The impacts of animal agriculture on One Health—Bacterial zoonosis, antimicrobial resistance, and beyond

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ABSTRACT

The industrialization of animal agriculture has undoubtedly contributed to the improvement of human well-being by increasing the efficiency of food animal production. At the same time, it has also drastically impacted the natural environment and human society. The One Health initiative emphasizes the interdependency of the health of ecosystems, animals, and humans. In this paper, we discuss some of the most profound consequences of animal agriculture practices from a One Health perspective. More specifically, we focus on impacts to host-microbe interactions by elaborating on how modern animal agriculture affects zoonotic infections, specifically those of bacterial origin, and the concomitant emergence of antimicrobial resistance (AMR). A key question underlying these deeply interconnected issues is how to better prevent, monitor, and manage infections in animal agriculture. To address this, we outline approaches to mitigate the impacts of agricultural bacterial zoonoses and AMR, including the development of novel treatments as well as non-drug approaches comprising integrated surveillance programs and policy and education regarding agricultural practices and antimicrobial stewardship. Finally, we touch upon additional major environmental and health factors impacted by animal agriculture within the One Health context, including animal welfare, food security, food safety, and climate change. Charting how these issues are interwoven to comprise the complex web of animal agriculture's broad impacts on One Health will allow for the development of concerted, multidisciplinary interventions which are truly necessary to tackle these issues from a One Health perspective.

1. Overview

With the rapid growth of Earth's population, there is a concomitant rapidly increasing demand to enhance agricultural productivity and quality [1–4]. In particular, there has been an unprecedented increased demand for animal protein and animal products [5]. In Asia, daily animal protein intake has more than tripled over the past fifty years, particularly among higher income demographics [6,7]. This increased demand has ultimately resulted in the global biomass of food animals surpassing that of humans, which has by necessity transformed the ways in which modern agriculture is conducted [6]. The significant progresses made in agricultural technologies, from CRISPR/Cas9 gene editing for breeding to harnessing the microbiome for promoting yield, have also revolutionized modern agriculture [8–11]. Although all agricultural transitions have aimed at improving human well-being, they also inevitably cause collateral damage to the health of animals, humans and the environment, which is the center of the One Health initiative. Although we recognize the importance of both crop and food animal production in agriculture and their impacts on One Health, we have focused this review primarily on animal agriculture, particularly livestock and poultry, and the critical interactions between these hosts and their pathogens from a One Health perspective. Aquaculture is another rapidly-growing

arm of the animal agriculture industry that also has important impacts on zoonoses and antimicrobial use, but which operates in unique ways relative to terrestrial agriculture [12,13], and therefore is not within the scope of this review.

One axis along which animal agriculture plays a vital role in animal and human health is zoonosis, infectious diseases transmitted between humans and animals. Zoonotic transmission can occur via direct or indirect contact with animals and their environments; consumption of animal products or water that has been contaminated by animals; as well as via an intermediate species such as an insect vector. Although zoonotic pathogens often require orchestrated alignment of environmental, pathogenic and host factors to overcome barriers to animal-to-human transmissions, they are capable of adapting to cause infections in humans [14–16], and are thought to account for an estimated two-thirds of recent major infectious disease outbreaks. The 2009 H1N1 "swine flu" influenza outbreak is a recent example of an agriculture-derived epidemic, although viral zoonoses will not be the focus of this review.

Bacterial zoonoses also have potential to act as "emerging" zoonoses; for example, the increasing prevalence of human tuberculosis infections resulting from infections with *Mycobacterium bovis* and *Mycobacterium caprae* that have crossed over from livestock and wild animals [17]. The infamous spore-forming bacterium *Bacillus anthracis* is causing increased livestock and zoonotic infections worldwide, often as a result of climate change-induced flooding which can liberate spores from the soil, as has been seen recently in Pakistan [18]. Endemic bacterial zoonoses often have the greatest impacts on human and animal health, particularly in low- and middle-income countries (LMICs). Foodborne pathogens, the majority of which are bacterial zoonoses, cause over 300 million human infections per year, often as a direct result of animal agriculture [19]. The growing scope of animal agriculture in recent history has changed the frequency and ways in which we interact with animals, in many cases increasing risks of zoonotic transmission. Although they often take a back seat to emerging viral zoonoses, endemic and emerging bacterial zoonoses also pose significant threats to public health and take major tolls on our economy and society.

Another major aspect of animal agriculture's impact on One Health, intimately connected to bacterial zoonosis, is the overuse and misuse of antimicrobials in agriculture that has exacerbated the rapid emergence of antimicrobial resistance (AMR). Here, the term "antimicrobial" will be used to encompass antibiotics and other drugs currently approved to treat bacterial infections. Antimicrobial use is essential for treating bacterial infections in animals to promote animal health and welfare, secure food production, as well as prevent spread of bacterial infections to humans through direct contact with animals and animal food products. However, the development of resistance renders antimicrobials ineffective and jeopardises their medical benefits.

Despite some debates on the direct contributions of antimicrobial use in food animals to antimicrobial infections in humans [20–24], it is generally accepted that the excessive use of antimicrobials in animal agriculture is concerning given multiple factors. First, the practicality of animal medication often necessitates group antimicrobial treatment, resulting in overuse as well as inconsistent dosing, major drivers of resistance development. In fact, the use of antimicrobials in animal agriculture vastly outstrips medical use in humans [6,25]. For example, in 2016, the total volume of antimicrobials used to treat Canadian livestock was nearly four times the amount used in humans, a number which is likely even greater in countries with less strict antimicrobial legislation [26]. Globally, antimicrobial use in livestock is predicted to increase over 67% by 2030, from approximately 63,000 tons in 2010 to over 105,000 tons in 2030 [6]. Second, antimicrobials are often unnecessarily used for purposes other than infection treatment, such as disease prevention and growth promotion, contributing to the huge volumes of their usage [27]. Recently, many countries, such as Canada, the USA, China and several countries within the EU have passed legislation to ban the use of antimicrobials for growth promotion in agriculture; however, the practice still persists in many countries around the world, particularly LMICs such as India, South Africa, and Brazil, where food production is intensifying [6]. Lastly, the majority of antimicrobials used in food animals are excreted and have the potential to persist in the environment, exerting selective pressure for the development of resistance in environmental bacteria [28,29]. Multiple lines of evidence have demonstrated that both the residues of antimicrobials and emerging antimicrobial resistant bacteria and resistance genes constantly circulate in the ecosystem and can reach humans and animals and affect their health negatively [30–32]. Globally increasing trends in antimicrobial usage in animals as well as in humans have driven alarming increases in resistance rates to both established common-use and sequestered last-resort antimicrobials, which pose profound threats to One Health [33].

The impacts of animal agriculture on One Health are far-reaching, and stretch beyond zoonoses and antimicrobial resistance to encompass other major societal and environmental issues. Modern animal agriculture practices have important impacts on animal welfare, part of which includes animal infections and their management. Food safety and security are impacted by animal agriculture broadly and also specifically by zoonoses and AMR. More indirectly, animal agriculture also affects One Health through its impacts on the environment, such as through climate change. Both deforestation and the emission of greenhouse gases caused by the expansion of animal agriculture have contributed to the climate change crisis [34], which increases the frequency of extreme weather events and causes longer-term environmental changes such as desertification, thereby leading to broad and substantial impacts on animal, human, and even microbial health.

It is worth noting that numerous perspectives on animal agriculture are interconnected to impact the ever-growing field of One Health. In this paper, we focused our discussions primarily on the angle of infectious diseases. Although we include some examples of mitigation strategies that aim to alleviate these impacts, it is critical to incorporate multidisciplinary and cross-sectional approaches to holistically address these One Health issues at the environment-human-animal interface.

2. Bacterial zoonotic infections

It is estimated that 60% of all human pathogens and 75% of emerging diseases affecting humans are zoonotic [35]. Many serious infections in human history have originated in animals [36]. Some, like highly pathogenic viruses, emerge from rare spillover events, whereas others, like many foodborne bacterial pathogens, are endemic zoonoses which infect humans as readily as animals. Both emerging and endemic zoonoses have critical impacts on human health, with endemic zoonoses having under-recognized impacts particularly in LMICs. It is estimated that about one billion cases of zoonoses occur worldwide each year [37]. Animal agriculture has played a critical role in supporting the progress of human civilization, but its intensification over the last century to keep pace with modern demands is introducing unprecedented risks for zoonotic infection. Intensive modern animal agricultural practices see animals kept in close quarters, alongside the global shipment of both animal products and animals themselves, increasing risks of not only local but global spread of zoonotic infections, as we have seen not only with outbreaks such as avian and swine influenza, but also the spread of many bacterial pathogens.

In this section, we will outline a range of animal agriculture-related zoonotic diseases of specifically bacterial origin (Table 1), elaborate further on several notable bacterial zoonoses, and connect mitigation and treatment strategies developed for zoonoses to the interdependent crisis of antimicrobial resistance.

Transmission through food products is one of the most important pathways of human infection by pathogens, particularly bacteria. The most common foodborne pathogenic bacteria include *Campylobacter* spp.*, Salmonella* spp.*, Listeria* spp.*, Shigella* spp.*,* and *Escherichia coli* [38]. In 2015, the World Health Organization (WHO) released their first ever global estimate of foodborne diseases, where they reported that approximately 600 million cases of foodborne illness, resulting in

Table 1
Animal agriculture-associated bacterial zoonotic diseases.

