Factors influencing emergence and spread of antibiotic resistance in Egypt using a one health approach

Mai Arafa

Egypt

55th Master of Science in Public Health/International Course in Health Development

KIT (Royal Tropical Institute)

Vrije Universiteit Amsterdam (VU)

“Factors influencing emergence and spread of antibiotic resistance in Egypt using a one health approach”

A thesis submitted in partial fulfillment of the requirement for the degree of Master of Science in Public Health

By

Mai Arafa

Egypt

Declaration:

Where other people’s work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.

The thesis **“Factors influencing emergence and spread of antibiotic resistance in Egypt using a one health approach”** is my own work.

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List of abbreviations

World Health Organization	WHO
Antibiotic Resistance	ABR
Food and Agriculture Organization	FAO
World Organization for Animal Health	OIE
Multi-drug resistant	MDR
Antibiotic resistance genes	ARGs
Horizontal gene transfer	HGT

List of figures, charts, tables and graphs

Glossary

Antibiotic resistance	It refers to alteration in bacteria in a way that cease the curative activity of medicines against these microorganisms and subsequently, the infections caused by those microorganisms became difficult or impossible to treat.
Antibiotics	Substances that are used for prevention and treatment of infections caused by bacteria.
One health	A multi-sectoral, multi-level and integrated approach aiming at planning and conducting effective programs and policies in order to reach greater public health outcomes for humans, animals and the environment.
Inappropriate use of antibiotics	It refers to unjustified use of antibiotics; such as, unneeded use, improper selection of antibiotic, overdosing or underdosing, inappropriate duration of antibiotic use and discontinuing antibiotics full course.

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Finally, I would like to dedicate my thesis to my mother's soul.

Praise be to God

Abstract

Background: Antibiotic resistance (ABR) is a huge threat to public health and leads to loss of thousands of human lives each year. Effect of ABR on animal health and environment is as harmful as its effect on humans.

Aim: To identify the main contributing factors to emergence and spread of antibiotic resistance in Egypt using a one health approach in order to develop useful recommendations for effective interventions to tackle the problem.

Methodology: A literature review of different published and unpublished articles, reports and documents was used. Lebov one health framework was adapted to match the study objectives and was followed to guide the review.

Results: Inappropriate use of antibiotics in humans, low awareness on antibiotics and their resistance, and uncontrolled antibiotic dispensing are the key human factors influence ABR. While unregulated agricultural practices, antibiotic residues in wastewater, resistant bacteria in water, soil and air, and horizontal gene transfer were the main environmental influencing factors. Extensive antibiotic use in animals and aquaculture were the major animal factors affect ABR. Challenges to controlling efforts were identified as lax regulations, lack of enforced policies and limited surveillance.

Conclusion and recommendations: ABR problem in Egypt is increasing and integrated interventions are needed to tackle it. National awareness campaign will help in behavior augmentation regarding antibiotic use. Encouraging research on ABR will find tailored opportunities based on the national situation. Strict regulations and regular monitoring will help in combating ABR in Egypt.

Keywords: Antibiotic resistance – One health – Egypt

Word count: 11,222

Introduction

Recently, antibiotic resistance became a global priority and a threat to million human lives. The problem of antibiotic resistance is increasing among both humans and animals. Since antibiotic resistance is a problem of humans, animals, environment and food, it cannot be tackled without integrated approach. This approach should aims to introduce interventions that would interfere the occurrence and spread of the resistant bacteria in both humans and animals with treating the facilitating environment. Therefore, there is a great need to study the problem in a comprehensive way from different dimensions. One health approach helps in understanding problems that influence public health with consideration of human, environment and animal health.

I worked as the one health focal point at the Egyptian ministry of health and population, which gave me the chance to participate in the initial steps towards establishment of the one health platform in Egypt. Additionally, it was a great opportunity to address the gaps in interventions aiming at reducing the burden of zoonotic diseases and health problems of zoonotic origin. I witnessed how some patients; particularly, patients with Tuberculosis and Pneumonia were suffering from multi-drug resistance due to infection with resistant bacteria.

This encouraged me to choose antibiotic resistance as my thesis topic to help in better and deeper understanding of the problem. Subsequently, find opportunities for useful interventions to decrease the intensity of the problem. Based on my previous observations, many efforts were exerted to tackle the problem of antibiotic resistance, yet still much more can be done especially regarding comprehensive and integrated regulations and policies.

I am willing to share the study results and the proposed recommendations with the decision-makers in Egypt. These recommendations might be useful in combating the antibiotic resistance problem in Egypt.

Chapter 1: Egypt Background

1.1. Geography

Egypt, officially the Arab Republic of Egypt, is one of the Middle East countries (1). It is located in the north-eastern corner of Africa with a part, Sinai Peninsula, is located in Asia (1,2). It covers a total area of 1.002.450 km^2 and it is bordered by the Mediterranean Sea at the north and the Red Sea at the East (1,3). It shares borders with other countries as demonstrated in Figure 1; 1273 km of its southern border with Sudan that is one of the longest land borders worldwide, 1.150 km of its western border with Libya and 255 km and 11 km of its eastern border in Sinai with Israel and Palestine (Gaza Strip), respectively (4–6).

Egypt has three geographical hallmark; Suez Canal, Nile River and Lake Nasser (2,4). The African and Asian parts of Egypt are separated by the Suez Canal, which plays a crucial role in Egyptian history, and political and economic situation (2,4). Nile River, the longest river in the world that rises from Lake Victoria in East Africa, runs through Egypt ending in the Mediterranean Sea through Rosetta and Damietta branches (2,4). As a result of construction of Aswan High Dam, Lake Nasser was formed to be one of the largest manmade lakes in the world, it helps in hydroelectric power generation, although, it smashed important historical sites (4,7). Those three main geographical landmarks divided Egypt into four main compartments; Upper Egypt, Lower Egypt, Western Desert, and Eastern desert and Sinai Peninsula, with 27 governorates (2).

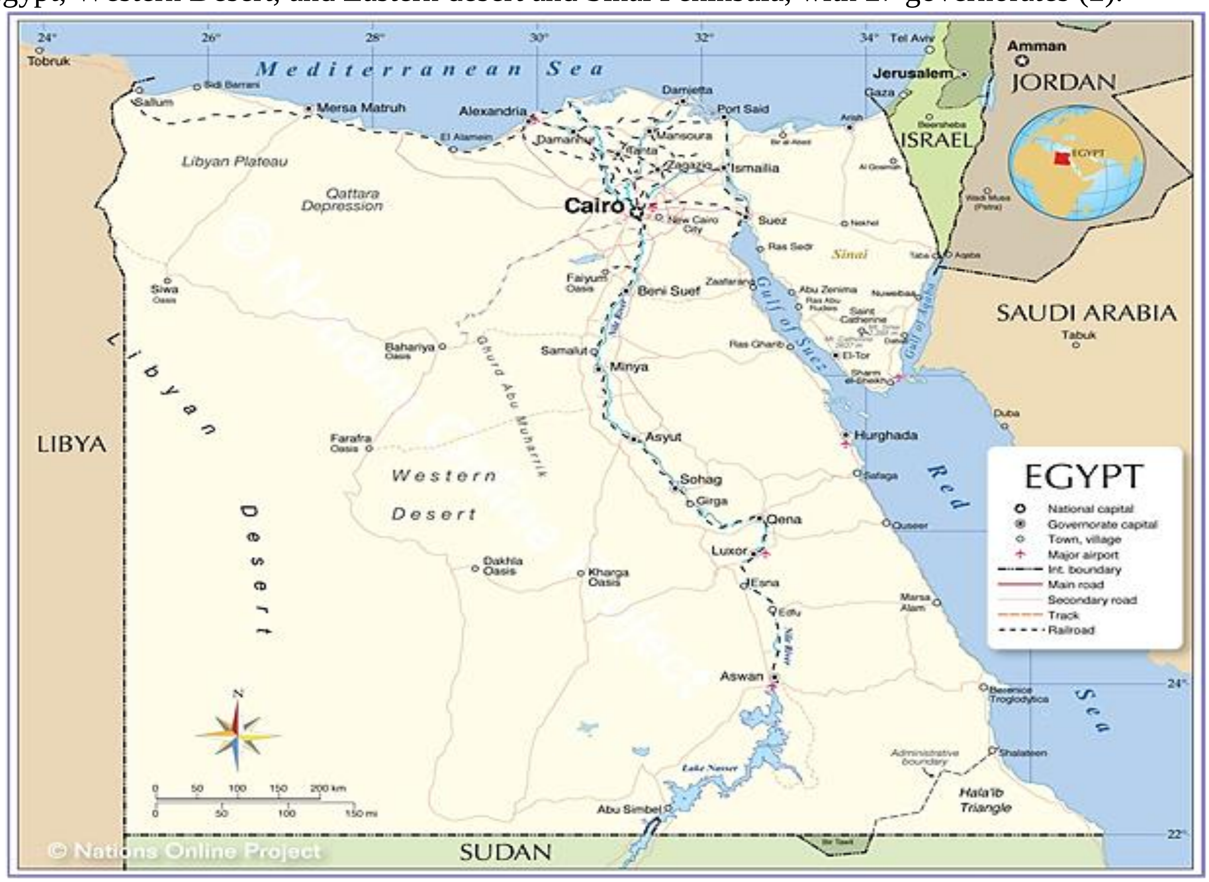

Figure 1: Egypt's map showing its situation, borders, geographical features and governorates (25)

1.2. Demography

According to latest census of 2018, the estimated population in Egypt is 98 million with an annual population growth rate of 1.93% and a male to female ratio of 1.08:1 (8,9). According to estimates in 2017, the total fertility rate is 2.7 and the average life expectancy is 68 years and 74 years for males and females, respectively (10). Nile delta represents 5% of total Egyptian surface area, however, 95% of Egyptians living in it making it one of the highest populated areas worldwide (11). Thirty three percent of the population are14 years of age and younger (12).

1.3. Sociocultural

About 95% of population in Egypt are Egyptians and around 5% of the population are from other ethnic groups; including, Berbers in Siwa Oasis, Bedouins in Sinai, Nubians in southern Nile and Copts who represents old Christians in Egypt (13). Arabic is the official language in Egypt and the majority of Egyptians speak the modern Egyptian Arabic (3). Whereas, people is Upper Egypt speak Saidi Arabic, Berbers minority speak Siwi and Nubian people in southern Nile speak Nubian (13). Besides, Egyptian Christians speak Coptic language during prayers and activities in churches (13). According to estimates in 2015, around 90% of Egyptians are Muslims (mostly Sunni) and about 10% are Christians (mostly Coptic Orthodox) (14).

1.4. Education and labor

The total education expenditure represents 8.9% of the total government expenditure (15). Literacy rate among population aged 15 years of age and older is 71% with 7.2 mean years of schooling (12,16). Egypt has unemployment rate of 11.4% which is more than two times the global unemployment rate (17). Labor market in Egypt is highly dominated by males representing 73.7% of labor force compared to 22.2% for females (16). Forty nine percent of labor force are working in service sectors, while 25.8% work in agriculture and 25% work in industry (14).

1.5. Economic and environmental characteristics

According to the World Bank classification for the fiscal year 2019, Egypt is categorized as a lower-middle income country (18). According to 2015 estimates, more than quarter (27.8%) of general population are below poverty line (international poverty line 1.9$ PPP) (8). The GDP[i] per capita in purchasing power parity is estimated at 12,390 USD with 5.3% GDP growth (19). According to human development index (HDI) global ranking, Egypt is ranked 115 with 36% inequality in income (11).

The main pillars of Egyptian economy are agriculture, tourism, Suez Canal revenues and Egyptians expats remittances (20). According to the latest Egyptian Central Agency for Public Mobilization and Statistics (CAPMAS) estimates, the total agricultural production in Egypt is estimated at 98.1 tons/hectare and the fish production in Egypt is estimated at 1.5 million tons (15). While, the Egyptian livestock production index was 123.35 in 2016 (21).

[i] GDP stands for Gross Domestic Product. It refers to the total financial worth of all produced services and commodities in a country per year.

