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International manufacturing and trade in colistin, its implications in colistin resistance and One Health global policies: a microbiological, economic, and anthropological study

Muhammad Umair, Brekhna Hassan, Refath Farzana, Qasim Ali, Kirsty Sands, Jordan Mathias, Seniyat Afegbua, Mohammad Nazmul Haque, Timothy R Walsh, Mashkoor Mohsin



Summary

Background The emergence of colistin-resistant Enterobacterales is a global public health concern, yet colistin is still widely used in animals that are used for food as treatment, metaphylaxis, prophylaxis, and growth promotion. Herein, we investigate the effect of colistin-resistant Enterobacterales in Pakistan, global trade of colistin, colistin use at the farm level, and relevant socioeconomic factors.

Methods We conducted a microbiological, economic, and anthropological study of colistin-resistant *Escherichia coli* in humans, animals, and the environment and international trade and knowledge of colistin in Pakistan, Bangladesh, Nigeria, China, India, and Viet Nam. We collected backyard poultry cloacal swabs, commercial broiler cloacal swabs, cattle and buffalo rectal swabs, human rectal swabs, wild bird droppings, cattle and buffalo meat, sewage water, poultry flies, chicken meat, and canal water from 131 sites across Faisalabad, Pakistan, to be tested for *mcr-1*-positive and *mcr-3*-positive *Escherichia coli*. We recruited new patients admitted to Allied Hospital, Faisalabad, Pakistan, with abdominal pain and diarrhoea for rectal swabs. Patients with dysentery and those who were already on antibiotic treatment were excluded. Data for colistin trade between 2017 and 2020, including importation, manufacturing, and usage, were accessed from online databases and government sources in Pakistan, Bangladesh, and Nigeria. We recruited participants from poultry farms and veterinary drug stores in Pakistan and Nigeria to be interviewed using a structured questionnaire. International manufacturing, import, and export data; value analysis; and trade routes of colistin pharmaceutical raw material (PRM), feed additive, and finished pharmaceutical products (FPPs) were accessed from 2017–21 export data sets.

Findings We collected 1131 samples between May 12, 2018, and July 1, 2019: backyard poultry cloacal swabs (n=100), commercial broiler cloacal swabs (n=102), cattle and buffalo rectal swabs (n=188), human rectal swabs (n=200), wild bird droppings (n=100), cattle and buffalo meat (n=100), sewage water (n=90), poultry flies (n=100), chicken meat (n=100), and canal water (n=51). We recruited 200 inpatients at Allied Hospital, Faisalabad, Pakistan, between Nov 15, 2018, and Dec 14, 2018, for rectal swabs. We recruited 21 participants between Jan 1, 2020, and Dec 31, 2020, from poultry farms and drug stores in Pakistan and Nigeria to be interviewed. 75 (7%) of 1131 samples contained *mcr-1*-positive *E coli*, including wild bird droppings (25 [25%] of 100), commercial broiler cloacal swabs (17 [17%] of 100), backyard poultry cloacal swabs (one [1%] of 100), chicken meat (13 [13%] of 100), cattle and buffalo meat (two [2%] of 100), poultry flies (eight [8%] of 100), sewage water (six [7%] of 90), and human rectal swabs (three [2%] of 200). During 2017–20, Pakistan imported 275.5 tonnes (68.9 tonnes per year, 95% CI 41.2–96.6) of colistin as PRM, all sourced from China, 701.9 tonnes (175.5 tonnes per year, 140.9–210.1) of colistin as feed additives from China and Viet Nam, and 63.0 tonnes (15.8 tonnes per year, 10.4–21.1) of colistin as FPPs from various countries in Asia and Europe. For Bangladesh and Nigeria, colistin PRM and FPPs were imported from China and Europe. Colistin knowledge and usage practices in Pakistan and Nigeria were unsatisfactory in terms of understanding of the effects on human medicine and usage other than for treatment purposes. China is the major manufacturer of PRM and feed additive colistin and exported a total of 2664.8 tonnes (666.2 tonnes per year, 95% CI 262.1 to 1070.2) of PRM and 2570.2 tonnes (642.6 tonnes per year, –89.4 to 1374.5) of feed additive in 1330 shipments during 2018–21 to 21 countries.

Interpretation Regardless of 193 countries signing the UN agreement to tackle antimicrobial resistance, trading of colistin as PRM, FPPs, and feed additive or growth promoter in low-income and middle-income countries continues unabated. Robust national and international laws are urgently required to mitigate the international trade of this antimicrobial listed on WHO Critically Important Antimicrobials for Human Medicine.

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For the Urdu translation of the abstract see Online for appendix 1

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Introduction

The emergence of *mcr-1*-mediated colistin resistance in *Escherichia coli* (MCRPEC) is thought to have been driven by the use of colistin in farming in China, not least in prophylaxis and animal feeds.¹ This notion was endorsed when China banned the use of colistin in agriculture in April, 2017, which subsequently resulted in a dramatic decrease in the prevalence of MCRPEC.^{2,3} However, colistin is still widely used in food-producing animals in countries other than China not only for treatment but also as prophylaxis and for growth promotion. The ongoing spread of plasmid-mediated colistin resistance in Enterobacterales in food-producing animals, humans, and the environment has raised serious public health concerns.⁴ Paradoxically, there is increasing reliance on colistin to treat multidrug-resistant Gram-negative bacterial infections, not least in low-income and middle-income

countries (LMICs) where other treatment alternatives (eg, tigecycline) are, when accessible, prohibitively expensive.⁵

Surveillance of antimicrobial consumption in food-producing animals and the reduction of antimicrobial use in animal husbandry are key strategic objectives indicated in many regional and global initiatives to address antimicrobial resistance.⁶ Global colistin production was 4292 tonnes in 2019, with 96% of this total consumption in poultry and pig farming.⁷ Antimicrobial stewardship programmes are not usually well practiced in LMICs, mainly due to the lack of infrastructure and government policies.⁸ Intensive livestock farming is increasing in Pakistan, making the country a notable consumer of antimicrobials in the farming of food-producing animals, where colistin is widely used to treat and control colibacillosis.^{9,10} Although colistin resistance reduced in China after banning the

Research in context

Evidence before this study

We searched Web of Science, Scopus, and PubMed from database inception to July 7, 2022, using structured queries built on keywords for articles, letters, and editorials on colistin. Search terms for Web of Science were “((ALL=(((Colistin Use) OR (Colistin Consumption)) AND ((Colistin Import) OR (Colistin Export)) AND (Colistin Resistance)))) OR (TI=(((Colistin Use) OR (Colistin Consumption)) AND (Colistin Resistance)))) AND DT=(Article OR Letter)”, for Scopus were “(ALL (Colistin W/5 Resistance AND Use OR Consumption AND Import OR Export)) OR (TITLE-ABS-KEY (Colistin W/5 Resistance AND Use OR Consumption)) AND (LIMIT-TO (DOCTYPE,“ar”) OR LIMIT-TO (DOCTYPE,“ed”) OR LIMIT-TO (DOCTYPE,“le”))”, and for PubMed were “((Colistin Us) OR (Colistin Consumption)) AND ((Colistin Import) OR (Colistin Export)) AND (Colistin Resistance)”. We did not exclude studies on the basis of region, language, or timeframe. A total of 174 articles (44 from Web of Science, 69 from Scopus, and 61 from PubMed) were analysed for evidence of colistin import or export, product manufacturing, colistin consumption, socioeconomic factors of colistin use, and One Health-based surveillance on colistin resistance. Several studies investigated the emergence and prevalence of colistin resistance in food-producing animals, different foods, humans, and the environment with a small sample size. There was a remarkable decrease in colistin resistance in China after the nationwide ban on colistin use as an antimicrobial growth promoter. International travel and the trade of food animals and feed products were also potential risk factors for the spread of mobile colistin resistance genes (*mcr*).

