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Antibiotic Resistance of Streptococcus Pneumoniae in the United States and Latin American Countries: Contributing Factors and Potential Solutions

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Antibiotic Resistance of *Streptococcus Pneumoniae* in the United States and Latin American Countries: Contributing Factors and Potential Solutions

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Table of Contents

Introduction……..3

Background……..5

Methods……..12

Discussion……..12

Conclusion……14

References……..16

Appendices……18

Introduction

Antibiotics have been heralded as one of the greatest contributions to modern medicine. While antibiotics have been documented throughout many parts of the world, it was the discovery of penicillin in 1928 that marked the modern era of medicine.[1] An antibiotic is a natural, semi-synthetic, or synthetic compound that interferes with the growth of, or results in the death of a microorganism, specifically bacteria.[2] These medications are used to treat or prevent infection of humans or animals. With the advent of antibiotics, many infections that would cause significant morbidity and mortality were greatly reduced. The 1930s-1960s is regarded as the "golden age" of antibiotics, when most of the antibiotics still used today were created.[2] Since then, there has been a dramatic slowing of antibiotic production. Several factors have contributed to this slowing, including their short-term nature which lowers their profit potential (compared to chronic disease medications), policies in place to reserve new antibiotics for use when current antibiotics fail, and increased regulations regarding antibiotic production. These factors have effectively dissuaded pharmaceutical companies from investing in novel antibiotics.[3] For example, in 2004, only 1.6% of drugs in clinical development by the world's fifteen largest pharmaceutical companies were antibiotics. Contrasted, antimicrobials account for more than 30% of hospital pharmacy budgets in the US.[3]

This is a large issue in medicine, as antibiotic resistance (ABR), or a pathogen's ability to evolve and withstand the effects of antibiotics, increases worldwide.[4,5] Several factors contribute to ABR including excessive use of antibiotics in humans and animals, poor sanitation, global migration, antibiotics sold over-the-counter, and release of nonmetabolized antibiotics into the environment through urine or feces.[1] When bacteria become resistant to conventional treatments, more expensive, and toxigenic drugs are needed to combat them. Compared to susceptible bacterial infections, resistant infections are associated with an increase in morbidity, mortality

and prolonged hospital stay.[4,5,6] The burden of ABR on society and their respective economies cannot be understated. In the US alone, antibiotic resistant hospital acquired infections cause 99,000 deaths annually, a total of $20 billion in economic losses annually, and a loss of $35 billion annually due to productivity loss.[1]

It has been estimated that the burden of ABR in developing countries is even higher due to lack of resources.[4,6] For example, in developed countries like the US, resistant bacterial infections may be treated with vancomycin or imipenem, which are more effective, but have increased cost and side effects. When contrasted in developing countries, many cannot afford these expensive treatments, preventing them from being readily available to the public.[6]

Streptococcus Pneumoniae (*S. Pneumoniae*) is a gram-positive organism which is responsible for several bacterial infections in humans.[7] 90 serotypes exist to date and the 10 most common account for approximately 62% of invasive disease worldwide.[7] *S. Pneumoniae* is the leading cause of pneumonia, meningitis, and bacteremia in adults and children. It is also the leading cause of otitis media (OM) in infants and children worldwide.[7,8] Pneumonia is the most common cause of death in children younger than 5 years, with 1.6 million deaths occurring annually.[8] People more likely to be infected with pneumococcal disease are children less than 2, adults 65 years or older, those with chronic conditions such as pulmonary disease, and those with immunosuppression.[8] Pediatricians, geriatricians, and internists have an obligation to stay current on data regarding ABR *S. Pneumoniae* given their susceptible populations.

S. Pneumoniae have become ABR to conventional treatments, including beta-lactams, macrolides, tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), erythromycin and others.[9] This is a trend worldwide and developing countries deserve special attention. Unlike developed countries like the US, there remain many barriers to effectively treating ABR *S.*

Pneumoniae infections such as cost of treatment, inaccessibility of healthcare and lack of infrastructure to analyze trends of ABR. This paper aims to identify some of the contributors to ABR *S. Pneumoniae* in developing countries with special attention to Latin America. In addition, this paper will explore some strategies that developed countries use to reduce or control ABR which developing countries can model.

