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ANTIMICROBIAL RESISTANCE IN THE DEVELOPING NATIONS OF BRICS

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ABSTRACT

Contemporarily, one of the most daunting challenges in the medical field is bacterial resistance to general antibiotics. Resistance is quickly evolving into an unsolved crisis in developed and developing nations alike, plaguing populations and preventing deliverance of effective health care. This thesis focuses on antimicrobial resistance (AMR) in five countries of comparable newly burgeoning economic status: Brazil, Russia, China, India, and South Africa. These developing countries, collectively coined by and known to economists as BRICS, have all reached a similar stage of newly advanced economic development in the past decade and are expected to become significant forces in the global economy. It is necessary to understand current trends in AMR in these nations to allow for the development of strong monitoring systems and to encourage an awareness of AMR-related issues facing these growing economic powers.

This thesis explores three commonly occurring infectious disease and their resistant counterparts: tuberculosis (TB), *Staphylococcus aureus* (Staph), and *Streptococcus pneumonia* (pneumonia). Each BRICS is analyzed according to factors that, according to WHO, have significant roles in the prevalence of AMR worldwide: surveillance and monitoring systems, medicine distribution methods, and diagnostic and therapeutic tools. To obtain an assessment of the current situation regarding each disease in each country, the primary literature regarding antimicrobial resistance is evaluated and potential trends in resistance are elucidated. Finally, suggestions for potential future work to combat the spread of resistance are made.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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INTRODUCTION

Antimicrobial Resistance

According to the World Health Organization (WHO), antimicrobial resistance (AMR) is a term used to describe a "resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive" ("Antimicrobial"). The unique ability of bacteria to become resistant to – or unaffected by – certain drugs is attributable to its biological structure. Bacteria are single-celled organisms without membrane-bound organelles belonging to the domain Prokaryota. Their chromosomal DNA, which stores their genetic information, is located in an area of the cell called the nucleoid.

Apart from the nucleoid, DNA is also contained in plasmids: circular structures that confer certain characteristics advantageous to the bacterium's survival such as genes for resistance to heat or drugs. Plasmids, and by association the traits they encode, may be transferred from one bacterium to another through a process called horizontal gene transfer (Figure 1, "Superbug").

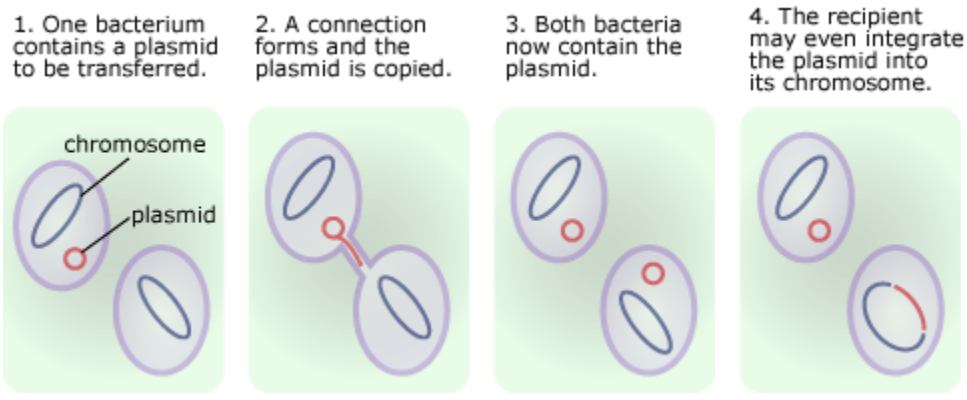

Figure 1. Horizontal gene transfer ("Superbug").

Evolutionarily, bacteria have ensured their survival over history through the combined influences of genetic mutations and natural selection ("Superbug"). All organisms are subject to natural mutations in their genes that, when expressed, result in altered or entirely new characteristics. When organisms face selective pressures such as changes in the environment, mutations that confer advantages to organisms' survival may be selected for, while mutations that negatively affect organisms' ability to survive may be selected against. The organisms that survive may then reproduce, passing on their mutations – or beneficial genes – to their progeny through horizontal gene transfer ("Superbug").

Prevalence and Scope of Antimicrobial Resistance

This information lays the groundwork for understanding AMR in the contexts of health and disease. Tuberculosis (TB), Staph infections, and pneumonia are infectious diseases caused by specific bacteria. Ideally, proper administration, oversight, and use of antimicrobial medicines should lead to consistent and successful cure rates for these diseases; however, these bacteria have been able to acquire resistance to them, resulting in increasing rates of MDR-TB, MRSA, PRSP, and other resistant strains of bacterial infections worldwide.

Microbes, Diseases, and Treatment Methods

Tuberculosis

Pulmonary tuberculosis (TB) is a contagious, infectious, and potentially lethal disease affecting the lungs caused by the microorganism *Mycobacterium tuberculosis* (World Health Organization [WHO], 2013). The disease is transmissible through air when those infected by

pulmonary TB expel the bacterium by coughing. It is most frequently identified in adults of economically productive ages and more common among men than women. Diagnoses are performed by utilizing sputum spear microscopies, molecular tests, or other culture methods to identify the bacterium in patients' sputum samples.

Without treatment, TB mortality rates are significant; 70% of those untreated are known to die within 10 years (WHO, 2013). Global treatment success rates for new cases average about 85-90%. In 2012, 8.6 million new TB cases and 1.3 million TB cases were reported (WHO, 2013).

There are 22 high burden countries (HBCs) for TB: Afghanistan, Bangladesh, Brazil, Cambodia, China, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russia, South Africa, Thailand, Uganda, Tanzania, Vietnam, and Zimbabwe (WHO, 2013). Together, these nations contain 80% of the world's TB cases; Brazil, Russia, India, China, and South Africa (BRICS) alone account for nearly 50% (WHO, 2013).

Drug treatments for TB were first developed in the 1940s. Rifampicin, one of the most powerful first-line anti-TB drugs available, was produced in 1959 and introduced into TB therapy in the 1960s (WHO, 2013). The second most powerful first-line drug used against TB is isoniazid. Other first-line oral drugs include pyrazinamide and ethambutol (WHO, 2013). The currently recommended treatment for TB, also described by the WHO, involves administering these four first-line drugs for a six-month period. Another, more general regimen involves combining four drugs from five different groups based on efficacy, safety, cost, and susceptibility of the specific strain of TB (Caminero et al, 2010). These groups are described in Table 1. Currently, no known vaccine for TB exists (WHO, 2013).

Table 1. Drug Regimens for TB

Group	Drugs	Description
Group 1	First-line oral drugs: rifampicin, isoniazid, pyrazinamide, ethambutol	Most powerful anti-TB drugs
Group 2	Fluoroquinolones: levofloxacin, gemifloxacin, moxifloxacin	First choice is levofloxacin
Group 3	Capreomycin, kanamycin, amikacin	Second-line drugs are used when first-line drugs prove ineffective (in cases of MDR-TB)
Group 4	Thioamides, cycloserine, aminosalicylic acid	
Group 5	Clofaximine, amoxicillin, clavulanate, linezolid, carbapenems, thioacetazone, clarithromycin	Group of drugs that are not very effective or are supported with limited clinical data

Rifampicin and isoniazid have been implemented through a program called Directly Observed Therapy Short-course (DOTS) to combat TB worldwide. In DOTS, doctors or trained assistants are responsible for the continued treatment of patients given antibiotics (Farmer and Kim, 1998). Health workers make house calls to each patient with antibiotics to ensure that doses are administered as prescribed and to educate patients about the necessity of faithful cooperation with treatment plans.

Multi-Drug Resistant Tuberculosis (MDR-TB)

MDR-TB is an advanced form of tuberculosis that is resistant to isoniazid and rifampicin, the two most powerful first-line drugs used in TB therapy (WHO, 2013). MDR-TB develops during the treatment of TB if the course of antibiotics is interrupted or the administered doses are insufficient to kill all the bacteria present so that the remaining bacteria are able to develop resistance (“Tuberculosis”).

Of the 450,000 new cases of MDR-TB in 2012 worldwide, more than half were reported in India, China, and Russia (WHO, 2013). MDR-TB is most frequently reported in Eastern Europe and central Asia: areas in which several countries report MDR-TB in greater than 20% of new cases and over 50% of previously treated cases (WHO, 2013).

MDR-TB is significantly more difficult to treat – and has lower treatment success rates – than TB for a number of reasons. First, treatment regimens are longer in duration; WHO recommends approximately two years, or 20 months, of continuous treatment (WHO, 2013). In addition, because the TB has grown resistant to two first-line drugs, more toxic second-line drugs become implemented in therapy. Second-line drugs are not only more toxic but also more expensive. According to Green Light Committee prices, they are 300 times the price of first-line drugs, and when estimating costs with market prices, this factor increases significantly to between 1000 and 3000 times (*Global Plan* 116). Common second-line drugs include Group 2 fluoroquinolones; Group 3 drugs including capreomycin, kanamycin, and amikacin; Group 4 drugs including thioamides, cycloserine, and para-aminosalicylic acid (PAS); ethionamide, cycloserine, ciprofloxacin, ofloxacin, levofloxacin, and clofazimine (Caminero et al, 2010). MDR-TB can be treated through a program known as DOTS-Plus: a DOTS-based strategy that uses these second-line drugs to oversee specific treatment regimens for individual patients (Farmer and Kim, 1998).

When MDR-TB is mismanaged – the appropriate drugs are not administered faithfully or the treatment program is terminated prematurely – extensively drug-resistant TB (XDR-TB) may develop (Figure 2). XDR-TB is defined as MDR-TB, or TB resistant to rifampicin and isoniazid, with further resistance to a quinolone drug and one or more of the second-line drugs kanamycin, capreomycin, or amikacin (“Tuberculosis”). Although WHO approximates that XDR-TB comprises 10% of global MDR-TB incidences, it is ultimately difficult to obtain a completely accurate estimation due to the fact that not all laboratories –particularly those in developing

nations – possess the necessary facilities, equipment, and detection and diagnosis methods for XDR-TB (WHO, 2013). It is therefore likely that many actual cases of XDR-TB are going undetected and subsequently unreported.

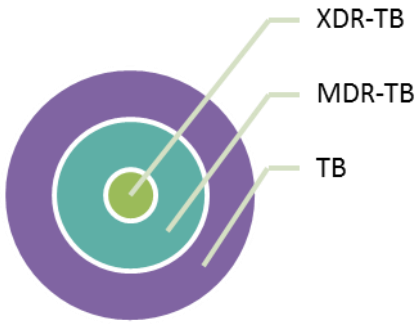

Figure 2. Representation of Forms of TB

Streptococcus Pneumoniae

Pneumonia is a respiratory condition caused by lung infection of *Streptococcus pneumoniae*, which is a bacterium also known to cause sepsis, meningitis, and other respiratory tract infections ("Pneumonia"). This invasive disease is most frequently identified in the youngest and oldest parts of the population as well as in those with immunodeficiencies (Bogaert, de Groot, and Hermans, 2003). Its impact is most significant in children under five years of age; pneumonia is the leading cause of death in this age group around the world. In 2008, pneumonia accounted for 1.575 million – or 18% – of all childhood mortalities, accounting for the most lives in resource-poor, developing countries (Adegbola, 2012). Pneumonia may be characterized by different serotypes. A serotype refers to a specific category of microorganisms that share a unique set of antigens (Bogaert, de Groot, and Hermans, 2003).