Added value of this study

Until now, no study has provided evidence on colistin trade, manufacturing, consumption, and socioeconomic factors

linked to colistin resistance. This study gives a panoramic overview of trade, manufacturing, and consumption of and resistance to colistin in Pakistan; additionally, we provide anecdotal data on colistin import to other low-income and middle-income countries, including Bangladesh and Nigeria. In this study we investigate community-based One Health surveillance and molecular epidemiology of colistin resistance in Pakistan with samples from humans, poultry, cattle and buffalo, meat, flies, wild birds, and fresh and wastewater. We critically discuss the global scenario of colistin manufacturing and its export, especially to low-income and middle-income countries without legislation or implementation of laws on imports, manufacturing, and use of important antimicrobials. Furthermore, we discuss the global initiatives on antimicrobial resistance and Europe's in-house laws on the veterinary use of last-resort antimicrobials and their approach to the rest of the world.

Implications of all the available evidence

Despite the global agreement and initiatives on curbing the international colistin crisis, we observed that the colistin manufacturing and trade of pharmaceutical raw material, finished pharmaceutical products, and feed additives or growth promoters for veterinary use was unchanged during 2017–19 in China, Pakistan, Viet Nam, and India. Our study has crucial implications on the global manufacturing and trade of colistin as pharmaceutical raw material for veterinary drug manufacturing and, more crucially, on the manufacturing and trade of feed additives or growth promoters. Strict laws should be internationally and globally implemented to mitigate widespread resistance to antibiotics listed on the WHO list of Critically Important Antimicrobials for Human Medicine.

use of colistin as a growth promoter in animals,² the manufacture and export of colistin as either pharmaceutical raw material (PRM) or feed additive still continues.¹¹

We aim to describe the molecular epidemiology of colistin-resistant *E coli* across humans, animals, and the environment in Pakistan; imports of colistin in Pakistan, Bangladesh, and Nigeria in 2017–20; farm-level colistin use, knowledge, and practices in poultry in Pakistan and Nigeria; exports of colistin from China, Viet Nam, and India in 2018–21; and situational analysis on international trading of colistin.

Methods

Study design

We conducted a microbiological, economic, and anthropological study into the epidemiology of colistin-resistant *E coli* in Pakistan; colistin use and knowledge in Pakistan, Bangladesh, and Nigeria; and the trade of colistin in Pakistan, Bangladesh, Nigeria, and China. Ethical approval was obtained from the Institutional Biosafety/Bioethics Committee of the University of Agriculture, Faisalabad, Pakistan (diary number 109/ORIC, dated Jan 5, 2018) and consent was taken from all human participants. The study outline is described in appendix 2 (p 28).

Procedures

We collected samples from ten sources: wild birds, backyard poultry, canal water, cattle and buffalo rectums, human rectums, commercial broilers, poultry flies, cattle and buffalo meat, chicken meat, and sewage water. All samples were collected, following a cross-sectional approach, from 131 different sites within a radius of 65 km from the University of Agriculture, Faisalabad, Pakistan (appendix 2 pp 9, 29). We recruited new patients admitted to Allied Hospital, Faisalabad, Pakistan, with abdominal pain and diarrhoea for rectal swabs (taken by QA). Patients with dysentery and those who were already on antibiotics were excluded. Only eligible patients were referred to us by the duty doctor.

All samples were cultured on UTI ChromoSelect Agar, modified (Merck, Darmstadt, Germany) supplemented without and with colistin (2 mg/L). Flies were incubated in 500 µL of Mueller Hinton Broth (Merck, Darmstadt, Germany) at 37°C for 4 h before plating on chromogenic agar without and with colistin (2 mg/L). The variants of *mcr* (*mcr-1* and *mcr-3*) were screened by PCR from the colonies recovered from media with colistin. Samples negative for colistin-resistance were plated on colistin-free chromogenic UTI to isolate *mcr*-negative *E coli* (MCRNEC) for risk analysis as described elsewhere.¹² Whole genome sequencing of MCRPEC and MCRNEC was performed on the MiSeq platform (Illumina, San Diego, CA, USA). Microbiology and genomics methods are detailed in appendix 2 (p 1).

Data for colistin imported in 2017–20 as PRM, feed additive, or finished pharmaceutical product (FPP) for Pakistan was accessed from the Pakistan EXIM Trade Info online database, which was accessible until July, 2021, whereas the imports data for Bangladesh and Nigeria were collected from government sources. Status of colistin product registration and manufacturing in Pakistan was accessed from the Drug Regulatory Authority of Pakistan available online data.¹³ We informally recruited managers or farm supervisors and drug store owners from poultry farms and drug stores in Pakistan and Nigeria to be interviewed using a structured questionnaire on colistin usage (appendix 2 pp 1–2).

Import data from Pakistan, Bangladesh, and Nigeria evidently showed that all colistin PRM was imported from China. To investigate production and international trade, colistin export data from China and its two major importers India and Viet Nam were retrieved from Exim Trade Data. The data contained shipments for colistin export as PRM, feed additive, FPPs, and laboratory reagents. Many variables available for each shipment can be widely categorised into exporter and importer information, item description, export quantities and value, and export route. All the shipments for laboratory purpose were excluded and others summed up as PRM, feed additives, and FPPs. For Indian exports, FPPs were further classified into human and veterinary products. The data were analysed for the years 2018–21 and choropleth maps were developed on the basis of the total number of export shipments available for each importing country. Frequency distribution using net or gross shipment weights and cost per kg (US\$/kg) for Chinese PRM and feed additive shipments was also performed.

Different trading and pharmaceutical companies purchasing colistin PRM or feed additive from China, and supplying it as is or after manufacturing FPPs to different parts of the world, were identified from the exporter information. The identified companies were searched online, and evidence was procured to categorise the company as an intermediate (ie, trader or FPP manufacturer) and to ratify a trade link to its country of origin or registration. Online drug stores from the Indian market were searched to look for available human colistin products. A colistin trade map showing exporter, intermediate, and destination countries was developed by use of QGIS 3.22.3 for Chinese exports using all the available trade data.

Total animal biomass for species most likely to be treated with antimicrobials was calculated using World Organisation for Animal Health methods to estimate country-level colistin consumption data on the basis of veterinary PRM imports for Pakistan and Bangladesh for the years 2017–20.^{11,14}

Statistical analysis

Fisher's exact test was performed using SPSS (version 28.0) to understand the associations of different antibiotic

