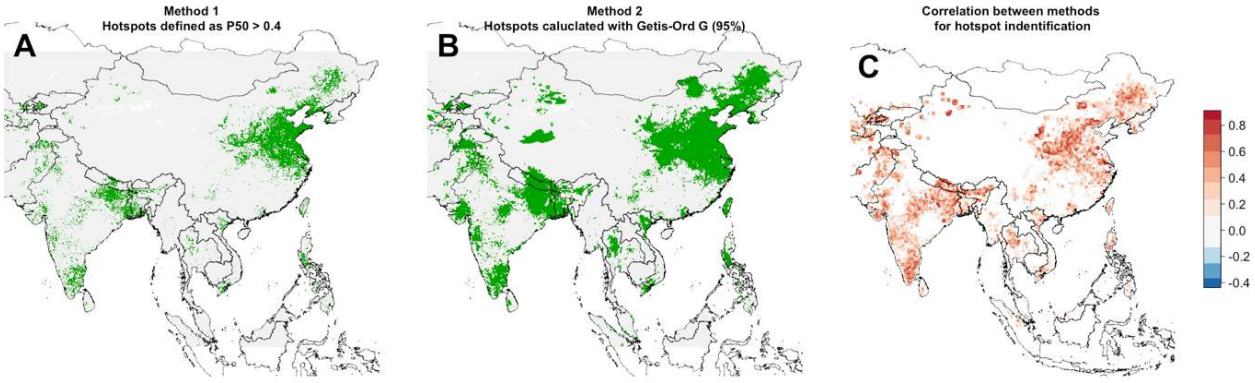

Fig. S10. Identification of hotspots using cutoff method (A), Getis-Ord Method (B), and local Pearson correlation coefficient between the cutoff method, and Getis-Ord G (C). A global map of hotspots is available in raster format.