Pathogen(s)	Disease in humans	Disease in animals	Agricultural animal host	Transmission
Bacillus anthracis	Anthrax	Anthrax	Livestock*	Respiratory (inhalation of spores from soil reservoir, animal products), oral (consumption of contaminated water), skin (contact with animal products)
Clostridium spp.	Gastroenteritis, tetanus	Gastroenteritis, blackleg	Poultry, livestock (cattle, sheep, pigs)	
Coxiella burnetti	Q fever	Abortion, infertility, mastitis	Livestock (cattle, goats, sheep)	Respiratory (inhalation of aerosols**)
Brucella spp. (*B. abortus, B. suis*)	Brucellosis	Abortions, infertility, decreased milk production, arthritis (lameness)	Livestock	Respiratory (aerosol), oral (consumption of infected milk or meat)
Mycobacterium bovis, Mycobacterium caprae	Tuberculosis	Tuberculosis	Livestock, llamas, camels, domestic cats	
Leptospira spp.	Leptospirosis, Weil's disease (severe form characterized by kidney, liver, heart failure)	Abortions and infertility (pigs and cattle), decreased milk production (cattle), gastroenteritis, kidney/liver disease	Livestock, dogs, rodents	Direct contact (through cuts in the skin, or via mucosal surfaces), oral (consumption of contaminated meat, milk, water)
Campylobacter spp. (*C. jejuni, C. colis*)	Campylobacterosis (gastroenteritis), Guillain-Barre Syndrome (*C. jejuni* specifically)	Largely asymptomatic	Poultry, livestock	Oral (consumption of infected meat, eggs, dairy; contact with feces)
Escherichia coli	Gastroenteritis	Largely asymptomatic	Poultry, livestock	
Listeria spp. (*L. monocytogenes*)	Listeriosis (gastroenteritis)	Encephalitis, abortions, myocarditis, septicemia, hepatitis (monogastric animals and poultry)	Poultry, livestock, rabbits, domestic cats and dogs	
Salmonella spp. (Non-typhoidal *S. enterica* subspecies, *S. bongori*)	Salmonellosis (gastroenteritis)	Asymptomatic in some species, but can cause gastroenteritis, abortions, septicemia	Poultry, livestock	
Shigella spp. (*S. flexneri*)	Shigellosis (gastroenteritis, dysentery)	Gastroenteritis, dysentery	Poultry, livestock (cattle, pigs)	
Yersinia enterocolitica	Yersiniosis (gastroenteritis)	Largely asymptomatic	Poultry, livestock	
Staphylococcus aureus	Pyogenic infection, Pneumonia, meningitis, endocarditis, Septicemia	Pyogenic infection, Septicemia	Poultry, livestock	Respiratory (aerosol), direct contact (through cuts in the skin, or via mucosal surfaces)

* Livestock animals encompass common livestock including cattle, pigs, goats, and sheep—less common livestock and/or particular livestock hosts are mentioned specifically where relevant.
** Aerosols can be generated from bedding soiled with manure or urine, birthing byproducts, unpasteurized milk, or other bodily fluids.

420,000 deaths, occur per year [19,39]. Of these, more than half are caused by pathogenic bacteria.

Farm animals, such as poultry, swine, and cattle, are the main reservoirs and sources of human infection with these pathogens. In addition, contaminated farming environments are also an important route of transmission, such as soil contaminated with *B. anthracis* or *Clostridium* spp. [40]. However, most of these pathogens, such as *Campylobacter* spp., *Listeria* spp., and *Shigella* spp., act as opportunistic pathogens, colonizing the intestinal tracts of agricultural animals often without exhibiting significant clinical symptoms [41,42]. The frequently subclinical presentation of these pathogens, alongside many other challenges, makes it difficult to administer targeted vaccines or drugs to prevent or control infection in animals. Contamination during slaughtering and processing can lead to spread of these pathogens to meat and other animal products, such as dairy or eggs. Risks of human infection are significantly greater in LMICs due to global gaps in food safety practices. Many of these bacteria are also able to spread from animals to humans through other pathways of transmission, including direct contact between secretions of infected animals and agricultural workers, and, more diffusely, through contamination of fomites, shared water sources, and soil. Common pathways of transmission for bacterial zoonoses in the specific context of animal agriculture are outlined in Fig. 1 below.

Campylobacteriosis and salmonellosis are two of the most prevalent human zoonoses, especially in developed countries, while tuberculosis and brucellosis are of growing concern in agriculture and public health. In the following section, we make a brief introduction to these four zoonoses.

2.1. Campylobacter spp.

Campylobacter are a genus of Gram-negative bacteria containing several species able to infect humans and cause a form of bacterial gastroenteritis known as camplyobacteriosis. *Campylobacter* species, alongside *Salmonella*, compose the most common foodborne bacterial zoonoses in the world [38,42]. The two most common culprits are *C. jejuni*, which is particularly prevalent in developed countries, as well as *C. coli* [41]. *C. jejuni* infects approximately 1% of the human population in Europe each year [38]. It is also estimated that campylobacteriosis affects approximately 1 million people per year in the USA, and over 200,000 cases are registered each year in Canada [38,42]. Poultry are the most common source of *Campylobacter* infections, accounting for 30% of all cases, followed by cattle at 20–30%, and then pigs and other sources, including game animals and water sources [38,42]. *Campylobacter* spp. are able to survive for several weeks in food products, especially when stored at low temperatures, resulting in a high risk of foodborne transmission [42].

Common symptoms of campylobacteriosis include gastrointestinal symptoms such as diarrhea and vomiting, but can also include fever, dehydration, and bloody stool. More rarely, campylobacteriosis can lead to development of long-term irritable bowel syndrome as well as reactive arthritis [42]. *C. jejuni* infection specifically can also induce onset of Guillain-Barre syndrome (GBS), a rare autoimmune disease characterized by immune cell destruction of myelin sheath proteins resulting in nerve damage and progressive, sometimes life-threatening muscle weakness [43]. Current statistics indicate that up to 30% of GBS cases are preceded by *C. jejuni* infection; however, only 0.25–0.65 per 1000 people infected with *C. jejuni* develop GBS [44,45].
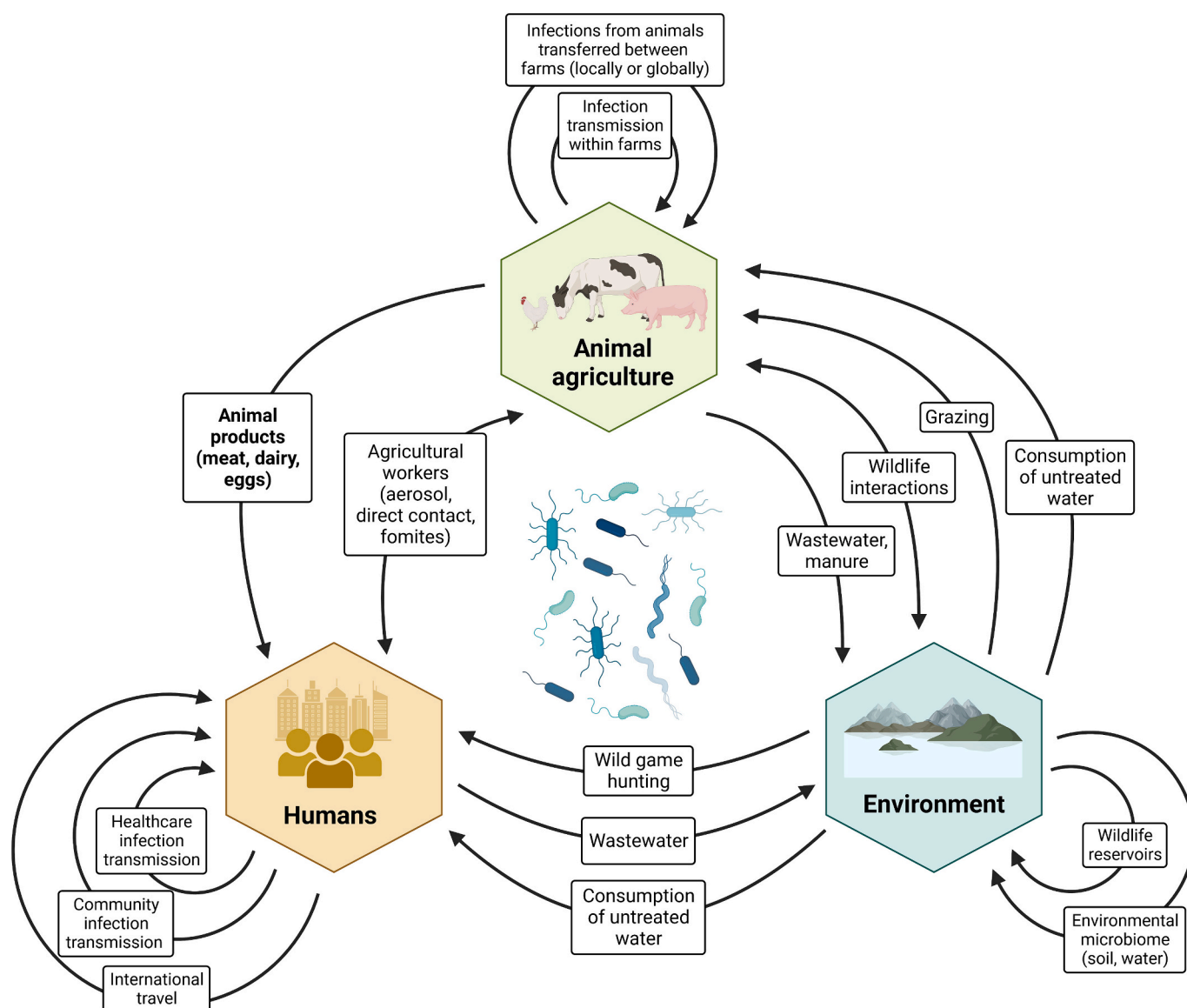
Fig. 1. Common transmission pathways for bacterial zoonoses in animal agriculture. Labelled arrows indicate common routes of bacterial transmission between the three key groups of agricultural animals, humans, and the environment, demonstrating how bacterial zoonoses can be transmitted both directly to humans via agricultural animals, as well as indirectly via environmental routes from animal agriculture. Arrows also indicate major routes of bacterial transmission and maintenance of bacterial reservoirs within each of these three groups. Figure created using Biorender.com.