For more on the Exim Trade Data see <https://eximtradedata.com>

See Online for appendix 2

	MCRPEC, n (%; n=75)	MCRNEC, n (%; n=73)	p value
Penicillins			
Antibiotic name			
Amoxicillin–clavulanic acid	69 (92%)	49 (67%)	0.0002
ARGs pertinent to phenotypic resistance patterns			
<i>bla</i> _{TEM-1b}	57 (76%)	20 (27%)	<0.0001
<i>bla</i> _{OXA-1}	0	10 (14%)	0.0009
Cephalosporins			
Antibiotic name			
Ceftriaxone	6 (8%)	29 (40%)	<0.0001
Ceftazidime	6 (8%)	28 (38%)	<0.0001
Cefotaxime	6 (8%)	30 (41%)	<0.0001
Cefepime	6 (8%)	27 (37%)	<0.0001
ARGs pertinent to phenotypic resistance patterns			
<i>bla</i> _{CTX-M-15}	6 (8%)	26 (36%)	<0.0001
Carbapenems			
Antibiotic name			
Imipenem	0	15 (21%)	<0.0001
Meropenem	0	15 (21%)	<0.0001
ARGs pertinent to phenotypic resistance patterns			
<i>bla</i> _{NDM-5}	0	13 (18%)	0.0001
Fluoroquinolones			
Antibiotic name			
Ciprofloxacin	66 (88%)	32 (44%)	<0.0001
Levofloxacin	66 (88%)	36 (49%)	<0.0001
Antibiotic name			
NA	NA	NA	NA
Aminoglycosides			
Antibiotic name			
Amikacin	1 (1%)	11 (15%)	0.0021
Gentamicin	31 (41%)	16 (22%)	0.014
ARGs pertinent to phenotypic resistance patterns			
<i>aac</i> (3)-Ild	15 (20%)	3 (4%)	0.0045
<i>aac</i> (6')-Ib-cr	0	10 (14%)	0.0009
<i>aph</i> (3'')-Ib	52 (69%)	22 (30%)	<0.0001
<i>aph</i> (3')-Ia	34 (45%)	8 (11%)	<0.0001
strB	53 (71%)	22 (30%)	<0.0001

(Table continues in next column)

resistance genes with MCRPEC compared to MCRNEC. Statistical significance was set at $p < 0.05$.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We collected a total of 1131 samples during different time periods between May 12, 2018, and July 1, 2019: backyard poultry cloacal swabs (n=100), commercial broiler cloacal swabs (n=102), cattle and buffalo rectal swabs (n=188), human rectal swabs (n=200), wild bird droppings (n=100), cattle and buffalo meat (n=100),

	MCRPEC, n (%; n=75)	MCRNEC, n (%; n=73)	p value
(Continued from previous column)			
Sulphonamides or dihydrofolate reductase inhibitors			
Antibiotic name			
Sulfamethoxazole–trimethoprim	69 (92%)	39 (53%)	<0.0001
ARGs pertinent to phenotypic resistance patterns			
<i>sul2</i>	49 (65%)	13 (18%)	<0.0001
<i>sul3</i>	37 (49%)	6 (8%)	<0.0001
<i>dfrA12</i>	26 (35%)	14 (19%)	0.034
<i>dfrA14</i>	16 (21%)	5 (7%)	0.012
Phosphonic acid derivatives			
Antibiotic name			
Fosfomycin	3 (4%)	1 (1%)	0.62
ARGs pertinent to phenotypic resistance patterns			
NA	NA	NA	NA
Glycylcyclines			
Antibiotic name			
Tigecycline	4 (5%)	0	0.12
ARGs pertinent to phenotypic resistance patterns			
<i>tet</i> (X4)	4 (5%)	0	0.045

p values for the difference in associations of ARGs between MCRPEC and MCRNEC are obtained from Fisher’s exact test. ARGs that had significant association with either MCRPEC or MCRNEC are listed in the table. Minimum inhibitory concentrations of selected antibiotics for 147 *Escherichia coli* isolates included in this study are shown in appendix 2 (pp 3–4). ARG=antibiotic resistance gene. MCRPEC=*mcr-1*-mediated colistin resistance in *Escherichia coli*. MCRNEC=*mcr*-negative *E. coli*. NA=not applicable.

Table: Antimicrobial resistance profile of MCRPEC by antimicrobial class

sewage water (n=90), poultry flies (n=100), chicken meat (n=100), and canal water (n=51; appendix 2 p 9). We recruited 200 inpatients at Allied Hospital, Faisalabad, Pakistan, between Nov 15, 2018, and Dec 14, 2018, for rectal swabs, which were taken at the time of recruitment. We recruited 21 participants between Jan 1, 2020, and Dec 31, 2020, from drug stores and poultry farms in Pakistan and Nigeria to complete the questionnaire. Participants were farm managers or supervisors and drug store owners representing 150 operational broiler houses, each with a capacity of 30 000 birds.

The prevalence of MCRPEC in this study was 7% (75 of 1131 samples). The only variant found was *mcr-1* on a plasmid of ~62 kb, IncI2(delta). MCRPEC was identified in one (1%) of 100 backyard poultry cloacal swabs, 17 (17%) of 102 commercial broiler cloacal swabs, zero of 188 cattle and buffalo rectal swabs, three (2%) of 200 human rectal swabs, 25 (25%) of 100 wild bird droppings, two (2%) of 100 cattle and buffalo meat samples, six (7%) of 90 sewage water samples, eight (8%) of 100 poultry flies, 13 (13%) of 100 chicken meat samples, and zero of 51 canal water samples. MCRPEC was most prevalent in environmental samples (39 [11%] of 341; ie, wild bird droppings, sewage water, poultry flies, and