Penicillin-Resistant Streptococcus pneumoniae (PRSP)

Pneumonia is treated using beta-lactams such as penicillin and macrolides, a class of drugs including erythromycin, clarithromycin, and azithromycin (Chiou, 2006). Resistant strains of *S. pneumoniae* may take various forms, one of the most prevalent of which is penicillin-resistant *S. pneumoniae* (PRSP). First detected in 1965 in Boston, penicillin resistance has been observed at steadily increasing levels worldwide since the popular introduction of penicillin into treatment regimens in 1943 (Applebaum, 1992; Chiou, 2006).

Staphylococcus aureus

A Staph infection, caused by the bacterium *Staphylococcus aureus*, affects the skin and other body tissues ("Methicillin"). Although it may be carried asymptomatically in approximately 25-30% of healthy individuals, boils on the skin are a characteristic indication of its presence (*Situation* 14). Because the infection occurs particularly commonly in surgical wound sites and is able to survive for long periods of time on dry surfaces like hospital sheets and equipment, high-risk populations for Staph include patients being treated in hospitals' surgical or burn wards (*Situation* 15).

Drugs most commonly administered in treatment are beta-lactams: a category of antibiotics including penicillin, amoxicillin, oxacillin, and methicillin (*Situation* 14). However, once strains of *S. aureus* began to develop resistance to these drugs, an invasive disease known as methicillin-resistant *S. aureus* (MRSA) emerged. MRSA, which first emerged in 1960, is now the most common antimicrobial-resistant disease plaguing most of the Eastern Hemisphere and the Americas (Carvalho, Mamizuka, and Filho, 2010). In addition, methicillin resistance is a good

indicator that the *S. aureus* possesses resistance to other beta-lactam drugs including penicillin (*Situation* 14).

Methicillin-Resistant Staphylococcus aureus (MRSA)

MRSA that is acquired through hospital exposure to *S. aureus* is termed hospital-acquired MRSA (HA-MRSA), and it currently is the most common type of MRSA identified. Rates of HA-MRSA have been increasing over the past few decades around the world (Carvalho, Mamizuka, and Filho, 2010). Community-acquired MRSA (CA-MRSA), which is transmitted primarily through high intensity physical contact, has historically been a lesser threat; however, gradually increasing rates of CA-MRSA have been recently documented, and many scholars assert that the distinction between HA and CA-MRSA is diminishing as more cases of CA-MRSA make their way into hospital and health care facility settings (*Situation* 14; Carvalho, Mamizuka, and Filho, 2010).

Overview

This paper will examine these three infectious diseases and their antimicrobial-resistant counterparts: Tuberculosis (TB), *Staphylococcus aureus* (Staph), and *Streptococcus pneumonia* (pneumonia). Each disease is characterized by unique symptoms, resistant forms, and treatment drugs (Table 2).

Table 2. Disease Summaries

	Description	Resistant Form	Treatment Antibiotics
Staph aureus	infection affecting the skin and other body tissues	MRSA	beta-lactams
Streptococcus pneumoniae	respiratory condition caused by lung infection	DRSP (or just antibiotic-resistant Strep. pneumoniae)	beta-lactams, macrolides
TB	contagious, infectious, potentially lethal disease affecting the lungs, spread via air, commonly linked to HIV, no vaccine	MDR-TB: resistant to 2 first-line drugs: isoniazid and rifampicin	isoniazid, rifampicin, pyrazinamide, ethambutol
		XDR-TB: resistant to isoniazid and rifampicin + any member of the quinolone family, and at least one second-line anti-TB drug	

The most commonly used antibiotics belong to three categories: beta-lactams, macrolides, and fluoroquinolones (Table 3).

Table 3. Drug Types According to Diseases

	Beta-lactams	**Macrolides**	**Fluoroquinolones**
Specific drugs	Methicillin Oxacillin Penicillin Amoxicillin	Erythromycin Clarithromycin Azithromycin	Levofloxacin Gemifloxacin Moxifloxacin
Used to treat	Staph infections Pneumonia	Pneumonia	TB

METHODS

Search Methodology

PubMed/MEDLINE were searched for primary literature published in English or translated into English within the last ten years that addressed the statuses of MDR-TB, MRSA, and PRSP in Brazil, Russia, India, China, and South Africa for human subjects. The search was conducted under the filters of "Most recent" and "Relevance." This literature encompassed studies that began over twenty years ago but have continued into a time falling within the last ten years. Therefore, papers from 2003-2012 constituting studies performed from 1993 to 2012 were examined. Each BRICS country was attempted to be characterized using three or more primary sources; however, for instances in which the literature for a specific country proved sparse, only one primary source may have been used.

Specific search terms were used to obtain literature from PubMed/MEDLINE for each disease. The keywords used were: *tuberculosis, MDR-TB, MRSA, MRSA surveillance, Staph aureus resistance, Streptococcus pneumoniae resistance, AMR, monitoring system, AMR prevalence*. Multiple forms, or serotypes, of resistant Streptococcus pneumoniae exist. Therefore, the scope of this thesis included data only regarding penicillin resistance. Furthermore, no specific serotypes were considered to the exclusion of others.

The location of each study, the scale of the study, the time period covered by each study, and the sample size used by each study were also taken into consideration when considering primary sources. Due to the large geographic scales of the BRICS nations and the subsequent extent of demographic, socioeconomic, and regional variations in each country, an attempt was made to select studies from different parts of each country to obtain a holistic view of AMR by taking regional differences into account. The scale of the study was defined by whether the study operated or examined a country on a national, sub-national, state, province, town, or county level.

Studies covering longer time periods were preferred because of their ability to provide more extensive data sets of their samples. Studies with larger sample sizes ($n \geq 100$) were preferred; the larger the sample size, the more weight was given to the results of the study. Studies with samples of patients over a broad age range – including children, adults, and the elderly – were selected. However, due to the sometimes limited nature of available studies based on the extent of research performed in a country or a country's technological or developmental standing, these qualifications for selecting studies were treated more as guidelines rather than as rigid rules.

Literature

The majority of sources were peer-reviewed papers and studies in published scientific journals. Review papers about the status of AMR prevalence in the countries of BRICS and the global condition of TB and MDR-TB were also included to obtain background information regarding these topics. Other sources included credible international organizations such as the World Health Organization (WHO).

Evaluating Disease Prevalence

Upon amassing data from relevant literature regarding the recent observed levels of MDR-TB, MRSA, and PRSP, trends in the prevalence of these diseases in each country were analyzed. Then, an overall perspective on the resistance status was provided through a graph that included all the rates detected by every study for each country.

Each individual country's rates of MRSA and PRSP, but not MDR-TB, over similar periods of time were graphed to explore recent trends in resistance rates. A graph of MDR-TB rates over time could not be produced because literature regarding different levels of MDR-TB in certain countries was lacking. Therefore, since only one reported level of MDR-TB from one point in time was available in some nations, analyses of MDR-TB trends over time were not made.

Evaluating Factors

The BRICS nations were ranked according to the current states of their surveillance and medicine distribution systems on a scale of 1 to 5. A ranking of 1 indicated that the status of the system was in the most optimal condition, and a ranking of 5 indicated the opposite. Then, overall rankings were determined by taking the average value of the assigned rankings. When the calculated average was not a whole number, the value was rounded down to the next whole number.

Disclaimer

Due to the developing natures of the BRICS nations and a lack of resources, the results and discussions featured in this thesis are not comprehensive of all the existing data and literature regarding AMR and thus may contain generalizations or inaccuracies. For instance, the current literature regarding MRSA and PRSP surveillance and monitoring systems is very limited; there were multiple instances in which no sources or studies regarding these resistant strains in the BRICS nations were able to be located. Furthermore, the BRICS nations are characterized by widespread regional variations in AMR rates and medical practices that may not be able to be captured by the scope of the available literature. However, a good-faith effort was made to obtain the most accurate, relevant, and significant information from the largest number of reliable studies possible to achieve the best results and conclusions possible.

TB AND MDR-TB

Brazil

According to the WHO, Brazil has a high TB burden and is therefore classified as a high-burden country (HBC): one of 22 nations that together possess 80% of the world's TB cases (WHO, 2013). However, at 20-49 cases per 100,000 people, Brazil presents markedly lower rates of TB infection than most of the other HBCs around the world, which have between 150 and 300 cases per 100,000 people (WHO, 2013). Brazil shows a sustained decline in TB rates over the past 20 years, and its treatment success rate in 2008 was 71% and showed an upward trend to 76% in 2011 (WHO, 2013).

The treatment program for MDR-TB was established in 2000 by the Brazilian Ministry of Health as an 18-month regimen consisting of 5 different drugs: amikacin, clofazimine, terizidone, ethambutol, and levofloxacin (Lemos and Matos, 2013). In 2012, the WHO found that less than 2.9% of new TB cases and 7.5% of retreatment cases in Brazil were drug-resistant (WHO, 2013). The rate of MDR-TB from new cases has increased slightly from 1.1% to 1.4% during a survey conducted a few years prior in 2007-2008 (Lemos and Matos, 2013). These data conclude that the prevalence of MDR-TB in Brazil among all new TB cases is approximately 1.4%.

Russia

Russia is also considered a HBC under the WHO Global TB Report. The country has approximately 50-124 new TB cases per 100,000 people per year, and in 2011 there were approximately 150,000 cases reported (WHO, 2013). These figures place Russia among the 22 HBCs with the highest rates of case detection (WHO, 2013). The treatment success rate in 2012

was reported to be 52%, showing a slight decline from the rates of 58% to 68% in the late 1990s and early 2000s (WHO, 2013).

The WHO estimates that 23% of new TB cases and 49% of retreatment cases were MDR in 2011. Certain areas of Russia that possess significantly high rates of MDR-TB are considered MDR-TB hotspots (Espinal, 2003). In 2011, the highest levels of MDR-TB detected in Russia were in the Ulyanovsk Oblast and the Yamalo-Nenets Autonomous Area, in which 74% and 41.9% of new TB cases were found to be drug-resistant, respectively (WHO, 2013).

India

India possesses 26% of the world's TB cases, which constitutes a significant portion of the TB disease burden (WHO, 2013). In 2012, India presented approximately 2.0 million cases: the largest number of cases among the HBCs. The treatment success rate for TB, which began at 25% in 1995, reached 88% in 2011 (WHO, 2013).

Approximately 2% of new and 15% of retreatment TB cases were MDR in 2011 (WHO, 2013). Furthermore, there was a significant increase in detected MDR-TB cases between 2011 and 2012 from 4,237 to 16,588 (WHO, 2013). India has displayed a sharp increase in both TB and MDR-TB cases from 2009 to 2012 (WHO, 2013).

One study conducted at one tertiary care hospital in East Delhi from November 2009 to October 2010 investigated 75 TB isolates and detected an MDR-TB rate of 1.30% (Sagar et al, 2013). Another study discovered varying levels of MDR-TB according to location; in a tertiary care center in Mumbai, one of India's largest cities, 51% of the 150 TB isolates were detected as MDR whereas 2% of 150 TB isolates in a rural health center were MDR (Almeida et al, 2003). The resistance rate found in the Mumbai center is one of the highest in the world and potentially implicates the development of a new MDR-TB hotspot in urban areas in India (Almeida et al,

2003). With the exception of the 51% MDR-TB rate detected in Mumbai, India's MDR-TB rate among new TB cases stands at approximately 2%.

China

China is also considered a HBC; the nation possessed 12% of the world's TB cases and approximately 1 million incident cases in 2012 (WHO, 2013). However, like Brazil, its rates of TB are fairly lower than most of the other HBC countries (WHO, 2013). Along with Brazil and 20 other countries, China has had a steady decline in TB cases over the past 20 years. The treatment success rate in 2011 was 95% (WHO, 2013).

The WHO reported that 5.7% of new and 26% of retreatment TB cases were multidrug-resistant in 2012 (WHO, 2013). India and China have the highest MDR-TB burden with an estimated 50,000 current MDR-TB cases each (WHO, 2013).

