Implementation of Tactics Employed by the European Union to Reduce Rates of Antibiotic Consumption and Resistance

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Antibiotic drugs were considered one of the greatest medical breakthroughs of the 20th century, providing mankind with reliable protection against devastating bacterial diseases. However, certain bacteria had developed resistance to many antibiotic treatments by 2000 due to overconsumption of these drugs. The European Union (EU) was the first multinational political organization to formally recognize the threat of drug-resistant bacteria. Efforts to fight this threat led to per capita antibiotic consumption and resistance rates for many bacteria stalling or decreasing in most member states by 2015 (ECDC, December 2019; Klein et al., 2018). The tactics employed by EU nations to curb antibiotic consumption and slow propagation of antibiotic resistance fall into four main categories: monitoring regional resistance rates over time (surveillance), improving infection control and protocols for proper antibiotic use (prevention), avoiding transfer of resistance genes between species and the environment (containment), and research into better diagnostics and alternative therapies (Bronzwaer, Lönnroth, & Haigh, 2004).

Comparing the effectiveness of these tactics is pertinent as there are currently dozens of nations that appear to be underprepared for the upcoming calamity or in the midst of a spike in antibiotic consumption (Klein et al., 2018; WHO, 2019). In many middle-income countries such as India and Russia, resistance rates for the most infectious drug-resistant bacteria had already surpassed EU levels by 2015 (OECD, 2018). Limited healthcare and sanitation infrastructure among low and middle-income countries preclude them from enacting plans as exhaustive as the EU's. Improving general population hygiene is known to be the most effective measure in these countries, as their high disease transmission rates drive bacterial resistance rates up faster than antibiotic consumption (Collignon et al., 2018). However, identifying other optimal ways to sustain meaningful efforts against the looming threat of drug-resistant bacteria may improve these countries' outlook.

As motor vehicle accidents still claim more lives than drug-resistant bacteria (even outside the EU), measures to lower rates of antibiotic consumption and resistance all fall under the umbrella of risk prevention (O'Neill, 2016). Ulrich Beck's risk society framework will be tested by following the processes of implementing these tactics (through organizational mechanisms). Beck infers that acceptance of risk by the general public is the primary impetus for risk prevention, while critics respond that acknowledgment of risk from those with economic power carries the most weight (Ormrod, 2013). The paper will describe specific tactics used by the EU for purposes of reducing antibiotic consumption and resistance rates, potential methods of comparing their effectiveness, and whether Beck's risk society framework accurately describes the implementation of interventions against the risk of drug-resistant bacteria.

Risk Society as a Framework for Managing the Hazards of Drug-Resistant Bacteria

"Reflexive modernity" is one of Beck's essential principles for a risk society, describing how unintended consequences of widescale production initiatives are dealt with (Wimmer & Quandt, 2006). Beck outlines a risk society where "a threatening future, still contrary to fact, becomes the parameter of influence for current action" (Adam, Beck, & Loon, 2000, p. 222). This framework seems especially applicable to Antibiotic Resistance (ABR), which was an unforeseen consequence of a global initiative to improve quality of life. Antibiotic drugs were used without foresight when governments assumed that obsolete drugs could continually be replaced; the slow progress of novel antibiotic research has forced modern societies to change course and preserve existing antibiotic usefulness.

Three other fundamental aspects of risk societies that apply to nations beset by the dangers of drug-resistant bacteria are: a latent time gap between the impact and symptoms of risk assumption, local decisions having global repercussions, and a "context of uncertainty" – wherein every informed decision is made with awareness that future circumstances could render the judgment erroneous (Adam et al., 2000, p. 217). In the case of ABR, the impact of overusing antibiotics occurs when a bacterial strain gains immunity to treatments. Symptoms are not realized until these bacteria infect a large population that is unable to properly defend itself. In this scenario, the time gap may be multiple years as resistance genes take time to propagate among microbial populations. Though scientists may pick up on the genes relatively quickly, the public perception of the risk may not be enough to force accountability until catastrophe strikes.

Local decisions concerning ABR will necessarily take on a global impact due to travel economies facilitating rapid spread of disease. In the case that a dangerous drug-resistant bacterium goes viral, heightened fear (which will certainly force additional action against ABR) may even be seen in areas mostly unaffected by the disease (Person et al., 2004). The concept of "organized irresponsibility" is observed during such events, where many institutions take part in risk assessment but no singular entity is actually held responsible for the damages incurred from risk assumption (Adam et al., 2000, pg. 224). Directives to slow antibiotic consumption rates evoke uncertainty because people who are affected by consumption limits will observe a strong disconnect between the powerful reward (elimination of disease) and the seemingly minute risk (proliferation of ABR) of their own treatment. As the threat of drug-resistant bacteria grows, societies must eventually choose to preserve present health or future health in some cases – choices that may be rendered faulty if treatments are later produced which are unaffected by ABR (such as vaccines).