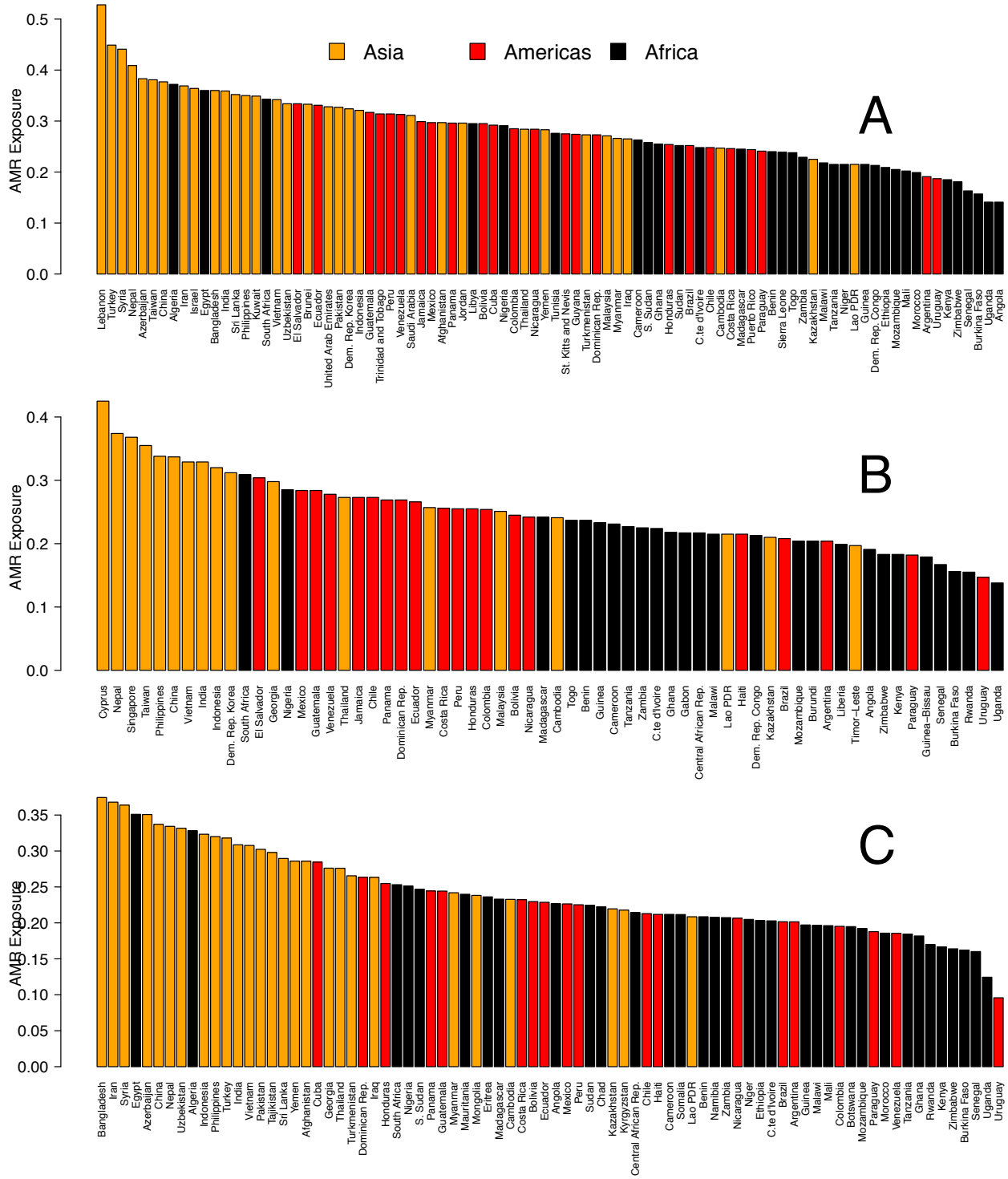

Fig. S11. Summary metric of country-level exposure to antimicrobial resistance in chickens (A), pigs (B) and cattle (C).

