

1 **Antimicrobial resistance dynamics and the one-health strategy: a review**

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11 **Abstract**

12 Antimicrobial resistance is a global threat that kills at least 75,000 people every year
13 worldwide and causes extended hospital stays. In coming 10 years, it is projected to have
14 huge health and economic burden on countries and the scarcity of available antibiotics
15 further worsens the situation. It is a result of many confounding factors that ranges from
16 indiscriminate antibiotic usage in humans, animals and agriculture and the rapid rate of
17 emergence and dissemination of the resistant pathogens. This menace is challenging
18 and urgent attention at many fronts such as antibiotic stewardship, strict regulations over
19 antibiotics usage, large-scale surveillance and responsible public behavior. This
20 demands international cooperation and integrated efforts under 'One-health' approach to
21 effectively mitigate the issue of antimicrobial resistance.

22 Here, we review the multifaceted nature of antimicrobial resistance and usefulness of the
23 'One-Health' approach to curb the origin and spread of antimicrobial resistance. The role
24 of antibiotics and antimicrobial resistance has been discussed with examples citing the
25 historical mistake of using antibiotics common between animal and humans. This
26 generated resistance against last-resort antibiotics and multiplier effects against related
27 classes of antibiotics. We highlight the effectiveness of hygiene in livestock rearing,
28 careful antibiotic usage and large-scale surveillance of animals, humans and environment
29 domains for understanding the emergence and spread of antimicrobial resistance.

30 Further, we focus on the steps taken for mitigation of antimicrobial resistance that
31 includes public awareness led successful ban of triclosan and the significant decrease in
32 resistant pathogens due to strict antibiotic stewardship. We emphasize the positive role
33 of inter-continental partnership such as Global Antibiotic Resistance Partnership and

34 international collaboration for high-throughput surveillance and continuous data
35 exchange for effective regulation of antimicrobial resistance. The last section underscores
36 the need for bringing all the mitigation steps proposed in the earlier sections under an
37 integrated approach called as One-health. 'One-Health' is a holistic and integrative
38 approach that can help in effective participation of stakeholders from public, health care
39 professionals and government to mitigate antimicrobial resistance. This is essential for
40 effective control and structured framework to tackle the issue of antimicrobial resistance.

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44 **Keywords**

45 antimicrobial resistance, one-health, antibiotics and agriculture, animal health, horizontal
46 gene transfer, environmental surveillance.

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51 **Abbreviations**

52 qnr : Quinolone resistance Gene

53 bla : Beta-Lactamase Gene

54 mec : Methicillin resistance gene

55 sul : dihydropteroate synthase gene for sulfonamide resistance

56 UN-FAO : United Nations Food and Agricultural Organization

57 GARP : Global Antibiotic Resistance Partnership

58 INSAR-India : Indian Network for Surveillance of Antimicrobial Resistance-India

59 NARMS-USA : National Antimicrobial Resistance Monitoring System-USA

60 ESAC-EU : European Surveillance of Antimicrobial Consumption-EU

61 SASCM-SA : South African Society for Clinical Microbiology-South Africa

62 PAHO : Pan American Health Organization

63 EARS-Net : European Resistance Surveillance Network

64 GLASS-WHO : Global Antimicrobial Resistance Surveillance System-WHO

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74 **1 Introduction**

75 There have been many stages of discovery and development in the knowledge and status
76 of antibiotics usage and menace of antimicrobial resistance. After the initial discovery of
77 Penicillin in 1928, many new antibiotics were found through intense industrial research
78 during 1950-1970. However, regulatory constraints, long development phase, accruing
79 financial inputs dampened the pharmaceutical interest into new antibiotics and fewer
80 antibiotics were developed after the mid-1980s (Spellberg & Gilbert, 2014).

81 On the other hand, indiscriminate antibiotics usage led to pollution by antibiotics and/or
82 their residues across all niches such as food, soil, aquatic water bodies and sewage (Shi
83 et al., 2020). These antibiotics originate from hotspots such as hospitals, pharmaceutical
84 units, agricultural setups and livestock farms. High antibiotic concentration is linked to
85 antimicrobial resistance often through horizontal gene transfer of antibiotic resistance
86 determinants such as genes, transposons, integrons, etc in deadly pathogens such as
87 *Acinetobacter baumannii* (Gillings, 2013); (Rodgers et al., 2019). Many such microbes
88 pass through overlapping ecological niches between humans, animals and environment,
89 thereby gaining resistance at even faster rate. Rapid emergence of resistant clinical
90 pathogens is an imminent threat to public health and 2.4 million people are predicted to
91 die due to antimicrobial resistance in Europe, North America and Australia over next 30
92 years (Bianco et al., 2020).

93 Improved international mobility, immigration and economic exchange further leads to
94 intercontinental distribution of resistant microbial phenotypes (Church, 2004). Since 1950,
95 many studies have reported increasing incidences of antimicrobial resistance (Davies &
96 Davies, 2010) and WHO has advocated research and antibiotics usage as per guidelines

97 (WHO, 2016). Subsequent research and attention to pharmaceutical neglect towards new
98 antibiotics has been recognized and efforts are directed towards aiding new antibiotic
99 development and understanding the antimicrobial resistance landscape between
100 animals, humans and the environment.