Critics of risk society theory have argued that greed and ignorance undermine risk planning more effectively than potential consequences can force it. Stakeholders with economic power can easily dissuade politicians from addressing risks and restrict the ability of consumers to understand risks. Beck indicates that free markets will eventually shift to accommodate known risks (in the absence of official policy), while critics argue that the public might still ignore recognized risks if there are no images associated with these risks which evoke fear (Ormrod, 2013). The nonprofit organization RAND Europe has painted a sobering picture where no additional action is taken against ABR before 2050. In that scenario, annual excess deaths from drug-resistant bacteria eventually surpass one million in the EU, costing the EU's economy trillions of dollars in the meantime (Taylor et al., 2014). Beck's risk society framework will be evaluated when examining how effective such gloomy predictions have been at inducing motivation to combat the ABR crisis. If noticeable progress has been made by the EU despite general indifference or ignorance to the risks posed by drug-resistant bacteria, significant flaws in the framework would be brought to light.

Case Context for Antibiotic Resistance

Antibiotic resistance is not a novel phenomenon. Strains of *Staphylococcus aureus* (staph) developing penicillin resistance had been observed as early as 1948 (Barber & Dowzenko, 1948), *S. aureus* strains resistant to methicillin and penicillin (MRSA) evolved by 1967 (Givney et al., 1998), and the first isolation of *Acinetobacter baumanii* with resistance to all known antibiotics (pandrug resistance) occurred in 2002 (Kuo et al., 2004). Individual EU member states had begun to take actions against the oncoming threat of ABR by 1995. In 1999, the European Commission (EC) attempted to unite these damage control efforts by drafting a consolidated strategy for the bloc. This plan identified five major areas for legislative action: research/development, international coordination, surveillance, prevention, and containment (Bronzwaer et al., 2004).

Antibiotic research groups in the 21st century have mostly produced compounds with minor differences to previously existing drugs; research into attacking various bacterial resistance mechanisms has proven even less fruitful (Lopatkin et al., 2017; Nicolas et al., 2019). Alternative treatments in the form of vaccines and bacteriophages have shown promise. However, these treatments usually cover only one bacterium at a time, take decades to develop in certain cases, and may not be a blanket replacement for antibiotics due to logistic difficulties in production or distribution (Henriques-Normark & Normark, 2014; Bragg et al., 2014). Other important ABR research concerns include improving the speed and quality of diagnostics to prevent dangerous hospital outbreaks and lower transmission rates in the larger population (OECD, 2018).

Coordination between countries primarily occurs in the context of surveillance; data must be harmonized to accurately track the relative growths of antibiotic consumption and resistance rates across multiple regions. There are currently 17 disease and laboratory surveillance networks operating in the EU, four of which deal directly with drug-resistant bacteria. These networks consolidate information from over 50 public health organizations across the EU (ECDC, 2012). The EU's primary surveillance system for ABR in humans is referred to as EARS-Net, the organization tracking human antibiotic consumption is designated ESAC-Net, veterinary drug consumption is tracked by ESVAC, and the European Food Safety Authority's (EFSA) Scientific Network for Zoonotic Monitoring tracks ABR in food animals. Secondary networks include the Food and Waterborne Diseases Network (FWD-Net) which involves some monitoring of ABR in the environment, and a network for comparing the relative contribution of different genes (EURGen-Net) to the overall resistance of bacterial species (ECDC, EFSA, & EMA, September 2017). Nations may also coordinate on developing/distributing alternative treatments and maintaining drug quality inspections; substandard antibiotics are a major issue in low-income countries (LIC) and may accelerate resistance propagation (OECD, 2018).

"Prevention" comprises two main realms: protecting the usefulness of antibiotics and strengthening infection control in specific sectors. Prevention is likely the most important aspect of ABR crisis mitigation; research has shown that limiting antibiotic consumption no longer slows ABR growth once concentrations of relevant resistance genes among bacterial populations reach certain thresholds (Lopatkin et al., 2017). Urbanization greatly exacerbates this problem, as population crowding (especially in areas unequipped for a bacterial outbreak) leads to increased disease transmission. Higher infection rates may precipitate a rise in antibiotic consumption to lower disease transmission rates, which strengthens ABR and eventually raises infection rates in a cyclical manner (Alirol et al., 2011; Bruinsma et al., 2003).

The most common prevention tactics in the healthcare "community" (facilities outside of hospitals) include diagnostics to guide antibiotic use and delaying prescriptions (in the absence of diagnostics). In localities that do not have enough capital to install and enforce these measures in the larger community, the most applicable ABR prevention methods are based in hospitals. Hand hygiene programs help prevent healthcare workers from spreading resistant pathogens, and stewardship programs are used to educate medical staff in order to prevent insufficient and unnecessary dosing of priority antibiotics (Bronzwaer et al., 2004).