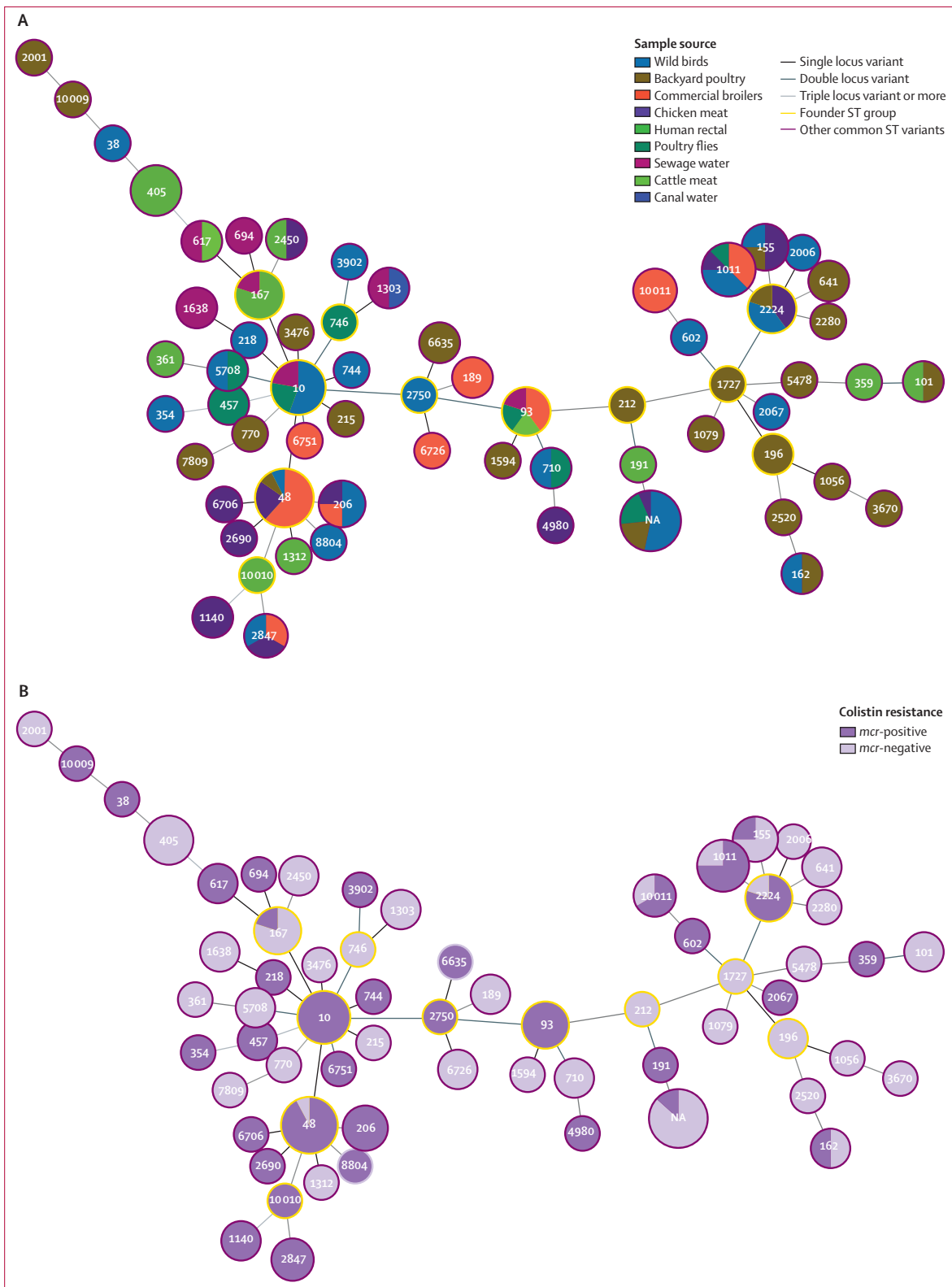


Figure 1: Distribution of sequence types among *Escherichia coli* isolates

Distribution of sequence types among *E. coli* isolates from different sources (A) and isolates with (n=73) and without (n=75) the *mcr-1* gene (B). Cattle and buffalo rectal samples were not sequenced, because the original remit of the study was primarily focused on poultry. NA=not applicable (ie, no sequence type match found in the database).

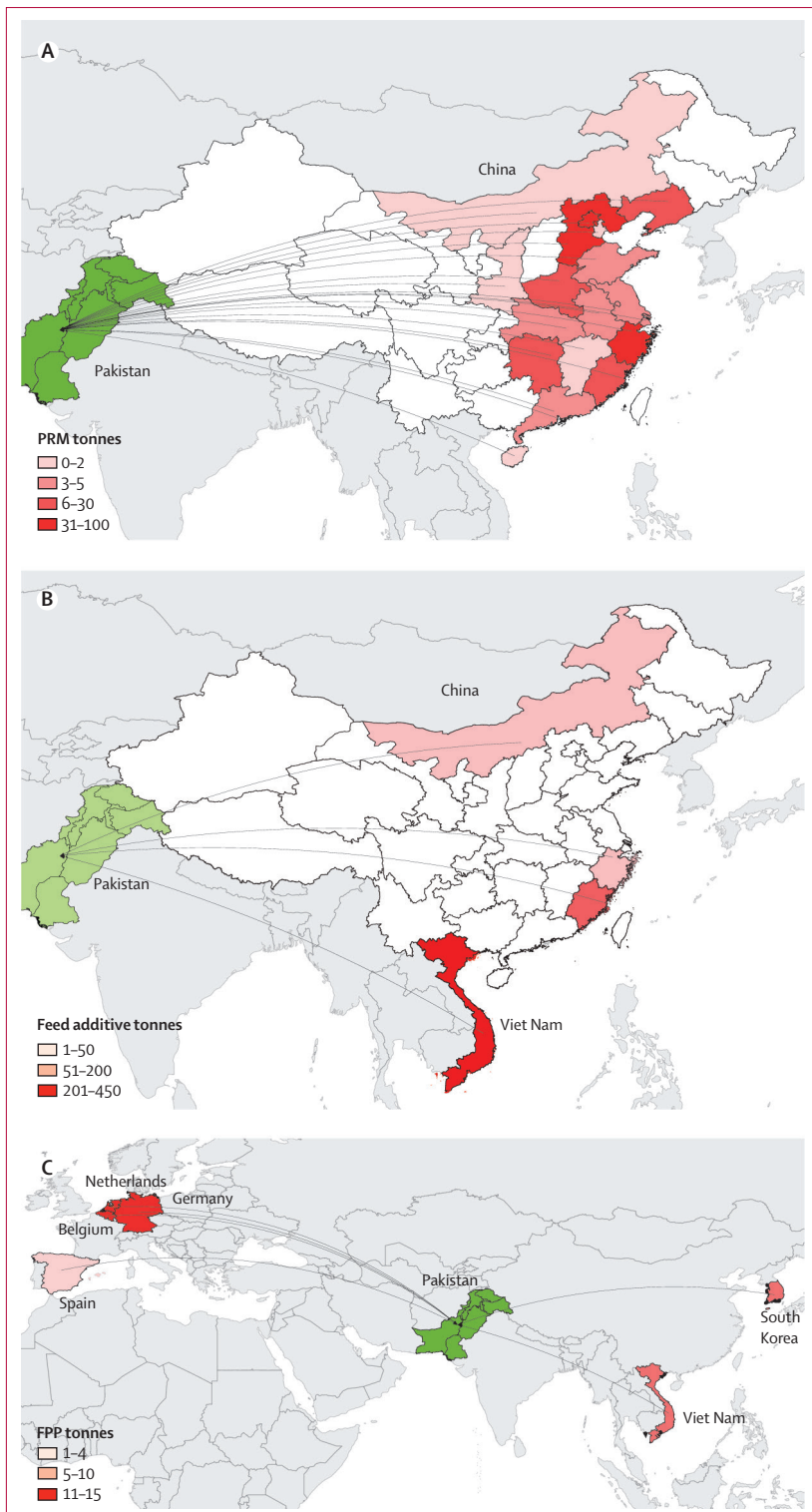


Figure 2: Colistin imports to Pakistan in 2017–20
Weight of PRM imports (A), feed additive imports (B), and FPP imports (C). Choropleth maps are based on the net weights for PRM and feed additives and gross weights for FPPs from the data retrieved from Pakistan EXIM Trade Info. FPP=finished pharmaceutical product. PRM=pharmaceutical raw material.

See Online for appendix 3

canal water) followed by samples from food-producing animals (33 [6%] of 590; ie, backyard poultry cloacal swabs, commercial broiler cloacal swabs, cattle and buffalo rectal swabs, cattle and buffalo meat, and chicken meat) and humans (three [2%] of 200). Wild bird (ie, crows and kites) droppings (25 [25%] of 100) and flies around poultry (eight [8%] of 100) were the major common sources of MCRPEEC in the environment. Chickens (31 [10%] of 302) were the higher reservoir of MCRPEEC than were cattle and buffalo (two [1%] of 288), with a difference in proportions of 0.1 (95% CI 0.06–0.13). *mcr-1* was more prevalent in commercial broilers (17 [17%] of 102) than in backyard poultry (one [1%] of 100; appendix 2 pp 9, 29).

Phenotypic resistance to colistin was linked to presence of only *mcr-1* in *E coli* (appendix 2 pp 4–5). Some MCRPEEC were multidrug resistant. Compared with MCRNEC, significant resistance was observed with amoxicillin-clavulanic acid, sulfamethoxazole–trimethoprim, ciprofloxacin, levofloxacin, and gentamicin (table). All MCRPEEC were sensitive to the carbapenems. Resistance to cephalosporins and carbapenems was significantly higher for MCRNEC than MCRPEEC. Antibiotic resistance genes pertinent to each resistance mechanism are specified in the table and appendix 2 (p 30). Results for sequence types and *mcr* plasmids are shown in figure 1 and appendix 2 (pp 3, 31–32).

During the years 2017–20, Pakistan imported a net total of 275.5 tonnes (68.9 tonnes per year, 95% CI 41.2–96.6) of pharmaceutical grade colistin PRM for animal use. The highest import volume of 91.7 tonnes was observed in 2017, whereas the import of colistimethate PRM for human use was 3.2 tonnes. All the colistin and colistimethate PRM was imported from China. A net total of 701.9 tonnes (175.5 tonnes per year, 95% CI 140.9–210.1) of colistin feed additive was imported from China (258.1 tonnes) and Viet Nam (443.8 tonnes) during the years 2017–20. During the same period, Pakistan imported 63.0 tonnes (15.8 tonnes per year, 95% CI 10.4–21.1) of 14 FPPs from Belgium, the Netherlands, Germany, South Korea, Spain, and Viet Nam (figure 2). On the basis of the total PRM imports and animal biomass for the years 2017–20, colistin consumption for Pakistan was estimated to be 2.5 mg/kg (appendix 2 p 9, appendix 3).