According to the latest estimates in 2017, the Egyptian consumption of poultry meat per capita is 11.4 kg/year, 8.8 k/year of beef and veal, 1.2 kg/year of sheep meat (22). Whereas, the Egyptian consumption of fish production per capita is 14.5 kg/year and the consumption of vegetative production per capita is 465.4 kg/year (15).

Egypt suffers from water scarcity due to poor water resources (23). According to CAPMAS, the total water quantity in Egypt was 76.3 billion m^3 in year 2015/2016, from which 82% are consumed in agriculture (15). The primary water source in Egypt is Nile River constituting 73% of total water quantity (15). Other water resources includes groundwater, treated wastewater, rains and desalination of seawater (15). Chart 1 shows the water quantity distribution in billion m3/year by resource in Egypt in 2015/2016 (15).

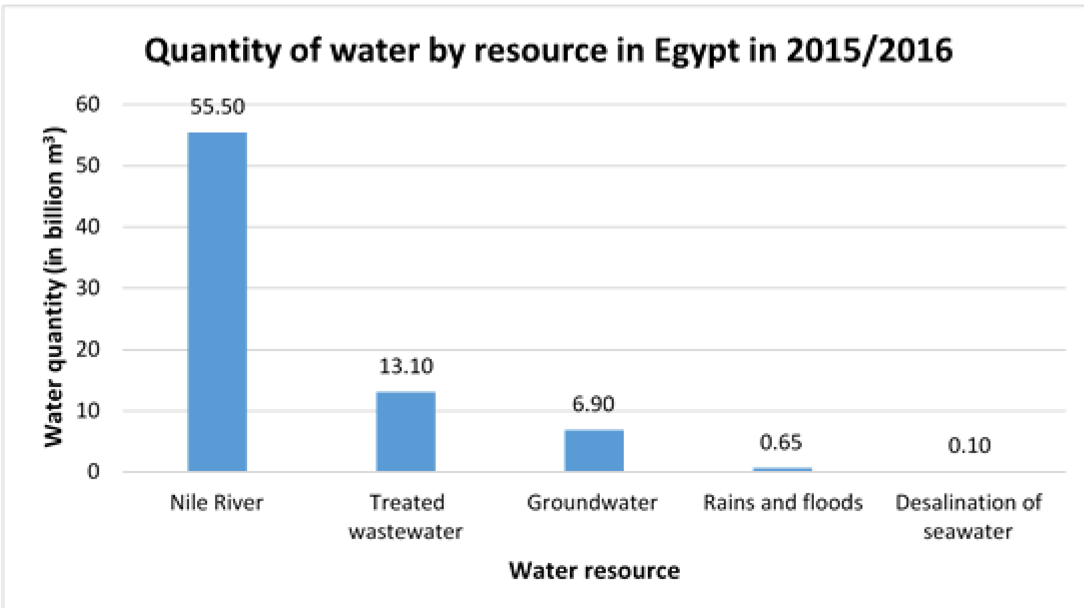

Chart 1: Distribution of water quantity in billion m^3 by water resource in Egypt in 2015/2016

1.6. Human Health status

Non-communicable diseases count 82% of the first ten causes of death in Egypt in 2017. While lower respiratory tract infections is the only communicable disease among the list ranking the fifth cause dropping from the fourth cause in 2007 by 24%. On the other hand, non-communicable diseases are responsible for 68% of the premature death. Whereas, lower respiratory tract infections ranked the third in the premature causes of death in Egypt. Diarrheal disease are among the first ten causes of premature death and infant mortality rate of 15.1 (10).

This indicates that the impact of non-communicable diseases is higher than communicable diseases in Egypt. However, this is due to the effective treatment, particularly, antibiotics and it therefore could be changed.

1.7. Human health system

Egypt has a powerful health system with multiple types of care providers; including mainly the public and the private providers. Public sector is funded and operated by the government and provide a cheap service of average quality. While, the private sector provide better services but with high costs. The public sector has 662 hospitals, which almost half the total number of private sector hospitals 1017 (15).

In fiscal year 2018/2019, the total health expenditure represents 4.3% from the total of the total government expenditure, which declined from 4.5% the previous year. Total number of healthcare professionals is 365 thousand, from which 102 thousand are medical doctors, 49 thousand pharmacists and 191 thousand nurses (15).

Only half of Egyptians are covered by the national health insurance (24). In 2017, Egypt released a health insurance law aiming to include more beneficiaries from people below poverty line in order to achieve universal health coverage by 2030 (25).

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Chapter 2: Problem statement, Justification and Objectives

2.1. Antibiotic resistance in the global context

According to the World Health Organization (WHO), antibiotic resistance refers to alteration in bacteria in a way that ceases the curative activity of medicines target these bacteria (26). ABR is a very old phenomena even older than discovery of antibiotics and it happens naturally (27). Bacteria can prohibit antibiotics to get across their cell walls by altering number or size of pores in their cell membranes. Bacteria can push antibiotics out of their cells using pumps located on their cell membranes. Some bacterial enzymes can abolish the antibiotic effect through devastating antibiotics or transforming its chemical structure. Bacteria can circumvent the antibacterial mechanisms of antibiotics by reshaping their targeted parts or generating new biological processes unlike the targeted ones by antibiotics (28).

ABR is increasing alarmingly and it causes 700,000 deaths annually (29). The latest report from Interagency Coordination Group on Antimicrobial Resistance (ICGA) indicated that available antibiotics are no more effective against up to 90% of human infections in low and middle income countries (30). Despite the global integrated surveillance system of WHO, Food and Agriculture Organization of the United Nations (FAO) and World Organization for Animal Health (OIE), the ICGA report noted that the global and the national integrated actions are not enough (30,31). ICGA called for investment in tackling the problem now to avoid the sever economic and health consequences later (30).

The integrated actions should be done through a one health approach since the main drivers of the problem includes human, animal, food and environment factors. One health is a multi-sectoral, multi-level and integrated approach aiming to plan and conduct effective programs and policies in order to reach greater public health outcomes for humans, animals and the environment (32,33).

2.2. Problem statement

ABR in Egypt is a huge threat to public health and many human cases were reported to have multi-drug resistant (MDR) pathogens of bacterial meningitis, enteric infections, tuberculosis and other respiratory infections (34). Thus, ABR has high health and economic burden due to severe health outcomes and increased costs of hospitalization and medical care; particularly, for severe cases who need to be hospitalized in intensive care units (35).

Limited studies on ABR prevalence and epidemiology were done in Egypt. During the period of 2006 to 2017, Egypt has the highest prevalence of ABR in Enterobacteria[ii] against Cephalosporins and Carbapenem antibiotics among the Arabic countries with estimates of 55% and 28% of the total tested human samples, respectively (36). Furthermore, during the period between 2008 and 2016, Egypt had the highest Carbapenem-resistant Acinetobacter baumannii among Arabic countries with estimate of 93% of the total tested human samples (36). Besides, Egypt had one of

[ii] Enterobacteria are a group of gram-negative bacteria that can cause multiple illnesses (161)

the highest Carbapenem-resistant Pseudomonas aeruginosa among Arabic states with estimate of 51% of the total tested human samples during the period of 2005-2015 (36). The previous findings were not done as a part of a national survey or a surveillance system, they were only done in some hospitals and for some organisms, which discourage the generalization of them to the whole Egypt. However, they highlight the seriousness of the problem.

There is no surveillance data on ABR prevalence among animals or in the environment. Poor coordination between different stakeholders plays a crucial role in ABR spread throughout Egypt as not sharing data between human health, veterinary and food safety authorities, results in exaggerated spread of resistant bacteria (1,37).

2.3. Justification

Most studies on ABR in Egypt examined the occurrence of resistance in specific bacteria, focusing on either humans only or animals only (35,37–40). Many studies focused on factors influencing antibiotics use in humans (41–44). Few studies connected animal and food determinants and fewer addressed the human in relation to animal causes, yet not from a one health perspective, which does not help in tackling the problem (45,46). This review was therefore designed to understand ABR problem in Egypt using a comprehensive one health approach to answer the question of: *What are the main influencing factors of ABR in Egypt and how these factors interact with each other?* Accordingly, using the results to suggest useful recommendations with integrated interventions that might help in decreasing the burden of the problem in Egypt.

2.4. Objectives

General objective:

To identify different contributing factors to emergence and spread of ABR in Egypt from a one health perspective, in order to develop useful recommendations that could help in tackeling the problem.

Specific objectives:

1- To identify human related factors that lead to occurrence and spread of ABR in Egypt; including, inappropriate use of antibiotics, health system factors, health-care acquired infections and occupational factors.
2- To identify different environmental related factors that lead to occurrence and spread of ABR in Egypt; including, antibiotic use in vegetation, water, soil, air, climate change.
3- To review and identify animal related factors that lead to occurrence and spread of ABR in Egypt; including, antibiotic use in animals, wildlife and aquaculture.
4- To analyze the intersection between previous factors and how they influence each other leading to ABR occurrence and spread.
5- Propose useful recommendations that might help decision-makers within involved stakeholders in decreasing the tense of the problem in Egypt.

Chapter 3: Methodology

Literature review was used as the methodology to perform this study in order to find different documents, articles, studies and reports on ABR problem and contributing factors worldwide and in Egypt. Data used for this study was obtained from published and unpublished literature, either through different organizational websites or through published studies. For the organizational websites, governmental websites WHO, Centers for Disease Control and Prevention, FAO, OIE, World Bank, and others were used to access different factsheets, reports, guidelines, articles, policy briefs and assessment tools. For the published studies, literature search was done using four main databases; Pubmed, Vrije Universiteit Library, Proquest and Google scholar. Literature search was limited to documents that are published in English and during the last 15 years only. Different keywords were used in different combinations; including, antibiotics, antimicrobial resistance, antibiotic resistance, prescription, use, human, animal, food, water, aqua, system, policy, interventions, worldwide, Africa, Egypt *(Refere to Annex 1 for detailed search strategy used till now).*

Exclusion criteria

Articles that focused on resistant bacteria were excluded as they are more related to microbiological background of the problem than the contributing factors. Articles published in languages other than English were also excluded. The literature search was limited to 15 years, so articles older than 15 years were excluded.

Analytical framework

In order to answer the study question, the J. Lebov et al framework (Annex 1) of one health was adapted by the author and adopted in the study (47). Lebov et al framework is a multidisciplinary approach to understand health problems and diseases that have zoonotic origin in a comprehensive way in order to discover hidden or missed factors that lead to the health problem of study, hence, useful interventions could be suggested (47).

Although the framework includes different contributing factors, it lack some crucial factors that influence the emergence and spread of ABR. On the other hand, it includes less relevant factors. Hence, to conceptualize the framework to the ABR problem and to achieve the study objectives, some factors were added and framework was reorganized as clarified in figure 2.

The original framework is flexible for changes to be conceptualized to studied problem. The main four domains of the framework include; human health, animal health, environment health and intersection between the previous three domains. The main four domains were not changed. Under each domain there are subdomains which the author advised to use at least one of them (47).

The first domain (human health) has four subdomains; occupational health, environmental health, lifestyle health and genetic susceptibility. Occupational health was included in the adapted framework, while environmental one (exposure to air) was moved to the environment. Lifestyle and genetic susceptibility were removed since they do not match with the ABR problem(47).

The second domain (environment health) has three subdomains; terrestrial health, soil/sediment and aquatic health. Soil and aquatic health were included in the adapted framework. Whereas, terrestrial health were removed since it is irrelevant to the ABR problem (47).

The third domain (animal health) has three subdomains; environmental health (food sources contamination), agricultural health and lifestyle health. Environmental health was moved to the intersection domain since it reflect the interaction between environment and animal domains in the context of ABR. Agricultural health was included in the adapted framework. While, lifestyle health was removed since it is not relevant to the problem of ABR (47).

The forth domain (one health) had multiple subdomains, they were therefore reorganized using the conceptualization model provided by Lebov (Annex 2). The newly reorganized subdomains are; human-environment intersection, human-animal intersection and animal-environment intersection (47).

Based on reviewing different articles, systematic reviews and reports on ABR using a one health approach the results are categorized as follows:

1- **Human health:** This section focuses on human-related factors that lead to emergence and spread of ABR; including:
   - 1.1. Antibiotic use pattern in humans with its influencing factors categorized as patient side, prescriber side and regulatory side.
   - 1.2. Human health system factors; including, legalizations and policies, surveillance and infection prevention and control.
   - 1.3. Health-care acquired infections since they are important in spread of resistant bacteria.
   - 1.4. Occupational health which play crucial role in spread of ABR.