Containment primarily concerns the minimization of resistance gene transfers from "resistance reservoirs" to their surroundings. The most common reservoirs of ABR are animal feeding lots and hospitals, where transfers mostly occur through environmental spread (such as waste discharges to watersheds) or contact with infected feeding animals and hospital patients (Silbergeld, Graham, & Price, 2009). Containment procedures include improving animal hygiene, limiting animal consumption, hospital surface decontamination, and farm waste management. These procedures are very important, as animals are estimated to consume more total antibiotics than humans in many countries across the income spectrum (including 13 EU member states) and the deadliest drug-resistant bacteria are still mostly limited to hospitals (ECDC, 2016; Van Boeckel et al., 2015). Unless massive support for plant-based diets negates a rapidly increasing demand for animal products, sustaining regulations to preserve animal hygiene in large production farms is crucial to stifle the demand for veterinary antibiotics - especially priority antibiotics designated essential for human safety such as fluoroquinolones and polymyxins (Maron, Smith, & Nachman, 2013).

STS Research Questions and Data Collection Methods

There were two central research questions to be answered:

1. Which were the most commonly applied tactics used by the EU to limit antibiotic consumption and resistance rates; is there a good way to compare their effectiveness?
2. Which sectors of European industry and society were most influential to success of the most common methods; does this align with Beck's risk society framework?

The first point of research was to investigate the EU databanks for relative trends in antibiotic consumption and resistance in human and animal populations over time. Consolidated data was located in reports released by the EFSA, European Medicines Agency (EMA), and/or European Centre for Disease Control and Prevention (ECDC). These reports originated from

ESAC (human consumption) in 2019, ESVAC (animal consumption) in 2019, EARS (human resistance) in 2019, EUSR (animal resistance) in 2020 and JIACRA (all together) in 2017. Following data collection, papers describing EU member states' initiatives to lower aspects of consumption and resistance rates were located. The starting points for locating these papers included the aforementioned reports along with the European Commission's 2011 action plan, 2016 evaluation, 2017 action plan, and 2020 Q1 action plan progress report. Klein et al. (2018) and Van Boeckel et al. (2015) also served as starting points. From the initial collection of papers, the reference lists of these papers were also scanned for articles which provided more detailed information on certain initiatives or examined societal aspects which might have influenced the effectiveness of these initiatives. "Effectiveness" of initiatives was implied by noticeable changes in drug consumption or resistance rates among humans or animals which the initiatives were designed to target. Public opinion data was obtained from Special Eurobarometer 338 (2010) and 478 (2018) to test if general viewpoints on ABR topics were affected by the EU's efforts.

Results

Defining a concrete metric for overall tactic effectiveness based on national results alone is impossible. While the ECDC and EFSA did release a report in 2017 describing sixteen Key Outcome Indicators (KOI) which are designed to summarize overall national progress against ABR in various sectors, the ECDC has noted that using these KOI's to compare specific tactics against ABR is fruitless. Aggregate results could arise from any combination of individual tactics (even within sectors). To make comparisons between individual ABR interventions, more focused meta-analyses are needed (ECDC, EFSA, & EMA, September 2017).

The Organisation for Economic Cooperation and Development (OECD) performed rigorous analyses in 2018 in order to model the potential effects on economy, morbidity, and mortality from implementing common tactics against ABR at the national level in all member states. One striking conclusion of the OECD's modeling is that annual excess deaths in the EU from ABR-related infections are unlikely to surpass 60000 by 2050 if no further action is taken against ABR; this death rate is notably less than a tenth of the rate predicted by RAND Europe for 2050 (Taylor et al., 2014). The OECD has speculated that this difference arises from other models overestimating the mortality of drug-resistant infections in the general population or overestimating the potential spread of dangerous diseases common in LIC (such as second-line resistant TB) to high-income countries (OECD, 2018).

However, the OECD only rigorously analysed the six interventions in the *human* sector which had a sufficiently large body of data for modeling. One of these tactics was containment based (hospital environmental cleaning), while the other five were prevention based (delayed prescriptions, mass media campaigns, hospital stewardship programs, improved hospital hand hygiene, and fast community diagnostics). Other prevention tactics noted by the OECD as common were communication initiatives between pharmacies and clinics, financial incentives (to induce a change in prescription trends), limiting counterfeit products, and limiting online (non-prescription) sales. These last two tactics are more applicable for middle-income countries, as counterfeit and non-prescription antibiotics comprise less than 10% of total antibiotics consumed in the EU (European Commission, 2018). Additionally, two significant containment tactics not analysed by the OECD were screening/isolation of hospital patients and application of topical antiseptics for patient visitations (OECD, 2018).

When comparing the results generated by the OECD model (Supplemental *Table 1*), it is obvious that the two most cost-effective ABR prevention tactics are improving hand hygiene in hospitals and delaying prescriptions. Because most of the "cost" of ABR is due to excess death, these are surely the two most attractive interventions for cash-strapped countries to implement. Besides mass media campaigns (which have long been suggested to be marginally effective at best), all six programs investigated by the OECD are estimated to reduce excess deaths from ABR by at least 16% when scaled up nationwide. The effect of assessing antibiotic usefulness in the community via fast (under one hour) diagnostics may seem weak, but the OECD model did not account for lower resistance rates in the community potentially translating to less resistance in hospitals. Additionally, the OECD model only incorporated C-reactive protein (CRP) diagnostics for presence of pathogenic bacteria. It is possible that expanding other fast diagnostic tests (such as those used to detect typical respiratory viruses) may have a more substantial effect (OECD, 2018).