101 The interconnections and microbial exchange between ecological niches involving
102 humans, animals and poultry, agriculture, environment and wastewater (sewage) cannot
103 be neglected. This is frequently underscored by recognition of animal carriers and
104 zoonotic sources during disease outbreaks (He et al., 2021). This scenario calls for
105 adoption of a powerful emerging concept called 'One Health'. It refers to a collaborative,
106 inter-disciplinary, and multi-domain approach of actions applied at local, national and
107 inter-national scale. This collaborative approach needs to be implemented for
108 antimicrobial resistance to tackle the omnipresence of drug resistant microbes (Fisman &
109 Laupland, 2010). The underlying principles of 'One Health' help to achieve long term
110 sustainability by strengthening human-animal bonds, providing safe food and water,
111 sustainable agricultural practices, surveillance of disease, antimicrobial resistance and
112 environment, alignment of government policies and regulations for efficient
113 communication and global outreach. Direct outcomes of this 'One Health' approach would
114 be interdisciplinary solutions emanating from strategic education, training, prevention,
115 diagnosis and novel therapies against antimicrobial resistance (Figure 1). The issue of
116 antimicrobial resistance can only be dealt through knowledge and multi-thronged
117 mitigation approaches and thus we discuss the overlapping landscape of antimicrobial
118 resistance and stakeholders in this review. This article is an abridged version of the book

119 chapter on antimicrobial resistance and One-health by Singh et al (K. S. Singh et al.,
120 2020).

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123 **Figure 1:** One-Health paradigm and stakeholders. 'One-health' refers to integrative
124 strategies in design and implementation of legislation, policies and research, which
125 facilitates communication between multiple sectors to achieve better solutions for public
126 health. This holistic approach can aid in integration of information from different
127 stakeholders such as regulatory agencies, economists, consumers and other contributors
128 to provide sustainable solutions against antimicrobial resistance.

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132 **2 Antibiotics and antimicrobial resistance**

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134 **2.1 Antibiotics in Humans, Veterinary and Agriculture**

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136 Various antibiotics are used for the treatment of infections in humans and animals. Some
137 of these antibiotics could be used in both animals and humans, whereas due to toxicity
138 and/or different incidences of infection in humans, some of them are restricted only for
139 use in animals (Church, 2004); (Davies & Davies, 2010); (Van Boeckel et al., 2015). Non-
140 therapeutic usage of antibiotics has been found disproportionately more in animals,
141 especially farm animals, as compared to humans because the antibiotics are added in

142 their water and/or feed to prevent them from various infections (Cully, 2014); (Van
143 Boeckel et al., 2015). In farm animals, antibiotics are also used at sub-therapeutic levels
144 as a growth enhancer (Landers et al., 2012) (Chattopadhyay, 2014), a procedure called
145 'metaphylaxis' (Butaye et al., 2003). The period of metaphylaxis may range from 2 weeks
146 to throughout the life of animals and increases their growth rate by up to 10% (WHO,
147 2003). All such activities lead to the direct or indirect leakage of antibiotics in the
148 environment and possess extreme threats to the human population.

149 What makes it more adverse is that certain antibiotics used on farm animals are reserved
150 for human usage to treat terminal infection or infections caused by multi drug-resistant
151 pathogens (MDR) (WHO, 2016). MDR pathogens have intrinsic resistance against many
152 antibiotics and they extensive usage of antibiotics increase their number in the farm
153 waste, thereby creating more number of microbes showing resistance against more than
154 one antibiotic (Tacconelli et al., 2018). According to a report published in the US, it is
155 been estimated that a large group of people may get affected by fluoroquinolone resistant
156 *Campylobacter* infections via chicken (Food and Drug Administration, 2000). It has been
157 reported from Canada and Europe, that poor hygiene and sanitation conditions lead to
158 excessive use of antibiotics (Health Canada, 2014; European Union, 2015). Without
159 compromising on economic front, antibiotic usage can be reduced largely by ensuring
160 hygiene and routine vaccination (World Health Organization, 2003; Tang et al. 2019).
161 Under the guidelines of WHO, many countries have started good practices in their farm
162 animals and have prohibited the use of certain antibiotics in their countries (Food and
163 Drug Administration, 2013; Health Canada, 2014; European Union, 2015).

164 The risks associated with metaphylaxis of common classes of antibiotics used between
165 humans and animals is clearly evident for third generation antibiotics such as
166 cephalosporins (WHO, 2016). Upon widespread metaphylaxis of cephalosporins in
167 animals, resistance across all cephalosporin antibiotics developed and spread to human
168 pathogens. Now, it has been reported that the cephalosporin dosage had to be increased
169 in humans as compared to animals (Food and Drug Administration, 2012) and two genes,
170 extended-spectrum beta lactamases (ESBLs) and AmpC, which both confer resistance
171 against these antibiotics, have been found on the bacterial plasmids in a highly mobile
172 genomic region (European Medicines Agency, 2009). ESBLs are a group of highly mobile
173 antibiotic resistance genes providing resistance against beta-lactem group of antibiotics
174 and it poses major health risk to humans (Rawat & Nair, 2010). Resistance in one class
175 of antibiotics can also result in emergence of resistance against other antibiotics due to
176 co-transfer of resistance genes, owing to their proximity in the genome, through plasmids.
177 One such example are the carbapenems, against which common human pathogens like
178 *E. coli*, *Salmonella* spp. and *K. pneumoniae* have gained co-resistance after overuse of
179 cephalosporins (Nordmann, 2014). Many studies have found similar ESBL-containing *E.*
180 *coli* strains between animal, food and humans (Tadesse et al., 2017); (Odsbu et al., 2018)
181 Rizzo, Horwich-Scholefield, and Epsom 2019). The mode of dissemination of resistance
182 genes between animals and humans has also been found to be through plasmids (de
183 Been et al., 2014). Thus, excessive use of these antibiotics as metaphylaxis further
184 aggravates the problem of resistant microbes in the environment (Canadian Integrated
185 Program for Antimicrobial Resistance, 2008) and urgently needs to be regulated. Many
186 studies done in Japan, Denmark and Canada have shown the positive impact on the

187 reduction of cephalosporin resistant microbes in food animals if it is not being used (Hiki
188 et al. 2015) and a similar pattern was observed with the usage of fluoroquinolones in
189 Australia (Nelson et al., 2007); (Rusu et al., 2015).

