

RESEARCH ARTICLE SUMMARY

ONE HEALTH

Global trends in antimicrobial resistance in animals in low- and middle-income countries

Thomas P. Van Boeckel*[†], João Pires[‡], Reshma Silvester, Cheng Zhao, Julia Song, Nicola G. Criscuolo, Marius Gilbert, Sebastian Bonhoeffer[‡], Ramanan Laxminarayan[‡]

INTRODUCTION: The global scale-up in demand for animal protein is the most notable dietary trend of our time. Since 2000, meat production has plateaued in high-income countries but has grown by 68%, 64%, and 40% in Asia, Africa, and South America, respectively. The transition to high-protein diets in low- and middle-income countries (LMICs) has been facilitated by the global expansion of intensive animal production systems in which antimicrobials are used routinely to maintain health and productivity. Globally, 73% of all antimicrobials sold on Earth are used in animals raised for food. A growing body of evidence has linked this practice with the rise of antimicrobial-resistant infections, not just in animals but also in humans. Beyond potentially serious consequences for public health, the reliance on antimicrobials to meet demand for animal protein is a likely threat to the sustainability of the

livestock industry, and thus to the livelihood of farmers around the world.

RATIONALE: In LMICs, trends in antimicrobial resistance (AMR) in animals are poorly documented. In the absence of systematic surveillance systems, point prevalence surveys represent a largely untapped source of information to map trends in AMR in animals. We use geospatial models to produce global maps of AMR in LMICs and give policy-makers—or a future international panel—a baseline for monitoring AMR levels in animals and target interventions in the regions most affected by the rise of resistance.

RESULTS: We identified 901 point prevalence surveys from LMICs reporting AMR rates in animals for common indicator pathogens: *Escherichia coli*, *Campylobacter* spp., nontyphoidal *Salmonella* spp., and *Staphylococcus*

aureus. From 2000 to 2018, the proportion of antimicrobial compounds with resistance higher than 50% (P50) increased from 0.15 to 0.41 in chickens and from 0.13 to 0.34 in pigs and plateaued between 0.12 and 0.23 in cattle. Global maps of AMR (available at resistancebank.org) show hotspots of resistance in northeastern India, northeastern China, northern Pakistan, Iran, eastern Turkey, the south coast of Brazil,

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Egypt, the Red River delta in Vietnam, and the areas surrounding Mexico City and Johannesburg. Areas where resistance is just starting to emerge are Kenya, Morocco, Uruguay, southern Brazil, central India, and southern China. Uncertainty in our predictions was greatest in the Andes, the Amazon region, West and Central Africa, the Tibetan plateau, Myanmar, and Indonesia. Dense geographical coverage of point prevalence surveys did not systematically correlate with the presence of hotspots of AMR, such as in Ethiopia, Thailand, Chhattisgarh (India), and Rio Grande do Sul (Brazil). The highest resistance rates were observed with the most commonly used classes of antimicrobials in animal production: tetracyclines, sulfonamides, and penicillins.

CONCLUSION: The portfolio of antimicrobials used to raise animals for food is rapidly getting depleted, with important consequences for animal health, farmers' livelihoods, and potentially for human health. Regions affected by the highest levels of AMR should take immediate actions to preserve the efficacy of antimicrobials that are essential in human medicine by restricting their use in animal production. In some middle-income countries, particularly in South America, surveillance must be scaled up to match that of low-income African countries that are currently outperforming them despite more limited resources. Policy-makers coordinating the international response to AMR may consider sparing African countries from the most aggressive measures to restrict access to veterinary drugs, which may undermine livestock-based economic development and rightfully be perceived as unfair. However, in regions where resistance is starting to emerge, there is a window of opportunity to limit the rise of resistance by encouraging a transition to sustainable animal farming practices. High-income countries, where antimicrobials have been used on farms since the 1950s, should support this transition—for example, through a global fund to subsidize improvement in farm-level biosafety and biosecurity. ■

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Animals raised for food use the majority of antimicrobials sold on Earth. The main article presents a map of antimicrobial resistance in animals in low- and middle-income countries where sales of veterinary antimicrobials remain largely unregulated. In this image, broilers are seen roaming freely outside of a family-owned farm in Kitwe, Zambia.