Addressing the specific KOI's for human consumption (total consumption, proportion of last-line antibiotics used in hospital and broad spectrum antibiotics used in the community), a survey of European agendas performed by the ECDC in 2017 showed that eight countries had already rolled out legislation for reducing at least one of these consumption measures. Another eight countries provided plans for future targets. At least four member states (Poland, Czech Republic, Ireland, and Hungary) had still not completed preliminary stages in developing national reduction targets for any specific antibiotics (D'Atri et al., 2019). Other countries such as Spain, Portugal, and Croatia had chosen to establish financial incentives for reduced consumption rather than include the targets in a national action plan (Howard et al., 2017).

Using recent EARS and ESAC data to compare progress between human consumption and resistance KOI's from 2015 to 2018, Supplemental *Table 2* shows that changes in human consumption don't immediately influence resistance rates in most cases. These outcomes suggest the existence of a long lag time between changes in consumption and resistance and/or a high influence of external confounders (such as environmental presence of drugs) on resistance rates. Most strikingly, Finland decreased all three consumption measures from 2015-2018 but saw >20% relative increases in most resistance KOI's during the same period. (ECDC, November 2019; ECDC, December 2019).

Comparing the efficacy of tactics in the animal sector is more challenging, as even the EFSA admits that the scope of animal sector data is very limited. The KOI's for monitoring animal resistance are all based around *E. coli*, as that was the only bacterium with a consistent body of data. Moreover, the 2017 JIACRA report demonstrates that the correlation of animal *E. coli* resistance to human *E. coli* resistance is much weaker than comparable correlations involving resistance rates of more zoonotic bacteria such as *Salmonella* or *Campylobacter* species (ECDC, EFSA, & EMA, June 2017). Collection of those bacterial resistance rates is not yet standardized, with less than ten countries reporting resistance rates for any *Salmonella* or *Campylobacter* species in all four important food animal types (chickens, pigs, cows, turkeys) along with humans in 2018 (ECDC & EFSA, 2020). There is also no reliable body of data as of 2018 that would allow for comparing the efficacy of tactics rooted in environmental protection, such as pharmaceutical companies committing to lower discharge from manufacturing facilities.

National efforts to reduce animal consumption of antibiotics have been very successful thus far. The earliest proof of concept came from Sweden, where a 1986 ban on "growth promoting" (low dosages) of antibiotics in farms did not substantially lower farm outputs.

Additionally, Denmark was able to lower animal consumption by 35% after instituting profit limits on antibiotic sales to veterinarians in 1995. These successes led the EU to ban common antibiotics for growth promoting in 1999 and all antibiotics for growth promoting in 2006. There is no evidence that either ban substantially affected meat production in the EU, as countries incorporated improved animal hygiene measures (such as lower density in feed areas) to offset the need for low dosages in feed stocks (Maron et al., 2013).

Progress in combating the misuse of antibiotics in animals did not stop with banning antibiotic growth promotion. In 2011, Germany greatly enhanced their national capability to monitor animal consumption and enforce restrictions on veterinary uses of certain antibiotics (Maron et al., 2013). This legislation appears to been impactful, as the 2019 ESVAC report shows a ~55% decrease in Germany's animal consumption between 2012-2016 – the largest drop during that time period. Norway, the Netherlands, Hungary, Latvia, France and the UK also observed significant (>20%) decreases in animal consumption between 2012-2016, though it is unclear what specific policies may have influenced these trends. Extreme (>75%) decreases in animal consumption of polymyxins in Italy and Spain between 2014-2017 suggests special legislation was passed there to preserve the usefulness of that last-line antibiotic class. Using this ESVAC report to track the animal consumption KOI's, Supplemental *Table 2* shows that substantial increases in animal consumption are currently rare in Europe. Lower total consumption tends to be accompanied by decreasing priority consumption, but "gaming" the system by swapping one priority antibiotic class for another is not unheard of (EMA, 2019).

In terms of surveillance programs, a method to compare their effectiveness would rely on quantifying their ability to transmit analyzable data. Because data reported by surveillance networks are necessary to assess tactic efficacy, better surveillance schemes will provide more robust proofs of concept for a given intervention. Between ESAC and ESVAC, the number of antibiotics tracked and harmony of the data could be starting points for comparison. Between EARS and EUSR, the number of drug/bacterium combinations tested for antibiotic susceptibility and the level of quality control in the susceptibility tests might be comparison points.

Both ESAC and ESVAC track all legal antibiotics in their domains, and include over 30 contributing nations as of 2017. However, ESAC data are much more harmonized, with the defined daily dose (DDD) per capita unit controlling for demographic variations between countries. The current consumption unit for ESVAC (mg drugs/kg biomass) does not incorporate specific dosing schemes for each type of animal, highlighting obvious problems with comparing data between countries with different livestock compositions. Less than ten member states are currently developing units comparable to the human DDD for animal consumption (ECDC, EFSA, & EMA, September 2017). The third JIACRA report expected in late 2020 would be the best place to check the EU's progress in this regard (as well as other persistent concerns with collection of animal sector data) since 2017 (European Commission, 2020).