An overview of ten Chinese provinces – Henan, Shandog, Zhejiang, Guangdong, Hubei, Liaoning, Henan, Inner Mongolia, Beijing, Shanghai, Heilongjiang – covering 38% of the total population from 1996 to 2004 found a MDR-TB rate of 5.4% among new TB cases and 25.6% among previously treated cases (He et al, 2008). In 2007, a study conducted on a national scale found very similar MDR-TB rates in the population: 5.7% among new and 25.6% among retreatment cases (Zhao, Y. et al, 2012). Other studies conducted in Shanghai from 2004 to 2007 and Lianyungang from 2011 to 2012 determined MDR-TB's prevalence to be 5.6% and 8.7%, respectively (Zhao et al, 2009; Liu et al, 2013). Overall, these studies show that the rate of MDR-TB in China is 5.6% of all new TB cases.

South Africa

South Africa is a HBC possessing the fourth largest TB-infected population in the world behind India, China, and Indonesia (WHO, 2013). Rates of TB are 1000 or more cases per 100,000 population, and there was an incidence rate of approximately 0.5 million in 2012 (WHO, 2013). The WHO reports that the nation has exhibited a steady upward trend in TB incidence rates from 1990 to 2012, with rates plateauing slightly in most recent years (WHO, 2013). The treatment success rate in 2011 was 79% (WHO, 2013).

Like India, South Africa showed the largest increases in MDR-TB detection from 10,085 to 15,419 cases between 2011 and 2012 (WHO, 2013). The WHO reported rates of MDR-TB in South Africa to be 1.8% of new TB cases and 6.7% of retreatment cases and demonstrated an upward trend in detected MDR-TB cases from 2009 to 2012 (WHO, 2013). One nationwide study, which spanned nine unique South African provinces and 920 people per province from 2001 to 2002, found overall MDR-TB rates to be 1.6% among new and 6.6% among retreatment TB cases (Andrews et al, 2007). Higher rates – 14.4% and 39%, respectively – were detected in the rural area of KwaZulu Natal between 2005 and 2006 (Gandhi et al, 2006). However, the majority of studies show that the prevalence of MDR-TB in new patients presenting with TB falls at approximately 2% of cases.

MDR-TB: BRICS

Each country and its unique rates of MDR-TB are presented in Table 4 and Figure 4. The various colors represent different studies, which are independent of each other from country to country. Thus, a green point for India represents one study related to India while the green point for South Africa represents an entirely different study related to South Africa.

Table 4. Rates of MDR-TB in BRICS According to Various Studies

Country	Rate of MDR-TB (New Cases)				
Brazil	1.4	-	-	-	-
Russia	23	-	-	-	-
India	2.2	1.3	51	2	-
China	5.7	5.6	8.6	5.7	5.4
South Africa	1.8	1.6	14.36	-	-

The rankings of the BRICS countries based on MDR-TB rate are as follows:

1. Russia (23%)
2. India (14.1%)
3. China (6.2%)
4. South Africa (5.9%)
5. Brazil (1.4%)

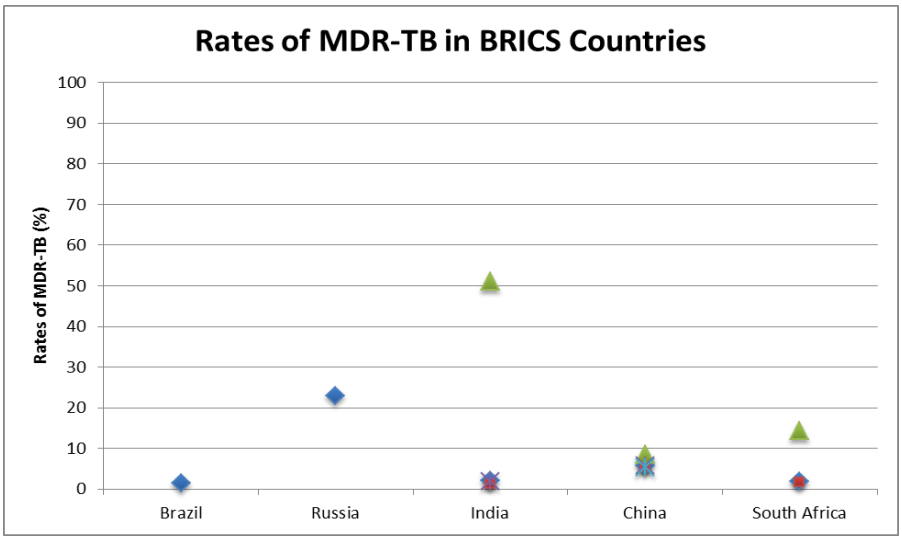

Figure 3. Rates of MDR-TB in BRICS

Russia possesses the highest average rate of MDR-TB according to the WHO Global TB Report while Brazil has the lowest rate of MDR-TB among new TB cases (Figure 3). Rates in China and South Africa are the most similar, with MDR-TB cases accounting for an average of 6% of cases.

STAPH AND MRSA

Brazil

In Brazil, *Staphylococcus aureus* – the bacterium responsible for Staph infections – accounts for 20% of nosocomial primary bloodstream and skin infections (Rossi, 2011). Two types of methicillin-resistant *Staphylococcus aureus* (MRSA) have emerged in Brazil: hospital-acquired (HA) and community-acquired (CA) (Carvalho, Mamizuka, and FIlho). HA-MRSA may be characterized by different genotypes and has been known to be more virulent. Studies done in hospitals have generally reported MRSA rates ranging between 30-60%, with higher rates reported in hospitals' intensive care units (ICUs) (Rossi, 2011). Risk factors for increased MRSA prevalence in ICUs include person-to-person spread from patient to patient, patient to healthcare professional, or healthcare professional to patient (Rossi, 2011).

Brazil was the source of the first CA-MRSA report in Latin America (Guzman-Blanco et al, 2009). Higher levels of CA-MRSA have been detected in populations with high levels of physical contact such as the homeless, prison inmates, military personnel, and children in care centers. In the past, CA-MRSA displayed more susceptibility to antibiotics; however, as these strains of MRSA evolve and come in contact with one another, studies are finding that the distinction between HA- and CA-MRSA is fading (Pacheco et al, 2011).

A total of 6 studies were reviewed to obtain more specific estimates of MRSA rates in Brazil. The first study, which was performed in 2003 throughout 16 ICUs in Brazil's Rio Grande do Sul, found that 64% of Staph infections were methicillin-resistant (Lisboa et al, 2007). Subsequently, MRSA rates generally showed a downward trend. In 2005, a study conducted in the dermatology unit of Hospital das Clinicas of the University of Sao Paolo – a major university

hospital – found a 45% resistance rate, which marked the beginning of the general decrease in detected rates (Pacheco et al, 2011). A couple of years later, the overall MRSA rate was significantly lower at 8.4% in a study conducted in Hospital de Clínicas in Porto Alegre, an urban tertiary-care, public university-affiliated teaching hospital (Santos et al, 2010). A 3-year study surveying four institutions across Brazil – two major teaching hospitals and two smaller centers that collected isolates from regional smaller public and private hospitals found a 31% MRSA rate (Gales et al, 2009). A 2009 study, again at the Hospital das Clinicas of University of Sao Paulo, detected a 15% MRSA rate (Rossi, 2011). Finally, in 2011, a study surveying five different regional sites across Brazil found a 29% MRSA rate (Jones et al, 2011).

Rates of MRSA in Brazil have generally decreased over time (Figure 4). Highest MRSA rates were detected in the early 2000s and became relatively lower with time. The relatively higher rates of MRSA between 2007 and 2011 occurred in studies of regional smaller hospitals across the nation while the lower rates were detected in large urban teaching hospitals.

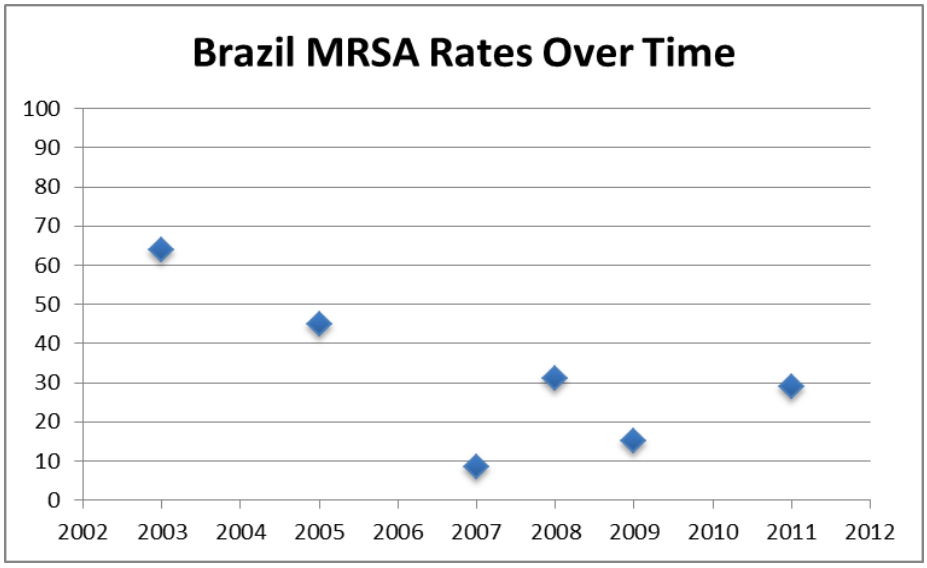

Figure 4. MRSA in Brazil, 2003-2011

Russia

A total of three studies were obtained to analyze the condition of MRSA in Russia. One study conducted in 2004 at the Regional Hospital of Arkhangelsk detected a 17.6% MRSA rate among 91 patients (Vorobieva et al, 2008). Then, between 2006 and 2007, 61 isolates of *S. aureus* derived from both hospitals and community centers were collected from hospital laboratories in Vladivostok and analyzed to demonstrate a 48% rate of MRSA (Baranovich et al, 2010). In this study, 28 of the 30 MRSA strains were proved to be hospital-acquired. The most recent study, which was performed in 2011 on a national level, estimated a MRSA rate of 50% (Jones et al, 2011a). Overall, MRSA rates in Russia have increased over time, and HA-MRSA appears to be the most frequently occurring form of resistance (Figure 5).

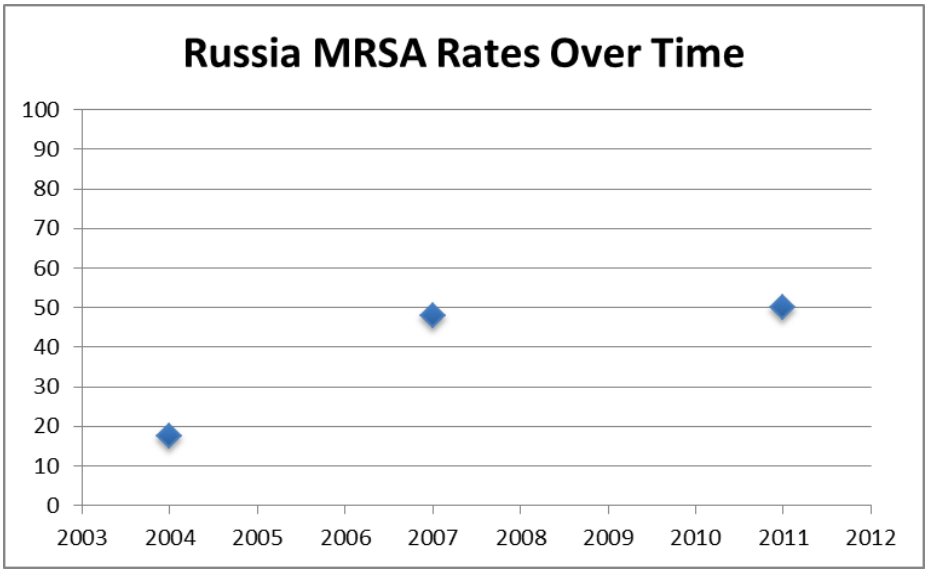

Figure 5. MRSA in Russia, 2004-2011

India

In India, MRSA is primarily hospital-acquired and transmitted among infected patients and hospital workers (Dar et al, 2006). MRSA is particularly exacerbated in ICUs; other factors to consider are the duration of hospitalization and extent of antibiotic exposure.

