1 **Abstract**

2 Despite political commitment to address antimicrobial resistance (AMR), countries are facing

3 challenges to implementing policies to reduce inappropriate use of antibiotics. Critical factors to the

4 success of policy implementation in low and middle income countries, such as capacity for

5 enforcement, contestation by influential stakeholders and financial interests have been insufficiently

6 considered.

7 Using Pakistan as a case study representing a populous country with extremely high antibiotic usage,

8 we identified 195 actors who affect policies on antibiotic use in humans and animals through a

9 snowballing process, and interviewed 48 of these who were nominated as most influential. We used

10 a novel card game based methodology to investigate policy actors' support for implementation of

11 different regulatory approaches addressing actions of frontline healthcare providers and antibiotic

12 producers across the One Health spectrum.

13 We found that there was only widespread support for implementing hard regulations (prohibiting

14 certain actions) against antibiotic suppliers with little power – such as unqualified/informal healthcare

15 providers and animal feed producers – but not to target more powerful groups such as doctors,

16 farmers, and pharmaceutical companies. Policy actors had limited knowledge to develop

17 implementation plans to address inappropriate use of antibiotics in animals, even though this was

18 recognised as a critical driver of AMR.

19 Our results indicate that local political and economic dynamics may be more salient to policy actors

20 influencing implementation of AMR national action plans than solutions presented in global guidelines

21 that rely on implementation of hard regulations. This highlights a disconnect between AMR action

22 plans and the local contexts where implementation takes place. Thus if the global strategies to tackle

23 AMR are to become implementable policies in LMIC, they will need greater appreciation of the power

24 dynamics and systemic constraints that relate to many of the strategies proposed.

Background

Despite high-level political commitment to tackle antimicrobial resistance (AMR), moving from rhetoric to action is proving to be far from straightforward [1,2]. In 2015, all 194 World Health Organization (WHO) member states endorsed the Global Action Plan on AMR, and committed to developing multisectoral national action plans (NAP) – considering human, animal and environmental drivers of AMR - within two years. The reason for this heightened attention to AMR is the huge predicted impact on morbidity and mortality in humans and animals, on food production, on economic growth and on global trade and travel [1]. However, only 79 countries had an action plan by 2017, with progress notably slower in low- and middle-income countries (LMIC) [3].

AMR is an archetypal 'wicked problem' [4] that presents major challenges for policy implementation as this requires engagement of many different actors, often with conflicting interests and the power to influence policymakers [5,6]. In particular, tackling one of the major drivers of AMR – inappropriate use of antibiotics – requires actions that affect multiple sectors, including human and veterinary medicine, agriculture, and trade [7,8]; this is why a One Health approach has been proposed. Inappropriate use encompasses clinically unwarranted or inappropriate dispensing for illnesses in humans and animals or without a confirmed diagnosis, as well as overuse in farming for growth promotion and prophylaxis of infectious diseases in animal populations through medicated feed and water. This contrasts with appropriate use of antibiotics, which is defined as access to quality-assured drugs, at an effective dose and treatment duration [9], supported by evidence collected through clinical and laboratory investigation.

There is insufficient evidence about how effective different types of regulatory approaches will be in moving statements about tackling inappropriate use of antibiotics from paper to practice in LMIC. Hard regulatory approaches, which appear frequently in Global Action Plan on AMR, typically consist of binding laws or guidelines with associated penalties for failure to comply, and therefore rely on monitoring and enforcement. An example is prescription only access to antibiotics in the UK through

50   licenced pharmacists, implementation of which is supported by clear antimicrobial stewardship

51   guidelines for secondary care (Start Smart then Focus) and primary care (TARGET antimicrobial toolkit)

52   [5]. Soft regulatory approaches, in contrast, rely on voluntary compliance often supported by training

53   [10]. Researchers have highlighted that approaches relying primarily on implementation (including

54   setting, monitoring and enforcement) of hard regulations in LMIC typically fail owing to interrelated

55   constraints: insufficient resourcing of regulatory bodies, contestation of regulatory policies by private

56   stakeholders, low technical capacity or power of regulatory bodies, and insufficient political support

57   owing to vested interests [5,6]. These issues are particularly salient in relation to addressing

58   inappropriate use of antibiotics, because suppliers of antibiotics may have a stake in preventing

59   implementation of regulations that they believe would reduce use to the detriment of their financial

60   interests. For example, doctors may receive incentives from pharmaceutical companies to over-

61   prescribe specific antibiotics and may oppose antimicrobial stewardship initiatives to check this

62   behaviour [11]. The political influence of different antibiotic suppliers can be critical in determining

63   which groups domestic policymakers choose to target with interventions and whether hard or soft

64   interventions are implemented. For example, interventions that prohibit dispensing of antibiotics by

65   a small number of drug sellers may receive a different level of opposition to hard interventions that

66   constrain incentives given to doctors by pharmaceutical representatives.