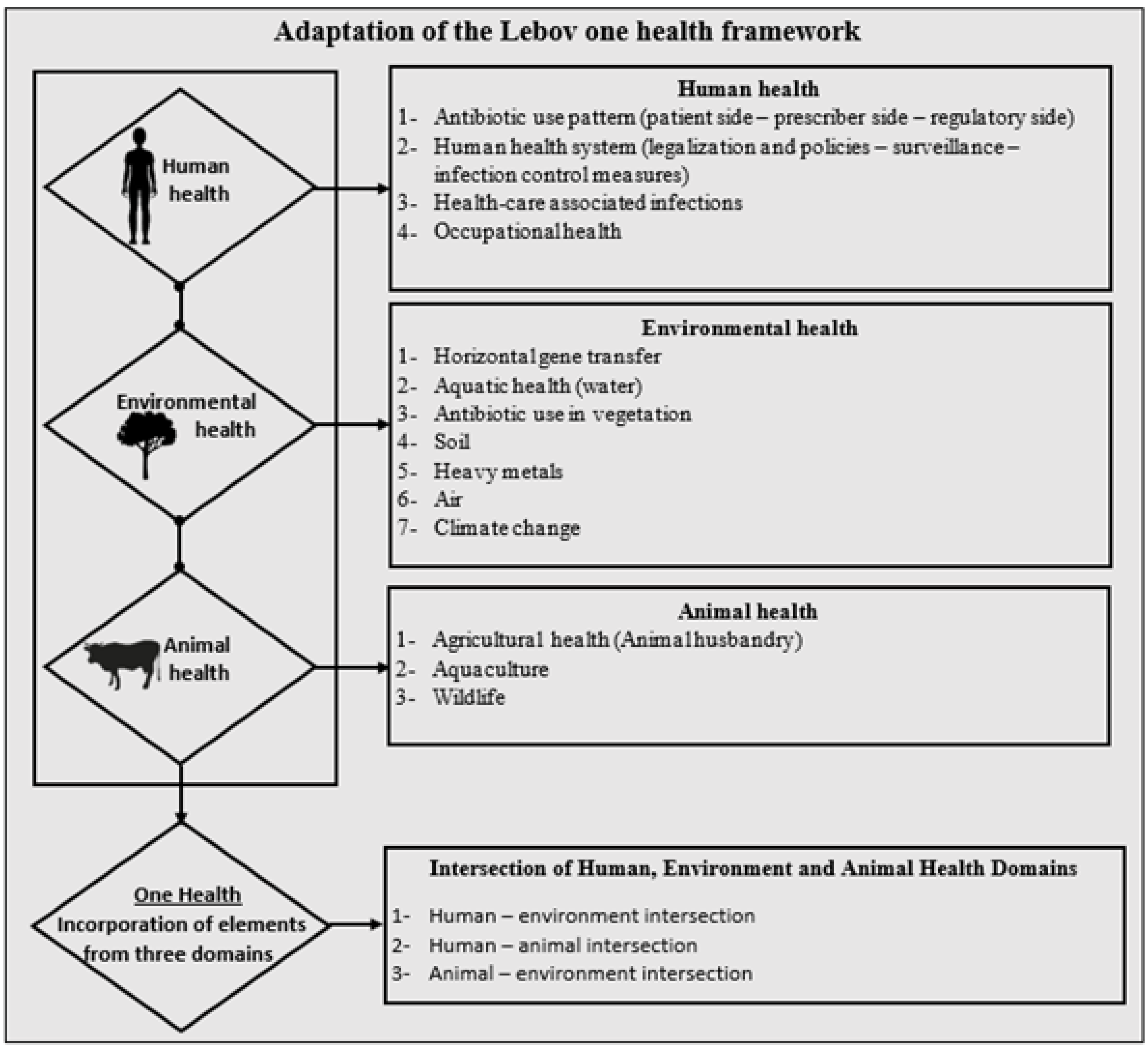
2- Environment health: This section focuses on environment-related factors that lead to emergence and spread of ABR; including:
   - 2.1. Horizontal gene transfer, which represent the natural phenomena of spread of ABR among bacteria.
   - 2.2. Aquatic health (water); including spread of ABR in different water types.
   - 2.3. Antibiotic use in vegetation
   - 2.4. Soil, discussing the presence of ABR in soil.
   - 2.5. Heavy metals, discussing the role of heavy metals in exacerbation of ABR problem.
   - 2.6. Air, discussing the role of as reservoir of resistant bacteria in the environment.
   - 2.7. Climate change, focusing on the relative association between climate and ABR spread.

3- Animal health: This section focuses on animal-related factors that lead to emergence and spread of ABR; including:
   - 3.1. Agricultural health; discussing the exposure of animal to antibiotics in animal husbandry.

3.2. Aquaculture; discussing exposure of aquatic creatures to antibiotics.
3.3. Wildlife; focusing on the role of wild animals in spread of ABR.

4- **Intersection between animal-human-environment:** This section focuses on relations between the previous domains resulting in emergence and spread of ABR; including:
4.1. Human-environment intersection; focusing of effect of human waste on environment and effect of air, water and plant consumption on humans.
4.2. Human-animal intersection; focusing on effect of food animals on humans and the bilateral effect of animal-human companion.
4.3. Animal-environment intersection; focusing on effect of animal waste on environment and effect of water and food plants on animals.

Figure 2: Adapted Lebov et al framework (adapted by the author)



Chapter 4: Results

4.1. Human-related factors

4.1.1. Antibiotic use in humans

Antibiotics prevented loss of many human lives due to infectious diseases, however, the inappropriate use of antibiotics; including, overuse and misuse of antibiotics, is a key driver of ABR emergence (48–50). Inappropriate use of antibiotics refers to unjustified use of antibiotics; such as, unneeded use, improper selection of antibiotic, overdosing or underdosing, inappropriate duration of antibiotic use and discontinuing full course of antibiotics (51–53). The inappropriate use of antibiotics increases the selectivity pressure of bacteria to resist and as a result exacerbates the ABR problem (54).

In 2015, the total antibiotic doses consumed by humans in Egypt was estimated at 24.9 DDD[iii] per 1000 population per day (9116 DDD/1000 population) (55). The most frequently used antibiotics were broad spectrum penicillin and quinolones and other antibiotics as illustrated in Chart 2 (55). Many factors determine the pattern of antibiotics use, which can be divided into; patient side, prescriber side and regulatory side (56).

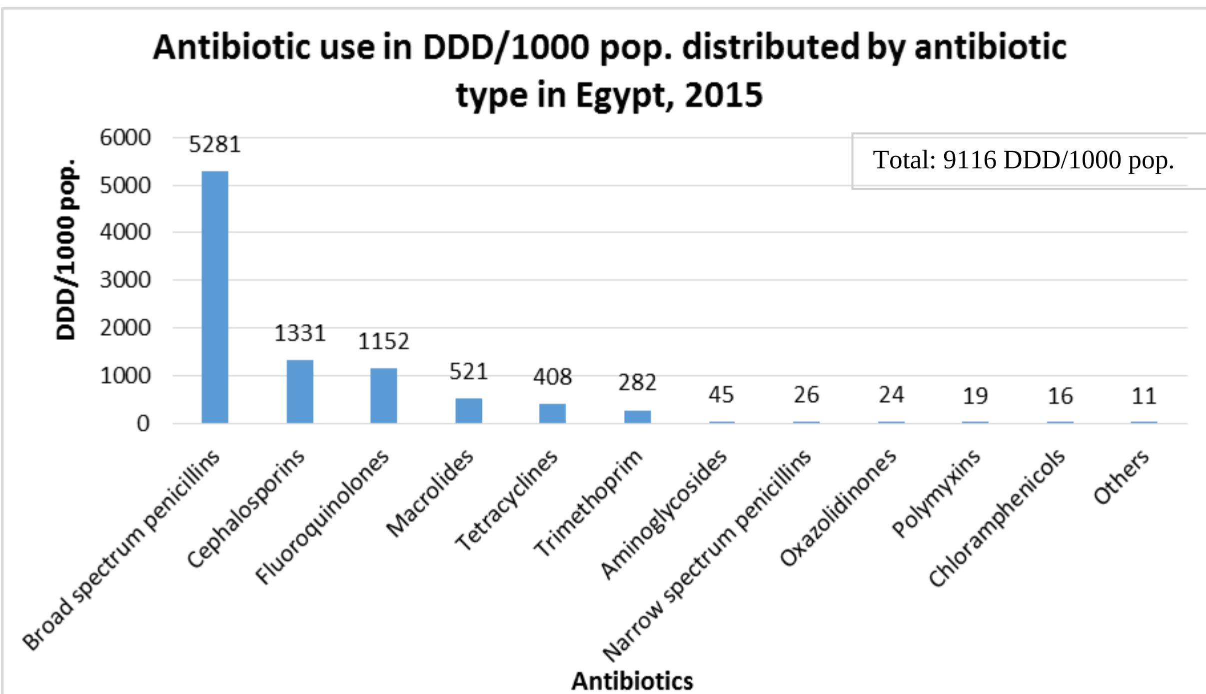


Chart 2: Distribution of consumed antibiotics in Egypt in 2015 (distributed by type in DDD/1000 population)

[iii] DDD stands for defined daily dose. According to WHO, it is the average daily drug maintenance dose utilized in adults for its primary intended purposes (162).

Patient side

Knowledge, attitude and behavior

A community-based survey in Egypt showed that 65.8% of participants lack the basic knowledge about antibiotics and ABR, however, 61% believed that irrational use of antibiotics has negative consequences (57).

Knowledge and attitude of public community in Fayoum[iv] regarding using antibiotics were examined by a cross sectional study. Fifty nine percent of all participants believed that antibiotics can treat any disease, regardless the disease nature or the causative agent, and 55.7% believed that newer and more expensive antibiotics are more effective. Forty seven percent of all participants believed that taking a small dose of the antibiotics would be helpful than getting nothing and about 60% expected to be prescribed antibiotics when consulting a physician. Besides, 42% knew nothing about ABR and 63.7% believed that taking antibiotics can prevent sever illnesses. Fifty four percent of participants reported discontinuing the antibiotic course in case of not getting better (58).

A mixed quantitative and qualitative study in Minya[v] showed that 61% and 44% of the caregivers and adult participants, respectively, believed that using antibiotics leads to quick recovery. Out of all caregivers and adult participants, 45% and 35% respectively believed that antibiotics could be used as a prophylaxis against common cold. Contrarily, 90% of all participants did not accept the idea of prescribing unneeded antibiotics (59).

The abovementioned study in Minya revealed that participants believed that antibiotics are powerful medicines and improve health, they also believed that antibiotics could be used as a preventive measure to prevent turning of simple symptoms into sever cases. The participants of this study agreed that acute illnesses and infections can only be treated by antibiotics with a preference of injectable and more expensive antibiotics since they are more effective, according to their perception. The participants preferred low doses with short course of antibiotics to avoid adverse effects of antibiotics overuse (59).

Many factors were found to be associated to the abovementioned findings. Patients with low income were found to discontinue the antibiotic course 1.6 times those with high income (58). Contrarily, there was no difference between different socioeconomic levels regarding practices related to antibiotic use in a population based survey in Cairo (60). Low education was significantly associated with discontinuing antibiotic course (OR: 1.93, CI 95% (1.30-2.72)) in Fayoum, however, previous practice was performed by individuals from all educational levels in

[iv] Fayoum is an Egyptian governorate. It is located in the West Desert (90 km away from the capital). It is classified as one of the Upper Egypt governorates (163).

[v] Minya is an Egyptian governorate. It overlooks Nile River and it is classified as one of the Upper Egypt governorates (164).

Minya (58,59). Unemployed patients in Fayoum opt to change their physician in case of no antibiotic prescribed 2.27 times higher than their counterparts (OR 2.27–95% CI (1.41–2.64)) (58).

