

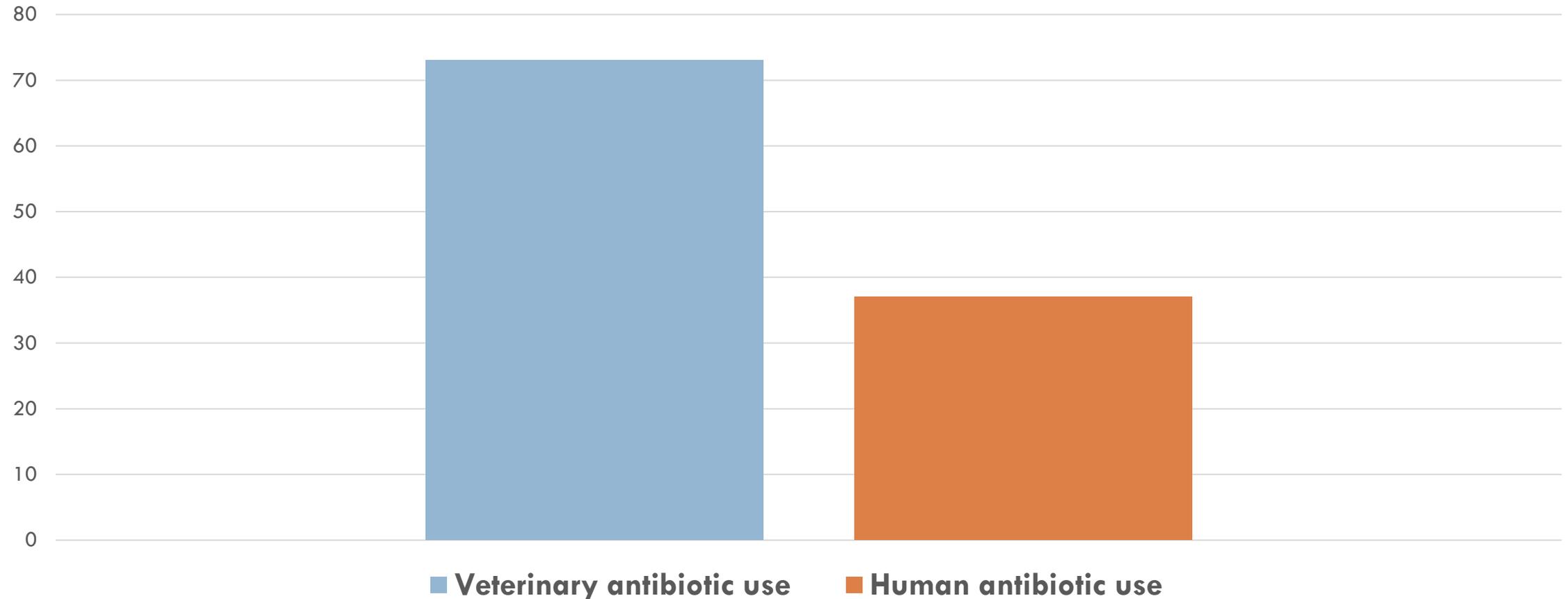
INTENSIVE FARMING, ANTIBIOTIC RESISTANCE AND PANDEMICS

**The need for a One Health approach
June 2020**

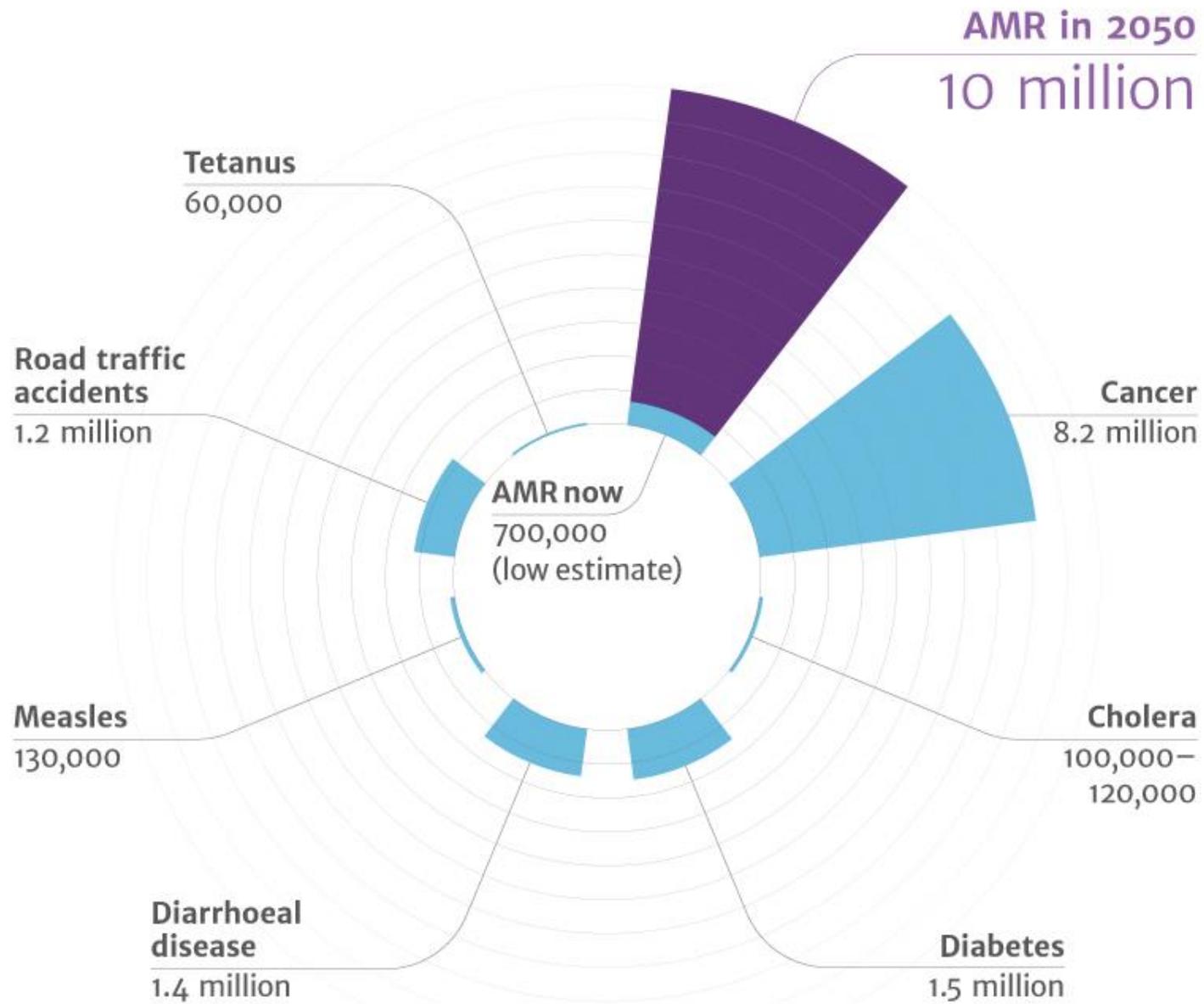


Antibiotic use in animals and humans globally

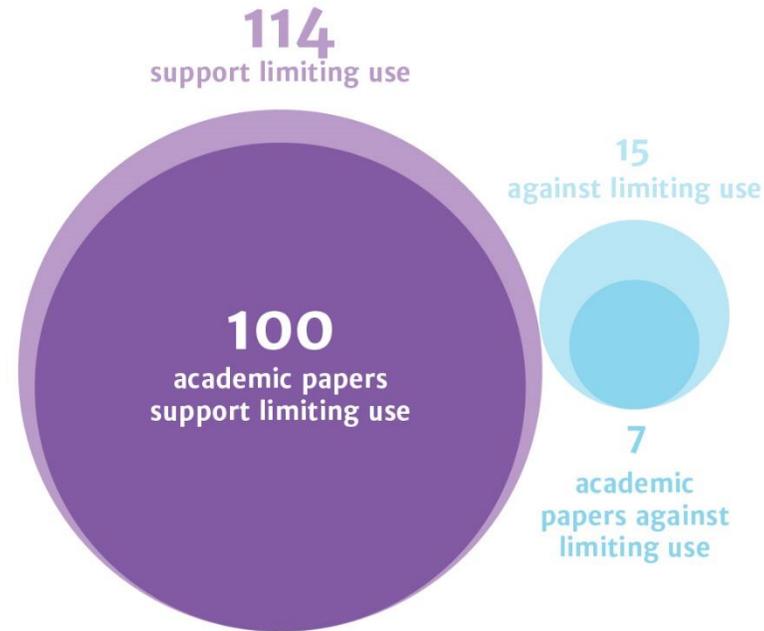
(Van Boeckel et al. 2017, Science and Van Boeckel et al. 2019, Science)



Farm antibiotic use projected to increase by 50% between 2013 and 2030 if we continue with business as usual (van Boeckel et al. 2017)



MOST PUBLISHED PAPERS PROVIDE EVIDENCE TO SUPPORT LIMITING USE OF ANTIBIOTICS IN AGRICULTURE



Based on a representative sample using the 280 papers from the NCBI's PubMed database found with the search terms "drug resistance, microbial" AND "agriculture", 88 of which were deemed not to be applicable as they did not address antibiotic use in agriculture. Papers were categorised as 'supportive', if they provided evidence to support limiting antibiotics in agriculture, 'against', if they provided evidence that we should not be concerned with limiting antibiotics in agriculture and 'neutral', if they did not explicitly take a stance. There were 63 papers that were categorised as neutral. Of the papers classified as neutral, 36 were written by academics. Academic papers are defined as those that were written by academics.