The EARS network tests eight bacteria (*E. coli*, *S. aureus, P. aeruginosa, A. baumanii,* 2 *Enterococcus* species, and *Klebsiella*/*Streptococcus pneumoniae*) for resistance against up to 45 different antibiotics in humans across all EU member states; 32 of the 315 possible drug/bacterium combos are detailed in EARS' annual epidemiological reports and five were adapted as human resistance KOI's. EUSR tests nine bacteria (*E. coli*, *S. aureus,* 5 *Salmonella* species, and 2 *Campylobacter* species) for drug resistance among humans and animals, but their data are far more disorganized with no substantial requirements for bloc-wide testing beyond *E. coli*. In harmonization terms, both networks usually follow EU antibiotic susceptibility testing committee (EUCAST) guidelines for reporting. External quality assessment teams facilitate harmonization by ensuring guidelines are followed properly and alternate collection methods are acceptable to include in annual reports (ECDC, December 2019; ECDC & EFSA, 2020).

On the research front, vaccines are currently in development for all eight of the bacteria investigated by EARS (however some bacteria, such as *Enterococci*, are more difficult to vaccinate against as those bacteria have a natural presence in the body) (OECD, 2018). One of these bacteria, *S. pneumoniae*, already has a decently effective vaccine known as the "pneumococcal conjugate vaccine" or PCV, which was credited with decreasing antibiotic consumption in the EU as immunizations were ramping up in the early 2000's (Huttner et al., 2010). The Innovative Medicines Initiative (IMI) was a partnership between governments and pharmaceutical companies designed in 2008 as a way to streamline clinical trials for promising new drugs. In 2012, the New Drugs for Bad Bugs (ND4BB) program became the arm of the IMI dedicated specifically to novel antibiotics with funding of around 650 million Euros. The ND4BB program also has other important research objectives which include faster diagnostics for hospital screening. The mission of IMI was later updated in 2014, attaching a goal of developing at least two new therapeutics for drug-resistant bacteria or Alzheimer's disease by 2024. Moreover, the program aims to develop an economic model which incentivizes pharmaceutical companies to fund antibiotics R&D, as rapid development of resistance during clinical trials and required product launch delays for any authorized antibiotics are often funding demotivators (European Commission, 2016).

Defining the "most important sector" for most of these policies appears simple. Drug-resistant infections advance along three lines of antibiotics. For stopping first-line resistant bacteria, the most important sector is primary care, specifically physicians who can influence prescription rate. For stopping second-line resistant bacteria, the most important sector involves drug dispensers, specifically mediators who can influence the burden of proof necessary for civilians to receive a second-line antibiotic. For stopping last-line resistant bacteria, the most important sector is the hospital, specifically staff in charge of maintaining hygiene of the workers and surfaces. The EU has placed special emphasis on surgical site infections, as drug-resistant bacteria make prophylactics useless (European Commission, 2017). If a last-line resistant bacterium were to spread among the general population, the most important sector for stopping it would be research teams to develop the alternative therapeutic and manufacturers to distribute the product. In all these important sectors, education of the "relevant stakeholders" on proper protocols is the main contributor to success of ABR interventions – implementing prevention tactics often requires considerable funding for worker training (OECD, 2018).

Beyond the most important sectors, there are many hidden factors at play. Despite carbapenems (another last-line antibiotic class) being banned for use outside of hospitals, carbapenemases have been spotted in animal bacteria on a few occasions, and carbapenem residues have been detected in nature. Though bacterial resistance rates to polymyxins in animals remain low, there are serious future implications for strengthening last-line resistant zoonotic bacteria (ECDC & EFSA, 2020). Lastly, when bacterial transmission rates are high enough, the consumption of antibiotics is mostly meaningless and the most important sectors all change to those involved with infection control (sanitation workers, water treatment, etc.). When the public's adherence to infection control guidelines is crucial to ABR interventions' success, then public perception of risk does indeed become the main factor in stopping drug-resistant bacteria. As this is not the case in the EU, it seems that public acceptance of ABR risks is a minor factor at most for ABR risk mitigation in the EU. To illustrate this point, 58% of residents surveyed in

Special Eurobarometer 478 (2018) were unaware of the 12-year-old EU ban on antibiotics in animal feed stocks (European Commission, 2018).

While these results appear in direct contrast to Beck's risk society framework, the public still has a passive influence on the actions of relevant stakeholders. Doctors' perception of patients' desire for antibiotics was by far the strongest predictor of prescription rates in a study of consultations for acute cough; physicians rarely preferred to risk patient satisfaction by not prescribing unnecessary drugs. In these cases, the public acceptance of risk for improper antibiotic use clearly overruled the doctors' informed opinions (Coenen et al., 2013). This phenomenon is likely responsible for the high proportion (41%) of superfluous antibiotic uses (for flu, cold, cough, or sore throat) seen in the 2018 Eurobarometer (European Commission, 2018).