During 2013–20, the Drug Regulatory Authority of Pakistan registered about 566 veterinary drugs containing colistin active chemical compound for local manufacturing and about 22 drugs to be imported from Europe and Asia. Because of the recommendation made by the Supreme Court of Pakistan, the Provincial Government of Punjab listed colistin as an impermissible antibiotic growth promoter; however, no national legislation exists on antibiotic growth promoters (appendix 2 pp 3, 46–48).

Data for 2017–20 retrieved from the Bangladesh national database, operated by the Directorate General

Drug Administration, indicated that eight pharmaceutical companies were approved to manufacture colistin products for veterinary use and were permitted to import 29.4 tonnes (7.3 tonnes per year, 95% CI -1.1 to 15.7) of colistin as PRM into Bangladesh. The import of colistin in Bangladesh was directly linked to 15 companies located in China. The Government of Bangladesh formulated a law in 2010 called the Animal Feed Act, in which the use of antibiotics, growth hormones, and pesticides were banned in animal feed (appendix 2 p 9, appendix 4).¹⁵

In January, 2019, a request regarding the ban of a few antibiotics, including colistin, was made by the Bangladesh Poultry Industries Central Council and therefore, on May 9, 2019, the Directorate General Drug Administration banned any combination of colistin in veterinary medicine and any single preparation of colistin except oral solution (≤ 1 L) and injectable dose form. On March 20, 2022, the Directorate General Drug Administration banned all preparations of colistin in veterinary medicine. During 2017–20, 71.1 kg of colistimethate FPPs (powder or solution for injection) for human use was imported from Denmark. On the basis of the total PRM imports and biomass in 2017–20, colistin consumption for Bangladesh was estimated to be 1.1 mg/kg (appendix 2 pp 10, 49–56).

During 2018–21, the Ports Inspection Directorate of the Nigerian National Agency for Food and Drug Administration and Control recorded a total of 37 import shipments containing colistin PRM or FPPs from the Netherlands (n=26), China (n=8), and Germany (n=3) to Nigeria. All the shipments from the Netherlands were of veterinary FPPs from three pharmaceutical manufacturing companies. Shipments from China included PRM (n=5) and FPPs (n=3), and two active pharmaceutical ingredient suppliers, from Switzerland and Germany, exported colistin PRM from China to Nigeria. All import shipments from Germany were of FPPs via a trading company that specialises in trading to and from Africa and from Asia to Europe. In overall colistin imports, FPP shipments were the most frequent (32 [86%] of 37), of which 26 (81%) shipments originated from the Netherlands, followed by PRM shipments (14% [5 of 37]), all of which were from China (appendix 2 p 10, appendix 5). In 2018, the Nigerian National Agency for Food and Drug Administration and Control issued a policy statement prohibiting the use of antimicrobials as growth promoters in animal feed, which is yet to become a law.

In Pakistan, poultry farmers were invariably unaware of the effect of colistin use on human medicine (18 [100%] of 18 respondents), which was not the case in Nigeria (3 [100%] of 3 respondents were aware of the effect). From both countries, farmers reported the use of colistin as a prophylactic measure (18 [100%] of 18 respondents in Pakistan; 2 [67%] of 3 respondents in Nigeria) and all respondents were satisfied with the outcomes of colistin. In both countries, respondents reported that colistin can be purchased without veterinarian's prescription (18 [100%] of 18 respondents in Pakistan; 3 [100%] of

3 respondents in Nigeria), and imported products were preferred (12 [67%] of 18 respondents in Pakistan; 3 [100%] of 3 respondents in Nigeria; appendix 2 pp 3, 27).

During 2018–21, the Exim Trade Data database recorded a total of 1420 colistin export shipments from China; 52 shipments that carried laboratory reagents and one shipment that contained colistimethate sodium were excluded. The remaining 1367 shipments carried PRM (n=1116), feed additive (n=214), and FPPs (n=37) to 22 countries in Asia, Europe, Africa, and Latin America. Most shipments were destined for Pakistan (n=380) followed by Viet Nam (n=337), the Philippines (n=99), Türkiye (n=78), and India (n=72; appendix 2 p 13); however, colistin export shipments varied in timescales and quantities. Viet Nam was the largest importer of feed-grade colistin shipments (n=105) followed by the Philippines (n=73) and India (n=23; figure 3). In 1116 PRM shipments, China exported approximately 2664.8 tonnes (666.2 tonnes per year, 95% CI 262.1 to 1070.2) of colistin to 21 countries and 617 (55%) shipments carried 0.5 to 5.0 tonnes of PRM. Total volume for 214 feed additive shipments (ie, 10% colistin sulphate formulation) exported to eight countries was approximately 2570.2 tonnes (642.6 tonnes per year, 95% CI -89.4 to 1374.5), and 130 (61%) shipments carried 5.0 to 50.0 tonnes of feed-grade colistin. For import volumes, Viet Nam (1353.3 tonnes; 451.1 tonnes per year, 95% CI -45.7 to 947.9) was the largest importer of colistin PRM followed by Pakistan (270.8 tonnes; 67.7 tonnes per year, 32.4 to 103.1) and Russia (256.7 tonnes; 64.2 tonnes per year, -7.7 to 136.1), whereas for feed additive import volumes, Viet Nam (1991.1 tonnes; 663.7 tonnes per year, -190.8 to 1518.2) was followed by India (228.0 tonnes; 114.0 tonnes per year; -102.0 to 330.0) and the Philippines (254.0 tonnes; 84.7 tonnes per year, -21.5 to 190.9; appendix 2 pp 13–14, 20; appendix 6).

The value of PRM exports, calculated against 1116 shipments, was \$17.3 per kg, with 870 (78%) of 1116 shipments valued between \$5.0 and \$15.0 per kg. Excluding 63 PRM shipments that were valued above \$100.0 per kg, the remaining 1053 shipments were valued at \$10.2 per kg. The value of feed additive exports for the 214 shipments was \$2.6 per kg, with 140 (65%) of 214 shipments valued between \$1.0 and \$3.0 per kg (appendix 2 p 20).

Although we requested data for 2018–21, data were available only for 2019–21. During 2019–21, a total of 219 colistin export shipments (73 shipments per year, 95% CI 37–109) were recorded from Viet Nam to 20 countries in Asia, the Middle East, and north Africa. Veterinary FPP shipments constituted a major proportion (133 [61%] of 219) of the total exports, followed by feed additive shipments (86 [39%]). For total export shipments, Laos (n=44), Pakistan (n=35), and Myanmar (n=33) were the major destinations. For feed additive shipments, Laos (n=44), Pakistan (n=21), and Cambodia (n=11) were the major

See Online for appendix 4

See Online for appendix 5

destinations (figure 4, appendix 2 p 21, appendix 6). Two feed additive colistin products imported in Pakistan are marketed as growth promoters (appendix 2 pp 39–40).

