


Geographically targeted surveillance of livestock could help prioritize intervention against antimicrobial resistance in China

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1 **Geographically-targeted surveillance of livestock could help prioritize intervention**
2 **against antimicrobial resistance in China**

3

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9

10 **Abstract**

11 The rise of antimicrobial resistance in animals is fueled by the widespread use of
12 veterinary antimicrobials. China is the largest global consumer of veterinary
13 antimicrobials – improving AMR surveillance strategies in this region could help
14 prioritize intervention and preserve antimicrobial efficacy. Here, we mapped AMR rates
15 in pigs, chickens and cattle in China using 446 surveys of event-based surveillance
16 between 2000 and 2019 for foodborne bacteria, in combination with geospatial models to
17 identify locations where conducting new surveys could have the highest benefits. Using
18 maps of uncertainty, we show that eastern China currently has the highest AMR rates,
19 and southwestern and northeastern China would benefit the most from additional
20 surveillance efforts. Instead of distributing new surveys evenly across administrative
21 divisions, using geographically targeted surveillance could reduce AMR prediction
22 uncertainty by 2-fold. In a context of competing disease control priorities, our findings

23 present a feasible option for optimizing surveillance efforts – and slowing the spread of
24 AMR.

25

26 **Main**

27 **Introduction**

28 Antimicrobials are used in agriculture as disease treatments, prophylactically to prevent
29 infections in healthy animals, and to increase productivity ¹. However, the routine use of
30 antimicrobials as surrogates for good hygiene practices on farms ^{2,3} is driving a rise in
31 antimicrobial resistance (AMR), with increasingly serious consequences for animal
32 health ^{1,4}, and potentially human health ^{5,6}.

33

34 Globally, 73% of antimicrobials are used in animals ⁷, with China being the largest
35 consumer of antimicrobials in absolute terms (41,967 tons in 2017) and the second largest
36 consumer in relative terms with 200 milligram used per kilogram of animal (mg/kg)⁸
37 (Supplementary Figure 1A, 1B). In comparison, Denmark and the Netherlands use
38 respectively 39 mg/Kg, and 56 mg/Kg ⁹ – while maintaining a productive livestock
39 sector. Multiple factors may contribute to antimicrobial overuse in China. Meat
40 production has grown by 560% since 1979 (FAOSTAT,
41 <http://www.fao.org/faostat/en/#data/QL>), which could have made farmers reliant on
42 antimicrobials to prevent infections. Veterinary antimicrobials are reportedly accessible
43 without prescriptions ¹⁰ and are sold at low prices in comparison to other countries ¹¹. As
44 in many other low- and middle-income countries (LMICs) ^{12,13}, farmers predominantly
45 obtain antimicrobials from local drug stores where vendors also provide medical advice

46 without veterinary training ^{10,14}. Additionally, enforcing the existing regulations ¹⁰ on the
47 compounds authorized in animals, or the recently announced ban on growth promoters ¹⁵
48 remain a formidable challenge in a country where 360 million people are active in
49 agriculture (World Bank, <https://data.worldbank.org/indicator/SL.AGR.EMPL.ZS>). In the
50 last 5 years, China has reported multiple first emergence of resistance genes to last-resort
51 antimicrobials such as colistin and tigecycline ^{16,17} and a recent global analysis suggested
52 that China may have become one of the largest hotspots of resistance among LMICs ⁴,
53 ranking 8th in relative terms, and 1st in absolute terms, for animal-associated burden of
54 AMR amongst LMICs (Supplementary Figure 1D, 1E).

55

56 In high-income countries, epidemiological evidence collected by surveillance systems
57 guides AMR responses and provides a baseline for evaluating policy targets. The US
58 Food and Drug Administration collects meat samples from retail and slaughterhouses to
59 monitor AMR levels ([https://www.fda.gov/animal-veterinary/antimicrobial-](https://www.fda.gov/animal-veterinary/antimicrobial-resistance/national-antimicrobial-resistance-monitoring-system)
60 [resistance/national-antimicrobial-resistance-monitoring-system](https://www.fda.gov/animal-veterinary/antimicrobial-resistance/national-antimicrobial-resistance-monitoring-system)); the European Food
61 Safety Authority (EFSA, [https://www.efsa.europa.eu/en/topics/topic/antimicrobial-](https://www.efsa.europa.eu/en/topics/topic/antimicrobial-resistance)
62 [resistance](https://www.efsa.europa.eu/en/topics/topic/antimicrobial-resistance)) serves a comparable role by amalgamating the surveillance efforts of its
63 member states. To the best of our knowledge, the majority of LMICs – including China –
64 either lack systematic surveillance systems or do not publicly report data from animal
65 AMR surveillance⁴. Despite these challenges, China could act as a leader for guiding the

66 international response to AMR – because its domestic policies may have far-reaching
67 benefits for neighboring countries, and its numerous trading partners¹⁸.

68

69 Point-prevalence surveys (PPS) published independently by veterinarians constitute an
70 alternative source for documenting AMR trends (Criscuolo *et al.* submitted) – and
71 inferences can be made to map AMR using a large collection of PPS⁴. However, adapting
72 this approach to the Chinese context requires building a critical mass of PPS, including
73 surveys in Chinese to train geospatial models. Accurate maps of disease prevalence have
74 been generated^{19–22}, but few used the associated uncertainty maps to inform field
75 sampling campaigns^{23,24}. In particular, as prediction uncertainty grows with distance
76 from existing surveys, an uncertainty map can help identify the location where
77 conducting new surveys could be most valuable to improve the confidence level of a
78 prevalence map. Repeating this process iteratively can guide long-term surveillance
79 efforts.

80

81 Here, we used event-based surveillance data to map trends in AMR in animals and
82 associated uncertainty levels. We identify regions where future surveillance efforts could
83 be intensified to reduce uncertainty on the geographic distribution of AMR in China. In a

84 context of competing disease control priorities, our approach helps optimally target the
85 limited resources dedicated to event-based surveillance of AMR.

