Agriculture and Human Values
https://doi.org/10.1007/s10460-021-10197-y

# How animal agriculture stakeholders define, perceive, and are impacted by antimicrobial resistance: challenging the Wellcome Trust's *Reframing Resistance* principles

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Accepted: 22 January 2021


## Abstract

Humans, animals, and the environment face a universal crisis: antimicrobial resistance (AR). Addressing AR and its multidisciplinary causes across many sectors including in human and veterinary medicine remains underdeveloped. One barrier to AR efforts is an inconsistent process to incorporate the plenitude of stakeholders about what AR is and how to stifle its development and spread—especially stakeholders from the animal agriculture sector, one of the largest purchasers of antimicrobial drugs. In 2019, The Wellcome Trust released *Reframing Resistance: How to communicate about antimicrobial resistance effectively (Reframing Resistance)*, which proposed the need to establish a consistent and harmonized messaging effort that describes the AR crisis and its global implications for health and wellbeing across all stakeholders. Yet, *Reframing Resistance* does not specifically engage the animal agriculture community. This study investigates the gap between two principles recommended by *Reframing Resistance* and animal agriculture stakeholders. For this analysis, the research group conducted 31 semi-structured interviews with a diverse group of United States animal agriculture stakeholders. Participants reported attitudes, beliefs, and practices about a variety of issues, including how they defined AR and what entities the AR crisis impacts most. Exploration of *Reframing Resistance*'s Principle 2, "explain the fundamentals succinctly" and Principle 3, "emphasis that this is universal issue; it can affect anyone, including you" reveals disagreement in both the fundamentals of AR and consensus of "who" the AR crisis impacts. Principle 2 may do better to acknowledge that animal agriculture stakeholders espouse a complex array of perspectives that cannot be summed up in a single perspective or principle. As a primary tool to combat AR, behavior change must be accomplished first through outreach to stakeholder groups and understanding their perspectives.

**Keywords** Antimicrobial resistance · Animal agriculture · Qualitative research · Antimicrobial use · Animal husbandry · One Health

**Abbreviations**

| | |
|---|---|
| AR | Antimicrobial resistance |
| Reframing resistance | How to communicate about antimicrobial resistance effectively |
| Wellcome | The Wellcome Trust |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| WHO | World Health Organization |
| OIE | World Organisation for Animal Health |
| NGO | Non-governmental Organization |
| FAO | Food and Agriculture Organization of the United Nations |

## Introduction

Antimicrobial resistant (AR) bacteria impact human, companion animal, and animal agriculture sectors (i.e. both terrestrial and aquatic settings) (Suzuki et al. 2017; Innes et al. 2020) and where those sectors interface (Magouras et al. 2017). Prescribers in the United States (U.S.) inappropriately

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administer antimicrobials to human patients in over 30% of outpatient settings, 50% of hospital settings, and 75% of long-term care settings (Hicks et al. 2010). Antimicrobial use in humans, especially when prescribed and consumed inappropriately, promotes selection of bacteria with antimicrobial resistance genes, which has been demonstrated across healthcare (Goossens et al. 2005; Riedel et al. 2007; Bell et al. 2014; Dadgostar 2019) and community settings (Furuya and Lowy 2006; Kallel et al. 2008; Olesen et al. 2018).

Inappropriate antimicrobial use extends into to the veterinary sector, where small animal veterinarians commonly prescribe antimicrobials discordant with established guidelines (Banfield Pet Hospital 2017). Over-use of antimicrobials in livestock production are also a concern among public health advocates (Silbergeld et al. 2008; Blanchette 2019; Kirchhelle 2020). Although animal agriculture's association with progression of AR in the human health sector is hotly debated among professionals in the industry, especially in the U.S. (Phillips et al. 2004; Ferguson 2019), robust scientific evidence suggests its undeniable contribution (Levy et al. 1976; Holmberg et al. 1984; Hummel et al. 1986; Castillo Neyra et al. 2012; Nordstrom et al. 2013). Authors in this manuscript also have contributed to the conversation (Davis and Rutkow 2012; Maron et al. 2013; Smith et al. 2018; Innes et al. 2020). Unlike in the human or small animal sectors, antimicrobial use in animal agriculture can be classified further into therapeutic and production justifications for use—although exact definitions for these two terms are controversial. Traditionally described as either "growth promotion" or "feed enhancement," subtherapeutic antimicrobial doses have been administered to animals to increase milk yield or weight-gain (Landers et al. 2012). Alternatively, animals may receive antimicrobials either for therapeutic or prevention justifications. Although antimicrobials are no longer labeled for growth promotion and cannot be used to enrich feed for such purposes (Food and Drug Administration (FDA) 2019), an effective "ban" on non-therapeutic uses, the U.S. agriculture industry has historically utilized antimicrobials to increase yield for meat and milk (Institute of Medicine 1989). In 2016, approximately 70% of the roughly 8.4 million kg of antimicrobials sold in the animal agriculture sector were for production or production/therapeutic reasons in contrast to therapeutic-only reasons (CVM and FDA 2017; Ferreira 2017). Antimicrobial use in animals leads to AR in animals, the same phenomenon which occurs in humans (Chantziaras et al. 2014; Pomba et al. 2017). However, antimicrobial use in animals has also been demonstrated to increase AR development in humans, either directly through contact or indirectly through animal products (Economou and Gousia 2015). A review written by several authors on this manuscript has described multiple routes whereby AR bacteria can transition from animals to human and compiled those scientific resources (Innes et al. 2020).

Regardless of the source, AR is a growing crisis. Current estimates suggest that annually over 700,000 human deaths worldwide are due to antimicrobial resistant infections (O'Neill 2016), which are projected to grow to 10 million by 2050 if no drastic interventions are implemented (O'Neill 2014) and likely exacerbated by climate change (MacFadden et al. 2018). This change starts with communication. Thoughtful, consistent dialogue to promote AR comprehension—what it is, who and what it impacts, and how and why it occurs—can alter trends, incentivize people to act, and establish a benchmark for change that stakeholders can espouse (Rochefort and Cobb 1994; Walker 2019). Communication is a pillar of behavior change and has been frequently included in developed public health frameworks (Maibach et al. 2007; Michie et al. 2011). Clear, intentional, and concise messaging can effectively promote education and incentivize behavior change, specifically in relation to AR (Hawkings et al. 2007; Edgar et al. 2009; Edgar 2012). In fact, previous research has found that farmers do consider the environmental and social impacts; given this, trusted, tailored messaging and targeted incentives are critical to the adoption of beneficial practices (Liu et al. 2018). At the current moment, however, no standardized, universal rhetoric exists to consistently define AR, describe its actual or perceived consequences, or identify strategies to reduce its transmission (Wellcome Trust 2019a), despite past attempts (Podolsky 2018).