For India, a total of 136 colistin export shipments (34 shipments per year, 95% CI 13–55) destined to 29 countries in Asia, the Middle East, Africa, and Latin America were recorded during 2018–21. Export shipments of human colistin FPP were markedly high

(106 shipments) compared with the FPP shipments for veterinary use (25 shipments), and one shipment was described as veterinary feed additive. Saudi Arabia (n=12), Malaysia (n=11), the Democratic Republic of the Congo (n=10), Nigeria (n=10), Oman (n=10), and Russia (n=10) were the major export destinations for total shipments (figure 5, appendix 2 pp 22–23, appendix 6). We searched at least 38 human FPPs (ie, colistin oral suspensions) available in the Indian market, 32 (84%) of

See Online for appendix 6

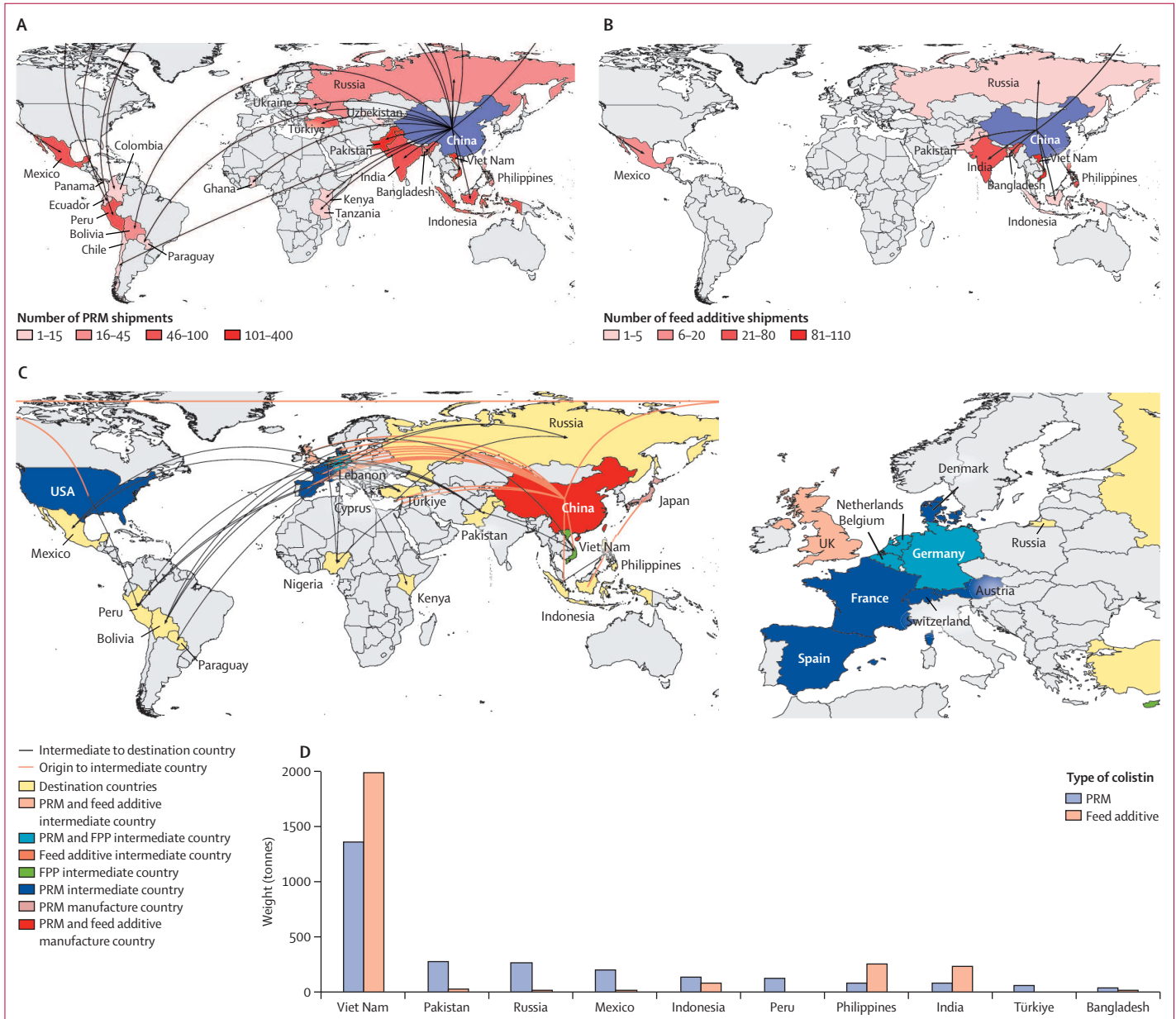


Figure 3: Colistin exports from China during 2018–21 and international trade routes

(A) Colistin PRM exports from China in 2018–21. (B) Colistin feed additive exports from China in 2018–21. (C) International colistin trade via intermediate or trading companies supplying PRM, FPPs, and feed additive colistin to the destination countries from PRM and feed additive manufacturing countries or couriers manufacturing FPPs. European companies' countries of registration are also shown close up. (D) Import weights to the top ten countries (ie, with the highest number of export shipments). Choropleth maps are based on the number of shipments recorded by Exim Trade Data for 22 countries. Trade routes are based on the trading and FPP manufacturing companies' countries of registration. The companies are identified from the export data recorded by Exim Trade Data for 22 countries and data received from other sources (appendix 2 p 1, appendix 3, appendix 4, appendix 5, appendix 6). FPP=finished pharmaceutical product. PRM=pharmaceutical raw material.

which were for paediatric use, and ten paediatric FPPs were marketed as antibiotic–antidiarrhoeal on the package label (appendix 2 pp 24, 44).

From the Chinese colistin export dataset, we identified 193 manufacturers or suppliers involved in international supply and trade of colistin. Export shipments from the top ten colistin manufacturers—ie, with the highest number of export shipments—constituted 610 (55%) of 1116 total PRM exports. For feed additive exports, we identified a total of 21 manufacturers or suppliers, and 154 (72%) of 214 exports were from seven manufacturers (appendix 2 p 19). Chinese active pharmaceutical ingredient or PRM manufacturers or suppliers export colistin directly to various countries in Asia, the Middle East, Europe, Africa, and America. We

identified at least 21 trading companies from Europe and one from the USA purchasing colistin from China and supplying it in Europe, Africa, Asia, and Latin America; these companies might have subsidiaries in other countries (figure 3, appendix 2 pp 25–26).

Discussion

This study uniquely combines evidence for One Health colistin resistance with specific colistin import or consumption data, or both, from Pakistan, Bangladesh, and Nigeria, and farmer feedback from Pakistan and Nigeria. We emphasise the worrying practice of international exports and imports of colistin as a feed additive and growth promoter. In the current climate of