To acquire an understanding of MRSA prevalence in India, five studies performed in various centers across the country were analyzed. The first study obtained data until 2003 in a hospital in northern India and detected a 35.1% MRSA rate (Dar et al, 2006). The next, which occurred in 2006 in Sir Sundar Lal Hospital, a tertiary care teaching hospital of Banaras Hindu University, detected a slightly elevated rate of resistance at 38.4% (Tiwari, Sapkota, and Sen, 2008). The next few studies were all conducted in 2008 in various tertiary care centers. The study that evaluated 15 tertiary care centers and around 14,000 isolates detected that 42% were methicillin resistant; the next year, the same study found that the MRSA rate in these centers decreased slightly to 40% (Joshi and Balaji, 2013). The other 2008 study examined two different areas in one tertiary care hospital: the ward, which produced a 35% MRSA rate, and the ICU, which had a relatively higher rate at 43% (Wattal et al, 2010).

Rates of MRSA in India have demonstrated a slight increase of 35% to approximately 40% over the past decade (Figure 6); however, there have been no radical changes like there have been in countries like Brazil. Highest MRSA rates were discovered in tertiary care centers and ICUs.

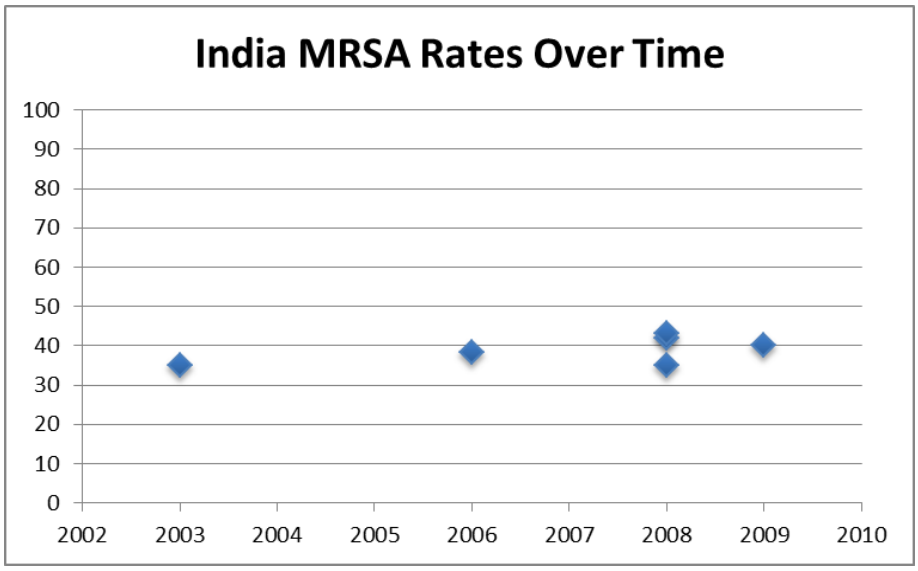

Figure 6. MRSA in India, 2003-2009

China

According to Chen et al, MRSA epidemiology in China is actively evolving. A 2005 study involving 16 centers in 12 different cities across China including Shanghai, Beijing, and Shenyang evaluated 800 *S. aureus* isolates and determined an average MRSA occurrence of 50.4% (Wang et al, 2008). Zou et al examined 11 hospitals in Changsha between 2006 and 2008 and found a MRSA rate of 27.5%. Four 2011 studies targeted various hospitals in unique areas and found similar MRSA rates. An evaluation of 16 different hospitals in the capitals of 12 provinces discovered a MRSA prevalence of 47.5% (He et al, 2013). Another study, which analyzed MRSA rates in 12 different hospitals located in Beijing, Shenzhen, Wuhan, Shenyang, Jilin, Hangzhou, and Zhengzhou, found an overall resistance rate of 45.3% (Jones et al, 2013a). The third study, which collected data until 2011 from 12 teaching hospitals across the country in Beijing, Shanghai, Hangzhou, Wuhan, Shenyang, and Guangzhou, discovered a 46.8% MRSA rate (Zhao et al, 2013). The final study evaluated the prevalence of MRSA in Huashan Hospital, a major teaching hospital in Shanghai, and discovered a rate of 68.1% (Li et al, 2013).

MRSA rates in China have demonstrated an upward trend between 2005 and 2008 (Figure 7). The majority of studies indicate that MRSA rates decreased in 2011; however, all three of the studies demonstrating a rate of approximately 46% were conducted in several hospitals throughout multiple cities while the significantly higher rate of 68.1% was detected in one teaching hospital in a major city. Such data may indicate that overall MRSA rates in China are lower when considering the country at large.

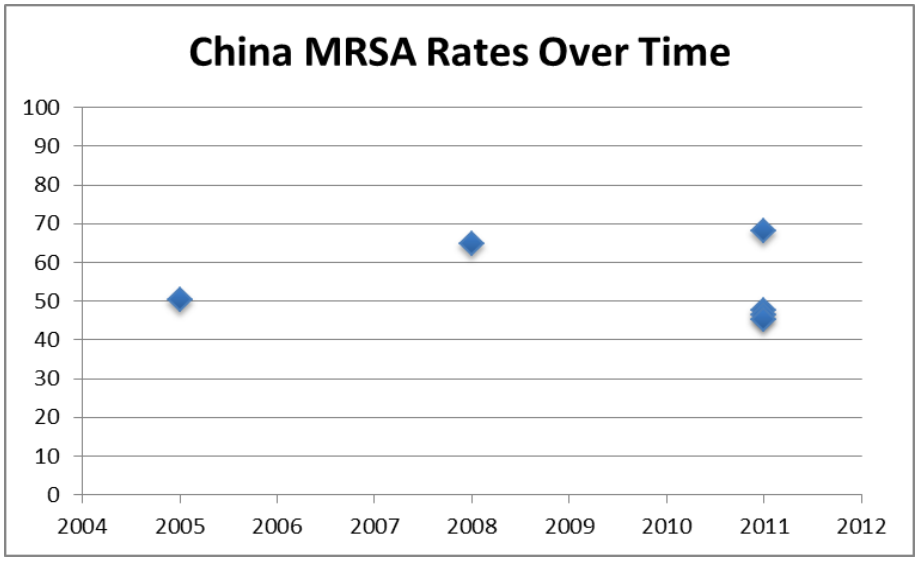

Figure 7. MRSA in Brazil, 2005-2011

South Africa

In the early 2000s, rates of MRSA in South Africa were relatively low. Perovic et al examined 2 academic hospitals in Johannesburg from 1999 to 2002 and discovered a 23.4% MRSA prevalence (2006). The next year, Shittu and Lin found a MRSA rate of 26.9% across 14 provincial hospitals in 7 districts of the KwaZulu-Natal province (Shittu and Lin, 2006). Falagas et al's study of 3 tertiary and 2 secondary-level public hospitals took place in two phases: the first occurred in 2006, and the second took place from 2007 to 2011 (2013). The MRSA rate in 2006 was 36% and 24% at the study's conclusion in 2011.

In South Africa, MRSA rates appear to have increased until the mid-2000s and then started to decrease in the past few years (Figure 8). Fairly similar MRSA rates have been detected in studies targeting both single and multiple regions.

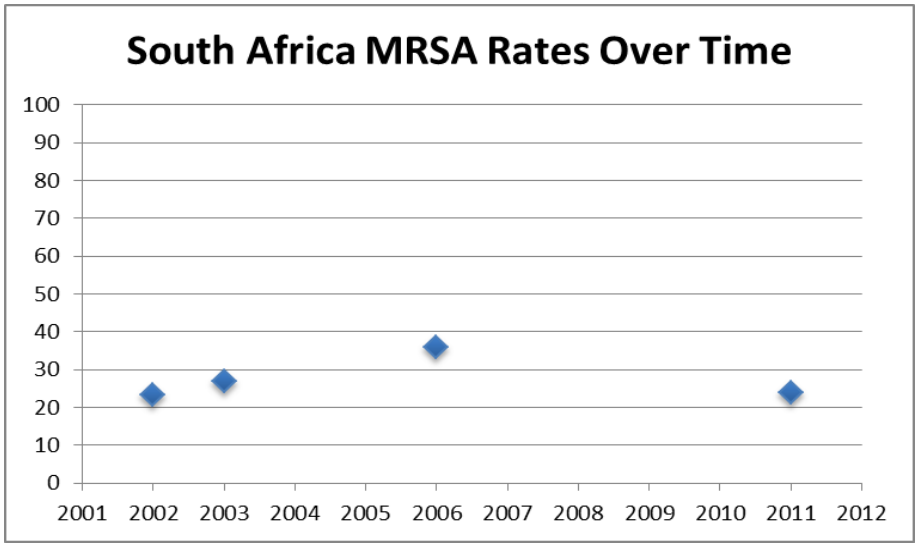

Figure 8. MRSA in South Africa, 2002-2011

MRSA: BRICS

Various rates of MRSA are detected in the BRICS nations by different studies over time (Figure 9). The highest rates tend to be located in China, and the lowest rates are in South Africa. Because rates reported in India, China, and South Africa tend to accumulate around certain values, they appear fairly precise; however, rates reported in Brazil and Russia are dispersed over a larger range of values.

The rankings of the BRICS countries based on their average MRSA rates are as follows:

1. China (53.8%)
2. Russia (38.5%)
3. India (38.3%)
4. Brazil (32.1%)

5. South Africa (27.6%)

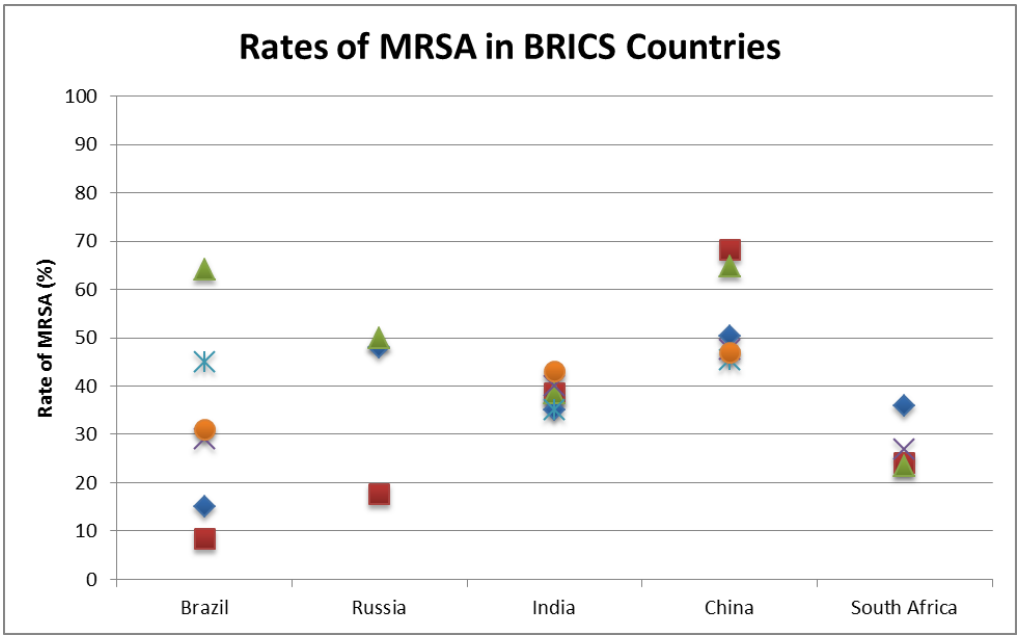

Figure 9. MRSA Rates in BRICS

PNEUMONIA AND PRSP

Brazil

Mantese et al reported a PRSP rate of 15% during a four-year study culminating in 2003 at Hospital de Clínicas of the Universidade Federal de Uberlândia (HCUFU), which is located in Brazil's second most populated state Minas Gerais (Mantese et al, 2003). Other studies that encompassed six to seven years and ended in 2004 found fairly similar rates in certain areas; Castanheira et al and Bedran et al found an 11% PRSP rate in Sao Paulo, the largest city in Brazil located in the southeast, and 11.8% rate in Minas Gerais, respectively (2006). Brandileone et al studied Brazil on a national scale (2006). Their examination of 72 hospitals and 23 public health labs across the nation – of which approximately half were from the southeast, a quarter from the northeast, and a minority were from the south, central-west, and north – found an overall PRSP rate of 27.9%, which was higher than the 10.2% detected by this study in 1993. Brandileone et al also determined that PRSP occurred at higher rates in southeast Brazil than any of the other regions. In 2008, Yoshioka et al studied isolates from Sao Paulo and found that 7.5% of isolates were penicillin-resistant.

