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Increased antibiotic resistance of Escherichia coli in Nicaragua: Potential Causes and Future Implications

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Increased antibiotic resistance of *Escherichia coli* in Nicaragua: Potential Causes and Future Implications

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Introduction

Since 1987, no new structural class of antibiotic has been introduced into human medicine. Aside from the absence of a new structural class of antibiotics, there has been a startlingly low number of new antibiotics approved since 1987. With the lack of new antibiotics, finding current antibiotics that are effective is becoming an alarming challenge due to the worldwide emergence of antibiotic resistance. Antibiotic-resistant bacteria presents a major threat to public health because they reduce the effectiveness of antibiotic treatment leading to increased morbidity, mortality, and healthcare expenditure.[1] The antibiotics most affected are often older, inexpensive antibiotics that are widely used throughout the world. As a result, developing countries face a higher burden as cost constraints prevent the patients in developing countries from getting access to the newer, more expensive antibiotics which act as broad spectrum or second-line therapies for infectious diseases.[2]

Without treatment for common infections, like uropathogenic *Escherichia coli* (UPEC), resistant infections will adversely affect mortality, disease transmission, and duration of illnesses. UPEC is usually obtained by fecal contamination of the urethra and bladder. The two most common causes of this are improper wiping and sexual intercourse. When urinary tract infections (UTIs) are untreated, UPEC will move superiorly to infect the ureters and the kidneys leading to pyelonephritis. In rare instances, the bacteria can leave the kidneys and enter the bloodstream leading to bacteremia. For years the mainstay treatment for UTIs has been a regimen of antibiotics. In the United States (U.S.), treatment guidelines for an uncomplicated UTI call for a 3-day course of trimethoprim-sulfamethoxazole (TMP-SMX).[7]

In the U.S., there are an estimated 8 million cases of UTIs per year.[3] Women have nearly a 50% lifetime risk of suffering from a UTI. This corresponds to a 10.8% annual risk for women aged 18 years and over to get a UTI.[3] In Nicaragua, data suggests this problem appears to be even more severe.[3] *Escherichia coli* is the most frequently isolated uropathogen in symptomatic UTIs worldwide, and in Nicaragua as well. In 2008 in Leon, Nicaragua, a study investigated the microbial cause in patients with symptomatic UTIs, and *Escherichia coli* was isolated 44.8% of the time to make it the most commonly isolated uropathogen in the country[3] (Table 1).

Globally, increasing resistance rates to frequently used antibiotics has hampered the clinical management of UTIs. In particular, Nicaragua has alarming resistance patterns of frequently observed uropathogens, like *Escherichia coli*. Bours et al. (2010) assessed antibiotic resistance in the *Escherichia coli* samples that were isolated (Table 2). The study showed high resistance rates to TMP–SMX (38.6%), which is commonly used as a first-line antibiotic for UTIs around the world. It also showed resistance to other common and inexpensive orally administered agents, such as ampicillin (61.4%) and ciprofloxacin (31.8%).[3] When using inadequate antibiotics, the risk of clinical failure is high, therefore, usage of these agents becomes clinically unacceptable.[3] The only drugs against *Escherichia coli* to which the susceptibility rate was high enough to be clinically acceptable to treat UTIs (higher than 80%) were nitrofurantoin (93.0%) and amikacin (95.3%).[3] Due to the high clinical rate and significance of *Escherichia coli* in UTIs, this data highlights the increased need to mitigate antibiotic resistance in Nicaragua.

If preventive and containment measures are not applied locally, nationally and internationally, the limited interventions in one country can compromise the effectiveness of antibiotics globally. Improper management of antibiotic resistance in Nicaragua and the rest of the developing world can endanger the policies of containment used by even the best-managed countries of the world. Antibiotic resistance is therefore a global problem, requiring integrated, global solutions, as there are no boundaries to its worldwide spread.[4] To help developing countries establish a system that can help curb antibiotic resistance, countries can turn to an approach recommended by the World Health Organization (WHO) called the 'One Health' approach. This approach is a cross-sectional, collaborative approach to improve health and well-being through the prevention of risks and the mitigation of effects of crises that originate at the interface between humans, animals, and their various environments.