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Global trends in antimicrobial resistance in animals in low- and middle-income countries

Thomas P. Van Boeckel^{1,2,6*†}, João Pires^{1,6†}, Reshma Silvester², Cheng Zhao¹, Julia Song^{3,4}, Nicola G. Criscuolo¹, Marius Gilbert⁵, Sebastian Bonhoeffer^{6†}, Ramanan Laxminarayan^{1,2,4†}

The global scale-up in demand for animal protein is the most notable dietary trend of our time. Antimicrobial consumption in animals is threefold that of humans and has enabled large-scale animal protein production. The consequences for the development of antimicrobial resistance in animals have received comparatively less attention than in humans. We analyzed 901 point prevalence surveys of pathogens in developing countries to map resistance in animals. China and India represented the largest hotspots of resistance, with new hotspots emerging in Brazil and Kenya. From 2000 to 2018, the proportion of antimicrobials showing resistance above 50% increased from 0.15 to 0.41 in chickens and from 0.13 to 0.34 in pigs. Escalating resistance in animals is anticipated to have important consequences for animal health and, eventually, for human health.

Antimicrobials have saved millions of human lives, yet the majority (73%) 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 scale-up in demand for animal protein. Since 2000, meat production has plateaued in high-income countries but has grown by 68%, 64%, and 40% in Africa, Asia, and South America, respectively (2). The transition to high-protein diets in low- and middle-income countries (LMICs) has been facilitated by the global expansion of intensive animal production systems, in which antimicrobials are used routinely to maintain health and productivity (3). A growing body of evidence has linked this practice with antimicrobial-resistant infections not just in animals but also, in some cases, in humans (4–6). Although the majority of emerging infectious disease events have been associated with drug-resistant pathogens of zoonotic origins (7), antimicrobial resistance (AMR) in animals has received comparatively less attention than in humans.

In LMICs, trends in AMR in animals are poorly documented. Colombia is currently the only country that has publicly available surveillance

data on AMR in animals (8). As in high-income countries, antimicrobials are used in LMICs to treat animals and as surrogates for good hygiene on farms. However, in LMICs, AMR levels could be exacerbated by lower biosecurity, less nutritious feed, and looser regulations on veterinary drugs (9). Conversely, in LMICs, AMR levels may also be reduced by less meat consumption and limited access to veterinary drugs in rural areas. Few studies have attempted to disentangle the effect of those factors and, thus far, expert opinion has prevailed over an evidence-based assessment of AMR in LMICs (10).

In 2017, The World Health Organization (WHO) called on its member states to reduce veterinary antimicrobial use (11, 12). 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) (13) has encouraged the 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 (14). However, in LMICs, similar surveillance systems are nascent at best, and building a globally harmonized surveillance system 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 with which to map trends in AMR in animals. Generating resistance maps from these surveys pre-

sents several challenges. First, surveys often differ in protocol, sample size, and the breakpoints used for antimicrobial susceptibility testing. Harmonizing these variations is a first step toward 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 (15). Third, because the problem of AMR affects many drug-pathogen combinations, it is difficult to communicate with policy-makers. Introducing composite metrics of resistance may help when summarizing 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.

Species distribution modeling can identify such associations for predictive mapping, and the development of ensemble geospatial modeling (16) has helped to improve their accuracy.

In this study, we address these challenges to mapping AMR in animals in LMICs at 10-km resolution using point prevalence surveys of common foodborne pathogens. The maps summarize current knowledge and provide policy-makers, or any future international panel (17), a baseline with which to monitor AMR levels in animals and to target interventions across regions.