2.2. Salmonella spp.

Salmonella is a genus of Gram-negative bacteria, of which *Salmonella enterica* is the type species. Within the subspecies of *S. enterica* exist more than 2600 different serotypes, and most of the serotypes, such as *S. enteritidis* and *S. typhimurium*, can infect both animals and humans [46]. Non-typhoidal *Salmonella* serotypes are zoonotic in origin, and cause a form of gastrointestinal disease referred to as salmonellosis. Common symptoms include diarrhea, vomiting, and fever, but complications arise in up to 10% of infections which can result in disseminated symptoms such as meningitis and arthritis [42]. As of 2010, it was estimated that non-typhoidal *Salmonella* spp. caused 93.8 million cases of diarrhea-associated diseases per year worldwide, resulting in 155,000 deaths, with 85% of those cases being linked to food [46]. *Salmonella* infections can be transmitted from a range of livestock, but poultry and eggs are a leading source [47,48]. Beyond human infection, certain *Salmonella* spp. (such as *S. gallinarium* and *S. pullorum*) are highly pathogenic in avians, resulting in severe and ongoing losses in the poultry industry [48].

2.3. Brucella spp.

Brucellosis, which is caused by the genus *Brucella*, is one of the most frequent zoonoses in LMICs, especially within the Middle East, Asia, Africa, and South America. The main species which can infect humans are *B. abortus, B. canis, B. melitensis*, and *B. suis*. Ruminants, including sheep, goats and cattle, are the main hosts of *Brucella* spp. *Brucella* spp. not only cause impaired fertility and abortions in ruminants, leading to both agricultural economic losses and food insecurity, but are also easily transmitted to humans through contaminated meat and unpasteurized milk, and less commonly through direct occupational contact and aerosol spread [49,50]. Brucellosis, also known historically as "Malta fever" or "undulant fever", causes fever and its associated symptoms in humans, including muscle pain, sweat, chills, fatigue, and frequently severe gastrointestinal symptoms. If left untreated, brucellosis can become chronic or lead to various inflammatory complications often

involving bones and joints, including the development of arthritis and spondylitis [51]. Rarely, brucellosis can also lead to cardiac complications such as endocarditis and myocarditis [52]. Farmers, abattoir workers, and veterinarians are the most vulnerable to *Brucella* spp. infection.

The likelihood of infection varies between countries, as many countries have implemented programs to eradicate *Brucella* spp. in livestock, including Australia, Canada, New Zealand, western Europe, and the United States [53]. However, brucellosis remains a significant concern in other regions, including Central America, Eastern Europe, Northern Africa, the Middle East, and China [54,55]. A recent meta-analysis reported that the seroprevalence of *Brucella* spp. in dairy cattle was on average 4% in Central America and the Caribbean, with Venezuela having the highest seroprevalence at 16% [56]. In Iran, unpasteurized milk samples have been identified as a major source of brucellosis [57]. Although there is no exact data, a WHO report estimated that the number of human brucellosis cases ranged between 340,000 and 19,500,000 in 2010, half of which were foodborne in origin [19].

In addition, resistance rates to antibiotics, which are the main choice for brucellosis treatment, are on the rise. A recent study found that 24.6% of *Brucella* isolates collected in northeast China were resistant to rifampicin [58]. In Bosnia and Herzegovina, 84.3% of *Brucella* isolates sampled from human patients were resistant to trimethoprim-sulfamethoxazole [59]. This situation exacerbates the threat of *Brucella* spp. to public health.

2.4. Mycobacterium spp.

Although *Mycobacterium tuberculosis* only infects humans, and is the primary cause of human tuberculosis (TB), other members of the *Mycobacterium tuberculosis* complex, such as *Mycobacterium caprae* and *Mycobacterium bovis*, can cause TB in both animals and humans. TB is characterized by fever, fatigue, muscle pain, and in chronic cases, can lead to extensive pulmonary fibrosis and inflammation. Zoonotic TB is becoming increasingly recognized as a significant infectious disease, not only in livestock, where it persists despite decades of eradication efforts, but also as an important contributor to human TB infections [17,60,61].

The main hosts of *M. caprae* are ruminants such as goats and sheep, as well as cattle, bison, and deer. The infection spectrum of *M. bovis* is even wider, encompassing cattle, goats, sheep, pigs, and horses; small mammals such as ferrets and cats; and even some avian species [62]. Contaminated food, especially milk, as well as direct occupational contact and aerosol transmission are the main routes of human infection from infected animals [62]. Because of these differences in transmission routes relative to *M. tuberculosis* which only infects humans, *M. bovis* and *M. caprae* are most often associated with extra-pulmonary TB in humans, which is more difficult to treat and has a higher mortality rate [17]. Our understanding of human TB caused by zoonotic *Mycobacterium* species remains highly incomplete. One review reported that the risk of human *M. bovis* infection at the animal-human interface ranged from 0.5 to 30% depending on risk factors including region of the world and income level, pointing out that while *M. bovis* infection has been reduced to a disease of economic importance in the developed world, it has much broader impacts in developing countries, rippling out beyond direct impacts on livestock and human health to affect livelihoods, communities, health systems, susceptible wildlife, and ecosystems [63].

2.5. Controlling zoonotic infections in animal agriculture

Prevention and treatment measures for zoonotic infections in agricultural animals are broadly interdisciplinary by necessity. From the top-down, such measures involve global, national, and regional systems of surveillance, healthcare systems to support infection treatment and prevention, and legislation regulating eradication programs, animal/animal product trade, farm management, animal handling, and

treatment guidelines, to provide an inexhaustive list. Key areas of improvement include the development of better surveillance and diagnostic strategies to understand zoonosis transmission, identify disease outbreaks, and inform policy decisions; strengthening of infrastructure, education, and access to therapeutics and other supports particularly in LMICs; best use guidelines for current preventative and therapeutic treatment options; and development of novel treatments to prevent and manage infections.

All of these approaches will be discussed in greater detail in Section 4, in order to present a more holistic view of the management of animal infections in agriculture from the perspectives of managing both bacterial zoonotic infections as well as collateral AMR. Integrating these two perspectives will allow us to better map the connections between human, animal, and environmental health within a One Health framework.

3. Antimicrobial resistance

Intimately connected to bacterial zoonosis is antimicrobial use and the rise of AMR. Antimicrobials, still our most important weapon against bacterial pathogens, are heavily relied on in animal agriculture to prevent and treat infections to ensure animal health and welfare, secure the food supply, and prevent further spread between animals or to agricultural workers or consumers. Antimicrobial use, in many ways, drives the agricultural industry—and vice versa. Of the tens of thousands of tons of antimicrobials used globally per year, it is estimated that 50–80% are used in animals raised for food [64]. Currently, the top three veterinary antimicrobial consumers are China, Brazil and the United States, which are among the world's highest food animal producers [65]. Commonly used antimicrobials in animal agriculture are listed below in Table 2.

Antimicrobial resistance is an inevitable result of antimicrobial use, but it has been accelerated by factors including misuse and overuse, which occur on a far greater scale in agriculture than in human medicine, for reasons that will be detailed below. Overuse of antimicrobials in animal agriculture has been directly linked to the rise of AMR. For example, synercid was approved by the US Food and Drug Administration (FDA) for growth promotion in poultry in 1974 and widespread resistance was observed at the beginning of approval of clinical use in 1999. Colistin was discovered in 1947, and then used as supplementation in swine and broilers (poultry bred for meat production) for many years. In 2013, the first plasmid carrying a mobile colistin resistance gene (*mcr-1*), was recovered from *E. coli* isolated from a pig in China, and since then *mcr-1* and its variants have been widely identified in animal breeding. Right now, *mcr-1* has been identified in humans, chickens, and pigs in 54 countries and on five continents [66]. In the 1990s, fluoroquinolones were developed as veterinary drugs for treating bacterial infection in animals, followed by rapidly increasing resistance over the next several decades. A meta-analysis on animals from developing countries during 2000 to 2018 revealed that the proportion of antimicrobials with resistance rates greater than 50% increased from 15% to 41% in chickens, from 13% to 34% in swine, and from 12% to 23% in cattle. Among them, the highest resistance rates in *Campylobacter* spp. were to tetracyclines and quinolones (both 60%). In *E. coli*, quinolone and gentamicin resistances were between 20 and 60%, while in *Salmonella* spp. resistance rates were 5–38%. In *Staphylococcus aureus*, the highest resistance rates were associated with penicillins (40–80%) [67]. Several of these important animal and zoonotic bacteria are also ESKAPE pathogens, an acronym devised to refer to six bacteria (*Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp.) which critically impact human health and exhibit high levels of AMR [68]. Increasing AMR, including carbapenem resistance, in these critical ESKAPE pathogens, can be linked to animal agriculture practices, particularly in LMICs [69,70].