The control of infectious diseases is seriously threatened by the steady increase in the number of microorganisms that are resistant to antimicrobial agents.[2] Antibiotics will be key to fighting these infections and preventing morbidity and mortality. This paper aims to highlight the problems Nicaragua and other developing countries face that can lead to antibiotic resistance in bacteria like *Escherichia coli*. In addition, this paper will explore what strategies might be used to reduce antibiotic resistance and the associated morbidity and mortality of infectious diseases, especially related to *Escherichia coli* infections.

Background

Treatment Guidelines

In modern medicine, treatment guidelines are often used as guidance for healthcare providers to select the appropriate medications for a particular infection. As a result, the use of guidelines has become a particularly effective way to control antibiotic use in healthcare. Practice and treatment guidelines have been shown to have a positive effect on the incidence of multidrug-resistant infections in both developed and developing countries.[4] Guidelines are based on current antibiotic susceptibility to infectious agents in a local community and should be adjusted based on this data.

Before 2003, no treatment guidelines were used for UTIs in Nicaragua. In 2003, Matute et al. showed the need for UTI treatment guidelines in Nicaragua due to the high resistance rates in *Escherichia coli* to commonly used antibiotics such as ampicillin, TMP-SMX, and ciprofloxacin (Table 2). In accordance to results of the study, new therapeutic guidelines were initiated. Ceftriaxone (0% resistance) was to be used for upper UTIs and nitrofuratoin (0% resistance) was to be used for lower UTIs.[6] These new guidelines would aim to reduce the use of ineffective antibiotics, therefore, decreasing antibiotic resistance in antibiotics not being used.

These guidelines were followed for 5 years until another study looking at *Escherichia coli* antibiotic resistance in UTIs was performed in 2008.[3] Reduced usage of β-lactam antibiotics had resulted in a decline in resistance to ampicillin (74% to 61.4%) and ampicillin–clavulanate (34% to 18.6%). Resistance to TMP–SMX has also declined (68.3% to 38.6%).[3,6] However, the opposite effect was seen in the guideline's first-line antibiotics. Globally, nitrofurantoin is the preferred treatment for lower UTIs.[7] An increase in resistance to nitrofurantoin was seen for *Escherichia coli* (0% to 7%) in Nicaragua.[3,6] Additionally, ceftriaxone was the preferred treatment for upper UTIs according to the 2003 guidelines. Ceftriaxone saw a large increase in resistance rates from 2003-2008 (0% to 20.5%). The increase made ceftriaxone no longer clinically acceptable, since it now had a resistance rate greater than 20%.[3,6] These results showed an increase in resistance to antibiotics used frequently and a decrease in antibiotics used less frequently. This highlights the power humans can possess in controlling antibiotic resistance by initiating and changing guidelines according to antibiotic resistance rates.

Surveillance

The power of guidelines emphasizes the need for frequent surveillance of the prevalence of antibiotic resistance in communities so treatment guidelines can be evaluated and changed accordingly. Bours et al. in 2010 showed the benefit of surveillance. With ceftriaxone being clinically unacceptable to treat upper UTIs at 20.5% resistance, new guidelines had to be made to mitigate resistance and to give patients appropriate antibiotic treatment that was at a low risk of clinical failure. Therefore in 2010, amikacin (2.8% resistance) became the new first-line treatment for upper UTI infections.[3] Although amikacin may be effective to fight against bacteria like *Escherichia coli*, amikacin may not be the best first-line treatment in countries like Nicaragua because it is an intramuscular injection. Amikacin must be given as an injection at a doctor's office where there are added costs for drug administration and clean syringes. If an individual is self-medicating for a UTI, an injectable antibiotic will not be the drug of choice at the counter and the individual will not be receiving a first-line treatment.

Without surveillance, suitable antibiotic choice for guidelines cannot be accessed. Setting up guidelines and surveillance protocols in developing countries like Nicaragua could be a useful strategy to reduce antibiotic resistance.

