Antimicrobial resistance in BRIC countries: what can be done with a one-health approach, a literature review

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Abstract

Introduction

Antimicrobial resistance is a worldwide problem but affects countries known as BRIC countries (Brazil, Russia, India and China) in particular. It is expected that from now until 2030 antibiotic use will double in these countries. Globally, there will be 10 million more deaths in 2050 due to antimicrobial resistance, which is more than cancer. This is a global threat and must be addressed as such. The review is written as a one-health approach that will encompass humans, animals and environment as starting point for interventions.

Methods

This is a literature review for which 13 articles are collected. Solutions mentioned in the articles are combined to create a bigger picture with respect to the one-health approach. Four themes are created that cover all the solutions mentioned in the articles.

Results

The first theme aims at avoiding infections. Clean water and sanitation are critical, especially because water is the most important carrier of resistant bacteria.

The second theme addresses what can be done to decline the use of antibiotics. Here especially legislative matters are important. National and international agreements on the use of antibiotics on humans, animals and agriculture should be created. It is also important to reduce intensive farming, because many antibiotics are used in this process.

Over half of all antibiotics used on humans are considered useless or marginal because, for instance, they are used for viral infections. The third theme is about using antibiotics the right way. This can be promoted through education and can be applied on medical students but also on kids.

New antibiotics will not be created in the next decades, but creating new antimicrobial medication is still necessary. The fourth theme addresses this topic. This should be a collaboration between many agencies trying to find good alternatives to antibiotics. Good results have been shown from phytogenic additives and other natural products, and these are worth investigating.

Conclusion

These interventions can start with international collaborations but should be continued nationally. Antimicrobial resistance seems to be reversible, but only if proper interventions are used.

Introduction

Probably the most challenging problem that will threaten global health in the next couple of decades is antimicrobial resistance. The consequence of this resistance is that antimicrobial medicine like antibiotics become useless against bacterial infections. This could mean that infections that are now effectively treated with antibiotics can become deadly again.

Antimicrobial resistance can be seen as an evolutionary response of bacteria. The compounds of antibiotics that kill bacteria are also compounds used by natural bacterial antagonists like fungi. Due to natural selection bacteria can become resistant to these antagonists and antimicrobial resistance develops. When antibiotics are used excessively it is inevitable that resistance will develop (Zinsstag et al., 2011). This is a well-known problem for pharmaceutical industries and health care workers; they have been coping with this problem for over 50 years (Bush et al., 2014).

Although it is a worldwide problem, it affects some countries in particular (Van Boeckel et al., 2015). These countries are referred to as BRIC countries because they consist of Brazil, Russia, India and China. Sometimes the term BRICS is used when South Africa is also involved. BRIC countries have in common that they are in a similar position of economic growth. This growth is thought to promote a different lifestyle in a fast-growing population. A bigger population with easier resources to medicine will contribute to more antibiotic use in humans. A different lifestyle is for instance a more protein-based diet, which will extend the use of antibiotics in agriculture; especially livestock (Van Boeckel et al., 2015). Intensive farming practices are now used to fulfill these demands but also contribute to high antibiotic use. Between 2000 and 2010 the global use of antibiotics has risen with 36%, three-quarters of this rise comes from BRICS-countries. There was also an increase of 45% in consumption of carbapenems, which are used as last resort antibiotics (Van Boeckel et al., 2014). If bacteria get resistant to last resort antibiotics, there is no treatment left against infections from this bacteria.

Although this is a big problem already, it is estimated that the use of antibiotics will rise from 2010 to 2030 with 67% globally. In BRICS countries the use will double. This is seven times more growth in antibiotic use than the estimated population growth in these countries (Van Boeckel et al., 2015). This extensive use of antibiotics will result in more resistant bacteria for which ultimately will be no cure if they cause infections. It is predicted that 300 million people will die prematurely between 2014 and 2050. In 2050 antimicrobial resistance will attribute 10 million deaths annually worldwide, almost 9 million of these in Africa and Asia (O'Neill, 2014). These numbers exceed deaths by cancer, which is the current leading cause of death worldwide (WHO, 2015).

