1   **Title:** Antimicrobial resistance surveillance: can we estimate resistance in bloodstream

2   infections from other types of specimen?

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40   Running title: AMR surveillane: non-sterile sites

41

42 **Synopsis**

43 **Background:** Antimicrobial resistance (AMR) surveillance of bloodstream infections is

44 challenging in low- and middle-income countries (LMICs), limited laboratory capacity

45 preventing routine patient-level susceptibility testing. Other specimen types could provide an

46 effective approach to surveillance.

47

48 **Objectives:** Our study aims to systematically evaluate the relationship between resistance

49 prevalence in non-sterile sites and bloodstream infections.

50

51 **Methods:** Associations between resistance rates in *Escherichia coli* and *Staphylococcus*

52 *aureus* isolates from blood and other specimens were estimated in Oxfordshire, UK, 1998-

53 2018, comparing proportions resistant in each calendar year using time series cross-

54 correlations and across drug-years. We repeated analysis across publicly-available data from

55 four high-income and 12 middle-income countries, and in three hospitals/programmes in

56 LMICs.

57

58 **Results:** 8102 *E. coli* bloodstream infections, 322087 *E. coli* urinary tract infections, 6952 *S.*

59 *aureus* bloodstream infections and 112074 *S. aureus* non-sterile site cultures were included

60 from Oxfordshire. Resistance trends over time in blood versus other specimens were strongly

61 correlated (maximum cross-correlation 0.51-0.99, strongest associations in the same year for

62 18/27 pathogen-drug combinations). Resistance prevalence was broadly congruent across

63 drug-years for each species. 276/312 (88%) species-drug-years had resistance prevalence in

64 other specimen types within ±10% of that blood isolates. Results were similar across multiple

65 countries and hospitals/programmes in high/middle/low income-settings.

66

67   **Conclusions:** Resistance in bloodstream and less invasive infections are strongly related over

68   time, suggesting the latter could be a surveillance tool for AMR in LMICs. These infection

69   sites are easier to sample and cheaper to obtain the necessary numbers of susceptibility tests,

70   providing more cost-effective evidence for decisions including empiric antibiotic

71   recommendations.

72

Introduction

Antimicrobial resistance (AMR) is among the top ten global health threats,[1] and is

particularly acute in low- to middle-income countries (LMICs).[2–4] Surveillance is a key tool

to combat rising AMR, as highlighted by the World Health Organization (WHO)[5] and

formalised in its Global Antimicrobial Resistance Surveillance System (GLASS),[6,7]

particularly in LMICs where lack of laboratory capacity prevents routine patient-level

antimicrobial susceptibility testing.[8] The lack of surveillance data was identified as a key

contributor to global AMR,[9] since the broad-spectrum empiric treatment approach that is

pragmatic in hospitals with limited laboratory facilities[2,10] generally results in

overtreatment.[11] Strengthening surveillance capacity in LMICs is therefore a major focus of

international initiatives. To date, these programmes have generally focused on improving

capacity for blood culture surveillance due to their high mortality; however, this requires

substantial capital investment and sustainable funding for LMICs, where baseline laboratory

functioning is poor.[12] Blood cultures are comparatively costly, require trained staff due to the

invasive nature of blood sampling, and can have slow turnaround times, reducing their ability

to inform individual clinical management. Additionally, the low positivity rate means that

very high sample throughput is needed to confidently estimate resistance prevalence.

Consequently, empirical treatment guidelines are largely uninformed by local resistance rates

in LMICs.

One way to address this would be to assess resistance rates using data from cheaper, easier

non-invasive samples. Reflecting this, the 2020 WHO GLASS report includes resistance

prevalence in urine cultures for key Gram-negative pathogens. However, associations

between resistance rates in blood and other specimens have been rarely studied

longitudinally. A 2018 report for South Korea observed similar resistance rates in *E. coli*

98   blood cultures and urine isolates in 2016.[13] A 2018 study showed statistical non-equivalence

99   of antimicrobial susceptibility in nontyphoidal *Salmonella enterica* from blood, urine and

100   faecal samples from 2015 U.S. National Antimicrobial Resistance Monitoring System data.[14]

101   Longitudinal surveillance of *Escherichia coli* bloodstream and urinary infections in a large

102   UK region (Oxfordshire) found similar trends in co-amoxiclav resistance over 19 years.[15]

103   Another Oxfordshire study also found similar trends over time in nosocomial methicillin-

104   resistant *Staphylococcus aureus* isolates from blood and non-blood clinical samples between

105   1998 and 2006,[16] but changes in trends were identified earlier from non-blood samples due to

106   higher numbers. This raises the broader question as to whether, for multiple pathogen-drug

107   combinations, the proportion of resistant bloodstream infections could be estimated by the

108   proportion of resistant isolates from other body-sites, that are easier to sample from, and

109   more often culture-positive, reducing the costs per drug phenotype obtained. Using the latter

110   as a surveillance method for the former is attractive because setting up a laboratory and

111   providing the infrastructure (e.g. reagents, personnel, electricity etc.) to conduct blood culture

112   surveillance in LMICs approximately doubles the costs compared to urine culture

113   surveillance.[17] Their large numbers make them ideal for developing locally relevant empiric

114   treatment guidelines.

115

116   We therefore investigated the annual prevalence of resistance in isolates from blood and other

117   body-sites for multiple pathogen-drug combinations in Oxfordshire (regional analysis, high-

118   income country (HIC)). We then extended the analysis, first to consider concurrent or

119   previous isolates in the same patient, and second to consider other world regions through

120   publicly available datasets (Antimicrobial Testing Leadership and Surveillance (ATLAS)[18])

121   and collaborating hospitals/programmes in LMICs with available data.

122

123 **Materials and methods**

124 We obtained antibiograms for *E. coli, Klebsiella* spp., *Staphylococcus aureus, Streptococcus*

125 *pneumoniae,* and *Enterococcus* spp. from the Infections in Oxfordshire Research Database

126 (IORD),[19] from 1 January 1998 to 31 December 2018, which includes all microbiology tests

127 performed for the region of approximately 680,000 individuals, and has Research Ethics

128 Committee and Confidentiality Advisory Group approval (19/SC/0403, 19/CAG/0144) as a

129 de-identified electronic research database. We compared *E. coli* and *Klebsiella* bloodstream

130 infections (BSI) versus urinary tract infections (UTI); and isolates from blood versus all other

131 body-sites of infection for other pathogens (non-blood infections; excluding surveillance

132 swabs), further sub-divided into sterile versus non-sterile for *S. aureus* (Supplementary

133 Methods). We estimated yearly resistance prevalence for all antimicrobials with

134 susceptibilities for >65% samples in that year (mostly >80%). Testing used manual disk

135 diffusion before 2013, and thereafter automated testing with the BD Phoenix[TM] Automated

136 Microbiology System, Beckton Dickinson. Resistance was as defined by the laboratory when

137 the test was done, using the same breakpoints regardless of specimen type, following

138 European Committee on Antimicrobial Susceptibility testing (EUCAST) recommendations

139 for bloodstream infections in each year.[20] We did not de-duplicate isolates by patient,

140 reflecting data that would be easily available from routine laboratory systems.