The previous findings demonstrated the low level of perceived knowledge about antibiotics and their indications. This shortage of knowledge leaded to certain attitude and behavior like antibiotic demand increase and taking occasional antibiotic doses or discontinuing antibiotics course. Increased antibiotic demand resulted in pressuring physicians to prescribe more antibiotics to promote patient satisfaction and strengthen doctor-patient relationship resulting in inappropriate use of antibiotics. Hence, the inappropriate use of antibiotics would lead to increase selectivity pressure leading to ABR occurrence. Knowledge, attitude and behavior were significantly associated to unemployment, on the other hand, merely some evidence supported their association to education and socioeconomic level (58,59,61).

Self-medication

Self-medication refers to consumption of medicines without consulting a physician based on self-diagnosis; including herbal and traditional remedies (62,63). It also refers to irregular or sustained use of previously prescribed medicines (62,64). Self-medication with antibiotics (SMA) leads to excessive human exposure to antibiotics influencing bacterial selectivity pressure leading to ABR (65,66). In Egypt, antibiotics for self-medication could be accessed through direct purchasing from community pharmacies, getting the antibiotic from a friend or a relative, or using a previously prescribed antibiotic that might be available at home (42,63,64,67).

Different studies assessed the prevalence of SMA and its underlying determinants in Egypt. The results revealed an SMA prevalence of 46.5%, 32.7% and 28% in Alexandria[vi], Fayoum and Cairo, respectively (58,60,63). SMA was found to be highly associated with occupation type with higher prevalence among students, retired people, farmers and skilled workers (63). A significant association between SMA and low education level was reported by two surveys in Cairo (63).

The previous results showed how SMA is widely spread in Egypt, which explains the extensive exposure of individuals to antibiotics leading to ABR emergence (64).

Sources of medical advice

The reviewed studies revealed that antibiotic users in Egypt seek medical advice through three main sources; physicians, pharmacists and friends or relatives (57,58,60). The prevalence of seeking medical advice through consulting a physician was 40.4% and 60.7% in Cairo and Fayoum, respectively (57,58). Two studies in Cairo showed that 48.3% and 24.6% of respondents approach pharmacists to seek advice on getting ill, while it was higher (53.7%) in Fayoum (57,58,60). Two studies in Cairo and Fayoum reported similar prevalence of consulting a friend or

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[vi] Alexandria is an Egyptian governorate. It is 190 km away from the capital of Egypt. It is classified as one of the central and west Delta governorates and it is bordered by the Mediterranean Sea in the north (165).

a relative on feeling sick (26% and 22.7% respectively), whereas another study in Cairo showed a lower prevalence of 9.8% (57,58,60).

Age, income, health insurance coverage, time and level of trust, were found to influence selecting the source of advice (60,61). Consulting physicians on feeling sick is more popular among children and elderly since children receive further care and elderly visit physicians regularly to follow up their chronic conditions (60). limited health insurance packages simultaneously with suffering from financial issues, encourage people to seek cheaper sources of advice (61). Limited trust in physicians along with avoiding long waiting time encourage some people to seek other sources for advice (60).

Prescriber side

This part focused on the role of prescribers[vii] in shaping the antibiotic use in Egypt through reviewing articles on knowledge, attitude and practice of physicians and pharmacists, pharmaceutical industry and profits pressures, and antibiotic dispensing pattern.

Knowledge, attitude and practice

In Minya, most of physicians and pharmacists showed good grasp of negative consequences of irrational use of antibiotics, however, the majority believed that antibiotics could be used against viral infections (68). In Fayoum, physicians showed sufficient knowledge about ABR and its contributing factors except for animal causes (69). In Alexandria, physicians showed poor knowledge about local patterns of ABR (70).

Only half of licensed pharmacists had satisfactory basic knowledge about antibiotics indications and ABR in Cairo (71). A study in Alexandria showed that all participants (pharmacists) were fully aware about the consequences of irrational use of antibiotics (44).

The previous results showed different levels of knowledge among both physicians and pharmacists about antibiotics and ABR. Thus, their decisions on antibiotic prescribing would be affected and might result in irrational use of antibiotics leading to ABR.

Almost quarter of physicians reported that they prescribed unindicated antibiotics in Minya (68). High prevalence of antibiotic prescribing in 18 hospitals in Cairo was reported with three hospitals exceeded 80% (72). A survey in Cairo showed that pharmacists were reported to replace the prescribed antibiotics by other antibiotics (57).

The previous results showed high prevalence of antibiotic prescribing among physicians that might be unneeded. Therefore, the human exposure to antibiotics increase influencing the bacterial selectivity pressure leading to emergence of ABR. Pharmacists may change the previously

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[vii] Prescriber refers to health personnel who can prescribe medicines including but not limited to physicians and pharmacists (166).

prescribed antibiotics by physicians, which might lead to wrong selection of antibiotics that could lead to ABR.

Patient request was one of the key factors that push physicians to prescribe antibiotics to gain patient trust and to promote doctor-patient relationship (70). Weak familiarity with guidelines leaded to wrong selection of antibiotics (73). Socioeconomic level of patients influenced the selection of antibiotics by some physicians to mitigate the economic burden on patients (70).

Pharmaceutical industry and profits

Pharmaceutical profits represent a pressure on the dispensing process of antibiotics in Egypt since antibiotics have a large share of pharmaceutical sales (71,74). Pharmacists have a substantial role in drug dispensing in Egypt including antibiotics (75). A study in Upper Egypt found that pharmacists dispensed antibiotics without prescription to increase their profits (76).

In Cairo, 49% of licensed pharmacists reported the negative impact of rejection of dispensing antibiotics without prescription on their profits (71). Owners of community pharmacies were found to encourage the antibiotic dispensing without prescription to increase profits as per a qualitative study in Alexandria (44).

The previous results showed how pharmaceutical industry and profits could affect the prescribed antibiotics and the dispensing of antibiotics in Egypt. The impact of this might lead to inappropriate use of antibiotics leading to ABR.

Antibiotic dispensing

Despite dispensing antibiotics without a prescription is legally forbidden in Egypt, it is very common (71). In Alexandria, 42% of dispensed antibiotics were without prescription (77). In Cairo, 52% of community individuals reported availability of antibiotics in pharmacies without prescription request (57)

Eighty percent of licensed pharmacists working in community pharmacies in Cairo believed that dispensing antibiotics without prescription increase the risk of antibiotic irrational use leading to ABR. However, most of them reported that they dispensed antibiotics without prescription. They believed that patients could simply obtain antibiotics from other pharmacies in case of refusal of dispensing antibiotics without prescription (71).

<u>Regulatory side</u>

Legally, antibiotics are prescription-only medicines in Egypt, although, dispensing antibiotics without prescription is frequent because of inoperative law and fragile policy enforcement (71). A survey in Alexandria revealed that the regulatory authority is fully responsible for the exacerbation of antibiotic dispensing problem in Egypt due to lack of monitoring (44). There is no governmental guidelines on antibiotic use in Egypt, thus, 90% of pharmacists in Cairo expressed their desire for receiving a national guideline regulating antibiotic dispensing (71).

4.1.2. Health system factors

This includes surveillance system, legalization and policies, and infection control interventions. **Legalization and policies** on regulated antibiotic use already reviewed early *(Refer to regulatory side under Antibiotic use in humans).*

Surveillance

Align with the global efforts, Egypt has been participating in GLASS since May 2016 with 15 surveillance sites, which were increased to 39 surveillance sites in 2017 (78,79). However, surveillance is still limited due to insufficient budget and limited human resources (76,80,81). Additionally, Egypt managed to develop a national plan to combat antibiotic resistance align with the global plan, however, this plan is not active till now (82). Weak surveillance provides limited information on the local ABR pattern, which interfere with developing proper interventions (83). Interventions that do not target the local ABR pattern and do not study the circulatory resistant strains, increase the emergence and spread of ABR.

Infection prevention and control

Infection prevention and control (IPC) plays a crucial role in preventing spread of resistant bacteria within health care facilities (84). In Egypt, IPC program was established in 2003 and there are extensive ongoing efforts to train healthcare professionals, and to monitor and evaluate the efficiency of the program (85). However, some studies reported some weaknesses in the implementation of the program. The identified pitfalls were linked to weak adherence of healthcare professionals to national IPC guidelines and laxity in following guidelines (86–88).

According to a cross sectional study in Cairo, 63.6% of total nurses at intensive care unit showed poor grasp of IPC guidelines (86). On the other hand, a cross-sectional study in Cairo revealed that 90% nurses at burn unit showed accepted level of knowledge on IPC standards, however, they showed poor performance (88). In Mansoura[viii], almost half of healthcare staff lacked basic knowledge about IPC standard precautions with limited practice of hand washing (87).

The previous results showed different levels of knowledge and performance of health care providers regarding IPC. Hence, poor performance might lead to spread of infections within health care facilities including infections with resistant bacteria resulting in spread of ABR in Egypt (84,89).

4.1.3. Health-care associated infection

Health-care associated infection (HAI) refers to acquired infections within any kind of health facility among patients or working staff. HAI spreads rapidly worldwide and are highly associated

[viii] Mansoura is a city in Dakahlia governorate. Dakahlia is an Egyptian governorate. It is 140 km away from the capital of Egypt. It is classified as one of Northwest Nile Delta governorates and it is bordered by Mediterranean Sea in the north. It is famous for agriculture (167).

with poor implementation of IPC standard precautions (90). *(Refer to Infection prevention and control under health system factors for more information on IPC in Egypt)*

HAI influences ABR through increasing the spread of resistant bacteria. The burden of HAI with resistant bacteria is hard to be determined due to poor surveillance. On the other hand, some studies investigated the prevalence of resistant bacteria within health care facilities in Egypt.

An interventional study in Egypt tested implementation of pilot surveillance units for HAI in 28 hospitals, showed high prevalence of MDR (92%) and resistant bacteria among bacterial HAI (91). High prevalence of resistant bacteria among patients who acquired HAI ranged from 49% to 77% was reported by a retrospective study in 5 hospitals in Cairo (92). Another study in Cairo showed high prevalence of extended ß-lactamase enzymes[ix] estimated at 25.7% and 33.7% in Klebsiella[x] and Escherichia coli[xi] (E.coli) bacterial isolates (93).

A prospective cohort study in Cairo showed a 22% prevalence of resistant bacteria among healthcare staff working in intensive care units without significant association with IPC measures (94). Two studies in Fayoum detected high prevalence of resistant bacteria in nasal and fecal samples among HCWs, which was attributed to poor IPC measures (95,96).

The previous results showed the high prevalence of resistant bacteria among HAI among both patients and healthcare professionals, which explains that HAI induce the spread of ABR. Poor implementation of IPC measures enhances the transmission of resistant bacteria from infected patients to healthcare staff through direct contact (95–97).

4.1.4. Occupational health

Many occupations were found to be related to spread of AMR. This includes healthcare staff, veterinarians, farmers and agriculture workers, butchers, animal transport workers, people with occupations related to animal-derived food processing and preparation and workers in water sanitation plants (94–96,98,99). *(Refer to Healthcare associated infection for possible occupational risk among healthcare professionals)*

A study in Mansoura studied ABR prevalence of enteric pathogens in skin swabs and stool samples from handlers of chicken raw meat (98). High levels of resistance, ranged from 49% to 100%, were found in all bacterial isolates against three antibiotics (98). On the other hand, a study in Dakahlia investigated the prevalence of Methicillin-resistant Stapylococcus Aureus (MRSA) on hands of dairy workers (99). The results showed high frequency of Staphylococcus aureus estimated at 80% of all hand swabs of dairy workers (99). However, none of them revealed positive results to the mecA gene, which is responsible for ABR activity (99).

[ix] Extended spectrum ß-lactamase enzymes are bacterial enzymes responsible for developing resistance against many of ß-lactam antibiotics (168).
[x] Klebsiella is a gram negative bacteria and it is classified as one of the Enterobacteria (169).
[xi] Escherichia coli is gram negative bacteria (170).