67   Our study systematically identifies policy actors that influence implementation of action plans on

68   inappropriate use of antibiotics in humans and animals in one high AMR burden LMIC – Pakistan – and

69   investigates the extent to which the most influential policy actors would support implementation of

70   different regulatory approaches. We also examine the use of an innovative methodological approach

71   using a card-sorting exercise to generate richer data from interviews with policy actors.

72   ***Characterising suppliers of antibiotics in LMIC***

73   We defined suppliers as organisations or individuals who play a role in the supply of antibiotics to

74   human or animal populations. In most LMIC with fragmented health systems, there is a large and

75   diverse set of 'proximate' suppliers of antibiotics, who are directly involved in providing antibiotics to

76   patients or farmers [12]. In contrast, 'distal' suppliers are organisations that typically provide

77   antibiotics to proximate suppliers but do not have direct contact with patients or farmers. Table 1

78   shows the key characteristics of the different suppliers across the One Health spectrum. A critical step

79   in developing an AMR NAP is to identify which of these suppliers to focus on as target groups of

80   interventions to reduce inappropriate use of antibiotics.

81   ***Interventions to address inappropriate use of antibiotics***

82   Potential interventions that could be implemented to reduce inappropriate use of antibiotics by

83   different suppliers were classified into three broad categories (Table 2, [13-15]): encourage (the

84   softest option, usually positive incentives to encourage adherence to regulations or guidelines without

85   any penalties); prohibit (the hardest regulatory approach, which typically includes a complete ban on

86   certain practices with penalties for failure to comply); and constrain (less severe than a complete ban

87   as it involves restriction of access). Policymakers developing and implementing AMR action plans have

88   two linked decisions to make: which suppliers of antibiotics should be targeted as a priority in their

89   context, and what type of intervention(s) should be used.

90   **Methods**

91   ***Study setting***

92   Pakistan, the sixth most populous country in the world, is facing challenges with high levels of drug

93   resistance. This was demonstrated by a recent outbreak of multidrug-resistant *Salmonella* Typhi,

94   which affected more than 300 patients in two cities within 6 months [16] and has continued to spread.

95   Pakistan was one of the earliest LMIC to initiate development of a national AMR action plan, being

96   recognised at the World Health Assembly in 2017 for proactively engaging in the Joint External

97   Evaluation (JEE) to assess preparedness to combat health emergencies including AMR [17,18].

98   Although the country performed well on some elements of the JEE, in the self-assessment Pakistan

99   had the lowest possible score on capacity and policies to combat AMR [19]. This partly reflected weak

100   regulations to monitor and control the use of antibiotics in human and animal sectors as noted in the

101   JEE[19]. For example, even though Drug Regulatory Authority of Pakistan (DRAP) was established

102   under the DRAP Act of 2012 to provide for effective coordination and enforcement of The Drugs Act

103   1976, the Pakistan AMR National Action Plan indicates that infectious disease expertise in DRAP and

104   implementation of the aforementioned regulations is lacking [18]. Similarly, surveys indicate that

105   human antibiotic consumption is extremely high in Pakistan, and data on use are limited [18,20].

106   Challenges to implementing large-scale interventions to reduce excessive antibiotic use in Pakistan

107   include the presence of very large, well-organised dairy and poultry industries [21], and a health

108   system that is dominated by for-profit providers; as a result of the lack of provision in the public sector

109   approximately 80% of the population visit private clinics, with out-of-pocket expenditure estimated at

110   56% [22,23]. These actors providing antibiotics to human and animal populations may perceive that

111   their profits are linked to continued overuse of antibiotics and oppose the introduction of specific

112   interventions.