141

142 For each pathogen-drug combination, we first estimated the proportion resistant in blood

143 versus other samples in each calendar year (with 95% confidence intervals (CI)) using Lin's

144 concordance correlation coefficient (CCC) for comparisons.[21] We used time-series cross-

145 correlation functions to identify the time differences at which the correlation between

146 resistance prevalence was strongest. As perfect agreement is unrealistic, we also considered

147 agreement within what might be considered clinically acceptable error ($\pm$5% and $\pm$10%

148   difference in prevalence), and agreement within arbitrary categories which may nevertheless

149   be clinically helpful, specifically: <5% resistance (most would readily prescribe an

150   antibiotic), 5-10% (most would prescribe for mild infections), 10-20% (unclear) and >20%

151   (many would not prescribe if other options were available). We used logistic random-effects

152   meta-analysis to estimate the overall difference between resistance prevalence in the two

153   sample types, treating every calendar year as an independent study, assessing heterogeneity

154   across years using the I^2 statistic.[22] We used meta-regression to estimate the effect of calendar

155   year on the proportion of resistant bloodstream isolates (with its standard error), assuming the

156   proportion of resistant isolates from other infection sites was known (given their greater

157   numbers). We also used meta-regression to directly estimate the association between log odds

158   of resistance in bloodstream infections (outcome, with its standard error) and the log odds of

159   resistance in other infection sites (explanatory variable, fixed). (Full details in the

160   Supplementary Material.)

161

162   One possibility is that resistance rates differ between blood and other infection sites because

163   of differences in the underlying populations being sampled. A secondary analysis therefore

164   considered matched pairs of isolates from the same patient, selecting the closest culture from

165   a different site up to 3 days before or 2 days after the blood culture,[15] assessing concordance

166   using McNemar's test. We also considered whether susceptibility of a previous *E. coli* UTI

167   could predict susceptibility of a subsequent *E. coli* BSI, by selecting the temporally closest

168   urine culture taken between 3-90 days before the blood culture.[15,23]

169

170   We also analysed pathogen-drug combinations at the country level (pooling multiple

171   hospitals/regions) using the ATLAS dataset, comprising 633,820 isolates from 73 countries

172   between 2004-2017.[18] We considered all years where at least 30 isolates were tested for a

173   given drug in LMICs (95% CI width around prevalence always <37%); and 100 isolates for

174   HIC (width <20%) given greater numbers from HIC and strong inverse association between

175   numbers tested and resistance prevalence in HIC, suggesting preferential testing of resistant

176   isolates. Finally, we also analysed microbiology data from Angkor Hospital for Children

177   (Siem Reap, Cambodia), Mahosot Hospital (Vientiane, Laos), and the Shoklo Malaria

178   Research Unit (Mae Sot, Thailand, serving migrant and refugee populations on the Thailand-

179   Myanmar border), including antibiotics tested for >40% of the isolates across all study years.

180   Antimicrobial susceptibility testing was conducted using disk diffusion and results

181   interpreted using Clinical and Laboratory Standards Institute (CLSI) 2019 breakpoints.

182   Intermediate isolates were considered non-susceptible. Extended Spectrum Beta-Lactamase

183   (ESBL) status was confirmed using the double disk method (ceftazidime+/-clavulanate and

184   cefotaxime+/-clavulanate) as a ≥5mm increase in a zone diameter for either agent with

185   clavulanic acid.

186

187   We conducted all analyses using R 3.5.1, using the metafor package for meta-analyses.[24]

188

189   **Results**

190   We focused initially on *E. coli* and *S. aureus* as two of the most common bacteria causing

191   BSI,[2,25,26] and often causing urine or skin and soft tissue infections, respectively. We included

192   8102 *E. coli* BSI and 322087 *E. coli* UTI (40-fold higher) from Oxfordshire (**Supplementary**

193   **Figure 1**); 4 antibiotics (amoxicillin, co-amoxiclav, ciprofloxacin, and trimethoprim) were

194   consistently tested in both between 1998-2018. Whilst absolute resistance prevalence was

195   generally slightly higher in bloodstream isolates, trends in the proportion of resistant BSI and

196   UTI were very similar, notably tracking substantial fluctuations over time in trimethoprim

197   resistance (**Figure 1**, **Supplementary Table 1, Supplementary Figure 2**), with resistance

198   rates in the same year most strongly correlated (maximum cross-correlation at lag 0). For

199   these four antibiotics, there was no evidence of strong variation in the relationship between

200   resistance rates over time (**Supplementary Table 1**).

201

202   Including a further six antibiotics (aztreonam, ceftazidime, ceftriaxone, co-trimoxazole,

203   ertapenem, gentamicin, meropenem and piperacillin-tazobactam) consistently tested between

204   2013-2018 (**Supplementary Figure 3, Supplementary Table 1**) increased the range of

205   resistance prevalences observed. Again, resistance rates were slightly higher in BSI and

206   showed reasonable concordance with resistance in UTI, with prevalences within 10% of each

207   other in 109/132 (89%) drug-years (**Figure 2**, left-hand panel, **Table 1**). Overall resistance

208   prevalence in BSI was highly correlated with resistance prevalence in UTI (CCC=0.93 (95%

209   CI 0.91-0.95) (**Table 1**). Agreement was also relatively high across our four pre-defined

210   resistance categories, with 83/132 (63%) drug-years in the same resistance category and

211   45/132 (34%) in adjacent categories (**Figure 2**, right-hand panel). Although numbers were

212   smaller, broadly similar results were seen for *Klebsiella* spp. (**Figure 2, Table 1,**

213   **Supplementary Figures 4&5, Supplementary Tables 1&2**).

214

215   Considering matched pairs of isolates from individual patients, there was no evidence that the

216   modestly different resistance rates seen in *E. coli* BSIs and UTIs overall were due to

217   differential sampling of intrinsically different underlying populations, given high but

218   similarly imperfect agreement in susceptibility (86-100% across 11 antibiotics for concurrent

219   infections, 80-94% for previous infections, **Supplementary Table 5**). In particular,

220   considering the closest prior *E. coli* UTI 3-90 days before a BSI, >80% resistant UTIs also

221   had a resistant BSI across these four drugs.

222

223   Between 1998-2018, there were 6952 *S. aureus* BSIs and 166179 *S. aureus* non-blood

224   cultures: 54105 (33%) from sterile sites and 112074 (67%) from non-sterile sites (8- and 16-

225   fold higher respectively, **Supplementary Figure 1**). Ciprofloxacin, erythromycin and

226   oxacillin presented similar trends in the proportions resistant over time in the different sample

227   types, which varied substantially over time (**Figure 1, Supplementary Table 1,**

228   **Supplementary Figure 6**), again supporting the plausibility of using non-blood cultures as a

229   proxy for blood culture surveillance. Agreement was poorer for gentamicin and tetracycline

230   resistance, although rates were low (<15%). As might be expected, agreement was slightly

231   better between resistance prevalence in blood and other sterile site cultures than blood and

232   non-sterile site cultures (**Supplementary Figure 7**). As agreement was reasonable in both,

233   and non-sterile site cultures would be more likely to be taken in LMICs, we focussed on this

234   group of infection sites. Overall, resistance prevalence was more similar in bloodstream and

235   other non-sterile infection sites in *S. aureus* than *E. coli* (**Supplementary Table 1**), but there

236   were also slightly stronger effects of calendar time for *S. aureus*, reflecting generally higher

237   rates of resistance in blood compared with non-sterile site cultures during the MRSA

238   epidemic in the mid-2000s, which then became more similar (**Supplementary Figure 3**).

239

240   For *S. aureus*, including other antibiotics tested between 2013-2018 only, resistance

241   prevalences in blood and non-sterile site cultures were within 10% of each other in 167/180

242   (93%) drug-years, with 132 (73%) drug-years in the same resistance category and 45 (25%)

243   in adjacent categories (**Figure 2, Table 1**). Overall resistance prevalence in blood was highly

244   correlated with resistance prevalence in non-sterile isolates (CCC=0.97 (0.95-0.97)) (**Table**

245   **1**). Overall agreement between resistance in concurrent blood and non-sterile cultures within

246   a patient was extremely high (96-100%) for *S. aureus*, with ciprofloxacin, erythromycin and

247   oxacillin having <5% of resistant blood cultures with susceptible non-sterile cultures and

248   <4% susceptible blood cultures with resistant non-sterile sites cultures (**Supplementary**

249   **Table 5**). Again, although numbers were smaller, broadly similar results were seen for *S.*

250   *pneumoniae*, *E. faecalis* and *E. faecium* (**Figure 2, Table 1, Supplementary Figure 8,**

251   **Supplementary Tables 1&2**).