86

87

88 **Results**

89 *Data*

90 We identified 446 point-prevalence surveys (PPS) reporting antimicrobial resistance
91 (AMR) in food animals in China between 2000 and 2019 (Supplementary Text S1). This
92 corresponds to one survey per 470,177 tons of food animals annually (28th rank amongst
93 low- and middle-income countries (LMICs); Supplementary Figure 1C). We collected data
94 on four common indicator bacteria: *Escherichia coli* (184 PPS), nontyphoidal *Salmonella*
95 spp. (131 PPS), *Staphylococcus aureus* (131 PPS), and *Campylobacter* spp. (33 PPS). The
96 446 PPS included 6,295 resistance rates. We defined a composite metric of AMR to
97 summarize trends in resistance across multiple drugs, and bacteria. For each survey, we
98 calculated the proportion of antimicrobial compounds with resistance higher than 50%
99 (P50; Supplementary Figure 2).

100

101 *Temporal trends*

102 In pigs, between 2000 and 2019, P50 increased significantly in *E. coli* (+59%), *Salmonella*
103 (+148%), and *S. aureus* (+85%) (Figure 1A, 1B, 1C). In contrast, in chicken, P50 was
104 stable in *E. coli*, *Salmonella*, and *S. aureus*, with mean P50 of 60%, 42%, and 37%,
105 respectively (Figure 1D, 1E, 1F). In cattle, P50 increased significantly in *E. coli* (+167%;

106 Figure 1G), and was stable in *Salmonella* and *S. aureus*, with mean P50 of 23% and 31%,
107 respectively (Figure 1H, 1I).

108

109 *Prevalence of resistance across antimicrobial classes*

110 For each drug-bacteria-animal combination, we estimated the prevalence of resistance
111 (R%), and calculated the center of mass of the probability density distribution of the
112 prevalence of resistance across PPS (Methods; Figure 2). Prevalence of resistance of
113 tetracyclines, sulfonamides, and penicillins was high across all tested bacterial species
114 between 2010 and 2019 (R% > 25%). In comparison, prevalence of resistance has remained
115 at low levels in polymyxins and cephalosporins (R% < 10% for at least one bacterial
116 species tested in one animal species). For all antimicrobial classes, prevalence of resistance
117 in *E. coli* in chicken and pigs increased after 2010, except tetracyclines with already high
118 prevalence of resistance (R% > 90%) in pigs before 2010. In *Salmonella*, increase in the
119 prevalence of resistance after 2010 was observed in penicillins in chicken, as well as in
120 sulfonamides, penicillins, and tetracyclines in pigs.

121

122 The prevalence of resistance in *E. coli* was higher than *Salmonella* for all antimicrobial
123 classes (Figure 2A, 2B). Across drug classes, the prevalence of resistance in *E. coli* was
124 18% higher than the prevalence of resistance in *Salmonella* in chicken, and 16% higher
125 than the prevalence of resistance in *Salmonella* in pigs. Prevalence of resistance for
126 individual antimicrobial classes differed between chicken and pigs. For *E. coli*,
127 cephalosporins and quinolones had respectively 20% and 27% higher prevalence of
128 resistance in chicken compared with pigs, while prevalence of resistance in other

129 antimicrobial classes differed by $< 6\%$ between chicken and pigs (Figure 2A). For
130 *Salmonella*, quinolones had 25% higher prevalence of resistance in chicken compared to
131 pigs, while for other antimicrobial classes, the difference in the prevalence of resistance
132 between chicken and pigs was smaller than 12%. (Figure 2B). This comparison was largely
133 influenced by the relative abundance of serotypes of *Salmonella* in different animal hosts
134 (Supplementary Figure 3). However, an in-depth investigation on its influence on
135 resistance trends was challenged by the fact that 70% of the surveys on *Salmonella* (93 out
136 of 131 surveys) did not report the prevalence of resistance broken down by serotypes.

137

138 *Geographic Distribution of Resistance*

139 We used a geospatial model (Supplementary Text S2) to map P50 at 10 Km resolution, and
140 combined information from PPS with environmental and anthropogenic covariates
141 (Supplementary Table 1). Hotspots of AMR – regions where more than 40% of drugs have
142 resistance levels above 50% ($P50 > 40\%$) – were found in 1) eastern China in the areas of
143 Heilongjiang, western Jilin, western Liaoning, southern Hebei, Shandong, eastern Jiangsu,
144 southern Anhui, Fujian and Taiwan, 2) central China in the areas of northern Shaanxi,
145 central Hunan and southeastern Sichuan, and 3) the northwestern Xinjiang Uyghur
146 Autonomous Region (Figure 3). Low levels of AMR ($P50 < 30\%$) were found in Tibet
147 Autonomous Region, northwestern Sichuan, and southern Guangxi (Figure 3). We
148 measured the association between P50 and covariates, using the decrease in area under the
149 receiver operator curve (AUC) by sequential permutation of each covariate
150 (Supplementary Text S2). The most important covariates associated with P50 values were:

151 the travel times to cities ²⁵ (-16% AUC), the minimum monthly temperature ²⁶ (-15%
152 AUC), and cattle population density ²⁷ (-13% AUC; Supplementary Figure 4).

153

154 *Optimal location for future event-based surveillance efforts*

155 We identified the locations of 50 hypothetical surveys to be conducted in China such that
156 these would minimize uncertainty on the current map of AMR. The uncertainty was
157 quantified using a map of “necessity for additional surveillance” (*NS*) – the product of the
158 kriging variance (a metric of interpolation uncertainty) and the population density
159 (Methods). The 50 locations for the hypothetical surveys were identified such as to
160 minimize the mean of NS_i across all pixels i in the *NS* map.