Source: Review's own analysis.



Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

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Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Methods The *mcr-1* gene in *E coli* strain SHP45 was identified by whole plasmid sequencing and subcloning. MCR-1 mechanistic studies were done with sequence comparisons, homology modelling, and electrospray ionisation mass spectrometry. The prevalence of *mcr-1* was investigated in *E coli* and *Klebsiella pneumoniae* strains collected from five provinces between April, 2011, and November, 2014. The ability of MCR-1 to confer polymyxin resistance in vivo was examined in a murine thigh model.

Findings Polymyxin resistance was shown to be singularly due to the plasmid-mediated *mcr-1* gene. The plasmid carrying *mcr-1* was mobilised to an *E coli* recipient at a frequency of 10^{-1} to 10^{-3} cells per recipient cell by conjugation, and maintained in *K pneumoniae* and *Pseudomonas aeruginosa*. In an in-vivo model, production of MCR-1 negated the efficacy of colistin. MCR-1 is a member of the phosphoethanolamine transferase enzyme family, with expression in *E coli* resulting in the addition of phosphoethanolamine to lipid A. We observed *mcr-1* carriage in *E coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection.

Interpretation The emergence of MCR-1 heralds the breach of the last group of antibiotics, polymyxins, by plasmid-mediated resistance. Although currently confined to China, MCR-1 is likely to emulate other global resistance mechanisms such as NDM-1. Our findings emphasise the urgent need for coordinated global action in the fight against pan-drug-resistant Gram-negative bacteria.

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A Role for Tetracycline Selection in Recent Evolution of Agriculture-Associated *Clostridium difficile* PCR Ribotype 078

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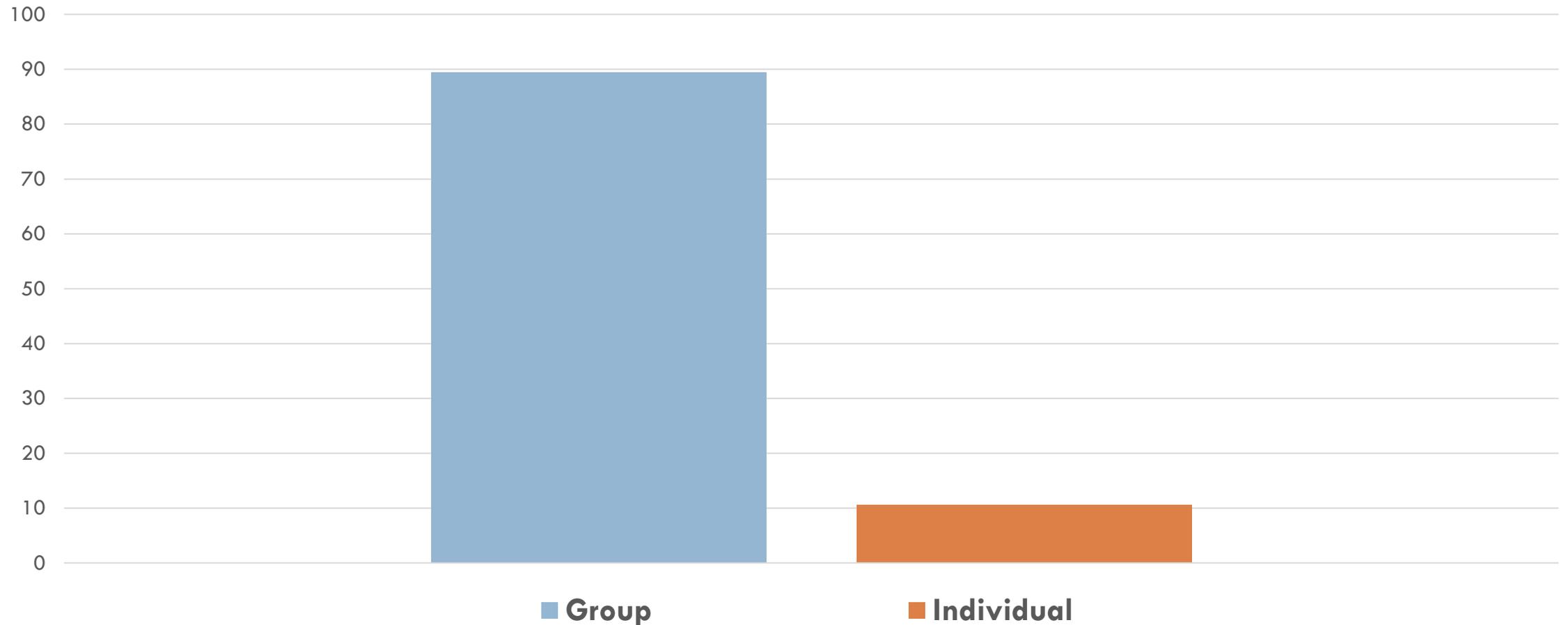
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ABSTRACT The increasing clinical importance of human infections (frequently severe) caused by *Clostridium difficile* PCR ribotype 078 (RT078) was first reported in 2008. The severity of symptoms (mortality of $\leq 30\%$) and the higher proportion of infections among community and younger patients raised concerns. Farm animals, especially pigs, have been identified as RT078 reservoirs. We aimed to understand the recent changes in RT078 epidemiology by investigating a possible role for antimicrobial selection in its recent evolutionary history. Phylogenetic analysis of international RT078 genomes (isolates from 2006 to 2014, $n = 400$), using time-scaled, recombination-corrected, maximum likelihood phylogenies, revealed several recent clonal expansions. A common ancestor of each expansion had independently acquired a different allele of the tetracycline resistance gene *tetM*. Consequently, an unusually high proportion (76.5%) of RT078 genomes were *tetM* positive. Multiple additional tetracycline resistance determinants were also identified (including efflux pump *tet40*), frequently sharing a high level of nucleotide sequence identity (up to 100%) with sequences found in the pig pathogen *Streptococcus suis* and in other zoonotic pathogens such as *Campylobacter jejuni* and *Campylobacter coli*. Each RT078 *tetM* clonal expansion lacked geographic structure, indicating rapid, recent international spread. Resistance determinants for *C. difficile* infection-triggering antimicrobials, including fluoroquinolones and clindamycin, were comparatively rare in RT078. Tetracyclines are used intensively in agriculture; this selective pressure, plus rapid, international spread via the food chain, may explain the increased RT078 prevalence in humans. Our work indicates that the use of antimicrobials outside the health care environment has selected for resistant organisms, and in the case of RT078, has contributed to the emergence of a human pathogen.