252

253   In the ATLAS dataset, there were 401 and 155 country-drug-years with >100 *E. coli* and *S.*

254   *aureus* isolates from HICs, respectively, from both bloodstream and urinary/non-sterile

255   infections (**Supplementary Table 3**). For *E. coli*, time trends could be estimated over 7 years

256   or more in four countries for 11 antibiotics, and were broadly similar (**Figure 3**; *S. aureus* in

257   **Supplementary Figure 9**). Across all drugs, prevalence of resistance in *E. coli* BSIs and

258   UTIs were within 10% of each other in 376/401 (94%) country-drug-years (**Figure 4**, left-

259   hand panel, **Table 1**); 326 (81%) country-drug-years were in the same resistance category

260   and 74 (18%) in adjacent categories (**Figure 4**, right column). For *S. aureus*, respective

261   figures were 147/155 (95%), 154 (99%) and 1 (1%). Agreement was similar in middle-

262   income countries where smaller numbers of isolates were available (**Figure 4**, **Table 1,**

263   **Supplementary Figures 10&11**) and in other pathogens (**Supplementary Figures 12-16**).

264

265   Considering hospital/programme-level LMIC datasets, numbers were smaller

266   (**Supplementary Table 4**) and hence estimates more variable, but both time trends (**Figure**

267   **5, Supplementary Figure 17**) and comparisons of individual country-drug-years (**Figure 6**,

268   **Table 1, Supplementary Figure 18**) supported overall findings that resistance profiles in

269   non-blood culture isolates correlate well with those in blood culture isolates over time.

270

271   **Discussion**

272   Here, we show that AMR prevalence from infections in sites other than blood could

273   potentially be used to infer AMR in bloodstream infections, which could reduce the initial

274   costs of AMR surveillance in LMICs. Focusing on two of the most common bacteria causing

275   serious infections, *E. coli* and *S. aureus*, we found that, whilst not perfect, agreement between

276   the resistant rates in blood cultures and in other clinical cultures was good for most

277   antibiotics, in terms of actual values, but, most importantly for surveillance, over time. This

278   suggests that changes in resistance over time could be monitored using samples that are

279   easier to collect than blood, and could also inform appropriateness of different empirical

280   antimicrobial therapies.

281

282   Whilst many studies estimate resistance prevalence in various infection sites, to our

283   knowledge, very few studies have directly compared resistance in blood versus other

284   infection sites, either focussing on one specific drug-pathogen combination,[16] or on

285   Enterobacterales and investigating metagenomics from pooled human samples from the UK,

286   Kenya and Cambodia as a predictor of resistance in invasive infections.[27] In 2011, Health

287   Protection Scotland and National Services Scotland published a protocol for the surveillance

288   of AMR in UTIs, arguing that it would be more appropriate to monitor resistance in other

289   sites where an infection initially starts before entering the bloodstream.[28] However, the

290   hypothesised relationship was not analysed using the data collected.[29] WHO piloted a similar

291   approach but did not compare with resistance rates in BSI.[30]

292

293   Current efforts on AMR surveillance in LMICs are directed towards building laboratories and

294   training staff to carry out antimicrobial susceptibility testing on blood cultures, arguing that if

295   this can be achieved, other types of culture will become possible too. However, setting up

296   such systems is very expensive, both in terms of infrastructural and running costs, and it will

297   be many years until sufficient data on blood cultures have been accumulated for surveillance

298   purposes, particularly given initial low uptake and low rates of positivity in these samples.

299   While longitudinal surveillance data is available at a limited number of research sites, these

300   programmes cover a limited geographic area and may not be representative of other locations

301   in a country. Incorporating blood culture testing into public hospitals may be further biased

302   by differences in ability to pay.[2] Collecting specimens from urine/skin surface/genital sites is

303   cheaper and less invasive than sampling blood, and therefore substantially easier to do on

304   large numbers from different communities, as well as having higher positivity rates,

305   increasing their utility for AMR surveillance. This is true even in HICs, with clearly narrower

306   confidence intervals from larger numbers of non-blood Oxfordshire isolates. Even allowing

307   for the greater manual processing needed for non-blood cultures, for example, obtaining 100

308   *E. coli* isolates would only require testing 361 urine samples assuming 37% are culture-

309   positive and 75% of these are *E. coli*, but 7693 blood cultures, assuming 13% are positive and

310   10% of these are *E. coli* (estimates based on Oxfordshire data 1998-2016). Whilst blood

311   cultures may be perceived as having greater diagnostic utility, this may be limited practically,

312   e.g. by long turnaround times.

313

314   One strength of our study is the different datasets used, and the robustness of findings across

315   these, including continuous surveillance of one large region (Oxfordshire), and global

316   analysis (ATLAS) albeit of a selection of infections within each country. The

317   hospital/programme-level LMIC datasets are highly curated, but relatively small. One crucial

318   underpinning assumption is that pathogens causing other infections are representative of

319   pathogens causing BSI in terms of antibiogram, either because the source of infection is

320   commonly from commensal colonising organisms that become pathogenic opportunistically

321   or because both types of infection arise from a similar reservoir. Even though this may hold

322   within the populations studied, it is possible, although fairly unlikely, that this may not

323   generalise more widely. Generalisability is supported by the good country-level agreement in

324   ATLAS, even though pooling different regions within countries, which could have

325   potentially differed further between blood and other infection sites. This raises an important

326   limitation of our approach, namely that different people were sampled for blood and other

327   specimens. However, our analysis of samples from the same patients suggests this is unlikely

328   to cause major bias. Another limitation is that we have only considered surveillance of the

329   proportion of resistant infections, not numbers or population-level rates of resistance;

330   however, in terms of empiric treatment recommendations, proportions rather than absolute

331   numbers that are generally of interest. We have not considered surveillance of AMR across

332   the entire antibiogram, i.e. patterns of resistance within one isolate across different

333   antibiotics. We also pooled all samples together: in future work we could consider whether

334   relationships are generalizable between different groups of patients (e.g. by age,

335   nosocomial/community infections). Finally, the thresholds we considered were arbitrary,

336   which is why we considered two different approaches (varying margins of error and varying

337   categorical thresholds).

338

339   One question is how good the agreement between resistance rates in isolates from blood

340   versus other specimens should be for surveillance of resistance in samples from other body-

341   sites to be useful – clinically and for understanding overall trends. In our dataset, different

342   resistance rates were observed in different sample types for many pathogen-drug

343   combinations, with some variation over time and less than perfect agreement. However,

344   cross-correlations were generally high, as was agreement within 10% and across categories

345   that could inform empirical antimicrobial therapy. Several biological reasons for the lack of

346   perfect agreement are plausible: for example, a large proportion of *E. coli* BSIs have a

347   urinary focus, but susceptibility and appropriate empiric treatment generally limit progression

348   to BSI, in contrast to resistant, and perhaps sub-optimally treated UTIs. Hence one might

349   expect the proportion of drug-resistant BSIs to be higher due to inadequate empiric treatment

350   of a drug-resistant UTI, but underlying time trends to track each other, as we observed. One

351   could ask whether blood is the best sample for AMR surveillance. BSIs are the most serious

352   infection, so risks associated with inappropriate antibiotic treatment are highest, but

353   potentially treating the many other less serious infections correctly might mean fewer

354   develop into BSI.

355

356   In HICs, susceptibility testing is still not instantaneous, with microbiology results generally

357   taking at least 48 hours, time during which empiric antimicrobials are administered,

358   potentially leading to poorer outcomes if the infection is caused by a resistant organism.[3]

359   However, increasing use of electronic health records means it is becoming much simpler to

360   check for previous UTIs and use this to guide empiric treatment. Our paired analysis

361   illustrates the potential of this approach based on an arbitrarily chosen interval of 3-90 days

362   prior to the BSI; future work could investigate how the strength of this association varies

363   further back in time, or using the most resistant rather than most recent urinary isolate.

364   Similarly, Yelin *et al.*[31] found that incorporating demographic information with susceptibility

365   results of previous UTIs and antibiotic purchases in a machine learning model improved

366   guidance of empirical treatment for new community-acquired UTIs.