Agriculturally, increasing AMR is expected to result in global

Table 2

Most commonly used antimicrobials in animal agriculture and their resistance mechanisms.

Antimicrobial class	Main animal drugs	Usage and specificity	Hazard of zoonotic relevance	Resistance mechanisms
Aminoglycosides	Streptomycin, spectinomycin, neomycin, gentamycin, kanamycin	Mainly act on aerobic Gram$^+$ bacilli by inhibiting protein synthesis.	*Enterococcus* spp.	(1) Enzymatic modification of aminoglycosides; (2) Target site modification via 16S rRNA methyltransferases; (3) Efflux systems [71].
β-lactams	Penicillin, amoxicillin	Act on aerobic bacteria, and some anaerobic bacteria by inhibiting cell wall synthesis.	*Enterococcus* spp.	(1) Modification of several classes of penicillin-binding proteins (PBPs); (2) β-lactamases [72].
Quinolones	Ciprofloxacin, enrofloxacin	Mainly act on Gram$^-$ bacteria by inhibiting nucleic acid synthesis.	*Campylobacter* spp., *Enterococcus* spp.	(1) Mutations in gyrase and topoisomerase IV; (2) Efflux-mediated resistance [73].
Macrolides	Tylosin, erythromycin, kitasamycin	Act on aerobic bacteria, and some *Mycoplasma* by inhibiting protein synthesis.	*Mycoplasma* spp., *Campylobacter* spp., *Salmonella* spp.	(1) Mutations in 23S rRNA; (2) Modification of the target by Erm; (3) Enzymatic inactivation by esterases; (4) Efflux-mediated resistance [74].
Tetracyclines	Tetracycline, oxytetracycline, chlortetracycline, doxycycline	Broad-spectrum antimicrobials, act by inhibiting protein synthesis.	*Brucella* spp., *Staphylococcus aureus*	(1) Efflux-mediated resistance; (2) Ribosomal binding site mutations; (3) Enzymatic inactivation [75].
Peptides	Virginiamycin, bacitracin, colistin	Virginiamycin and bacitracin mainly acts on G$^+$ bacteria; colistin mainly acts on Gram$^-$ bacilli.	*Enterobacteriaceae*	(1) Efflux pumps-mediated resistance to bacitracin [57]. (2) Mobile colistin resistance (MCR) [76].
Chloramphenicols	Florfenicol	Broad-spectrum antimicrobial, acts by inhibiting protein synthesis.	*E. coli*, *Fusobacterium necrophorum*	(1) Efflux pumps and ABC transporters (floR, fexA, optrA, etc.); (2) Modification of the target by cfr [77].
Lincosamides	Lincomycin	Mainly act on Gram$^+$ bacteria and Gram$^-$ anaerobic bacteria by inhibiting protein synthesis.	*Mycoplasma* spp., *Leptospira* spp.	(1) ABC transporter (2) modification of the target by a nucleotidyl-transferase [78].
Sulfonamides	Sulfadiazine, sulfametoxydia-zine, sulfadimidine	Broad-spectrum antimicrobial, inhibits the synthesis of folate.	*Chlamydiae*, *Toxoplasma*, *E. coli*, *Salmonella* spp., *Shigella* spp.	Presence of dihydropteroate synthase in a form that the drug cannot inhibit [75].

declines in livestock production between 2.6% to 7.5% annually, which will have serious ramifications for food security especially as global food production is already struggling to meet the demands of the growing human population [26]. Many of these resistant bacteria are also relevant human pathogens, as described in the previous section on zoonoses, and resistance genes are highly capable of spreading into other human pathogens, resulting in dwindling efficacy of antimicrobials critical for human medicine. Antimicrobial resistance is predicted to result in 10 million human deaths annually by 2050, with expected global healthcare costs in excess of $1 trillion USD per year [26].

This section will outline factors driving antimicrobial use and overuse in animal agriculture as well as key pathways of resistance development and transmission.

3.1. Antimicrobial use in agriculture

Numerous factors influence the overuse and misuse of antimicrobials in animal agriculture, many of which are challenging to address given the scale of modern agriculture. Over the past century, animal agriculture has shifted from primarily pastoral and smallholder farming systems to widespread industrialization driven by technological and scientific advancements which allow for unprecedented numbers of animals to be bred and housed in both intensive and extensive farming systems that allow for unparalleled yields of animal products.

One significant challenge to the correct application of antimicrobials is the difficulty of diagnosis. Many livestock pathogens present similarly, and diagnostic lab tests are frequently inaccessible or impractical, particularly from an economic standpoint, as many antimicrobials are comparatively inexpensive relative to laboratory testing, especially at a herd scale [79]. Inaccessibility of diagnostic testing, beyond its obvious connections to misdiagnosis and thus antimicrobial misuse, also has implications for pathogen surveillance programs in animal agriculture. This often results in the metaphylactic and prophylactic use of

antimicrobials, to either prevent spread from a subpopulation of symptomatic to asymptomatic animals in a herd or flock, or to prevent the onset of symptomatic infection in a group of ostensibly healthy animals assumed to be at high risk [79]. These practices, while they clearly contribute to antimicrobial overuse, also frequently have no better alternatives, and are necessary to ensure security of the food supply and maintain animal welfare, particularly in high-density intensive farming systems where quarantine and other biosecurity measures may not always be feasible [80]. These intensive farming systems also frequently rely on inefficient delivery systems for antimicrobials, such as feed and water, which result in suboptimal dosing as well as downstream environmental contamination with antimicrobial residues.

Antimicrobials have also historically been used as growth promoters in animal agriculture, with some examples being oxytetracycline, chlortetracycline and tylosin in cattle, and virginiamycin and bacitracin in poultry. Sub-therapeutic use of antimicrobials in animal feed has been shown to reduce morbidity and mortality, increase daily growth rates, and the conversion of feed to animal product, which significantly increases poultry and livestock production. However, with the growing AMR crisis, the usage of antimicrobials as growth promoters has been gradually banned in many countries, beginning with Sweden in 1986, several European countries in 2006, the USA in 2015, and China in 2020, resulting in significant decreases in antimicrobial consumption in these countries [79,81]. These bans, however, are yet to reach many LMICs which possess some of the fastest-growing animal agriculture industries in the world.

Despite these successes, the use of therapeutic antimicrobials is still unavoidable and significant in animal agriculture, especially under conditions of inadequate biosafety. In order to safeguard critical antimicrobials for human use, some antimicrobials have been banned in animals, particularly the newest generations of antimicrobials, or those seen as the last line of defense in human medicine, such as linezolid, tigecycline, and vancomycin. However, some resistance genes have been

found which allow cross-resistance between therapeutic antimicrobials in animals and protected human antimicrobials, such as *tetX* (tetracycline and tigecycline), *cfr* and *optrA* (florfenicol and linezolid) [82,83], indicating that these safeguarding practices may not be adequate to protect critical last-resort antimicrobials for human health. Additionally, such regulations on antimicrobial use require countries to possess adequate regulatory frameworks to enforce bans, which are frequently absent in LMICs.

Complexities of the factors driving antimicrobial use in animals have been further reviewed from additional interdisciplinary perspectives, including detailed sociological [80], economic [84], and policy-design [85] frameworks, which must be taken into account in order to develop holistic, multimodal One Health approaches to antimicrobial stewardship and regulation in animal agriculture. Some of these approaches will be outlined in more detail in Section 4.

3.2. Antimicrobial resistance development and transmission in animal agriculture

The spread of AMR in bacteria occurs primarily through the horizontal transfer of resistance genes, which can occur anywhere bacteria are able to colonize, including within humans, livestock, wild animals, and in the environment, including soil and water, depending on the bacterial species. Under the pressure of antimicrobial selection, bacteria acquire resistance genes and mobile genetic elements (MGEs) that can spread to other bacteria of the same or different genus. Antimicrobial use and overuse in food animals, as described above, are important drivers of resistance gene acquisition in animal and zoonotic bacteria. Animal bacteria have become one of the most important reservoirs for the horizontal transfer of resistance genes, and share most of their resistance genes and mobile genetic elements with human pathogens [86].