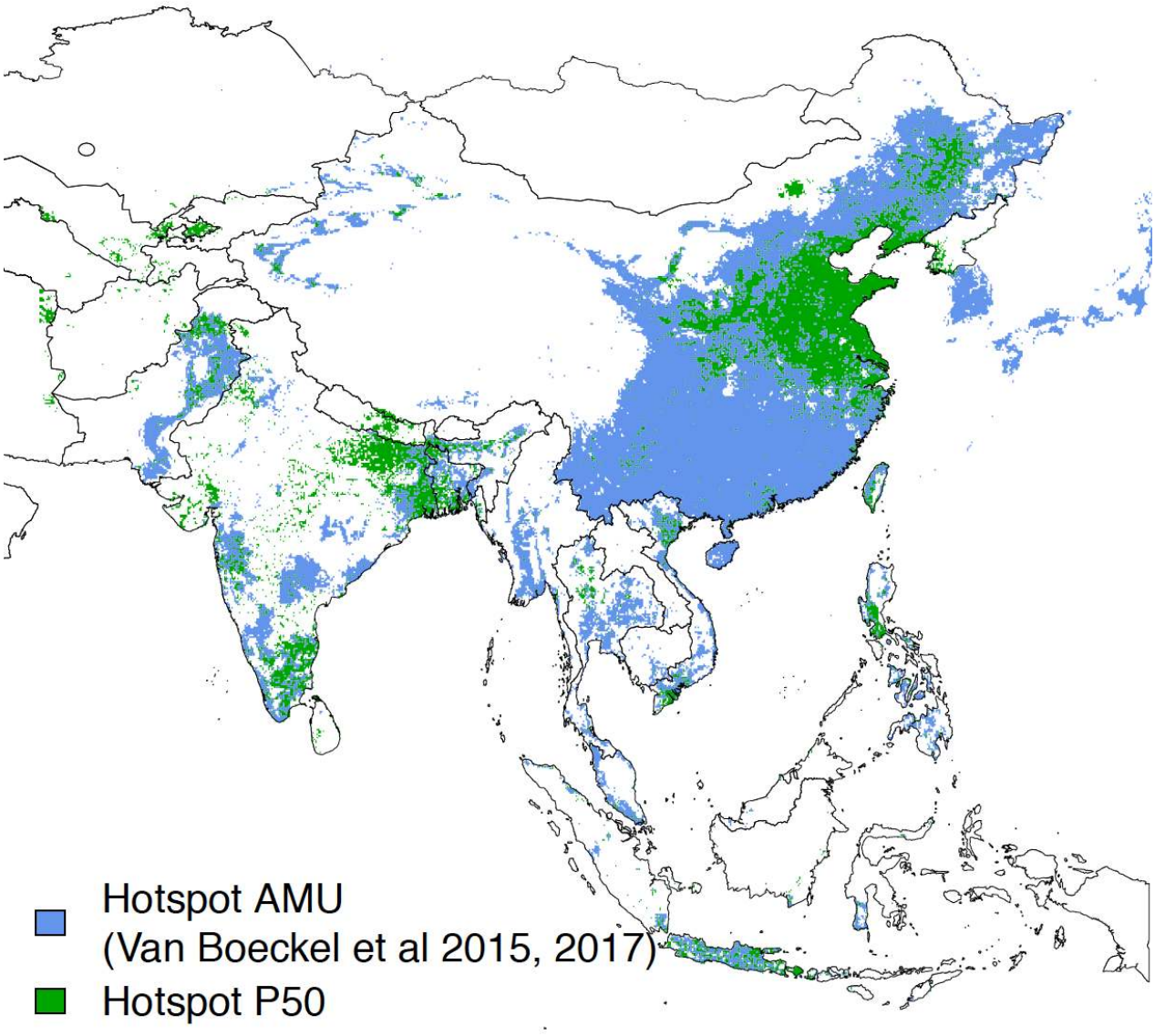

Fig. S12. Association between hotspots of antimicrobial resistance (P50 > 0.4, green), and hotspots of increased antimicrobial use (blue) in Asia. Hotspots of increased antimicrobial use (AMU) are areas where consumption could surpass 30 kg per 10 km^2 by 2030, as estimated by Van Boeckel et al 2015 (*49*), and updated with the latest global antimicrobial use data (*1*). Three quarters (74%) of the P50 hotspots are in hotspots of increased antimicrobial use, albeit the association between P50 and antimicrobial use was moderate (Kappa = 0.28), and consistent with the moderate importance of antimicrobial use in used child-models for global geospatial models (Table S5).

Geographic Region	End Date[a]	PubMed	ISI Web of Science	Scopus	Total Hits	Studies Screened
South America	28.03.19	2206	930	1129	4265	260
Central America, Mexico, Caribbean	28.03.19	694	257	322	1273	53
Africa	28.03.19	2217	1677	2520	6414	457
India and South East Asia	28.03.19	4763	1147	2164	8074	543
West and Central Asia, Arabian Peninsula	28.03.19	2297	1359	1409	5065	275
China	28.03.19	5067	873	999	6939	404
Grey Literature	-	-	-	-	-	178

[a]Data collection end date for the corresponding region. For search dates were limited from 2000/01/01 to 2018/12/31.

Table S1. Number of hits across literature databases and geographic regions

Antimcirobial Classes	ATC-Code	*Salmonella* and *E. coli*	*Campylobacter* spp.	*Enterococcus* spp.	*Staphylococcus aureus*
Aminoglycosides	J01GB03 J01GA01	Gentamicin	Gentamicin Streptomycin	Gentamicin Streptomycin	Gentamicin
Amphenicols	J01BA01	Chloramphenicol	-	Chloramphenicol	Chloramphenicol
Carbapenems	J01DH51 J01DH02	Imipenem Meropenem	-	-	-
Cephalosporins	J01DC01 J01DD01 J01DD04 J01DD02 J01DE01	Cefoxitin Cefotaxime Ceftriaxone Ceftazidime Cefepime	-	-	Cefoxitin
Glycopeptides	J01XA01 J01XA02	-	-	Vancomycin Teicoplanin	Vancomycin
Glycylcyclines	J01AA12	Tigecycline	-	Tigecycline	-
Lincosamides	J01FF01	-	Clindamycin	-	Clindamycin
Lipopeptides	J01XX09	-	-	Daptomycin	-
Macrolides	J01FA10 J01FA01	Azithromycin	Erythromycin	Erythromycin	Erythromycin
Nitrofurans	J01XE01	Nitrofurantoin	-	-	-
Oxazolidinones	J01XX08				Linezolid
Penicillins	J01CA01 J01CA04 J01CA17	Ampicillin Amoxicillin Temocillin	Ampicillin	Ampicillin	-
Polymyxins	J01XB01	Colistin	-	-	-
Quinolones	J01MA02 J01MB02 J01MA03	Ciprofloxacin Nalidixic acid Pefloxacin	Ciprofloxacin Nalidixic acid	Ciprofloxacin	Ciprofloxacin
Rifamycins	J04AB02	-	-	-	Rifampicin
Streptogramins	J01FG02	-	-	Quinupristin-Dalfopristin	Quinupristin-Dalfopristin
Sulfonamides[a]	J01EB05[a]	Sulfisoxazole[a]			Sulfisoxazole
Tetracyclines	J01AA07	Tetracycline	Tetracycline	Tetracycline	Tetracycline
Trimethoprim	J01EA01	Trimethoprim	-	-	Trimethoprim
Sulfonamides+ Trimpethoprim	J01EE01	Sulfonamides-Trimethoprim	-	-	-

