INTRODUCTION

Nowadays, the development of antibiotic resistance represents one of the most important issues of the global public health. The incorrect use of antimicrobial drugs is recognized as one of the leading causes of antibiotic resistance.

It was estimated that 80% of antibiotic use is in the community while only 20% in the health care facilities. ***(Kotwani and Holloway, 2011).*** Therefore, a better understanding of the existing pieces of evidence pertaining knowledge, attitudes and practice 'KAP' regarding antibiotic and antibiotic resistance in the population and particularly for children who frequently receive antibiotics is important.

Antibiotics invention transformed the practice of medicine, as they have improved morbidity and mortality all over the world so they are considered one of the blesses to humanity. But the drawbacks of its use are considerable, whether, on the individual or the community basis. Such as adverse effects, allergic reactions and importantly the resistance.

By definition "Antimicrobial resistance is the resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it" ***(WHO, 2015).***

The cost of the problem is lives, each year, in the United States, at least 2 million people become infected with resistant bacteria and at least 23,000 people die as a direct result of these infections ***(CDC, 2016).*** While it is about 25,000 deaths in Europe with multidrug-resistant bacteria ***(ECDC, 2009).*** This can affect any individual whether he is a regular antibiotic consumer or not.

Resistance is complex and multi-factorial, but relation between misusing antibiotics and the development of resistance has been proved. Higher antibiotic consumption is sufficient to cause resistance in the community on a long term ***(Goosens et al., 2005; Chung et al., 2007).***

Public awareness gains more importance in the developing countries where antibiotics are one of the most commonly sold drugs ***(Buke et al., 2003).*** With no strong regulatory machanisms to limit their use, antibiotics are perceived as Over the Counter "OTC" drugs. It was estimated that nonprescription use of antibiotics can range from 19 percent to well over 90 percent outside the United States and Europe ***(Morgan et al., 2011).***

Variable misconceptions regarding antibiotics were reported, including beliefs and expectations for their effectiveness against several minor illnesses as flu, up to using them as analgesics, antipyritics and for prophylaxis ***(Aboul Fotouh et al., 1998; Shehadeh et al., 2012),*** despite that physicians are the main source of knowledge about antibiotics as showed by many KAP studies for adult patients or parents ***(Pavydė et al., 2015; Al Dossary, 2013).***

As regards practice, self medication with antibiotics is considered a routine practice for many patients (78.7%) and parents (53.8%) as showed by Saudi studies of ***(Al Rasheed et al., 2016; Eldalo, 2013)*** respectively**,** using un-prescribed antibiotics, left-overs from previous illness or even using other adult relative's or friend's antibiotic for children ***(Abobotain et al., 2013)*** and lack of proper adherence to antibiotics regimens and instructions for use were reported.

Self medication with unprescribed antibiotics is evident in Egypt as proved by a study in Cairo that showed 53.7% of the respondents used antibiotics over the past 3 months, 29.8% were un-prescribed. Survey of 6 pharmacies revealed antibiotics to be 22.5% of the total sales with 86% of them un-prescribed. Highest sales were for Penicillins, for both prescribed and un-prescribed ***(El Masry et al., 2013).***

Orientation about antibiotic resistance and the fact that all antibiotic use, appropriate or not, "uses up" some of the effectiveness of that antibiotic, diminishing our ability to use it in the future is important to fight against resistance, as the lack of knowledge positively correlates with a higher prevalence of resistance ***(Grigoryan et al., 2007).***

In a WHO multicountry survey, only 22% of participants from Egypt knew the term antibiotic resistance "the lowest proportion of any country included in the survey" ***(WHO, 2015).***

Although when most of parents thought that antibiotic misuse increases bacterial resistance, in Cyprus 85% of them believed scientists always discover antibiotics against resistant microorganisms ***(Rousounidis et al., 2011),*** and in Palestine 70.1 % would still give antibiotics to their child because they thought this would lead to a faster recovery ***(Zyoud et al., 2015),*** so comprehensive knowledge of the real impact is needed.

AIM OF THE WORK

Research question:

Do the Egyptian parents have the appropriate knowledge, attitude and practice about antimicrobials use for their infants and children?