Global trends

We identified 901 point prevalence surveys reporting AMR rates in animals and food products in LMICs. Our analysis focused on resistance in *Escherichia coli*, *Campylobacter* spp., nontyphoidal *Salmonella* spp., and *Staphylococcus aureus*. The number of published surveys on resistance to these pathogens in LMICs increased from three 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).

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 and 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 the 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 materials).

In LMICs, resistance levels showed considerable geographic variations (see Fig. 3A and fig. S1 for country-level indexes). Regional hotspots (P50 > 0.4) of multidrug resistance were predicted in south and northeast India, northeast China, north Pakistan, Iran, Turkey, the south coast of Brazil, Egypt, the Red River delta in Vietnam, and the areas surrounding Mexico

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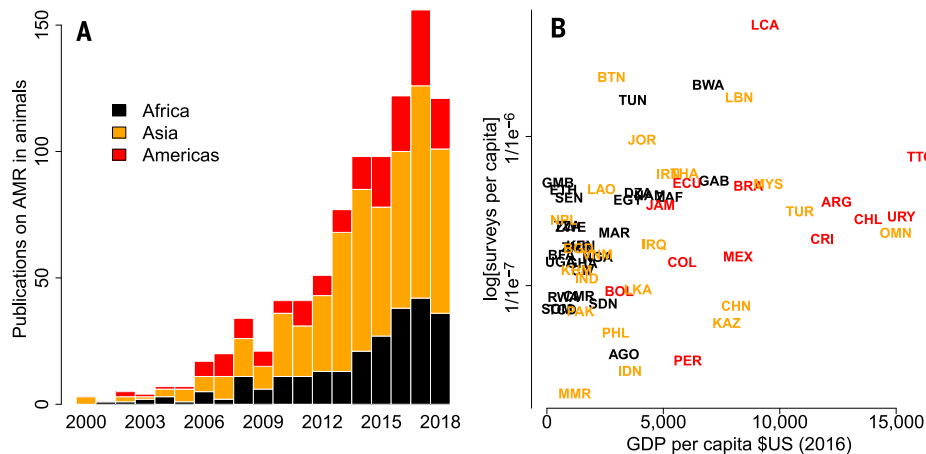


Fig. 1. Number of surveys conducted on AMR in animals. (A) Publications by continent. (B) Publications per capita versus GDP per capita; each country is designated by International Organization for Standardization (ISO3) country code.