However, there are also subliminal economic elements to this phenomenon: prescribing drugs quickly allows for doctors to see more patients and installing financial incentives to lower prescription rates can help doctors overcome "psychological barriers" to denying drugs (OECD, 2018). Additionally, governmental efficiency plays a big part in ABR risk mitigation. A study by Collignon et al. (2015) showed that "quality of governance" measures (as defined by the International Country Risk Guide) were a much stronger predictor of antibiotic resistance rates in Europe than antibiotic consumption rates. In other words, more antibiotics used more responsibly are not necessarily more dangerous.

Discussion

The suggestion that Beck's framework is inaccurate for the ABR situation in the EU neglects the fact that antibiotic consumption is not influenced by a "free market" there. Most of the sale power is already in the hands of doctors: over 90% of antibiotics in the EU for both humans and animals are obtained with consent from a medical provider (EMA, 2019; European Commission, 2018). Additionally, most of the actual *risk* of drug-resistant bacteria in the EU currently stems from the hospital sector, where the public generally has little influence. The ECDC predicts that the most important tactics for stopping last-line resistant bacterial outbreaks will be improving speed of antibiotic susceptibility tests and screening/isolation of hospital patients, which the OECD did not investigate (ECDC, 2016).

The counterpoint that economic stakeholders' perceptions of risk will drive ABR response is also not entirely accurate for the EU. Despite the OECD insisting that delaying prescriptions and improving hospital hand hygiene will likely *save money*, efforts to scale up these policies in deficient areas are still stuck in legislative circuits (OECD, 2018). In fact, the response to the ABR crisis has been noticeably slow due to the relative lack of attention paid to ABR by governments compared to other public health issues. This is likely to continue if the OECD predictions for ABR growth are accurate (European Commission, 2017; OECD, 2018).

The principle of Beck's risk society framework that most strongly applies to the ABR situation is "glocality". The 2017 EC action plan for ABR management (modeled from the 2015 WHO global plan) clearly describes how substantive actions in human healthcare, veterinary healthcare, and the environment are all necessary to turn the tide against drug-resistant bacteria – neglecting one area means resistance genes circulating there will continue to spread to the other areas. Local efforts must be combined to make a global difference (European Commission, 2017;

WHO, 2015). The concept of "manufactured uncertainty" also comes into play, as increasing the coverage of surveillance systems almost always illuminates more shortcomings in data collection than the upgrades had corrected for (European Commission, 2016). "Organized irresponsibility" may be applicable as well. Given the nature of a problem like ABR where deficiencies in one aspect of control can cause problems in many other seemingly unrelated areas, it is simply not reasonable to assign specific blame for overall control failures. Tracing the breakdown to a specific source is effectively impossible (Adam, Beck, & Loon, 2000).

The immense density of layers to the ABR problem inhibits development of a comprehensive analysis, especially in single author papers with a nonexistent budget. In the future, perhaps only one of the critically important drug-resistant bacteria identified by WHO (such as carbapenem resistant *K. pneumoniae*) would be the focus of a paper, with all analysis being done on measures to combat the spread of that specific bacterium, develop alternative therapies, and lower consumption of the essential antibiotic (WHO, 2017). However, even this style of paper may be subject to limitations. A study on point prevalence surveys of animal resistance done by Tang et al. (2017) showed that decreasing consumption of a specific drug had a much higher effect on incidence rates of bacterial resistance to *multiple drugs* than resistance to the drug in question. This suggests that the phenomenon of co-selection (where taking one drug in places where many resistance genes are present also boosts resistance to other drugs) is not an insignificant factor in the propagation of ABR. As the most severe drug-resistant bacteria are limited to hospitals, and critically important antibiotics are mostly consumed in hospitals, co-selection would certainly be a confounding factor when studying a specific drug/bacterium resistance combo (ECDC, November 2019; Silbergeld, Graham, & Price, 2009).

One current issue that will relate to antibiotic resistance is the pandemic of COVID-19. Given antibiotics are frequently prescribed to treat viral infections of the respiratory tract with symptoms similar to those of COVID-19, it would be interesting to see if the pandemic caused a noticeable rise in any of the three human consumption KOI's. It may also be interesting to investigate if resistance rates for dangerous last-line resistant bacteria rose as a result of the spike in hospitalizations and shortages of protective equipment for medical staff. As secondary drug-resistant bacterial infections often cause pneumonia, the excess death rate from pneumonia in hospitals attributed to COVID may be influenced by ABR. Additionally, it may be worthwhile to investigate if some of the manufacturing facilities set up for failed COVID vaccines could be repurposed for distribution of the PCV to LIC's. This paper is unlikely to inform the author's future engineering practice. Though there are many public health concerns in chemical engineering, antibiotic resistance is only really a contributing factor in drug manufacturing plants, waste management, and antibiotic research. Were the author to enter into any of these fields, the knowledge of environmental vectors for spreading antibiotic resistance would play a factor in designing and following failsafe/cleanup protocols.