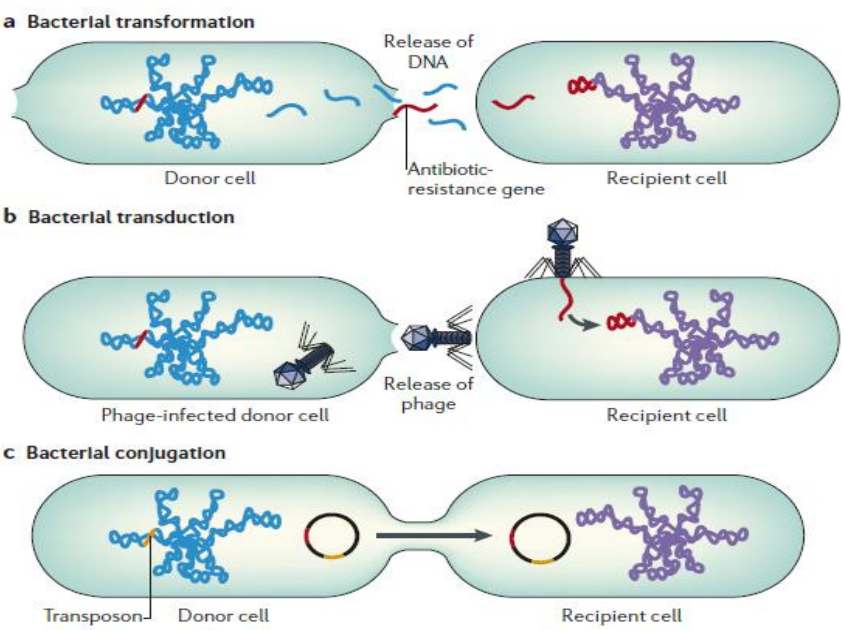
4.2. Environmental Factors

This section focused on the possible sources of ABR in the environment. Based on the reviewed articles the key sources include the natural phenomena of horizontal gene transfer between bacteria, water, soil, heavy metals and using of antibiotics for agricultural activities.

4.2.1. Horizontal gene transfer

Horizontal gene transfer (HGT) or lateral gene transfer refers to transmission of genes or mobile genomic elements between unrelated organisms (100). It is considered one of the major environmental determinants of ABR spread (101). The three main mechanisms of HGT as clarified in figure 3 are; a) bacterial transformation, b) bacterial transduction, and c) bacterial conjunction (101). A study in Giza[xii] and Kaluobaia[xiii] focused on ARGs in pathogenic E.coli bacteria isolated from broilers revealed that the resistance rate of E.coli ranged from 30% to 85% against twelve types of antibiotics (102). Besides, the detection rate of six ARGs ranged from 40% to 70% (102).

Figure 3: Different mechanisms of horizontal gene transmission; a) bacterial transformation: ARGs pass from a bacteria to another on a whole DNA strand, b) bacterial transduction: ARGs pass from a bacteria to another on a phage, and c) bacterial conjunction: ARGs pass from a bacteria to another through a plasmid (101)



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[xii] Giza is an Egyptian governorate. It overlooks Nile River, which separate it from the capital of Egypt (171).
[xiii] Qaliubiya is an Egyptian governorate, 40 km from Egypt capital. It lies in Delta region to the east of Nile River (172).

A study in Cairo showed that 90% of the isolated E.coli from clinical and food samples were resistant against at least one of the 26 tested antibiotics with 35% prevalence of MDR against at least 3 antibiotics (103). A further study using the same samples studied the potential transmission mechanisms of the ABR characteristics to non-resistant E.coli strains, showed evidence that ARGs were transferred from resistant E.coli to non-resistant E.coli through HGT by conjunction (104).

The previous results explains the phenomena of ABR development and transmission of ARGs between different bacteria through a horizontal approach in Egypt (101,104).

4.2.2. Water (Aquatic health)

Antibiotic residues were investigated in wastewater collected from multiple pharmaceutical factories in Egypt. The results showed high levels of antibiotic residues, which would be a dangerous source of ABR in the environment (105).

A study in Suhag[xiv] aimed to detect the antibiotic resistance level among Pseudomonas aeruginosa[xv] strains isolated from water. The water samples were taken from multiple natural sources; including, wastewater (treated and untreated), agriculture drainage water, irrigation water and Nile River surface water. The results showed high resistance rates among the isolates from different water sources against tested antibiotics, particularly, from treated and untreated wastewater. Table 1 displays the antibiotic resistance rates of the isolates from different sources against different antibiotics. While antibiotic resistance rate of the bacteria was the highest against Tetracyclin (estimated at 96.3%), it was the lowest against Norfloxacin (estimated at 1.7%) (106).

Table1: Antibiotic resistance rates per water source in Suhag

Water source / Antibiotic	Wastewater Treated and Untreated	agriculture drainage water	irrigation water	Nile River water	Overall
Ampicillin	96.7%	93.3%	83.3%	90%	**90.8%**
Streptomycin	98.3%	91.7%	57%	93.3%	**92.2%**
Gentamycin	60%	35%	18%	40%	**41.3%**
Norfloxacin	5%	0%	0%	1.6%	**1.7%**
Kanamycin	91.7%	90%	85%	91.7%	**89.6%**
Tetracyclin	100%	95%	91.7%	98.3%	**96.3%**
Chloramphenicol	100%	83.3%	86.7%	96.7%	**91.7%**
Rifampicin	86.7%	66.7%	75%	78.3%	**75%**

[xiv] Suhag is an Egyptian governorate. It overlooks the Nile River and 476 km away from the country capital. It is classified as one of the Upper Egypt governorates (31).

[xv] Pseudomonas aeruginosa is a gram-negative bacteria, belongs to Pseudomonas species. It can lead to plant disease and it may spread through water. It cause sever illnesses in patients with low immunity and mild illnesses in other people (173,174)

For the previous results in Suhag, the high resistance rate in wastewater might be attributed to the antibiotic residues and resistant bacteria from human and animal excreta and industrial waste (105,106). Additionally, this high resistance rate in irrigation water may increase the risk of transmission of resistant bacteria to humans later by consumption of the crops irrigated by this water (106).

A study aimed to identify the possible risks of ABR to environment due to wastewater drainage in Nile River was conducted at Rosetta branch of the river. Samples were collected from surface water and drainage site along the branch. Results showed that 60.8% of total bacteria were isolated from Rosetta branch surface water, while merely 39.2% from drainage sites. Results showed MDR of a high risk contamination from antibiotics with MAR index[xvi] of 0.25. Based on bacterial classification and antibiotic susceptibility testing, the study determined sewage as the major source of water pollution by antibiotic residues and resistant bacteria. These results clarified the role of drains in increasing the risk of ABR by transmitting the resistant bacteria to surface water threatening aquatic health (107).

A study in Cairo aimed to find an evidence of existence of resistant bacteria in drinking water (even after treatment) showed that 40% to 70% of the samples found to carry resistant bacteria (108). Groundwater in Egypt showed high levels of bacterial pollution, which is attributed to its direct contact with sewage and industrial waste (109). It can therefore carry resistant bacterial strains that will subsequently consumed by humans enhancing ABR spread (109).

In Suhag, 32 bacterial strains were isolated from water samples collected from Nile River and groundwater. The isolated strains were resistant against 50% of tested antibiotics. However, the samples from treated tap water for the same study were negative to bacterial strains. Despite the negative results of tap water sources, people with limited access to tap water will use other alternatives like direct consumption of surface water. The bacterial isolates from surface water showed high levels of resistance, this bacteria could be transmitted to humans increasing the ABR burden (110).

The previous results showed the ABR risk that threaten the environment and the probable sources. The identified probable sources of antibiotic residues and resistant bacteria were mainly; human and animal waste, pharmaceutical waste.

4.2.3. Antibiotic use in vegetation

Antibiotics are crucial for plant growth and crops production because they protect plants and crops from infections (111,112). Despite their importance, even low doses influence the bacterial selection pressure resulting in developing of ABR in bacteria living on plants surfaces (111–113).

[xvi] Multiple antibiotic resistances index (MAR index), it equals the number of antibiotics the isolate was resistant to divided by the total number of antibiotics the isolate was tested to. MAR index of ≥ 0.2 is considered high risk contamination source (1).

A study was done in Mansoura aimed to estimate the prevalence of food borne pathogens and their antibiotic resistance activity. The results revealed that outer surface of potatoes has the highest prevalence of viable bacteria and the least were found in the inner tissue of cucumber. Those bacteria were tested against twelve antibiotics. Two types of the isolated bacteria showed resistance activity against three of the tested antibiotics (114).

Another study was done to determine the prevalence of Listeria monocytogenes pathogenic bacteria and their resistance activity in the Egyptian market. It showed that 14.7% of total frozen vegetable samples were positive to the Listeria monocytogenes bacteria, which were tested against 10 antibiotics. All isolates were resistant against Amoxicillin, Gentamycin and Norfloxacin, while resistance against other antibiotics showed variable degrees (115).

The previous results explains the risk of ABR in pathogenic bacteria attached to plants and vegetables. Hence, this bacteria could be transmitted later to animals and humans by consumption of this type of food or by direct contact for farmers (114,115).

Different hypothesis may clarify the causes of previous results. Spraying plants and soils with antibiotics as a preventive measure leads to antibiotic aggregation that enhance bacterial resistant reaction (112). Due to water scarcity in Egypt along with poor sanitation system, waste is directly released in agricultural drains and wastewater is being used in irrigation of soils and plants (116,117). Wastewater contains dozens of pathogenic bacteria with high resistant activity and antibiotic residues, which induces the ABR risk in soils and plants that would be transmitted to humans and animals (116,117). Organic fertilizers may increase the risk of ABR of plant origin since they contain numerous bacteria derived from animals or humans (118). Pollution due to direct contact with infected humans during preparation and handling of plant food might cause the abovementioned results, however, it is not sufficiently studied (118).

4.2.4. Soil

Soil is a key reservoir of resistant bacteria and ARGs that can be easily spread from non-pathogenic to pathogenic bacteria (119,120). Thus, harmless bacteria might be the origin of ABR. Soils are naturally rich in both pathogenic and non-pathogenic bacteria that are important for soil nourishment and productivity (119,120). Bacteria develop resistance naturally when some bacteria in the environment release antibacterial compounds to inhibit the virulence activity of other bacteria as part of a competition on nourishment (121). Actinomycetes are gram-negative bacteria that present extensively in soil (122). Actinomycetes are the main source of antibiotics and are considered the source of almost 80% of all antibiotics (123,124).

Antibacterial activity of isolated Actinomycetes from soil from 9 governorates in Egypt was tested (125). The results showed that the Actinomycetes were bioactive and produced antibacterial activity against many pathogens (125). In Beni-Suef, the isolated Actinomycetes from soil had antibacterial activity against pathogenic strains of E.coli and Staphylococcus aureus (126). This means that these bacteria may develop resistance against the antibiotics synthesized out of the

Actinomycetes later leading to spread of ABR through transmission to humans and animals (121,126).

The previous findings showed evidence on antibacterial activity of isolated bacteria from soil in Egypt. This might affect the selectivity pressure of other bacteria resulting in emergence of ABR (121,125,126). There are different factors influence soil as a reservoir of ABR; including, over use of antibiotics for soil treatment and HGT from resistant to non-resistant bacteria (127).

4.2.5. Heavy metals

Heavy metals were found to be associated with high prevalence of ABR in environmental reservoirs; including, soil and water. They act as co-selecting agents in bacteria due to the indefinite selection feature of bacteria against heavy metals and antibiotics since ARGs lie close to heavy metals encoding genes (128,129).

A study in Cairo and Sharkia found that there is a bacterial co-resistance against both heavy metals and antibiotics in isolated bacteria from soil in different localities (129). In Suhag, resistance rates against heavy metals and antibiotics from different water sources was tested (106). The results revealed that there was high metal-antibiotic double resistance rate ranged between 56.5% to 100% (106). The previous results show how presence of heavy metals in ABR environmental reservoirs promote the emergence of ABR in Egypt.