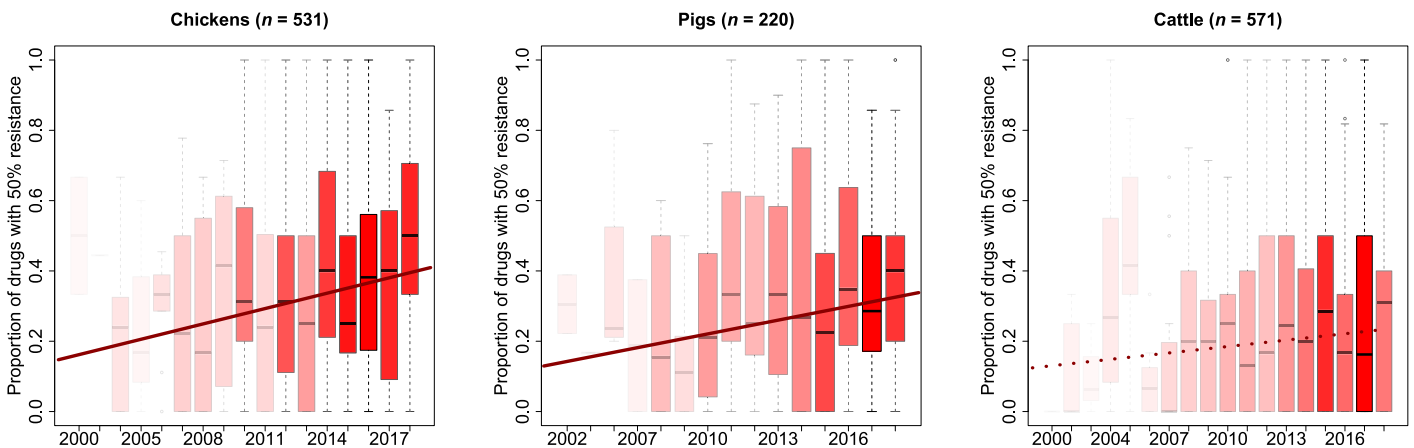


Fig. 2. Increase in antimicrobial resistance in LMICs. Proportion of antimicrobial compounds with resistance higher than 50% (P50) is shown. Solid lines indicate statistically significant (5% level) increases of P50 over time; shading indicates the number of surveys per year relative to total number of surveys per species.

City and Johannesburg. Low P50 values were predicted in the rest of Africa, Mongolia, and western China. On the basis of maps of animal densities (fig. S2), we estimate that across LMICs, 9% [95% confidence interval (CI), 5 to 12%] of cattle, 18% (95% CI, 11 to 23%) of pigs, and 21% (95% CI, 11 to 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 the global average in China [38% (95% CI, 24 to 46%)], Egypt [38% (95% CI, 22 to 55%)], and Turkey [72% (95% CI, 41 to 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 and eastern Brazil, central India, Iran, Chile, and southern China, the difference between P10 and P50 was high (>0.5), indicating that these regions are emerging AMR hotspots. Conversely, established hotspots of AMR where the difference between P10 and P50 was low

(<0.1) included northeastern China, West Bengal, and Turkey.

Uncertainty

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 materials). All geospatial models had limited accuracies (areas under the curve, 0.674 to 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 less influence (table S1).

Uncertainty in the map of P50 was high (95% CI > 0.3) in the Andes, the Amazon region, West and Central Africa, the Tibetan plateau, Myanmar, and Indonesia. Dense geographical coverage of surveys (>4 point prevalence surveys/100,000 km²) did not systematically correlate with high

P50 values (Ethiopia; Thailand; Chhattisgarh, India; and Rio Grande do Sul, Brazil).

Classes of drugs

The highest resistance rates were observed in the most commonly used classes of antimicrobials in animal production (Fig. 4): tetracyclines, sulfonamides, and penicillins (7). Among antimicrobials considered critical to human medicine (18), the highest resistance rates were found for ciprofloxacin and erythromycin (20 to 60%) and moderate rates were found for third- and fourth-generation cephalosporins (10 to 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 (14, 19) for tetracyclines, sulfonamides, and third- and fourth-generation cephalosporins, but differences also exist for quinolones and aminoglycosides.

In *E. coli* and *Salmonella* spp., quinolone resistance in LMICs (20 to 60%) was comparable