Background

Antibiotic Use in Food and Animal Agriculture

One of the largest contributors to ABR is the use of antibiotics in agriculture. While *S. Pneumoniae* is human specific, and has no animal vector, the concept of antibiotic use in agriculture is still worth investigating due to its large impact on a global scale. Concomitant infection of *S. Pneumoniae* with ABR pathogens related to agriculture are possible and pose serious risk.

Antibiotic use puts selective pressure on bacteria, eliminating susceptible bacteria while favoring the survival of resistant strains that have physiologic protective mechanisms against them. In agriculture, not only are antibiotics used for treatment of livestock, but also for proactive purposes. In metaphylaxis, if a farmer sees disease symptoms in one animal, they will treat all other animals with an antibiotic to prevent spread of that disease. Physiologic stress is commonly experienced by livestock due to their living conditions, which can cause immunosuppression. In order to combat this, farmers will often utilize prophylactic treatments, where a sub-therapeutic dose of an antibiotic is given to the immunocompromised animals to prevent infection.[2]

Antibiotics have also been used in agriculture as a growth promoter leading to rapid growth in food animals and fish, while also contributing to an increase in ABR.[2] This is a

frightening realization, as humans can become infected from ABR pathogens indirectly along the food chain through ingestion of food products or directly from colonized biological substances from animals such as blood, urine, feces, saliva and semen.[2] Given the expansion of the global population, globalization of trade (especially food animals) and international travel, this is a problem that extends beyond borders. Every nation can be affected by this mounting issue. For this reason, it is imperative that local, regional, national and international regulations be put in place to monitor and regulate ABR.

Developed countries, such as Denmark, Sweden, and the US have systems and programs in place to monitor antibiotic use in agriculture and ABR in food animals and products.[2] Developed countries such as these can analyze trends and implement national-level regulations to reduce the use of antibiotics in this sector. Denmark, for example, banned avoparcin in 1995, and in 2008 it was found that poultry production increased slightly, while reducing antibiotic consumption by 90%.[2] These surveillance systems have proven to be effective in the management of antibiotic use in agriculture.

In contrast to developed countries, most developing countries have no systems or programs that monitor antibiotic use or ABR in agriculture.[2] In developing countries, there seems to be a large emphasis on antibiotic use for growth-promotion. A study by Eagar et. al. determined that two thirds of 1500 tons of antibiotics sold for animal use in South Africa over a three-year period were for growth-promotion purposes.[2] It is also estimated that from 2010 to 2030, up to a third of the global increase in antibiotic consumption in food animals will be attributed to lower-middle income countries.[2] This is alarming as the majority of developing countries are major exporters of animals and their products. Brazil, for example, is the world's

largest exporter of chicken meat.[2] Any ABR bacteria seen in the chickens of that region, will surely reach across the globe.

Unrestricted Access and Self-Medication

One of the unique challenges that developing countries face regarding ABR is the unrestricted access to antibiotics. It is known that justified and controlled use of antibiotics contributes to ABR, however, widespread and unnecessary use exacerbates the situation. In many developing countries, the public have access to antibiotics over the counter without the need of a prescription. This problem is exacerbated by the fact that many of these antibiotics are acquired through unregulated supply chains.[10,11] In general, the public acquires antibiotics from non-professional sources and their education surrounding when an antibiotic is indicated, how much to take, the side effects associated with them, and the duration of use is lacking.[10,11]

To make factors worse, when antibiotic use is recommended, locals often prefer treatment from traditional healers who provide herbal supplements.[11] This is especially true in rural areas, where many do not have adequate access to healthcare. While studying abroad in Costa Rica on July 7th, 2019, a rural resident of Longo Mai named Mercedes reported her preferences regarding treatment of illnesses, "I always prefer natural medicine over going to the doctor. This is because doctors give us chemicals which are bad for us. Also, it is at least 30 minutes to the nearest clinic in Buenos Aires. I always choose natural medicine". The composition and potency of these herbal remedies are unknown, therefore, the effects they exert on pathogens are also unknown. It is plausible these herbal remedies might produce antimicrobial effects, but, if given at sub-therapeutic doses, may confer ABR.[11]