Overall, PRSP rates in Brazil are varied according to time and location (Figure 10). Although the national study by Brandileone et al found that PRSP was most prevalent in the southeast in part due to the increased accessibility to penicillin in this developed region, a slight decrease has been found in recent years in Sao Paulo (Yoshioka et al, 2011). The national-scale study generally reported a higher rate of PRSP than the regional studies in Sao Paulo and Minas Gerais, which may indicate that there are significant regional differences in penicillin resistance in Brazil.

Figure 10. PRSP in Brazil, 2003-2008

Russia

A study conducted from 1998 to 2003 in Moscow, Russia's capital and a highly populated city, found 18.6% of isolates to be penicillin-resistant (Grudinina et al, 2004). Other studies in various regions detected increasingly higher resistance rates. In 2004, an examination of isolates from Vladivostok Naval Hospital in Far East Russia found a 23.1% PRSP rate (Martynova and Turcutyuicov, 2004). Between 2003 and 2005, a significantly higher PRSP rate of 64.5% was detected in the central and northwestern regions of Russia, which included the cities of Moscow, St. Petersburg, and Yaroslavl (Reinert et al, 2008).

These three studies indicate the presence of an upward trend in PRSP between 2003 and 2005 (Figure 11). The highest prevalence of penicillin resistance has been detected in cities with the heaviest population densities in Russia such as Moscow.

Figure 11. PRSP in Russia, 2003-2005

India

A study that concluded in 2002 in North India obtained a PRSP rate of 18.3% (Goyal et al, 2007). Six years later, two studies were performed in separate tertiary care hospitals: one in Karnataka, on the south coast of India, and the other in New Delhi, India's capital and largest city. The prevalence of PRSP in the Karnataka hospital was reported to be 4%, and the rate detected in New Delhi center was slightly more than double the Karnataka rate at 9.5% (Chawla et al, 2010; Wattal et al, 2010). The most recent study, which finished in 2010, obtained isolates from New Delhi and found a 5% resistance rate (Shariff et al, 2013).

Overall, penicillin resistance rates from 2002 to 2010 exhibit a downward trend (Figure 12). The highest rates were detected over a decade ago and have subsequently decreased. Resistance has been most prevalent in heavily populated areas; New Delhi has consistently had higher rates of resistance than other regions (Wattal et al, 2010; Shariff et al, 2013). However, the detected rate of PRSP in New Delhi has decreased by half between 2008 and 2010.

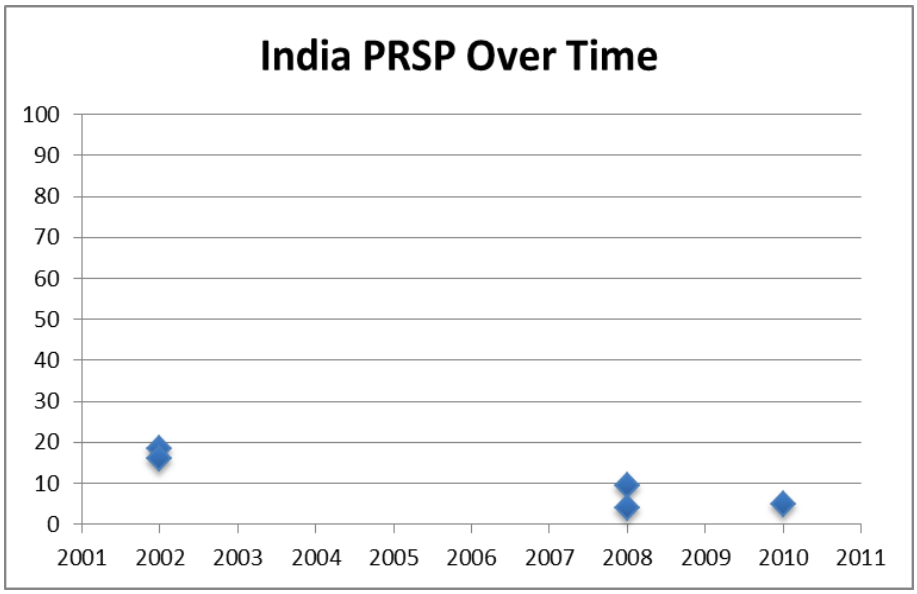

Figure 12. PRSP in India, 2002-2010

China

Five studies conducted across several hospitals throughout China were analyzed to obtain an overview of penicillin-resistant *S. pneumoniae* in China. A study beginning in 2005 that included isolates from 12 different teaching hospitals throughout China found a PRSP rate of 27% in 2005; five years later, this rate was more than doubled to 60% (Zhao et al, 2012). The other four studies all culminated in 2011. Zhao et al examined 12 major cities along the east and eastern coast – Beijing, Shanghai, and Guangzhou among them – and detected a 66% PRSP rate (Zhao et al, 2013). A similar study, performed by Jones et al, surveyed over ten hospitals also throughout Eastern China and found a 49% PRSP rate (2013a). An examination of the central and eastern regions in 7 hospitals detected a 61.5% PRSP rate (Zhang et al, 2013). Lastly, Wang et al surveyed 13 hospitals across China for a 50% overall PRSP prevalence (2013).

Rates of PRSP in China display an upward trend from 2005 to 2011 (Figure 13). The majority of studies were conducted in Eastern China, a region adjacent to the coast that contains

many of the nation's cities and is therefore the most heavily populated; this area was the source of the highest rates of PRSP. Most recently, more than half of all *S. pneumoniae* infections have been detected to be penicillin-resistant.

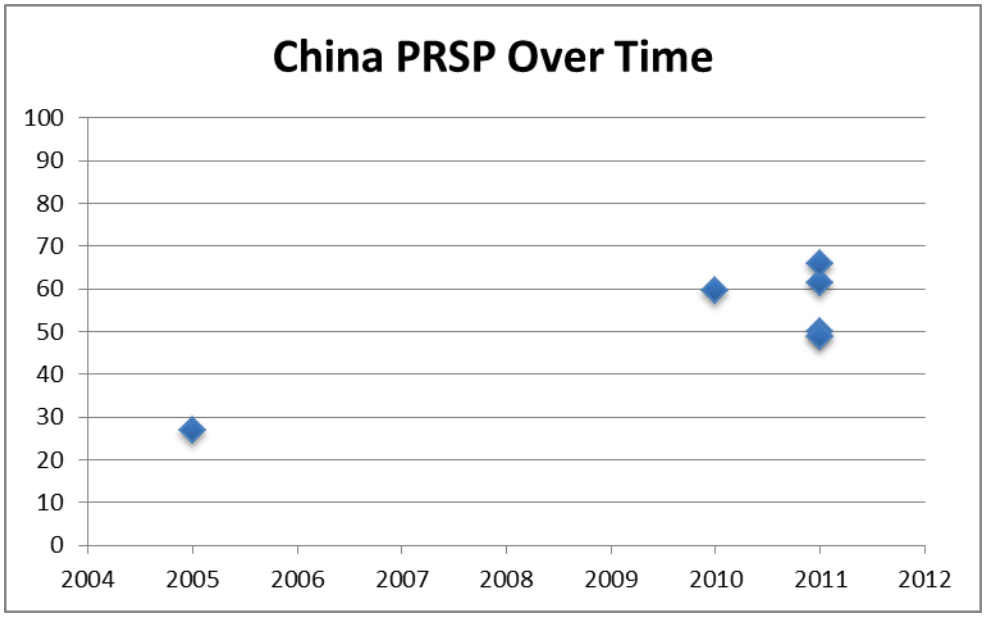

Figure 13. PRSP in China, 2005-2011

South Africa

In South Africa, the PRSP rate detected in 2002 by a national program surveying multiple centers throughout the country was 46% (Leibowitz, Slabbert, and Huisamen, 2003). The following year, Schito and Flemingham reported a slightly elevated penicillin resistance rate of 51% from various centers across the nation (2005). In 2005, a study of over a hundred laboratories throughout South Africa detected a PRSP prevalence of 25% (Wolter et al, 2008).

According to these studies, the rate of PRSP was highest in the early 2000s and appears to have been approximately 50% (Figure 14). Although Liebowitz, Slabbert, and Huisamen report

a reduced rate of resistance in 2005, it is difficult to ascertain whether or not rates have continued or will continue to decrease consistently.

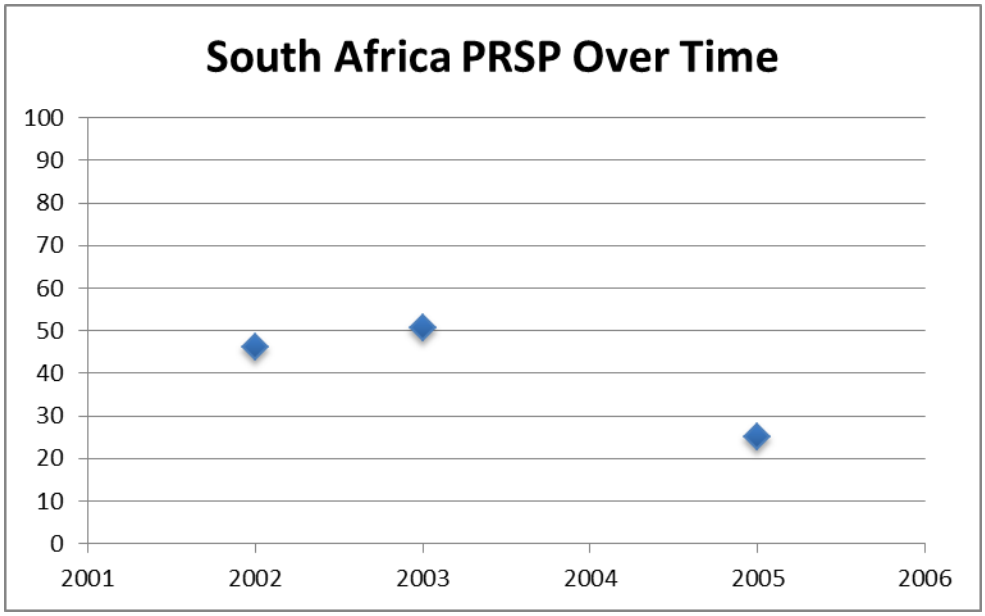

Figure 14. PRSP in South Africa, 2002-2005

PRSP: BRICS

Of the BRICS nations, Brazil and India have the most precise values of PRSP rates across studies (Figure 15). These two countries also have the relatively lowest and most constant rates over time; PRSP rates generally fall below 20%, with Brazil's ranging between approximately 10% and 20%, and India's between 5% and 20%. Russia, China, and South Africa have values for PRSP rates over larger ranges, which may be either due to the fact that there have been more changes in resistance rates over the past decade or because there are inherently greater levels of regional variation in penicillin resistance in these countries. Of these three countries, Russia has the largest spread followed by China and then South Africa; however, these countries' values all

fall between 20% and 65%, which is a higher range than that of the values detected in both Brazil and Russia.