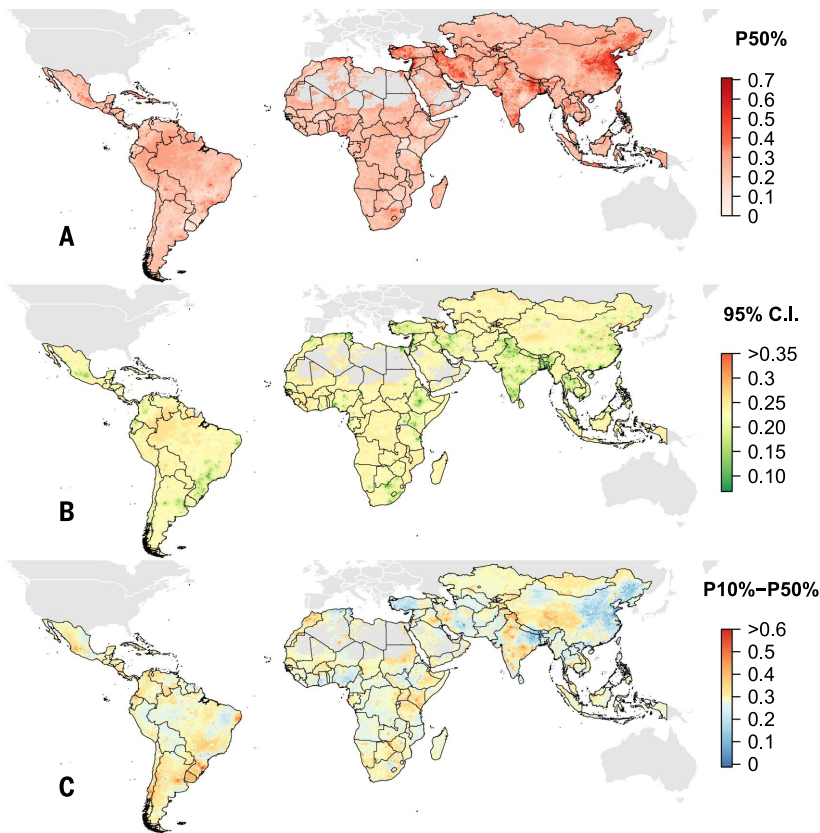


Fig. 3. Geographic distribution of antimicrobial resistance in LMICs. (A) P50, the proportion of antimicrobial compounds with resistance higher than 50%. **(B)** 95% confidence intervals on P50 (supplementary materials). **(C)** Difference in the proportion of antimicrobials with 10% resistance and 50%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

with European levels [59.8 to 64% (14)], but gentamycin resistance was higher in LMICs (5 to 38%) than in Europe (2.4 to 8.9%). The reverse situation was observed when comparing LMICs and the United States, where quinolone resistance is low (2.4 to 4.6%) and gentamycin resistance higher [22.1% and 41.3% for *Salmonella* and *E. coli*, respectively (19)]. In LMICs, high resistance in third- and fourth-generation cephalosporins in *E. coli* was high (~40%). Resistance to carbapenems was low in all host species in LMICs, as previously reported in animals (20). Asia and the Americas currently have the highest rate of colistin resistance (~18 to 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 United States [49.1 to 100% (19)], but lower for quinolones in chickens (20%). Resistance to erythromycin was moderate (<30%) in LMICs but higher than in high-income countries (0.3 to 22% in the United States and 0 to 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 to 80%), erythromycin (20 to 60%), tetracycline (20 to 60%), and oxacillin (20 to 60%). For *S. aureus*, unlike other pathogens, resistance rates among antibiotics (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 susceptibility testing was typically restricted to methicillin-resistant *S. aureus*, which has considerable variation in prevalence [0% in Irish cattle and chickens to 40 to 87% in Danish pigs (14)].

Depletion of the drug portfolio

In most high-income countries, AMR has been monitored in animals for over 10 years (14). Here, we used point prevalence surveys to conduct a global assessment of the 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 a summary metric of resistance, P50, which reflects the ability of veterinarians to provide effective treatment solutions. On the basis of the evidence assembled, P50 increased in LMICs from 0.15 to 0.41 (+173%) in chickens and from

0.13 to 0.34 (+161%) in pigs and plateaued between 0.12 and 0.23 in cattle. Rapid increases in AMR in chickens and pigs are consistent with the intensification of livestock operations for these species compared with cattle (21). The main consequence of those trends is a depletion of the portfolio of treatment solutions for sick animals. This loss has economic consequences for farmers because affordable antimicrobials are used as first-line treatment (22), 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. S3A). 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- to 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 among LMICs (23).

Geography of resistance

The largest hotspots of AMR in animals were in Asia, which is home to 56% of the world's pigs and 54% of the chickens. In Asia, targeted interventions such as legislative action and subsidies to improve farm hygiene could reduce the need for antimicrobials in animal production (1), thereby preserving important drugs for human medicine and the treatment of sick animals. We identified hotspots for the emergence of AMR including central India and Kenya, where resistance to multiple drugs has appeared but not yet reached 50% (Fig. 3C). In these regions, meat consumption is still low and animal production is gradually intensifying. Here, there may be a window of opportunity to contain AMR by imposing strict hygiene standards in newly built farms. This approach could reduce the risk of the spread of resistant pathogens such as *mcr-1*-carrying *E. coli* (6) that have emerged in regions where intensive meat production has been facilitated by enormous quantities of veterinary antimicrobials (1).