Self-medication practices have been shown to be excessive in Latin American countries.[10] Several authors have attributed high prevalence of self-medication with antibiotics to

poor access to healthcare in several countries, such as Costa Rica, Nicaragua, Chile, Argentina, Brazil, and Colombia.[10] Many developing countries, especially those in Latin America, seem to prefer unrestricted access to antibiotics in an effort to maintain reasonable access to medications. This is due to a recognition that if regulations were put in place, many would not have adequate access to receive the medications they may need.[10] A study done in Guatemala by Ramay et. al. in 2015 revealed the top four antibiotics used in self-medication were: amoxicillin, tetracycline, TMP-SMX, and erythromycin. (Table 1)[10] These are some of the first line medications used in the treatment of *S. Pneumoniae* infections, which is problematic.

ABR Serotypes and Pneumococcal Conjugate Vaccine

Although all pneumococcal infections can be treated with antibiotics, the available choices are limited for some strains. While antibiotics are used as a reactive approach to treatment of bacterial infections, vaccinations are a proactive approach to prevent bacterial infections from happening in the first place. Pneumococcal conjugate vaccines (PCVs) are effective against invasive pneumococcal disease (IPD) and have a significant effect directly on those who acquire them as well as indirectly.[8]

In the US, multi-drug resistant strains of *S. Pneumoniae* were first isolated in children and are predominantly associated with pediatric serotypes (6A, 6B, 9V, 14, 19A, 19F and 23F).[8] Because of the pneumococcal vaccine, less multi-drug resistant strains of *S. Pneumoniae* were reported in the US within 14 years of its introduction. A shift of multi-drug resistant strains has now been reported in serotypes 15A, 15B, 15C, 6C, 23A, and 35B. Multi-resistant serotype 19A isolates are still reported with the highest resistance to beta-lactams, macrolides, tetracycline, co-trimoxazole and lincosamides.[8] Just 4 years after the introduction of the pneumococcal conjugate vaccine-7 (PCV-7) in 2000, which covers the most common ABR serotypes (4, 6B, 9V, 14, 18C,

19F, and 23F) the US witnessed a decrease in penicillin-resistant *S. Pneumoniae* infections from 6.3 to 2.7 per 100,000, and multi-drug resistant *S. Pneumoniae* infections (4.1 to 1.7 cases per 100,000). (Figure 1)[8] Vaccine-type resistant *S. Pneumoniae* disease decreased by 87% following the introduction of the PCV-7 in the US.[8] Similar findings can be seen throughout the world. For example, after the introduction of the PCV-10 in Brazil, there was a decrease in penicillin and ceftriaxone resistant *S. Pneumoniae* infections.

In Latin America, most ABR *S. Pneumoniae* infections are caused by serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F. Serotype 23F, a clonal serotype from Spain, which is resistant to penicillin, chloramphenicol, tetracycline and erythromycin, has had a large impact on this region.[6,9] These serotypes reflect similar trends in developed countries such as the US. In Latin America, countries with the highest percentage of penicillin-resistant isolates are Puerto Rico (35%) and Peru (27%). The highest median percentage of *S. Pneumoniae* isolates with high-level resistance was found in children less than 5 years of age. Mexico reported the highest rate of penicillin-resistant pneumococcal isolates (22%) and 47% overall ABR. Argentina reported the highest penicillin resistant OM isolates (80%). It is worth noting that OM represents 79% of all infections caused by *S. Pneumoniae* in Latin America and the Caribbean. Consequently, this results in most of the consumption of antibiotics in the region.[9] Providing PCVs in this region is therefore of utmost importance.