Antimicrobial resistance also causes problems on financial level. It is estimated that in 2050 the worlds GDP will be 2 to 3,5% smaller than it would have been without this problem; this is about 100 trillion USD (O'Neill, 2014). People who die early or are sick cannot contribute to the country's economy. Also, treating an infection of a resistant bacterium is much harder and will lead to more hospital days. In 2007, Europe had 2,5 million extra hospital days because of multidrug resistant bacteria with losses exceeding 1,5 billion (Bush et al., 2014).

This review is written with a 'one-health' approach. This means that besides human interventions, animal and environmental interventions will be reviewed. The importance of such an approach is because antibiotic use in one sector will automatically influence another sector (Zinsstag et al., 2011). For instance, use of antibiotics in agricultural livestock will produce antimicrobial resistant bacteria in meat, which then will be eaten by humans. Antibiotics will also be found in waterways after excretion, which in turn will be drunk by humans and animals. This is one of the many ways that these three sectors interact. This explains the necessity of an approach that includes human, animals and environment combined; also because antibiotics are used in all three of these sectors (Collignon, 2012). This means there will have to be close collaboration between physicians, veterinarians and environmentalists, but also between governments and universities with citywide, countrywide and international agreements. "This is a worldwide, international problem and must be treated as such" (Bush et al., 2014, p. 5).

Antimicrobial resistance will cause a lot of problems and avoidable deaths. Still, little is done in countries where the consequences will be the biggest. Four themes will be addressed within these interventions: avoid infections; use fewer antibiotics; use antibiotics the right way; and create new medicine. These themes are selected because the solutions in the articles fell into one of these four patterns. Articles that were found where either about the one-health approach, antimicrobial resistance or solutions in one of the three one health areas. In this article these factors are combined for a broader view.

Methods

Introduction

The focus of this review is to see what interventions are still possible to make a change. This article is a literature review for which 13 articles are selected.

Search strategy

The entire search for this literature review is done in PubMed and Google Scholar to find all relevant articles on this topic from 2010 until 2015. Mesh-terms used are "Drug-resistance, Bacterial" and "Anti-bacterial agents". Other key words used are: Anti-biofilm, Review, Antibiotics, Antimicrobial, Crisis, Resistance, Management, BRIC and One-health approach. Both the articles from van Boeckel et al. were found through other articles in a snowball search manner found in the review of O' Neill. Professionals in the field of antimicrobial resistance gave this last article to me.

Selection process

Too specific articles about one country or one bacterium were excluded and more general articles about different bacteria and interventions on healthcare systems were included. Only the article about triclosan resistance was published before 2010, because this one was the best research on this topic.

Analysis

All the solutions that were found in the articles fell into one of the four categories that were addressed. These solutions were categorized in one of the four themes and

combined with all the other solutions in that category to put in the article. Some solutions were mentioned in different articles. These solutions were then combined as one solution with different perspectives.

Results

In this section the four themes will be addressed with the solutions from that theme. Each theme can contain interventions on human, animal and environmental level, which is usual with the one-health approach.

Avoid Infections

This theme is important because it is a solution in which no antibiotics are needed at all. It will focus on measures that can kill resistant bacteria before they get infectious or on interventions that prevent bacteria to spread.

Water is the most important carrier of pathogens within and between animals and humans. Salmonella Typhi is a good example of this problem. "We need clean water to be available for people and for animals. Failure to do this will result in huge numbers of people entering a "post-antibiotic era" for too many common infections" (Collignon, 2012 p.32). Local governments will have to be motivated to invest in better infrastructure and sanitation (Bush et al., 2014).