In bacteria, horizontal transfer is achieved through the concerted activities of MGEs. MGE are composed of insertion sequences (IS), transposons (Tn), gene cassettes and integrons (In). These MGEs are highly prevalent in animal bacteria, and are associated with multiple resistance genes, such as *cat* (chloramphenicol), *tet* (tetracycline), *aphA* (kanamycin), *bla* (carbapenems), *mcr* (colistin), and *erm* (macrolides, lincosamides, streptogramins (MLS) antimicrobials) [87]. Genomic islands, mainly including Integrative Conjugative Elements (ICE) and Integrative Mobilizable Elements (IME) are another important mechanism for horizontal transfer of resistance genes. For example, staphylococcal cassette chromosome element (SCCmec) is a typical example of a resistance island carried on methicillin-resistant *S. aureus* (MRSA), which is widespread in pig farms and hospitals [88]. Resistance plasmids are also important vehicles for the transfer of acquired antimicrobial resistance genes (ARGs) and MGEs, which are able to transfer between bacterial cells. For example, plasmid-mediated quinolone resistance (PMQR) is one of the most important causes of quinolone resistance in both human and animal Enterobacterales [89]. In addition, ARGs can also be transferred between bacteria via phages. Many ARGs, such as *mcr-1* have been detected in phage genomes or phage-like plasmids isolated from animal farms, and the relative abundance of bacteriophages has been positively correlated to the relative abundance of ARGs in animals, which suggest that phages play important roles in the spread of resistance as well [90,91].

The spread of antimicrobial resistance between humans and animals can occur through several routes, the most straightforward of which is direct infection with resistant bacteria. In the case of zoonotic pathogens, this most commonly occurs through consumption of contaminated meat and other animal products, such as eggs and dairy. As described above, many zoonotic pathogens are multidrug resistant. For example, with the increase in resistant *Campylobacter* spp. in chickens, many of the *Campylobacter* spp. isolated from diarrhea patients are quinolone-resistant [92,93]. Genomic analysis showed that the genotypes of some human and avian *Campylobacter* strains are overlapping.

Foodborne illnesses resulting from this consumption can be severely complicated if the bacteria ingested are resistant to various antimicrobials. The relevance of this route of antimicrobial resistance transmission to human health is further highlighted by findings that some antimicrobial-resistant bacteria found in hospitals can be traced back to animals [94]. In addition to foodborne infection, direct exposure to the farm environment can also shape the human gut microbiota and antimicrobial resistome. There is direct evidence of the spread of antimicrobial-resistant plasmids from chicken to chicken and from chicken to handlers [95]. An investigation in swine farms also showed that resistance genes and bacteria in guts of veterinary students changed after three months of exposure to the farm environment, and shared extensive similarities with the microbial composition and drug resistance gene composition isolated from farm workers and local environmental samples [96].

In addition to direct human infection, waste, debris, and pollutants from animal farms, which contain antimicrobial residues as well resistant bacteria, can infiltrate the environment and lead to the establishment of new resistance reservoirs and novel opportunities for the direct and indirect spread of resistance. Resistant bacteria from livestock animals can in this way enter the environment and infect plants, vegetables, and fruits, as well as persist in soil and water if they are capable of doing so. Animal manure from farms is often used to fertilize crops, but it is one of the most important concentrators of bacteria, especially enteric zoonotic pathogens, such as pathogenic *E. coli*, *Salmonella* spp., *Klebsiella* spp., *Campylobacter* spp., and *Proteus* spp., which harbour many ARGs, therefore posing a latent risk for transferring ARGs from animals and animal products to soil and crops, and then to the human microbiome. As reported, the concentrations of ARGs from manured soil are approximately 28,000 times higher than in un-manured soil [97]. An investigation on the resistomes of lettuce growing in animal manure-amended soil showed 144 ARGs in this plant or around its root system, and the ARG profiles were significantly correlated with the bacterial community [98]. An investigation into fresh vegetables and fruit also showed a high abundance of tetracycline and aminoglycoside resistance genes, providing evidence for ARG transmission in the food chain [99]. Animal waste also leads to contamination of water sources around farms, furthering transmission cycles. A study on the antimicrobial resistome in a swine feedlot water treatment environment showed that the wastewater from a breeding farm was a reservoir of resistance genes, and that phage-mediated transduction was one of the important causes of resistance spreading [100]. Resistome profiling showed that ARGs in microbiome samples from livestock manure, lagoon, and treated wastewater along the west coast of the United States belonged to four core resistance classes: aminoglycosides, tetracyclines, β-lactams, and macrolides, which correlate closely to antimicrobials used in animal agriculture [101].

More than 70% of administered veterinary antibiotics are not digested fully by the animal system, but excreted out into the environment as either the original compound or their metabolic product [102]. Soil and water contaminated with just antimicrobial residues can also lead to selection of resistant variants in environmental bacteria, which has been shown to affect aquatic and soil environmental microbiomes [103,104]. Under antimicrobial pressure, soil microflora including bacteria and other organism can be changed, and some essential microbes needed for supplying nutrients to plants can be killed in addition to increases in resistant bacteria [105]. In addition, these antimicrobial residues also can be absorbed and accumulated by plants, exacerbating their potential spread to humans [106].

In all of these ways, antimicrobial resistance can be easily transferred to different ecosystems and populations where it can establish reservoirs of resistant bacteria and resistance genes. Fig. 2 summarizes key routes of AMR development and transmission in the context of animal agriculture.

a) Mechanisms driving development of AMR in an animal agriculture context
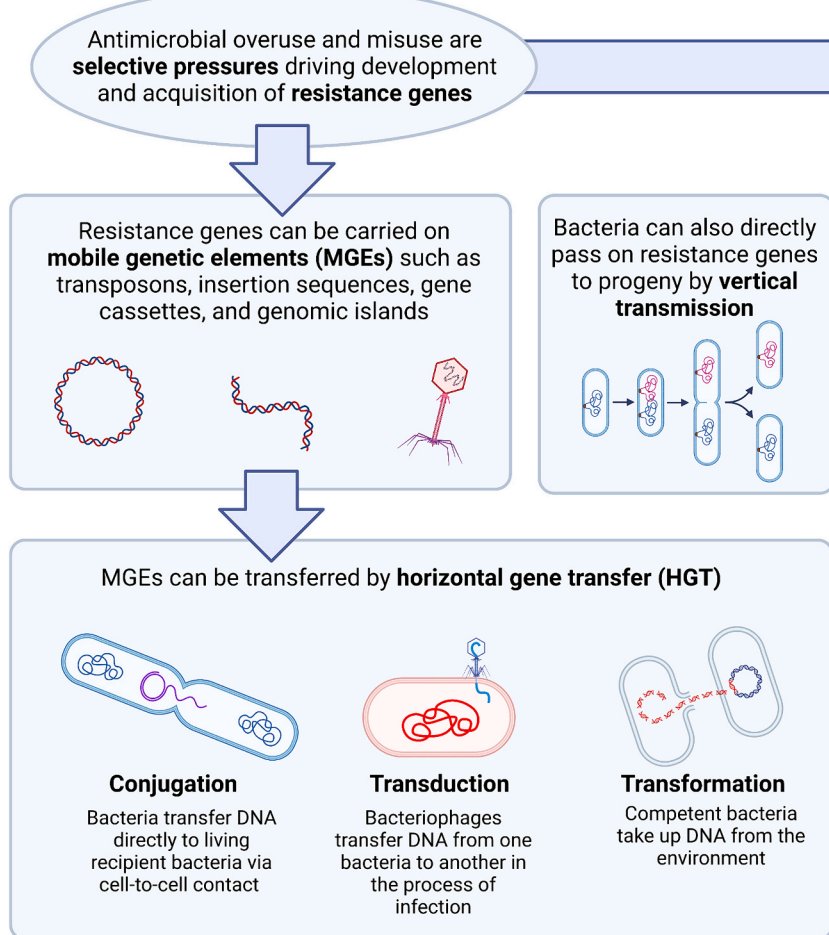
b) Factors driving development of AMR in an animal agriculture context
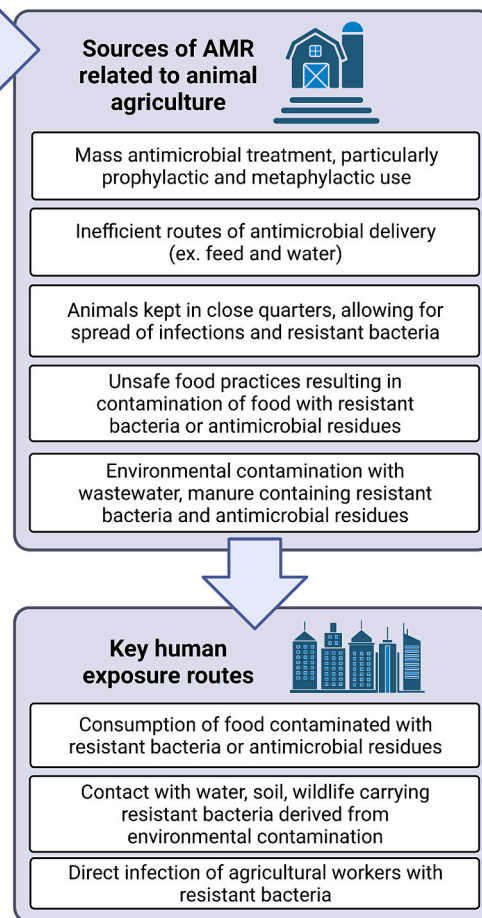

Fig. 2. Roles of animal agriculture in the development and spread of AMR. a) Mechanisms which drive the spread of AMR, including horizontal gene transfer of mobile genetic elements as well as vertical transmission. b) Factors driving the development of AMR in animal agriculture and routes of AMR spread from animal agriculture to the human population. Figure created using Biorender.com.