Unfortunately, many developing countries, and Latin American countries specifically, do not have adequate access to these vaccines. For example, the PCV-7 became available to Costa Rica in 2004. While this is beneficial for the country, it was estimated that only 10-15% of children in Costa Rica had access to this vaccine.[12] This was attributed to economic limitations,

leaving the vaccine available only to children who had private insurance. Proper access to PCVs in developing countries would decrease the burden of pneumococcal disease as well as ABR.

Clinical Practice Guidelines, Surveillance and Improper Prescribing Practices

In modern medicine, the use of empirical treatment guidelines for specific infections is an important part of quality healthcare. The same is true for *S. Pneumoniae* infections. In developed countries such as the US, societies like the Infectious Disease Society of America and the American Thoracic Society (IDSA/ATS) have provided specific treatment guidelines for practitioners to use in the treatment of pneumonia infections.[14] These guidelines are generated based upon current data highlighting effective antimicrobial agents. In the US, pneumococcal disease data is constantly monitored using the population-based survey system called Active Bacterial Core Surveillance Program (ABC).[8] The US then uses this data to update and educate medical providers on trends of ABR pneumococcal disease and provide appropriate treatment guidelines.

According to the IDSA/ATS, recommended treatment guidelines for pneumonia are: macrolide or doxycycline in a previously healthy person with no risk factors for ABR *S. Pneumoniae* infection, a respiratory fluoroquinolone or beta-lactam plus a macrolide if the patient has comorbidities such as heart disease or been previously exposed to antibiotics in the previous 3 months, and use of the previous agents mentioned if local macrolide-resistant *S. Pneumoniae* infections are prevalent (>25%).[8] Guidelines, therefore, depend on adequate surveillance in order to be effective.

Many Latin American countries do not have adequate surveillance systems in place to make proper treatment guidelines for their area. Because of this, much of the rudimentary data in these countries are based solely on point-prevalence assessments or case studies.[6] For this

reason, the IDSA/ATS guidelines for pneumococcal disease have been used by Latin American countries as a reference for treatment.[14] While this is a valuable resource and much of the trends of pneumococcal infections and ABR patterns in the US have been similar in Latin American countries, proper prescribing practices are necessary on the part of medical providers.

A study done in 2015 by Gattarello et. al. demonstrated that when physicians from Latin American countries were given fictional patient cases with community-acquired pneumonia (CAP) and nosocomial pneumonia, 31% of CAP cases and only 3% of nosocomial pneumonia cases were considered adequate treatments following the IDSA/ATS guidelines. (Table 2)[14] This reflects the need for not only proper surveillance and guidelines in Latin American countries, but for adequate and ongoing education for medical providers. Without continuing education, medical providers will continue to prescribe improper treatments for *S. Pneumoniae* infections, further contributing to burden of disease and ABR.

Methods

This was a literature review conducted using PubMed. A search was done using keywords such as "antibiotic resistance, *Streptococcus Pneumoniae*, developing countries, Latin America, Costa Rica and clinical guidelines". Initially, 27 articles were collected and filtered based upon relevance to the topic, date of publication and redundancy of information to other articles used during June and July of 2019. Fourteen articles were used in this literature review. Some government websites were utilized for general background information on healthcare. A brief interview was conducted with Mercedes, a resident of a rural community called Longo Mai in Costa Rica, regarding her opinion on healthcare and antibiotics. Another interview was conducted with Dr. Jose Alejandro Madrigal Lobo, a member of the Costa Rican Doctor's Association regarding the healthcare system in Costa Rica.

Discussion

While modern medicine has made large impacts on global health, finances are a consistent barrier to adequate access to healthcare. Specifically, the advent of antibiotics introduced new challenges to the medical community. Antibiotics are a mainstay to the treatment of infectious disease but have contributed to global ABR pathogens. As previously stated, ABR infections increase morbidity and mortality worldwide, require constant surveillance and necessitate novel treatments. Countries in Latin America are still considered developing and just don't have the ability to combat ABR like developed countries. While barriers exist, small policy changes could have positive impacts on these countries.