367

368   AMR surveillance plays a key role in optimising the use of antibiotics and hence reducing

369   resistance: asking clinicians to reduce antibiotic use and running successful stewardship

370   programmes cannot be done in an information vacuum, and lack of microbiology facilities

371   and unwillingness of patients to have samples taken (often due to cost) have been identified

372   as key factors influencing antibiotic use.[32,33] LMICs face numerous challenges in setting up

373   surveillance systems similar to those in HICs, including lack of coherent governance, budget,

374   technical expertise, information technology systems and co-ordination. Our study shows that

375   body-sites which are easier to sample, cheaper, faster and easier to grow from compared to

376   blood could provide a feasible approach to AMR surveillance, providing evidence for empiric

377   treatment recommendations. They could also be amenable to survey-type approaches which

378   could be particularly valuable as setting up a local laboratory infrastructure for successful and

379   useful antibiogram production is challenging. Using population level surveillance as a

380   substitute for individual patient testing could be considered a pragmatic steppingstone in

381   improving a site's diagnostic capacity for individual patient management. Nevertheless, the

382   urgent threat posed by AMR demands that we not let the perfect be the enemy of the good.

383

Transparency declaration

Karina-Doris Vihta affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted;

408   and that any discrepancies from the study as planned (and, if relevant, registered) have been

409   explained.

410

411   **Contributors**

412   K-DV, NJW, TEAP, and ASW designed the study. TPQ prepared extracts from the Infections

413   in Oxfordshire Research Database. K-DV obtained data from the Antimicrobial Testing

414   Leadership and Surveillance (ATLAS). Data from the Angkor Hospital for Children was

415   provided by PT, from the Mahosot Hospital Microbiology Laboratory by MV, EAA, VC, and

416   from the Shoklo Malaria Research Unit by CL. K-DV, TEAP and ASW analysed the data. K-

417   DV, TEAP, and ASW prepared the figures. K-DV, DE, TEAP, and ASW prepared the first

418   draft of the manuscript. All authors commented on the data and its interpretation, revised the

419   content critically, and approved the final version. *NIHR Health Protection Research Unit*

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421

422   **Declaration of interests**

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428

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530

531 **Figure legends**

532 **Figure 1** Resistance prevalence in *E. coli* and *S. aureus* in blood and non-blood cultures in

533   Oxfordshire, 1998-2018

534 **Figure 2** Resistance in blood and non-blood cultures (A) *E. coli*, (B) *Klebsiella* spp., (C) *S.*

535   *aureus*, (D) *S. pneumoniae*, (E) *E. faecalis* and *E. faecium*, Oxfordshire 1998-2018

536 **Figure 3** Resistance prevalence in *E. coli* in blood and non-blood cultures in high-income

537   countries present in the ATLAS dataset, 2004-2016

538 **Figure 4** Resistance in blood and non-blood cultures (A) *E. coli*, (B) *S. aureus,* ATLAS

539   dataset split into high-income countries and middle-income countries

540 **Figure 5** Resistance prevalence in *E. coli* in blood and non-blood cultures in three

541   hospitals/programmes in LMICs

542 **Figure 6** Resistance in *E. coli* blood and non-blood cultures in three hospitals/programmes in

543   LMICs

544 **Table legends**

545 **Table 1** Resistance prevalence in blood and non-blood cultures across drug-years,

546   Oxfordshire 1998-2018

547

548 *Figure 1 Resistance prevalence in E. coli and S. aureus in blood versus non-blood cultures in*
549 *Oxfordshire, 1998-2018*

550 *E. coli*   *S. aureus*

551
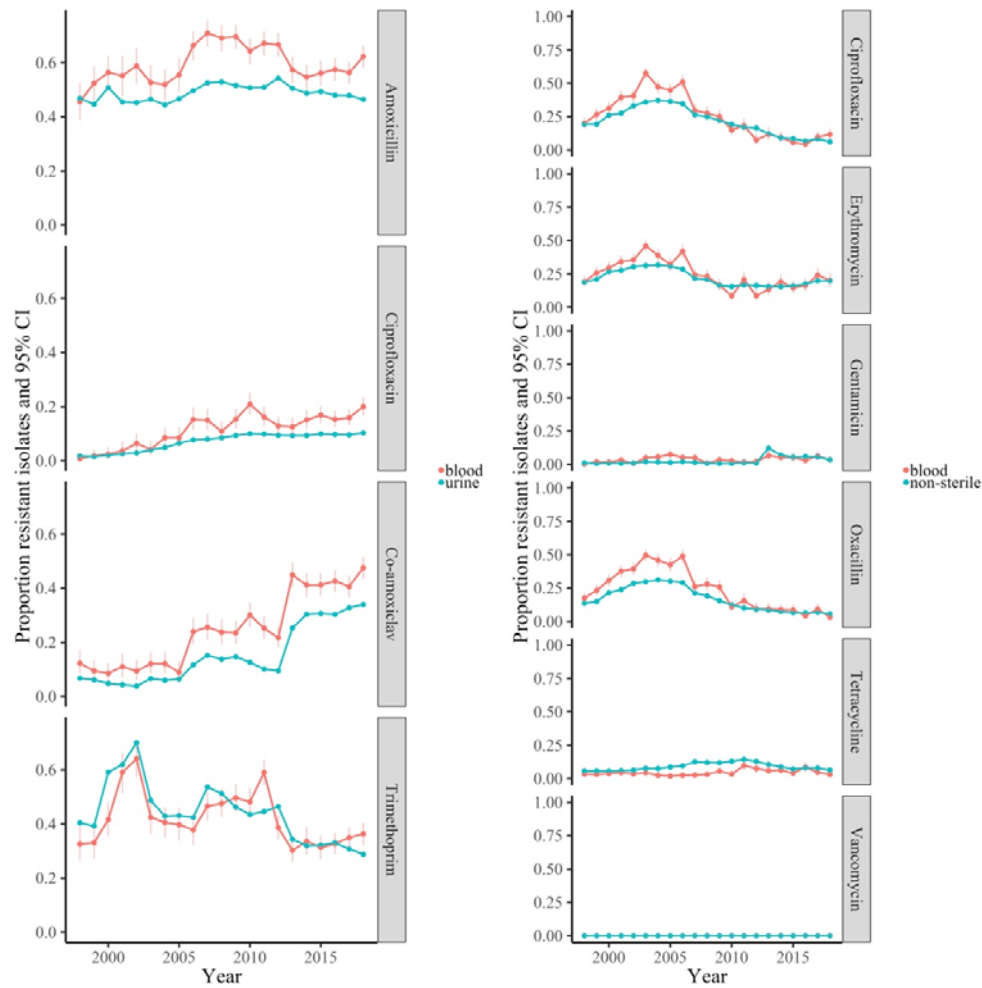
552 Note: maximum cross-correlation at time lag 0 in 3/4 drugs for *E. coli* and 4/6 drugs for *S. aureus*; cross-
553 correlation 0.77 at lag 1 (0.75 at lag 0), 0.95, 0.96, 0.80 for *E. coli* and 0.95, 0.93, 0.54, 0.75, 0.69 at lag -4, 0.60
554 at lag 3 for *S. aureus* from top to bottom respectively.

555

556 *Figure 2 Resistance in blood and non-blood cultures for (A) E. coli, (B) Klebsiella spp., (C)*
557 *S. aureus, (D) S. pneumoniae, (E) E. faecalis* and *E. faecium, Oxfordshire 1998-2018*

