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Use of polymyxins in Chinese hospitals

We acknowledge the Comment from Federico Perez and Robert A Bonomo[1] regarding our Article[2] on the decline of colistin resistance and *mcr-1* abundance in *Escherichia coli* from animal and human origins following the ban of colistin as an animal growth promoter in China. We appreciate their suggestion that the insufficient data on clinical polymyxin use is a limitation of our study.

From the introduction of polymyxin in the 1980s, its use in China was restricted to food-producing animals. However, in January, 2017, the China Food and Drug Administration (CFDA) approved polymyxin B as a therapy in humans,[3] and injectable polymyxin B (lyophilised powder, 500 000 units per dose) became available for clinical use in October, 2017. In May, 2018, the CFDA also approved colistin (polymyxin E) for exclusive use in humans,[3] and injectable colistin (lyophilised powder, 500 000 units per dose) became available for clinical use in December, 2018.

We collected hospital consumption data for polymyxins, including polymyxin B (2018–19) and colistin (2019), from 26 Chinese provinces using the CHINET surveillance system, and compared the data with samples that were positive for colistin-resistant *E coli* from the corresponding provinces in 2018–19.[2]

In total, 354 442 polymyxin doses were administered between 2018 and 2019. More than 10 000 doses were given to patients who were hospitalised in ten provinces. Nine of the ten provinces (except Beijing) were among the top ten wealthiest areas in China (by gross domestic income in 2019, appendix p 1). Hospitals in Zhejiang, Jiangsu, Beijing, Shanghai, and Guangdong consumed over half (196 018 [55·3%] of 354 442 doses) of all polymyxin used for the treatment of serious multidrug-resistant infections, mainly caused by carbapenem-resistant Gram-negative bacilli. Notably, hospitals from five of these provinces are major referral centres and have some of the best resources in China. Based on consumption data, we conclude that Chinese clinicians should consider polymyxin as a last resort antibiotic, and that clinical polymyxin use should be heavily restricted.

To understand the relationship between polymyxin use and infections caused by colistin-resistant *E coli* in Chinese hospitals, we did a correlation analysis. Spearman's correlation coefficient showed no significant correlation between polymyxin use and colistin-resistant *E coli* (Spearman's ρ=0·18, p=0·389). We propose three possible reasons for the absence of correlation. First, a large number of inpatients receiving polymyxin were treated in intensive care units and had little or no similarities of ward to inpatients who were positive for colistin-resistant *E coli* from other hospital units, including the intensive care unit.[3] Second, some inpatients who were positive for colistin-resistant *E coli* were administered antibiotics that were not polymyxin, including tigecycline and carbapenem plus fosfomycin combination therapies. Third, unlike animals, in which large quantities of colistin were used and associated with colistin resistance, the short term and smaller amounts of polymyxin used in Chinese hospitals had little direct pressure on the emergence of colistin-resistant *E coli*.

Nevertheless, our data will be useful baseline data for future studies. With the increase in carbapenem-resistant pathogens causing clinical infections,[4,5] polymyxin use in Chinese hospitals is also expected to increase; therefore, continuous surveillance of both polymyxin use and colistin-resistant *E coli* infections is warranted.

For the **CHINET surveillance** system see http://www.chinets.com

See **Online** for appendix

RZ and YW report grants from the National Natural Science Foundation of China (81861138052 and 81861138051), as part of the submitted work. TRW reports a UK–China joint project obtained in 2018 from the UK Medical Research Council (MR/S013768/1), under the name "Determining the clinical and environmental impact, burden and cost of Extensively Drug Resistant Enterobacteriaceae in China HUB" (DETER-XDRE-CHINA-HUB). YS and FH declare no competing interests.

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mcr-1 and plasmid prevalence in *Escherichia coli* from livestock

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We read with interest the Article by Yang Wang and colleagues,[1] in which they assessed the effects of the withdrawal of colistin as a feed additive on the prevalence of colistin-resistant *Escherichia coli* (CREC) and *mcr-1*-positive *E coli* (MCRPEC) in China. The authors found that this policy positively contributed to a reduction in the prevalence of CREC and MCRPEC in animals and humans, as reported in other studies.[1–3] However, as the authors noted, in their analysis of *mcr-1* abundance in farms, their sampling timepoints were 3 months and 15 months after colistin withdrawal and did not include a baseline analysis before the policy was enforced. Furthermore, trends in the prevalence of *mcr-1*-associated plasmids have yet to undergo validation.

We did a 7-year continuous surveillance study of the prevalence of colistin resistance and *mcr-1* and its associated plasmids among *E coli* isolates randomly collected from pigs and chickens between July 11, 2013, and Dec 6, 2019, in China. 4569 *E coli* isolates were recovered from pigs at slaughter in the Guangdong (n=2196) and Liaoning (n=1171) provinces and pigs from two farms located in the Guangdong (n=719) and Anhui (n=483) provinces (appendix p 1). Additionally, 598 *E coli* isolates were obtained from chickens living in one chicken farm located in the Anhui province.

Generally, the prevalence of CREC and MCRPEC in the five sampling sites showed a similar trend: a gradual increase before 2015–16, when the peak was reached (38–45%), and then a decrease towards a trough (<2%) in 2018–19 (appendix p 2). The CREC and MCRPEC prevalence peak coincided with our first report of the emergence of *mcr-1* and the decree by the Chinese Government for cessation of the use of colistin as a feed additive in response.[4,5] The continuous increase in CREC and MCRPEC prevalence from 2011 to 2015 (appendix p 2)[4] indicates that *mcr-1* can spread quickly under colistin selective pressure. Thus, without prompt government action, CREC and MCRPEC prevalence would probably have kept increasing, raising the risk of *mcr-1* spread from animals to humans and threatening colistin efficacy in human medicine. Our data further show that this policy implementation was both prompt and effective.

Furthermore, after 2015–16, we also observed a significant reduction in the frequency of the IncI2 and IncX4 plasmids (appendix p 2), reported to be the dominant vectors driving the dissemination of *mcr-1* worldwide.[6] In line with this finding, our correlation analysis showed that *mcr-1* was most associated with IncX4 plasmids, followed by IncI2 (appendix p 3). These results suggest that the prevalence of *mcr-1*-associated IncX4 and IncI2 plasmids decreased as a consequence of a reduction in the use of colistin. Although the toxic effects of MCR-1 might explain in part the rapid reduction in the prevalence of *mcr-1*-bearing plasmids,[7] the underlying mechanism needs to be further studied.

Overall, our results suggest that the withdrawal of colistin as a feed additive had a positive effect on the reduction in the prevalence of colistin resistance, *mcr-1*, and IncX4 and IncI2 plasmids. Whether the same policy applied to the use of other antimicrobials will have a similar effect on the prevalence of resistance and resistance determinants needs to be further evaluated.

This work was supported in part by grants from the National Natural Science Foundation of China (31830099, 31625026, and 31902322), the Guangdong Special Support Program Innovation Team (2019BT02N054), the 111 Project (D20008), and the Innovation Team Project of Guangdong University (2019KCXTD001). We declare no competing interests.

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