161

162 We compared four approaches to distribute hypothetical future surveys (Methods): first a
163 ‘greedy’ approach that tested all possible locations for new surveys but was associated with
164 high computational cost. Second, an “overlap approach” based on mutual zones of
165 exclusions for consecutive surveys to be conducted. This approach was a computational
166 approximation to the greedy approach. Third, an ‘administrative’ approach where surveys
167 were distributed equally across administrative divisions. These three approaches were
168 compared with a “null model” consisting of randomly distributing 50 surveys across China.
169 The greedy ‘optimal’ approach achieved the greatest reduction of the mean necessity for
170 additional surveillance (*NS*) (Figure 4B, dark red). The greedy approach reduced *NS* by
171 56% more than the null model (Figure 4B, blue). However, the greedy approach was
172 associated with a considerable computational burden (Figure 4C, 4.5×10^5 CPU minutes).
173 The overlap approach reduced the mean *NS* by 44% more than the null model (Figure 4B,

174 blue), thus achieving near-optimal reduction of NS, but with a considerably lower
175 computational burden than the greedy approach. The overlap approach also outcompeted
176 the administrative approach (Figure 4B, green): it reduced the mean *NS* by 104% more than
177 if surveys had been distributed equally between administrative divisions.

178

179 The overlap approach predicted locations for a large number of new surveys in the
180 southwest (21/50 surveys) and northeast (11/50 surveys) of China. The surveys were
181 predominantly distributed in Yunnan Province (10 surveys), Tibet Autonomous Region (9
182 surveys), Xinjiang Uyghur Autonomous Region (7 surveys), and Heilongjiang Province (5
183 surveys) (Figure 4A). These locations were determined using animal population densities
184 as the metric of exposure (Methods). Additionally, we calculated the locations by province
185 for individual animal species, respectively (Supplementary Figure 5). The locations were
186 mainly distributed in Yunnan and Heilongjiang (exposure by chicken or pigs), and in Tibet
187 Autonomous Region (exposure by cattle). If human population was considered to
188 determine exposure (Supplementary Figure 6), then the locations predicted by the overlap
189 approach to conduct new surveys were mainly distributed in Heilongjiang Province (8
190 surveys), Xinjiang Uyghur Autonomous Region (8 surveys), Yunnan province (7 surveys),
191 and Inner Mongolia Autonomous Region (5 surveys).

192

193

194 **Discussion**

195 We identified geographical gaps in event-based surveillance of food animal AMR in
196 China, using a map of AMR derived from 446 PPS, and its associated map of uncertainty,

197 identifying where surveillance scale-up would be the most valuable to reduce
198 uncertainties in the current trends of AMR.

199

200 *Trends of AMR across animals and bacteria*

201 Between 2000 and 2019, in pigs, P50 doubled in *Escherichia coli*, *Salmonella*, and
202 *Staphylococcus aureus*. This increase in AMR occurred in a period of considerable
203 intensification of pig production in China, and the number of pigs slaughtered in China
204 increased by 45%²⁸. Traditional backyard systems were gradually replaced by large-scale
205 intensive farms to support the growing domestic demand for pork²⁹. However, as in other
206 countries currently transitioning from extensive to intensive farming, improvements in
207 biosecurity may have lagged behind improvements in productivity³⁰. Future
208 improvements in biosecurity may reduce farmers' dependency on antimicrobials for
209 disease prevention, and have potentially indirect benefits for managing AMR in the long-
210 term. Future biosecurity improvements can reduce the risk of diseases introduction
211 through strict hygiene requirements for personnel who enter the farms, appropriate
212 carcass management, and reducing the spread of diseases inside the premises through
213 establishing pig compartments, and regular cleaning and disinfection³¹.

214

215 Between 2000 and 2019, in chicken, P50 remained stable in *E. coli*, *Salmonella*, and *S.*
216 *aureus*, albeit at high levels. In 2000, P50 in *E. coli*, *Salmonella*, and *S. aureus* in chicken
217 were already at 58%, 48%, and 56%, respectively, double the levels of resistance in pigs
218 (35%, 15%, and 30%). This suggests that the intensification process (and the routine use
219 of antimicrobials for production) occurred earlier and faster in the poultry sector than for

220 pigs³². Excessive use of quinolones (e.g. norfloxacin and ofloxacin) and cephalosporins
221 (e.g. ceftriaxone) in chicken¹⁰ may have caused much higher resistance rates of these two
222 antimicrobial classes in chicken, compared with pigs (Figure 2). Our analysis suggests
223 that the antimicrobials that maintained low prevalence of resistance in chicken are
224 expensive and are seldom available on the Chinese market (Supplementary Text S3),
225 impeding overuse and also preventing the further AMR increases.

226

227 Prevalence of resistance for *E. coli* were higher than for *Salmonella* in pigs and chicken
228 (Figure 2), possibly influenced by commensal *E. coli* being associated with lower
229 resistance levels than pathogenic *E. coli*³³. However, due to the non-systematic nature of
230 the PPS sampling schemes (event-based surveillance), disentangling how resistance rates
231 differ between bacteria exhibiting commensal or pathogenic behavior remains
232 challenging. We attempted to mitigate this potential bias by focusing our analysis
233 exclusively on bacteria isolated from healthy animals.

234

235 Resistance levels (P50) in cattle were lower than in chicken and pigs (Figure 1).
236 However, P50 in *E. coli* grew by 81% between 2000 and 2019, while globally the P50 in
237 cattle was stable over the same period⁴. This may be associated with the increasing
238 demand for cattle product in China – cow milk production increased by 261% from 2000
239 to 2019²⁸. Despite this rapid expansion, the current per capita consumption of dairy
240 products in China is still only one fifth of the dairy consumption in the US and the EU²⁸
241 – leaving room for further expansion. Thus, a window of opportunity may exist at the

242 current stage to slow the rise of AMR in cattle, while resistance rates are still low (22% in
243 *E. coli*) – and immediate action could help secure a sustainable dairy intensification.