[a]Only sulfisoxazole shown, but any combination of sulfonamides can be used to test for this class and were included in the analysis

Table S2. Antibiotics suggested by the WHO-AGISAR for surveillance in foodborne bacteria (adapted from (*14*))

Name	Acronym	Year	Original Resolution	Source
Antimicrobial use in animals	use	2013	0.083333 decimal degrees	Van Boeckel et al 2017 (*1*) http://science.sciencemag.org/content/357/6358/1350.full
Travel time to cities	acc	2015	30-arcsec resolution	Weiss et al 2018(*26*) https://www.map.ox.ac.uk/accessibility_to_cities/.
Yearly average of minimum monthly temperature	tmp	1970-2000	**2.5 minutes**	Worldclim (*50*) http://worldclim.org/version2
Percentage irrigated areas	irg	2005	0.083333 decimal degrees	Global Map of Irrigation Areas (GMIA) (*51*) http://www.fao.org/nr/water/aquastat/irrigationmap/index10.stm
Population density pigs, chickens and cattle (extensive vs intensive systems)	ChExt ChInt PgExt PgInt Ca	2013	0.083333 decimal degrees	Gridded Livestock of the World v3 (*52*, *53*) https://livestock.geo-wiki.org/
Percentage of tree coverage	veg	2013	0.008333 decimal degrees	https://earthenginepartners.appspot.com/science-2013-global-forest/download_v1.2.html (*54*)

Table S3. Environmental and anthropogenic covariates used for training the child models

Name	Acronym	Year	Original Resolution	Source
Urban Areas	Urban	2009	~ 300m at equator	GlobeCover 2009 (*55*) http://due.esrin.esa.int/page_globcover.php
Human population density (n/km^2)	Hpop	2015	30 arc-second	GPW v4 http://sedac.ciesin.columbia.edu/data/set/gpw-v4-population-density-rev10

Table S4. Covariates used for the stratified sampling of pseudo-absence points

	Use*	acc	tmp	irg	PgExt	PgInt	ChExt	ChInt	Ca	veg
Relative Influence (%)										
BRT	3.8	68.1	7.4	5.2	1.5	2.0	2.4	6.4	1.8	1.3
Frequency of selection after regularization (%)										
LASSO-GLM	-30	-100	-70	100	0	10	90	50	0	-50
LASSO-GAM (linear)	0	50	80	60	0	10	100	50	0	10
LASSO-GAM (non-linear)	90	50	10	40	0	0	0	0	0	60

*Predicted antimicrobial use in animals (use), travel time to major cities (acc), yearly average of minimum monthly temperature (tmp), percentage of pixel area irrigated (irg), population densities of extensively raised pigs (PgExt), intensively raised pigs (PgInt), extensively raised chicken (ChExt), intensively raised chicken (ChInt), Cattle (Ca), and percentage are covered in vegetation (veg).