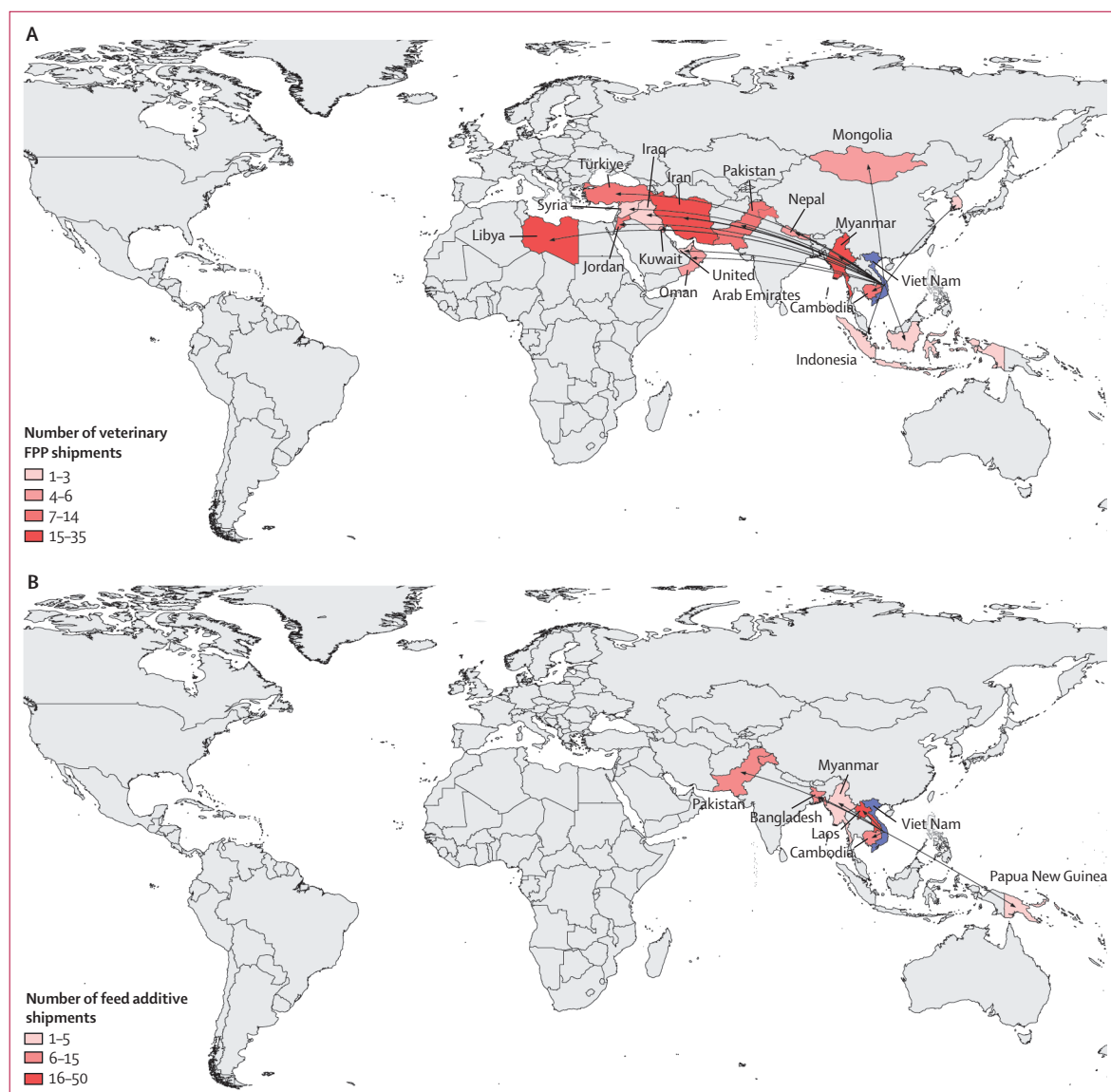


Figure 4: Colistin exports from Viet Nam in 2019–21

Exports of veterinary FPPs (A) and feed additives (B). Choropleth maps are based on the number of shipments recorded by Exim Trade Data to 20 countries from Viet Nam. FPP=finished pharmaceutical product.

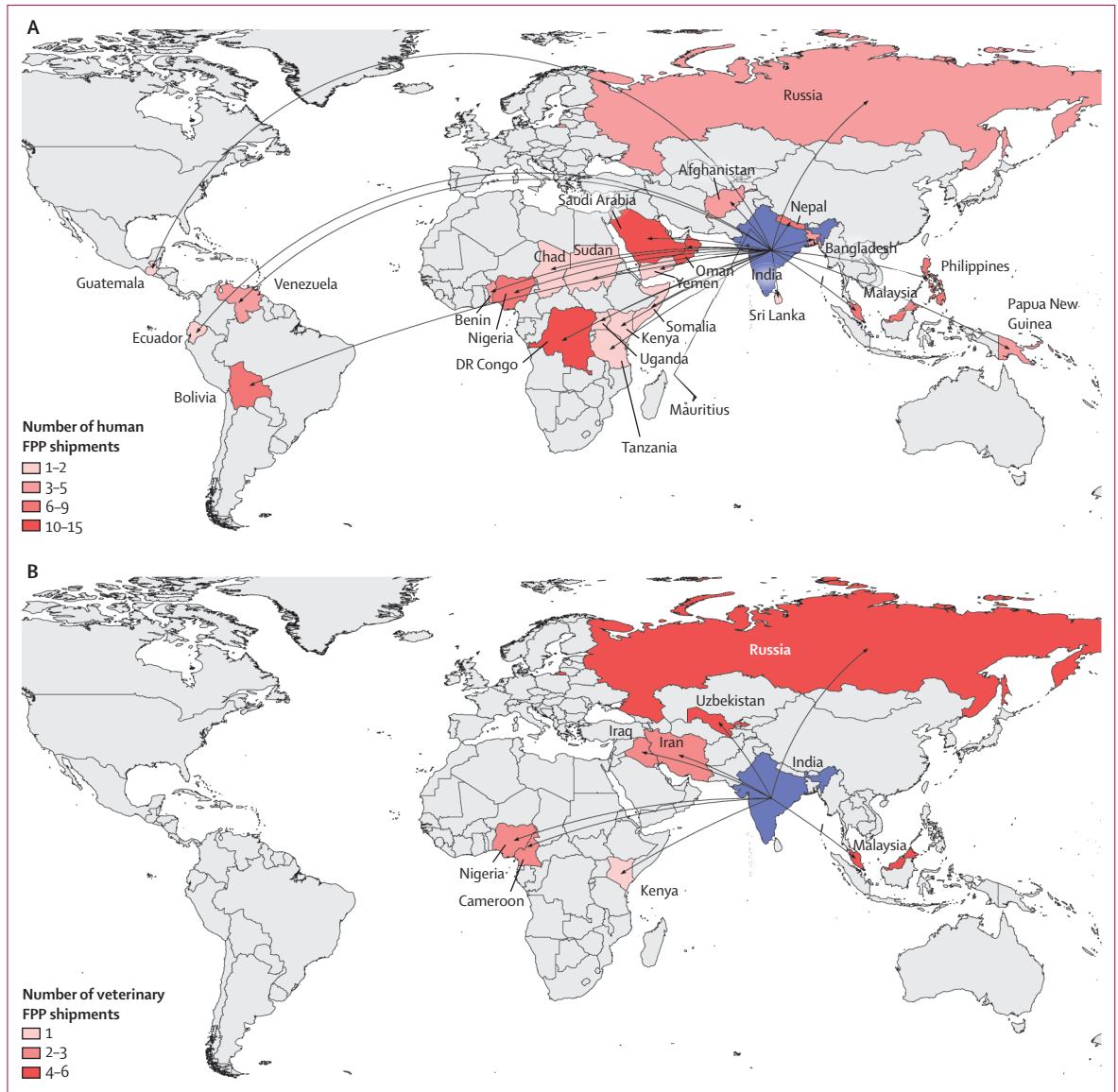


Figure 5: Colistin exports from India in 2018–21
Exports of human FPPs (A) and veterinary FPPs (B). Choropleth maps are based on the number of shipments recorded by Exim Trade Data to 29 countries from India. FPP=finished pharmaceutical product.

One Health antimicrobial resistance awareness, it is counterintuitive that, in 2022, colistin, an antibiotic that is listed as a WHO Critically Important Antimicrobial for Human Medicine,¹⁶ is still sold and disseminated as an antimicrobial growth promoter. This study also reports Pakistani and Nigerian farmers’ understanding of colistin and its consequences on colistin resistance, which was mostly poor, emphasising the need for improved public awareness on antibiotic consumption across all cultures and socioeconomic sectors.