558 **(A)** *E. coli* bloodstream infections versus urinary tract infections
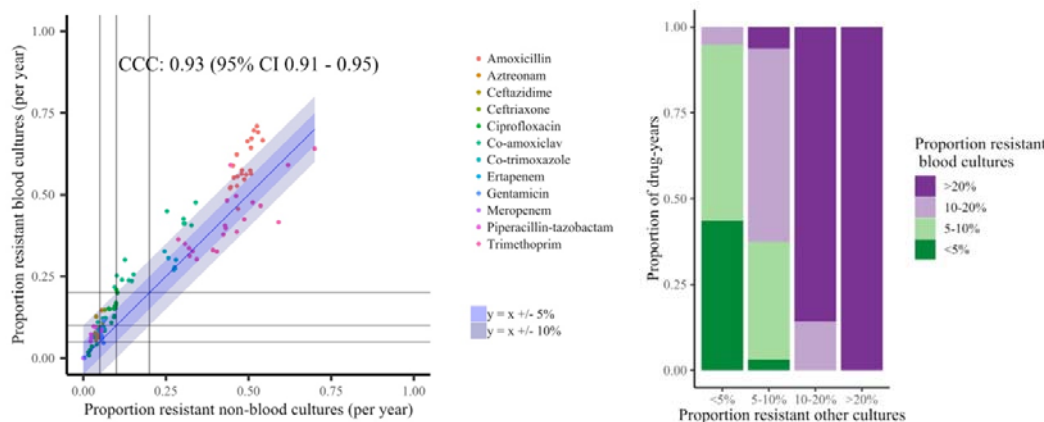
559
560 **(B)** *Klebsiella* spp. bloodstream infections versus urinary tract infections
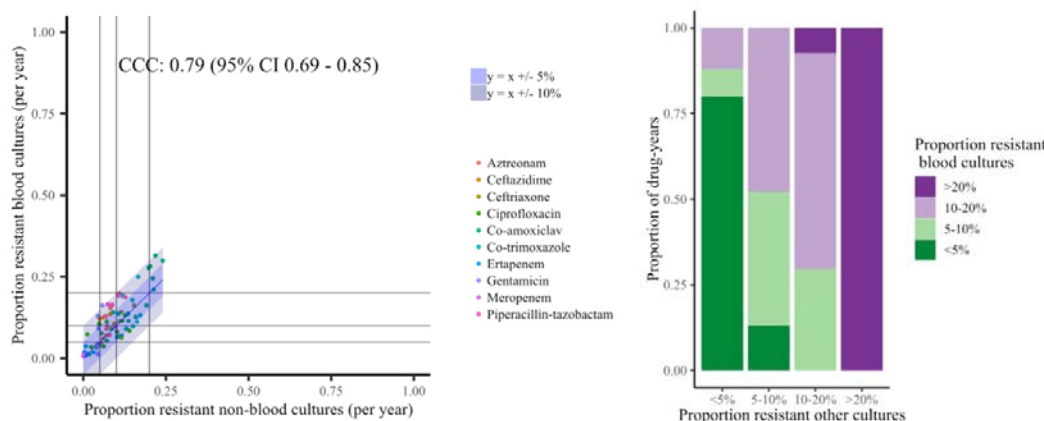
561
562 **(C)** *S. aureus* bloodstream infections versus non-sterile site infections

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564
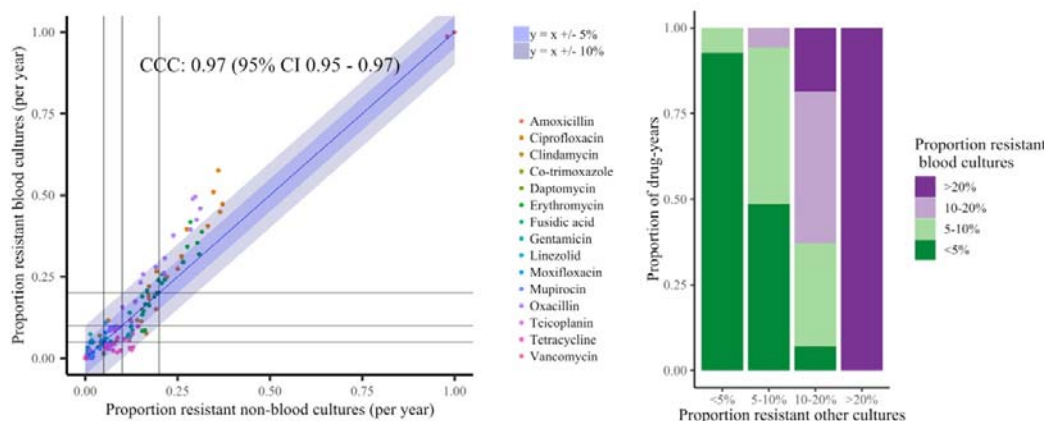
(D) *S. pneumoniae* bloodstream infections versus non-blood infections
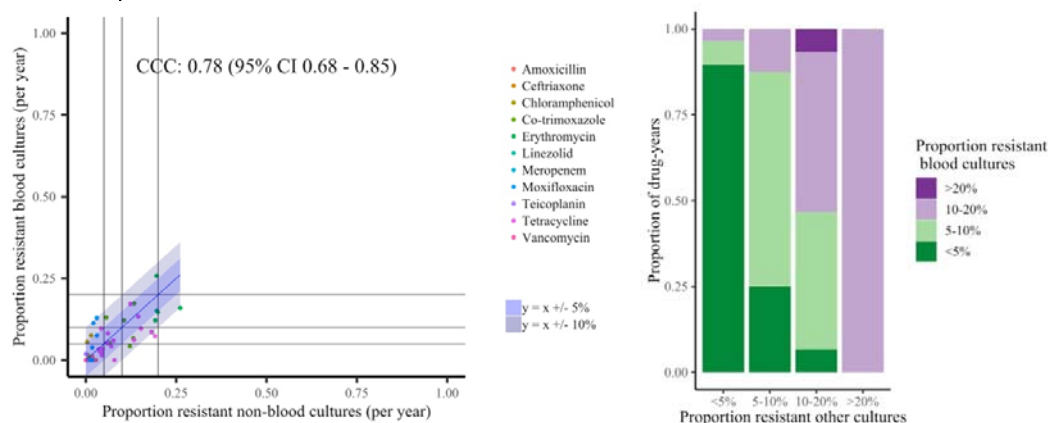
(E) *E. faecalis* (denoted _S) and *E. faecium* (denoted _M) bloodstream infections versus non-blood infections
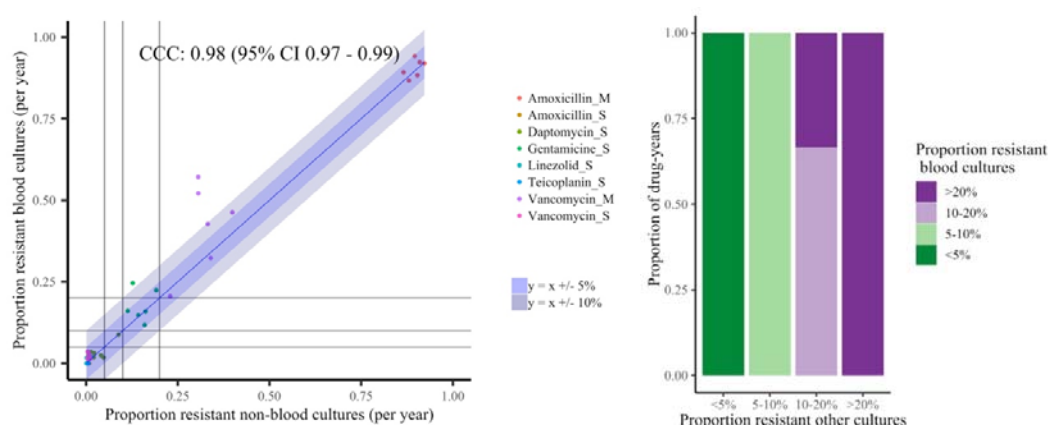
Note: Left: Proportion resistant non-blood cultures versus proportion resistant blood cultures per year for all antibiotics. Each dot reflects resistance prevalence for one antibiotic in one specific year. Line of identity, +/- 5% and 10% shown in blue. Lines are drawn at 0.05 (5%), 0.1 (10%) and 0.2 (20%) resistance prevalence in each of blood versus non-blood cultures for ease of visualisation of agreement between clinically meaningful resistance categories in these two types of samples. Right: Grouping points from left column into clinically meaningful resistance categories; classifying resistance prevalence in blood cultures by the proportion in urine/non-sterile site cultures.