244

245 *Improved maps of AMR in China*

246 Currently, AMR levels in animals are the highest in the east (43%), moderately high in the
247 northwest (40%), and lowest in the southwest (34%; Figure 3). These geographical trends
248 are in agreement (Pearson correlation coefficient 0.48) with the previous attempts to map
249 AMR in China ⁴. However, the present map is considerably more robust because it is
250 exclusively based on surveys conducted in China (446 surveys, including 318 publications
251 in Chinese). In comparison, previous maps were produced with just 101 surveys from
252 China supplemented by surveys from other LMICs ⁴. The revised maps of AMR help
253 identify hotspots of AMR (Figure 3) where intervention could be targeted immediately as
254 part of domestic policies ³⁴. Travel time to cities was the factor with the highest influence
255 on resistance levels ²⁵. The clustering of intensive farms in major consumption centers
256 during industrialization ³⁵, and the ease of access to drug stores in peri-urban areas ^{10,36}
257 may drive AMR level upwards³⁷. High AMR levels were also associated with high minimal
258 monthly temperature ²⁶ – high temperatures may lead to increased stress and conflicts
259 among animals, with risk of animal injuries requiring antimicrobial treatment ³⁸.

260

261 *Key locations for conducting event-based surveillance*

262 Amongst LMICs, China ranks 28th for the number of surveys in event-based surveillance
263 per kilogram of food animals (population corrected units of food animals; PCU), and 36th
264 for the number of surveys per PCU relative to average resistance level (P50) per country

265 (Supplementary Figure 1). We identified locations where additional surveys on AMR in
266 animals could be conducted in the future to minimize uncertainty associated with the
267 geographical trends in AMR – representing a gain in information given the resources
268 spent on event-based surveillance. Current patterns resulting from event-based
269 surveillance are “sub-optimal” as surveys are clustered around veterinary institutes,
270 mainly in the east (Supplementary Figure 7), where sampling to investigate AMR in their
271 vicinity is easier (Supplementary Text S4) – and may have contributed to geographical
272 information gaps on AMR trends in the southwest and northeast. Cross-provincial efforts
273 between institutes are needed to coordinate future event-based surveillance efforts into
274 these regions, which may be far from existing institutes, but where the gain in
275 information by additional surveys would be the highest.

276

277 Our approach for assigning future surveys works by minimizing an index of “need for
278 additional surveillance (NS)” based on a map of AMR (China for this example).
279 However, testing exhaustively all possible location for future surveys (“greedy
280 approach”) incurs considerable computational cost. We developed an ‘overlap approach’
281 which is a rapidly implementable approximation of a greedy approach. The overlap
282 approach achieved 93% of the reduction of the uncertainty in AMR trends achieved by
283 the greedy approach, albeit using just 15% of total computation time required by the
284 greedy approach (Methods). This not only makes the approach faster but also applicable
285 with limited computational resources, and was developed in the context of event-based
286 surveillance, which was abundant in China with 446 PPS and served as a proof of
287 concept. However, the approach could also be used with systematic surveillance data or

288 in other countries with event-based surveillance. In addition, the ‘overlap approach’ is
289 flexible with respect to exposure. In this analysis we used animal densities as metric of
290 exposure, but this variable could easily be substituted by other criteria that are relevant
291 for epidemiological or environmental assessments.

292

293 *Limitations and Future Directions*

294 Although steps are taken (Supplementary Text S1) to ensure comparability between
295 surveys, there remain potential sources of bias in variations in the accuracy of
296 susceptibility testing. These include potential difference in laboratory equipment, and
297 compliance to analysis protocols across regions in China. The World Health Organization
298 assesses the quality of antimicrobial susceptibility testing across countries ³⁹, but to the
299 best of our knowledge, such within-country assessment is not currently available to
300 account for laboratory practices that could lead to variations in the accuracy of
301 susceptibility testing. These ‘hidden’ variations between surveys may influence the
302 accuracy of the spatial distribution of P50. Inherent to event-based surveillance, a
303 subjective summary metric “P50” was used in the absence of publicly available
304 systematic surveillance data. P50 could be affected by the different antimicrobials subject
305 to susceptibility testing in each survey. The potential bias was reduced by using the drug-
306 bacteria combinations recommended by the WHO Advisory Group on Integrated
307 Surveillance of Antimicrobial Resistance⁴⁰ to calculate P50. Insufficient and irregular
308 geographic coverage of data points may affect the accuracy of the estimations of model
309 parameters. The risk of local overfitting is attenuated by using spatial cross-validation in
310 the models. Finally, future mapping efforts could integrate surveys on AMR in

311 aquaculture, because aquatic animals are important food animals in China, with at least
312 20 antimicrobials involved in their production ⁴¹. Complementary to phenotypic
313 resistance, AMR surveillance could be expanded to include genomics data, through
314 metagenomic analysis of wastewater ⁴² from farms, although issues about harmonization
315 remain an active field of analysis (Pires *et al.* submitted).

316

317 The health challenges that China currently faces are multifaceted and burdensome, both
318 in humans (e.g. COVID-19 ⁴³), and in food animals (e.g. African Swine Fever ⁴⁴). With
319 limited resources to allocate between competing priorities for disease surveillance, our
320 approach identifies locations where conducting new surveys of AMR in animals could
321 have the highest benefits, particularly in southwestern and northeastern China. Timely
322 policy intervention could curb AMR in China, as illustrated by the significant reduction
323 in colistin resistance after the colistin withdrawal policy ⁴⁵. Our analysis helps to
324 optimally deploy the limited resources dedicated to event-based surveillance of AMR –
325 improving chances for successful intervention for curbing AMR development and
326 providing data to inform policy.