Winning the battle with ABR infections such as *S. Pneumoniae* require national and international efforts. Surveillance systems that monitor ABR patterns from major regions throughout the country will determine proper therapeutic guidelines. While many Latin American countries do not have this in place, it is a goal that should be worked on to improve outcomes regarding ABR infections. Placing surveillance programs at large tertiary hospitals throughout Latin American countries where proper microbiological testing is available could help the situation. When patients with severe infections go to the hospital, often they will receive cultures and other laboratory tests to determine the nature of the disease. Implementing a recording program in these countries could help better understand local and regional patterns of ABR.

While many medical providers have understanding regarding treatments for common infections, it is apparent that many do not stay current with therapeutic guidelines, especially more complex cases. Continuing education for medical providers is imperative so they can make the best recommendation for their patients. International cooperation from medical providers in

developed, high-income countries may be a feasible way to ensure medical providers in developing countries like Latin America stay current on treatment guidelines.

Antibiotic use in agriculture is a large issue in developing countries that has major implications across the world. As previously stated, *S. Pneumoniae* is a human-only pathogen and doesn't reside in animals, however, due to the global implications of antibiotic use in agriculture, and the risk of multiple infections, it is important to address. Developing countries could benefit from the replication of models used in developed countries. While there are barriers to implementing complex infrastructure involving cost and human resources, it is a goal that is imperative to achieve. One policy that could be implemented in developing countries is restricting access of antibiotics to farmers. Currently, most developing countries do not require veterinarian oversight to access antibiotics. Adding nation-wide regulations that strictly prohibit access to antibiotics without veterinary oversight in developing countries like Latin America could be a step towards effective management of this issue. Also, providing farmers with education surrounding ABR is important. Countries should also implement policies that restrict the use of antibiotics as growth promoters, like many developed nations.

The use of over-the-counter antibiotics for human consumption is another issue that needs to be addressed in developing countries. Uneducated and unrestricted use of antibiotics can contribute to ABR in *S. Pneumoniae infections*. The absence of healthcare professionals in pharmacies and lack of regulations for antibiotic prescriptions is a contributing factor. If the role of the pharmacist became more integral to the acquisition of antibiotics, patients would likely become more educated surrounding them.[10] In order to do this, developing countries need to develop laws that regulate the dispensing of medications. Like many developed countries that require prescriptions for acquisition of antibiotics, a stricter policy along with the integration of

pharmacists would improve safety, rational use, and affordability of antibiotics.[10,11] One might question how policies introducing more regulations would be cost effective. Up front cost would surely rise, but the benefits it would impose by decreasing overall ABR infections, the need for more invasive and costly treatments, and hospitalizations would make up for upfront costs.

Vaccine programs are important for protection of the population and prevention of ABR pneumococcal infections. While implementing PCVs in developing countries like Latin America may be difficult due to financial constraints, it is still important to continue to advocate for them. Pneumococcal disease represents a large majority of infectious disease across the world. With the introduction of the PCV-7 vaccine in the United States, pneumococcal infections dropped significantly. Much of the cost required to treat those who become infected is therefore abated. Research on cost-effective implementation of vaccines in developing countries will be more productive than treatment of pneumococcal infections themselves.

Conclusion

ABR is a global issue and persists despite advanced efforts to control it. This is compounded by the fact that there has been little development of new antibiotics to combat this. ABR infections pose significant morbidity and mortality worldwide as conventional antibiotics have become less effective. This is especially true for *S. Pneumoniae*, which as previously stated causes most invasive disease worldwide. The problem of ABR *S. Pneumoniae* becomes exponential in developing countries where they lack the proper resources to implement surveillance infrastructure to track ABR, development of proper guidelines based upon local data, education for medical providers on current empiric treatment guidelines, access to vaccinations and more costly treatments. These problems are further exacerbated by the high

prevalence of self-medication of antibiotics which are frequently acquired over-the-counter, without education regarding these medications.

ABR is an issue that spans across borders and global efforts should be implemented to improve these disparities for developing countries such as Latin America. Joint global funding, research, and education guidelines could be implemented in developing countries to improve outcomes, with a priority to common infectious diseases that cause significant morbidity and mortality, such as *S. Pneumoniae*. Understanding the disparities that developing countries face regarding ABR is an instrumental part to the creation of a solution. Now that many disparities are understood, implementation of nation-wide policies aimed at reducing ABR needs to be investigated. It is easy to say such policies need to be created but the actual implementation of them is far more challenging. Future research should focus on feasible ways to implement the strategies outlined in this paper to improve healthcare in developing countries. Even small changes in policy will help decrease ABR and improve global health.

