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New Initiative in Ecuador, The Creation of a National Reference Laboratory for Antibiotic Resistance

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Abstract

Antibiotic resistance is a serious issue everywhere. Today, highly resistant strains are not just found in hospitals but are ever more present in the community. Immediate action is required to understand the true state of resistance and minimize the risks of further escalation of the problem. Throughout the world there is concern that resistance to high spectrum Carbapenem antibiotics is on the rapid increase. Latin America has more reason than most to be alarmed as there is a higher rate of these enzymes being reported there than in any other continent, with some enzymes solely found in Latin American countries.

To date, there have been no comprehensive epidemiological studies published internationally on the state of antibiotic resistance and carbapenems resistance from Ecuador. Apart from the obvious need to observe and control resistance and outbreaks within the country, Latin America having high rates of resistance makes any additional data invaluable to the international scientific community. Due to the serious concerns growing over antibiotic resistance, the Ecuadorian government has appointed the laboratory of the National Institute of Research in Public Health (INSPI) Quito, the national antibiotic reference lab.

Keywords: Antibiotic resistance; Latin America; Ecuador; Carbapenemases

Introduction

The era of antibiotics started in 1940 with the introduction of penicillin [1]. Diseases that use to cause millions of deaths started to fade in importance as these potent therapies started to cure diseases previously untreatable. But soon, abuse, lack of effective antibiotic usage policies, together with the ability of bacteria to adapt and evolve, have created a new reality; the era of resistant superbugs.

Super-resistant bacteria are not just nosocomially acquired [2,3], but are also present in the community, meaning that super bugs are no longer concentrated and therefore are unmanageable and disastrous prognoses more frequent. The mechanisms of action of different antibiotic families are shown in (Table 1) and the mechanisms of resistance to them in the (Table 2).

The causes of the increase in antibiotic resistance are diverse, auto-medication, inadequate usage, increased usage of antibiotics in livestock as a growth promoter are to name but a few [4].

Antibiotic target	Antibiotic famiy
Celular Wall	β-lactams and vancomicin
Synthesis DNA/RNA	Fluoroquinolones, Rifamicin
Synthsis folato	Trimetropin, Sulfonamides
Cellular membrane	Daptomicin, Polimixin
Protein synthesis	Linezolid, Tetraciclins, Macrolides, Aminoglicosides

Table 1: Mechanisms of action of the most frequently used family of antibiotics.

Mechanism of resistance	Antibiotic family
Efflux pumps	Fluoroquinolones, Aminoglicosides, Tetraciclin, Beta-lactams, Macrolides
Inmunity and Bypass	Tetraciclines, Trimetropin, Sulfonamides
Modification of the target	Fluoroquinolones, Rifamicin, Vancomicin, Penicilin, Macrolides, Aminoglicosides
Inactivation of the antibiotic by enzymes	Beta-lactams, aminoglicosides, Macrolides, Rifamicin

Table 2: Mechanisms of resistance of the different antibiotic families.

Some groups are working in the development of new therapies, one example is quorum sensing as a target, this is just the beginning, but some papers have shown promising results *in vitro* [5].

Nanotechnology is another line of research that has shown great promise *in vivo* in animal models, where drug delivery systems have been developed to release antibiotic in a specific manner [6,7]. Nano coatings have also shown great potential in medical devices, in the prevention of biofilm formation.

On the 21st of April 2004 the "Centre for Diseases Prevention and Control" started with the purpose of performing epidemiological studies. Soon after beginning its' task it became clear that decisions needed to be made and antibiotic policies adjusted. Since then their reputation as leading experts in disease control policies has increased world-wide.

However antibiotic resistance is one of the biggest threats facing our world. A WHO article published by the Latin America network of antibiotic resistance on the 7th of April 2011 [8], advised that 80% of medical treatments are empiric. Empiric treatment of patients relies on unnecessary guess work that can seriously delay correct treatment, to the detriment of the patient's health, but other unintended effects are an increase in the creation of resistant strains and an increase in cost of patient care due to change of therapy and increased time hospitalized.

In the report of, Ears-net reporting protocol 2013, the "European antibiotic resistance surveillance network" [9], established that

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antibiotic resistance and other infectious diseases treatments, are causing big problems in European health care because of the cost increases attributed to patient care, failure of treatment and in worst case scenario, the death of the patient.

The aim of this paper is to evaluate the situation of Ecuador, the lack of resistance data nationally and internationally, the need for a national reference laboratory capable of characterizing antibiotic resistance as well as possible new mechanisms.