The rankings of the BRICS countries based on their average PRSP rates are as follows:

1. China (49.3%)
2. South Africa (40.5%)
3. Russia (35.4%)
4. Brazil (12.9%)
5. India (9.2%)

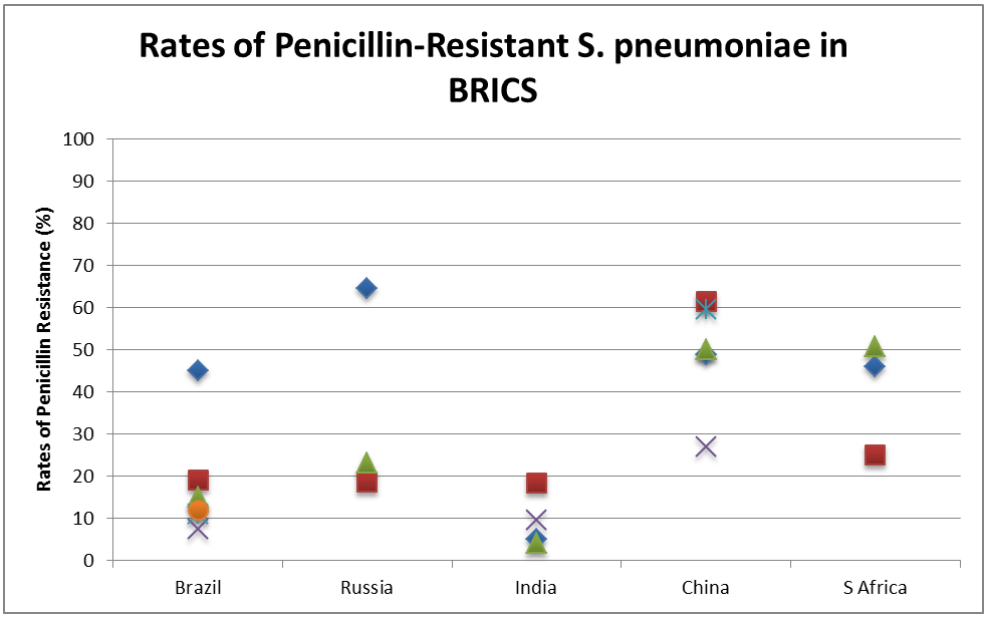

Figure 15. Rates of PRSP in BRICS

FACTOR 1: SURVEILLANCE AND MONITORING SYSTEMS

The first of three major factors in the development, growth, and spread of antimicrobial resistance in a nation is its surveillance and monitoring systems ("Antimicrobial"). According to Health Protection Scotland, the ideal surveillance and monitoring systems will have "consistent data reporting by labs to highlight extent and nature of resistance, provide early warning system for emerging resistance, and enable measurements of effects of intervention strategies for resistance."

Brazil

MDR-TB

According to the WHO, Brazil currently performs MDR-TB surveillance on a sub-national level and the most recent data received by the WHO from Brazil is from between 2005 and 2009 (*Situation* 46). Because Brazil possesses a limited understanding of its overall MDR-TB burden, it is considered less able to detect and address emerging resistance quickly. About 80% of MDR-TB laboratory centers are covered by external quality assessment programs (*Situation* 61).

MRSA

Surveillance of MRSA is similarly limited to specific regions. From 1997 to 2001, four hospitals in various cities across Brazil contributed data to the SENTRY Antimicrobial Surveillance Program, which aimed to monitor the local resistance levels of a number of pathogens including *S. aureus* (Gales et al, 2009). MRSA is also monitored through local and national laboratories associated with the Pan-American Health Organization (PAHO) (Guzman-

Blanco et al, 2009). However, surveillance of MRSA is again limited by the lack of even distribution of hospitals equipped with necessary technology to send data throughout the country.

PRSP

The last noted effort to survey PRSP on a regional level was accomplished from 1993 to 2004 by the SIREVA (Sistema Regional de Vacunas) project, which was sponsored by the PAHO (Mantese et al, 2003). Data from pneumococcal isolates were collected and sent to a public health laboratory in Sao Paulo for analysis.

Russia

MDR-TB

The most recent surveillance data for MDR-TB from Russia was conducted sub-nationally and reported between 2010 and 2012; therefore, like Brazil, Russia is not currently optimally equipped to respond to MDR-TB (WHO, 2013). The WHO also noted that data from remote areas of Russia lacking proper laboratory facilities were more likely to be unreliable. External quality assessment programs monitor approximately 95% of MDR-TB laboratory centers across Russia (WHO, 2013).

MRSA

In 2011, a Regional Resistance Surveillance study of various disease agents, one of which was *S. aureus*, was conducted throughout 21 countries including Russia (Jones et al, 2013). No other national efforts to survey MRSA have been identified.

PRSP

No existing national or regional efforts to survey the prevalence of PRSP in Russia were able to be identified.

India

MDR-TB, MRSA, PRSP

The WHO reported that India conducted its first survey for MDR-TB in 2013, the data for which were received from facilities nationwide. Quality assessment programs cover all labs in India (WHO, 2013). According to the Ministry of Health and Family Welfare, "[India has] no accepted national database of antimicrobial resistance in different pathogens" (India). Specific pathogens may be monitored and tested periodically according to localized interest; however, this data is neither centralized by the nation nor made available for public health purposes (India). No national or regional efforts to monitor MRSA or PRSP could be identified.

China

MDR-TB

China has performed repeat nationwide surveys of MDR-TB that have continued throughout 2013 (WHO, 2013). Of the non-European HBCs, China had the highest coverage of MDR-TB testing (WHO, 2013). The Chinese Center for Disease and Control includes a National Tuberculosis Reference Laboratory (NTRL), which also conducted a national survey of MDR-TB in 2007 (Zhao, Y. et al 2012). Furthermore, China has implemented external quality assessment programs to evaluate 95% of its laboratory centers throughout the country (WHO, 2013).

MRSA

No national or regional efforts to monitor MRSA in China could be identified.

PRSP

No ongoing national or regional methods of PRSP surveillance could be identified. From 2008 to 2009, trends in PRSP in China were monitored through an external entity: the Asian Network for Surveillance of Resistant Pathogens (ANSORP) (Kim et al, 2012).

South Africa

MDR-TB

Like China, South Africa runs repeat MDR-TB surveys that have continued in 2013 across the country (WHO, 2013). External quality assessment programs are available for 95% percent of South Africa's surveillance laboratories (WHO, 2013).

MRSA

According to Nyasulu et al, there are no centralized laboratories or data collection methods that are able to monitor MRSA accurately and consistently in South Africa (2012).

PRSP

SENTRY's Antimicrobial Surveillance Program has conducted PRSP surveillance since 1998 (Nyasulu et al, 2012).

Summary of Surveillance Systems for MDR-TB, MRSA, and PRSP

Tables 5 through 7 provide overviews of the surveillance systems in place for MDR-TB, MRSA, and PRSP in the BRICS countries.

Table 5. MDR-TB Overview

	Surveillance (Y/N)	National-level surveillance data	Most recent data	Coverage of MDR-TB testing (new cases)	Labs with external quality assessment programs
Brazil	Yes	No	2005-2009	-	> 80%
Russia	Yes	No	2010-2012	79%	> 95%
India	Yes	Yes	2013	-	100%
China	Yes	Yes	2013	3.60%	> 95%
South Africa	Yes	Yes	2013	-	> 95%

Table 6. MRSA Overview

	Surveillance (Y/N)	Surveillance Scale	Most recent data
Brazil	Yes	Regional	1997-2001
Russia	Yes	Regional	2011
India	No		
China	No		
South Africa	No		

Table 7. PRSP Overview

	Surveillance (Y/N)	Surveillance Type	Most recent data
Brazil	Yes	Regional	1993-2004
Russia	No		
India	No		
China	No		
South Africa	Yes	Regional	Since 1998

FACTOR 2: MEDICINE DISTRIBUTION

Proper medicine distribution, another integral component to managing the occurrence of AMR, may be described as the regulation and quality of drugs available to people in communities, hospitals, and health centers across a nation. Prescriptions are an essential component of drug management because they have a significant influence on drug accessibility; a lack of proper prescribing practices by physicians contributes to higher rates of antimicrobial resistance among patients who engage in inappropriate self-medication and irrational drug use (Wang, H. et al, 2013).

Brazil

No prescriptions were necessary to obtain antibiotics in Brazil until 2010. On October 26 of that year, the Brazilian National Agency of Health Surveillance (ANVISA) passed an act eliminating the distribution and sale of antibiotics over-the-counter (OTC) and establishing the need for prescriptions (Santa-Ana-Tellez et al, 2013). The Act was specifically collaborated with pharmacies, the dispensing centers for antibiotics among other drugs, stating that pharmacies were to make two copies of a prescription: one to be kept by the pharmacy and another to be stamped and issued back to the consumer. Pharmacies that do not cooperate with these regulations may be fined up to $1.5 million BRL and have their supplies taken. The Institute for Healthcare Informatics evaluated the impact of the Administrative Act and found that the consumption level of antibiotics in 2012 was 18% lower than the level that had been predicted in Brazil if the policy had not been in place; specific decreases in the use of penicillins and macrolides, which are both antibiotics used in the treatment of pneumonia, were noted.

ANVISA is responsible for regulating drug manufacture through the Brazilian Public Pharmaceutical Manufacturing Laboratories (PPML) (Santa-Ana-Tellez et al, 2013). Furthermore, a national WHO-approved authority is responsible for overseeing a network of manufacturers that produce antibiotics to treat TB (Gemal et al, 2013).

Russia

The acquisition and consumption of antibiotics do not require prescriptions in Russia; antibiotics are available for purchase in drug stores without restriction, and people choose to purchase drugs based on pharmacists' recommendations or information obtained from the mass media, which is often inaccurate or low quality (Stratchounski et al, 2003). Stratchounski et al conducted an extensive study of Russian households in 2003 and found 83.5% of the families that were surveyed kept antibiotics – some of which were expired or discontinued – in their home medicine cabinets for regular use.

According to Ulla Pape, "no obligatory guidelines or general quality standards" exist in Russia (2013, p. 107). Mossialos et al also note significant lacks of documentation and enforcement of safety and quality standards for drugs in the nation (2004, p. 274, 343).

India

Although prescriptions are administered, they are effectively non-functional in medicine distribution and regulation systems due to the absence of a stringently applied or effective prescription monitoring system in India. Antibiotics may be purchased OTC, with a previously used or outdated prescription, with a prescription from a non-allopathic doctor, or no physician signature at all (*Situation*). Pharmacists who are unqualified to provide healthcare

recommendations to patients routinely influence patients' decisions on which antibiotics to use. Between 2005 and 2009, the number of antibiotics sold increased by 40% (*Situation*).