Conclusion

The original purpose of this paper was to illuminate the best practices outside of general infection control that LIC's could utilize to halt rapid growth of ABR. The author's research has demonstrated that such "best practices" are nonexistent. Self-medication without prescription may appear to be a big problem in LIC's (along with financial incentives to sell off antibiotic stocks), but more people still die from a lack of access to quality antibiotics in LIC's than from drug-resistant bacteria – a situation that will likely persist long past 2030. LIC's often use antibiotics as a substitute for infection control due to the drugs' comparatively low cost. Limiting consumption in LIC's will likely not be possible; the two best options for improving their prospects against ABR are immunization initiatives and improving drug quality to slow resistance against higher-line antibiotics. Both options will require internationally coordinated humanitarian and regulatory aid to implement (OECD, 2018; Van Boeckel et al., 2014).

The situation for middle-income countries is more promising but still dubious. Although interventions based around delayed prescription regulations and hospital hand hygiene are technically affordable, they still require a substantial amount of training and capital to introduce and enforce. Additionally, antibiotics in middle-income countries are under more of a "free market" regime, in which Beck's risk society principles are more applicable to ABR. Citizens in these nations may respond to prescription limitations by bribing doctors or purchasing antibiotics from less regulated drug stores (which have financial incentives to sell stock). Moreover, civilians could switch to alternative medicines that are more dangerous. Hospitals may rely on pharmaceutical sales to operate, or staff may be too underpaid and overworked for hand hygiene campaigns to be effective. In any case, there are significantly more logistical hurdles to overcome for middle-income countries to implement ABR interventions than there are for EU member states (OECD, 2018; Van Boeckel et al., 2014).

If this paper has demonstrated one thing (besides reinforcing the importance of hand cleaning), it is that Beck's theory does not always apply when the risks are too complicated for "the public" to properly understand. As was the case for ABR propagation in the EU, more educated stakeholders will enforce risk mitigation measures on their own when the risks are sufficiently complex. Edgar, Boyd, and Palame (2008) have argued that public awareness campaigns would work much better if they were constructed using proper social marketing techniques, but the general failure of European "Antibiotic Awareness Days" to dramatically inform public opinion since 2010 casts doubt on the authors' conclusions. Though there was a decrease in participants seeking antibiotics for superfluous reasons from 58% to 41% between 2010-2018, the proportion of participants considering antibiotics useful against viruses only dropped by 5% in that frame (European Commission, 2010; European Commission, 2018). Delayed prescription guidelines are very effective (not to mention cheaper than awareness campaigns) because they prevent infections which would have resolved naturally from contributing to ABR without sacrificing patient safety. These policies remove the burden of understanding the dangers of antibiotic misuse from patients, and the burden of explaining why antibiotics might not be helpful from doctors (OECD, 2018).

The best continuation for this work (in the human sector) would involve an investigation into the individual action plans of EU member states. Selected countries should include those that have made the best progress against ABR recently as defined by the KOI's in Supplemental *Table 2* (such as France or Belgium), or were already at low values of human resistance KOI's as defined by the 2019 EARS report (such as the Netherlands, Scandinavia or UK) (ECDC, December 2019). As successfully implementing tactics against ABR heavily depends on training, auditing and feedback, it would be helpful to see how more successful countries' approaches to promoting compliance to the six tactics in Supplemental *Table 1* differ from less successful countries (such as Poland or Hungary). It would also be beneficial to study the effect of income metrics like GDP on national ability to maintain compliance and effectiveness for the cheaper tactics; this analysis should produce more substantial implications for the ability of middle-income countries to combat the ABR crisis than the analyses in this paper.

In the animal sector, this work could be continued by studying the effects of regulations passed by countries outside the OECD for reducing antibiotic consumption (such as China's ban on polymyxins for veterinary use in 2016) on farm output. The investigation could also explore the costs of improving animal hygiene in the countries that limited animal consumption; both inquiries might also yield significant implications for the ability of middle-income countries to fight ABR (Van Boeckel et al., 2019). Additionally, the effects of the EU's recent activities concerning ABR in Latin America (detailed in the 2020 Q1 progress report) on ABR preparation in Latin America could be studied (European Commission, 2020). As Latin America appears to be the least prepared region for an ABR crisis when studying action plans submitted to the WHO, it will be important to assess the effectiveness of the EU's agenda there (WHO, 2019).

Supplemental Tables

Table 1. Comparison of Tactic Effects Modeled by the OECD

Tactic Code	Cost per Capita (2017 USD)	Reduction in ABR excess deaths (%)	Reduction in sector antibiotic resistance (%)	Benefit/Cost ratio (USD/ Death %)	Benefit/Cost ratio (USD/ Resistance %)	Cost Saving Probability* (%)
HHH	2.5	58	48	23.2	19.2	60-70
HEC	65.0	53	38	0.8	0.6	10-20
HSP	12.0	54	46	4.5	3.8	25-35
CMMC	2.7	9	9	3.3	3.3	<5
CDP	1.3	16	50	12.3	38.5	25-60
CFDT	12.7	25	22	1.9	1.7	12-25

*Assuming 50 percent compliance at the national level, 25-75 percentile for OECD countries.
Abbreviations | HHW: Hospital Hand Hygiene; HEC: Hospital Environmental Cleaning;
HSP: Hospital Stewardship Programs; CMMC: Community Mass Media Campaigns;
CDP: Community Delayed Prescriptions; CFDT: Community Fast Diagnostic Tests.
Source: OECD, 2018.