Alarming Increase of Carbapenemases

Carbapenems are a group of high spectrum antibiotics that are often used in infections produced by gram negative bacteria that harbour high resistance to other antibiotics such as cephalosporin. The increase in the resistance to cephalosporins and the high antibiotic pressure that exists today has made bacteria quickly evolve several mechanisms of resistance to these high spectrum antibiotics.

Resistance to carbapenems can be due to chromosomal AmpC overexpression; reduction in porins or efflux pumps but alarmingly the number of enterobacteriaceae that carry a carbapenemase is increasing rapidly. KPC (carbapenemase form *Klebsiella pneumoniae*) was first identified in North Carolina (USA) in a *K. pneumoniae* that had been isolated in 1996 [10]. Since this mechanism of resistant was identified, the number of isolates that carries KPC has increased all around the world. KPC was first reported In Colombia in 2005 [11].

Already Fritsche et al. [12], reported the increase in the number of isolates that carried carbapenemase. In the results obtained by the SENTRY network, that compiled samples from all around the world, they reported that throughout South America there were high rates of *P. aeruginosa* isolates resistant to imipenem, 44.8% of all Brazilian *P. aeruginosa i*solates were found to resistant. As a conclusion they reported an alarming increase in the number of isolates that produced metalo-betalactamases in three continents; Asia, Europe and South America.

In 2013 in Expert Reviews, a paper published by Maya et al. [13], stated the situation of Latin America with the carbapenemases and the results are shown in the (Table 3). They reported the threat to Latin America but in this study no data from Ecuador was included. Even so, the data was alarming as some of the carbapenemases were only found in Latin America.

Preliminary results have shown that in just one Hospital in Quito, from a sample of six months, the number of enterobacteriaceae that carried a carbapenemase was 123 isolates. More studies need to be done; characterization, rates, and of course samples throughout the whole country. These further studies will help us to understand the situation but also to improve the antibiotic policy to try to control the increase and dissemination of this type of resistance.

Actual Situation of the Resistance in Ecuador

The reality in Ecuador is that there is no knowledge of the national state of the resistance; there are only some local studies that are published in local journals and there are few published in journals with impact factor. Furthermore the works that have been published are comprised of data from Latin America and not just Ecuador, data solely from Ecuador is not national data, but from individual hospitals [14-17].

From 1990 until 2010 the first network of antibiotic resistance was working in Ecuador under the leadership of Jeannete Zurita [14-17], using a limited number of sample hospitals (Figure 1) they were able

Class A carbapenemases	KPC	Colombia
		Brazil
		Argentina
	GES	Brazil
		Argentina
Class B carbapenemases	VIM	Chile
		Venezuela
		Mexico
		Brazil
		Colombia
	SPM	Brazil
	IMP	Brazil
		Mexico
		Puerto Rico
		Argentina
	NDM	Guatemala
		Colombia
Class D carbapenemases	OXA-23	Brazil
		Argentina
		Chile
		Colombia
	OXA-24	Mexico
		Puerto Rico
		Brazil
		Colombia
	OXA-51	Argentina
	OXA-58	Brazil
		Chile
		Argentina
		Puerto Rico
		Venezuela
	OXA-48	Argentina
	OXA-143	Brazil
	OXA-235	Mexico
	OXA-247	Argentina

Table 3: Different carbapenemases isolated in Latin America.

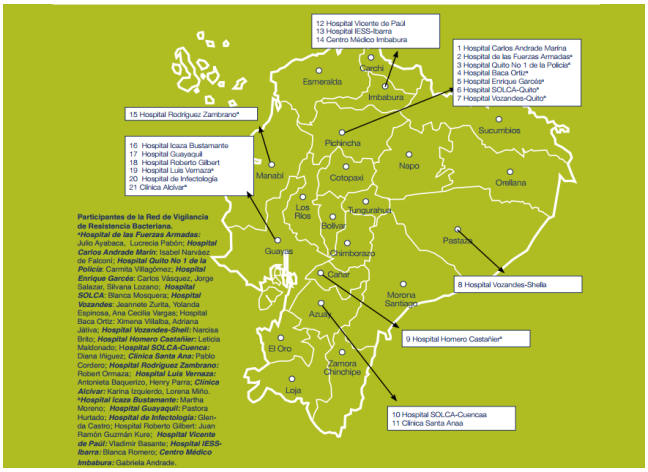

Figure 1: Map that indicates the Hospitals that had participated in the Ecuadorian Network until 2010.

to start to build a picture of resistance in the country. Unfortunately this network was stopped and since then there has been a void that now will be cover. The Ministry of Public Health (MPS) in Ecuador are making a big effort to understand the levels of resistance in the country and desperately want to improve in this area so they can contribute

more fully, as a nation to the network call ReLavra, which studies the rate of resistance in Latin American countries. It is time for change in Ecuador and they have recognised that now is the moment to create a central lab that will concentrate all resistant strains and data from all over the country and that will provide a reliable source of data to control resistance and outbreaks.