Citation Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Marwick CA, Cola J, Brown D, Buchanan S, Ijaz UZ, Goswami C, Douce G, Fawley WN, Wilcox MH, Peto TEA, Walker AS, Crook DW. 2019. A role for tetracycline selection in recent evolution of agriculture-associated *Clostridium difficile* PCR ribotype 078. mBio 10:e02790-18. <https://doi.org/10.1128/mBio.02790-18>.

Editor Paul Kelm, Northern Arizona University

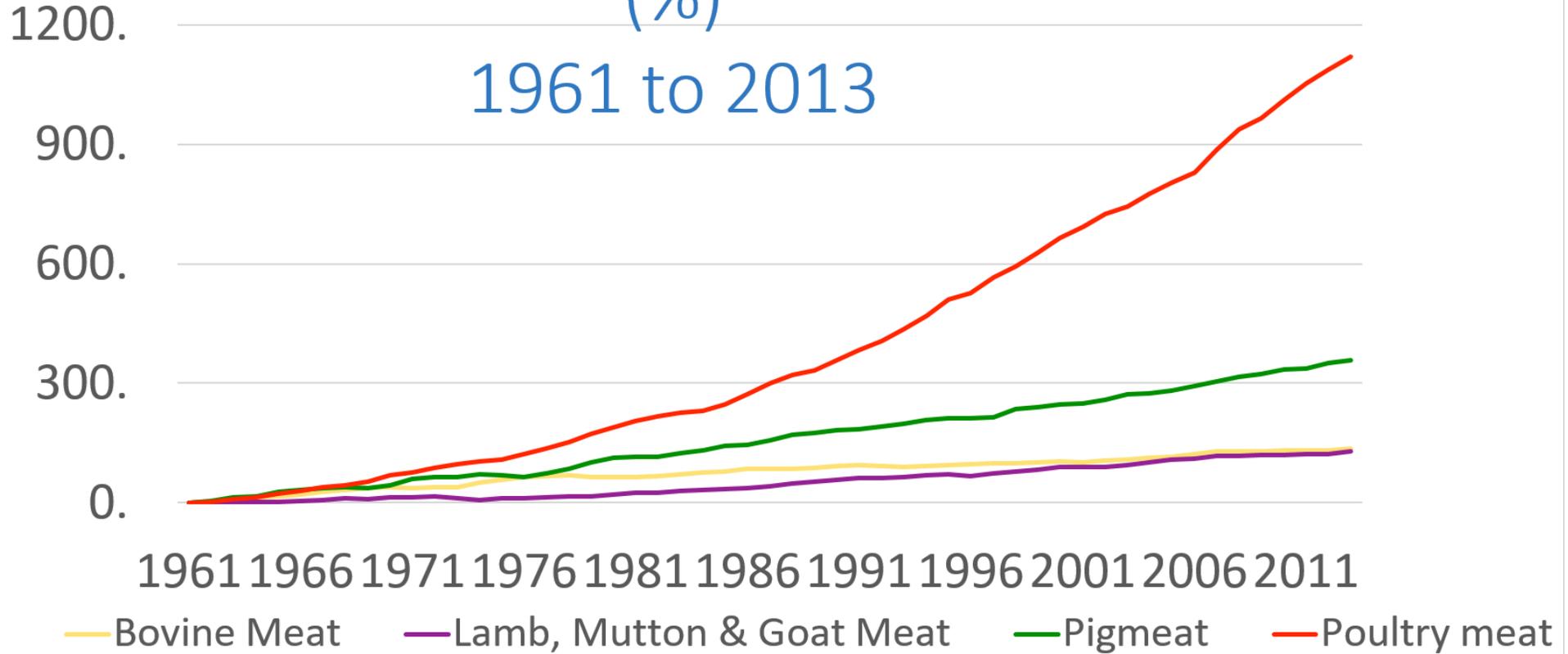
Farm antibiotic treatments in Europe – group v individual (ESVAC 2019)



