Antibiotics

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We certify that this entire work is our own doing and all members have contributed equally.

Intro to Antibiotics – Historical Aspects

Antibiotics are a class of chemical compounds that can specifically inhibit bacterial growth and therefore treat a variety of bacterial infections. Before Antibiotics came into the picture, bacterial infections from Staphylococcal and Streptococcal bacteria loomed as major killers. Even minor injuries could become infected and once the infection had developed, there was no reliable way to treat patients.

Alexander Fleming, a professor at Saint Mary's Hospital, London is credited with the discovery of the very first antibiotic Penicillin. Like many major scientific discoveries, this one too was rather accidental in nature. On returning from a holiday in 1928, Fleming noticed that the region around a blob of mold growing on one of his Stappylococcus bacteria plates was free of bacterial colonies [1].

Further investigation revealed that the mold was a strain of *Penicillin notatum*[1] and the secretion it produced was capable of killing a wide range of harmful bacteria. Hence the term 'Penicillin' was coined. However, extraction proved difficult and without a deeper understanding of how Penicillin really worked, its enormous therapeutic benefits could not be foreseen by Fleming. At the time, its primary application seemed to be in bacterial isolation rather than as a life-saving drug.

It was over 10 years later in 1939 that Howard Florey and his colleagues from Oxford University began working earnestly on the purification of Penicillin and understanding its chemistry [1]. Newly discovered purification techniques like Alumina Column Chromatography aided in the process and helped the scientists reach a purity level that was fit for clinical trials; something that would not have been possible at the time of its discovery. The drug was tried successfully on patients in 1941 and soon after there were plans to make it available to troops on the battlefield.

One of the key motivating factors for the sudden interest in Penicillin production was the possible benefit that it would provide soldiers during the war. Administering Penicillin to wounds could greatly reduce the risk of Gangrene and other bacterial infections, for which the only cure was for a long time the highly undesirable process of amputation.

War time conditions in Britain were however not suitable for mass production of Penicillin and this led the Oxford researchers to try their luck in the US. They were referred to the National Regional Research Laboratory (NRRL) in Illinois. The expertise of the Fermentation Division of this Lab, combined with its willingness to contribute the goal of mass producing Penicillin proved to be a crucial step in the history of the drug. The combined efforts of the Oxford Researchers and the NRRL scientists led to a complete revamping of the production process including the identification of the most suitable mold strain for mass production.

Meanwhile, three pharmaceutical companies- Merck, Squibb and Lilly – began to take interest in Penicillin research. The representatives of these three companies along with several others attended a meeting in Washington DC to plan a collaborative research program in order to produce penicillin [1]. The various firms agreed to conduct independent research activities but share developments with each other. However, some firms like Heatley and Merck went a step further by exchanging research staff for several months.

These efforts bore fruit when production of Penicillin in the US jumped from around 21 billion units in 1943 to 6.8 trillion units by 1945. Though penicillin was administered only for life or death situations from 1941 to 1944, on 15th March 2015 penicillin was made available to all consumers in the US at local pharmacies.

Though Penicillin may have been the first antibiotic to have been discovered, the Sulpha drug Prontosil preceded Penicillin, albeit by just a few years, in therapeutic use[2]. Gerhard Domagk is credited with its development and won the Nobel Prize in 1939 for its discovery.

The events leading up to the discovery of Prontosil began in 1931 when Domagk and his team developed a compound they called KL695 which showed weak antibiotic properties when tested on mice. After making several substitutions in the molecule, they came up with KL730 which displayed enormous antibacterial effects on laboratory mice[3]. KL730 was patented as Prontosil and in the following years was used to treat a variety a human diseases of Staphylococcal and Streptococcal origin successfully, including those affecting the soldiers of the allied troops during World War II.

We have come a long way since Penicillin and Prontosil and till date over a 100 antibiotics have been brought into therapeutic use[4]. These include familiar names such as amoxicillin, ciproflaxin, azithromycin, levofloxacin and many more[5]. A large number of these drugs are affordable and in several regions, procurable even without a doctor's prescription.