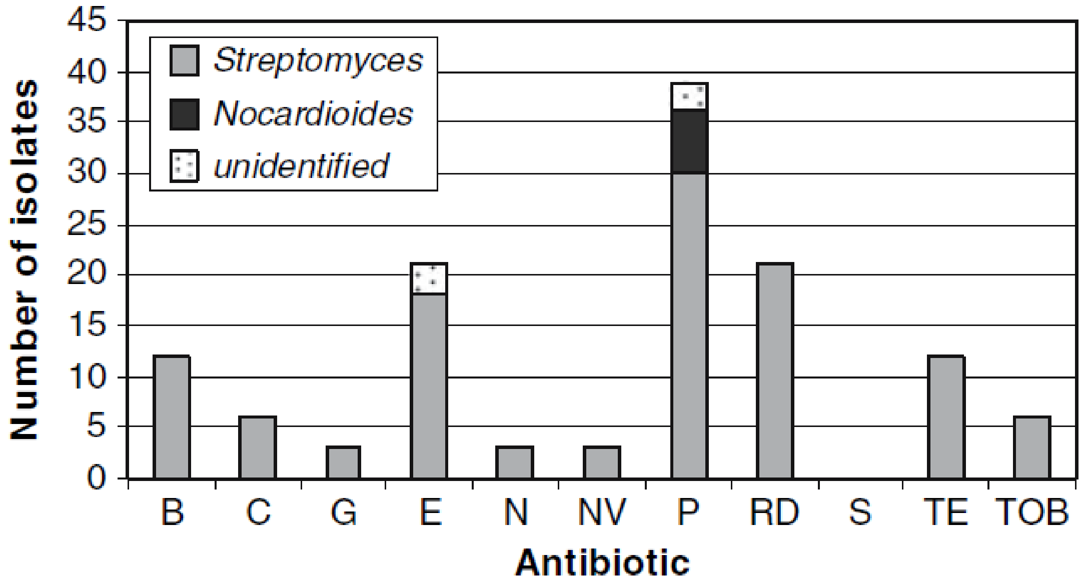
4.2.6. Air

A global survey tested air samples from 19 cities around the world for ARGs. The results showed that the samples were positive to 77% of the tested ARGs. A notable point here is that the air samples were collected from different 8 climate regions. Hence, presence of ARGs in air is a worldwide issue and air is an important reservoir of ARGs and facilitate spread of ABR (130).

A study in South Sinai investigated the resistance rates of isolated bacteria from indoor air of a church. Almost three quarters of the 56 bacterial isolates were resistant to the eleven tested antibiotics with varied rates as illustrated in Figure 4.

Figure 4: Antibiotic resistance of bacterial isolates against 11 tested antibiotics

B, Bacitracin; C, Chloromphenicol; G, gentamicin; E, Erythrouycin; N, neomycin; NV, Novobocin; P, Pencillin G; RD, Rifampecin; S, Streptomycin; TE, Tetrocyclin and TOB, tobromycin



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4.2.7. Climate change

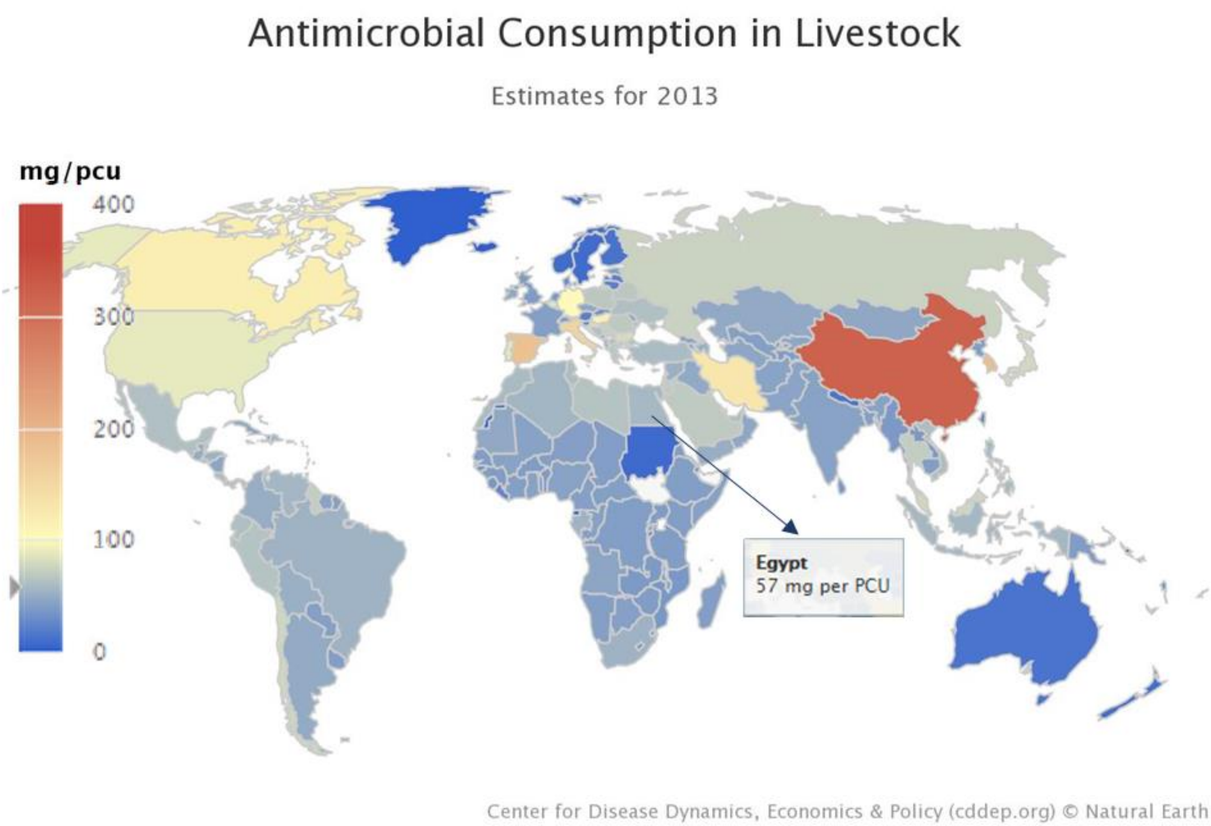
A study in the United States of America found that there was a positive relation between antibiotic resistance rates and rising in temperature (131). A recent study across Europe supported the association between global warming and ABR (132). No evidence was found in Egypt but it might be due to limited research.

4.3. Animal Factors

4.3.1. Agricultural health (Animal husbandry)

Antibiotics are commonly used in livestock as a prophylaxis, a growth enhancer in animal feed or for treatment (133). In 2013, the global consumption of antimicrobials (including antibiotics) in livestock was estimated at 131,109 tons and it is assumed to reach 200 thousand tons in 2030, Figure 5 (134). According to 2013 estimates, the antimicrobial consumption in livestock in Egypt was 57 mg per PCU[xvii] and it is predicted to increase by 11% by 2030 (134). The broad use of antibiotics in animals influence the selectivity pressure leading to emergence of ABR in animals through the regular resistance mechanisms.

Figure 5: Antimicrobial consumption in livestock per country in 2013, with focusing on Egypt (134)



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In Dakahlia, 2% of 600 bovine giblet samples contained Oxytetracycline residues with 1.3% of the total samples were higher than the maximum limits (135). A cross sectional study in Sharkia investigated antibiotic residues in broilers poultry farm samples by testing samples from litter and

[xvii] PCU stands for population correction unit. According to FDA, 1 PCU = 1 kilogram (kg) of biomass of different live and slaughtered animals. It is calculated by multiplying the estimated average weight of animals at time of antibiotic treatment in kg by the total number of live and/or slaughtered animals in the country.

bird droppings (136). Results showed high levels of Tetracycline and Ciprofloxacin residues in poultry waste (136).

Fresh chicken meat and liver samples from retails in Cairo governorate were tested for Tetracycline residues. Forty four percent of total samples showed positive results to Tetracycline with higher incidence in liver samples. Residues that exceeds maximum limits were found in fresh muscle tissues and liver (137).

A study in Alexandria aimed to detect antibiotic residues in laying chicken and their commercial eggs after administration of Amoxicillin. Ninety six percent of fecal samples of the tested laying chickens were positive to the antibiotic residues. Antibiotic residues were detected in white and egg yolk of the chicken eggs, stored in room temperature and at 4°C, up to seven days after last administration with higher amounts in the white eggs than the egg yolks. This explains how the antibiotic use in chickens could spread to its excreta and eggs, which can be transmitted to environment, other animals and humans later worsening ABR problem (138).

The previous results showed that the antibiotic residues detected in animals exceeded the maximum limits, which refers to overuse of antibiotics in animals in Egypt (135,137). They also elaborated how antibiotic residues could spread to animal flesh, products and excreta (135,137). This explains how these residues might later spread to environment through contamination of soil, water and air, and subsequently to humans (136,138). It may also spread directly to humans through consumption of these animals or their products (135,137).

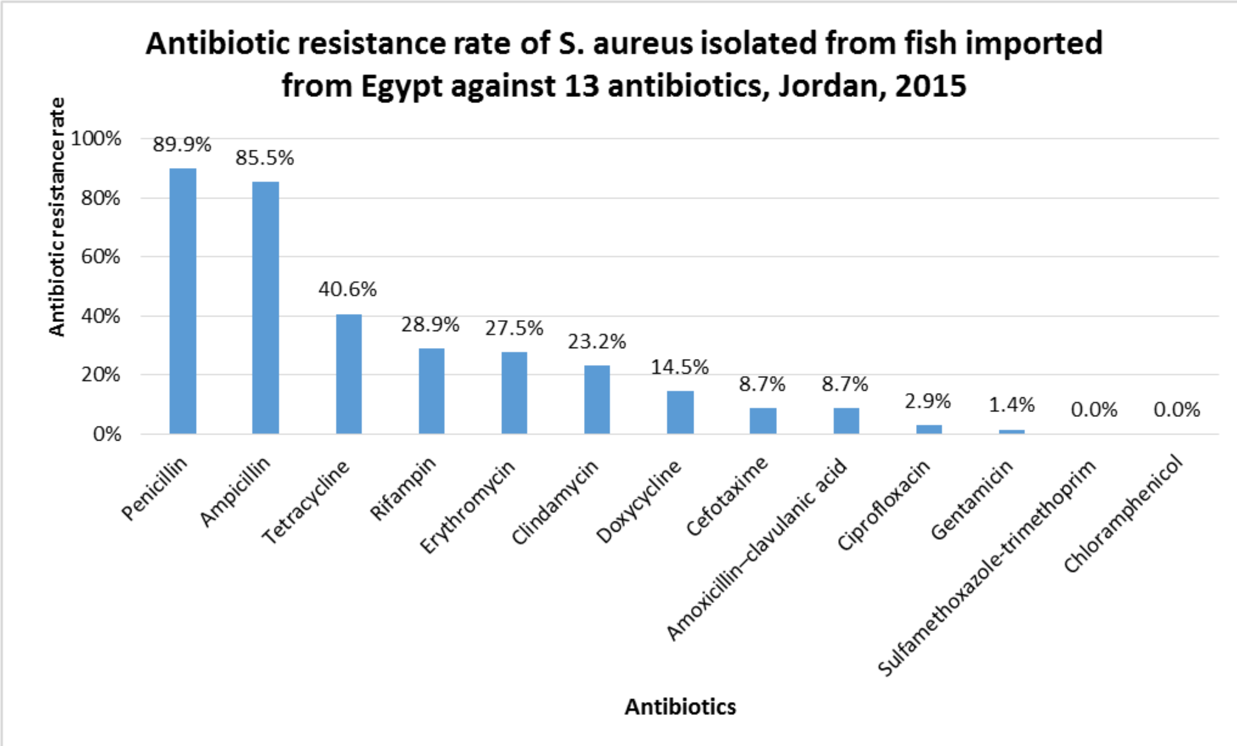
4.3.2. Aquaculture

Antibiotics are used in Egyptian fish farms for preventive and curative purposes, in addition to act as food supplements (139). Using antibiotics in fish farms has a harmful effect since it help in spread of ABR due to antibiotic remnants in fish and the huge amounts of antibiotic residues excreted in water (133).

A study in four Egyptian governorates showed that the prevalence of bacteria in Nile Tilapia fishes was 17.5% (Enterococcus, Streptococcus and Lactococcus species). The Streptococcus isolates were tested against 18 antibiotics revealing the highest resistance against Tetracycline with 94% of the isolates showed multiple resistance activity. The multi-resistance was explained by possible HGT of ARGs (140).

A study in Jordan investigated antibiotic resistance rates of S. aureus isolates from samples collected from fish imported from Egypt. The results showed high resistance rate against Penicillin and Ampicillin, while no resistance at all against Sulfamethoxazole-trimethoprim and Chloramphenicol as shown in Chart 3 (141).