4. Prevention and control of zoonoses and antimicrobial resistance in animal agriculture

Underlying both the issues of agricultural zoonoses and AMR are questions of how to better prevent, survey, and manage infections in animal agriculture. As discussed above, many key agricultural zoonoses are bacterial, particularly foodborne zoonoses, and the use of antimicrobials to treat and control transmission of these zoonotic bacteria has clear ramifications for resistance development. Considering ways to better prevent and manage zoonoses in agriculture will reduce antimicrobial usage and thus AMR. Addressing these issues together, from an integrated One Health perspective, will be necessary to develop more effective systems for surveillance, antimicrobial stewardship, policy design, infection prevention, treatment, and beyond. The following section will discuss some of these key approaches to address issues of both zoonoses and antimicrobial resistance in animal agriculture and highlight areas where these two topics should be considered jointly to provide a more holistic perspective on managing infections in animal agriculture.

4.1. Surveillance programs

Surveillance systems in animal agriculture are necessary to monitor

emerging and existing zoonoses, as well as antimicrobial usage and resistance spread. Surveillance systems provide critical information for identifying concerns including disease outbreaks and AMR development; directing treatment and mitigation efforts; evaluating the efficacy of current practices; and developing new policies and regulations.

Surveillance systems primarily operate at national or subnational levels, and survey farm animals for infections and AMR, as well as farm workers for evidence of zoonotic spread. Surveillance programs also exist to monitor zoonotic infections as well as AMR in the general human population, as well as at the interfaces of livestock and human populations with wildlife and the environment. These surveillance networks have historically been disconnected and independently-developed, though several countries, particularly high-income countries, are now developing integrated surveillance systems for both zoonoses and AMR. Canada, for example, has the Canadian Animal Health Surveillance System (CAHSS), under Animal Health Canada (AHC), which defines itself as an integrated network that has linked together numerous self-organizing animal health surveillance networks from a regional to national scale, encompassing surveillance of both animal infections, zoonotic and otherwise, as well as antimicrobial usage and resistance [107]. In the United States, the National Animal Health Surveillance System (NAHSS) monitors livestock animal infections including zoonosis, and the National Animal Health Monitoring System (NAHMS) collects

information on health and health management of livestock including antimicrobial stewardship, usage, and resistance, though these systems do not appear to have the same integration as the CAHSS [108]. The development of integrated, multi-sector (i.e., agricultural, veterinary, and human healthcare) networks addressing both zoonoses and AMR is a critical One Health priority, and is especially important for LMICs which face intensified hurdles to the development of effective surveillance and response systems. Integration of these systems results in better use of resources, and coordination across sectors helps strengthen health systems, as has been seen in countries such as Tanzania [109]. Integrating surveillance of humans, food products, farm animals, wildlife, and ecosystems will also allow for better understanding of the pathways driving pathogen transmission and resistance development and identifying animal agriculture's roles in those pathways.

In LMICs, there are still significant challenges to the development of robust national surveillance systems for zoonoses and AMR [109]. Such challenges include limited resources and funding to support surveillance as well as infrastructure gaps such as veterinary laboratory or healthcare diagnostic capacity [110]. However, novel strategies are being developed to circumvent these challenges. One project taking place in Ethiopia, Mozambique, Nigeria, Tanzania, known as the Foodborne disease epidemiology, surveillance, and control in African LMIC (FOCAL) project, is aiming to analyze sewage samples using short-read next generation sequencing (NGS) to identify the population prevalence of bacterial infections including those of zoonotic origin, as a less resource-intensive surveillance method [111,112]. Another platform implemented in Kenya involved a mobile phone-based reporting application which collected environmental and livestock monitoring data from resident veterinary officers connected to a network of farmers across several counties [110]. Another option under development for high-throughput AMR surveillance are robotic platforms. One robotic platform (RASP), while adhering to internationally recognized standards (CLSI and ISO 20776-1:2019), was superior in throughput, cost, and data resolution when compared with an experienced human technician. Integration of robotics platforms in the microbiology laboratory is a necessary advancement for future One Health AMR endeavors, and can also be adapted to screen for zoonotic pathogens [113]. Developing novel surveillance platforms that are both cost-effective and high-throughput, as well as platforms that are feasible for implementation in LMICs, will improve the scope of zoonosis and AMR monitoring worldwide, allowing for the collection of data that will inform efficient treatment response rates, as well as future policy, education, and other prevention and control efforts.

4.2. Policy and education

Once surveillance data has been collected, it is able to inform policy decisions that affect prevention and treatment of infections in agricultural animals, including vaccination programs; eradication programs; access to veterinary antimicrobials; regulations surrounding food handling and trade; education and antimicrobial stewardship efforts; and beyond.

Successful policy decisions rely on concerted efforts from a wide range of disciplines. Here, we aim to very briefly highlight examples of how various disciplines contribute to policy development, to outline what a truly multidisciplinary One Health approach to these issues looks like in practice. Policy development often starts with interpretation of surveillance data, which relies on bioinformatics and statistical modeling. For example, Opatowski et al. [114] proposed a stochastic quantitative risk assessment model for the different components at play in AMR selection and spread, which computes the incidence of AMR colonization in humans from water or food consumption, contacts with livestock, and interhuman contacts in hospitals or the community, and combines these incidences into a per-year acquisition risk. This work highlights the importance of modeling to harness the predictive power of surveillance data for future decision-making.

An entirely different approach by Ida et al. [80] investigated risk assessment and understanding of antimicrobial stewardship policies through ethnographic fieldwork conducted on dairy farmers in Alberta, Canada. This approach highlights the importance of local context to inform the most effective policy decisions on regulating antimicrobials. Previous related work by Lam et al. [115,116] in the Netherlands incorporated local farmers' perspectives on antimicrobial usage to inform antimicrobial-reducing legislation, resulting in a highly successful 47% decrease in antimicrobial use over a 6-year period. Approaching yet another angle of this issue, to improve the accessibility of education and antimicrobial stewardship efforts, Wernli et al. [117] created an international One Health platform for online learning, which could synthesize the evidence for actions on AMR into a fully accessible database and generate new scientific insights into the design, implementation, evaluation, and reporting of the broad range of interventions relevant to addressing AMR. This platform or one like it will hopefully ultimately contribute to the goal of building societal resilience to this central challenge of the 21st century. Similar interdisciplinary work has been carried out from the perspective of zoonotic disease, from policy process analysis in Uganda and Nigeria which elucidated key political factors governing decisions made about zoonoses control measures [118] to socioeconomic studies outlining the non-disease burdens of zoonoses such as *Brucella* spp. and the relevant social, economic, and educational interventions required to address those additional burdens [119].

An in-depth discussion of the numerous factors influencing the success of policy decisions and educational efforts related to agricultural zoonoses and antimicrobial resistance is beyond the scope of this review, but has been reviewed extensively elsewhere [26,79]. What this brief snapshot is intended to highlight is that an integrated One Health approach to zoonoses and antimicrobial resistance in animal agriculture must recognize the importance of these multidisciplinary approaches to developing and communicating the most effective policies preventing and controlling the spread of zoonotic and antimicrobial-resistant pathogens between animal, human, and environmental interfaces.

4.3. New therapeutic targets and strategies

The global increase in AMR has resulted in the loss of efficacy of many once-frontline antimicrobials, which has important implications for the treatment of human and animal disease, as well as preventing the spread of bacterial zoonoses. As a result, when compared to a single prevention and control strategy, "multi-pronged" measures based on collaboration between human, animal, and environmental sectors will be needed to fully address the ongoing rise in AMR [120]. Another critical element of this crisis is the fact that the development and introduction of new antimicrobials has slowed significantly over the past several decades. Few novel classes of antibiotics have been discovered since 1960, and there are limited pipelines to develop new agents [121,122]. Between 1983 and 2007, the number of new antibiotics developed decreased from approximately 20 every five years to only 5 every five years [123]. Moreover, once a new drug is introduced to the clinic, AMR can arise rapidly via strong selective pressure soon after use [124]. This means that AMR is developing at a faster rate than new antibiotics, indicating that new strategies and platforms are required to expedite the development of novel antibiotics and non-antibiotic anti-infective drugs.

Conventional antibiotics target cell viability, either by killing (bactericidal) or by inhibiting growth (bacteriostatic). These modes of action impose a high degree of selective pressure that ultimately fosters the growth of antimicrobial-resistant strains [124]. A novel antibacterial drug is defined by the following criteria: (1) it belongs to a novel chemical class and interacts with a new target, (2) works via a new mechanism or binding to new target sites, and/or (3) is biochemically modified to re-sensitize a previously resistant pathogen. In the past ten years, several promising strategies for non-antibiotic therapies have

shown potential in circumventing the rapidly looming post-antimicrobial era. These novel strategies and targets, which include combination therapies, anti-virulence drugs, bacteriophage therapy, and microbiome modulators, will be discussed below. Even though most of these new developments focus on human use, some approaches can potentially be applied in animal agriculture to fight pathogenic bacteria.

4.3.1. Combination therapy

Some drugs cannot be used directly as antibiotics but may be used as potentiators or synergists because they increase membrane permeability, reduce efflux pump activity, inhibit kinase activity, or inhibit intrinsic antimicrobial resistance. Examples of recent drugs which have shown promise as combination therapies pre-clinically and in clinical trials will be briefly outlined.