*Reframing Resistance: How to communicate about antimicrobial resistance effectively* (henceforth *Reframing Resistance*), The Wellcome Trust (henceforth Wellcome) sponsored report released in October 2019, proposes the need to establish a consistent and harmonized messaging effort that describes the AR crisis and its global implications for health and wellbeing across all stakeholders, while also being uniformly approachable. Wellcome as an organization is well-placed to synthesize and disseminate AR recommendations, as they have expertise in AR and vast experiences in global health challenges. Wellcome is committed to conducting and funding research that fulfills the United Nations' resolutions on AR; develop, improve, and assess AR treatments and technologies; and support national and global strategies and policies to combat AR (Wellcome Trust 2020).

In planning *Reframing Resistance,* Wellcome had two main aims: (1) increase public comprehension of the problem of antimicrobial resistance and (2) persuade the public that AR is something that should be the focus for political action. These objectives were initiated to improve awareness and support among the general public to encourage effective policy (Wellcome Trust 2019b).

*Reframing Resistance* posits the necessity to include partners in the animal, human, and environmental sectors to ameliorate the AR crisis. The concept of "One Health" harmonizes these three sectors and is recognized as an essential strategy to approach the AR crisis (McEwen and Collignon 2018; Thakur and Gray 2019). Unfortunately, few representatives in the animal agriculture sphere were involved in Wellcome's expert panel, and the agriculture community at large was not specifically targeted in their messaging panels. Additionally, no animal agriculture producers who intimately and directly worked with animals were consulted. The involvement of the agriculture community—a complex network of professionals encompassing many disciplines—is essential to extinguish the propagation and spread of AR. Regardless, Wellcome asserts that five principles should be used to communicate AR ideas and promote action universally: (1) "frame AR as undermining modern medicine," (2) "explain the fundamentals succinctly," (3) "emphasise [sic] that this is a universal issue; it can affect anyone, including you," (sometimes worded alternatively in the document as "emphasise that this is a universal issue; it affects everyone, including you") (4) "focus on the here and now," and (5) "promote immediate action" (Wellcome Trust 2019a).

Two principles are of primary relevance to animal agriculture stakeholders who work in the U.S.: Principle 2—"explain the fundamentals succinctly"—encourages a firm understanding of the AR concept, and Principle 3—"Emphasise that this is a universal issue; it can affect anyone, including you"—acknowledges that human and animal sectors are impacted by and contribute to global AR development and ubiquity. Both of these principles are important, specifically in the sectors which utilize antimicrobials and therefore contribute to AR selection and spread.

Using qualitative data collected from key stakeholder interviews from the U.S. animal agriculture sector, we questioned and explored how Wellcome's global messaging framework in *Reframing Resistance* applies to the interviewee's profession and livelihood. We aimed to describe animal agriculture stakeholders' AR definitions and perceptions to determine existent gaps in language consistency and to assess whether using different language in messaging would make it more effective at recruiting the U.S. agriculture sector. Understanding animal agriculture stakeholders' insights regarding AR fundamentals and AR spread can contribute to the formulation of an effective process to engage AR stakeholders, particularly those within the animal agriculture industry. Since the agriculture sector plays a key role in the use of antibiotics, the ability to successfully address AR hinges on their inclusion.

## Methods

### Setting

We initially designed this study to understand how U.S. animal agriculture stakeholders, including animal agriculture producers, veterinarians, educators (e.g. consultants, extension agents and specialists, and subject-matter expert lecturers), academics, pharmaceutical representatives, and industry representatives perceive the impact of U.S. federal and state policies and regulations that promote judicious use of antimicrobials. We also sought to understand whether perspectives varied across states that have adopted various levels of stringent antibiotic-use policies. Maryland and California were among the first states to enact and promulgate antimicrobial judicious-use policies, and therefore industry stakeholders within those states are among the most experienced with compliance and results. We considered Maryland and California as the "policy" states, and other states (i.e. Delaware, Georgia, Iowa, Nevada, New York, North Carolina, Oregon, Pennsylvania, Utah, Virginia, Washington, and West Virginia) as controls. We aimed to encompass a wide swath of states to capture the plurality of perspectives in the U.S. food system.

Wellcome released their *Reframing Resistance* report during the initial interviewing phase of this research, which then generated conversations in the literature and media regarding the principles and their application to the animal agriculture sector (CIDRAP 2019; Glover et al. 2019; Williams 2019). Although this study was not originally developed to investigate *Reframing Resistance*, our study aims were primarily to investigate how policy and regulation messaging may be interpreted by the U.S. animal agriculture sector. Broadly speaking, both *Reframing Resistance* and our research explored effective communication and messaging around AR. Thus, the release of *Reframing Resistance* provided a unique opportunity to compare the results from this pilot study to their internationally recognized guidelines.

Some of the interview questions posed in our research offered direct insights into the principles recommended by the *Reframing Resistance* reports. In particular, our interview question "how do you define antibiotic resistance?" tied to Principle 2. In addition, some interview responses were also relevant to Principle 3, in particular responses that discussed the etiology of AR and its impacts on the animal agriculture industry.

### Participants

We identified animal agriculture stakeholders through a combination of purposive and snowball sampling techniques (Miles and Huberman 1994). We began by listing stakeholders' professions in the animal agriculture industry (i.e. producers, veterinarians, educators, and industry representatives). We recruited and approached potential interviewees at professional meetings and through publicly available information (e.g., websites and reports). We contacted several stakeholders who were acquainted through the authors' networks. After being interviewed, we asked all participants to identify other contacts who could inform this work (i.e. snowball sampling).

Inclusion for participation was based upon current or recent professional experience within the animal agriculture sphere, with at most one degree of separation from direct contact with animals—meaning that the participants own, produce, and/or treat animals or that they work with people who own and/or produce animals. We sought to include established professionals who may have been less well-known but who have considerable subject-level experience, and stakeholders who interact in large- and small-scale operations. Participants were not triaged based upon antimicrobial administration practices, and thus included users and non-users. We called and/or sent emails to potential interviewees to explain the research and invite them to participate in an in-person or remote interview—depending on their location and preference—at a time convenient for them. For those who did not initially respond, we sent follow-up communications. Prior to in-person interviews, the research team offered a meal (typically breakfast or lunch) as an incentive.

We invited 43 stakeholders to participate in the study either via email, telephone, or in-person. Stakeholders included animal agriculture producers, veterinarians, educators (e.g. consultants, extension agents and specialists, and subject-matter expert lecturers), academics, and pharmaceutical representatives. Thirty-one animal agriculture stakeholders participated in a series of in-depth, semi-structured interviews between February 2018 and February 2020. The interviews ranged between 11 min (due to recording technology failure) and 100 min with a median of 43.5 min. Table 1 describes the participants according to key demographics. One or more co-authors (GKI, MFD, KRD) participated in each interview and interviewed participants alone or within small groups. GKI and MFD conducted most interviews—14 and 13 interviews, respectively. For two interviews, GKI and MFD were both present, one of which included KRD. GKI was joined by CAG in seven interviews. The two remaining interviews were conducted individually by KRD. No follow-up interviews were performed.