Table S5. Relative influence of individual covariates in child models

Pathogen	Continent	Species	Studies per compound
Ecoli	Africa	Cattle	AMP(n=16),AMX(n=13),CAZ(n=14),CHL(n=35),CIP(n=33),CRO(n=10),CST(n=10),CTX(n=26),FEP(n=3),FOX(n=14),GEN(n=41),IPM(n=11),MEM(n=3),NAL(n=26),NIT(n=7),SOX(n=1),SSS(n=8),SXT(n=34),TET(n=49),TIG(n=2),TMP(n=9)
Ecoli	Africa	Chicken	AMP(n=15),AMX(n=15),CAZ(n=18),CHL(n=31),CIP(n=43),CRO(n=7),CST(n=15),CTX(n=29),FEP(n=3),FOX(n=12),GEN(n=43),IPM(n=14),MEM(n=6),NAL(n=30),NIT(n=5),SSS(n=10),SXT(n=35),TET(n=37),TIG(n=2),TMP(n=10)
Ecoli	Africa	Pig	AMP(n=3),AMX(n=1),CAZ(n=3),CHL(n=6),CIP(n=8),CRO(n=1),CST(n=2),CTX(n=6),FOX(n=2),GEN(n=8),IPM(n=1),MEM(n=2),NAL(n=4),SSS(n=1),SXT(n=4),TET(n=7),TIG(n=2),TMP(n=2)
Ecoli	Asia	Cattle	AMP(n=70),AMX(n=27),AZM(n=7),CAZ(n=29),CHL(n=68),CIP(n=67),CRO(n=30),CST(n=16),CTX(n=45),FEP(n=7),FOX(n=10),GEN(n=83),IPM(n=24),MEM(n=11),NAL(n=35),NIT(n=13),SOX(n=3),SSS(n=2),SXT(n=41),TET(n=50),TIG(n=2),TMP(n=12)
Ecoli	Asia	Chicken	AMP(n=60),AMX(n=18),AZM(n=7),CAZ(n=29),CHL(n=57),CIP(n=70),CRO(n=25),CST(n=19),CTX(n=36),FEP(n=11),FOX(n=14),GEN(n=72),IPM(n=21),MEM(n=12),NAL(n=32),NIT(n=11),SOX(n=1),SSS(n=6),SXT(n=45),TET(n=46),TIG(n=1),TMP(n=10)
Ecoli	Asia	Pig	AMP(n=36),AMX(n=9),AZM(n=1),CAZ(n=18),CHL(n=31),CIP(n=39),CRO(n=14),CST(n=11),CTX(n=29),FEP(n=6),FOX(n=13),GEN(n=42),IPM(n=13),MEM(n=9),NAL(n=19),NIT(n=6),SOX(n=1),SSS(n=1),SXT(n=30),TET(n=34),TIG(n=5),TMP(n=9)
Ecoli	Americas	Cattle	AMP(n=33),AMX(n=5),CAZ(n=13),CHL(n=20),CIP(n=29),CRO(n=16),CST(n=2),CTX(n=16),FEP(n=10),FOX(n=13),GEN(n=37),IPM(n=11),MEM(n=5),NAL(n=24),NIT(n=8),SOX(n=3),SSS(n=1),SXT(n=35),TET(n=30),TIG(n=1),TMP(n=2)
Ecoli	Americas	Chicken	AMP(n=18),AZM(n=1),CAZ(n=10),CHL(n=21),CIP(n=25),CRO(n=8),CST(n=4),CTX(n=16),FEP(n=5),FOX(n=10),GEN(n=27),IPM(n=4),MEM(n=1),NAL(n=16),NIT(n=6),SOX(n=3),SSS(n=1),SXT(n=20),TET(n=25),TMP(n=2)
Ecoli	Americas	Pig	AMP(n=14),AMX(n=1),CAZ(n=4),CHL(n=12),CIP(n=11),CRO(n=4),CST(n=5),CTX(n=8),FEP(n=2),FOX(n=3),GEN(n=16),MEM(n=1),NAL(n=10),NIT(n=4),SOX(n=1),SSS(n=2),SXT(n=14),TET(n=14),TIG(n=1),TMP(n=2)