190 With the emergence of many multi-drug resistant pathogens, the effectiveness of many
191 general use antibiotics has largely reduced. Thus, certain antibiotics with high side effects
192 in humans, such as colistin, are now being approved as last resort antibiotics against
193 resistant pathogens. Colistin was only limited for metaphylaxis in food animals and thus
194 high levels were being used. Its overuse in food animals led to many colistin resistant
195 pathogens and reports of horizontal transfer of colistin resistance gene (*mcr-1*) via
196 plasmid (Liu et al., 2016) prompted the regulatory agencies of many countries to reduce
197 colistin administration in food animals. Likewise, the extensive use of avoparcin, a
198 glycopeptide antimicrobial, in food animals (Aarestrup et al., 1996) has created the
199 problem for other candidates of the glycopeptide class of antibiotics. One such case is
200 vancomycin (also a glycopeptide antibiotic), which is being used in case of multi-drug
201 resistance and is now facing the problem of losing its effectiveness on humans as well as
202 animals (S. S. Tang, Apisarnthanarak, and Hsu 2014). Altogether, careful regulations
203 need to be put in place for the use of veterinary antibiotics especially when they are highly
204 potent and widespread surveillance of antibiotic seepage into the environment needs to
205 be done.

206 **2.2 Antimicrobial resistance, bacteriophages, animals and public health**

207 The indiscriminate use of antibiotics has led to the increased prevalence of antibiotic
208 resistance genes among pathogens (Figure 2). In livestock, antibiotics are said to

209 stimulate overall body development by improving digestion or preventing bacterial
210 infections. This is postulated to be caused by suppression of unwanted intestinal bacteria
211 which otherwise will cause infections leading to release of certain cytokines which
212 reduces muscle mass (Liao & Nyachoti, 2017); (Gonzalez Ronquillo & Angeles
213 Hernandez, 2017). In pork industry, China's use of the antibiotics for growth is four times
214 higher than the US (Cully, 2014). Since antibiotics are often used for metaphylaxis in high
215 levels, but they are poorly absorbed in the animal body. Most of the antibiotics are
216 excreted in feces which leads to emergence of resistant bacteria in the animal manure.
217 In accordance, Denmark and the European Union have forbidden the use of 11 antibiotics
218 since 1995, causing a decrease of up to 50% in antibiotic resistance (Hollis & Ahmed,
219 2013).

220 It has been observed that manure enhances antibiotic genes transfer to bacteria infecting
221 human populations and even exposes soil to it, causing a build-up of antibiotic-resistant
222 genes in the environment (Zhu et al., 2013); (Pruden et al., 2012). These antibiotics along
223 with metals used in livestock feed such as Cu, Zn, As, Cr, Cd, Pb, , further generate a
224 co-selection pressure on bacterial populations by hindering their growth and are positively
225 correlated with antibiotic resistance genes (*suIA* and *suIII*) (Baker-Austin et al., 2006);
226 (Zhang et al., 2012) ; (Seiler & Berendonk, 2012). Even the unculturable portion of the
227 microbiome of niches potentially houses antibiotic resistant genes (Enne et al., 2008) ;
228 (Zhu et al., 2013) and is speculated to act as sink for them. Further, it has been noted
229 that human waste processed in sewage treatment plants results in less frequent
230 antimicrobial resistance than untreated animal waste (Di Cesare et al., 2016).

231 Bacteriophages (bacteria-killing viruses) are an often ignored but important player in the
232 antimicrobial resistance landscape. They carry many antibiotic resistance genes and they
233 can mobilize these genes similar to plasmids and integrons through horizontal gene
234 transfer (Brabban et al., 2005). Phage-mediated transfer of resistance genes has been
235 found responsible for conferring resistance against ampicillin in *Escherichia coli*
236 (Colomer-Lluch et al., 2011), multiple drugs in *Salmonella enterica* (Schmieger &
237 Schicklmaier, 1999) and *Pseudomonas aeruginosa* (Blahová et al., 2000). Their attribute
238 as vectors for gene transfer has been reported from many niches including sewage, which
239 also has high numbers of resistant microbes and genes (*qnrS*, *bla*_{TEM}, *bla*_{CTX-M}, *bla*_{SHV},
240 *mecA*, *sul1*) conferring multi drug resistance (Colomer-Lluch et al., 2011); (Marti et al.,
241 2014); (Calero-Cáceres & Muniesa, 2016). More research needs to be done on the extent
242 of involvement of phages, but their omnipresence and high capacity for gene mobilization
243 between microbes make them important in animal, human and environmental niches.

244 Another interesting study argues that street food indirectly exposes humans to antibiotics
245 (Campos et al., 2015), owing to compromising practices in hygiene. This also relates to
246 storage and purchase of raw materials from farms using cheaper farm practices,
247 unregulated antibiotic use and diseased animals with high antibiotic levels (Pham Kim et
248 al., 2013). One striking example of feed is the use of poultry litter as protein supplement
249 for farm animals in South Africa, which is often contaminated with residues of antibiotics
250 to which the poultry was exposed (Soto, 2013). Food from animal origin can carry major
251 proportions of antibiotic resistant bacteria with about 47% of resistant *Salmonella* being
252 isolated from meat and milk in Ethiopia (Ejo et al., 2016) and 14% of resistant *E. coli*
253 isolated from chicken, milk and eggs in India (Laxminarayan & Chaudhury, 2016).