Several polymyxin derivatives such as SPR741 have been developed to serve as antibiotic adjuvants and have recently finished Phase 1 clinical studies [125]. SPR741 lacks direct antibacterial activity but potentiates antibiotic activity by disrupting the bacterial outer membrane, permeabilizing it to antimicrobials [126].

Penicillin-binding-proteins and Ser/Thr kinase-associated (PASTA) kinases of Gram-positive pathogens, which have been shown to regulate biofilm formation, cell wall homeostasis, metabolism, and virulence, may also have potential as a target for combination therapies. An imidazopyridine aminofurazan-type kinase inhibitor GSK690693 can dramatically increase the sensitivity of the intracellular pathogen *Listeria monocytogenes* to various β-lactams by inhibiting the activity of PASTA kinase PrkA [127], and pyrazolopyridazine GW779439X was found to re-sensitize MRSA to various β-lactams through inhibition of the PASTA kinase Stk1 [128].

A number of potent efflux pump inhibitors (EPIs) against antimicrobial-resistant Gram-negative bacteria have been reported. EPIs compete with antibiotics to be the substrate of efflux pumps, reducing efflux of antibiotics from the cell and thus increasing their intracellular concentration, eventually leading to cell death. Some EPIs include chemicals such as 1-(1-naphthylmethyl) piperazine (NMP), carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), phenylalanyl arginyl β-naphthylamide (PAβN), and quinoline derivatives; plant extracts and phytochemical products, such as curcumin; and microbial fermentation extracts EA-371α and EA371-δ [129,130]. However, no EPI has been clinically approved to date, mainly due to toxicity, low in vivo efficacy, or poor pharmacokinetic properties [131].

4.3.2. Anti-virulence

Targeting pathogenic mechanisms, such as virulence factors, represents a very attractive alternative for the development of new antimicrobial agents, because they do not directly kill bacteria and thus exert reduced selective pressure for resistance development [124]. Several compounds have been discovered which inhibit key regulators of bacterial virulence and pathogenesis or target the virulence factors and toxins directly.

The expression of two main virulence factors involved in *Vibrio cholerae* pathogenesis – cholera toxin (CT) and toxin-coregulated pilus (TCP)— is regulated by the master regulator ToxT. Hung and colleagues [132,133] identified virstatin (4-[N-(1,8 naphthalimide)]-n-butyric acid) as a compound which inhibits ToxT dimerization and thus reduces colonization *of V. cholera* in a murine model of infection. Secreted toxins also play a major role in the pathogenesis of many bacterial pathogens. Several toxins have been targeted by blocking mechanisms which fall into 2 categories: chemical inhibitors and anti-toxin antibodies. The most clinically advanced antitoxin antibody, raxibacumab, was approved by the US Food and Drug Administration in 2012 for use in combination with appropriate antimicrobials to treat anthrax disease caused by *Bacillus anthracis* anthrax toxin. Raxibacumab is a fully humanized immunoglobulin G1 (IgG1) monoclonal antibody that prevents anthrax toxin binding to its host cell receptor [134]. Extensive studies have been done on several classes of small molecules with inhibitory

activity against type 3 secretion system (T3SS) of several Gram-negative pathogens [135]. For *Salmonella*, sanguinarine chloride, Cytosporone B, fusaric acid, and thymol affect the secretion of T3SS effectors. Cinnamaldehyde, paenol, syringaldehyde, and licoflavanol inhibit the *Salmonella* Pathogenicity Island 1 (SPI-1) regulatory genes. Additionally, the 2-imino-5-arylidene thiazolidinone and TTS29 are ATPase (motor) inhibitors of T3SS [135].

Other anti-virulence strategies target bacterial adhesion and motility. For example, the surface protein sortase A (SrtA) is not required for growth or viability but is involved in biofilm formation and adhesion of several pathogens. Quercitrin (QEN), a natural bioflavonoid, remarkably inhibits the enzymatic activity of purified SrtA. *S. aureus* treated with QEN showed a significant reduction in their attachment to fibronectin/fibrinogen-coated surfaces [136]. Flagella motility has also been shown to play a critical role in the pathogenicity of bacteria such as *C. jejuni*. Ménard et al. [137] found three inhibitors (CD24868, CD26839, and CD36508) that effectively inhibit *C. jejuni* flagellin production in a dose-dependent manner by screening small-molecule inhibitors for pseudaminic acid (Pse) biosynthetic enzymes using a combination of high-throughput and in silico screening.

Quorum sensing (QS) is a bacterial cell-cell communication process that controls bacterial bioluminescence, biofilm formation, toxin secretion, motility, and virulence factor expression. Thus, anti-QS compounds are another promising way to selectively counter bacterial virulence. LED209, a small molecule, can inhibit signal binding to the *E. coli* sensor kinase QseC, preventing autophosphorylation and thus inhibiting QseC-mediated activation of virulence factor expression [138]. The bacterial two-component system also plays an important role in bacterial physiological function, including AMR, biofilm formation, virulence, and cell division. Carabajal et al. [139] identified a series of quinazoline compounds that showed selective and potent down-regulation of PhoP/PhoQ-activated genes, which were noncytotoxic and exhibited anti-virulence effects ex vivo by blocking *S. typhimurium* intramacrophage replication.

4.3.3. Bacteriophage therapy

The use of lytic bacteriophage as antimicrobial agents against multidrug resistant bacteria has been extensively investigated over the past several decades. Even though phage therapy has been shown to be safe and effective for treating patients with bacterial infections in numerous studies, many nations have not yet approved its use clinically [140]. Before phage therapy is implemented in clinical settings, there are still a number of other concerns that need to be resolved, including rapid pathogen resistance to phage after phage treatment [141]; a limited range of target bacterial species/strains [142]; unknown immunogenicity of phage therapy leading to unexpected outcomes [143]; and the unintentional spread of antimicrobial resistant determinants through phage, potentially expediting AMR.

4.3.4. Modulating the microbiome

Human and animal bodies contain a complex population of bacteria with a wide range of species, known as the microbiome. Bacteria and the chemicals they produce affect homeostasis and these effects can have both positive and negative impacts on human and animal health [144]. The composition of the microbiome can be manipulated in various ways to prevent or treat bacterial infections. The treatment of recurrent *C. difficile* infections (CDI) with fecal microbiota transplant (FMT) is the most successful use of microbiome manipulation as a therapeutic, which has recently been approved by the FDA [145]. FMT has recently been investigated in animal agriculture as well, particularly in poultry. Recent studies have found that FMT improved weight gain and overall health of broiler chickens by reshaping the gut microbiota composition; specifically protected chicks from *Salmonella enteritidis* infection; and improved egg-laying performance in broiler breeders [146–148]. Besides FMT, probiotics can also be used to alter the microbiome and thus prevent or eradicate infection. According to several studies, *Lactobacillus*

species and *Saccharomyces boulardii* can effectively reduce the risk of CDI and antibiotic-associated diarrhea. Overall, the incorporation of healthy donor flora, either specifically through probiotics or broadly through FMT, is able to act as a "broad-spectrum antibiotic" capable of eradicating pathogens by competition for replicative niches, thus rebalancing the homeostasis of the body and microbiota and improving its future resilience to infections [149].

4.3.5. Implications in animal agriculture

Several of these novel options lend themselves particularly well to use in animal agriculture, such as microbiome-modulating approaches which could be applied at a herd or even farm-wide scale to help prophylactically counter colonization with both harmful animal bacteria as well as bacteria of zoonotic importance, as has already been demonstrated [150]. Strategies such as pre-biotics and other microbiome-modulating compounds are being applied to replace antimicrobial use for growth promotion in poultry farming [151]. Phage therapy approaches, as well, could potentially be developed to allow for local transmission within a herd or flock, taking advantage of high-density farming systems to improve dosing and coverage. Overall, animal agriculture represents an important site for the development of novel therapies to reduce global antimicrobial consumption in order to slow the development of resistance.

5. Other health issues

Although zoonoses and AMR are the core impacts that have drawn vast attention, many emerging aspects of One Health, including animal welfare, food security, food safety, and climate change, are also profoundly affected by animal agriculture. It is worth noting that these effects are highly interconnected and often influence each other. This section highlights some non-exhaustive examples of the broader impacts of animal agriculture on One Health at the human-animal-environment interface.

5.1. Animal welfare

There has been increasing awareness of the importance of One Health when addressing the sustainability of animal agriculture systems [152,153], because of the clear bidirectional relationship between the two aspects. While animal welfare, which includes animal health, has been inevitably influenced by modern animal agriculture practices, improving animal health also represents an opportunity to develop a more productive and sustainable animal agriculture.

Compared to the traditional family farming and "free-range" farming modes, concentrated animal feeding operations (CAFOs) are more efficient and economically more competitive, thus dominating in countries with increasing populations as well as increasing standards of living and animal product consumption such as China [154]. However, the growth of food-producing animals at high densities may enhance the occurrence and spread of both infectious and non-infectious diseases. One of the most discernible impacts on animal welfare by the industrialization of animal agriculture is confinement and segregation from natural environments and behaviors. These alterations can lead to secondary health issues, such as promotion of disease transmission, abnormal metabolism, and altered growth and development of farm animals [34]. For example, animals raised in confinement and overcrowded settings have restricted movement, often resulting in failure to develop normal muscle tissue [155]. In addition, many natural behaviors, such as grazing, suckling, perching, and nesting, are frustrated in animals raised in such environments, negatively affecting animal welfare [156]. In these environments, traditional grazing and foraging are also replaced by artificial feeds consisting of highly processed mixtures of corn, soybeans, and other supplements including slaughterhouse renderings and medications [157,158], causing various health problems in livestock. Digestive disorders are commonly found in cattle and pigs fed with these artificial

feeds [159–161]. The microbiota of livestock can also be adversely affected by artificial feed, resulting in increased risk of colonization with pathogenic bacteria, which has consequences that loop back to issues of zoonosis and AMR.