113   *Data collection*

114   We first conducted a snowballing exercise to identify the range of actors that could influence

115   operationalisation of government strategies to reduce inappropriate use of antibiotics in both humans

116   or animals (thus applying a One Health lens). We started with a list of 12 'seed' informants covering a

117   range of core sectors related to AMR, including infectious disease physicians, clinical microbiologists,

118   veterinarians, government policymakers working in human and animal health, civil society

119   organisations, media representatives and the pharmaceutical industry. This group included members

120   of the committee tasked with developing Pakistan's national AMR action plan. We asked informants

121   to identify people or organisations that are shaping the approach taken by the government to reduce

122   inappropriate use of antibiotics in human and animal populations in Pakistan. We contacted all

123 nominees by email or telephone and continued the snowballing process until no new actors were

124 identified.

125 During the second stage of the study, we contacted actors identified as influential (mentioned at least

126 twice during snowballing) and interviewed those who agreed to participate in the research. This is the

127 stage at which we applied our methodological innovation, which allowed us to collect rich qualitative

128 and quantitative data simultaneously. During the interview we asked actors their views on what types

129 of interventions – encourage, constrain, prohibit – they would support to address the actions of

130 specific antibiotic suppliers, explicitly focusing on antibiotic use in human health and animals. If the

131 interviewee agreed, we used a 'thinking aloud' approach in which they were asked to place cards

132 representing the suppliers listed in Table 1 on pieces of paper printed with Encourage, Constrain or

133 Prohibit to indicate what type of intervention they would propose to reduce inappropriate use of

134 antibiotics by that supplier, while talking through their thought process [24,25] (Figure 1). Details of

135 where each interviewee placed each card were noted and entered into an Excel spreadsheet. The

136 methodology was piloted in Pakistan by the research team before two researchers conducted the

137 interviews. Since we were seeking to solicit interviewees' thoughts about preferred policy options and

138 contextual factors influencing these thoughts, possible unspoken prior to the interview, we designed

139 the card-sorting task to help interviewees forget they were being recorded. We anticipated that they

140 would possibly more open about their views on recommended interventions owing to the

141 incorporation of this methodological innovation into our interviews.

142 Interviews lasted 45 to 60 minutes and were run jointly, with the aid of a semi-structured interview

143 topic guide, by two or three researchers (all female) with post-graduate level training in qualitative

144 research. The researchers had no prior relationships with the interviewees and had not conducted

145 research on this topic previously.

146 All except one interview were conducted face to face. All interviewees gave permission to record the

147 interviews. Participants were able to choose the location of the interview, which usually took place at

148   their workplace. Brief notes were taken by the researchers during the interview and these were

149   written up immediately after each interview.

Data management and analysis

151   The interviews were transcribed and translated into English (when required) before thematic analysis

152   was conducted. All authors, including a veterinarian to ensure a One Health approach during the

153   analysis, collectively identified and validated emerging themes across a sample of transcripts before a

154   line-by-line analysis was conducted by two researchers on all 48 interview transcripts, using NVivo 12

155   qualitative data analysis software (QSR International Pty Ltd. Version 12, 2018). Data from the card

156   sorting exercise were used to construct bar charts to quantitatively compare responses of actors to

157   potential interventions addressing different target groups.

158   We sought feedback on our preliminary results from interviewees and government policymakers from

159   human and animal health during two consultation workshops that took place at the National Institute

160   of Health in Islamabad and Aga Khan University in Karachi (November 2018).

161   The study was approved by the Research Ethics Committees of the Pakistan and UK-based primary

162   investigators' institutions.

163

Results

Who has influence over policy interventions to reduce antibiotic misuse?

166   195 policy actors were nominated in total during the snowballing process. The majority of these

167   worked in the field of human health (n=149), and about one quarter in animal health (n=46). The

168   pattern of nomination indicated that human health and animal health/livestock actors were typically

169   not well connected to each other.

170   Of the 195 actors, we identified 48 as 'most influential' based on the frequency of nomination being

171   greater than or equal to two (Table 3), and summarise below findings about their reactions to the

172   proposed implementation of different approaches to address inappropriate use of antibiotics by each

173   group of suppliers.