## Data collection

Invitees who agreed to participate were interviewed using one of three interview guides developed by three co-authors (GKI, KRD, MFD) who are licensed veterinarians and public health researchers. Three guides were employed to account for differences among occupations within the industry and whether the participants worked in states with or without antibiotic-use policies. Guides varied slightly to incorporate pointed questions based on specific professional experiences among producers, veterinarians, or others in the industry. Similarly, participants with experience working in states with specific antibiotic-use policies were questioned to reflect upon their perspectives. We used a modified grounded theory approach that was informed by available literature on animal agriculture perspectives to develop the guides, focusing questions on three domains: antibiotics, animal welfare, and relevant legislation/regulation (Baron and Frattaroli, 2016; Coyne et al. 2014; Mas et al. 2017; Table 1).

We obtained written or verbal informed consent, although the Johns Hopkins Bloomberg School of Public Health's Institutional Review Board (IRB) determined this project to be "Not Human Subjects Research" (IRB# 00,008,466). Prior to each interview, participants completed a survey which assessed demographic, profession, job title, and industry information. During the interviews, participants recounted general feelings about governmental regulation, antibiotic-use, and animal welfare, particular topics within those domains, and the overlap among those three topics. Follow-up questions not included on the interview guides were asked in accordance with semi-structured interview methodology. Flexibility in data collection that is responsive to unanticipated findings is a key characteristic of qualitative methods (Miles and Huberman 1994). We continued to recruit and interview informants until reaching data saturation (Miles and Huberman 1994).

## Data analysis

A third-party transcription service (Production Transcripts, Glendale, California) transcribed the interviews. GKI and AM analyzed data with NVivo software (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 11, 2017). GKI and AM reviewed every recorded interview and read the transcribed interviews (Saldana 2015). They recorded analytical notes and synthesized content into categories and themes based on the two investigated *Reframing Resistance* principles. GKI and AM discussed the identified preliminary themes and agreed upon categories and codes, which they developed into a codebook. Themes and subthemes were iterative and data-driven; if any subthemes were to emerge outside of the *Reframing Resistance* framework, new subthemes would be documented and be described. All disagreements were discussed and resolved. In accordance with the finalized codebook definitions, GKI and AM recoded all transcripts, and MFD reconciled any discrepancies (Saldana 2015). GKI and AM then re-assessed the transcripts for the frequency and strength of preliminary themes and finalized the themes presented herein (Creswell

**Table 1** Participant demographics

| | Total | Intervention State[a] | Control State[b] |
|---|---|---|---|
| **Total** | 31 | 21 | 9 |
| California | 11 | 11 | |
| Maryland | 11 | 10 | |
| Control state | 9 | | 9 |
| ***Facility tours*** | 8 | 6 | 2 |
| **Sector**[c] | | | |
| Dairy | 8 | 6 | 2 |
| Cow | 5 | 3 | 2 |
| Small ruminant (goat, sheep) | 3 | 3 | 0 |
| Meat | 7 | 5 | 3 |
| Beef (cattle) | 7 | 5 | 3 |
| Small ruminant (sheep, goat) | 2 | 1 | 1 |
| Swine | 5 | 3 | 3 |
| Poultry | 6 | 3 | 4 |
| Aquaculture/Fisheries/Shellfish | 7 | 3 | 2 |
| **Mixed production sectors** | 6 | 4 | 3 |
| ***Producer or farmer*** | 10 | 7 | 4 |
| Large-scale (≥ 1000 animal units) | 2 | 2 | 1 |
| Mid-scale (≥ 100 animals but < 1000 units) | 6 | 5 | 1 |
| Small-scale (< 100 animals) | 1 | 0 | 1 |
| Not answered | 1 | 0 | 1 |
| **Veterinarian** | 5 | 2 | 3 |
| ***Non-veterinarian educators***[d] | 6 | 6 | 0 |
| **Government representative** | 4 | 4 | 0 |
| ***Industry representative*** | 4 | 2 | 2 |
| **Interview type** | | | |
| Key informant interview | 21 | 16 | 5 |
| Focus group interviewees (# of groups) | 9 (4 groups) | 5 (2 groups) | 4 (2 groups) |

[a]California (SB27), Maryland (SB422)

[b]Delaware, Georgia, Iowa, Nevada, New York, North Carolina, Oregon, Pennsylvania, Utah, Virginia, Washington, West Virginia, or national institution, organization, or company

[c]Numbers within animal production sector may not sum to the total due to mixed production facilities (facilities or stakeholders who produce more than one animal species)

[d]Non-veterinary educators include professions such as consultants, and education agents and specialists, and subject matter experts who teach animal agriculture practices

2003). This manuscript was written in accordance with COREQ guidelines for best practice of conducting and writing qualitative research (Tong et al. 2007).

## Research team and reflexivity

When conducting the interviews, we sought to establish a neutral environment so that participants would be comfortable sharing their thoughts, feelings, perspectives, and insights on these sometimes-controversial topics. We worked to maintain this neutrality throughout the interview and the analysis. In the interest of transparency, we provide a summary of the authors' relevant skills and training for readers' consideration (Table 2).

# Results

We first present our findings that are relevant to Principle 2 from *Reframing Resistance,* and next present our findings that are relevant to Principle 3. Results are further organized by emergent themes and, when applicable, subthemes.

## Defining Antimicrobial Resistance; Principle 2

"Explain the fundamentals succinctly"
– *Reframing Resistance,* Principle 2

Definition is a fundamental means to both comprehend and express an idea (National Institute of Child Health and

**Table 2** Research Team (in order of authorship)

| Author | Education | Profession | Relevant Experience |
|---|---|---|---|
| Gabriel K. Innes | VMD PhD | Epidemiologist | Veterinary medical training in large animal medicine<br>Fellowship in dairy production and medicine<br>Qualitative analysis training<br>Published peer-reviewed research on animal agriculture and antimicrobial resistance<br>Antimicrobial resistance and stewardship epidemiologist |
| Agnes Markos | MPH | Public Health Analyst | Qualitative analysis training |
| Kathryn R. Dalton | MPH VMD PhD | Postdoctoral Fellow | Veterinary medical training in large animal medicine<br>Small animal medicine practitioner<br>Published peer-reviewed qualitative research, on animal agriculture, and antimicrobial resistance |
| Caitlin A. Gould | MPPA DrPh(c)* | Doctoral Candidate | Aquaculture experience<br>Qualitative analysis training |
| Keeve E. Nachman | PhD | Associate Prof | Published peer-reviewed research on animal agriculture and antimicrobial resistance |
| Jessica Fanzo | PhD | Prof | Published peer-reviewed research on animal agriculture industry |
| Anne Barnhill | PhD | Core Faculty | Published peer-reviewed research on food policy and animal ethics |
| Shannon Frattaroli | MPH PhD | Associate Prof | Published peer-reviewed qualitative research and on animal agriculture |
| Meghan F. Davis | MPH DVM PhD | Associate Prof | Veterinary medical training in large animal medicine<br>Mixed animal practitioner<br>Published peer-reviewed research on animal agriculture and antimicrobial resistance<br>Qualitative analysis training |