577 *Figure 3 Resistance prevalence in E. coli in blood versus non-blood cultures in high-income*
578 *countries present in the ATLAS dataset, 2004-2016*
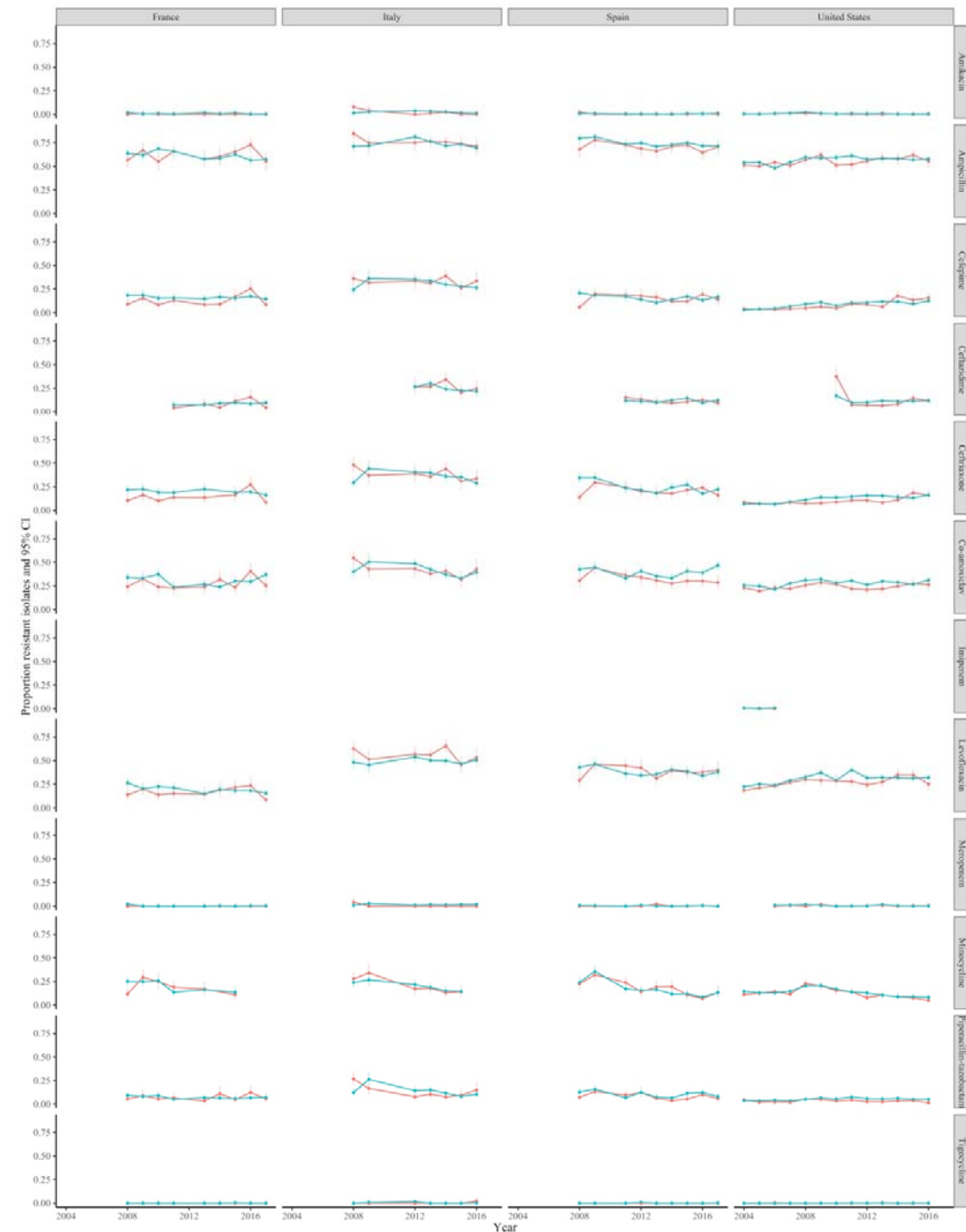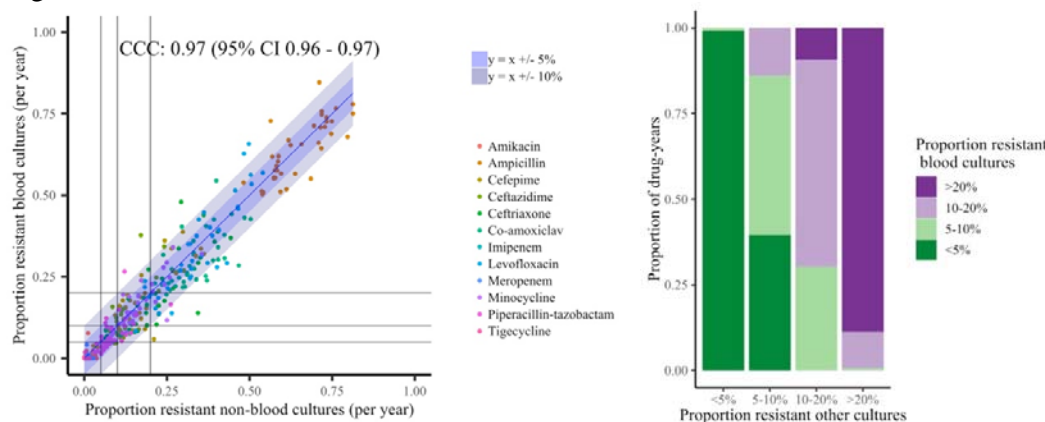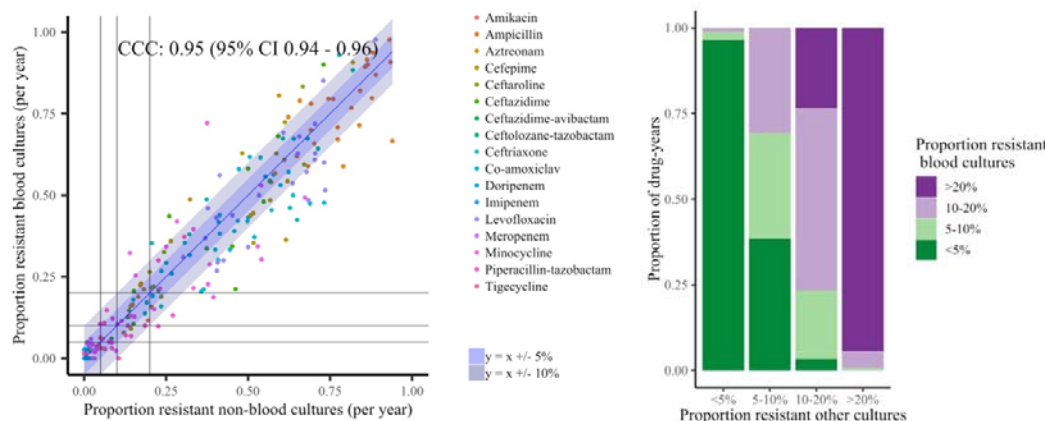

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580

581   *Figure 4 Resistance in blood and non-blood cultures (A) E. coli, (B) S. aureus, ATLAS*
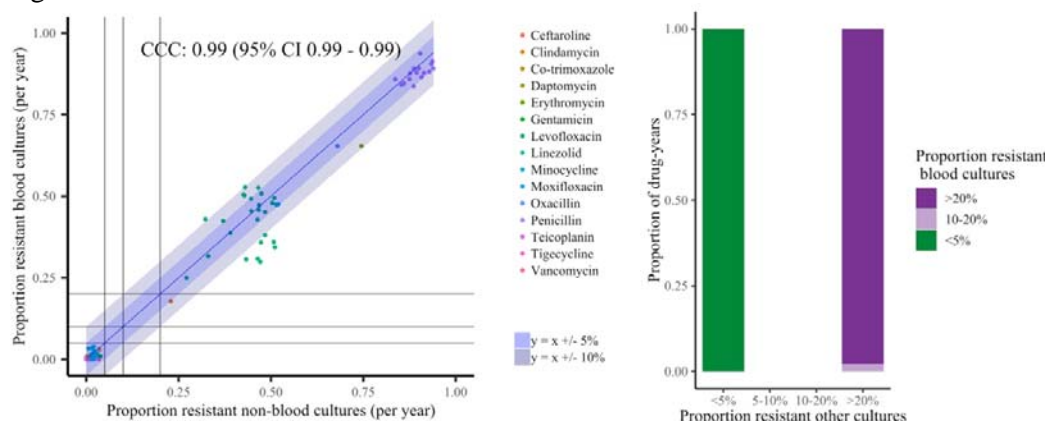582   *dataset split into high-income countries and middle-income countries*