In Africa, resistance maps reveal the absence of major AMR hotspots, except for the Johannesburg metropolitan area. This suggests, on the basis of the regions surveyed, that Africa probably bears proportionately less of the current global burden of AMR than high- and upper- to middle-income countries. Policy-makers coordinating an international response to AMR might therefore spare Africa from the most aggressive measures, which may undermine livestock-based economic development and rightfully be perceived as unfair.

In the Americas, where the number of surveys was limited (Fig. 3B), the observed low AMR levels could reflect either good farming practices (low antimicrobial use) or the absence of surveys conducted in the areas most affected by AMR. Considering that Uruguay, Paraguay, Argentina, and Brazil are net meat exporters (2), it is of concern that little epidemiological surveillance of

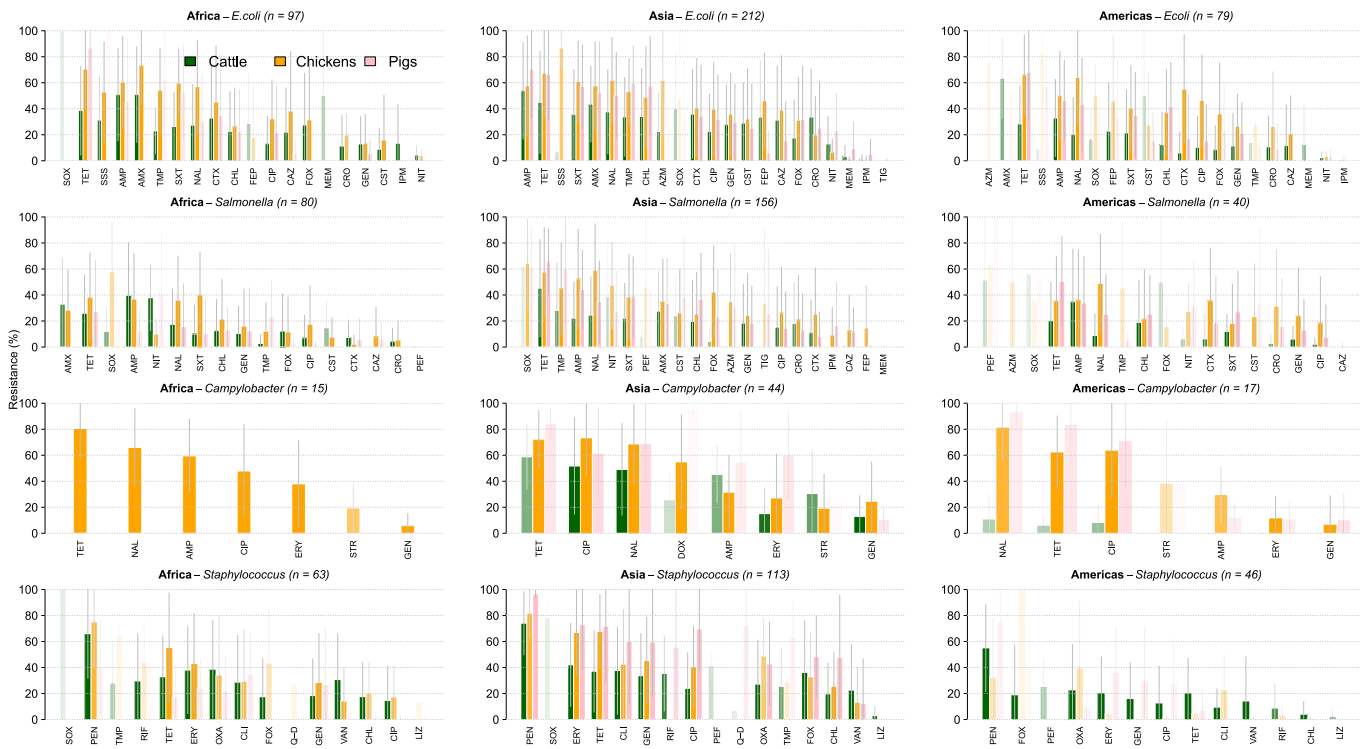


Fig. 4. Resistance in foodborne pathogens recommended for susceptibility testing by the WHO. Shown are resistance rates and number of surveys (n) by region. Transparency levels reflect sample sizes for each animal-pathogen combination (for drug acronyms, see supplementary text, protocol S1).

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, 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 predictions from geospatial models to map P50 and P10 in LMICs. The moderate accuracy of these models reflects the challenge of associating the spatial distribution of AMR with environmental and socioeconomic factors (24). AMR in animals may be driven by factors known to influence antimicrobial use in humans—such as cultural norms, the presence of drug manufacturers in the 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 affluent city dwellers. We also found a positive association between P50 and temperature. Evidence for a link with temperature in animals is less established than in humans (27), but it has been suggested that high temperature causes stress and conflicts in animals, thus increasing the risk of wounds that require preventive antimicrobial treatment (28). Finally, in Asia, 74% of

P50 hotspots corresponded to areas previously identified for their projected increase in antimicrobial use (fig. S4). The relative influence of antimicrobial use on the spatial distribution of P50 was limited to 3.8% (table S1), but this association should be treated with caution given the scarcity of original data on antimicrobial use in LMICs (29).

We identified diverging patterns of resistance across combinations of pathogens and drugs. For *S. aureus*, geographic differences in AMR levels could be explained by sublineages carrying different *SCCmec* cassettes that are specific to certain regions (30). Of greater concern for public health is the presence of resistance to third- and fourth-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 (6), as well as by the widespread use of this cheap antimicrobial. The recent Chinese ban on colistin (31), 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, in LMICs, *E. coli* and *Campylobacter* 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 in