327

328 **Methods**

329 *Data*

330 We reviewed point-prevalence surveys (PPS) reporting rates of antimicrobial resistance
331 (AMR) in healthy animals, and animal food products in China between 2000 and 2019
332 (Supplementary Text S1). We focused on three common food animal species, including
333 chicken, pigs, and cattle. Here, dairy cattle and meat cattle were pooled in this study, in

334 consistency with the categorization adopted in the maps of livestock created by the Food
335 and Agriculture Organization²⁷. The review focused on four common foodborne bacteria:
336 *Escherichia coli*, nontyphoidal *Salmonella*, *Staphylococcus aureus* and *Campylobacter*.
337 We recorded resistance rates reported in PPS, defined as the percentage of isolates tested
338 resistant to an antimicrobial compound. In addition, we extracted the anatomical
339 therapeutic chemical classification codes of the drugs tested, the year of publication, the
340 guidelines used for susceptibility testing, the latitude and longitude of sampling sites, the
341 number of samples collected, and the host animals. We recorded sample types for each
342 survey, including live animals, slaughtered animals, animal products, and fecal samples.
343 Each sample was taken from one animal or animal product. These sample types were
344 pooled in the current analysis. 10,747 rates of AMR were extracted from 446 surveys
345 (Supplementary Figure 8), including 318 surveys from China's National Knowledge
346 Infrastructure (CNKI), the leading Chinese-language academic search engine. All data
347 extracted in the review are available at <https://resistancebank.org>.

348

349 Two steps were taken to ensure comparability of the resistance rates extracted from the
350 surveys. First, the panel of drug-bacteria combinations extracted from each survey was
351 that recommended for susceptibility testing by the WHO Advisory Group on Integrated
352 Surveillance of Antimicrobial Resistance (AGISAR)⁴⁰. This resulted in the extraction of
353 6,295 resistance rates for 76 drug-bacteria combinations. Second, resistance rates were
354 harmonized using a methodology⁴ accounting for potential variations in the clinical
355 breakpoints used for antimicrobial susceptibility testing (Supplementary Text S1). There
356 are two major families of methods used for susceptibility testing in this dataset -diffusion

357 methods (e.g. disc diffusion) and dilution methods (e.g. broth dilution). Previous works
358 have shown good agreement between the two approaches in measuring resistance in
359 foodborne bacteria^{4,46}. For each family of methods, variations of breakpoints may result
360 from differences between laboratory guidelines systems (European Committee on
361 Antimicrobial Susceptibility Testing; EUCAST vs Clinical and Laboratory Standards
362 Institute; CLSI), or from variations over time of clinical breakpoints within a laboratory
363 guidelines system (CLSI or EUCAST). Here, we accounted for both situations using
364 distributions of minimum inhibitory concentrations, and inhibition zones obtained from
365 *eucastr.org* (Supplementary Text S1).

366

367 *Trends in Antimicrobial Resistance*

368 We defined a composite metric of AMR to summarize trends in resistance across
369 multiple drugs and bacterial species. For each survey, we calculated the proportion of
370 antimicrobial compounds with resistance higher than 50% (P50). For each animal-
371 bacteria combination, we assessed the significance of the temporal trends of P50 between
372 2000 to 2019 using a logistic regression model, weighted by the log10 transformed
373 number of samples in each survey.

374

375 For each bacteria-drug (antimicrobial class) combination, we estimated prevalence of
376 resistance by calculating a curve of the distribution of resistance rates across all surveys
377 (Figure 2). The analysis was conducted for surveys published between 2000 and 2009,
378 and between 2010 and 2019, respectively. The distribution was estimated at 100 equally
379 spaced intervals from resistance rates of 0% to 100%, using kernel density estimation.

380 We used the center of mass of the density distribution to estimate prevalence of
381 resistance. The calculation was conducted for six animal-bacteria combinations. This
382 included *E. coli* in chicken, pigs and cattle, as well as *Salmonella* in chicken and pigs,
383 and *S. aureus* in cattle. The remaining animal-bacteria combinations were excluded due
384 to limited sample size, only represented in 32 out of 446 PPS. The analysis was restricted
385 to antimicrobial classes represented by at least 10 resistance rates. In addition, we
386 estimated the association between resistance rates and the ease of obtaining
387 antimicrobials from the market, using data from online stores (Supplementary Text S3).

388

389 *Geospatial modelling*

390 We interpolated P50 values from the survey locations to create a map of P50 at a
391 resolution of 10 x 10 Km across China. The approach followed a two-step procedure ⁴⁷:
392 In step 1, three ‘child models’ were trained using four-fold spatial cross validation to
393 quantify the relation between P50 and environmental and anthropogenic covariates
394 (Supplementary Text S2; Supplementary Table 1). In step 2, the predictions of the child
395 models were stacked using universal kriging (Supplementary Text S2). This approach
396 combined the ability of the child models to capture interactions and non-linear
397 relationships between P50 and environmental and anthropogenic covariates, as well as
398 the ability to account for spatial-autocorrelation in the distribution of P50.

399

400 The outputs of the two-step procedure were: a map of P50 (Figure 3), and a map of
401 uncertainty on the P50 predictions (Supplementary Figure 9, Supplementary Text S2).

402 The overall accuracy of the geospatial model was evaluated using the area under the

403 receiver operator curve (AUC). The contribution of each covariate was evaluated by
404 permuting sequentially all covariates, and calculating the reduction in AUC compared
405 with a full model including all covariates (Supplementary Figure 4). The administrative
406 boundaries used in all maps were obtained from the Global Administrative Areas
407 database (<http://www.gadm.org>).