254 Unregulated antibiotic use can cause emergence of resistant pathogens like *Salmonella*
255 spp., *Enterococcus* spp., *Yersinia enterocolitica*, *Listeria monocytogenes*,
256 *Staphylococcus* spp. and many more (Phillips et al., 2004) which generally have higher
257 recombination frequency and gene transfer ability thus indicating fecal, soil and water
258 contamination. Also the lack of quick and effective antibiotic resistance detection
259 techniques, complex patterns of exchange of antibiotic resistance genes, unreliable
260 prediction tools to understand the consequences of human mortality and morbidity, and
261 fluctuating costs of care are associated with infections induced by such pathogens
262 (Wegener, 2012).

263

264 **Figure 2:** Inter-connectedness and transferability between the different niches. Many
265 routes of transmission exist for exchange of antimicrobial resistance determinants such
266 as antibiotic resistance genes (ARGs) between animals, humans and the environment.
267 Anthropogenic activities remain at the center of all major activities related to antimicrobial
268 resistance.

269

270 Residues of antibiotics such as tetracycline and chloramphenicol (Cameroon, Iran, Egypt)
271 above their maximum residue limit (European Union standards) have been detected in
272 muscle, heart and kidney of farm chicken (Daghrir & Drogui, 2013) ; (Tavakoli, 2015) ;
273 (Guetiya Wadoum et al., 2016). Similarly, ciprofloxacin has been detected in eggs of
274 terminally ill birds receiving antibiotic treatment (Billah et al., 2015), quinolones inside
275 chicken and beef in Turkey (Er et al., 2013), amoxicillin in milk and eggs in Bangladesh
276 (Chowdhury et al., 2015), sulfonamides and quinolones in milk in China, Malaysia and

277 India (Cheong et al., 2010); (Zheng et al., 2013); (Kumari Anjana & C. Jayachandran,
278 2017). This exposure of antibiotics to humans can lead to neuropathological problems,
279 drug hypersensitivity, aplastic anemia, mutagenesis, disturbance of normal gut flora and
280 many more such complications (Lee et al., 2001); (Nisha, 2008); (Beyene, 2015).
281 European Union and other authorities have recommended a maximum residue limit for
282 antibiotics in animal-derived food but it is quite difficult to ascertain their safe level and
283 thus monitoring antibiotic use and their clearance period from animal becomes crucial
284 (Alimentarius 2012). Many such guidelines on the use of medically important antibiotics
285 in food producing animals have been recommended by WHO in 2016 (Table 1) (Aidara-
286 Kane et al., 2018). The historical linkage of antibiotic and antimicrobial resistance in the
287 modern age could not be overstated and direct effects of antibiotics and interconnected
288 microbial entities on human health must be considered when probing the emergence and
289 spread of antimicrobial resistance.

290

291 **2.3 Antimicrobial resistance in soil and water bodies**

292 Soil is a complex ecological niche and acts as source and sink for physical exchange
293 between the living and non-living components of the earth. Naturally, it also serves as a
294 reservoir for antibiotic resistance genes and determinants coming from various sources
295 (Figure 1, 2) (Monier et al., 2011). Metagenomic studies of soil have shown that many
296 antibiotic resistance genes exist which are yet to be fully characterized (Riesenfeld et al.,
297 2004). Agriculture land may receive antibiotics washed off from other sources, but
298 manure-supplemented soil especially with inputs from animal farms often contain high
299 concentration of antibiotics (Marti et al. 2013), such as tetracycline residues and resistant

300 microbes (Zhu et al., 2013). Antimicrobial resistance in soil is further aggravated if
301 improperly treated wastewater which is a nutrient-rich niche for microbes is used for
302 irrigation (Chee-Sanford et al. 2009; Oluyeye, T, and C 2015). Many antibiotics and
303 resistance genes such as the *bla*_{CTX-M} gene (confers resistance against cefotaxime) have
304 been reported from soil near pig farms and even rice fields (Xiao et al., 2016).

305 The waste generated from farms, manures, irrigation water, drug manufacturing plants,
306 hospitals, humans, and antibiotic contaminated ground surfaces often ends up in
307 agricultural land which increases the level of antibiotics (Rodgers et al., 2019). Depending
308 upon class of antibiotics, they degrade at different rates and thereby aggravate resistance
309 against antibiotics (Du & Liu, 2012) such as ampicillin, tetracycline, sulphamethoxazole,
310 nalidixic acid and chloramphenicol (Carballo et al. 2013). The vegetables and fruits from
311 these farming lands often pick up the antibiotics and resistant microbes present in the soil
312 and pose risk of transmission of antimicrobial resistance to humans during transport and
313 storage (Beuchat, 2002); (Kumar et al., 2005). Although data for direct use of antibiotics
314 in agriculture is limited, inputs from aforementioned antimicrobial resistance sources are
315 often ignored and there is hardly any surveillance for resistance in agricultural land.

316 Water bodies such as freshwater lakes, rivers, artificial water systems and sea also act
317 as dynamic reservoirs for antibiotic-resistant bacteria, antibiotic resistance genes and
318 antibiotics owing to multiple edaphic and biotic factors (Ding & He, 2010); (Cizmas et al.,
319 2015) (S. Khan et al., 2019). Many resistance determinants such as ESBLs (*bla*_{CTX-M-15},
320 *bla*_{CTX-M-15} *bla*_{OXA-58}) were found from rivers and drinking water sources, which exposes
321 a large population to resistant microbes (Cacace et al., 2019). This is particularly
322 worsened if animal farms, pharmaceutical plants, manure storages, wastewater treatment

323 plants are in close vicinity of these water bodies (Kümmerer, 2009). Very diverse and high
324 numbers of MDR strains have often been reported from ground water and rivers across
325 the world (Mulamattathil et al. 2014; (Wahome, 2013). Certain mass gathering events
326 such as religious congregations, sports, water parks, beach sports, etc near water bodies
327 witness a huge influx of resistant microbes such as *Enterobacter*, *Serratia*, *Klebsiella*,
328 *Citrobacter* and *Pantoea* and inter-mixing of large populations in such hotspots also
329 facilitates the spread of antimicrobial resistance (Khan, Memish, et al. 2010; Jani et al.
330 2018). These reports indicate towards the enormous effects of the antimicrobial
331 resistance in the soil and water bodies and the role of environment as a source-sink pair
332 for antimicrobial resistance. This demands for careful surveillance, strategic management
333 of public events for effective control over spread of antimicrobial resistance.