Due to its importance in agriculture, animal welfare has gained considerable attention from relevant stakeholders, including farmers, the public, and international/government organizations, which collectively shape animal welfare promotion practices. The mandate of the Food and Agriculture Organization (FAO) of the United Nations is to improve animal health, contributing to a productive and sustainable animal agriculture [162]. To achieve this, FAO together with the WHO and the World Organization for Animal Health (WOAH, founded as OIE) formed a global partnership to promote the One Health initiative, emphasizing the importance of animal health among the unified health of humans, animal and the environment [163]. Non-profit charity organizations, such as Compassion in World Farming and the International Fund for Animal Welfare, are also strong advocates for animal welfare campaigning. When it comes to farmers and the public, some studies have found that they share common interests in promoting animal welfare, despite different perceptions of their welfare priorities [164,165]. An important factor for improving animal welfare is the balance of costs and benefits, such as the obvious costs in infrastructure and human resource and production gain. A recent study also elaborated on some indirect economic and social benefits associated with better animal welfare [166]. More studies providing empirical evidence is necessary to enable informed decisions on the optimal course of action to improve animal welfare, which is undoubtedly an important link of the One Health initiative and a critical foundation for developing a sustainable animal agriculture.

5.2. Food security

Animal welfare and disease also has clear economic ramifications for both the farmers who depend on animals for their livelihood and consumers who depend on animal products. It is challenging to accurately quantify the overall economic burden of all livestock diseases. Some studies estimated that the annual cost of zoonoses in developing countries is in excess of $85 billion USD per year, accounting for productivity costs, livestock costs, and human health costs [152], which poses significant risks to food security and the livelihoods of impacted farmers, especially in LMICs [153,167]. For example, outbreaks of viral infections caused by highly pathogenic avian influenza (HPAI) have caused significant losses of poultry [168,169]. HPAI H5N1 viruses have been detected in US wild aquatic birds, commercial poultry and backyard or hobbyist flocks since the beginning of January 2022, and have recently spread to cattle [169]. Two human infections have been recorded as of April 2024 [169]. This ongoing HPAI outbreak has affected over 90 million birds in the US by April 2024, causing increased prices for eggs and poultry meat and prompting precautionary measures by zoo aviaries [169]. On a less dramatic scale, other animal pathogens, including bacteria of zoonotic relevance such as *C. burnetti, Brucella* spp*.,* and *Listeria* spp*.,* which cause abortions and impaired fertility in animals, also contribute to significant ongoing losses in animal agriculture over time [170]. Thus, the critical impact of animal disease (zoonotic or otherwise) and death on food security is another factor which drives use and overuse of antimicrobials in agriculture to stabilize and secure the food supply.

5.3. Food safety

For all of the reasons outlined above, veterinary drugs—both antimicrobials and other non-antimicrobial drugs such as hormones and growth stimulants—are widely used to treat diseases in food-producing animals and maximize yields. However, the use of veterinary drugs in food-producing animals has the potential to generate residues in animal-origin food [171]. These residues may result from inappropriate or

extra-label drug usage, failure to maintain drug withdrawal periods, or poor livestock production practices [172], and can cause public health hazards such as hypersensitivity reactions, cancer, mutagenicity, reproductive challenges, disruption of normal intestinal flora, and resistance (in the specific case of antimicrobials) [173]. Additionally, since only a fraction of administered veterinary drugs can be metabolized in food-producing animals, the rest ends up in urine and feces, which can pollute soil, surface water, and groundwater through wastewater discharge and land application of manure, negatively impacting wildlife and environmental health as well [154].

Given these potential health effects, various regulatory bodies exist to ensure the safety of animal food products and environmental health. On an international level, the Joint Food and Agricultural Organization/ World Health Organization Expert Committee on Food Additives (JECFA) carries out risk assessments to develop maximum residue limit (MRL) recommendations for veterinary drugs in various food products, which are then published by the Codex Alimentarius Commission (CAC) [174]. These recommendations are often followed by countries in the developing world which do not set their own MRLs, whereas several high-income countries such as the US and European Union set their own limits by different metrices [175]. The establishment of MRLs or tolerances for various veterinary drugs relies on a complex array of toxicological, pharmacological, dietary exposure, and microbiological risk assessment studies. These regulatory bodies also oversee a range of other measures, including improving access to veterinary services, strengthening supervision of veterinary drug production and distribution, and increasing the scope of animal-based food and environment monitoring, to promote rational use of veterinary drugs, and to reduce public health risks in animal agriculture. The residues of veterinary drugs commonly used in food-producing animals, as well as those not approved for use, are regulated in the major categories of animal products and are monitored using both general screening methods (i.e., microbial screening methods, immunological techniques and biosensors) and more sensitive quantitative measurements (chromatography-mass spectrometry based methods) [174].

5.4. Environmental health

Growing numbers of people worldwide are adopting animal resource-based diets, leading to significantly increased meat production in the last 50 years [176]. Despite some controversy, the impacts of meat consumption on the environment have been widely accepted [177]. Animal agriculture requires natural resources to support the growth of farm animals and to provide energy for meat production and consumption-related services [178]. These activities will inevitably cause significant changes in the environment, some of which are discussed below.

First, animal production has a significant impact on land and water use [179]. It is estimated that 75% of the world's agricultural land is devoted to feed production and grazing, and 20% of green water, which is main source of water to produce food, feed, fiber, timber, and bioenergy, is dedicated to livestock feed production [180], which directly competes with the land and water required to produce crops that feed the human population [181]. Moreover, the excessive land use for meat production is responsible for the majority of deforestation due to the rapid expansion of pastures as well as the increasing demand for high-quality protein feeds, such as soybean [182].

Livestock production also leads to other secondary impacts on the environment, including ecosystem corruption and environmental pollution from animal waste and emissions [177]. For example, the conversion of natural habitats for agricultural use causes ecological changes that can lead to increases in zoonotic disease host diversity [183]. Animal agriculture also produces vast amounts of waste, including manure, urine, greenhouse gases (GHGs), and excess feed [184]. Runoff waste containing chemicals, pathogens, and nutrients often spill into and contaminate the environment, which is not only a

mechanism for the spread of antimicrobial resistance, as discussed above, but also can have broader negative consequences on environmental health [185]. For example, excess nitrogen and phosphorus from agricultural runoff cause eutrophication in nearby water bodies, posing significant health risks to animals in aquatic ecosystems as well those reliant on those ecosystems, from wildlife to humans [186].

Animal agriculture also affects environmental health through its impacts on climate change. It contributes significantly to global warming via two layers of negative impacts. The historical displacement of terrestrial biomass carbon in native ecosystems that were converted to support grazing and feed production of livestock is responsible for approximately a third of all anthropogenic CO_2 emissions to date [187]. It was suggested that food animals, especially large ruminants, also contribute significantly to ongoing emissions of potent GHGs methane and nitrous oxide [188]. The FAO reported in 2006 that food animal production generates between 4.6 and 7.1 gigatons of GHGs each year that account for between 15% and 24% of total GHG emissions into the atmosphere [189], which was suggested to be underestimated for the present day [190]. A recent study modelled the combined, long-term effects of emission reductions and biomass recovery and suggested that a hypothetical rapid global phaseout of animal agriculture has the potential to stabilize greenhouse gas levels for 30 years and offset 68% of CO_2 emissions this century [191]. Climate change also plays a role in altering ecosystems and driving the emergence of novel zoonotic pathogens—which once again highlights the cyclical and interwoven nature of these issues.

6. Conclusion

The issues of zoonoses and antimicrobial resistance in animal agriculture should be considered interdependently in order to develop a true One Health approach to the challenges of preventing and monitoring infections at the interfaces between animal agriculture, human health, and the environment. This review aimed to provide a broad overview of some of the major bacterial zoonoses in animal agriculture, as well as key antimicrobials and pathways of resistance development. Approaches to combat these interrelated issues were considered, including the development of novel treatment strategies as well as non-drug interventions including surveillance and policy development, highlighting the importance of multidisciplinary research efforts to develop well-rounded approaches to these complex issues. Finally, additional factors influenced by and influencing animal agriculture were discussed, including animal welfare, food security, food safety, and climate change, to provide an even broader snapshot of the many facets which need to be accounted for when addressing issues of animal agriculture and infection from a One Health perspective. This review aimed to highlight the importance of considering how various issues, such as zoonoses and antimicrobial resistance, relate to one another within specific contexts such as animal agriculture, and the importance of multidisciplinary approaches to tackle the full complexity of these issues. The growing issues of both zoonoses and antimicrobial resistance are only two of many "ticking time bombs" which highlight the current unsustainability of modern animal agriculture and underscore the urgent need to systematically reconsider animal agricultural practices in our world today.

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