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(c)*—author is seeking degree

Human Development 2000). During interviews, we asked participants to define AR in order to characterize the nuances among individuals and professions and explore reasons for why stakeholders adopted specific definitions. Every participant succinctly defined AR. Participants' ability to define AR readily demonstrated their mindfulness about the concept and the realities of the AR issue. However, participants' definitions of AR varied. We identified three distinct categories of definitions, which centered around three different entities (or "protagonist") in AR: the pathogen (according to the "microbiological" definition), the patient (according to the "clinical" definition), or the antibiotic drug (according to the "pharmaceutical" definition). These definitions, and those who use them, position either the pathogen, patient, or antibiotic drug as playing the central role in the problem (Fig. 1). Some participants used multiple definitions. We investigated whether varied definitions could be attributed to demographics and found that although the study group represented multiple generations, AR definitions did not group by age, which suggests similar AR knowledge across generation. Similarly, producer scale (i.e. small versus large) and type (i.e. United States Department of Agriculture (USDA)-certified Organic versus conventional) did not cluster around specific AR definitions.

Study participants had varying opinions and practices regarding appropriate antimicrobial use. Some producers indicated that they either produced in accordance with USDA-certified Organic (Ricke 2012) and/or "antibiotic free" labeled protein (FSIS 2019). No producers indicated that they utilized antimicrobials for growth promotion, and furthermore most verbalized this sentiment: "…we don't rely on antibiotics for growth promotion or anything like that" [Producer]. Others indicated that they administered antibiotics only when their animals had symptoms such as fever, self-described as a "minimalist" approach [Veterinarian], and others attested to using antibiotics when animals have subclinical signs such as high somatic cell count in milk [Producer]. Some producers—and most other stakeholders—indicated that they would like to maintain the option to administer antimicrobials preventively: "We know that… these birds are going to get sick…we know what's going to happen to them, but now you've taken the tool of being preventive away…" [Producer]. Additionally,

> We don't have vaccines to control all diseases…and so they're one important factor but they're not the only way that we can prevent disease. …We look for alternatives to antibiotics, but there are times that animals do get sick and we need to make sure that we continue

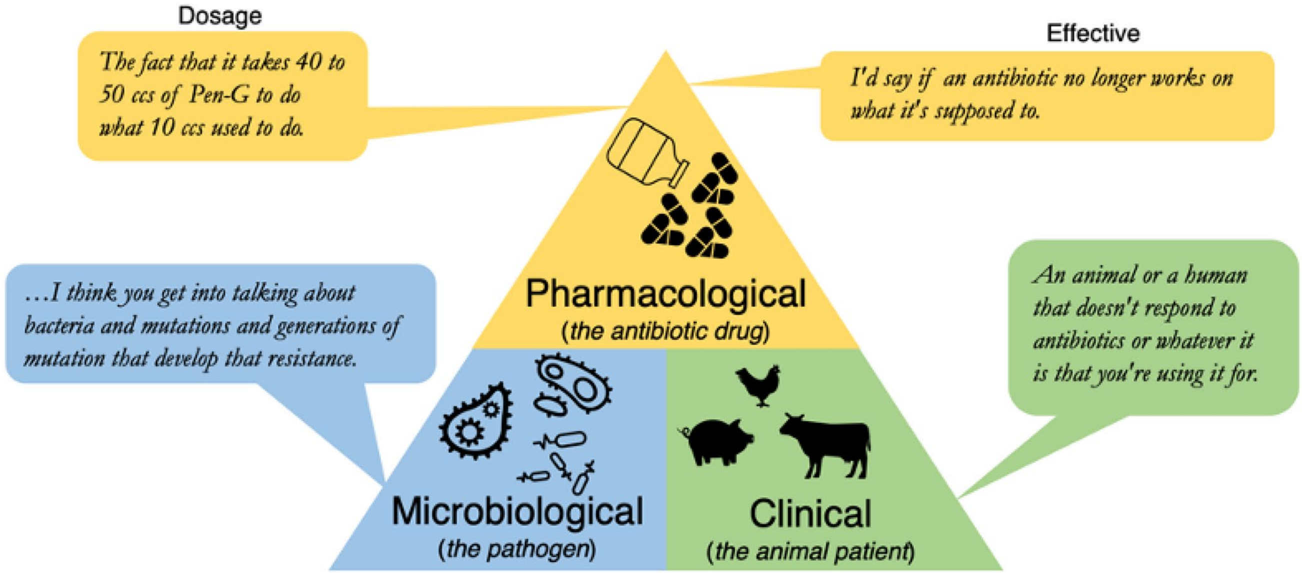


**Fig. 1** ***Refraining Resistance,*** **Principle 2 — "Explain the fundamentals succinctly."** Stakeholders perspectives could be categorized into three major facets: Pharmacological (a failure within the drug itself), Microbiological (genetic resistance development in bacteria), and Clinical (refractory treatment efforts) AR definitions. The majority of stakeholders utilized the clinical AR definitions, which may reflect their direct and consistent contact with livestock animals

> to be able to [prescribe] antibiotics…to prevent and treat and control disease when it does occur. [Pharmaceutical Representative]

### Microbiological definition of AR

Wellcome urges stakeholders to frame AR as an evolutionary phenomenon within distinct bacteria populations. *Reframing Resistance* emphasizes that AR is a manifestation within bacterial genetics and therefore should not be confused with misconceptions that resistance occurs within the animal's biology. Many participant's description of AR aligned to this definition, where bacteria are the protagonist. These respondents centered AR as the transference of resistance genes or mutation mechanisms that develop within bacteria populations: "bacteria and mutations and generations of mutation that develop that resistance" [Government Researcher].

Notably, all stakeholder professions within our small sample contained individuals who incorporated the microbiological definition. The variety of industries within animal agriculture who utilized the microbiological definition was also wide; stakeholders from poultry, beef, dairy, swine, and aquaculture entities all prioritized this definition category. Similarly, participants from six of the seven participating states defined AR in microbiological terms. All veterinarians in our study, independent of their practice species, communicated the microbiological definition.

### Clinical definition of AR

The clinical definition of AR highlights the patient, in this case the animal, as the protagonist. A minority of participants adopted the clinical definition. For example: "[The diseased animal] is not responding to the antimicrobial that we are choosing*"* [Educator].