334

335 **2.4 Antimicrobial resistance and humans**

336 Antibiotic consumption varies across the world owing to differences in incidences of
337 infectious diseases, living standards, community hygiene and often broad-spectrum
338 antibiotics are unnecessarily prescribed. Although, new treatments alternatives such as
339 use of probiotics (Hatakka & Saxelin, 2008), probiotics surface proteins such as mucus
340 binding protein (K. S. Singh et al., 2018) (K. S. Singh et al., 2017), fibronectin binding
341 protein (Bisht et al., 2018) or oligosaccharides (Anand et al., 2018) has been proposed,
342 but they are still far from being commercial therapeutic success. This leaves fewer options
343 to treat MDR strains and extensive antibiotic stewardship of health professionals is
344 needed. Antibiotic stewardship approach can be further augmented by increasing
345 awareness in the general public about responsible usage of antibiotics. Humans can

346 potentially act as most aggressive vectors for transmission of antimicrobial resistance,
347 given their omnipresence, long distance travel, socializing and work. Human activities
348 around antimicrobial resistance hotspots such as farms, drug manufacturers, hospitals,
349 further loads them with resistant microbes. Resistant pathogens can affect humans
350 directly (Scallan et al. 2011), use them as transmission vectors (Spoor et al., 2013) and
351 also utilize humans as niche for example 'human gut' for the exchange of antibiotic
352 resistance genes among microbes (Willems et al., 2011). It is correctly reasoned that
353 antimicrobial resistance in humans is linked to high exposure of antibiotics either by drugs
354 or contaminated food or water. The antibiotic prescription pattern, market dynamics and
355 disease state of patients decide antimicrobial resistance in humans, which directly affects
356 patient's amicableability for vital invasive procedures in cancer and transplantation (Friedman
357 et al., 2016).

358 Many nations have taken steps to curb indiscriminate antibiotic usage at both pre-
359 prescription and post-prescription levels, by strengthening public health and structured
360 antibiotic stewardship (Garnacho-Montero et al., 2015) (Dyar et al., 2017). This has been
361 further augmented by strict laws and regulations on the sale without prescription and over-
362 the-counter antibiotics in many countries including Thailand, Mexico and Brazil (Santa-
363 Ana-Tellez et al., 2013); (Holloway et al., 2017). Similar strides have bene initiated in India
364 (Laxminarayan & Chaudhury, 2016) and South Africa (Gelband & Laxminarayan, 2015)
365 for strengthening of antibiotic stewardship programme, tight regulatory control over
366 antibiotics usage and data register of antibiotics sale (Masterton, 2011) ; (Valsamatzi-
367 Panagiotou et al., 2021). The direct effects of anthropogenic activities and fast transfer of
368 antimicrobial resistance through food and drinking water to humans is easily perceptible.

369 Apart from strategic antibiotic stewardship in hospitals, there is a need to adopt safe
370 handling practices of antibiotic-polluted environmental samples originating from soil,
371 water, etc.

372

373 **3 Prevention and regulation of antimicrobial resistance**

374 The issue of antimicrobial resistance needs to be tackled both at prevention and
375 mitigation levels, which needs awareness in general public, tight regulatory measures and
376 responsible antibiotics usage. Sensitization of the public towards antimicrobials could be
377 done through radio, TV and awareness campaigns by non-governmental organizations
378 and can result in success stories such as of 'triclosan'. Earlier, triclosan was a widely used
379 antimicrobial in many countries but it was banned for use when its role in antimicrobial
380 resistance became public and public pressure mounted on the government (McGinley,
381 2016). Healthcare systems could benefit from antibiotic stewardships, identification of
382 critical control points and strict adherence to regulatory measures (Uchil et al., 2014). A
383 major preventive measure to mitigate antimicrobial resistance is surveillance, further
384 augmented by use of high-throughput technologies such as next generation DNA
385 sequencing and inclusive classification systems such as Rescon (resistance readiness
386 condition), which links severity and spread potential of antimicrobial resistance (Martínez
387 et al., 2015). This applies directly to resistance determinants and mobilizing elements like
388 plasmids, transposons and integrons and also to other environmental stress factors like
389 heavy metals, temperature (Vorholt, 2012). Other omics technologies further resolve
390 information about antibiotics levels, mobile genetic elements, resistance genes and their

391 expression patterns coupled with actual antibiotic residues present in the niche (Spicknall
392 et al., 2013).