Increases in global meat consumption

(%)

1961 to 2013





Bureau of Investigative Journalism



Bureau of Investigative Journalism



Compassion in World Farming



Compassion in World Farming

Alliance to Save our Antibiotics June 2020



UNEP FRONTIERS 2016 REPORT

Emerging Issues of Environmental Concern



“Demand for livestock products leads to more intensive production, that is greater populations of high yielding and genetically similar stock kept close together.

Thus the animals are not only exposed to more contact opportunities but they also lack the genetic diversity that helps resist the spread of disease, a vulnerability known as the monoculture effect.”

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About this content

Michael Standaert

Wed 27 May 2020 08.30 BST



1,580

'Unstoppable': African swine fever deaths to eclipse record 2019 toll

With world's attention on Covid-19, warnings that lack of measures to contain pandemic could lead to culling of record number of pigs



▲ A pig is tested for African Swine Fever in Manila, Philippines, during the 2019 outbreak. Photograph: Rolex dela Peña/EPA

The African swine fever (ASF) pandemic will be even worse this year than in 2019, say experts, warning that the spread of the highly contagious virus, which is fatal to pigs, is unrelenting.

With world attention on the human viral pandemic of Covid-19, concern is growing that countries are not focusing enough on halting the spread of ASF through better biosecurity practices, cooperation on intensive vaccine development, or transparency regarding outbreaks.

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UNEP FRONTIERS 2016 REPORT

Emerging Issues of Environmental Concern



“Around 60 per cent of all infectious diseases in humans are zoonotic as are 75 per cent of all emerging infectious diseases. [...]

While many originate in wildlife, livestock often serve as an epidemiological bridge between wildlife and human infections. This is especially the case for intensively reared livestock which are often genetically similar within a herd or flock and therefore lack the genetic diversity that provides resilience: the result of being bred for production characteristics rather than disease resistance.”

When low pathogenic viruses are transmitted to vulnerable poultry species, only mild symptoms such as a transient decline in egg production or reduction in weight gain are induced.

However, where a dense poultry environment supports several cycles of infection, the viruses may mutate, adapting to their new hosts, and for the H5 and H7 subtypes these mutations can lead to generation of a highly pathogenic form.

Thus, highly pathogenic avian influenza viruses are essentially products of intensively farmed poultry, the incidence of which has increased dramatically with the greatly enhanced volume of poultry production around the world. [...]

In general, they should be viewed as something artificial, made possible by intensive poultry production techniques.”