Goal:

The aim of this study is to improve KAP of Egyptian parents regarding antimicrobials for infants and children, so as to help decreasing antimicrobials resistance and their adverse effects.

Objectives:

1. To asses knowledge, attitude and practice of parents about antimicrobials use for their infants and children.
2. To identify factors affecting knowledge, attitude and practice of the parents about antimicrobials use.

Chapter 1
OVERVIEW OF ANTIBIOTICS

Antimicrobials include among others: Antibacterials (The so often called antibiotics), Antimycobacterial drugs, Antivirals, Antifungals and Antiparasital drugs ***(ECDC, 2016).***

Historical Preview

Antimicrobials are probably one of the most successful forms of chemotherapy in the history of medicine. Significantly they have contributed to the control of the leading cause of human morbidity and mortality along human existence, the infectious diseases. Perhaps equally important, they have facilitated the vast expansion of other medical interventions, such as kidney and heart transplants, by allowing clinicians to prevent surgical site infections and infections in immuno-suppressed patients, such as organ recipients ***(Aminov, 2010).***

The era of antibacterials began with the discovery of arsenic-derived synthetic antibiotics by Alfred Bertheim and Paul Ehrlich in 1907. in 1909 they came across the sixth compound in the 600th series tested, thus numbered 606 that showed significant promise for the treatment of patients with Syphilis in trials on humans ***(Ehrlich and Hata, 1910).*** Despite its side effects, the drug, marketed under the name Salvarsan, was a great success and, together with a more soluble and less toxic Neosalvarsan, became the most frequently prescribed drug until its replacement by penicillin in the 1940s ***(Mahoney et al., 1943).***

In 1942, Penicillin G was the first successfully purified penicillin as a therapeutic drug by Chain and Florey after the accidental discovery of the penicillin by Sir Alexander Fleming in 1928. The three shared the Nobel Prize in 1945 ***(Florey, 1945).***

With its development, infections that were previously severe and often fatal, like bacterial endocarditis, bacterial meningitis and pneumococcal pneumonia, could be easily treated.“the difference with treatment was so clearly apparent that no one even thought of doing a randomized controlled trial” **(Theodore C. Eickhoff. MD)** ***(Kalvaitis, 2008).***

New paradigms were set for future drug discovery research. The period between the 1950s and 1970s was indeed the golden era of novel antibiotic classes discovery, with nearly no discovered new classes since then. Therefore, with the decline of the discovery rate, the main approach for the development of new drugs to combat pathogen’s emerging and re-emerging resistance to antibiotics has been the modification of existing antibiotics ***(Chopra et al., 2002).***

In fact, many of the antibiotics developed and approved in recent years did not respond to needs and were withdrawn for lack of market share and safety issues ***(Gelband et al., 2015).***

Adverse effects of Antibiotics

Among children antibiotics are the most common drug class implicated in Emergency Department (ED) visits for adverse drug events (ADEs) ***(Shehab et al., 2016).***

Antibiotic Associated Diarrhea (AAD) is not uncommon side effect, with estimated overall incidence of 6.2% to 11% in two pediatrics outpatient care settings. A higher incidence is associated with the amoxicillin/clavulanate ***(Turke et al., 2003). (Damrongmanee and Ukarapol 2007)*** and with intravenous broad-spectrum antibiotic therapy ***(Haran et al., 2014).***

In general, pediatric AAD have a more rapid onset of symptoms, a shorter duration and fewer complications than in adults ***(McFarland et al., 2016).***

Most of the AAD would respond to only discontinuation or change of the antibiotic, while 15% will appear in the week following stopping antibiotic ***(Turke et al., 2003).***

Antibiotic treatment destabilizes the balance of intestinal microflora by killing off large numbers of bacteria, allowing C. difficile, which is naturally resistant to most antibiotics, to proliferate. C. difficile can be thought of as a serious adverse event related to antibiotic use, whether appropriate or inappropriate ***(McDonald et al., 2012; CDC, 2013).*** The infection can be lethal, especially to those with impaired immune systems or other serious comorbidities ***(Fridkin et al.,***

2014), and is responsible for more than 14,000 deaths and 250,000 infections per year in the United States ***(CDC, 2013).***

Although hospitals are the source of most C. difficile infections, those infections may originate in outpatient settings ***(Lessa et al., 2015; McDonald et al., 2012)***. Antibiotic use increases the risk of C. difficile infections by seven- to 10-fold for up to one month after discontinuation ***(Brown et al., 2015; Hensgens et al., 2012).*** A 30 percent reduction in the use of broad-spectrum antibiotics in hospitalized patients could reduce the incidence of C. difficile infection by 26 percent ***(Fridkin et al., 2014).***

Hypersensitivity (HS) may occur causing rashes, phlebitis or angioedema and even anaphylaxis. Cross allergy can happen between beta lactam antibiotics.