Some respondents using the clinical definition of AR posited that bacterial infections and the antibiotic tools used to fight the infections detract from the larger picture—animal health and production—a problem that those who interact directly with animals encounter regularly: "Antibiotics are a tool and…we should always have all our tools in our toolbox…" [Educator]. In this sense, some stakeholders reported that infections physically harm animals and interfere with husbandry, thus positioning antibiotics as necessary "tools" to reestablish animal health. Animals are the central entity of the industry, which may be why some stakeholders underscored them in their AR definitions. Interviewees who used the clinical definition were producers and educators: professionals who often work directly with animals and their welfare. Producers, who most regularly interact with their animals, visualize the impact of AR in their animals firsthand: "That cow just keeps coming back and doesn't respond to something… and then at some point, which is usually by the third time when we followed the vet directive and we're not seeing any improvement, then we cull that cow" [Producer]. At a certain point, AR overwhelms the resources of producers and the immune system of their animals. Of note, no veterinarian respondents defined AR with a clinical perspective.

While only some respondents used the clinical definition of AR, most respondents considered optimal animal health paramount within the industry. Stakeholders noted that animals were inextricably linked to their own livelihood, and some suggested that welfare was their life's purpose. After one producer was asked how they viewed animal welfare, they responded, "it's literally what I do for a living" [Producer].

In centering animals and animal health in their understanding of AR, these respondents did not articulate AR fundamentals in alignment with *Reframing Resistance*'s emphasis that AR is a manifestation within bacterial genetics.

#### Pharmaceutical definition of AR

The majority of participants concentrated on the functionality of antibiotic agents when describing AR fundamentals. These stakeholders asserted antibiotic drugs as their protagonist, and they connected AR with the ability of antibiotic agents to treat illness. This orientation addresses antibiotic tools as failures to perform as intended, which one participant noted: "[AR is] when you need to take antibiotics and they don't work" [Non-governmental organization (NGO) representative]. This description of antibiotic inadequacy was always in relation to their efficacy to treat infections over time as opposed to failures in the pharmaceutical industry or active drug components themselves.

Within the pharmaceutical definition, two sub-themes emerged termed *effective* (the loss of antibiotic drug function) and *dosage* (the necessity to increase volume or dose to achieve the same effect, or dose-dependency). Both sub-themes stressed the importance of temporality and thus the transition to a level of resistance from a susceptible state. Among participants who incorporated the effectivity sub-theme in their AR fundamental descriptions, they included derivations of the word *effective*: "[AR is a] situation where an antibiotic that would normally work and help eliminate an infection no longer is effective" [Educator]. Participants opined that that the antibiotic itself failed to perform as expected. Some participants elaborated that antibiotics failed entirely. Others inferred that *effective* is a non-binary term to describe a gradient where antibiotics' effects progressively decline, as opposed to an all-or-nothing mechanism.

Only three participants—one educator and two producers—stressed the *dosage* sub-theme. They described the necessity to administer a higher dosage or volume of antibiotics to achieve the same result: "The fact that [treatment] takes 40 to 50 ccs of Pen-G to do what 10 ccs used to do [to treat infection]" [Producer].

#### Multiple definitions of AR

Many of those who used the pharmaceutical definition bolstered and amended perspectives with the microbiological definition. Two quotes are shown below:

> Broadly I think it's when certain bugs are no longer, or certain antibiotics are no longer effective against certain bugs (Pharmacological) or the pathogens have developed resistant patterns to certain antimicrobials. (Microbiological) [Veterinarian]

And, "I'd say if an antibiotic no longer works on what it's supposed to (Pharmaceutical)…if the bacteria has developed a resistance to it (Microbiological)" [Producer].

Of those who began defining AR through the pharmaceutical definition, many corrected, modified, and/or reinforced their definitions with the microbiological definition. However, those who used the microbiological definition did not necessarily follow-up with the pharmaceutical definition.

### Universality of AR; Principle 3

> "Emphasise that this is a universal issue; it can affect anyone, including you"
> – *Reframing Resistance,* Principle 3

Because Principle 3 asserts two independent ideas, we analyzed responses accordingly. First, did stakeholders perceive the AR issue as being a universal, One Health problem? To affirm this question, stakeholders must have verbalized or alluded to a One Health vision of AR development and transmission that includes both human and animal agriculture sectors. For example: "This isn't just a [veterinary] problem but a human [problem, too]" [Educator].

Second, did stakeholders express and understand that AR, in some capacity, affects their industry? To meet this criterion, stakeholders must have shared a One Health view of AR consequences (the *One Health acknowledgement* theme), acknowledged that AR develops within animal agriculture (*animal centrality* theme), or recognized that animal agriculture affects the transmission of AR to humans and/or the environment (the *overflow* theme). One beef producer demonstrated the overflow theme consistent with these standards,

> [AR is a] scare for society, especially with the antibiotics we use in beef or in chickens. ***It's trailing over into humans as well***. And we're seeing a lot of resistance from what I have read anyway from antibiotic use in animals, the same things we use in humans… [Producer]

A vast majority of stakeholders acknowledged AR as a problem, a finding aligned with other research (Pearson and

Chandler 2019). However, when asked, few participants described AR as a crisis. A few participants were unphased by AR, solely respondents within the shellfish aquaculture sector, where AR was less of a perceived threat to the industry: "I don't think [AR] is something that really has come up that much in that [shellfish aquaculture] realm" [Aquaculture Educator]. The terrestrial animal agriculture counterparts shared contradicting views from the shellfish stakeholders. We constructed four main themes based upon stakeholder opinions about AR sector involvement: One Health acknowledgment, animal centrality, human centrality, and overflow (Fig. 2).

### One Health acknowledgement

*One Health acknowledgment* is at the root of the first phrase in Principle 3, "Emphasise that this is a universal issue." This theme recognizes that AR development is a One Health problem in that it both develops within and impacts humans, animals, and the environment. Those with a *One Health acknowledgement* of the AR problem acknowledged the other themes—*animal centrality*, *human centrality,* and *overflow*—as parts to a process that occurs in all sectors (Fig. 2). These participants discussed the human and animal connections that result in transmission of AR genes and/or pathogens.

> We need to look at [AR] not only in the veterinary setting but also in the human setting and try to continue to further understand how those interplay with each other and understand what are the biggest drivers [its development]. [Pharmaceutical Representative]

This stakeholder articulated that veterinary and human medicine have AR challenges and described its exacerbation through the "interplay"—or overlap—between sectors. They demonstrated a level of understanding that *Reframing Resistance* professes in Principle 3′s first statute by capturing the issue's universality. Although only one-third of the participants adopted *One Health acknowledgement* to describe the AR crisis outright, no one demographic stood out; those who expressed this sentiment spanned six states (both in those with statewide antibiotic-use policies and those without) and multiple industries and professions. Further investigation of the stakeholder category based on their state policy indicated no differences in the proportions who used the *One Health acknowledgement* theme. Use was consistent among animal agriculture producers who self-identified as Organic and those who were conventional, and across professions.