Salmonella	Africa	Cattle	AMP(n=13),AMX(n=7),AZM(n=1),CAZ(n=9),CHL(n=28),CIP(n=30),CRO(n=15),CST(n=4),CTX(n=12),FEP(n=2),FOX(n=11),GEN(n=34),IPM(n=5),MEM(n=2),NAL(n=27),NIT(n=9),PEF(n=1),SOX(n=5),SXT(n=27),TET(n=30),TIG(n=2),TMP(n=10)
Salmonella	Africa	Chicken	AMP(n=14),AMX(n=16),CAZ(n=14),CHL(n=38),CIP(n=33),CRO(n=11),CST(n=10),CTX(n=24),FEP(n=1),FOX(n=15),GEN(n=40),IPM(n=8),MEM(n=3),NAL(n=34),NIT(n=8),PEF(n=2),SOX(n=4),SXT(n=35),TET(n=38),TIG(n=2),TMP(n=21)
Salmonella	Africa	Pig	AMP(n=4),CAZ(n=4),CHL(n=6),CIP(n=7),CRO(n=2),CST(n=1),CTX(n=6),FEP(n=1),FOX(n=2),GEN(n=8),IPM(n=4),MEM(n=2),NAL(n=9),NIT(n=2),SOX(n=1),SXT(n=6),TET(n=7),TIG(n=2),TMP(n=4)
Salmonella	Asia	Cattle	AMP(n=23),AMX(n=8),AZM(n=2),CAZ(n=6),CHL(n=20),CIP(n=21),CRO(n=8),CST(n=3),CTX(n=10),FEP(n=1),FOX(n=4),GEN(n=23),IPM(n=1),NAL(n=15),NIT(n=2),PEF(n=1),SOX(n=1),SXT(n=14),TET(n=18),TIG(n=1),TMP(n=9)
Salmonella	Asia	Chicken	AMP(n=94),AMX(n=26),AZM(n=8),CAZ(n=25),CHL(n=81),CIP(n=95),CRO(n=29),CST(n=21),CTX(n=41),FEP(n=9),FOX(n=11),GEN(n=98),IPM(n=18),MEM(n=6),NAL(n=72),NIT(n=9),PEF(n=2),SOX(n=7),SXT(n=56),TET(n=70),TIG(n=3),TMP(n=26)
Salmonella	Asia	Pig	AMP(n=43),AMX(n=8),AZM(n=4),CAZ(n=10),CHL(n=33),CIP(n=40),CRO(n=21),CST(n=4),CTX(n=25),FEP(n=4),FOX(n=8),GEN(n=36),IPM(n=7),MEM(n=3),NAL(n=35),NIT(n=4),PEF(n=1),SOX(n=3),SXT(n=35),TET(n=39),TIG(n=4),TMP(n=6)
Salmonella	Americas	Cattle	AMP(n=12),CAZ(n=2),CHL(n=14),CIP(n=11),CRO(n=6),CST(n=2),CTX(n=8),FOX(n=2),GEN(n=12),IPM(n=4),NAL(n=11),NIT(n=3),PEF(n=2),SOX(n=1),SXT(n=12),TET(n=12)
Salmonella	Americas	Chicken	AMP(n=20),AMX(n=2),AZM(n=2),CAZ(n=5),CHL(n=20),CIP(n=21),CRO(n=7),CST(n=8),CTX(n=12),FEP(n=1),FOX(n=3),GEN(n=21),IPM(n=4),MEM(n=2),NAL(n=18),NIT(n=5),PEF(n=1),SOX(n=1),SXT(n=20),TET(n=20),TIG(n=1),TMP(n=2)
Salmonella	Americas	Pig	AMP(n=13),AMX(n=1),CAZ(n=1),CHL(n=13),CIP(n=13),CRO(n=6),CST(n=2),CTX(n=8),FOX(n=1),GEN(n=14),NAL(n=13),NIT(n=3),PEF(n=1),SOX(n=1),SXT(n=10),TET(n=13),TMP(n=3)
Campylobacter	Africa	Chicken	AMP(n=10),CIP(n=15),ERY(n=13),GEN(n=11),NAL(n=12),STR(n=6),TET(n=10)
Campylobacter	Asia	Cattle	AMP(n=5),CIP(n=10),DOX(n=2),ERY(n=9),GEN(n=10),NAL(n=10),STR(n=6),TET(n=5)