It is not a goal to live bacteria free because this also leads to problems. Besides commercial pressure to use antibiotics there also is similar pressure to use different types of disinfectants. It is sometimes advised to cleanse your body once in a while and always keep you tables and floors disinfected. Bacteria have gotten much negative attention, which makes it logical to think that eradicating all bacteria is a good thing. This is not the case, however: bacteria outnumber human cells ten to one in a human body, and many bacteria are needed for homeostasis. This cautious approach tends to have a paradoxal effect. Humans need to get exposed to antigens to strengthen the immune system; this is comparable with vaccinations. If this does not happen people are more likely to get infections by microbes (Michael et al., 2014). Also, in antibacterial hand soaps, bacteria are getting resistant to the active ingredients like triclosan. This can also result in cross-resistance with other antimicrobials (Braoudaki & Hilton, 2004). A good alternative for antibacterial soaps is normal soap.

This does not mean that eradicating bacteria is a bad thing, especially when they are pathogenic it can be life-saving. Hygiene and infection control interventions are very important in declining the number of infections. For instance, between 2003 and 2007 after interventions in the UK there was a decline of 40% of the MRSA bacteremia (Collignon, 2012).

In food production, animal and human manure is sometimes used for the fertilization of food. This is no problem unless resistant bacteria are still present when it is sold or used. Prevention of livestock infections can be accomplished through good husbandry of animals and immunization.

A little further down the line in the food business are possibilities in the preservation of the food. Options are pasteurization of milk and eggs and heat treatment for meat products (Collignon, 2012). Education about clean ways to eat your food can also

help, especially with food like lettuce which is not cooked when eaten (Collignon, 2012).

Use fewer antibiotics

If we want to deal with antimicrobial resistance, we will need to use fewer antibiotics in all three of the one-health sectors. Two-third of the manufactured antibiotics are used is in food animals (Collignon, 2012). They are used as therapeutics, grow promoters, prophylactics and metaphylactics, which are used to treat a whole flock when one animal is sick. Especially the use of antibiotics for growth is controversial: it accounts for more than 50% of all the antibiotics used worldwide (Bush et al., 2014). It is said that it promotes growth by 15-20% of which the mechanism is uncertain. Antivirals and antifungals do not have the same effect.

The best way to reduce antibiotic use is to develop laws. These legislative interventions have proven to be difficult. A first step could be to investigate stakeholder perception on antimicrobial resistance in order to address this and inform them on responsible antibiotic usage (Michael et al., 2014). Legislative measures can then be used to control and restrict antibiotic use in human and veterinary medicine.

Stopping all antimicrobials in animals at once is not recommended because it will influence the health, productivity and well-being of animals, which will cause a rise of food prices (Woolhouse et al., 2015). Reducing antibiotic use is possible though, if used together with complementary antibiotic alternatives to reduce the negative effects. The use of antibiotics as therapeutics could be continued in usual manner. Bush et al (2014) state that a good way of controlling antibiotic use is to make sure that only people who are competent are authorized to prescribe antibiotics. These include veterinarians and physicians. Nowadays many antibiotics are sold over the counter, even last resort antibiotics like carbapenems (Van Boeckel et al., 2014). This is alarming because this leads to overuse and misuse.

34% of the global increased antibiotic use will be due to the change of farming practices (Van Boeckel et al., 2015). There will be a shift to more intensive farming towards 2030, which countries need to reconsider because this is not a long-term solution. Intensive farming is an important risk factor for antimicrobial resistance and reducing this is an important step forward.

The remaining 66% will be due to more food animals and this will be harder to address. An international agenda can be formulated to regulate antibiotic use in livestock. Also, internationally funded surveillance can be implemented to control antimicrobial use in food animals (Van Boeckel et al., 2015). "The ultimate phasing out of antimicrobial use for growth promotion, based on the successful experience in the European Union and the new biological and economic evidence challenging the purported benefits of antimicrobial use in food animal production" (Van Boeckel et al., 2015, p. 5). This means that with the proper interventions it may be possible to reverse resistance in bacteria. Especially the extensive use of antibiotics in food animals as growth promoters is controversial.