A minority of this respondent subset alluded to the universality of the AR issue through other means, either through personal experience or metaphor to describe antibiotic judicious-use or "minimalism" to lessen AR development: "Yeah, so I'll just tell you my own experience with human antibiotics, I'm kind of a minimalist, it's the way I practiced veterinary medicine" [Academic]. Although this group of stakeholders did not explicitly draw a connection between humans and animals when describing AR, their response nonetheless suggested that they recognized that AR implicates humans, animals, and the environment.

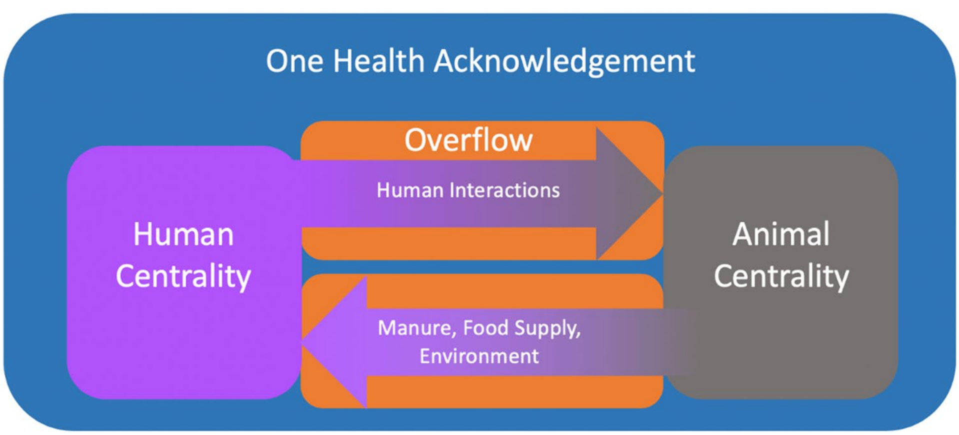


**Fig. 2** ***Reframing Resistance*** **Principle 3 — "Emphasis that this is a universal issue; it affects everyone, including you."** Stakeholders must have shared a One Health view of AR consequences (the *One Health acknowledgment* theme), acknowledged that AR develops due to veterinary (*animal centrality* theme) or human medical (*human centrality* theme) misuse, or recognized that sources of AR development directly or indirectly spills into a different sector—either animals, humans, and/or the environment (the *overflow* theme). Most stakeholders, in alignment the Wellcome Trust's *Reframing Resistance* report, agreed that AR is a One Heath problem which requires a multisectoral response

### Overflow

Some respondents articulated a specific idea—that AR bacteria, genes, or antibiotics themselves fluctuate from one sector to another dynamically, which can be seen as a specific manifestation of a One Health understanding of AR. We termed this idea *overflow*. One producer explains the *overflow* of specific pathogenic bacteria, made less treatable to antibiotic intervention, from the animal sector into the human sector.

> I mean you go through the Salmonellas and the Listerias and it's deadly and it didn't use to be. So I think the regulation is good to keep the public safe with the products that we're trying to sell them. [Producer]

Specifically, two types of *overflow* were described: AR bacteria and the antibiotic drugs via residues. Most participants suggested that AR bacteria developed in the animal agriculture setting and then *overflowed* into the human sector. Participants cited this *overflow* could occur through foodborne and/or manure-borne routes:

> [AR] is a concern of everybody, … if we overuse [antibiotics]… that's really more of the concern of environmental impact, like getting into the manure,… it just doesn't seem like it's as big of an issue as the antibiotic resistance directly in the food supply would be. [Producer]

This participant expressed primary concern about contamination of the food supply with AR bacteria and a secondary concern about AR contamination into the environment. They verbally ranked the importance of which *overflow* pathway—manure and food supply—had more significance in the AR problem. Although they stated that the risk of food-related contamination may not warrant a large concern, they nonetheless acknowledged its existence. Other participants ranked risks and benefits similarly: "I think there's a higher foodborne illness risk with tainted meat than I do with superbug creation through judicious use" [Industry Representative]. All but one participant cited AR *overflow* directionality from the animal sector into the human sector, who described transmission of AR from humans into the animal sector:

> I find it interesting [that] a lot of organizations are looking at farmers, but these same organizations work at research facilities that use antibiotics, but they don't look at themselves. Is antibiotic resistance leaving the hospital in our doctors and our nurses and our researchers? [Educator]

This participant highlighted a transmission pathway which not many individuals or organizations elaborated upon: anthroponosis—the transmission of infectious disease from humans to animals. It is notable that *Reframing Resistance* also neglects this type of *overflow*.

### Animal centrality

*Animal centrality* entirely focuses on the animal agriculture sector. Participants' comments categorized into this theme included little or no mention of the human contribution to AR development nor of the connection between the human and animal sectors. For example, "I would define it as producers or people giving so much that the animals, you know, don't respond to it anymore" [Producer].

Although these stakeholders spoke only about AR development in animal agriculture, it satisfied statute two in Principle 3 because these respondents recognized that AR has consequences in their industry. Stakeholders who incorporated *animal centrality* agreed that AR development in animals impacts them and their industry directly. These participants acknowledged that the use and sometimes misuse of antibiotics in animal agriculture has led to resistance and the loss of function in antibiotics:

> If there's a Gram-negative infection, for example, that doesn't respond to antibiotics, then there's no point in using antibiotics, using supportive therapy and things like that rather than—anti-inflammatories—that helps the cow get back to health rather than just automatically defaulting to antibiotic therapy. [Educator]

### Human centrality

The *human centrality* theme encompasses language that focuses on the human involvement in the AR crisis. Two participants articulated this theme:

> I believe we have a much, much worse problem—and I feel much more at risk within human overuse and misuse of antibiotics and the creation of antibiotic-resistant bacteria due to overuse and misuse in humans than I've ever thought about in animals. [Educator]

Both participants, an educator and an aquaculture representative modified this statement, elaborating that human misuse was not in isolation and that animal agriculture may also conduct practices that contribute to AR development, consistent with the *animal centrality* theme. These respondents additionally cited the connections between animals and humans through the *overflow* theme. These three themes, which acknowledged humans, animals, and their connections, is the main message behind *One Health acknowledgement*. Therefore, interviewers who utilized the *human centrality* theme language, were also coded as having *One Health acknowledgement* when aggregating their perspectives.