408

409 *Identifying (optimal) locations for future surveys on AMR*

410 We identified the locations of 50 hypothetical new surveys – the rounded average number
411 of surveys conducted per year (54 surveys/year) between 2014 and 2019 in China. The
412 location of each new survey was determined recursively such that it minimized the
413 overall uncertainty levels on the geographical trends in AMR across the country. This
414 process took into account the locations of existing surveys, as well as the location of each
415 additional hypothetical survey. The objective of this approach was to maximize gain in
416 information about AMR given the resource invested in conducting surveys.

417

418 The map of uncertainty consisted of the variance in the child model predictions
419 $Var(P_{BRT}, P_{LASSO-GLM}, P_{FFNN})$ (step 1) across 10 Monte Carlo simulations, and the
420 kriging variance Var_K (step 2):

421

$$422 \quad Var_{total} = Var(P_{BRT}, P_{LASSO-GLM}, P_{FFNN}) + Var_K$$

423

424 In this study, the location of hypothetical surveys was solely based on Var_K , instead of
425 the sum of both terms. This approach was preferred, because including both terms would

426 have required to hypothesize P50 values associated with the surveys to be conducted in
427 the future, adding an additional source of uncertainty that cannot be quantified. In any
428 case, the uncertainty attributable to Var_K was 4.1 times of
429 $Var(P_{BRT}, P_{LASSO-GLM}, P_{FFNN})$ (Supplementary Text S2).

430

431 The allocation of new surveys was based on a map of “necessity for additional
432 surveillance” (NS), defined as:

433

$$434 \quad NS = Var_K \cdot W$$

435

436 Where Var_K reflected the uncertainty of the spatial interpolation, and W is log10
437 transformed population density of humans⁴⁸, animals²⁷ in total, as well as in chicken,
438 pigs, and cattle, separately, which reflected exposure (Supplementary Figure 10). Here,
439 animal population density was calculated as the sum of population corrected units (PCU)
440 of pigs, chicken and cattle, using methods described in Van Boeckel et al. 2017⁷. We
441 adjusted the values of W , such that its density distribution equals that of Var_K .
442 Concretely, for each pixel i , we calculated the quantile of Wi on the map of W , and
443 replaced the value by the corresponding value of Var_K at the same quantile. Var_K and W
444 were both standardized to range [0,1], thus given each term equal weight in the need for
445 surveillance.

446

447 Four approaches were used to distribute 50 surveys across China based on the map of NS .

448 The reduction in uncertainty on AMR level associated with each of the four spatial

449 configurations of the hypothetical surveys was evaluated, by calculating the reduction in
450 the mean values of NS across 7,857 possible pixels on the map of China.

451

452 First, we used a “greedy” approach where all possible locations for additional surveys
453 were tested. Concretely, the first hypothetical survey was placed at each of the 7,857
454 possible pixel locations, and a revised map of $NS_{(+1\ survey)}$ was calculated for each of the
455 placements. The survey was eventually placed in the pixel that led to the largest reduction
456 in $NS_{(+1\ survey)}$. The map of NS was then revised to account for the reduction in
457 uncertainty in the neighborhood of the new survey. The process was repeated recursively
458 for the next hypothetical surveys (2nd -50th). This approach, by definition, yields the
459 optimal set of locations to reduce uncertainty, but it also bears a considerable
460 computational burden, because every possible location is tested ($N_{pixels}= 7,857$) by the
461 geospatial model for each hypothetical survey.

462

463 The second approach developed was a computational approximation to the greedy
464 approach, hereafter referred to as the ‘overlap approach’. This approach exploits a key
465 feature of the kriging procedure: the decrease of the kriging variance (Var_K) with
466 increasing proximity to existing survey locations. Each additional survey reduces the
467 variance of the geospatial model at its own location, but also in its surrounding area
468 (Supplementary Figure 11). The ‘overlap approach’ selects an optimal set of locations
469 that reflect a compromise between high local NS and distance to other surveys. It
470 iteratively selects new locations based on the highest local NS penalized by the degree of

471 overlap between the hypothetical new surveys and existing surveys (Supplementary
472 Figure 12). The first survey was placed at the location X_p, Y_p with the highest local NS
473 (Supplementary Figure 12, Part 1). Then, the value of NS at each pixel location X_i, Y_i was
474 recalculated as (Supplementary Figure 12, Part 2):

475

$$476 \quad NS_{(+1 \text{ survey}) X_i, Y_i} = NS_{X_i, Y_i} \times \left(1 - \frac{\text{overlap area}}{\text{neighborhood area}}\right)$$

477

478 Where the neighborhood area was the circular area of decreased kriging variance around
479 a new survey, and its radius was the distance until which NS decreased due to this new
480 survey; “Overlap area” is the shared area of the neighborhoods of location X_p, Y_p and of
481 location X_i, Y_i . The radius of the neighborhood was determined using a sensitivity
482 analysis, optimized by approximate Bayesian computation (sequential Monte Carlo) ⁴⁹
483 (ABC-SMC; Supplementary Text S5). The optimal neighborhood radius was chosen such
484 as it minimizes reduction in NS across all pixels. The procedure (Supplementary Figure
485 12, Part 1 and Part 2) was repeated recursively for the hypothetical surveys (2nd -50th).

486

487

488 The third approach tested consisted of distributing surveys equally between provinces, to
489 reflect a common approach to disease surveillance based on equal allocation of resources
490 between administrative entities. Here, 22 provinces with the highest human population
491 were assigned 2 surveys, and the remaining 6 provinces were assigned one survey per
492 province. The exact location of each survey was randomly selected inside a province.

493 Finally, all approaches were compared with the fourth approach (the random approach)
494 as a ‘null-model’, in which the 50 hypothetical surveys were located randomly across the
495 country without any geographic weighting criteria. The reduction in *NS* associated with
496 the third and fourth approach, which was compared to the greedy approach and overlap
497 approach, was the average over 50 simulations.