393 These approaches are important to identify patterns and overlapping ecological factors
394 involved in emergence and spread of antimicrobial resistance including those due to
395 biofilms, phyllosphere and water bodies (Calero-Cáceres et al., 2014). Overall, this helps
396 in precise statistical prediction of abundance and mobilization of resistant genes and
397 accessory genetic elements, spread between humans, animals and environment and
398 predictive model to aid in the design of mitigation strategies and critical regulatory policies
399 against antimicrobial resistance. These surveillance measures are not effective in
400 standalone countries and thus inter-continental partnerships between regulatory
401 agencies of different countries are being strengthened (Rogers Van Katwyk et al., 2020).
402 Some examples are GARP (Global Antibiotic Resistance Partnership) - (Ganguly et al.,
403 2011); (Leung et al., 2011), INSAR-India, NARMS-USA, ESAC-EU, SASCM-South
404 Africa, PAHO (Pan American Health Organization) and EARS-Net (European Resistance
405 Surveillance Network), GLASS – WHO. All of these networks focus on information
406 exchange and partnership in research and action for efficient tackling of antimicrobial
407 resistance (Berendonk et al., 2015). These preventive measures need a boost from
408 another front, which is the development of novel and potent antibiotics augmented with
409 improved drug delivery strategies to bypass biofilms (B. P. Singh et al., 2021). Reducing
410 the mass usage of antibiotics by imposing extra charges on non-human antibiotic usage
411 and strict regulations to encourage raising animals in clean, hygienic conditions would
412 also help the overall effort (Hollis & Ahmed, 2013). However, all such efforts need to be
413 integrated under 'One Health' approach across the world with further consideration of

414 other ecological factors and niche diversity to customize the prevention and mitigation
415 plan against antimicrobial resistance. The effectiveness of high-throughput surveillance
416 and public awareness is paramount and we need to consider the interplay of ecological
417 factors in the antimicrobial resistance landscape. The discernible need for worldwide
418 networks to fight against antimicrobial resistance is also a pertinent concern and recent
419 efforts by many countries need to be continued and strengthened.

420 **4 Antimicrobial resistance and One health approach**

421 The 'One health' concept offers multiple benefits in systematic dealing with the menace
422 of antimicrobial resistance. A big concern in the antimicrobial resistance issue is the
423 acquisition of resistance by human pathogens from their non-pathogenic relatives in the
424 environment (Forsberg et al. 2012). There are many direct evidences for human-animal-
425 environment interrelatedness and inclusive strategies such as 'One health' have to be
426 adopted for effective control and mitigation of antimicrobial resistance. The 'One health'
427 approach is directly beneficial for humans when applied to surveillance network and
428 public awareness programmes where it facilitates precise understanding of the pattern
429 and active dynamics of antimicrobial resistance. For example, documentation of resistant
430 microbes from human origin in an area provides ideas about endemic patterns of such
431 resistant microbes (Critchley & Karlowky, 2004). This information could be utilized for
432 prioritizing antibiotic susceptibility screens for infection in incoming patients and would
433 promote evidence-based antibiotic prescription by physicians. Furthermore, the
434 sensitized physicians themselves can encourage patients to adopt good hygiene
435 practices, safe disposal of animal waste and general behavior during zoonotic disease
436 outbreaks, thereby leading to low infections and robust addressal of public health issues.

437 Although not considered as measure of antimicrobial resistance, the antibiotics and their
438 degraded products largely drive resistance in all niches (Subbiah et al., 2016) and are
439 sometimes responsible for activating biofilm formation, motility and stress response in
440 microbes (Romero et al., 2011). There are myriad types of applicable regulations and
441 stakeholders in areas related to human, animals and environmental health, which handle
442 the issue of antimicrobial resistance with different levels of seriousness. The regulation
443 on use of last resort antibiotics (for humans) such as carbapenems and colistin in
444 agriculture settings is very relaxed and allows mass level usage (Pereko et al., 2016).
445 Less regulatory oversight into agricultural systems and their neglect towards recognizing
446 it as reservoir of antimicrobial resistance further worsens the situation. The risks
447 estimated due to pathogens arising from these domains directly affect humans involved
448 in handling agriculture products during production, transport and even the disposal of
449 agricultural wastes. Careless antibiotic prescription to animals without giving any
450 consideration for resistance against carbapenems and colistin in case of veterinary
451 pathogens still ends up being part of the animal-human-environment interplay and
452 aggravates the development of resistance. The antibiotic administration pattern at
453 individual animal and herd levels also differs and integrated approaches to understand
454 long-term effects in the context of antimicrobial resistance must be considered.

455 Across many developing nations, hunting of wild animals for food also referred as 'bush
456 meat' has been linked with infections including e.g. Ebola virus (Peterson, 2003). Low
457 vaccination, frequent mixing of animal-human habitats and poor hygiene in such countries
458 further drives infections and concomitantly complicates the issue of antimicrobial
459 resistance. Such situations have prompted many agencies such as WHO and UN-FAO

460 (United Nations Food and Agricultural Organization) to join hands and design strategies
461 using the 'One health' approach to deal with endemic diseases such as echinococcosis,
462 bovine tuberculosis, rabies and brucellosis in Africa while considering animal interactions
463 (Aidara-Kane et al., 2018). Similar strides have been initiated by UN-FAO and WHO to
464 tackle the risk of avian influenza (influenza virus A) in humans by collaborative efforts of
465 veterinarians and physicians (OFFLU-OIE/FAO, 2019).

466 Given the multidimensional issue of antimicrobial resistance and overlapping spheres of
467 its sources, treatment regimen and control of regulations demands inclusive mitigation
468 under the 'One health' framework. This framework collates information from all
469 stakeholders and fills knowledge gaps (Fisman & Laupland, 2010) to compare regulatory
470 standards for resistant strains isolated from human, animal and environmental sources.
471 This facilitates clarity in mitigation strategy and design of logic-based risk mitigation
472 policies for precise administrative and structural support in dealing with antimicrobial
473 resistance (McLain et al., 2016). The One health model can effectively mitigate the issue
474 of antimicrobial resistance and is equally applicable to developed, developing and under-
475 developed countries (Gebreyes et al., 2014) which is necessary for a sustainable control
476 of mankind over antimicrobial resistance. The overreaching arc of 'One health' to provide
477 effective control over the confounding factors of antimicrobial resistance is widely
478 recognized. It is prudent to work within the integrated framework of 'One health' and
479 mitigate antimicrobial resistance in a sustainable and long-term fashion.