The skin tests are safe, and successfully diagnose immediate hypersensitivity reactions to beta-lactam antibiotics in children, with low diagnostic and predictive values for nonimmediate HS. In contrast, most accelerated and delayed reactions can be diagnosed by Oral Challenge test ***(Ponvert et al., 1999).***

Drug-induced eosinophilia is common with parenteral antibiotics. Although most patients with eosinophilia do not have HS reactions, eosinophilia increases the hazard rate of having rash and renal injury ***(Blumentha et al., 2015).***

Long term antibiotic therapy in pediatrics is associated with development of ADEs to 42% of patients, with a fourfold increase in the rate of ADEs with I.V. antibiotic agents compared with oral agents ***(Murphy et al., 2016).***

Various long term associations with antibiotics use were proved, such as increased risk of early-onset childhood asthma that began before 3 years of age with dose response relationship when antibiotics were used in the first year of life ***(Ong et al., 2014).***

Also, early exposure to antibiotics is associated with increased body mass in healthy 24 months children ***(Saari et al., 2015),*** and in boys aged 5-8 years in a large international cross-sectional survey on a total of more than 70000 children from 31 centers in 18 countries ***(Murphy et al., 2014).***

Chapter 2

ANTIBIOTICS CONSUMPTION

A major driver of antibiotic resistance is antibiotic use which is fueled by the high background burden of infectious disease in low and middle income countries (LMICs) and easy access to antibiotics in much of the world, which increases both appropriate and inappropriate use.

Two trends are contributing to a global scale-up in antibiotic consumption. First, rising incomes and increasing access to antibiotics. Second, the increased demand for animal protein and resulting intensification of food animal production is leading to greater use of antibiotics in agriculture ***(Gelband et al., 2015).***

Between 2000 and 2010, total global antibiotic consumption grew by 36 percent, based on data from 71 countries, including most high population countries ***(Van Boeckel et al., 2014).*** In most countries, antibiotic consumption varied significantly with seasonal infections, such as influenza ***(Polgreen et al., 2011).*** Per capita consumption is generally higher in high-income countries, but the greatest increase in antibiotic use between 2000 and 2010 was in LMICs, where use continues to rise.

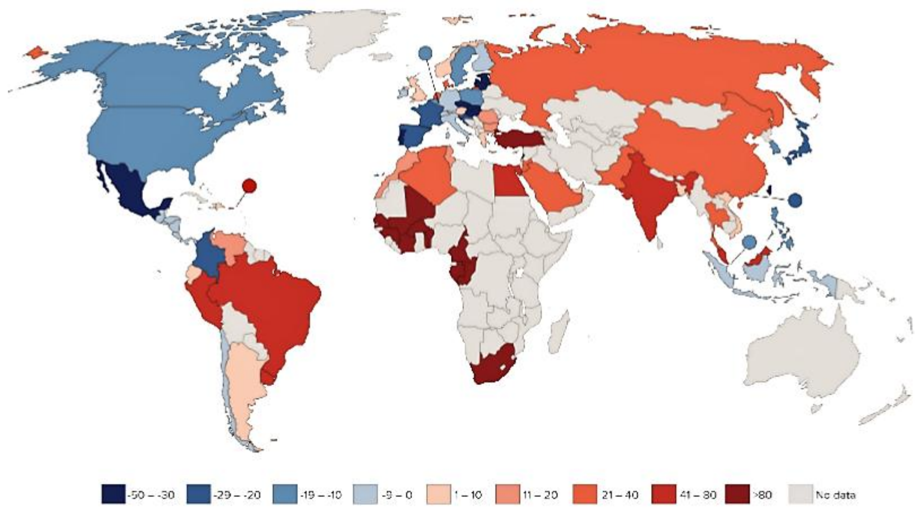

Figure (1): Percentage change in antibiotic consumption per caplta 2000-2010*, by country ***(Van Boeckel et al., 2015).***

Penicillins and cephalosporins accounted for nearly 60 percent of total consumption in 2010, increasing by 41 percent from 2000. Among the oldest antibiotics on the market, these are still the most common first-line antibiotics and the primary treatment for common infections around the world ***(Van Boeckel et al., 2014 based on IMS).*** This applies for Egypt as shown in figure (2).