## Discussion

### *Reframing Resistance*'s Principle 2—"Explain the fundamentals succinctly"

#### Microbiological definition of AR

High-level organizations, such as governmental entities, NGOs and international health entities, promote the microbiological definition of AR. The World Health Organization (WHO) describes AR as "the ability of a microorganism to stop an antimicrobial [drug] from working against it" (WHO et al. 2016) and World Organisation [sic] for Animal Health (OIE) defines AR as "microorganisms that cause disease stop responding to drugs and medicines that were once effective in treating them"(World Organisation for Animal Health 2016). *Reframing Resistance* likewise adopts this framing. However, a disconnect existed between the author group of the Wellcome report—professionals who may or may not have direct interaction with livestock—and participants in this study who have explicit and frequent interaction with animals or stakeholders who work with producers. The microbiological definition, although adopted by some participants, was not expressly communicated by the majority of stakeholders, those within the stakeholder groups, nor within either state-policy category. True, shared language may be an effective way to communicate (Thomas and McDonagh 2013); however, we speculate that this may degrade a multi-culture environment and could be construed as forced assimilation and subduction of one's identity and opinions (Oishi 1984). In turn, this may create a splintered front against AR as opposed to a united one, hypothesized to be detrimental in effective AR messaging efforts (Edgar et al. 2009).

#### Clinical definition of AR

Although Wellcome encourages AR communication with a microbiological framing, this may not resonate with many animal agriculture stakeholders for whom optimal animal health and welfare are paramount. We found this perspective to be independent of profession: in the absence of health, animals cannot efficiently or effectively build meat, produce milk, or grow fiber. Further, sick animals translate to financial losses for producers and result in a cascade of problems for other animal agriculture stakeholders (Sinclair et al. 2019). Because animal health exists at the center of the animal agriculture nexus, the pattern of health and illness influences stakeholder perspectives, especially for producers. If animals do not recover after antibiotic administration, producers may assume that AR is to blame; however other explanations exist for refractory illness and treatment failures. One possible reason may be that the symptomatic animal may not have a bacterial infection; the etiologic agent of their illness may be viral or parasitic. In these case, antibiotic agents would be useless. Alternatively, the animal may have had a different bacterial infection previously, and antibiotic agents used to treat this new infection may not be indicated for the new bacteria. Therefore, AR may not explain refractory illness. Unfortunately, inappropriately administered antimicrobials are commonly cited in the human health literature but are widely absent in animal livestock medicine (TNS Opinion & Social 2010).

#### Pharmaceutical definition of AR

Although the pharmaceutical definition, similar to the clinical definition, does infer processes that occur as the result of AR development, the underlying AR fundamentals may not be well-articulated through this perspective. Antibiotic "failure" is a symptom, but not the cause of AR. Similar to explanations in the clinical definition theme, other factors may contribute to the poor performance of antibiotics.

Why do producer stakeholders reference the *dosage* subtheme within their pharmaceutical definition? Many producers have the legality, resources, and wherewithal to administer treatments to their own animals (Ekakoro et al. 2019). It is possible that over time, the lack of pharmaceutical response may require administration at a larger volume or a higher dosage to reach the same effect. This is a manifestation of AR consequences in animals. Similarly, educators and NGO representatives, who are directly involved with producers, may hear similar anecdotes from their constituents, as reflected by the many participants who cited current or prior production experiences themselves during the course of data collection for this study.

#### Multiple definitions of AR

*Reframing Resistance* emphasizes that communicators who define AR discordant with the microbiological theme or use multiple definitions confuse their audience about AR fundamentals, consequences, and intervention strategies such as antimicrobial stewardship. Based upon interview analysis of the interview data, an alternative conclusion may be that communicators who use mixed definitions express a more systems-level understanding (Peters 2014), and/or attempt to establish connections with an audience where the receptivity to the different definitions is unknown. Specifically, it is possible that respondents framed AR in multiple ways to capture different facets of the AR problem and convey the message to people with different perspectives. This is an inclusive strategy because animal agriculture stakeholders speak to people with so many backgrounds in education, from different professions, and with a range of biases.

### *Reframing Resistance's* Principle 3—"Emphasise that this is a universal issue; it can affect anyone, including you"

Principle 3 asserts two sub-principles, implied by the placement of a semicolon. The first phrase—*emphasise that this is a universal issue*—implies that the global community should accept the One Health, all-encompassing nature of AR development. Similar to collaborative messaging from WHO, OIE, and Food and Agriculture Organization of the United Nations (FAO), this idea acknowledges that humans, animals, and the environment play significant roles in AR development that must be communicated in AR messaging strategies.

In the second phrase, Wellcome clarifies: *[AR] can affect anyone, including you.* The first piece in this phrase—*it can affect anyone*—narrows the message. Unfortunately, by integrating the word "anyone," Wellcome directs attention only to the human consequence of AR, and thus fails to acknowledge the scope of AR as a One Health, ubiquitous issue. However, the use of "anyone" neglects the relationship among animals and the environment *with* humans as related to the AR issue. Instead, Wellcome could have harnessed the word "everything" to demonstrate inclusivity and the One Health significance of AR development and spread.

The second phrase—"including you"—confronts the audience directly. The audience is told to recognize that "anyone" should not be interpreted with equivocation. Wellcome asserts that AR impacts each person individually and directly. The tone is forthright and may be an attempt to engage and educate stakeholders. However, some stakeholders could interpret this directness as demeaning and aggressive. Exactly *how AR* "affects even you," is left ambiguous. Economic externalities exist in the agriculture sector, where animals infected with AR pathogens cause economic losses for producers. Animal agriculture stakeholders absorb these economic externalities. Producers may become burdened and suffer economically from AR infections in their animal populations. Therefore, the statement—*it can affect anyone, including you*—may resonate with individuals differently, and could be understood that AR directly, via physical health, or indirectly, via economic or mental health, affect the population. Regardless of the mechanisms by which stakeholders connected with this phrase, "including you," the vast majority verbalized AR's consequence in their own lives independent of profession and operation type (e.g., USDA-certified Organic and conventional). Interestingly, this is somewhat inconsistent with literature that investigated nuanced perspectives, which indicates that stakeholders had varied opinions based on profession and operation type (Fortané 2019; Pearson and Chandler 2019). However, the same literature (Pearson and Chandler 2019) has noted that stakeholders were uniformly aligned with AR as a problem, which is consistent with findings in this research. Possibly, our interviews did not distinguish specific justifications for perspectives. However, we theorize that the disentangling of a targeted message may in fact fragment the response overall, and therefore do not believe this is exceptionally salient to this research.

The WHO, OIE, and FAO have proposed solutions and action plans for the AR crisis. The tripartite recommends that countries promote AR surveillance, monitoring, and containment in the agriculture, human, and environmental spaces. AR is a global issue and a One Health issue. Next steps require that AR development has wide-reaching repercussions and etiologies that should be acknowledged by all stakeholders. Acknowledgement that AR has universal roots and repercussions contributes to Wellcome's Principle 3, which was widely adopted among respondents, independent of individual demographics and state-level policy adoptions.