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483 **5 Conclusion**

484 Numerous studies have established overlapping interactions between humans, animals
485 and the environment, especially in the context of emergence and spread of antimicrobial
486 resistance. Frequent outbreaks of zoonotic diseases and their clear association with both
487 environmental and human domains underscores their interwoven relationship. Clinicians,
488 veterinarians and regulatory agencies have achieved wonderful milestones in infectious
489 diseases, but quantifiable and integrated measures against antimicrobial resistance
490 between human, animals and environment are largely missing. Due to this, even though
491 the link between these ecological domains is obvious, only few predictive models exist
492 which could inform about their source-sink-reservoir relationships during most disease
493 outbreaks. A big reason for this knowledge gap is due to focus on human research and
494 complete ignorance of other stakeholders spanning the animal, plant and environmental
495 niches. This ignorance has been rampant at almost all levels including relaxed
496 regulations, indiscriminate antibiotic usage, surveillance, control and research.

497 Recent studies on the rapid rate of exchange of antimicrobial resistance determinants
498 between these spheres of life further underscores futility of all domain-limited efforts and
499 demands inter-sectoral focus for tackling antimicrobial resistance. Recent research has
500 shown that strict regulatory control, antibiotic stewardship, novel antibiotic development
501 and widespread surveillance have to be adopted. The multi-domain nature of the issue of
502 antimicrobial resistance demands its handling through an inclusive approach called 'One
503 health', which provides integrated solutions with multi-sectoral representation at the level
504 of surveillance, detection and targeted mitigation. This deals comprehensively with the

505 biotic and abiotic confounding factors involved in antimicrobial resistance and provides
506 sustainable solutions. One health approaches are useful for all countries at different
507 economic levels and are particularly suitable for effective implementation in low and
508 middle-income countries that often tend to have high disease burden and worse situations
509 of antimicrobial resistance.

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877 [_HPLC_method_in_chicken_and_calves_meat_in_diet_of_a_military_center_in_Tehran](https://www.researchgate.net/publication/291835452_Detecting_antibiotic_residues_by_HPLC_method_in_chicken_and_calves_meat_in_diet_of_a_military_center_in_Tehran)

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916 **Declarations**

917 **Funding:** No funding from any source.

918 **Conflicts of interest/Competing interests:** All authors declare no conflict/competing
919 interest.

920 **Ethics approval:** Not applicable.

921 **Consent to participate:** All authors have given consent for participation, if applicable.

922 **Consent for publication:** All authors have given consent for publication.

923 **Availability of data and material:** All data has been assessed from open/public domain
924 and no data/material needs to be made available from our side.

925 **Code availability:** Not applicable.

926 **Authors' contributions:** *KSS, SA and SD* wrote the manuscript. *JKS* made the figures.
927 *WB* and *YS* edited the manuscript with comments and changes as and when required.

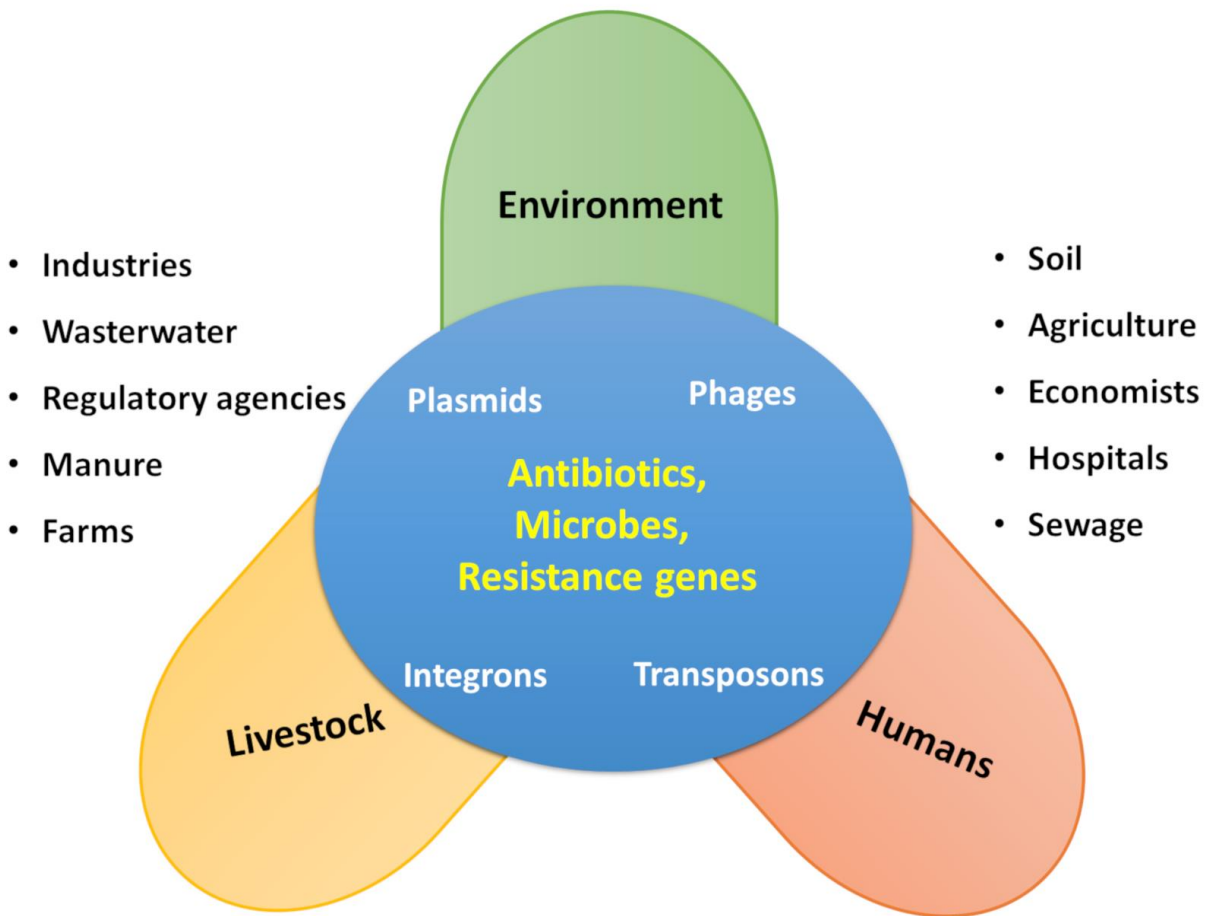
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932 **Legend of figures:**