Improper Prescribing

Guidelines can be very helpful, but are only helpful if followed correctly. Improper prescribing in Nicaragua and developing countries is another source contributing to antibiotic resistance. den Engelsen et al. investigated antibiotic prescribing in an emergency department of a hospital in Leon, Nicaragua in 2005. The most prevalent infections at this emergency department were respiratory tract infections, urogenital infections, and GI infections. The study looked specifically at UTI treatments in the emergency room (ER). According to the national guidelines, nitrofuratoin is the first-line antibiotic choice in uncomplicated UTIs. Only 5.3% of patients in the ER received the first-line antibiotic. Approximately a quarter of patients did not receive the top three recommended antibiotics (nitrofurantoin, ciprofloxacin, and amoxicillin/clavulanic acid) according to the guidelines from 2005.[8] According to den Engelsen et al., a possible reason for the misuse of antibiotics in the Leon ER is due to physicians and healthcare providers having a lack of awareness of the guildelines, lack of familiarity with the guidelines, or lack of agreement to the guidelines.[8] If healthcare providers fail to follow treatment guidelines and effective antibiotics are not used, there is an increased risk of clinical failure, which will lead to increased morbidity, mortality and healthcare expenditure.

Research shows that the use of antibiotics in Nicaragua is not optimal. Antibiotics were prescribed too frequently and not according to national guidelines when treating for UTIs, exacerbating the growing antibiotic resistance problem in Nicaragua.

Access to Medications and Healthcare Providers

Infectious diseases are the fifth leading cause of death in Nicaragua and continue to be a leading cause of death in the developing world.[6,7] Therefore, antibiotics are a crucial resource in fighting infectious disease. However, antibiotics are not always easy to obtain for Nicaraguans and citizens in developing countries.

Nicaragua's health system exists of 32 hospitals, 176 health centers and 849 health posts.[7] Most of the hospitals are concentrated in the cities, which makes healthcare access difficult for individuals in rural areas of the country. Nicaragua has 0.91 physicians per 1,000 inhabitants. Comparatively, the United States has 2.55 physicians per 1,000 inhabitants. Sweden, considered the second best healthcare systems in the world (US news), has 4.11 physicians per 1,000 inhabitants.[11]

Inaccessibility of healthcare providers and facilities in the developing world is one of several factors that may have a role in the development of antibiotic resistance. Professional healthcare providers are often not the first point of care. With the lack of practitioners and access to healthcare, patients often obtain their drugs and medical advice from unsanctioned stall keepers, itinerant vendors, hawkers, and purveyors of other materials.[5] This is a problem because drug vendors are licensed to sell antimicrobials such as antibiotics, but lack the knowledge to dispense or offer proper drug treatment advice.

In developed countries, the desire to self-medicate with antibiotics is present, but individuals are limited to do so by prescription-only regulations. Although enforcing national regulations is effective in curbing self-medication, it is not easily accomplished in developing countries.[8] When enforcement is present where antibiotics are usually freely available, there have only been rare reports of reduction in antibiotic use.[5] The sale of antibiotics is a lucrative business as long as the demand for antibiotics is high. The best way to approach this would be through consultation, education, and cooperation among all interest groups. Although cooperation between all groups is ideal, it requires a level of commitment that is not the norm in countries like Nicaragua.[5]

Due to the presence of self-medication and lack of healthcare providers to give proper drug treatment advice, patients do not always take their antibiotics properly, which can lead to increased antibiotic resistance. In a Mexican study, 60% of patients failed to adhere to their antibiotic regimen. One of the predisposing factors was inadequate provider-patient relations, which in developing countries often arises because of low physician/patient ratios.[5] As stated earlier, this low physician/patient ratio is present in Nicaragua, so individuals often seek out unsanctioned healthcare providers in order to get the treatment they believe they need.

Antibiotics Use in Agriculture

Another source of antibiotic resistant *Escherichia coli* in Nicaragua and other countries seems to come from agriculture. Extensive antibiotic use in agriculture as growth promoters in animals and as prophylactics against infectious diseases has lead to an increase in antibiotic resistance in the food chain, which is often neglected and under-estimated. [4] Antibiotic resistant bacteria present in the food chain infect humans indirectly through consumption of contaminated food products or directly through exposure to biological substances such as blood, urine, feces, and saliva.[4] Since antibiotics are widely used in aquaculture, livestock production, and crops, the occurrence of antibiotic resistance in the food chain is considered a cross-sectoral problem.[4]

Several studies having reported food animals and products being colonized and contaminated by deadly antibiotic-resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Campylobacter* spp.[4] When specimens are taken from our food animals and products, *Escherichia coli* is one of the most prevalent antibiotic resistant organisms found in livestock in the developing and developed world (Table 3).[4] With the world being more interconnected with the expansion of the human population and international travel, antibiotic resistance can easily spread globally via the food chain.