498

499 **Data Availability**

500 Resistance rates and related information extracted from all point-prevalence surveys can
501 be accessed in the Supplementary Data file, and at <https://resistancebank.org>.

502

503 **Code Availability**

504 The codes used to generate the results are available at Zenodo
505 (<https://doi.org/10.5281/zenodo.4940089>).

506

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511

512 **Author Contributions**

513 CZ, TVB and JP developed the analytical framework. CZ, YW and KT conducted the
514 literature review. CZ conducted the analysis and wrote the first version of the manuscript.

515 NC incorporated all data into resistancebank.org. All authors contributed to the final
516 version of the manuscript.

517

518 **Competing interests:**

519 No competing interests declared.

520

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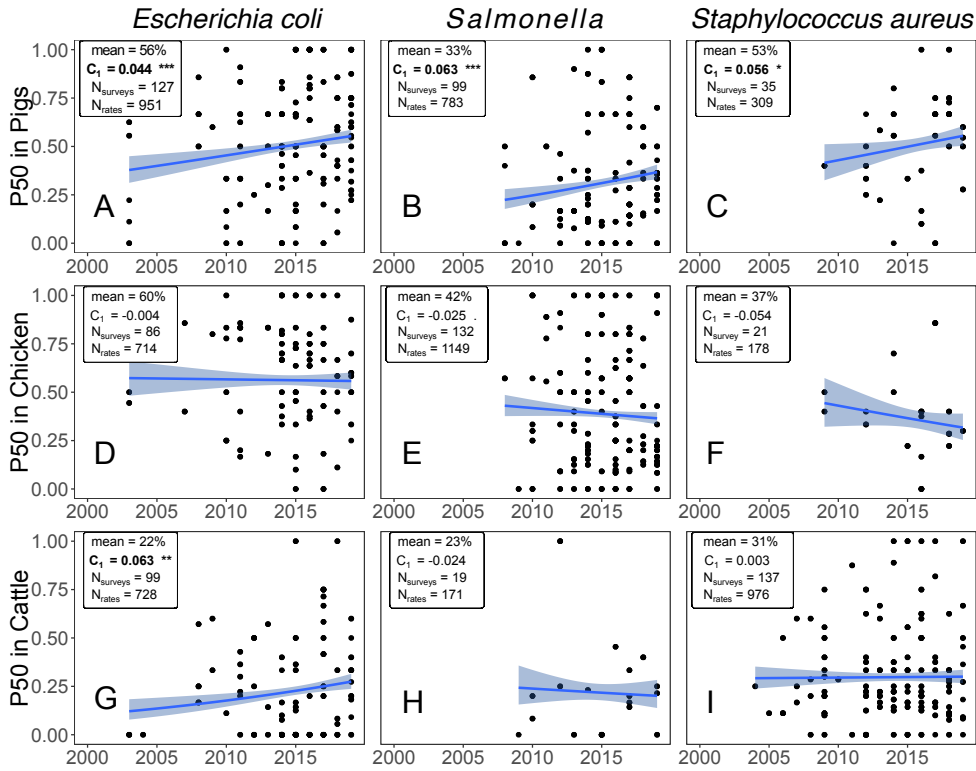
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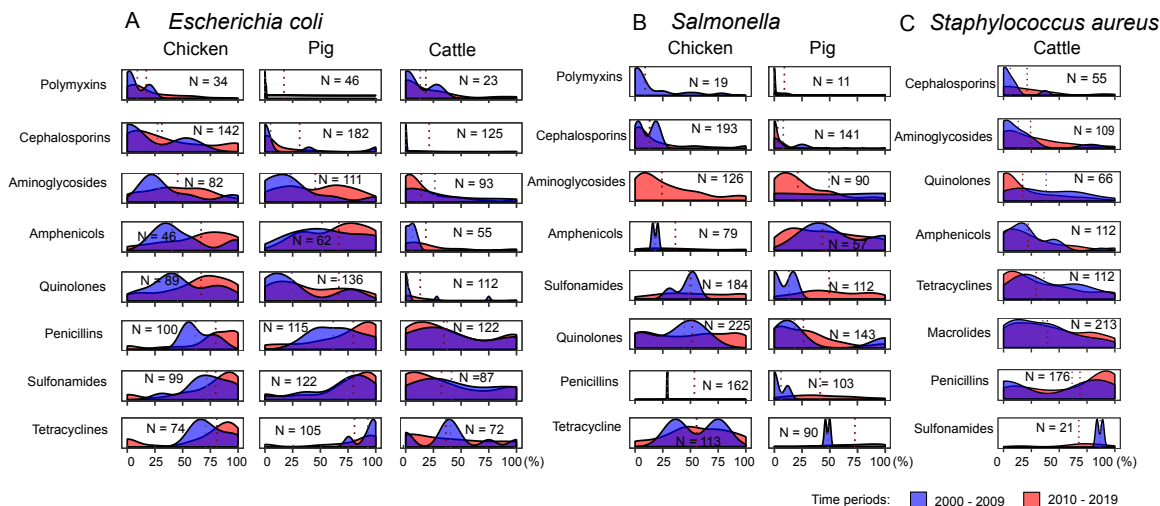


633

634 **Figure 1. Antimicrobial resistance between 2000 and 2019.** P50 is the proportion of
 635 antimicrobials with resistance higher than 50% (P50). Mean refers to the mean P50 value
 636 of all surveys. C₁ is the coefficient associated with the temporal trend in a logistic
 637 regression model weighted by log₁₀ transformed sample size in each survey. Shaded area
 638 indicates 95% confidence intervals. *** p < 0.001; ** p < 0.01; * p < 0.05. N_{surveys} is the
 639 number of surveys, and N_{rates} is the total number of resistance rates reported in the surveys.
 640 Surveys conducted at multiple locations in the same publication are considered multiple
 641 surveys.