The emergence of MCRPEEC throughout the agriculture sector is likely to be driven by the use of colistin in animal feed, as has been shown by studies before and after the ban of colistin in China.² Knowing that colistin was widely

used in Pakistan, we undertook a One Health surveillance study for MCRPEEC in Faisalabad, Pakistan. Our data showed that carriage was highest in wild birds (ie, crows and kites), which possibly scavenge from farm waste and dead poultry from farms in which colistin is used and are also capable of flying large distances and spreading MCRPEEC through faecal waste. High MCRPEEC carriage was also found in healthy commercial broilers (17%) and chicken meat (13%), which is consistent with previous reports.¹⁷ Among the countries importing colistin that were included in this study, Bangladesh has a high prevalence (25%)¹⁸ of *mcr-1* among *E coli* sourced from commercial chicken compared with a lower prevalence (2.8%)¹⁹ in Nigeria. The 8% carriage in flies

also testifies to the One Health aspect of MCRPEC, because flies feed off of faeces and farmyard organic matter, and as previously shown, insects are disseminators of extremely drug-resistant bacteria in surgical infections in south Asian hospitals.²⁰

We found a large diversity in sequence types of MCRPEC; however, *mcr-1* was consistently found on Inc12 (~62 kb) plasmids among MCRPEC recovered from different niches. We identified an inverse association between MCRPEC and antimicrobial class cephalosporins, carbapenems, phosphonic acid derivatives, and glycolcyclines, which are infrequently used in food-producing animals,^{10,21} indicating independent selection and horizontal transmission of *mcr-1*, possibly due to colistin pressure. Our findings indicate the wide dissemination of *mcr-1* in different niches, emphasising the urgent need for effective implementation of antimicrobial resistance control policies by use of One Health surveillance.

In this study, we observed high *mcr-1* prevalence (7%) compared with the global figure (4.7%) reported by Elbediwi and colleagues in 2019.²² Bastidas-Caldes and colleagues reported 6.5% prevalence of MCRPEC and Asia had the largest diversity of *mcr* variants,²³ and Dadashi and colleagues reported 1.3% global prevalence of colistin-resistant *E coli* with a high prevalence observed in Asia and Africa.²⁴ After the discovery of *mcr-1* in 2015, China banned the use of colistin as a growth promoter in 2017,³ and in 2019, the Chinese Ministry of Agriculture and Rural Affairs introduced new regulations on the administration of feed and feed additives to ensure the safety of food derived from animal sources and public health.²⁵ A significant decrease in MCRPEC prevalence (from 14.3% to 6.3%) was observed between 2016 and 2019 after the ban of colistin as a growth promoter.² Accordingly, although China has been proactive in ensuring that animal feeds in poultry (and pig) production are free of antimicrobials within China, paradoxically it continues to manufacture non-human colistin for international export. Antimicrobial resistance is a One Health, one-world phenomenon without international borders; therefore, these practices appear counterintuitive.

In the beginning of 2019, the EU attempted to address the issue of veterinary medicines with respect to the health consequences in both humans and animals;²⁶ however, the text is non-committal and not enforced by EU law. Consequently, companies operating in Andorra, Austria, Belgium, Denmark, France, Germany, the Netherlands, Spain, and Switzerland import and export colistin to be used in LMICs, which has been repeatedly shown to drive colistin resistance from the animal sector into communities.²⁷ Despite European manufacturing and exports of colistin FPPs (including to Africa and Asia), we observed that PRM imports data were not readily available for Europe, which should be regulated under antimicrobial surveillance programmes.

Although this study is unique and multifaceted, we note that it has limitations. Firstly, the export data have variable coverage for different countries. Additionally, the export data were retrieved on the basis of the search word “colistin” and do not cover the trade (ie, exports and imports) of colistin PRM, feed additives, or FPPs under harmonised system codes or the colistin products marketed under different brand names. Secondly, the data are not representative of the total colistin production, which also includes domestic use and exports, due to fragmented coverage of the export and import databases of China, Viet Nam, and India; however, the findings can be used as an estimation of the international trade of colistin among different countries. Indeed, our findings are likely to underestimate its international trade. Finally, the questionnaire responses might have been subject to bias in terms of participant selection and interviewer interactions with the respondent.

Antimicrobial use in food systems is common practice, and projections suggest that use will increase by 11.5% from 2017 to 2030.²⁸ The Global Leaders Group on Antimicrobial Resistance have called on all countries to end the use of medically important antimicrobials (eg, colistin) for growth promotion entirely, reduce antimicrobial prophylaxis and metaphylaxis, eliminate the use of antimicrobials to compensate for inadequate agricultural practices, and markedly reduce the use of antimicrobials, particularly those on the WHO priority list.⁶ However, although these esteemed notions might be implementable in high-income countries, in LMICs, their execution will result in decreased meat production and increased meat prices, with an inevitable increase in local poverty. Notably, feed additive antimicrobials are not being registered and regulated by the Drug Regulatory Authority of Pakistan, because they are imported under the import item category of feed additives. Therefore, it is imperative to understand country-specific antimicrobial supply chains and veterinary practices before embarking on any legislation and trade control strategies. Regulatory laws and structures in LMICs are often inadequate to monitor and enforce antimicrobial growth promoter restrictions, and antimicrobial growth promoter use is further abetted by poor governance, counterfeit medicines, and unregulated internet sales.²⁹ Moreover, despite the agreement of 193 countries on the UN declaration to combat antimicrobial resistance in 2016,³⁰ the manufacturing and trade of colistin (listed on the WHO list of Critically Important Antimicrobials for Human Medicine) as PRM, FPPs, and feed additives still continues.

Global meat consumption is projected to increase by 14% in 2030,³¹ and LMICs in particular will need to ensure that farming practices meet the demands of a growing human population. Farmers in LMICs will need support to make the necessary improvements in farm hygiene, management, and animal husbandry to enable

restrictions on the use of antimicrobials while still protecting animal welfare and avoiding catastrophic losses of livestock from disease. One obvious solution would be to use animal feed additives containing antimicrobials that are not used in humans and, crucially, do not select for resistance against human antibiotics.³² However, the 2022 European Medicines Agency update on veterinary medicinal products still advocates the use of many human antibiotics in veterinary practices, including colistin.³³ The support needed to deliver changes in the manufacturing, trade, and veterinary use of antimicrobials that are essential for human medicine is insufficient and will take considerable commitment from all global stakeholders, including adequate financial support (in some countries, pharmaceutical raw colistin for animal use costs approximately \$10 per kg)³⁴ to ensure rigorous implementation and sustainability. Any global solution should not mitigate animal welfare nor negate the alleviation of poverty in LMICs, which is a key Sustainable Development Goal. Therefore, alternative, cost-effective solutions should be found to prevent diseases and thereby sustain global poultry production without inducing collateral resistance to human antibiotics.

Contributors

MM, TRW, BH, and MU conceived and designed the study. QA, BH, MU, RF, KS, and JM collected and processed the samples. MU and BH curated the genomic data, and BH and RF did the analyses and representation. MU, MM, RF, SA, and MNH collected the manufacturing and trade data, and MU did the analysis and representation. MU, BH, RF, and KS wrote the method and results. MM, TRW, MU, RF, BH, KS, and SA reviewed the method and results. TRW and MM wrote the introduction and discussion. MU, RF, and TRW formatted the manuscript. MU curated and formatted the appendices. MM, TRW, MU, RF, and BH critically reviewed the manuscript and appendices. MU, BH, RF, TRW, and MM accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All the Excel metadata workbooks and government documents are in the appendices. Database datasets, Excel analysis workbooks, and other data can be requested via email to the corresponding authors. Whole genome sequencing data is submitted to NCBI and can be accessed via BioProject accession number PRJNA871112.

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