However, the story of antibiotics is not as rosy as it may seem at first glance. Antibiotic Resistance is on the rise and has become a cause for major concern in recent years. The first case of a Penicillin resistant infection surfaced a good 22 years after its introduction[6]. However, in recent times resistance to antibiotics is developing much faster. Resistance to Levofloxacin(1996), Linezolid(2000) and Ceftaroline(2010) began to develop within a year after their introduction. The phenomena of antibiotic resistance will be discussed in more detail in the third section of this paper.

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[1] https://www.acs.org/content/acs/en/education/whatischemistry/.../flemingpenicillin.htm

[2] www.discoveriesinmedicine.com › Ra-Thy

[3] https://www.chemheritage.org/historical-profile/gerhard-domagk

[4] www.emedicinehealth.com/antibiotics/page2_em.htm

[5] http://medshadow.org/features/pros-cons-of-antibiotics/

[6] https://thefern.org/wp-content/uploads/2013/11/Timeline-of-Antibiotic-Resistance.png

Research and Development in Antibiotics

‘Antibiotics technology’ requires a lot of research at every stage of its development and is also a very time consuming process. Since its use is directly on humans it has to be tested and verified thoroughly before it can reach the market and thus has a very long time gap from its discovery till it is sold as a product. Various fields in which R&D is required are:

- Discovery of antibacterial substance.
- Its mode of attack on the bacteria.
- Animal and human testing.
- Isolation and purification of the substance.
- Large scale manufacture.
- Waste management.

Most antibacterial substances are obtained from natural sources such as plants, soil, animals etc. but recent developments have also made possible the complete synthesis of antibiotics through artificial chemical means.

The different modes of action on the bacteria are:

1. Inhibition of Cell Wall Synthesis (most common mechanism)
2. Inhibition of Protein Synthesis (Translation) (second largest class)
3. Alteration of Cell Membranes
4. Inhibition of Nucleic Acid Synthesis
5. Antimetabolite Activity

Different modes of action have different resistances from bacteria and need to be dealt with in an appropriate manner.

This raw substance is converted to a prototype and is tested on animals and humans in a very controlled environment to observe its effects. This is then modified to appropriate needs by changing its composition and varying doses till it is deemed fit for use.

Isolation of pure substance is needed for large scale manufacture of the drug. It is first allowed to grow in a seed tank at optimum conditions and then it is used in the fermentation process where large amounts of desired antibiotic are excreted.

This production results in creation of toxic waste of different kind which can prove to be very harmful for the environment as well as humans and animals if left untreated in water bodies, soil, air etc. This can also promote antibiotic resistance as the waste also contains antibiotics and this when let into soil and water increases the resistance of the bacteria in them. Therefore, a lot of research is also being carried out in the waste management of the pharma industry.

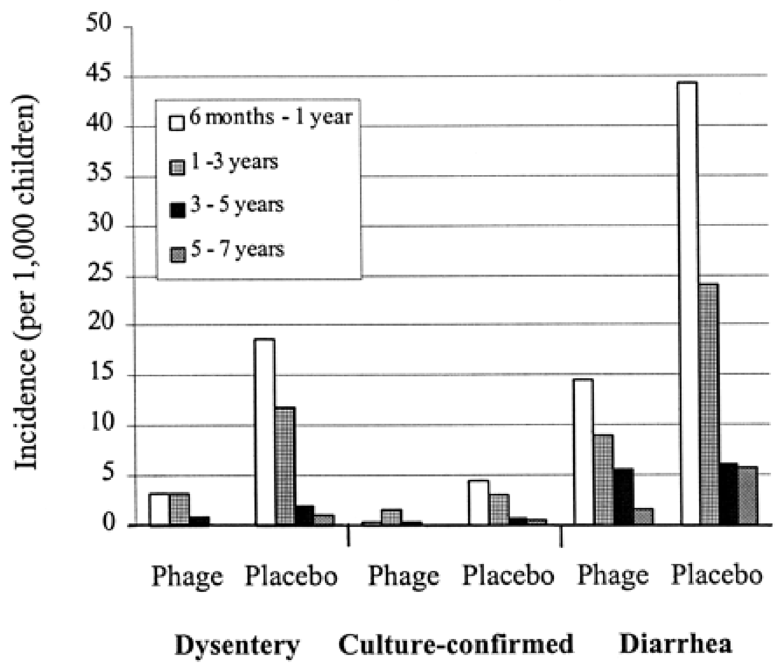
Discovery of new Antibiotics:

The biggest challenge that the antibiotics face is discovery of an entirely new class. Most of the naturally found antibacterial substances have been discovered and the bacteria have developed resistance to many of them. Two areas which have not yet been fully discovered are marine life and synthetic methods for new antibiotics.
The marine life contains a vast variety of microscopic life. The marine organisms are under a constant threat of infection by microbes which are different from the set of terrestrial microbes and in response they have developed antibacterial compounds from a varied set of biological predecessors.

Recent advances in science has enabled us to produce more chemicals and compounds and also new production methods. This approach can help in synthesis of new antibiotics which are either not easily available or entirely new kind.

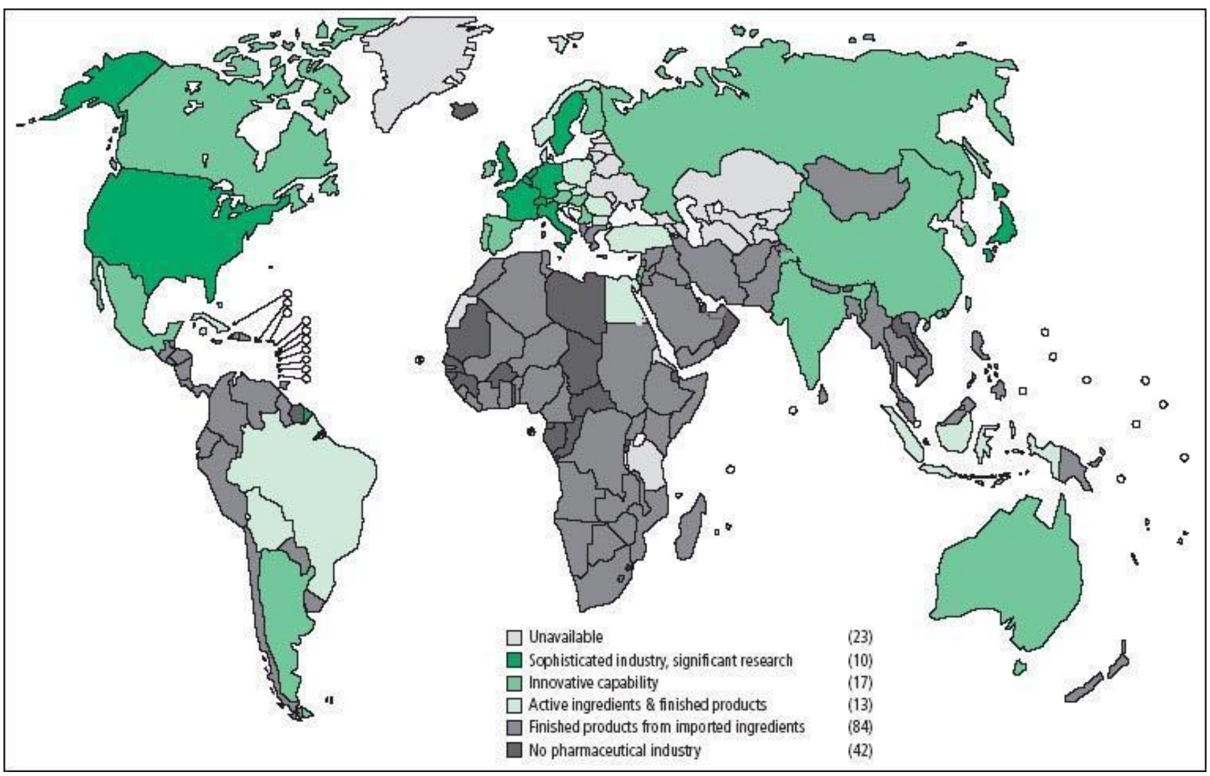
Bacteriophage Therapy:

Bacteriophages are bacterial viruses which disrupt the bacteria's metabolism and lyse them.
It is very specific in its action, the phages replicate at the site of infection, have very few side effects, phage-resistant bacteria remain susceptible to other phages and development of new phage to counter phage resistant bacteria is a rapid process. Despite of all these perks, the narrow host range, insufficient purity and lack of understanding of mode of action has held back this method of treatment and thus there is research going on to improve this method to tackle the problem of antimicrobial resistance.
The below graph shows the effectiveness of phage therapy against dysentery over placebo:



World medicine production

Pharmaceutical companies are an integral part of the world's GDP accounting for almost $1 trillion, 2-3 % of which is antibiotics production. Two thirds of the world production takes place in only five major countries: USA, Japan, Germany, France and UK. Share of high income countries is around 90% by value and is constantly increasing with USA dominating with a third of world's production. India contributes to merely 1% of the pharmaceutical production and ranks 12th but it contributes 8% of production by volume and ranks 3rd. The pharmaceutical industry is also a very fast growing one. Between 1985 and 1999 the real growth of GDP was 3.6% per annum whereas the real growth rate of pharmaceutical industry was 14.9% per annum. A small number of transnational companies dominate world production, ten of these accounting for almost 50% of world sales. The top ten medicines alone account for 14% of production. Nine of the top 100 transnational corporations (ranked by foreign asset value) were pharmaceutical companies. But merely cost of drugs and volume doesn't reflect its therapeutic value. Measurement of therapeutic value is a complex process and various method can be used such as fever reduction, time of recovery, healthy life years gained, disability adjusted life years etc.



The above image shows how the world production is divided across the globe.

Economic issues in production of antibiotics

Pharmaceutical companies have less incentives to produce antibiotics because antibiotics offer a relatively poor return on investment when compared to any other type of and for two main reasons. First, antibiotics are taken for a short period of time unlike drugs for chronic diseases which continue for decades. Second, prices for antibiotics are set lower than other drugs because of their importance. However, antibiotics are still third highest earning drugs. Another major problem seen in the past decade is the withdrawal of antibiotics from the market. Of the 61 new approved antibiotics in past 30 years 26 have been withdrawn by 2010. The main reason for withdrawal of these products is that most these new products don't give a great advantage over the existing ones and are also expensive. These new products are also susceptible to the resistance of their predecessors and re therefore of very little use.

The cost of bringing a new antibiotic to the market is more than $ 1 billion and delaying the need for one is worth conservative $60 million per year. Yet in recent years, the U.S. Centres for Disease Control and Prevention has spent only about $5 million per year on antibiotic conservation. Thus there is a need for innovation incentives.

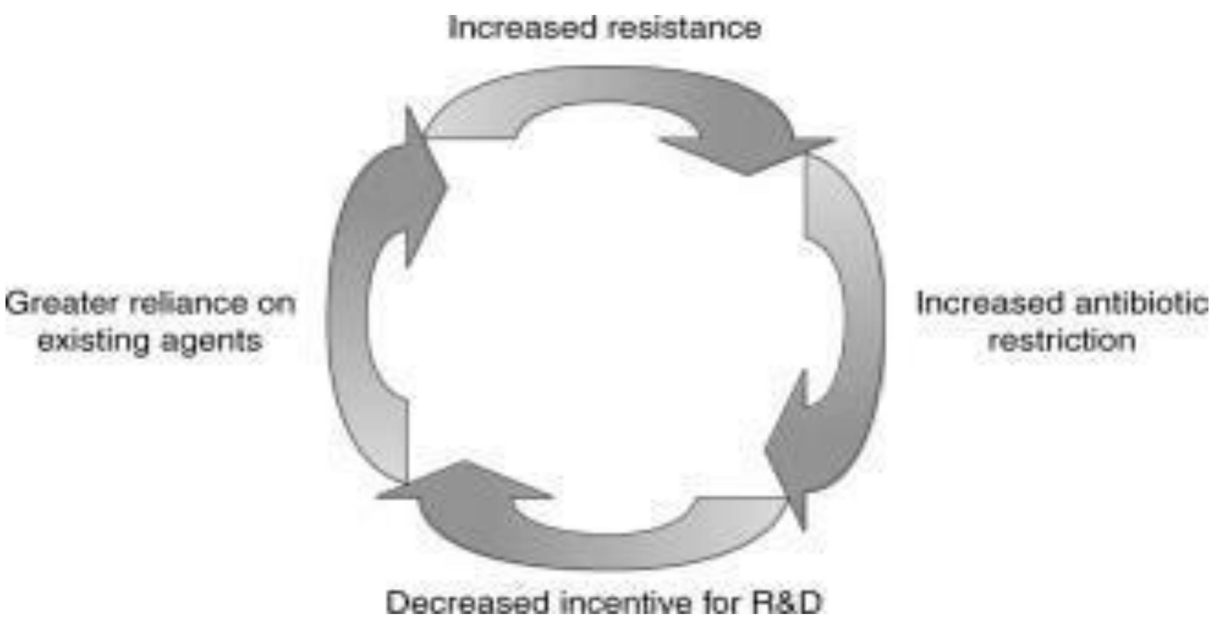
Conserving and restoring antibiotic effectiveness