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Appendices

Table 1. Reported most common antibiotic purchases when self-medicating.[10]

Table 2 Number of respondents purchasing antibiotics when self medicating

Antibiotic purchased for use in self-medication	Suburb (n = 221)		City center (n = 197)	
	Number of respondents	%	Number of respondents	%
Amoxicillin	114	51.58	82	41.62
Tetracycline	34	15.38	55	27.92
Trimethoprim-sulfamethoxazol	13	5.88	20	10.15
Erithromycin	11	4.98	18	9.14
Ciprofloxacin	9	4.07	9	4.57
Cefadroxil	0	0.00	4	2.03
Cefixime	0	0.00	4	2.03
Amoxicilin/Clavulanic Acid	9	4.07	3	1.52
Azithromycin	5	2.26	2	1.02
Secnidazol	8	3.62	0	0.00
Albendazol	6	2.71	0	0.00
Metronidazol	6	2.71	0	0.00
Levofloxacin	3	1.36	0	0.00
Ceftriaxone	2	0.90	0	0.00
Clarithromycin	1	0.45	0	0.00
Total	221	100	197	100

Table 2. Antibiotic prescription, dose and duration in the case of CAP.[14]

Table 2 - Antibiotic prescription, dose and duration in the case of community-acquired pneumonia

Antibiotic	N indications	Dose*	Indicated dose ≥ recommendation	Duration < 7 days	Duration 7 - 10 days	Duration > 10 days
Beta-lactams	29/68 (42.7)					
Ceftriaxone	20/68 (29.4)	2.0 (2.0 - 3.5)	19/20 (95.0)	0/20 (0)	17/20 (85.0)	3/20 (15.0)
Cefepime	5/68 (7.4)	6.0 (5.0 - 6.0)	4/5 (80.0)	0/5 (0)	3/5 (60.0)	2/5 (40.0)
Meropenem	4/68 (5.9)	3.0 (1.9 - 3.0)	3/4 (75.0)	0/4 (0)	3/4 (75.0)	1/4 (25.0)
Macrolides	19/68 (27.9)					
Clarithromycin	10/68 (14.7)	1.0 (0.9 - 1.0)	8/10 (80.0)	0/10 (0)	8/10 (80.0)	2/10 (20.0)
Azithromycin	9/68 (13.2)	0.5 (0.5 - 1.0)	9/9 (100)	0/9 (0)	7/9 (77.8)	2/9 (22.2)
Quinolones	8/68 (11.8)					
Levofloxacin	4/68 (5.9)	0.8 (0.6 - 0.8)	3/4 (75.0)	0/4 (0)	4/4 (100)	0/4 (0)
Moxifloxacin	4/68 (5.9)	0.4 (0.4 - 1.3)	4/4 (100)	0/4 (0)	4/4 (100)	0/4 (0)
Glycopeptides	4/68 (5.9)					
Vancomycin	4/68 (5.9)	2.0 (2.0 - 2.0)	4/4 (100)	0/4 (0)	3/4 (75.0)	1/4 (25.0)
Others	8/68 (11.8)					

Results are expressed as the absolute values and percentages: n (%); * result is expressed as the median and interquartile range.