Healthcare providers supplying antibiotics to humans

175   (i)   Unqualified healthcare providers

176   The majority of interviewees who engaged in the card sorting exercise favoured strong measures

177   (prohibit or constrain) to deal with unqualified providers in the human health sector, specifically drug

178   sellers and 'unqualified doctors' (quacks; Figure 2). Those who did not favour complete banning of

179   unqualified providers suggested that these suppliers might be allowed to sell a very limited set of

180   medications such as painkillers but not 'critical drugs' such as antibiotics.

181   When arguing for constrain-type interventions some interviewees expressed reluctance to support

182   the hardest regulatory measures owing to concerns about lack of universal health access to qualified

183   providers. Two medically trained interviewees emphasised that quacks and drug sellers provide a

184   useful service in remote rural areas where there is no other access to the health system.

185   *'for quackery you not only need to provide more access for the general population to good quality*

186   *services in the public sector, but you also need to educate the masses …' [A47, International*

187   *agency].*

188   (ii)   Qualified doctors

189   In contrast, when asked about measures to address inappropriate prescribing of antibiotics by

190   qualified doctors, interviewees favoured softer measures (encourage) such as update training or

191   awareness raising and systems to track prescribing practices to increase transparency. There was a

192   commonly held view that doctors were 'doing their best', sometimes with limited diagnostic (and

193   other) resources. A range of interviewees highlighted that the lack of resources to guide diagnosis and

194   decision-making was compounded by inadequacies in medical education; two senior medical

195   professionals asserted that doctors in Pakistan often practise medicine in a way that reflects gaps and

196   a need to strengthen training: 'you know, unfortunately, I even call the doctors quacks […] because

197   the way they prescribe is like quacks' [A18, Human health government official].

198   However, not all interviewees favoured a soft approach to doctors. Several focused on the 'unethical'

199   relationship between pharmaceutical companies and medical professionals. They argued that stricter

200   regulation was required to constrain the incentives provided by these companies that encourage

201   doctors to prescribe antibiotics.

202   Interviewees from the public human health sector and the domestic pharmaceutical industry were

203   more reluctant to support constraints on doctor-pharmaceutical company relations than other actors

204   such as those representing international agencies and non-profit organisations, perhaps reflecting

205   their own interests. The Pakistan Medical Association and the Pakistan Medical and Dental Council

206   were identified by interviewees as having the potential to play a stronger role in improving antibiotic

207   use by doctors.

208   (iii)   Pharmacies and drug shops

209   It was widely felt that private pharmacies, with a qualified pharmacist needed to be encouraged, to

210   support qualified pharmacists in taking over jobs from untrained drug sellers, and that strict

211   enforcement measures were required to prevent antibiotic dispensing without an appropriate

212   prescription. Over-the-counter sale of antibiotics was mentioned frequently as a key issue to be

213   addressed through 'constrain' interventions. It was suggested that pharmacists could monitor what

214   doctors were prescribing and discuss any discrepancies with them.

215   ***Providers supplying antibiotics to livestock***

216   When discussing suppliers in the animal health or livestock sectors, a large proportion of interviewees

217   declined to comment due to a perceived lack of expertise.

218   (i)   Veterinarians

219   Among those who did express a view, veterinarians were commonly perceived to be responsible users

220   of antibiotics and thus as needing to be supported with 'encourage' measures that would allow them

221   to play a larger role in controlling use of antibiotics in animals (Figure 3). The current limited role of

222   veterinarians in Pakistan was explained by interviewees to be related to farmers' tendency to avoid

223   the expense of paying for a veterinary consultation and instead going directly to pharmacies to buy

224   antibiotics without a prescription.

225   (ii)   Farmers

226   Opinions on measures to tackle self-prescription of antibiotics by farmers were divided, mainly

227   between 'encourage' and 'constrain' approaches. Approximately half of those who responded opted

228   for encourage measures based on educating farmers to be able to diagnose and treat their animals

229   (without veterinary input) more effectively. This group of interviewees asserted that harder measures

230   to prohibit self-prescribing by farmers would not be feasible given how common it is, and instead

231   better use of antibiotics by farmers should be facilitated:

232   *'There are huge numbers of farmers and breeders […] they get all these antibiotics [..] so just*

233   *prohibit or constrain would not be that much important here […] they should be encouraged*

234   *and educated not to use antibiotics, just to give them when needed' [A11, Animal health*

235   *government official].*

236   Others felt that stronger regulations were needed to prevent overuse of antibiotics, particularly in the

237   poultry sector, where farmers were believed to administer large quantities of antibiotics to bird

238   populations via medicated feed]. Several interviewees indicated that the poultry industry is hard to

239 regulate due to its economic power, professional organisation, and the fact that some large poultry

240 farms are owned by politicians [A11 and A12, Animal health government official; A52, Human health

241 government official].