Chart 3: Antibiotic resistance rate of S. aureus isolated from fish imported from Egypt in Jordan



The previous studies showed high resistance rates among bacterial isolates from fish in Egypt. This was attributed to the high antibiotic use in aquaculture as a preventive measure against infections. The resistant bacteria may subsequently spread to fishermen or handlers through direct contact and to consumers as well (140,141).

4.3.3. Wildlife

Antibiotics are not used in wildlife, however, ARGs and resistant bacteria have been detected in wild animals (142). Thus, they are important reservoirs for resistant bacteria and have a crucial role in global transmission of ABR, for instance, migratory birds travel thousands miles carrying resistant bacteria (142).

Despite limited data on transmission pathways of ABR to wildlife, probable routes have been identified (143). Direct contact with infected animals or their waste could spread the resistant bacteria to wild animals (144). Exposure to polluted water with antibiotic residues and resistant bacteria as a result of drainage of animals effluents or treated sewage water in rivers and lakes, leads to ABR transmission to wildlife (143). Wild animals may get resistant bacteria through feeding on animals, animal giblets or aquatic creatures living close to polluted fish farms (143). Exposure to human waste, animal fertilizer or polluted soil can spread ABR to wild animals (142). Wild animals that are close to human life have higher and significant rates of ABR (143).

These wild animals can spread resistant bacteria to other animals through direct contact or through environment; including, water and soil (142). Subsequently, resistant bacteria would spread to humans through food animals, direct contact with carrier and infected animals or through water and environment (142).

No literature found about the relation between wildlife and antimicrobial resistance in Egypt, which might be due to limited research. For this reason studies from other countries were used to find the association. A study in Saudi Arabia found that bacterial isolates from some migratory birds showed MDR activity, thus, it represents a threat to international spread of ABR (145). Another study in Spain showed that samples from Egyptian vultures[xviii] contained antibiotic residues of Fluoroquinolone, which is used frequently in animal husbandry (146). Those findings support the role of wild life in spread of ABR.

4.4. Intersections between different factors

This section discussed the interactions between the previously discussed three factors; human, environment and animal. Some of the previously discussed points were highlighted here again but through relating them to other factors.

4.4.1. Human – Environment interactions

The main human effect on environment leading to spread of ABR is the human waste that might contain antibiotic residues or resistant bacteria. Human waste may be excreted in water of lakes, rivers or seas leading to water pollution. Organic fertilizers might be used form human excreta and irrigation water could be derived from human waste drainage.

Working in farming and plant food processing facilitates the transferring of resistant bacteria and ARGs from soils, drainage water and plants to humans (118,147).

Human waste to environment

According to the WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene (JMP) data in 2015, 61% of Egyptian households have proper safe sanitation properties. On the other hand, 33% have basic latrines, while the data showed that there is no open defection in Egypt (148).

In Alexandria, wastewater of human origin was investigated and the results showed high prevalence of resistant bacteria and ARGs. This results mean that the human waste represent a risk for the environment and could later spread to soil and worsen the ABR problem in Egypt (149).

Industrial waste to environment

[xviii] Egyptian vultures can migrate up to 90 miles a day and a project showed that Egyptian vultures with GPS transmitters traveled from Spain and reached Senegal and Mali (175).

Industrial effluents are discharged in lakes, rivers or seas which increase the risk of ABR emergence and spread especially pharmaceutical industry (105). *(Refer to water section under environment for evidence on presence of pharmaceutical industry waste in water)*

Water to humans

Different channels of exposure to contaminated water with resistant bacteria and ARGs contribute to emergence and spread of ABR from environment to humans.

A study in Egypt examined the prevalence of ABR in indoor and outdoor swimming pools. The study showed that 34.6% of total P. aeruginosa isolates showed MDR activity against tested antibiotics. This result illustrates the probable risk of transmission of resistant bacteria through swimming or bathing in contaminated water (150).

Different studies detected resistant bacteria in drinking water *(Refer to section water under Environment factors).* These results showed how ABR could spread from environment to humans through water consumption (102).

Food plants to human

ABR could spread through human consumption of vegetables or fruits that contain resistant bacteria or ARGs. This might be attributed to use of contaminated water in irrigation or extensive use of antibiotics in vegetation for nourishment purposes of soil (114,115).

4.4.2. Human – Animal interactions

Food animals

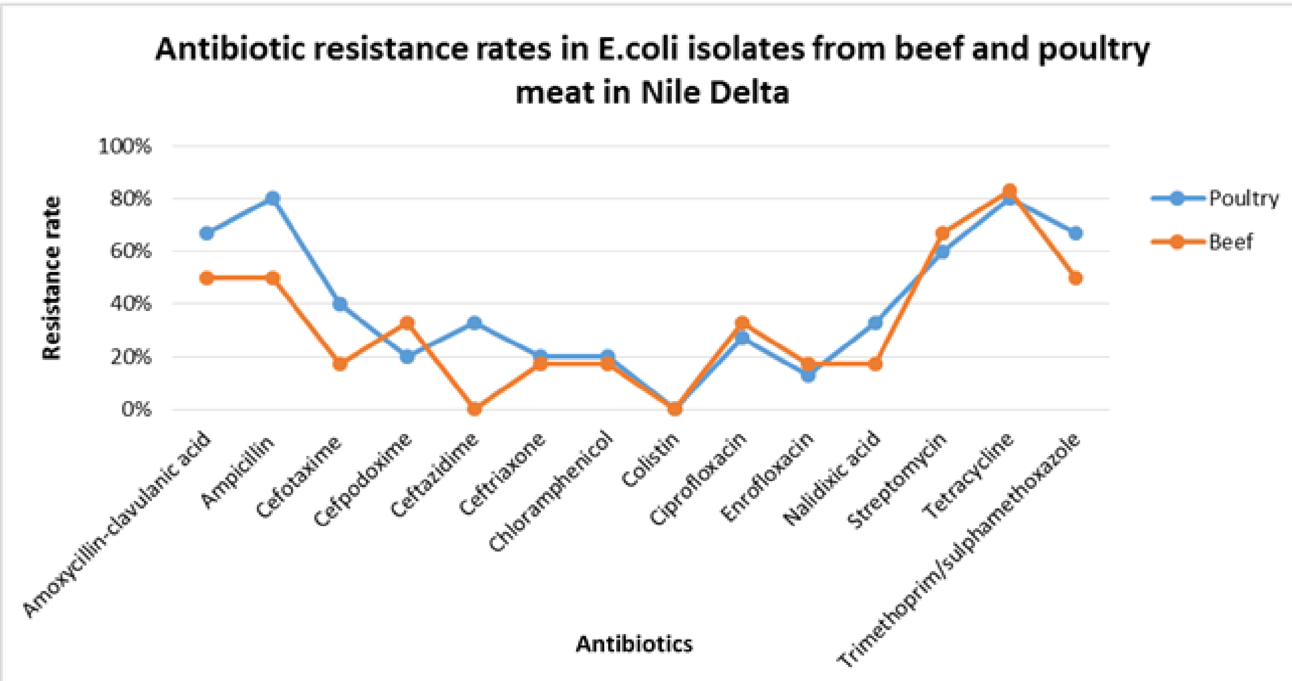
Human consumption of food containing antibiotics residues or ARB leads to ABR spread from animals to humans (151). This includes eating of contaminated raw or undercooked meat, meat products and fish (151,152). Food could be contaminated through different ways; including, unsanitary slaughtering and food processing practices, antibiotic residues in water and animal tissues (152).

According to the previously mentioned study in Alexandria *(under animal husbandry section)*, antibiotic residues in boiled commercial eggs whose laying chicken received Amoxicillin for three days were recorded (138). The results showed that the amount of Amoxicillin residues that were detected in raw eggs for up to seven days after last administration were the same after boiling eggs for ten minutes (138). The previous results demonstrate that antibiotic residues in eggs can stand under high temperatures (138). Thus, it could be transmitted to humans by eating those eggs leading to ABR through previously illustrated mechanisms (138,153).

A study in Cairo investigated the resistance pattern of isolated foodborne bacteria from beef meat samples from retails. All bacterial isolates showed different resistance rates ranged from 14.8% against ampicillin-sulbactam to 100% against sulphamethoxazole/trimethoprim. All isolates except one species had at least two ARGs in addition to the MDR pattern. Hence, resistant bacteria and ARGs could spread to humans through consumption of undercooked meat, direct contact or from aerosols (154).

A study aimed to determine the prevalence of ABR in two types of enteric bacteria isolated from fresh beef and chicken meat was conducted in Nile Delta. Both bacterial species (E.coli and Salmonella Enterica) showed different ABR rates with detection of ARGs in all beef and chicken meat samples. E.coli isolates from poultry meat showed higher resistance rates than isolates from beef meat as clarified in Graph 1 (155).

Graph 1: Antibiotic resistance rates in E.coli isolates from beef and poultry meat samples in Nile Delta against 14 antibiotics



In Dakahlia, 5.3% of total S.aureus isolates were positive to mecA gene[xix], the S.aureus were isolated from raw milk, Kariesh local cheese and ice cream (99). Other studies in Egypt showed high ABR rates and isolation of ARGs from dairy products and local cheese (156–158). The previous findings might be attributed to poor hygiene practices during processing of dairy products (158). Studies showed the probable risk of ABR in fish were discussed before *(Refer to aquaculture section under animal factors).*

The previous results showed how ARGs and resistant bacteria could spread from animals to humans through consumption of food animal. The results also suggested that lack of hygiene may transfer the resistant bacteria to humans.

[xix] mecA gene is the methicillin resistance gene which is present on bacterial DNA and responsible for generating resistance against different antibiotics (176).

Animal companion

Direct contact between animals and humans may result in transmission of resistant bacteria or ARGs from animals to humans or from humans to animals. Occupations involve close contact with animals and animal products induces the transmission risk of resistant bacteria increasing ABR prevalence (98,99,147). *(Refer to occupational health section under human factors)*. The increasing number of owing pets or domestic animals increase the risk of spread of ABR between humans and animals (133).

A study in Cairo investigated the probable relation between human health and existence of MRSA[xx] in pet animals; dogs and cats (159). Results showed a positive dog sample to MRSA and a positive human sample of its companion person to MRSA. Both MRSA isolates from the dog and its companion person were phenotypically the same and showed identical antimicrobial reactions to the thirteen tested antibiotics, as illustrated in Table 2. This highlights the probability of cross infection in between animals and humans of serious pathogens like MRSA, which exacerbates the ABR problem (159).

Table 2 : The Antibiotic susceptibility pattern of methicillin-resistant Staphylococcus Aureus isolates from pet and human samples (A study in Cairo) (159)

Tested Antibiotics	Antibiotic susceptibility pattern	
	Dog 2 oral isolate	Human (contact to dog 2) nasal isolate
Ampicillin	Resistant	Resistant
Ciprofloxacin	Sensitive	Sensitive
Gentamicin	Sensitive	Sensitive
Cefoxitin	Resistant	Resistant
Clindamycin	Sensitive	Sensitive
Rifampicin	Sensitive	Sensitive
Sulphamethoxazole/trimethoprim	Sensitive	Sensitive
Tetracycline	Sensitive	Sensitive
Oxacillin	Resistant	Resistant
Vancomycin	Sensitive	Sensitive
Erythromycin	Resistant	Resistant
Penicillin	Resistant	Resistant
Cefotaxime	Resistant	Resistant

[xx] MRSA stands for Methicillin-resistant staphylococcus aureus. It is gram positive bacteria and it causes serious illnesses that might lead to death due its high virulence and resistance against different antibiotics (177).

4.4.3. Animal – Environment interactions

Food and water sources from environment to animals

Animals might feed on the natural plants, which might carry ARGs and resistant bacteria. These bacteria could be passed to humans through different ways; such as, direct contact with this polluted soil, consumption of plants cultivated in this soil, consumption or consumption of water from wells attached to this soil (127,160).

Animal waste to environment

Different studies in Egypt showed evidence of high prevalence of ABR in animal waste, which can be easily spread to environment and increase ABR. Additionally, animal waste might be used as manure to soil increasing the risk of ARGs and resistant bacteria transmission from animal to environment (136,138).