Europe, where this compound is banned for use in poultry and cattle (32). These findings suggest that regional restrictions on the use of specific compounds are associated with lower AMR rates.

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 using spatial cross-validation. Second, temporal variation in AMR over the period 2000–2018 was not accounted for. As more surveys become available, spatiotemporal, model-based geostatistics approaches could help to overcome this limitation. Third, in slaughterhouse surveys, most did not perform molecular typing longitudinally throughout the different processing stages, which would have enabled us to assess potential cross-contamination. Although cross-contamination may generally affect AMR rates, in the absence of international benchmarking, it is unknown whether it could systematically bias our result in any single country. Finally, our analysis raises renewed concerns about the pace of increase of AMR in animals, but it is beyond the scope of this study to draw conclusions about the intensity and directionality of transfer of AMR between animals and humans,

which should be further investigated using robust genomics methods (33).

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 diseases of global importance, such as malaria (34). In human medicine, point prevalence surveys of AMR in hospitals have generated snapshots of AMR across regions (35).

This initial assessment outlines three global priorities for action. First, our maps show regions that are poorly surveyed and 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. These countries should take immediate actions 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 the transition to sustainable animal production in LMICs—for example, through a global fund to subsidize improvements in farm-level biosafety and biosecurity (36).

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 to S12
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Global trends in antimicrobial resistance in animals in low- and middle-income countries

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Livestock antibiotic resistance

Most antibiotic use is for livestock, and it is growing with the increase in global demand for meat. It is unclear what the increase in demand for antibiotics means for the occurrence of drug resistance in animals and risk to humans. Van Boeckel *et al.* describe the global burden of antimicrobial resistance in animals on the basis of systematic reviews over the past 20 years (see the Perspective by Moore). There is a clear increase in the number of resistant bacterial strains occurring in chickens and pigs. The current study provides a much-needed baseline model for low- and middle-income countries and provides a "one health" perspective to which future data can be added.

Science, this issue p. eaaw1944; see also p. 1251

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