When it comes to human health, in most countries the decline will have to be up to 50%, because many antibiotics in people are used for viral infections and other ineffective treatments (Collignon, 2012). Therefore it is recommended to invest in diagnostic techniques (Michael et al., 2014). This will result in more specific, small-

spectrum antibiotic use. Extensive broad-spectrum antibiotics use can be problematic because they cause resistance in different bacteria, because of which even more broad-spectrum antibiotics will be used (Pulcini & Gyssens, 2013). Whole genome sequencing of bacteria has found to have good result in finding which antibiotic is most effective. This way it is possible to determine the best treatment quicker and more accurate (Woolhouse et al., 2015). Also, starting an antibiotic will be much earlier. Both will result in less antibiotic resistance.

Use antibiotics the right way

Up to half of the use of human antibiotics are considered as misuse. Both in the community as in the hospital the benefits of these are non-existent or marginal (Collignon, 2012). In 1993 it was already established that the lack of knowledge about infectious diseases and prescribing antibiotics is a major factor in this misuse. It seems obvious that the solution for this problem is educational measures, also because educational measures amongst physicians are mostly more successful than restrictive measures (Pulcini & Gyssens, 2013). This can even start at child age where children are learned that antibiotics are not useful against viral infections. This is a long-term plan because when these kids get older they can use this knowledge when they get kids themselves (Pulcini & Gyssens, 2013). A European example on this topic is the 'e-Bug programme', a site that teaches children about diseases and pathogens (Bush et al., 2014).

In a research in America 75 % of the medical students agreed on the fact that they want to learn more about prescribing antibiotics. 83% said they wanted to have this in the third year, before internships start (Pulcini & Gyssens, 2013). This is a responsibility of the universities but political support is needed as well. Currently this education mostly happens postgraduate, which can be continued. Not only physicians should be educated but all health professionals who interact with the patient. This will lead to consistent messages towards the patient (Pulcini & Gyssens, 2013). Hopefully this education will make sure physicians know when to prescribe antibiotics and when not to. In India 51-69% of patients with dengue fever that come to the hospital get antibiotics. Dengue has no treatment and is a virus so prescribing antibiotics is useless. Also, in China and India it is not uncommon to prescribe antibiotics for self-limiting diarrheal diseases (Van Boeckel et al., 2014). In hospitals, core groups should be assembled which focus on education about antibiotic resistance and antibiotic prescribing. These can include al kinds of specialists teaching evidence based information about this subject (Pulcini & Gyssens, 2013).

Recently the clinical relevance of biofilm has been discovered. Biofilm is a layer of slime that bacteria can create wherein they can exchange information through a mechanism called 'quorum sensing'. This is a way in which resistance spreads easily because this information can include resistance genes. Biofilm covers bacteria and also precludes the immune system. The metabolism of the bacteria is very low in a biofilm. Most antibiotics work on metabolism, like beta-lactams on cell wall synthesis and aminoglycosides on protein synthesis. This means that when bacteria are in a biofilm these antibiotics do not work and prescribed antibiotics are useless. This will increase the odds that infections will become recurrent or chronic. "Currently, biofilm infections are usually treated with combinations of antibiotics" (Chung & Toh, 2014 p. 231). Many alternatives have been created like silver nanoparticles, bacteriophage

therapy, quorum sensing inhibitors and plant derived compounds. Studies have found anti-biofilm properties in horse chestnut, cranberry and cinnamon oil for drug resistant Staphylococcus Aureus. The biofilm inhibiting mechanisms of these products are still unknown (Chung & Toh, 2014). Biofilm inhibitors can act solely or in combination with antibiotics. Especially with chronic biofilm infections it is useless to use antibiotics without biofilm inhibitors.