242   (iii)   Animal feed producers

243 There was greater support for stronger measures to address use of antibiotics by animal feed

244 producers than farmers, with some interviewees expressing concern about the lack of implementation

245 of regulations by the government:

246   *'In the animal feed mills the government should check the ingredients... they [animal feed*

247   *producers] are using different drugs and also they are using chemicals in the feed' [A40, Domestic*

248   *non-profit organisation].*

249   (iv)   Animal drug shops and pharmacies

250 Interviewees commonly stated that shops selling animal drugs need to be regulated and monitored,

251 and that over-the-counter sales without a prescription should be prohibited. Informal drug sellers,

252 without a qualified pharmacist, were recognised as a major issue in the animal as well as the human

253 health sector and most interviewees who responded stated that they should be prohibited from

254 selling antibiotics:

255   *'[informal drug sellers] need strict legislation about prohibition because these things should*

256   *not exist in the first place… this is a big problem in both humans and animals' [A11, Animal*

257   *health government official].*

258 The support for stringent measures to reduce inappropriate access to antibiotics for animals through

259 pharmacies and drug sellers contrasted with commonly expressed reluctance to limit access to

260 antibiotics for farmers. Larger farmers purchase antibiotics directly from pharmaceutical companies

261 or drug ingredient wholesalers, and therefore prohibition of over-the-counter animal antibiotic sale

262 by pharmacies would largely impact small-sized farmers.

263 ***Distal suppliers of antibiotics***

264   (i)   Supplier of raw materials for pharmaceutical products

265 There was a general consensus that companies involved in the supply of raw materials for

266 manufacture or packaging of antibiotics in Pakistan should be constrained (to meet minimum quality

267 standards) or prohibited (if supplying substandard raw materials) (Figure 4). Our interviews indicated

268 that it is common practice for pharmaceutical companies to import raw materials and package drugs

269 for sale in Pakistan. An international agency representative explained that import of raw materials

270 typically involves a bidding process that selects companies that can supply raw materials at the lowest

271 price, irrespective of quality. The same interviewee suggested that the government should enforce a

272 minimum quality standard on suppliers of raw materials that are imported into Pakistan. In general,

273 quality control was considered an issue both in the animal and human health sectors:

274   *'We must do something to them, to stop, to prohibit... to stop them preparing compromised*

275   *drug[s], which are not quality controlled so I think legislation should be very strict about the drug*

276   *ingredient'* [A22, Senior doctor]

277   (ii)   Pharmaceutical companies

278 The pharmaceutical industry was mentioned frequently as a key actor both in driving inappropriate

279 use of antibiotics, particularly through using bribes to doctors as a standard practice, and having the

280 opportunity to affect positive change. Most interviewees chose encourage, constrain or a mixture of

281 the two to address the role of the pharmaceutical industry and were reluctant to opt for harder

282 measures:

283   *'In general encouraging them [pharmaceutical companies] I think, or saying what are best*

284   *practices, rather than saying 'you get kickbacks because you do such and such'* [A16, Senior

285   doctor].

286 Interviewees indicated that the limited resources available to the DRAP when compared to those

287 available to the pharmaceutical industry mean implementation of more stringent measures are

288 unlikely to be effective. Specifically, it was highlighted that resources available to pharmaceutical

289 companies could be used to influence doctors' prescribing behaviour through sponsorship of

290 continuing medical education and financial incentives offered in return for prescription of their

291 proprietary medicines, as well as to bribe officers responsible for enforcing rules. In this context, DRAP

292 was considered necessary to implement measures to address both quality issues and inappropriate

293 marketing practices by pharmaceutical companies, but was commonly described as ineffectual,

294 understaffed, and open to influence in its current form:

295 *'DRAP […] are lacking in human resources. One person, one drug inspector in the whole district,*

296 *maybe looking after two to three districts. How can he manage?'* [A35, Human health

297 government official].

298 Some actors were bolder in suggesting that marketing practices of sales representatives giving

299 financial incentives to doctors, pharmacies or drug sellers to overuse specific antibiotics should be

300 prohibited.