Drug quality in India is largely compromised. The national government estimated that approximately 10% of drugs being produced and sold in India between 1995 and 2003 were either counterfeit or substandard (Bate et al, 2009). Due to the geographically vast nature of the country, there are also considerable variations in drug quality between states that are unable to be regulated. The establishment of a National Drug Authority that would enforce quality control for antibiotics has been proposed in the past; however, it has yet to be created (Bate et al, 2009).

China

Prescriptions are necessary to purchase antibiotics in China, but prescribing practices vary widely according to the region. For example, Dong, Yan, and Wang found that rural village clinics in certain provinces of Western China had higher rates of prescribed antibiotics than others (2008). Yin et al report that higher antibiotic use is also recommended by less educated physicians working in lower-level hospitals in more rural areas (2013). Such variation may exacerbate the prevalence of AMR by encouraging self-medication practices instead of adherence to a specific regimen.

This variation in prescribing practices is partially due to the inadequate nature of national guidelines concerning antibiotic use. The Chinese Ministry of Health has attempted to regulate the utilization of antibiotics on various occasions; it published a report containing guidelines for physicians regarding antibiotic use in 2004 and enacted clinical antibiotic control practices in 2012 (Xiao and Li, 2013). Furthermore, physicians report being commonly influenced by pharmaceutical companies that urge physicians to prescribe one antibiotic over another for financial purposes (Reynolds and McKee, 2009).

The Chinese State Food and Drug Administration (SFDA) monitors drug circulation and quality standards through Good Supply Practices (GSP) regulations ("Newly"). However, because there is no general population-based drug database, the formation and management of a comprehensive drug management system to explore regional variation in drug use are difficult (Zhang et al, 2008).

South Africa

In South Africa, prescriptions are required to gain access to antibiotics. Pharmacies generally enforce prescription-based administration, so OTC sale of antibiotics is very limited ("Situation").

Antibiotics are regulated differently in the public and private spheres. The South African government has published an essential drugs list (EDL) – an enumeration of drugs that "satisfy the health care needs of the majority of the population [and] should therefore be available at all times in adequate amounts" at affordable prices – and standard treatment guidelines (STGs) to oversee antibiotic use in the public sector (*Selection*; "Situation"). In the private sector the EDL and STGs are neither followed nor enforced. According to the Global Antibiotic Resistance Partnership (GARP)'s evaluation of South Africa, one in five medicines is believed to be counterfeit ("Situation"). Universities that are contracted by the Medicines Control Council (MCC) own centers that perform drug quality testing; the government does not have such labs ("Situation").

FACTOR 3: DIAGNOSTIC AND THERAPEUTIC TOOLS

The third vital feature of effective AMR management is the proper use of diagnostic and therapeutic tools. Successful implementation of diagnostic and therapeutic methods involves the correct analysis of patients' conditions, determination and implementation of appropriate treatments, the prevention of blind use, overuse, and misuse of antibiotics, and patient compliance.

Brazil

Antibiotic overuse and underuse both occur frequently in the sphere of Brazilian healthcare. One study of a university hospital showed that the administration of antibiotics as considered therapeutically inadequate in 27% to 31% of cases (Fonseca and Conterno, 2004). Rossi noted the prevalence of overuse in the high consumption of last-resort drugs in a hospital ICU. Inappropriate prescribing practices, which also contribute to overuse and underuse, are prevalent in Brazil and vary from region to region (Da Cunha, Amaral, and Silva, 2003). Patient compliance, though difficult to measure accurately, is known to be lower in pediatric patients (De Sa Del Fiol et al, 2013).

Russia

Rates of overuse in the community are generally high because antibiotics can be obtained over the counter in Russia. Overuse is also prominent in hospitals; a study conducted by Balabanova et al in Samara City, Russia discovered that 25% of the patients who received an

antibiotic for their condition did not require one (2004). There is also a pervasive lack of knowledge regarding AMR among the general population, and information from the mass media about this topic is limited in scope and accuracy (Balabanova et al, 2004; Stratchounski et al, 2003).

General practitioners in Russia report that external factors can influence the decisions they make when prescribing antibiotics. For example, doctors may over-prescribe when they feel pressured by pharmaceutical companies to endorse certain drugs; one study found that companies engage in a variety of activities from paying direct visits to physicians or funding physicians' educations (Jaruseviciene et al, 2013). Balabanova et al also determined that 80% of 425 doctors made prescribing decisions based on information promoted by pharmaceutical companies (2004). In addition, certain antibiotics are reimbursable through insurance policies and therefore are prescribed more frequently. Physicians who desire financial protection from external auditors will prescribe antibiotics even when they are clinically unnecessary (Jaruseviciene et al, 2013).

Finally, the lack of national guidelines detailing the latest proper treatment regimens exacerbates physicians' confusion regarding proper prescribing practices (Jaruseviciene et al, 2013).

India

A survey of prescriptions administered by physicians in a pharmacy serving the state of Goa, India demonstrated a significant lack of quality instructions and information regarding various drugs (Patel et al, 2005). A majority of prescriptions were characterized by polypharmacy: the administration of more than one drug per patient and often a sign of irrational drug use; 80% of the prescriptions were for more than one drug, and approximately 50% of the prescriptions were for at least three (Patel et al, 2005). Instructions for the patient regarding the

medications – most of which were antibiotics and branded medicines – were frequently illegible, unclear, or lacking significant information (Patel et al, 2005). These findings indicate that physicians may not be administering the most substantiated or cost-effective remedies for their patients.

Communities possess limited knowledge regarding the proper therapeutic use of antibiotics; therefore, misuse and blind use is often observed and compliance is neither commonly observed nor enforced (Kotwani et al, 2010). In the face of diagnostic and subsequently therapeutic uncertainty, physicians have been observed to tailor their treatment recommendations to perceived patient expectations (*Situation*).

China

In China, several considerations – many of which are common to the other BRICS nations – influence how physicians prescribe antibiotics. One factor is financial; the fact that physicians split profits with pharmaceutical companies over certain medications drives over-prescribing practices and therefore overuse of antibiotics (Reynolds and McKee, 2009). A lack of thorough knowledge about AMR exacerbates this issue. Another significant factor is the patient himself. Studies in China have found that, like in India and other countries, physicians are affected by their patients' expectations (Reynolds and McKee, 2009). Furthermore, the physician-determined use of antibiotics varies considerably according to region (Zhang et al, 2008).

Due to the promotion of antibiotics in the media, self-medication is a common practice among communities that also acts as an enabling factor for the overuse, underuse, and blind use of antibiotics (Wang, H. et al, 2013; Reynolds and McKee, 2009).

South Africa

One study conducted throughout ICUs in South African hospitals demonstrated that over 50% and 80% of prescribing practices in the public and private sector respectively were determined to be erroneous (Paruk et al, 2012). In 72% of cases examined, patients were using antibiotics over inappropriate durations, and instances of polypharmacy – in this case specifically, the prescription of more than four antibiotics at a given time for a patient – were detected (Paruk et al, 2012). Polypharmacy to this degree is considered a reasonable indication of diagnostic and therapeutic uncertainty among physicians in both the public and private spheres (Patel et al, 2009).

The proper consumption of antibiotics and regimen compliance among patients is hindered by the fact that many people lack reliable access to diagnostic facilities or health clinics ("Situation").

DISCUSSION

Comparative Analyses of Factors

Surveillance and Monitoring Systems

The first factor considered when evaluating the relative effectiveness of surveillance in the BRICS nations was whether or not monitoring was possible on a national level. According to the WHO, the countries with national-scale surveillance have the best understanding of antimicrobial-resistant pathogens and are subsequently most able to detect and respond to emerging trends in resistance. Table 8 provides a summary of surveillance systems of the examined diseases in BRICS.

Table 8. Summary of Surveillance Systems in BRICS for MDR-TB, MRSA, PRSP

	MDR-TB Surveillance	MRSA Surveillance	PRSP Surveillance
Brazil	Yes (sub-national)	Yes	Yes
Russia	Yes (sub-national)	Yes	No
India	Yes (national)	No	No
China	Yes (national)	No	No
South Africa	Yes (national)	No	Yes

Although Brazil was found to operate on the basis of sub-national data collection for MDR-TB, it is the only nation to possess monitoring systems for both MRSA and PRSP as well (Table 8). Therefore, Brazil was ranked first over the other nations for the first factor. India and China both have national surveillance systems in place for MDR-TB but no noted monitoring of either MRSA or PRSP; thus, they were ranked lowest of the BRICS nations. No information regarding the coverage of MDR-TB testing is available for India whereas a value of 3.6% is reported for China. Thus, China was ranked over India.

Complete monitoring systems are not available for both MRSA and PRSP in either South Africa or Russia; South Africa has no system to track MRSA while Russia lacks one for PRSP. However, South Africa has national-scale surveillance in place for MDR-TB whereas Russia does not. Therefore, South Africa was ranked relatively higher than Russia.

The overall ranking for the best surveillance and monitoring systems in the BRICS nations was as follows:

1. Brazil
2. South Africa
3. Russia
4. China
5. India

Medicine Distribution

Due to the significant role that prescriptions have in regulating drug accessibility and consumption, the medicine distribution systems of the BRICS nations were first compared according to whether or not prescriptions were necessary to obtain antibiotics. They were then evaluated according to how they monitored drug quality. Table 9 provides a summary of the data used in this analysis.

Table 9. Medicine Distribution Analysis of BRICS

	Prescription needed?	Drug quality	Result
Brazil	Yes	Strong network of WHO-certified public sector drug manufacturers	1
Russia	No	Regulations lacking in both public and private sectors	4
India	No	High rates of counterfeit or substandard drugs	5
China	Yes	Policies in place for drug quality management	2
South Africa	Yes	No government labs for quality testing	3

Prescriptions were effectively required in Brazil, China, and South Africa. Brazil was ranked first because it possesses a WHO-approved system of drug quality evaluation, and China was placed over South Africa because of South Africa's lack of quality control and testing. Though drug quality is not well supervised in either Russia or India, Russia was ranked over India due to India's documented high prevalence of counterfeit and substandard drugs.

The overall ranking for the best medicine distribution systems among the BRICS nations was as follows:

1. Brazil
2. China
3. South Africa
4. Russia
5. India

Diagnostic and Therapeutic Tools

Overall, the state of diagnostic and therapeutic tools in Brazil, Russia, India, China, and South Africa is similar. According to multiple case studies and literature reviews, the incorrect analysis of patient conditions, the administration of inappropriate treatments in the face of diagnostic uncertainty, and antibiotic misuse – which includes overuse, underuse, and blind use – are all commonly noted in the BRICS nations. Because no significant distinctions could be determined between the nations' diagnostic or therapeutic circumstances, no relative rankings were established.

Summary of Rankings of AMR Factors

Of the BRICS nations, Brazil possesses the best AMR surveillance and antibiotic distribution systems while India has the poorest quality surveillance and drug regulation systems in place. Russia's monitoring and medicine distribution frameworks are in slightly better condition than India's. China and South Africa's systems are on comparable levels with each other, less effective than those in Brazil, and more successful than those in Russia and India. These rankings, which operate on a scale of 1 for highest to 5 for lowest quality, are summarized in Table 10.