Although this laboratory has only been working for 3 months, preliminary studies have shown that there is a real need for the services the national reference lab provides. Auto-medication, poor completion rates of treatment, unrestricted medication to farms animals and poor previous antibiotic policies have created a worrying situation where preliminary results seem to indicate dangerously high levels of resistance. But understanding the situation is the first step towards combating resistance.

Organization of the Reference Laboratory

The objectives of the new reference laboratory are based in 8 main principles that are listed below:

1. Increase the efficiency and effectiveness of the Public Health system

2. Increase the Access to the public health services

3. Increase the vigilance, regulation, control and prevention of emergent diseases

4. Increase the satisfaction of the patients

5. Increase the ability and training of professionals

6. Increase the efficient usage of the Budget

7. Increase the efficiency and effectiveness of Ministry and associated entities programs

8. Development of science and technologies important for the area of public health

To achieve this, the reference laboratory works directly in coordination and under the responsibility of the epidemiological vigilance department in the MPS.

The reference laboratory offers several services, detection of outbreaks, characterization of mechanism of resistance, identification of atypical strains, serotyping of *Salmonella spp*, *Shigella spp*, *Escherichia coli* and other strains; fingerprinting assays, and analysis of the monthly microbiology isolates of Hospitals.

The future perspective is to create a centre of control of diseases based on the National Institute of Health of the USA. In the NIH there are four main focus of action: surveillance, prevention and control, research and finally product development.

Based on these four principles the Ecuadorian reference lab is starting to produce results. Since March the laboratory has identified, fingerprinted and identified the mechanisms of resistance for more than 150 different strains, as shown in (Figure 2).

After analyzing the initial batch of data from hospitals an outbreak in one of the hospitals was detected and after studying the risk factors and advising the professionals, an immediate decrease in the number of this type of isolate was observed. Two months later, the outbreak has been controlled and the lab has its first success.

The laboratory is a certified part of the PulseNet network, this is a Latin American network based in the use of Pulsed Field Electrophoresis for the study and detection of food transmitted diseases infections.

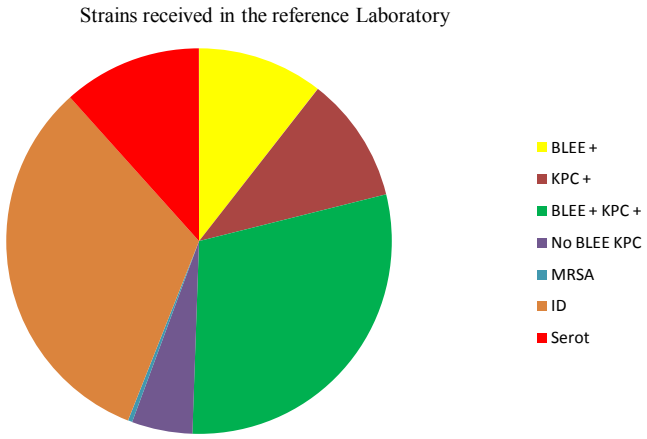

Figure 2: It shows the percentage of the test that the reference lab has been doing since March of this year.

As a part of the objectives to improve health care as well as efficiency they run several courses for professionals with the purpose of keeping the professionals to up to date with the latest developments in microbiology, improving their techniques and finally to build up an open network built upon good communication. This laboratory is still in its early stages but the preliminary results are showing already the potential of this project as a vital resource to save lives and government expenditure.

Conclusion

The high increase in antibiotic resistance worldwide is alarming. Resistance to carbapenems is one of the greatest problems in the fight against resistance, as effective treatments are reduced to polimixin B or tigeciclyne. Several studies have been done around the world, including Latin America but there exists a lack of data when looking to Ecuador. But soon with this new initiative, results will follow and with them the need to adjust policies and implement new ones as a response to the individual needs of Ecuador.

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