Create new medicine

Creating new medicine has been the solution for antimicrobial resistance in the last decades. "There are not likely to be many new classes of antibiotics becoming available in the next few decades" (Collignon, 2012 p. 19). With this speed of resistance development it is not profitable for pharmaceutical companies to create new antibiotics. There has been found scientific evidence for phytogenic food additives in animals. These additives contain herbs and plants and can improve food animal production and also strengthens their immune system (Seal et al., 2013). Phytogenic additives are sometimes referred to as alternative medicine but are used for thousands of years in many countries. With a growing economy farmers tend to switch to antibiotics for growth promotion because this is based on scientific evidence. With growing research about phytogenic additives and the scientific evidence that comes with it, this can be a good replacement for antibiotic use in food animals in BRIC countries.

The most effective way of avoiding infections is immunization. The easiest way of doing this is with vaccination. Many vaccinations still have to be developed. Also passive immunization is possible in which antibodies are injected specific to one microbe type. This is only possible if the infection you want to avoid always happens by one type of microbe species, like E. Coli with mastitis in cows (Seal et al., 2013). But even if vaccinations are available, it is very hard to persuade farmers to use them. "As long as antibiotics are still available and effective, there is arguably little commercial incentive either to use existing or to develop new antibacterial vaccines for farm animals" (Woolhouse et al., 2015, p. 5). This means that besides vaccination development and distribution, with easy availability to antibiotics it is hard to make vaccinations an effective tool.

If new medication is to be created, it will have to be a big project involving many different disciplines. The private sector will have to partner with governments or universities (Seal et al., 2013). "There is a clear need for research input from a range of disciplines, not only clinical and veterinary medicine, epidemiology, microbiology and pharmacology, but also health economics, international law and social science. However, effective action on antimicrobial resistance will require a coordinated response from governments, industry and international agencies as well as scientists. That action will need to involve and will affect clinicians, pharmacists, patients, veterinarians and farmers, all of whom have contributed to the current antimicrobial resistance problem and all of whom will be part of a long-term solution" (Woolhouse et al., 2015, p. 5). This is a big project with big costs, but this will still be really small compared to the costs of doing nothing (Bush et al., 2014). This means that it is advised that a collaboration has to be assembled with many different disciplines. This will be very expensive, but is better than doing nothing.

Discussion, recommendations and conclusion

The results in this review are meant to give a scientific base on the possibilities for BRIC countries to prevent an antimicrobial resistance crisis. Most articles are about ways of preventing antimicrobial resistance, but not about BRIC countries. It was hard to find specific information about these countries. Also between these countries are cultural differences, which can make it difficult to generalize. What they have in common is fast economic growth. Interventions needed to avert a resistance crisis might slow down economic growth short term, which makes it hard to convince these countries (Van Boeckel et al., 2014). International legislative measures can be effective if it affects these countries economically. Much knowledge is available but also needs to be taught. This can be accomplished by international exchange projects. Still, the biggest interventions will be responsibilities of the BRIC countries themselves.

There is still much research to be done. The mechanism in which antibiotics promote growth is still unknown. Antibiotic use in livestock could benefit from knowing this mechanism so that a different product might be created.
Phytogenic additives could be the best alternative right now because they are easy and cheap. These additives are known to have an anti-biofilm ability, so they can help treating therapy-resistant chronic infections. Still, more research has to be done on this as well to have a scientific basis on which guidelines can be created.

Especially in livestock antibiotic use and antimicrobial resistance are still badly documented. It is necessary that this use will be mapped, similarly as is done with malaria and tuberculosis (Van Boeckel et al., 2015).

There are things that I have not addressed in my review which need mentioning. We are failing to control 'the big three' global infectious epidemics tuberculosis, malaria and HIV because of resistance development to the current medication. Resistance is not only a problem of bacteria, but of all microbes like viruses and worms. With many infectious diseases it is shown that it is possible to eradicate them with proper management. The interventions that have to be started must be long-term and intensive to make sure that after the disease gets eradicated the medication is still working.

With the proper interventions antimicrobial resistance seems to be reversible (Van Boeckel et al., 2015). This means that it is possible not to end in a post-antibiotic era if we address this problem properly.

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