301 Differences between the domestic and international pharmaceutical industries were also noted in the

302 qualitative analysis. Many interviewees perceived international companies to be better regulated than

303 domestic companies and more likely to be following international guidelines on marketing practices

304 and internal drug quality controls (e.g. bar coding) to enable better detection of counterfeit drugs. In

305 contrast, there was a common feeling that domestic companies were often not following ethical

306 marketing practices, largely because they do not have to abide by the standards that international

307 companies have signed up to in recent years.

Discussion

This study used a novel approach to systematically investigate support (or lack thereof) for different interventions to reduce inappropriate use of antibiotics among actors who can influence implementation of policies in Pakistan, applying a One Health lens by including eligible human and animal health actors in our study. Our findings are novel, timely, and policy-relevant as the majority of countries report that they are still to develop a strategy to operationalise their AMR NAPs [3], and there is limited attention given to supporting countries in navigating major political and economic barriers to implementing actions that potentially reduce the use of antibiotics [5,8,9]. Existing literature documents a gap in evidence about the types of interventions that might be locally appropriate in LMIC [26] and about strategies to tackle 'local barriers' [11]; our findings address this gap in evidence for Pakistan, and have implications for other LMIC developing AMR action plans.

Although enactment and enforcement of regulations has been advocated as an important approach to tackle inappropriate use of antibiotics, many interviewees suggested that doctors and the pharmaceutical and livestock industries may be too powerful for government agencies to enforce rules on; the latter were presented as under-resourced, poorly organised, and lacking in authority to implement the existing regulations, which is similar to the status of regulatory bodies in many LMIC [22]. Instead, interviewees expressed support for awareness-raising interventions to address inappropriate prescribing by doctors and farmers, which was acknowledged as a serious issue. Although resource constraints of regulatory agencies were certainly salient in the Pakistani context, some interviewees working outside government agencies highlighted that vested interests connecting politicians and health policymakers with the pharmaceutical and livestock industries may also explain the reluctance to support harder regulatory approaches. The tendency to take a softer approach based around awareness raising for doctors, as demonstrated by the placement of cards in the card-sorting exercise and/or comments in interviews, may also reflect the composition of interviewees who were mostly medically trained. However, evidence of a substantial and sustained impact on antibiotic

333   prescribing by doctors in LMIC owing to soft interventions that encourage responsible use is currently

334   lacking [26]. It is important to consider that there is a lack of evidence of a substantial and sustained

335   impact of awareness campaigns on sustained impact on prescribing practices in LMIC, even though

336   this is often a politically palatable intervention [26]. In contexts such as Pakistan where doctors rely

337   on continuing medical education sponsored by pharmaceutical companies, awareness campaigns

338   alone are unlikely to be effective [27,28].

339   Out study identified a number of interventions for which there was widespread support from

340   interviewees across different stakeholder groups, and these could be prioritised as strategies to

341   address AMR in Pakistan. Among these were prohibition of untrained doctors and unlicensed drug

342   sellers from providing healthcare services. However, several interviewees highlighted that a major

343   impediment to implementing a complete ban on unqualified healthcare providers is the lack of public

344   health services, particularly in rural areas of the country, and therefore preferred to constrain the

345   types of services provided or to provide basic training to unqualified providers. Our thinking aloud

346   interviews revealed that this was a major concern for some civil society organisation representatives.

347   Geographical differences in the distribution of qualified or licenced providers is a well-documented

348   issue in Pakistan [22,23] and other countries in the region, rendering groups of the population

349   dependent on unqualified healthcare providers who tend to inappropriately use antibiotics [29,30].

350   Our findings from Pakistan indicate that although there is impetus to prevent untrained providers

351   from operating, a sizeable group of actors may not support a full ban owing to concerns about the

352   government's ability to provide health services [31].

353   Pharmacists and veterinarians were identified two groups that could be empowered to play a bigger

354   role in ensuring appropriate access, with many interviewees expressing concern that these are often

355   bypassed by patients and farmers in favour of unqualified drug sellers and self-medication, resulting

356   in this cadre of health professionals being devalued in Pakistan.