In high-resource developed countries, a variety of systems to monitor antibiotic resistance in food animals, food products, and humans have been implemented. In contrast with developed countries, the majority of low-income developing countries have no systems to monitor antibiotic resistance in food animals, food products, and humans. Therefore, antibiotic resistance in developing countries is only partially documented, and is dependent on point-prevalent data rather than long-term data. To help limit the spread of antibiotic resistance in the food chain, integrated food chain surveillance systems and well-controlled extensive farming practices must be implemented.

In developing countries, controlled use of antibiotics in animal farming is not being practiced. One policy that could be implemented is the unrestricted access of antibiotics to farmers, which should be prohibited unless under veterinary prescription or oversight.

Waste Water Plants

Residues of human and veterinary drugs are primarily introduced into the environment via discharges from waste water treatment plants or land application of sewage sludge and animal manure.[9] With agriculture and medical waste comes a route by which resistance genes can be introduced into natural bacterial ecosystems where antibiotic resistance can proliferate.[9]

A study was performed in Leon, Nicaragua looking at various water sources and found high levels of antibiotic resistant *Escherichia coli* in hospital sewage water and in 8 of 87 well-water samples.[9] The most common resistance was to ampicillin, chloramphenicol, ciprofloxacin, nalidixic acid, and TMP-SMX. Of the isolates, 19% had multi-resistant profiles to ampicillin, ceftazidime, ceftriaxone, cefotaxime, chloramphenicol, ciprofloxacin, gentamicin, nalidixic acid and trimethoprim-sulfamethoxazole.[9]

Research shows that waste water treatment plants provide a reservoir for bacteria and favorable conditions for the proliferation of antibiotic resistance and spread of resistance genes to non-resistant bacteria. Thus, it highlights the importance of creating risk management strategies to monitor waste water environments for the spread of antibiotic-resistant bacteria.

Methods

This research was conducted through a review of the literature including a PubMed search using the search operators “antibiotic resistance, *Escherichia coli*, urinary tract infections, Nicaragua, developing countries, and clinical guidelines" were used, and articles were filtered based on relevance and date of publication during June and July 2017. Articles over 15 years old were not referenced. Government websites were utilized to obtain background information on healthcare and poverty. In addition, interviews were conducted with Karla Rias Cisneras, a pharmacist in Managua, Nicaragua, on July 11th, 2017 and with Dr. Leonel Arguello, epidemiologist and president of the Nicaraguan Association of General Practioners, on July 14th, 2017.

Discussion

In Nicaragua, approximately 30% of the population lives on less than $2 per day. In rural areas, poverty rates are especially high, where 50% of households live in extreme poverty.[8] Poverty is a key reason why developing countries are at a higher risk for increased antibiotic resistance. Nicaragua simply lacks the resources to fight antibiotic resistance the way the developed world does. In an ideal world, developing countries would have the resources needed to implement strategies and programs, such as surveillance protocols, waste water management, and healthcare provider education programs. If initiated, these programs could improve the healthcare system and prevent the development of antibiotic resistance organisms.

Therapeutic guidelines can have a powerful role on the control of antibiotic resistance. However, without the resources and personnel to perform antibiotic resistance research in the community, proper guidelines cannot be made or updated according to current trends in antibiotic resistance. In an interview with Dr. Leonel Arguello, epidemiologist and president of the Nicaraguan Association of General Practioners, he confirmed that there is not enough research being done in the field of antibiotic resistance in Nicaragua. He also emphasized the lack of concern towards antibiotic resistance in the healthcare community. Lack of concern by healthcare providers may lead to prescribing practices that negatively effect antibiotic resistance. To combat these problems, consultation, education, and cooperation must be initiated in the healthcare community.