583   *E. coli* bloodstream infections versus non-blood
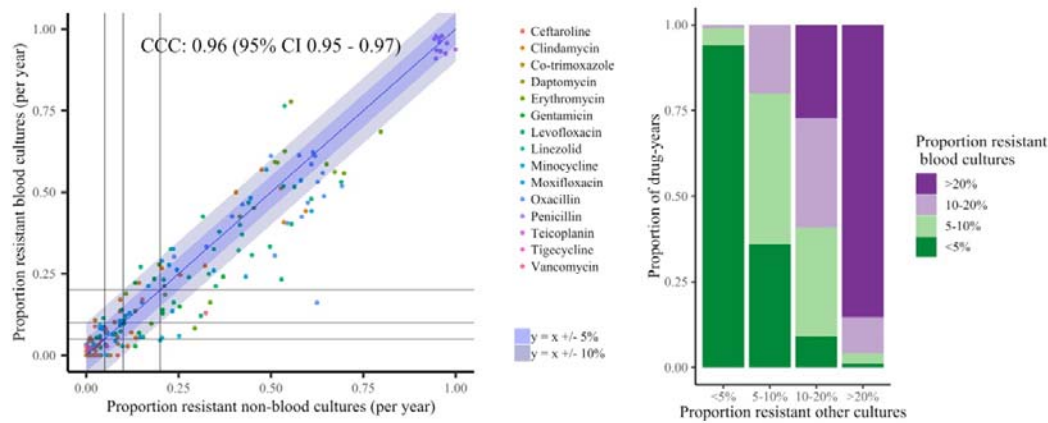584   High-income countries

585
586   Middle-income countries

587
588   *S. aureus* bloodstream infections versus non-blood
589   High-income countries

590
591

592   Middle-income countries

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594   Note: Left: Proportion resistant non-blood cultures versus proportion resistant blood cultures per year for all
595   antibiotics. Each dot reflects resistance prevalence for one antibiotic in one specific year. Line of identity, +/-
596   5% and 10% shown in blue. Lines are drawn at 0.05 (5%), 0.1 (10%) and 0.2 (20%) resistance prevalence in
597   each of blood versus non-blood cultures for ease of visualisation of agreement between clinically meaningful
598   resistance categories in these two types of samples. Right: Grouping points from left column into clinically
599   meaningful resistance categories; classifying resistance prevalence in blood cultures by the proportion in
600   urine/non-sterile site cultures.

601

602   *Figure 5 Resistance prevalence in E. coli in blood versus non-blood cultures in three*
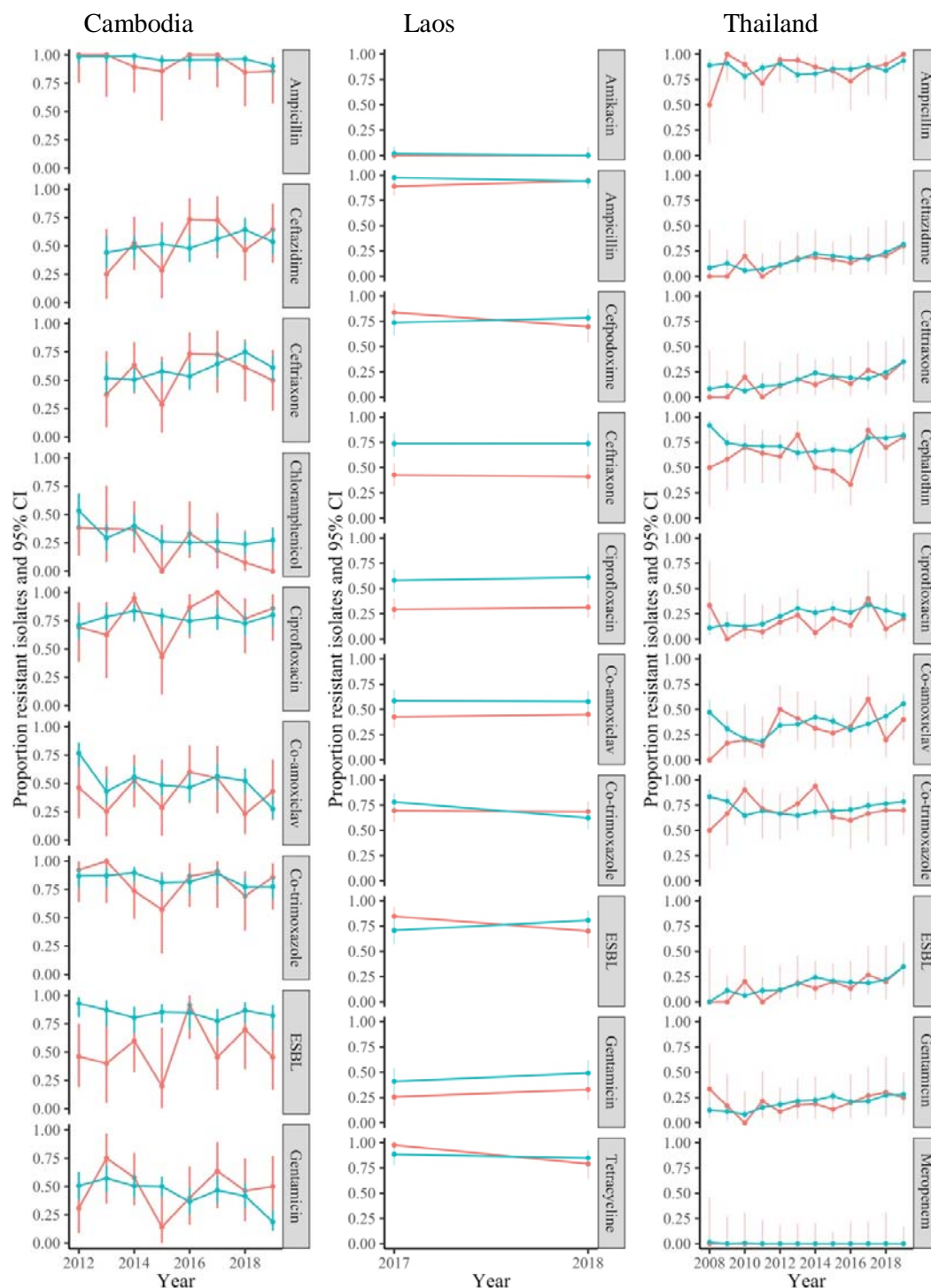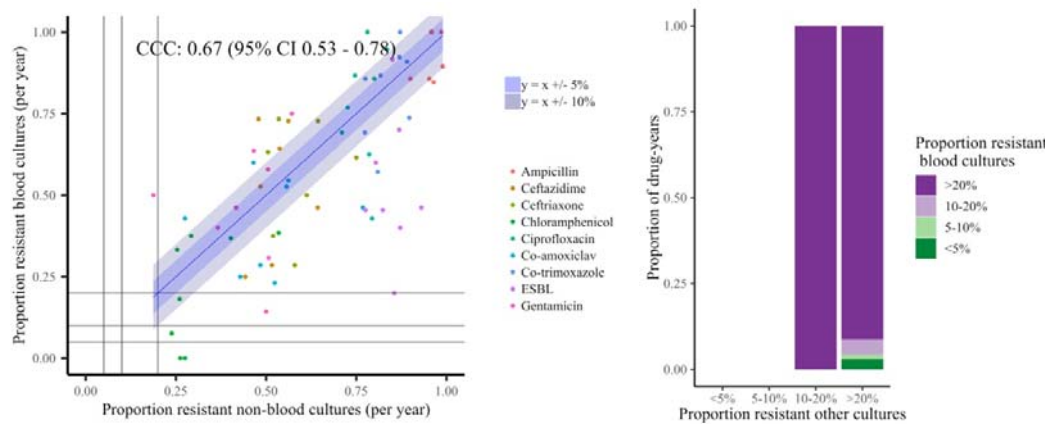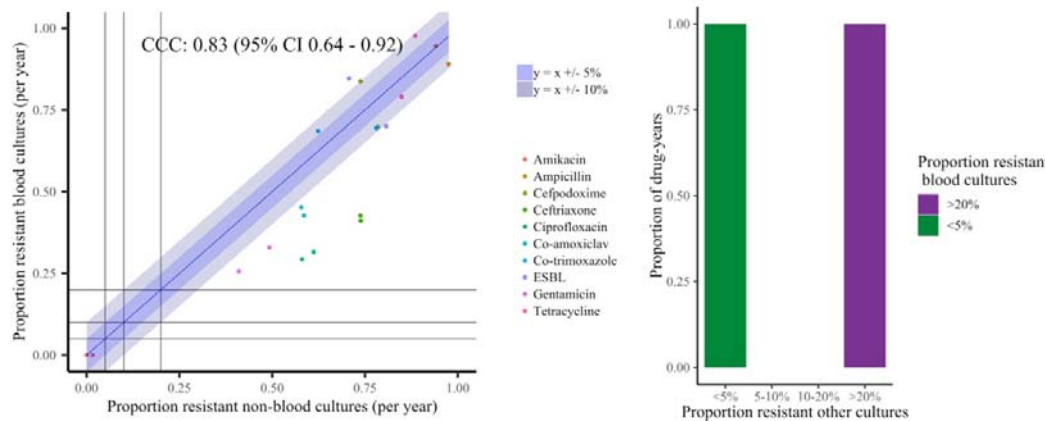603   *hospitals/programmes in LMICs*