357   A striking finding from the card-sorting exercise was that many that many policy actors, owing to their

358   human healthcare background, did not feel knowledgeable enough to discuss interventions targeting

359   suppliers of antibiotics to animals and that actors with animal health expertise were lacking in

360   regulatory agencies such as DRAP; this may hinder implementation of effective strategies to address

361   inappropriate use of antibiotic use in animals, despite commitments to applying a One Health

362   approach by international agencies [3]. Other studies have also reported a (perceived) imbalance in

363   power and representation between human and animal health stakeholders [32].

364   We developed and applied a novel method, which benefitted from an initial network analysis that

365   enabled us to systematically identify actors that were perceived to be most influential, combined with

366   an innovative card sorting exercise that aimed to facilitate open discussion by policy elites during

367   interviews [33]. There were two main advantages of our novel methodology. First, the card-sorting

368   exercise enabled the interviewer and interviewee to follow a more systematic approach to discussing

369   each supplier of antibiotics one by one. Even if some interviewees were unable to comment on the

370   role of a particular supplier, the card-sorting exercise allowed this finding to be captured explicitly.

371   This helped to reveal that many of the influential policy actors did not feel knowledgeable to comment

372   on interventions addressing antibiotic use in the livestock sector. Second, the card sorting exercise

373   allowed us to gain information based on where interviewees placed cards (along the spectrum of hard

374   to soft interventions) even if they did not fully verbalise their rationale.

375   Reflecting on the value of the card sorting exercise in generating richer qualitative data, we felt that

376   it did help to initiate dialogue, but it was time-consuming, so some of the interviewees were not able

377   to complete the exercise. Although the majority of interviewees spoke openly about their support or

378   opposition for different types of interventions some respondents involved in the implementation of

379   regulations stated that they were reticent to speak freely while being recorded. In terms of limitations,

380   this study was conducted in one country, Pakistan, and findings may not be representative of other

381   LMIC. However, we have successfully adapted and applied the novel methodology in Cambodia and

382   Indonesia. In the Cambodian study we reduced the number of cards used, in order to shorten the time

383   taken, and had cards representing different types of healthcare providers (formal and informal) to

384   understand policy actors' support for interventions to reduce inappropriate use of antibiotics

385   targeting each type of healthcare provider [34]. In terms of future work, evidence from this study

386   about political support for specific interventions targeting individual antibiotic supplier groups could

387   be coupled with quantitative epidemiological studies of the likely impact on overall inappropriate

388   antibiotic misuse from these interventions to design evidence-based and politically acceptable policies

389   to operationalise the national AMR action plan. We found that our methodological innovation could

390   easily be adapted to study policy actors' views on interventions to address inappropriate use of

391   antibiotics, and we would encourage application of the novel method to study other wicked problems

392   such as tobacco control or regulation of medical education in LMIC contexts.

393   **Conclusion**

394   Our study provides new insights about challenges to implementing hard regulatory approaches to

395   address inappropriate use of antibiotics in LMIC with weak governance structures, and additionally

396   developed a new methodology that can be applied to support policy research in other countries. In

397   Pakistan we found that measures to prohibit untrained drug sellers and untrained doctors were clearly

398   more palatable to influential policy actors than implementation of strong regulations targeting groups

399   perceived to be powerful such as (qualified) doctors, pharmaceutical companies and the livestock

400   industry. Hard regulatory approaches – such as prescription-only access to antibiotics or banning of

401   growth promoters in livestock – were considered 'technical' solutions which do not take account of

402   the political opposition these may face.

403   These findings have implications for other countries developing AMR NAP as they highlight the need

404   for a clear understanding of socio-economic context, policy processes and underlying interests and

405   power [33]. We conclude that in each country prioritising development of a NAP, an analysis of the

406   key stakeholders and their interests is a prerequisite step for global health actors wishing to support

407 national efforts to tackle AMR. Such an analysis will enable development of more effective strategies

408 that that will incorporate a greater appreciation of the power dynamics and systemic constraints that

409 relate to many of the strategies proposed. Ultimately, if ambitious global strategies to tackle AMR,

410 such as the Global Action Plan on AMR, are to become implementable in LMIC, they will need to strike

411 a balance between technically ideal solutions and options that are feasible to implement.

412 **List of abbreviations:** AMR: Antimicrobial resistance; DRAP: Drug Regulatory Authority of Pakistan;

413 JEE: Joint External Evaluation; LMIC: Low and middle income countries; NAP: National Acton Plan;

414 WHO: World Health Organization.

415

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