Campylobacter	Asia	Chicken	AMP(n=14),CIP(n=35),DOX(n=10),ERY(n=34),GEN(n=31),NAL(n=25),STR(n=10),TET(n=30)
Campylobacter	Asia	Pig	AMP(n=3),CIP(n=6),DOX(n=1),ERY(n=4),GEN(n=4),NAL(n=6),STR(n=1),TET(n=4)
Campylobacter	Americas	Cattle	AMP(n=1),CIP(n=4),ERY(n=3),GEN(n=4),NAL(n=3),STR(n=1),TET(n=3)
Campylobacter	Americas	Chicken	AMP(n=7),CIP(n=15),ERY(n=13),GEN(n=12),NAL(n=8),STR(n=3),TET(n=12)
Campylobacter	Americas	Pig	AMP(n=3),CIP(n=5),ERY(n=3),GEN(n=5),NAL(n=3),STR(n=1),TET(n=4)
Staphylococcus	Africa	Cattle	CHL(n=34),CIP(n=25),CLI(n=21),ERY(n=37),FOX(n=11),GEN(n=31),LIZ(n=2),OXA(n=26),PEF(n=1),PEN(n=35),RIF(n=10),SOX(n=1),TET(n=36),TMP(n=3),VAN(n=25)
Staphylococcus	Africa	Chicken	CHL(n=6),CIP(n=7),CLI(n=7),ERY(n=10),FOX(n=3),GEN(n=11),LIZ(n=1),OXA(n=7),PEN(n=8),Q-D(n=1),RIF(n=2),TET(n=10),TMP(n=1),VAN(n=9)
Staphylococcus	Africa	Pig	CHL(n=2),CIP(n=3),CLI(n=3),ERY(n=3),GEN(n=4),LIZ(n=1),OXA(n=3),PEN(n=2),RIF(n=1),TET(n=3),VAN(n=1)
Staphylococcus	Asia	Cattle	CHL(n=44),CIP(n=46),CLI(n=28),ERY(n=40),FOX(n=25),GEN(n=63),LIZ(n=9),OXA(n=37),PEF(n=2),PEN(n=52),Q-D(n=1),RIF(n=8),SOX(n=1),TET(n=37),TMP(n=6),VAN(n=31)
Staphylococcus	Asia	Chicken	CHL(n=11),CIP(n=12),CLI(n=9),ERY(n=10),FOX(n=7),GEN(n=14),LIZ(n=3),OXA(n=6),PEN(n=8),TET(n=12),TMP(n=2),VAN(n=9)
Staphylococcus	Asia	Pig	CHL(n=13),CIP(n=16),CLI(n=14),ERY(n=15),FOX(n=12),GEN(n=18),LIZ(n=9),OXA(n=10),PEN(n=10),Q-D(n=3),RIF(n=6),TET(n=17),TMP(n=2),VAN(n=12)
Staphylococcus	Americas	Cattle	CHL(n=10),CIP(n=18),CLI(n=17),ERY(n=30),FOX(n=11),GEN(n=31),LIZ(n=4),OXA(n=27),PEF(n=3),PEN(n=31),Q-D(n=2),RIF(n=7),TET(n=29),TMP(n=1),VAN(n=15)
Staphylococcus	Americas	Chicken	CHL(n=3),CIP(n=3),CLI(n=3),ERY(n=2),FOX(n=1),GEN(n=3),OXA(n=3),PEN(n=3),RIF(n=3),TET(n=2),VAN(n=3)
Staphylococcus	Americas	Pig	CHL(n=2),CIP(n=2),CLI(n=2),ERY(n=3),FOX(n=1),GEN(n=3),LIZ(n=2),OXA(n=2),PEN(n=2),Q-D(n=1),RIF(n=1),TET(n=3),TMP(n=1),VAN(n=3)

Table S6. Number of point prevalence surveys per pathogens, continent, host species and antimicrobial compound (See Protocol S1 for drug acronyms**)**