Chapter 5: Discussion

ABR is a major risk to public health of humans, animals and environment. ABR leads to hundred thousands of humans each year. This review showed a comprehensive view about the contributing factors of ABR emergence and transmission in Egypt.

Reviewing human-related factors revealed that the pattern of antibiotic use in humans has a huge role in ABR emergence and transmission. Evidence showed that antibiotics in Egypt are irrationally consumed. The individual factors precipitate to that pattern of use included lack of knowledge and misleading beliefs, and wrong practices.

Different studies supported the low level of knowledge of among community members about antibiotics proper use with opposing information. For instance, the individuals practiced self-medication and believed antibiotics is a prophylaxis against common cold, refused unneeded prescription of antibiotics. Additionally, others who knew consequences of misuse of antibiotics, were discontinuing antibiotic course on feeling better. Additionally, some studies found a significant relation between lack of knowledge and level of education while others not.

These results highlighted the poor perceived knowledge among community members regardless their educational level or socioeconomic level. This urges the need of a mass campaign to raise awareness about antibiotic use and resistance. This action would engage community in the process of combating ABR in Egypt. Furthermore, better health insurance coverage may encourage people to visit physicians and continue antibiotic courses when properly prescribed. A noteworthy point here about consulting pharmacists for medical cases, many of community pharmacy attendants in Egypt are not pharmacists nor health-affiliated staff (74,76). Thus, getting and advice from pharmacy attendants would exacerbate the inappropriate antibiotic use.

Other determinant of antibiotic use pattern was the prescribers themselves. Evidence showed average level of knowledge among healthcare professionals which negatively affect their decision on antibiotic prescribing. Moreover, weak monitoring and enforcement of laws and regulations regarding antibiotic dispensing has a rough influence on ABR in Egypt. Hence, the proper regulations, guidelines and strong monitoring system would help in addressing this point.

Additionally, absence of well-structured surveillance system for ABR in Egypt is a huge barrier to introduce useful interventions due to lack of information about ABR pattern in Egypt. Establishment of a reliable surveillance system would help in combating ABR. Not to mention the important role of research gap in Egypt, which needs strong support by the government.

The reviewed studies about environment-related factors highlighted the gap in surveillance of ABR in environment. All the studies were independent work, yet no national surveys by the authorities was found. This refers to the lack of well-established surveillance system to estimate the burden of ABR on the environment in Egypt.

No studies were found by literature search about the regulations on antibiotic use in cultivation. This refers to weak regulatory system along with lack of research on antibiotic and ABR in plant environment in Egypt. However, some evidence was found about the presence of antibiotic residues in plants, which might be later consumed by animals or humans leading to emergence of ABR.

The results from wastewater showed resistance among bacterial isolates against the highly used antibiotics by humans. This means that at some point no antibiotics would work against any human infection leading to high morbidity and mortality rates. The evidence of association between ABR and climate change would be really important with the ongoing global warming and needs further researches.

Strong regulations on waste water treatment is needed with proper and clear guidelines, also, the water treatment plants could be used as surveillance sites. This would help in better understanding of ABR pattern in Egypt. Due to scarcity in water resources in Egypt, wastewater is used in irrigation, which increase the probability of ABR transmission.

The immense amount of antibiotics used in animals threatening the animal lives as much as human lives and environmental ecosystem. Limited surveillance data about ABR among animals is a big gap and needs to be tackled.

Limited surveillance data among animals prevent effective interventions due to absence of information on ABR pattern and resistance rates. Results of possible risk of pets and domestic animals should be taken seriously since there is increasing rate of getting domestic animals. Serious precautions should be taken towards wild animals since they can spread the ABR globally and not only on local level.

Research focus on detection of resistant bacteria or antibiotic residues, although, limited researches focused of relating them to each other to give clear evidence about the relation in Egypt to design tailored interventions to the situation in Egypt.

Interventional studies would help in understanding the environmental contributing factors to ABR in Egypt. Additionally, they will lead the authorities to the proper interventions. A good example of that the surveillance pilot in hospitals in Egypt, which gave a good grasp about ABR pattern among patients in these hospitals.

Chapter 6: Conclusion and recommendations

Conclusion

The review showed the main contributing factors to emergence and spread of antibiotic resistance (ABR) in Egypt from a one health perspective. Extensive and inappropriate use of antibiotics in humans, animals and farming is one of the key drivers of ABR. Poor awareness among community members and healthcare professionals increase ABR emergence and spread.

Lack of strict regulations and monitoring on antibiotic dispensing facilitates ABR emergence. On the other hand, lack of data about ABR pattern in Egypt due to limited surveillance system acts as a barrier to effective interventions and hinders efforts to combat ABR in Egypt.

Research should be encouraged for better understanding of the leading causes to cover the gaps and to design useful interventions fits in the current situation in Egypt. Strict regulations and policies on antibiotic use in humans, animals and for farming purposes would help in decreasing the spread of antibiotic residues and as a result decreasing emergence of ABR.

Urgent integrated interventions are needed from all involved stakeholders to combat the problem of ABR in Egypt. Strong surveillance system should be implemented to detect the prevalence and incidence of ABR in humans, animals and environment. Decision-makers in Egypt should commence and enforce the drafted national comprehensive action to fill in gaps and tackle ABR.

Recommendations

This review is an individual step to give a comprehensive view about the ABR problem in Egypt. Yet authorities in Egypt should take serious interventions to address knowledge gaps and to combat ABR.

Based on the results of this review, the following recommendations are suggested to decision-makers in different involved stakeholders in Egypt to help in tackling the problem of ABR:

1- **Egyptian ministry of health and population (MOHP) should regulate the antibiotic dispensing in Egypt.**
   This could be done through development of proper policies, reinforce the law and publish national guidelines on antibiotic use with strict monitoring of antibiotic prescribing and dispensing.
2- **MOHP, ministry of agriculture and land reclamation, ministry of environment should cooperate to combat the ABR in Egypt.**
   This could be done through enforcing the drafted action plan to combat the ABR in Egypt in addition to establish an integrated surveillance system to provide information about the ABR pattern in Egypt.
3- **Research on ABR should be increased to find the actual relations between different contributing factors and to define gaps in current interventions.**

This could be done through increasing allocated fund to research in Egypt, particularly, on ABR problem since this is considered an investment to avoid the huge economic costs in the future.

4- **Increase community and health professional knowledge about antibiotics and ABR.** This could be done through mass campaign to promote community awareness about antibiotics and ABR. Additionally, provide intensive training programs for healthcare professionals on antibiotics and proper prescribing.

Study Limitations

Since interventions to tackle and combat ABR was initiated in recent years, there is no clear or definite data on prevalence of the problem, subsequently, data from different studies cannot be generalized. Figures used in this review indicates to the magnitude of the problem, however, they are not precise since surveillance data are limited.

Finding a suitable framework to use it as a guidance through the review was challenging. Lebov framework was found to be the best organized framework to follow, however, it lacked serious factors and included less relevant factor. To address this limitation, the framework was adapted.

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100. Supratim Choudhuri, Chapter 2 - Fundamentals of Molecular Evolution**The opinions expressed in this chapter are the author’s own and they do not necessarily reflect the opinions of the FDA, the DHHS, or the Federal Government., Editor(s): Supratim Choudhu.

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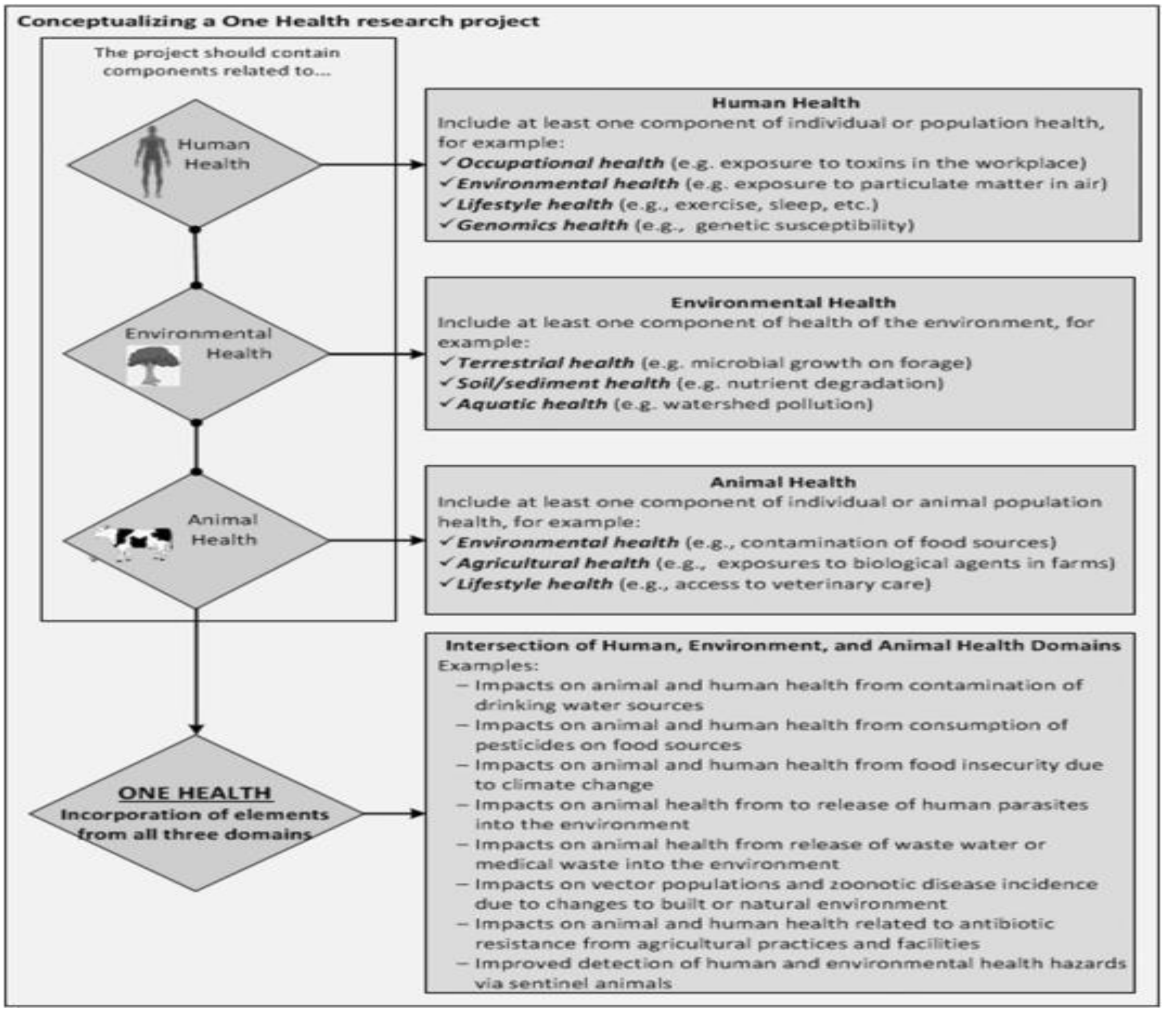
Annexes

Annex 1: Detailed literature search strategy

Problem	AND	Search words	AND	Geography

- Antimicrobials - Antimicrobial resistance - Antibiotics use - Antibiotics prescription - Antibiotics misuse - Antibiotics remnants	OR	- Epidemiology - Trends - Incidence - causes - Age - One health - Humans - Human factors - Human health - Policy - Policy gaps - Strategies - Stewardship - Surveillance - Infection control - Health system - Occupational health - Hospital-acquired - Genomic health - Culture - Community awareness - Human lifestyle health - Health professionals awareness - Industry factors - Interventions - Human to human transmission - Gene mutations - Human waste residues - Hygiene - WASH measures - Animals - Animal factors - Animal health - Animal to human transmission - Animal lifestyle health - Environment health - Agricultural health - Food - Food consumption - Food safety ± policy - Soil health - Agriculture - Growing corps - Fertilizers - Terrestrial health - Aquatic health - Water - Drinking water - Aqua	OR	- Global - Worldwide - Middle east - Africa - North Africa - Egypt - Lowe-middle income countries

Annex 2: A developed framework for one health research by *J. Lebov et al*



Annex 3: Conceptualization model of *J. Lebov et al* framework for one health research by