Table 10. AMR Factors Ranking

	Factor 1 Ranking	Factor 2 Ranking	Factor 3 Ranking	Overall Ranking
Brazil	1	1	N/A	1
Russia	3	4	N/A	4
India	5	5	N/A	5
China	4	2	N/A	Tie
South Africa	2	3	N/A	Tie

Comparative Analyses of Diseases

Overall, the highest resistance rates of the examined pathogens in the BRICS nations were detected in *S. aureus* for methicillin; this finding may be related to the fact that MRSA surveillance systems in each country were either limited or non-existent. Conversely, the BRICS nations all exhibited relatively low rates of MDR-TB, which may partially be because each country is equipped with MDR-TB surveillance systems. The three countries that monitor MDR-TB on a national level – India, China, and South Africa – record three of the lower MDR-TB rates, which is consistent with the WHO's assertion that implementation of national-scale surveillance is a fundamental part of controlling the spread of AMR. Although Brazil monitors MDR-TB on a sub-national level, it currently possesses the lowest rate of MDR-TB among the five countries. A potential explanation for this finding is that a WHO-approved network strictly regulates that Brazil's anti-TB drugs, and strong drug management is a significant way to limit AMR.

The lowest rates of resistance were consistently identified in Brazil; it has the lowest detected rate of MDR-TB at 1.4%, the second-lowest rates of MRSA and PRSP, and an average resistance rate of the three surveyed diseases of 15.47% (Figure 17). These observations correlate with the finding that Brazil has the best surveillance and monitoring systems in place and regulates drug quality and distribution most effectively of the BRICS nations.

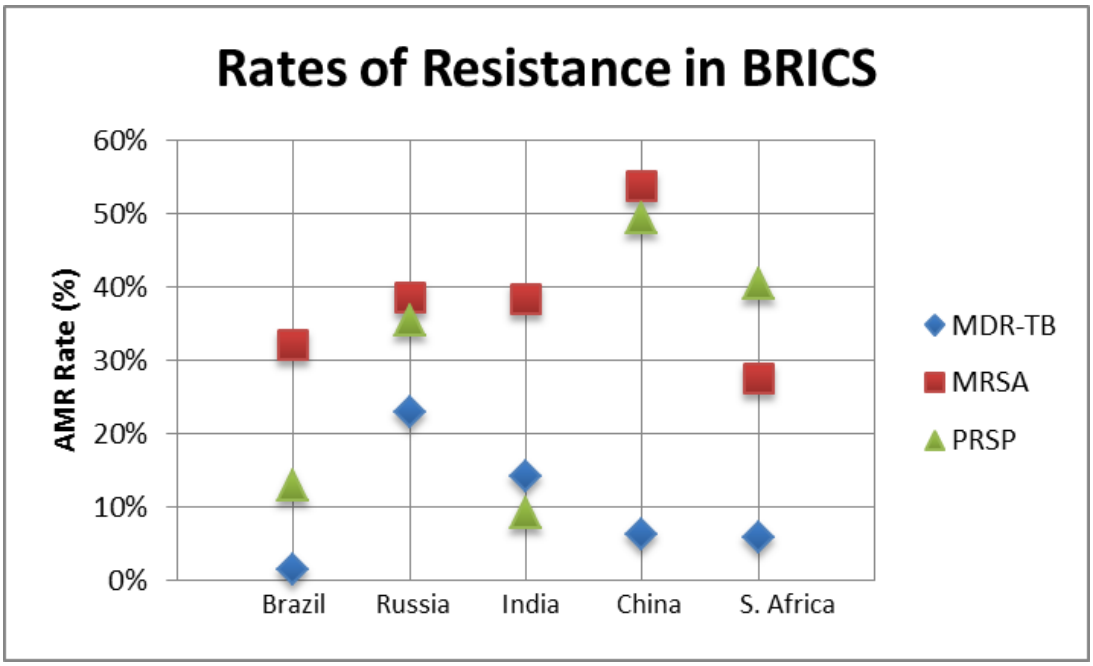

Figure 16. Rates of Resistance in BRICS

Table 11. Rates of Resistance in BRICS

	MDR-TB	MRSA	PRSP	Average AMR Prevalence
Brazil	1.4%*	32.1%	12.9%	15.47%
Russia	23%**	38.5%	35.4%	32.3%
India	14.1%	38.3%	9.2%*	20.5%
China	6.2%	53.8%**	49.3%**	36.4%
South Africa	5.9%	27.6%*	40.5%	24.7%

** Identifies the highest value in column
* Identifies the lowest value in column

Conversely, China had the highest detected prevalence of MRSA and PRSP among the five countries with rates for both reaching greater than equal to 50% of *S. aureus* and *S. pneumoniae* cases examined (Figure 16, Table 11). Although China's rate of MDR-TB was relatively low, the high detected rates of MRSA and PRSP contributed to its standing as the country with the highest average rate of antimicrobial resistance. Interestingly, China tied with South Africa in the effectiveness of its surveillance and drug regulation systems, and South Africa had fairly similar rates of MDR-TB and PRSP as China. South Africa and China's MDR-

TB rates were both approximately 6%, and the two nations had PRSP rates of between 40% and 50% (Table 11). The presence and absence of PRSP surveillance systems in South Africa and China respectively may account for the slightly lower PRSP prevalence detected in South Africa. However, there was significant a contrast between the two countries' MRSA rates. Neither country has monitoring systems for MRSA, so this difference may exist because of variation in how MRSA specifically is diagnosed and treated between China and South Africa: a factor that was unable to be elucidated in the scope of the current existing literature.

The conditions of surveillance and drug distribution systems in Russia are better than those in India but poorer than those in Brazil, China, or South Africa. Russia's overall AMR prevalence and rates of MRSA and PRSP are all second highest among BRICS, which demonstrates that the strengths of surveillance and distribution systems are correlated with the prevalence of resistance in Russia.

India's overall ranking of surveillance system and medicine regulation efficacy was the lowest of the BRICS nations; however, it presented scattered results. Although India possessed the lowest PRSP rate and the second lowest average rate of AMR, its MDR-TB and MRSA burdens were higher than the other nations'. India's MDR-TB prevalence of 14% was particularly high considering that India has national TB surveillance systems in place. One possible explanation for this finding is that there is a differential approach in how MDR-TB, MRSA, and PRSP are being controlled. A difference in the availability of antibiotics – for example, easier accessibility of either rifampicin or methicillin over penicillin – would allow for a higher rate of MDR-TB or MRSA development than PRSP development. Another possible explanation is that cases of PRSP in India are detected and reported less frequently than cases of MDR-TB and MRSA so that, though high levels of PSRP may exist, they are not being accounted for. Furthermore, it is important to note that the rates reported in the analyzed studies may not be reflective of that the actual rates of AMR in India due to the influence of regional variation.

Overall, the statuses of surveillance and medicine distribution systems were correlated to the presence of resistance in TB, *S. aureus*, and *S. pneumoniae* throughout BRICS. Other factors such as regional variation and specific inconsistencies in case detection rates may partially account for observed deviations.

RECOMMENDATIONS FOR THE FUTURE

Improving Surveillance Systems

Both regional and national systems of data collection must be strengthened in order to curb the development of resistance in BRICS; such change also involves the funding and development of national microbiology laboratories to analyze and centralize the data for use by public health authorities (Global Antibiotic Resistance Partnership (GARP), 2011; Kotwani et al, 2010). Diagnostic testing methods of diseases must be standardized and used on a broader scale, eventually reaching health care facilities in even rural regions. The creation and utilization of infection control committees would also help to trace the development of AMR in hospitals, where antimicrobial-resistant strains have been known to emerge and proliferate (Paruk et al, 2012).

Regulating Medicine Distribution

A medicine distribution system in any of the BRICS nations, which encompasses control of drug quality and prescribing practices, may be strengthened through policies that require prescriptions to obtain antibiotics at pharmacies (Stratchounski et al, 2003). Necessary enforcement measures such as fines or other penalties on non-compliant pharmacies may be used to ensure that this ban of over-the-counter sales is effective. Other policies might include creating financial or other incentives to motivate record keeping and adherence to prescription monitoring. An example of such a policy is the 2010 Administrative Act in Brazil, which was able to temper the overall use of antibiotics in the years after its implementation (Santa-Ana-Tellez, 2013; *Advancing*).

In Russia, South Africa, India, the regulation of antibiotics may also be significantly improved by the development of quality assessment programs such as those that exist in Brazil and India to detect counterfeit and substandard drugs.

Utilizing Diagnostic and Therapeutic Tools

All of the BRICS countries would benefit from publishing and distributing national guidelines regarding treatment. These guidelines would act to decrease irrational antibiotic use by alleviating physicians' uncertainties and reducing disparities in treatment methods between physicians and across regions.

According to physicians in nearly all the BRICS nations, an important external influence on prescribing practices is the relationship between physicians and pharmaceutical companies (Jaruseviciene et al, 2013; Reynolds and McKee, 2009; Paruk et al, 2012). Regulations to this part of the healthcare system must be formed and applied to curb the monetary or other incentives offered by pharmaceutical companies to physicians who prescribe their drugs (Kotwani et al, 2010).

It is also crucial that effective treatment plans, such as DOTS for MDR-TB, are implemented and enforced with increased efforts directed toward ensuring patient compliance throughout each nation. This step is markedly more difficult in areas with restricted access to health care facilities; however, proper patient compliance is ultimately necessary to limit the spread resistance.

Educating the Community

Self-medication poses a significant threat to resistance prevention (Stratchounski et al, 2003). This practice is common in communities of each BRICS country but must be stopped through effective community health education about the consequences of improper antibiotic use on both an individual and national level. Community education will also help bring accuracy to patient expectations, bridging the gap between the understandings of physicians and patients regarding treatments and prescribed medications.

Continuing Physician Education

Improving and continuing physician education are crucial to limiting AMR in BRICS (GARP, 2011). Specific areas to target through education are the nature of the diseases – which include but are not limited to TB, *S. aureus*, and *S. pneumoniae* – and the antibiotics used to treat them, the principles behind AMR and its potential consequences, and proper prescribing practices. An evaluation of pharmaceutical services in Brazil showed that education level was an important indicator of how a physician administered drugs in his practice (Emmerick, Luiza, and Pepe, 2009). Educational materials could be most effective if distributed through various means such as lectures, handouts, emails, web-based or physical newsletters, conferences, and verified reports delivered through news outlets or the mass media.

Cooperating with the Press

In China and Russia, the media was an important influence on both patient and physician understanding of antibiotics (Stratchounski et al, 2003; Reynolds and McKee, 2009). Therefore, an effective measure to target resistance may come through the popular press. The government

could authorize public health officials to cooperate with the media to ensure that only accurate information about AMR or antibiotics was released to the public. Such regulation might be able to have a far-reaching effect on educating physicians and communities alike.

Encouraging Research

The resistance of pathogens to general antibiotics is an important public health matter that must be analyzed, understood, and addressed. The WHO has determined that the absences of surveillance and monitoring structures, medicine distribution systems, and diagnostic and therapeutic tools exacerbate AMR trends in countries worldwide. Upon reviewing the existing literature regarding the diseases caused by *M. tuberculosis*, *S. aureus*, and *S. pneumoniae* and examining levels of their resistance to treatment antibiotics over recent years, correlations were discovered between the WHO factors and AMR in Brazil, Russia, India, China, and South Africa. Various changes in policy to promote regional and national monitoring systems, community and physician education, the improved quality of drugs and prescribing practices are required to temper the development of resistance in BRICS.

CONCLUSION

The resistance of pathogens to general antibiotics is an important public health matter that must be analyzed, understood, and addressed. The WHO has determined that the absences of surveillance and monitoring structures, medicine distribution systems, and diagnostic and therapeutic tools exacerbate AMR trends in countries worldwide. Upon reviewing the existing literature regarding the diseases caused by *M. tuberculosis*, *S. aureus*, and *S. pneumoniae* and examining levels of their resistance to treatment antibiotics over recent years, correlations were discovered between the WHO factors and AMR in Brazil, Russia, India, China, and South Africa. Various changes in policy to promote regional and national monitoring systems, community and physician education, the improved quality of drugs and prescribing practices are required to temper the development of resistance in BRICS.

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