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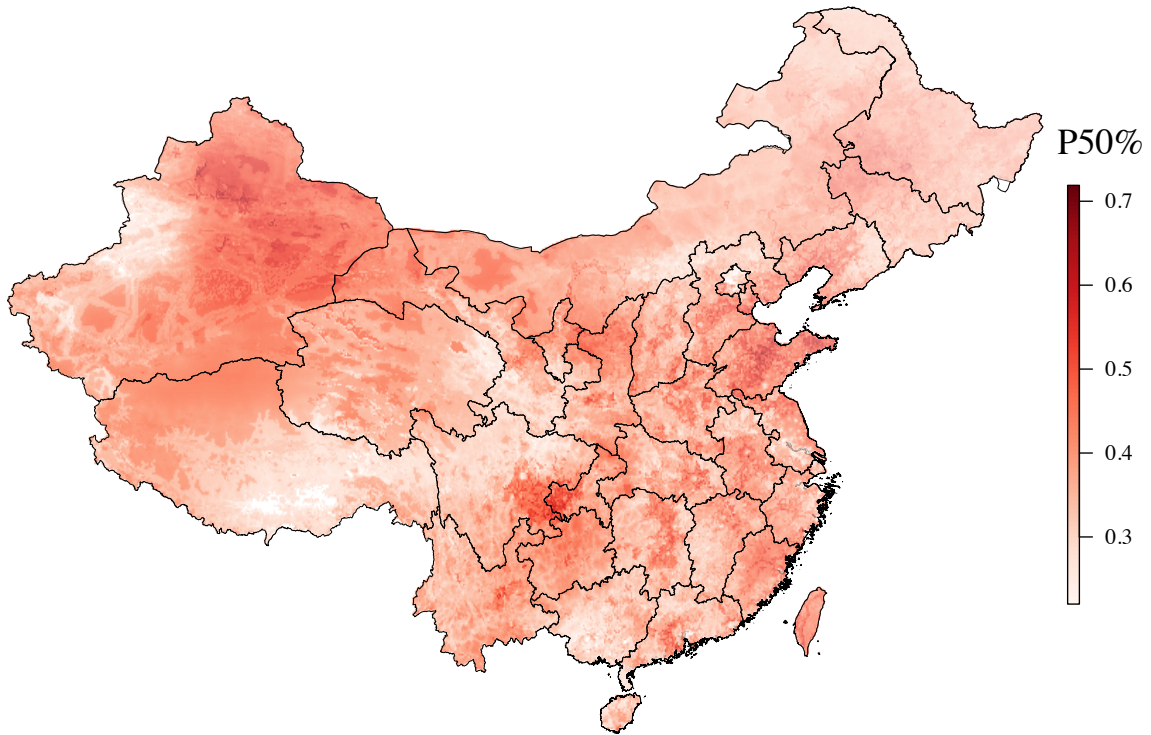
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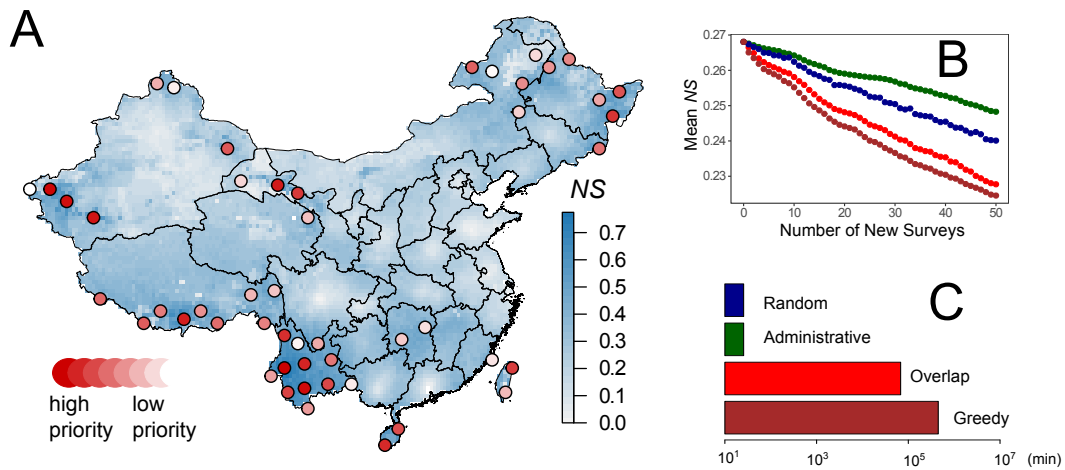
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645 **Figure 2. Prevalence of resistance per antimicrobial class.** In each panel, x-axis
 646 represents resistance rates, and y-axis represents the probability density. (A) *Escherichia*
 647 *coli* in chicken, pigs and cattle; (B) *Salmonella* in chicken and pigs; (C) *Staphylococcus*
 648 *aureus* in cattle. The x-axis represents resistance rates, and the area under the curve
 649 between two resistance rates represents the probability for resistance rates to fall within the
 650 interval. N: number of resistance rates used to calculate the density distribution. Dashed
 651 lines represent the center of mass of each distribution.

652



653
654 **Figure 3. Geographic distribution of antimicrobial resistance.** Color represents the
655 proportion of antimicrobials with resistance higher than 50% (P50).
656



657 **Figure 4. Predicted Locations for Future Surveys.** (A) Predicted optimal locations for
 658 future surveys using the “overlap approach”. The background color represents the
 659 “necessity for additional surveillance” (*NS*): the product of the kriging variance and animal
 660 population density (standardized from 0 to 1). (B) Reduction in the mean *NS* with 50
 661 hypothetical additional surveys. The 50 additional survey locations were identified using
 662 the greedy approach (dark red), the overlap approach (red), the administrative approach
 663 (green), and the random approach (blue). (C) Total CPU (central processing unit) time for
 664 computing the four approaches (log 10 scaled).

666