Figure 1. ABCs IPD rates in 1999, 2009 (9 years after PCV7 introduction), and 2013 (3 years after PCV13 introduction).[8]

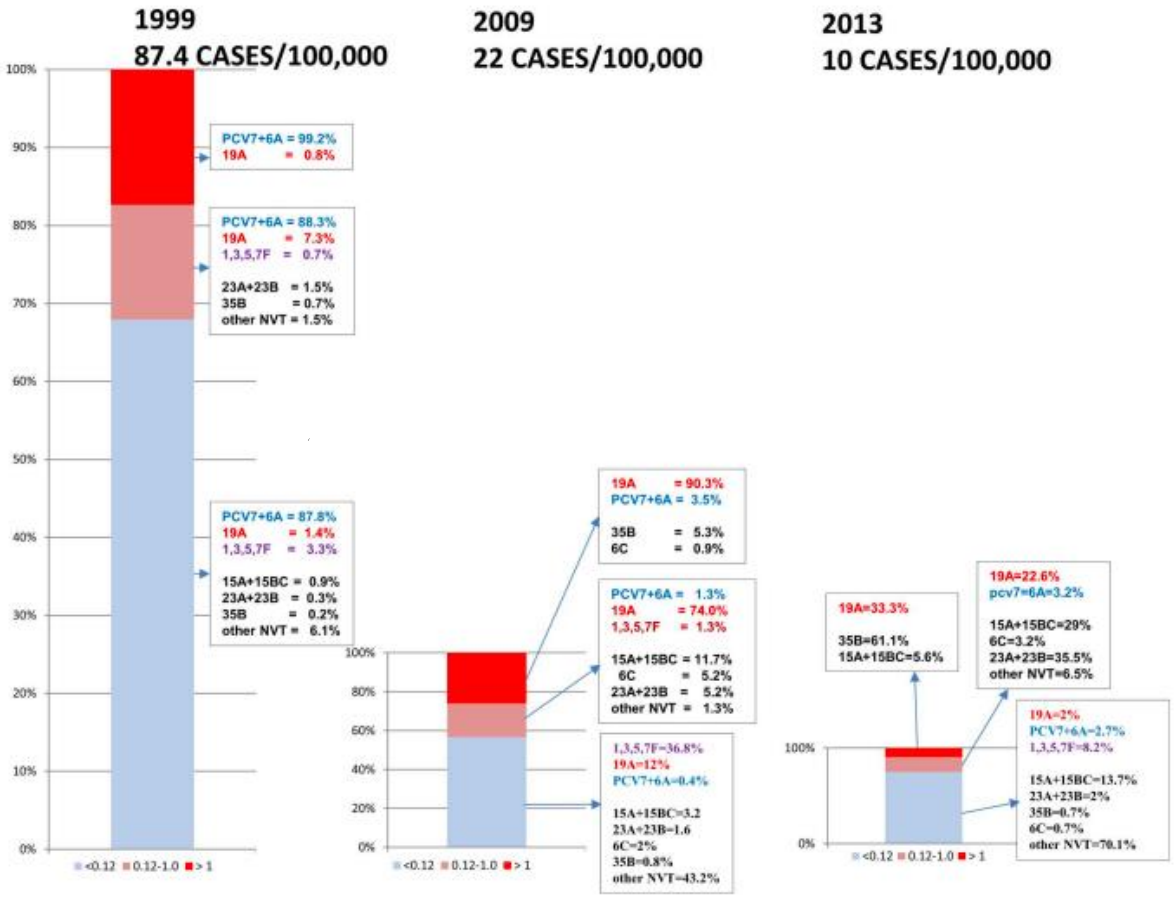

FIG 2 ABCs IPD rates in the population of individuals <5 years of age in 1999 (before PCV7 introduction), 2009 (9 years after PCV7 introduction), and 2013 (3 years after PCV13 introduction). The bright red portions indicate penicillin resistance (MICs of ≥2 μg/ml), lighter red indicates intermediate resistance (0.12 to 1.0 μg/ml), and gray indicates sensitivity (≤0.06 μg/ml). PCV13 types, besides those targeted by PCV7, are indicated in red and purple. Only nonvaccine types (NVT) that are found associated with intermediate or high penicillin resistance are specifically indicated in black boldface type.

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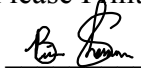
Author's Signature:  Date: 08/16/2019

If the Deposit Agreement is executed by the Author's Representative, the Representative shall separately execute the Following representation.

I represent that I am authorized by the Author to execute this Deposit Agreement on the behalf of the Author.

Author's Representative Signature: _____ Date: _____