Scientific Task Force on Avian Influenza and Wild Birds (UNEP/FAO/CMS), 2008

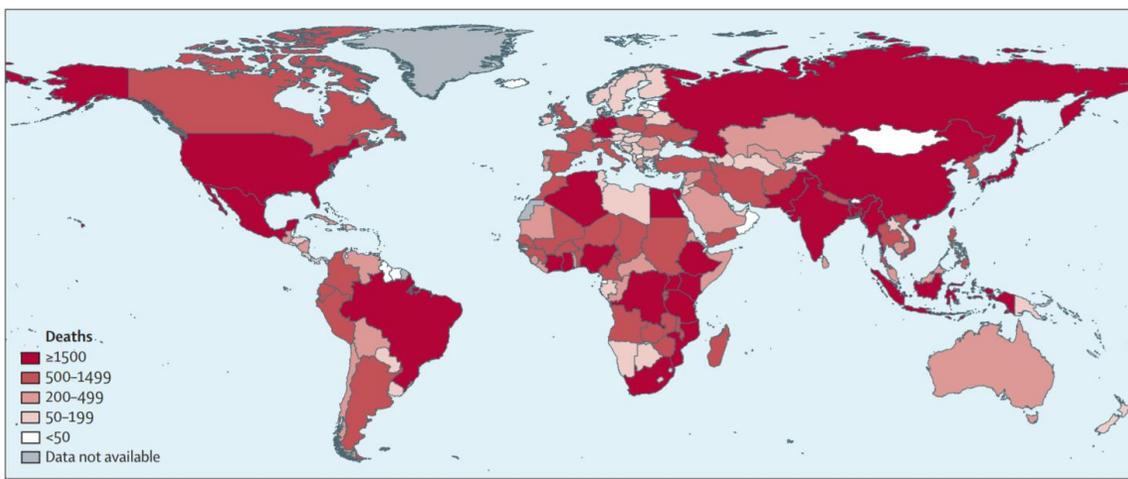
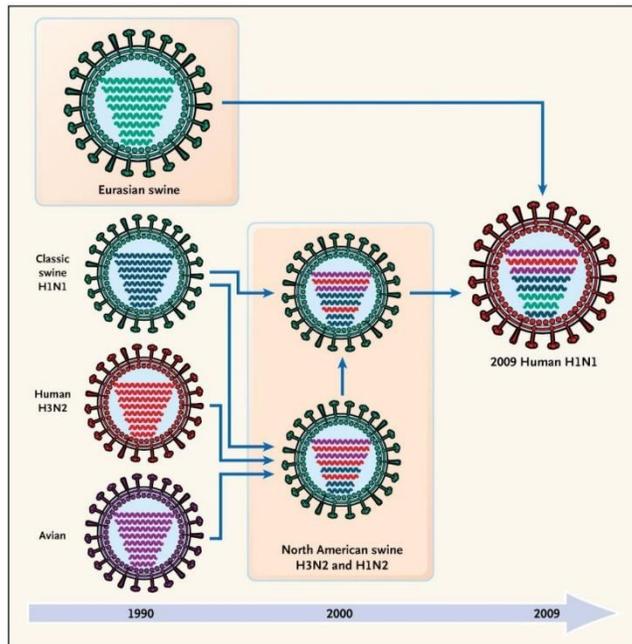


Figure 1: Global distribution of deaths associated with 2009 pandemic influenza A H1N1 during the first year of virus circulation by country

Dawood et al. 2012

- In 2009, a new pandemic strain of influenza H1N1 emerged in North America.
- Spread around the world, affecting mainly younger and middle-aged people.
- Study co-authored by CDC estimated pandemic killed between 150,000 and 575,000 people.



Trifonof et al. 2009

- Of animal origin and genetic analyses linked the new pandemic influenza to a “triple reassortment” strain that had circulated in pigs for years (a mix of pig/avian/human influenza viruses) which combined with another pig strain. Pigs are “mixing vessels” for influenza.
- Influenza is a seasonal disease in humans, but in intensive pig farming flu viruses circulate all year round, providing many opportunities for the emergence of new pathogenic strains which may spread to humans.

Nipah virus: spread from bats to pigs to humans

- Emerged in pigs Malaysia in 1999 and is believed to have spread from bats. Associated with the encroachment of large commercial pig farms into forested areas of high fruit bat activity (Field 2009).
- Malaysian outbreak killed over 100 humans, many of them pig farmers.
- High pig and farm density led to rapid spread in pigs. Over 1 million pigs were culled.

Covid-19 is a zoonosis too

- Origin is still unproven, but is believed to have transmitted from bats via an intermediate species, possibly pangolins.
- Attempts to experimentally infect small numbers of various animals with the new virus failed to infect pigs or chickens (Shi et al. 2020). This suggests that livestock may not be involved in the emergence of this new pathogen.
- However, an in vitro study looking at cell lines from many different animals found that "SARS-CoV-2 replicated most robustly in non-human primate cells and pig cells" (Chu et al. 2020).

Coronaviruses in pigs

- Pigs are susceptible to infection by at least six different coronaviruses (believed to be of bat or bird origin). These have caused huge economic costs and some are considered public-health threats (Pan et al. 2020).
- Sudden re-emergence of porcine epidemic diarrhea (coronavirus) in US piglets in 2013 caused death of over 8 million pigs. May have originated from bats in China (Huang et al. 2013).
- Porcine deltacoronavirus emerged in pigs China in 2012. Believed to have spread from birds. In vitro tests suggest humans may be susceptible. Potential for spreading to other species, including humans, described as “alarming” (Li et al. 2018).
- In 2017, “Swine acute diarrhoea syndrome” coronavirus emerged in pigs in China, killing 25,000 piglets. Shown to have spread from bats (Zhou et al. 2018). “Might transmit to humans in the future”.
- Co-infection with different types of coronavirus also occurs in intensively farmed pigs, raising the possibility of viral recombination (Leopardi et al. 2020).

“Given that pigs are in frequent contact with human and multiple wildlife species, and that pork is one of the most commonly consumed meats in non-Muslim countries, it is important to assess whether pigs could be mixing vessels for the emergence of novel coronaviruses with high agricultural impact and risks to public health.”