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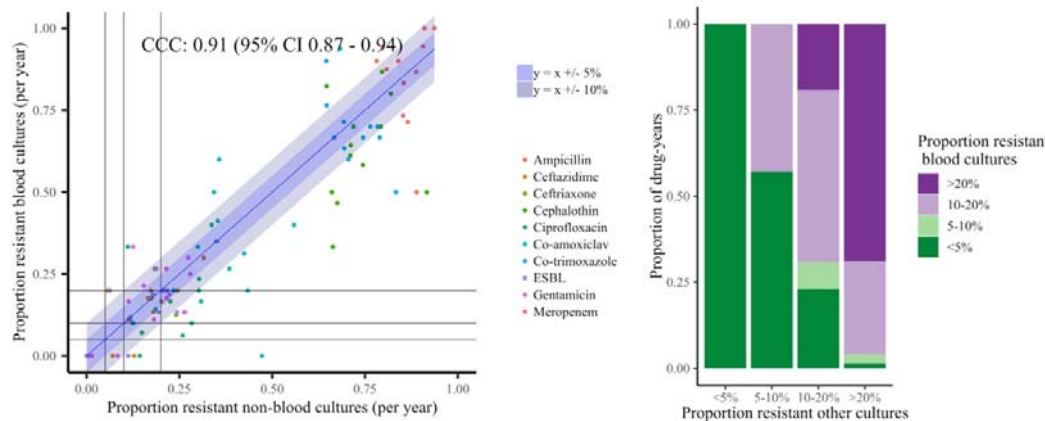607 *Figure 6 Resistance in E. coli blood and urine cultures in three hospitals/programmes in*
608 *LMICs*

609 Cambodia

610
611 Laos

612
613 Thailand

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615 Note: Left: Proportion resistant non-blood cultures versus proportion resistant blood cultures per year for all
616 antibiotics. Each dot reflects resistance prevalence for one antibiotic in one specific year, with 21 dots per
617 antibiotic (one for each year 1998-2018). Line of identity, +/- 5% and 10% shown in blue. Lines are drawn at
618 0.05 (5%), 0.1 (10%) and 0.2 (20%) resistance prevalence in each of blood versus non-blood cultures for ease of
619 visualisation of agreement between clinically meaningful resistance categories in these two types of samples.
620 Right: Grouping points from left column into clinically meaningful resistance categories; classifying resistance
621 prevalence in blood cultures by the proportion in urine/non-sterile site cultures.

622   Table 1 Resistance prevalence in blood and non-blood cultures across drug-years, Oxfordshire 1998-2018

Pathogen	Lin's concordance coefficient (95% CI)	<5% difference in prevalence	<10% difference in prevalence	Same resistance category*	One resistance category* different	Two resistance categories* different
Oxfordshire						
E. coli	0.93 (0.91-0.95)	67/132 (51%)	109/132 (83%)	83/132 (63%)	45/132 (34%)	4/132 (3%)
Klebsiella spp.	0.79 (0.69-0.85)	54/80 (68%)	79/80 (99%)	51/80 (64%)	26/80 (32%)	3/80 (4%)
S. aureus	0.97 (0.95-0.97)	140/180 (78%)	167/180 (93%)	132/180 (73%)	45/180 (25%)	3/180 (2%)
S. pneumoniae	0.78 (0.68-0.85)	63/81 (78%)	79/81 (98%)	63/81 (78%)	15/81 (19%)	3/81 (4%)
E. faecalis	0.90 (0.82-0.94)	35/36 (97%)	35/36 (97%)	34/36 (94%)	2/36 (6%)	0/36 (0%)
E. faecium	0.92 (0.77-0.97)	8/12 (67%)	9/12 (75%)	12/12 (100%)	0/12 (0%)	0/12 (0%)
ATLAS high-income countries						
E. coli	0.97 (0.96-0.97)	302/401 (75%)	376/401 (94%)	326/401 (81%)	74/401 (18%)	1/401 (0%)
S. aureus	0.99 (0.99-0.99)	140/155 (90%)	147/155 (95%)	154/155 (99%)	1/155 (1%)	0/155 (0%)
K. pneumoniae	0.89 (0.86-0.92)	135/186 (73%)	172/186 (92%)	134/186 (72%)	51/186 (27%)	1/186 (1%)
P. aeruginosa	0.89 (0.80-0.94)	27/35 (77%)	34/35 (97%)	25/35 (71%)	10/35 (29%)	0/35 (0%)
ATLAS middle-income countries						
E. coli	0.95 (0.94-0.96)	157/268 (59%)	213/268 (79%)	234/268 (87%)	31/268 (12%)	3/268 (1%)
S. aureus	0.96 (0.95-0.97)	260/344 (76%)	308/344 (90%)	289/344 (84%)	47/344 (14%)	8/344 (2%)
K. pneumoniae	0.86 (0.82-0.89)	87/228 (38%)	146/228 (64%)	170/228 (75%)	53/228 (23%)	5/228 (2%)
P. aeruginosa	0.77 (0.60-0.88)	20/36 (56%)	31/36 (86%)	32/36 (89%)	4/36 (11%)	0/36 (0%)
E. cloacae	0.96 (0.93-0.97)	31/61 (51%)	45/61 (74%)	49/61 (80%)	10/61 (16%)	2/61 (3%)
Cambodia						
E. coli	0.67 (0.53-0.78)	16/70 (23%)	27/70 (39%)	63/70 (90%)	4/70 (6%)	3/70 (4%)
S. aureus	0.97 (0.95-0.98)	22/48 (46%)	39/48 (81%)	30/48 (62%)	15/48 (31%)	3/48 (6%)
Laos						
E. coli	0.83 (0.64-0.92)	3/20 (15%)	10/20 (50%)	20/20 (100%)	0/20 (0%)	0/20 (0%)
S. aureus	0.96 (0.85-0.99)	4/10 (40%)	8/10 (80%)	7/10 (70%)	3/10 (30%)	0/10 (0%)

Pathogen	Lin's concordance coefficient (95% CI)	<5% difference in prevalence	<10% difference in prevalence	Same resistance category*	One resistance category* different	Two resistance categories* different
			Thailand			
E. coli	0.91 (0.87-0.94)	48/120 (40%)	77/120 (64%)	77/120 (64%)	34/120 (28%)	9/120 (8%)
S. aureus	0.97 (0.96-0.98)	56/84 (67%)	72/84 (86%)	55/84 (65%)	21/84 (25%)	8/84 (10%)

623   * Resistance categories are: <5%, 5-10%, 10-20%, >20%
624   Note: in the Oxfordshire dataset, non-blood cultures are urine for *E. coli* and *Klebsiella* spp., other non-sterile sites for *S. aureus* and all other body sites for other gram-
625   negatives and *S. pneumoniae*, *E. faecalis* and *E. faecium*; in the ATLAS dataset non-blood cultures are all other body sites for all pathogens; in the three hospitals from
626   LMICs non-blood cultures are urine for *E. coli* and swabs/pus for *S. aureus*

627