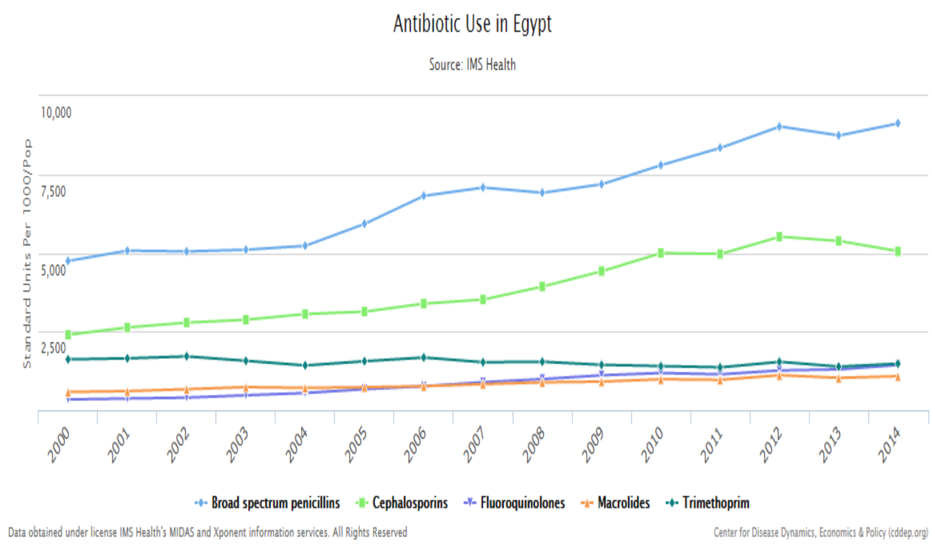

Figure (2): By Resistance Map, an interactive, data-rich visualization tool, brings together the most current antibiotic resistance surveillance statistics from the United States, Europe, and many LMICs (www.resistancemap.org). Data about resistance in Epypt was deficient.

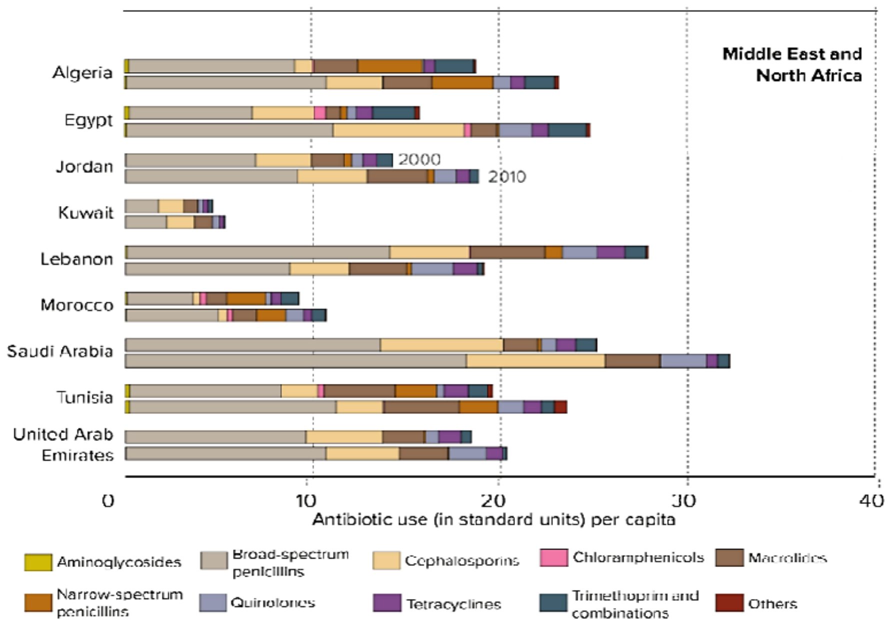

Figure (3): Antibiotic consumption per capita by class and country, 2000 and 2010, Source: ***Van Boeckel et al. (2014)*** (adapted; based on IMS)