## Reframing *Reframing Resistance*

Wellcome scrubbed social media for AR-focused posts and garnered participation from over 12,000 people across Germany, India, Japan, Kenya, Thailand, United Kingdom, and U.S. via survey dissemination and general public focus groups. Wellcome then contextualized findings with a group of 33 experts, three of whom worked in the private sector and none who could represent the expansive animal agriculture industry. However, *Reframing Resistance* did not assess how more direct stakeholders (such as those in the medical, veterinary, and animal agriculture field) perceive their five principles. Understanding the perspectives of specific stakeholders who prescribe and use antibiotics (i.e. administer to others or consume themself) is critical in order to target specific populations for intervention. *Reframing Resistance* has overlooked an important stakeholder sector that could play a key role in dampening AR development and spread. Over half of the participants who were interviewed agreed with *Reframing Resistance*'s Principle 3, that AR should be acknowledged by all sectors as a One Health problem. With the exception of shellfish aquaculture stakeholders, an industry that claims negligible antibiotic-use, all stakeholders understood that AR affects them and their industry either solely through animal agriculture therapeutics, connections between human and animal use, or both. Therefore, animal agriculture stakeholders are unified in agreement with Principle 3; findings were independent of state policy categories.

In this study, animal agriculture stakeholders were less unified when describing AR fundamentals, a finding consistent with other studies (Fortané 2019). Roughly half of the participants defined AR in accordance with Wellcome's microbiological definition in Principle 2. Although *Reframing Resistance* pushes the importance of having a standardized understanding of AR aligned with the microbiological definition, they neglect the multitude and the importance of stakeholders' perspectives. Simply because animal agriculture stakeholders may share alternative understandings of AR fundamentals, they should not be considered inherently wrong in their definitions or views, nor classified as denialists about the overall crisis and the impact that AR has on their industry, their personal livelihood, and/or their animals. One example that is rarely researched is the transmission of human-originated pathogens into animals, or anthroponosis, which includes methicillin-resistant *Staphylococcus aureus*, influenza A virus, *Cryptosporidium parvum*, and *Ascaris lumbricoides* infections (Messenger et al. 2014). This relationship received acknowledgement in our study but has been perpetually absent in governmental and NGO reports.

## Research limitations and future research

This research did not aim to reach conclusions about which messaging techniques can promote behavior change in the U.S. animal agriculture industry; thus we do not reach such conclusions. Rather, the intention of this research was to describe perspectives from the many facets of animal agriculture. A limitation of this research is that perspectives from 31 individuals may not be generalizable to the larger animal agriculture stakeholders within the U.S. or globally (Knights et al. 2012; Norris et al. 2019) or to the diversity of all animal agriculture stakeholders. However, we did aim to represent a variety of viewpoints to predict animal agriculture stakeholders' responses to this report in the hopes to predict *Reframing Resistance's* ability to elicit behavior change. By selecting participants who hold positions in eight unique stakeholder professions, five animal industry types, and six states with different levels of judicious-use policies, we deliberately recruited individuals with knowledge and experience that span the political spectrum and include a range of animal agriculture sectors. Additionally, we intentionally recruited producers with diverse husbandry methods, which may influence antibiotic-use philosophies (i.e. producers who used USDA-certified Organic, antibiotic-free, and conventional antibiotic use practices were represented within stakeholders interviewed for this study). However, we were unable to obtain perspective from the vast stakeholder profession and industry combinations, nor were we able to speak with finfish or freshwater aquaculture representatives, despite attempts to do so. Similarly, although we had a high response rate (72%), selection bias may have occurred, which would be reflected by a lack of diverse viewpoints, specifically in relation to Principle 3 from *Reframing Resistance*. Unfortunately, we were unable to evaluate concordance with our data to other research that has evaluated the impact of Wellcome's *Reframing Resistance* to elicit behavior change, due to an absence of peer-reviewed publications at the time this manuscript's acceptance. This may be due lack of widespread dissemination, poor adherence, or insufficient time from adoption to analysis. Regardless, the authors sincerely hope that *Reframing Resistance* will inspire communication efforts that motivate individuals to acknowledge that common illnesses caused by AR pathogens are once again becoming dangerous and untreatable, and to ensure that current drugs maintain effectiveness. Further yet, regardless of top-down interventional effectiveness, professionals who work on the ground may benefit most through collaborations and communications with each other, which could create a fluid dialogue and information-disseminating opportunity that is initiated from the grassroots level.

## Conclusions

This research explores how the framework in *Reframing Resistance* may be applied to high-priority stakeholder groups and identifies the potential for gaps in Wellcome's approach. Further research to understand the opinions of stakeholders in more states and more countries may provide insight into additional gaps. Although we included all regions in the continental U.S. in this study, state- and country-specific sentiments may convey alternative perspectives that offer novel themes that were not discussed at the global scale. Larger recruitment among unrepresented states may validate the findings or offer new themes. We recommend that the remaining *Reframing Resistance* Principles (one, four, and five) be queried among animal agriculture stakeholders in their country-wide assessments to assess its alignment within the industry. Regardless, findings in this analysis indicate that although Wellcome and animal agriculture stakeholders are in agreement about "who" the AR crisis impacts, dissent still exists regarding AR fundamentals, which may impede adoption efforts within certain members of the animal agriculture community. No significant differences existed between animal agriculture producers, veterinarians, educators' perspectives in defining AR. Results in this study can dovetail with other studies that explore relevant stakeholders to identify groups who may require the largest attention for intervention and inform communication efforts like Wellcome's *Reframing Resistance*.

Animal agriculture stakeholders are a high-priority group in AR efforts, and ideally, they would have a unified understanding of the AR problem, one which would promote antimicrobial stewardship and judicious use. However, this collection of stakeholders espouses a complex array of perspectives that cannot be merged into a single perspective or principle, nor should it. The animal agriculture nexus encompasses many disciplines with a variety of socioeconomic statuses, types of education, cultures, attitudes, and philosophies, especially as it relates to antibiotic use in animals. This plenitude of perspectives, along with evidence to suggest that antibiotic use in animal agriculture plays a measurable role in the development or promotion of AR pathogens in the human sector (Innes et al. 2020), necessitates further investigation into the many perspectives that exist within the animal agriculture stakeholder groups.

**Acknowledgements** We thank all of the animal agriculture stakeholder participants who were gracious and willing to speak their minds and thoughts on record, despite obvious controversies around these issues. We are grateful of Caitlin Ceryes for her help and guidance in qualitative analysis and research. We also acknowledge Joan Casey, Christopher Heaney, and Sara Tartof for their instrumental roles in the ARES Grant and the progression of the ARES project.

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**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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