The following table describes 28 European countries' recent progress towards 12 Key Outcome Indicators as of early 2020. "nc" means no significant (<10%) change in either direction, n/a means data was nonexistent or unavailable, a single arrow indicates at least 10% relative change across the three-year period, and a double arrow indicates at least 20% relative change in that timeframe. All KOI's are expected to decrease (down arrow) if improvement has been made in the sector that the KOI involves, and increase for vice versa. Note that this chart describes relative changes for specific nations, and does not consider the large variance in starting points for each country's KOI's in 2015. Sources: ECDC, EFSA, & EMA, September 2017; ECDC, November 2019; ECDC, December 2019; EMA, 2019.

Table 2. Progress of EU Countries on Combating ABR as Defined by KOI's from 2015-2018

	Human			Human					Animal					
	total consumption	Community Broad/Narrow Ratio	Hospital Last Line Proportion	% MRSA incidence	% E. coli cephalosporin resistance	% K. pn. carbapenem resistance	% K. pn. full 2nd line resistance	% S. pn. full 1st line resistance	total consumption	cephalosporin consumption	fluoroquinolone consumption	polymyxin consumption	Total Up	Total Down
Austria	↓	↓	n/a	↓	nc	nc	nc	↑↑	↓	nc	nc	nc	1	4
Belgium	nc	nc	nc	↓↓	nc	↑	nc	↓↓	↓	↓↓	↓↓	↓↓	1	6
Bulgaria	nc	↑↑	nc	↑↑	nc	↑↑	↑↑	↓↓	nc	nc	↑↑	↑↑	6	1
Croatia	nc	↑	nc	nc	↑	nc	↓	↑↑	↓↓	↑↑	↓↓	↓	4	4
Cyprus	nc	↑	n/a	nc	↑↑	↑↑	↑↑	n/a	nc	↓↓	↑↑	nc	5	1
Czech Rep.	n/a	n/a	n/a	nc	nc	nc	nc	↑	↓↓	nc	nc	↓↓	1	2
Denmark	↓	nc	nc	nc	nc	↑↑	↑↑	↓↓	↓	↓↓	n/a	↓↓	1	5
Estonia	nc	↑	nc	↓	↓	↑↑	↓↓	↓↓	↓	↑↑	↓	↓↓	3	7
Finland	↓	↓	↓	nc	↑↑	↑↑	↑↑	↓	↓	↓↓	↓	n/a	3	7
France	nc	↓↓	nc	↓↓	↓	nc	nc	↑	↓↓	↓↓	↓↓	↓↓	1	7
Germany	nc	↓	n/a	↓↓	↑	nc	↑↑	nc	↓	nc	↓	↓↓	2	5
Greece	nc	nc	↑	nc	nc	nc	nc	n/a	↑↑	nc	↑↑	↓↓	3	1
Hungary	nc	↑	nc	nc	↑↑	↑	nc	↑↑	nc	↑↑	nc	↑↑	6	0
Iceland	↑	↓↓	n/a	nc	↑↑	n/a	n/a	n/a	nc	↓	n/a	n/a	2	2
Ireland	nc	nc	nc	↓↓	↑	nc	nc	nc	nc	nc	nc	n/a	1	1
Italy	↓	↑	↑	nc	nc	↓↓	↓	↓	↓	nc	nc	↓↓	2	6
Latvia	nc	↑↑	nc	nc	↑	nc	↓↓	↑↑	nc	nc	↓↓	↑↑	4	2
Lithuania	↑	↑↑	↓	nc	nc	nc	↑	↑	nc	nc	↓↓	↑↑	5	2
Luxembourg	nc	↓	nc	↓	nc	nc	↑	nc	↓	nc	nc	↓↓	1	4
Netherlands	nc	nc	nc	nc	↑↑	↑↑	↑↑	nc	↓	n/a	nc	↓	3	2
Norway	nc	↓	nc	↓	↑	nc	↑↑	↑↑	nc	n/a	n/a	n/a	3	2
Poland	nc	↑↑	↑	nc	↑↑	↑↑	nc	↓↓	↑	↑	↑↑	↑↑	8	1
Portugal	nc	↓↓	nc	↓	nc	↑↑	nc	↑↑	nc	↑	↓↓	↓↓	3	4
Romania	↓	↑↑	n/a	↓↓	↓↓	↑↑	nc	nc	↓	↑↑	↓	↓↓	3	6
Slovakia	nc	↑↑	↑	nc	nc	↑↑	↓	n/a	nc	nc	↓	↑	4	2
Slovenia	nc	nc	nc	↑↑	↓	↓↓	↓↓	nc	nc	nc	↓↓	↑	2	4
Spain	nc	nc	nc	nc	↑	↑↑	↑	↓	↓	↓	↓↓	↓↓	3	5
UK	nc	nc	nc	↓↓	nc	↑↑	↑↑	↓↓	↓↓	↓	↓↓	↓↓	2	6

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