Wang et al. 2018

“Subclinical circulation of coronaviruses in pigs might present a risk to animals and, potentially, to human health.[...] The cocirculation of coronaviruses is worrisome as it might favour the emergence of potential epidemic strains through recombination events”

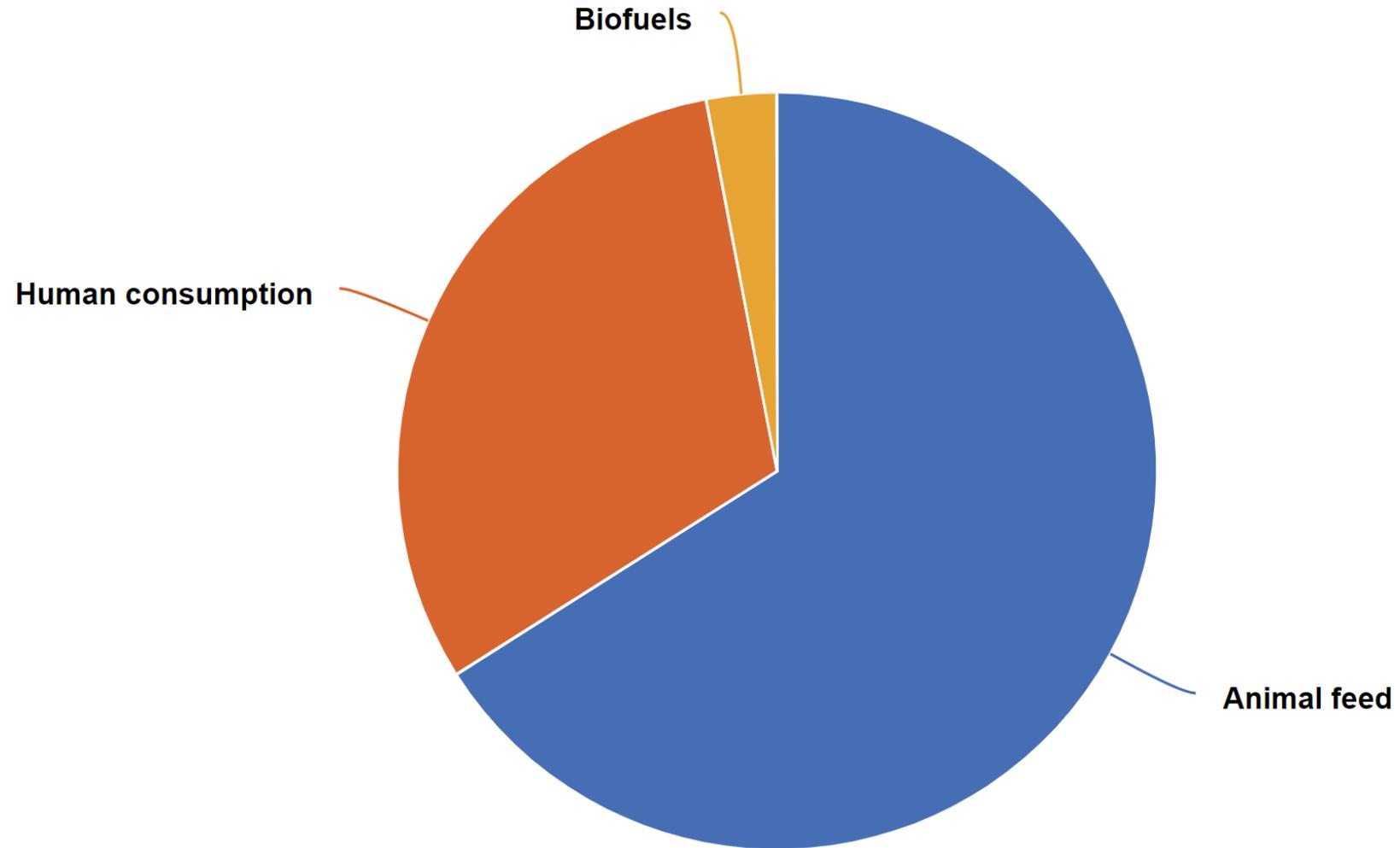
Leopardi et al. 2020

Habitat loss, deforestation and emerging infectious diseases

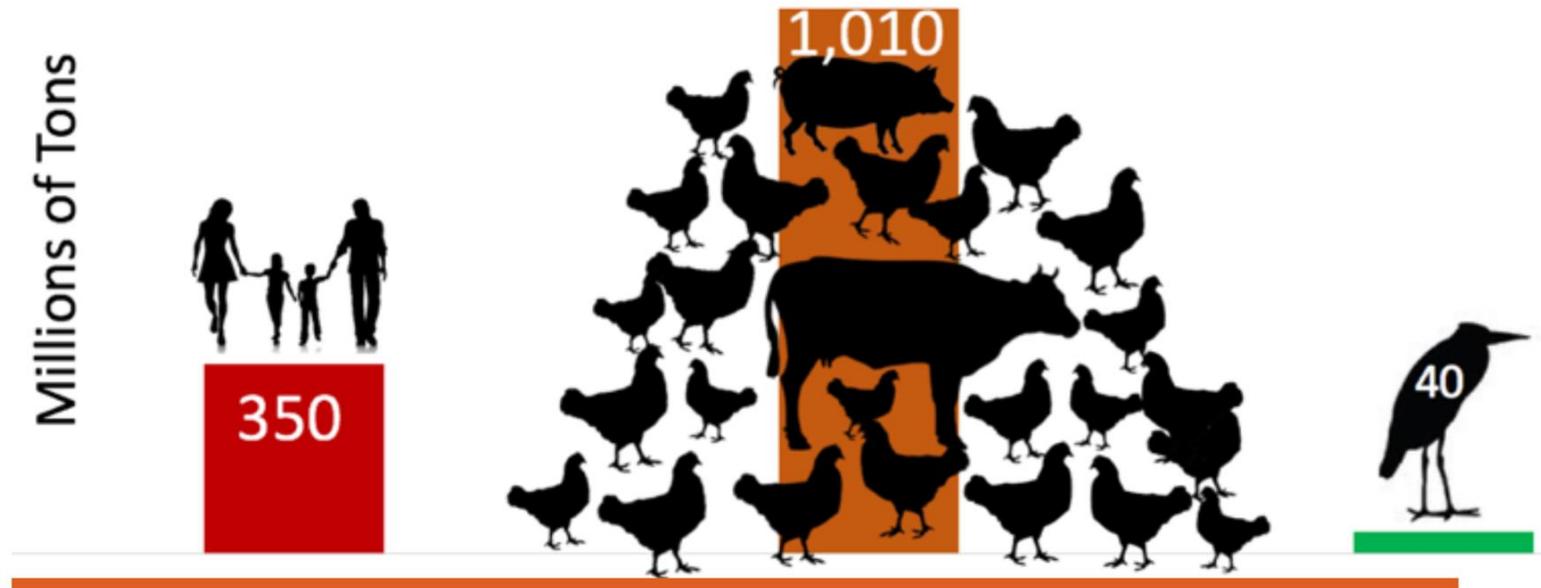
- Scientists increasingly say that habitat loss, deforestation and the loss of biodiversity caused by population growth, road building, logging, mining and agriculture is a major cause of new pathogens spreading from wildlife to humans (UNEP 2016). This process may explain the emergence of Covid-19.
- According to the Food and Agriculture, 80% of global deforestation is occurring to clear land for agriculture.

EU's cereals consumption

Source: European Commission



Estimated total weight of humans, livestock and terrestrial vertebrate wildlife



Van Boeckel 2017, adapted from Smil 2002

Media centre

Stop using antibiotics in healthy animals to prevent the spread of antibiotic resistance

News release

7 NOVEMBER 2017 | GENEVA - WHO is recommending that farmers and the food industry stop using antibiotics routinely to promote growth and prevent disease in healthy animals.

The new WHO recommendations aim to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their unnecessary use in animals. In some countries, approximately 80% of total consumption of medically important antibiotics is in the animal sector, largely for growth promotion in healthy animals.

— [WHO guidelines on use of medically important antimicrobials in food-producing animals](#)

Over-use and misuse of antibiotics in animals and humans is contributing to the rising threat of antibiotic resistance. Some types of bacteria that cause serious infections in humans have already developed resistance to most or all of the available treatments, and there are very few promising options in the research pipeline.

“A lack of effective antibiotics is as serious a security threat as a sudden and deadly disease outbreak,” says Dr Tedros Adhanom Ghebreyesus, Director-General of WHO. “Strong, sustained action across all sectors is vital if we are to turn back the tide of antimicrobial resistance and keep the world safe.”

A systematic review published today in *The Lancet Planetary Health* found that interventions that restrict antibiotic use in food-producing animals reduced antibiotic-resistant bacteria in these animals by up to 39%. This research directly informed the development of WHO's new guidelines.

WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

A real One Health approach is needed

- Routine antibiotic use in livestock must end, including preventative mass medication and growth promotion.
- Major improvements to animal husbandry needed. Intensive indoor farming is unhealthy for animals and humans. We recognise the importance of “social distancing” and the safety of the outdoors for limiting Covid-19 spread, so why do we think disease spread for livestock is any different?
- Ecosystems must be protected as diversity provides resilience which helps limit the spread of disease. Ecosystems are likely to suffer further damage if global expansion of intensive livestock farming continues.