The presence of self-medication in Nicaragua was confirmed in an interview with Karla Rias Cisneras, a pharmacist in Nicaragua. Many sick individuals in Nicaragua will receive their medical advice and treatment from local pharmacies where they can buy any antibiotic without a prescription. Pharmacists are not as well trained in medical diagnoses in Nicaragua and most seem to just be aware of only the most basic antibiotics. For instance, Ms. Cisneras said she would recommend azithromycin for any problem related to the throat or neck region. To make matters worse, a lot of these pharmacies do not have pharmacists working, and storeowners with no education will be the ones that recommend antibiotic treatments to sick individuals. With the level of poverty in Nicaragua, these storeowners are simply trying to move their antibiotics off the shelves for profit.

Poverty can also drive people from only purchasing a partial antibiotic regimen, which is human behavior that can lead to antibiotic resistance. For instance, if an individual needed a 10-day course, they may only buy 3 days worth to save money. With the lack of proper resources and infrastructure, developing countries struggle to initiate proper waste water management to combat antibiotic resistance. The government also lacks the resources and awareness to initiate enforcement of antibiotics used in agriculture.

Since humans, animals, agriculture, and the environment all contribute to antibiotic resistance, it can be difficult to contain. If possible, developing countries should use the One Health approach endorsed by the World Health Organization (WHO). 'One Health' is an approach to designing and implementing programs, policies, legislation and research in which cross-sectional collaborations between groups involved in humans, animals, and their various environments, come together to achieve better public health outcomes. An example would be programs that would monitor antibiotic resistance in humans, animals, and water environments.

Although monitoring antibiotic resistance in humans, animals, and their various environments would be helpful in a developing country like Nicaragua; monitoring every source is not possible with funds being so scarce. Surveillance programs would be most helpful in the hospital and clinical settings where patients with UTIs could receive urine cultures and bacteria like, *Escherichia coli,* could be tested for their susceptibility to various antibiotics used to treat UTIs. With antibiotic susceptibility information, individual patients would not only receive targeted antibiotic therapy based on the results, but antibiotic resistant strains could be recorded and sent to a database where trends in resistance could be evaluated. With frequent monitoring, treatment guidelines could be more effectively evaluated and changed according to the current antibiotic resistant trends.

Another useful strategy would be starting an educational program for physicians and healthcare providers to provide information to emphasize the significance of antibiotic resistance and the importance of using treatment guidelines appropriately and religiously. Based on experiences in Nicaragua and interviews with Dr. Arguello and Ms. Cisneros, antibiotic resistance had minimal to no coverage during healthcare training in Nicaragua. Therefore, an effective strategy may be to educate healthcare providers on the importance and relevance of antibiotic resistance during their initial training. By including antibiotic resistance in the curriculum, all healthcare providers would be covered during their initial training, and it would be cost-effective, since no new educational outreach program would have to be created.

Conclusion

With the increasing threat of antibiotic resistant bacteria and the decreasing production of new and effective antibiotics, the world is in an evolutionary arms race against some of the smallest organisms on earth. Developing countries are at the frontlines of the war. In order to take the lead in the war, more must be done in antibiotic resistance research and antibiotic development. Governments must be educated on the threat of antibiotic resistance so they can help implement appropriate public health programs, policies and legislation. Although there are a myriad of things that could be done to combat antibiotic resistance in developing countries like Nicaragua, countries unfortunately lack the resources and infrastructure to do so. Since antibiotic resistance is a global issue that crosses national borders, international financial support could help developing countries fight at the frontlines of the war against antibiotic resistance.

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Appendices

Table 1. The most frequently isolated microorganisms from UTIs in Leon, Nicaragua.[3]

Uropathogens

Pathogens	No. of samples (%)
Escherichia coli	44 (48.4)
Serratia spp	11 (12.1)
Escherichia fergusonii	10 (11.0)
Enterobacter spp	6 (6.6)
Cedecea davisae	4 (4.4)
Klebsiella spp	3 (3.3)
Staphylococcus aureus	3 (3.3)
Kluyvera spp	3 (3.3)
Proteus mirabilis	2 (2.2)
Other pathogens	5 (5.5)
Total	91 (100)

Table 2. Antibiotic resistance from isolated *Escherichia coli* from UTIs in Leon, Nicaragua.[3]