Worldwide, increases were also significant for two "last-resort" antibiotic classes: carbapenems (approximately 40 percent) and polymixins (13 percent) ***(Van Boeckel et al., 2014).*** The growth in retail carbapenem (which is a class of beta-lactams chiefly employed against Gram-negative infections) sales was particularly steep in India, Pakistan, and Egypt (some drugs may have been prescribed in hospitals and filled at a pharmacy) ***(Laxminarayan et al., 2013).***

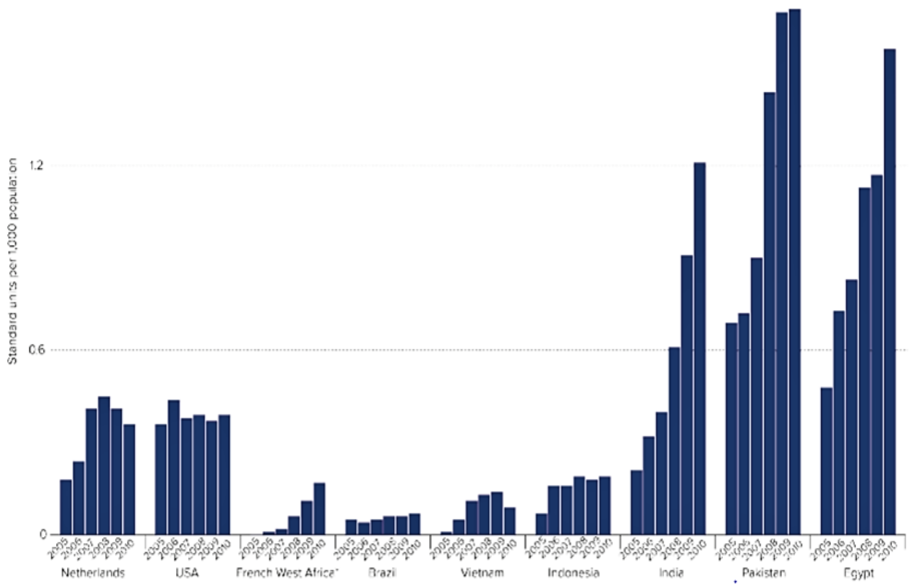

Figure (4): Carbapenem retail sales in selected countries, 2005-2010 (per 1,000 population) ***(Laxminaravan et al., 2013)*** (Based on IMS MIDAS).

In most countries, about 20 percent of antibiotics are used in hospitals and other healthcare facilities, and 80 percent are used in the community, either prescribed by healthcare providers or purchased directly by consumers or caregivers without prescription ***(Kotwani and Holloway, 2011).***

The prevalence of antibiotic use in Egyptian hospitals was high with obvious targets for antimicrobial stewardship activities including provision of antibiotic prescription guidelines and optimization of surgical and medical prophylaxis practices ***(Talaat et al., 2014).***

Antibiotics in Animal Production

Antibiotics have been used to treat and prevent infections in animals for as long as they have been widely available. They also have a surprising ability to accelerate animal growth. Currently, more antibiotics are used in poultry, swine, and cattle to promote growth and prevent disease than are used by the entire human population. Though the figure is based on incomplete data, an estimated 80 percent of all antibiotics consumed in the United States are used in food animals ***(U. S. FDA, 2010).*** Worldwide, in 2010, at least 63,200 tons of antibiotics were consumed by livestock, likely to be more than all human consumption ***(Van Boeckel et al., 2015),*** this is projected to rise to meet the demands of the increasing human population.

Proof that antibiotic use in animals (particularly for growth promotion, and to a lesser extent for prevention) has a significant effect on human health has been growing. Poultry, cattle, and swine raised with antibiotics harbor populations of antibiotic-resistant bacteria, which are transmitted to humans through direct contact with the animals and through their meat, eggs, and milk ***(Marshall and Levy, 2011).***