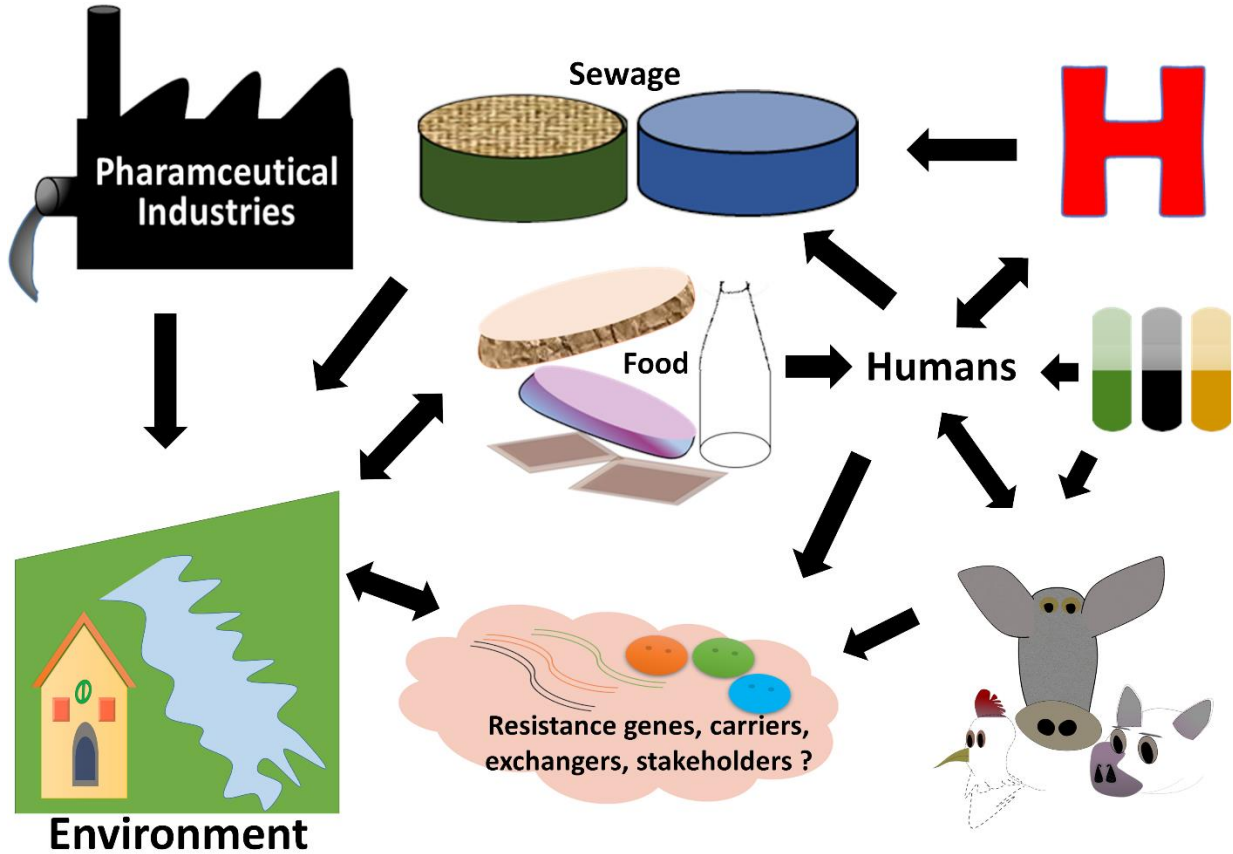
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934 **Figure 1:** One-Health paradigm and stakeholders. 'One-health' refers to integrative
935 strategies in design and implementation of legislation, policies and research, which
936 facilitates communication between multiple sectors to achieve better solutions for public
937 health. This holistic approach can aid in integration of information from different
938 stakeholders such as regulatory agencies, economists, consumers and other contributors
939 to provide sustainable solutions against antimicrobial resistance.

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945 **Figure 2:** Inter-connectedness and transferability between the different niches. Many
 946 routes of transmission exist for exchange of antimicrobial resistance determinants such
 947 as antibiotic resistance genes (ARGs) between animals, humans and the environment.
 948 Anthropogenic activities remain at the center of all major activities related to antimicrobial
 949 resistance.

954 **Table 1:** WHO recommendations on the use of medically important antimicrobials in
 955 food-producing animals

1	The Guideline Development Group (GDG) recommends an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.
2	The GDG recommends complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.
3	*The GDG recommends complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.
4a	*The GDG suggests that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals.
4b	*The GDG suggests that antimicrobials classified as critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease.

956 *Specific considerations: when a veterinary professional judges that there is a high risk
 957 of spread of a particular infectious disease, use of antimicrobials for disease prevention
 958 is justified, if such a judgement is made on the basis of recent culture and sensitivity
 959 testing results.

960 *To prevent harm to animal health and welfare, exceptions to recommendations 4a and
 961 4b can be made when, in the judgment of veterinary professionals, bacterial culture and
 962 sensitivity results demonstrate that the selected drug is the only treatment option.
 963

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