Antibiotic resistance

	% Susceptible 2008	% Resistant 2008	% Resistant 2003	Difference (*p*-value) [b]
Escherichia coli	(*n* = 44)	(*n* = 44)	(*n* = 35)	
Ampicillin[a]	31.8	61.4	74.0	0.34
Amoxicillin–clavulanate[a]	69.8	18.6	34.0	0.12
Ceftriaxone	72.7	20.5	0	0.04
Gentamicin	72.7	25.0	11.0	0.16
Trimethoprim–sulfamethoxazole[a]	59.1	38.6	63.0	0.04
Nitrofurantoin[a]	93.0	7.0	0	0.25
Ciprofloxacin[a]	68.2	31.8	30.0	1.0
Cefalothin	45.5	45.5	58.0	0.37
Amikacin	95.3	2.3	0	1.0

Table 3. Prevalence of antibiotic-resistant bacteria isolated from food animals and products in developed and developing countries.[4]

Country	Isolation year	Origin/type of specimens	Antibiotic-resistant bacteria	Prevalence (%)	References
DEVELOPING COUNTRIES					
China	2015	Pig	Plasmid mediated colistin resistant *E. coli*	21	Liu et al., 2016
		Raw meat	Plasmid mediated colistin resistant *E. coli*	15	
Thailand	2007	Poultry	ESBL-producing *S. Typhimurium*	77.3	Padungtod et al., 2008
		Pig	ESBL-producing *S. Typhimurium*	40.4	
	2012–2013	Pig	ESBL-producing *E. coli*	77	Boonyasiri et al., 2014
		Pork	ESBL-producing *E. coli*	61	
		Pork	MDR-*A. baumannii* and *P. aeruginosa*	40	
		Poultry	ESBL-producing *E. coli*	40	
		Poultry meat	ESBL-producing *E. coli*	50	
Vietnam	2007	Poultry	MDR-*E. coli*	91.5	Usui et al., 2014
Indonesia	2007	Poultry	MDR-*Enterococcus faecalis*	84.5	
Brazil	2000–2016	Pigs	Plasmid mediated colistin resistant *E. coli*	1.8	Fernandes et al., 2016
		Chicken	Plasmid mediated colistin resistant *E. coli*	5	
Egypt	2010	Meat and dairy products	MDR-Shiga-toxin-producing *E. coli* O157:H7	57.4	Ahmed and Shimamoto, 2015a
	2010	Meat and dairy products	MDR-*Shigella spp.*	89	Ahmed and Shimamoto, 2015b
Algeria	2005–2006	Broilers	MDR- *Salmonella spp.*	51	Elgroud et al., 2009
Tunisia	2010–2011	Raw meat	MDR-*Enterococcus spp.*	24.5	Klibi et al., 2013
		Raw meat	LA-MRSA ST398	0.6	Chairat et al., 2015
South Africa	2014	Cattle	MDR-*E. coli*	100	Iweriebor et al., 2015
	2015	Poultry	Plasmid mediated colistin-resistant *E. coli*	79	Coetzee et al., 2016
DEVELOPED COUNTRIES					
European Union	2014	Broiler meat	MDR-*Salmonella Infantis*	>70	EFSA and ECDC, 2016
		Broiler meat	MDR-*E. coli*	55	
Norway	2014	Broiler	ESBL-producing *E. coli*	36	NORM/NORM-VET, 2015
		Broiler meat	ESBL-producing *E. coli*	30	
		Broiler	Vancomycin resistant *Enterococcus* spp.	7	
Netherlands	2014	Poultry	ESBL-producing *Salmonella* spp.	12	NethMap-MARAN, 2015
		Poultry	Fluoroquinolone-resistant *Salmonella* spp.	43	
		Pig	ESBL/AmpC-*E.coli*	18	
		Dairy cow	ESBL/AmpC-*E.coli*	9	
		Turkey meat	ESBL/AmpC-*E.coli*	51	
		Poultry meat	ESBL/AmpC-*E.coli*	67	
Denmark	2014	Pigs	MDR-*Salmonella* spp.	7	DANMAP, 2014
		Broiler meat	ESBL-producing *E. coli*	9	
United States	2012–2013	Turkey	MDR-*E. coli*	62	FDA, 2014
		Turkey	MDR-non-typhoidal *Salmonella*	34	
		Chicken	MDR-*E. coli*	62	
		Pig	MDR-*E. coli*	22	
		Ground beef	MDR-non-typhoidal *Salmonella*	20	

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