Antibiotic conservation requires both reducing the need of antibiotics as well as reducing inappropriate use. Antibiotic need can be reduced by improved sanitation, cleaner and safer water supply and vaccinations for prevention of diseases. Inappropriate use of antibiotics can be reduced by increasing awareness among people about the side effects, enforcing prescribing restrictions and active participation by hospital staff and pharmacies to maintain control over proper use of the prescribed drugs.

Impact of regulations and restrictions on antibiotics

New regulations on the production of new drugs have created obstacles for antibiotics production. New antibiotics have to go through more tests therefore almost doubling the number of patients for clinical trials. Already increasing costs of trials hugely add to the cost of manufacture of new drugs. Also recruiting patients with some uncommon diseases consumes more time and thus delays the entry of product into the market.

New restrictions on prescription to antibiotics require need for antibiograms which are not usually available in primary practice, omission of newer antibiotics from hospitals to prevent their resistance, quotas for generic substitutions and parallel imports. These restrictions make assumptions on population basis which may not be justifiable on an individual. This creates a conflict in the two agendas of antibiotic management i.e. to reduce the dependence on newer agents to counter resistance spread against demand of newer antibiotics to fight resistance. This creates a negative feedback which will eventually lead us to pre-antibiotic era conditions.



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Impact on Hospitals and Medical Professional

Being the connecting link between production and consumers, Hospitals play a central role in influencing antibiotic use and consumption, while also facilitating their demand. This two-fold aspect makes them the choke point for antibiotic flow in the community.

Antibiotic manufacturers have always had a deep relationship with hospitals and doctors, be it related to lobbying for their drugs, a feedback mechanism or even suggestions for future development.

But, in recent years, due to a multitude of consumer awareness and rights movements, doctors are now more scared than ever to definitively prescribe medicine, lest it adversely affect the patient. So, in recent times, doctors, especially in the more developed countries, give each patient a choice of medicines to cure his ailments, and leaves the choice, the blame to him.

Now, the inherent flaw with this is that consumers being uneducated about this are at a severe disadvantage regarding this decision. So, since the decision making power shifted to the consumers, so did the lobbying of the pharmaceutical companies. Now, prescription medicine is being advertised, and the consumers actually demand certain medication, even though it might not be the best for them.

In this plethora of choice, hospitals have done very little to adapt with the changing times. Being the birthplace of antibiotic resistances, Hospitals did very little, save identifying the problem early on. Similarly, hospitals gave up their decision making power, and left the burden of decision onto the consumers. This move was completely counterintuitive, since doctors had all the medical knowledge and expertise as compared to the simple minded consumers.

In a time where most people prefer to self-medicate rather than see a doctor for everything but serious illnesses, the hospital community has once again done nothing to discourage such practices from emerging and progressing.

So, hospitals, which were once the common link between the manufacturers and consumers, have almost broken their links with both these spheres, through small but efficient strides in these directions. So, once an integral part of the antibiotics supply cycle, hospitals are now just overlooked in this aspect.

Antibiotic Policies

Introduction

With great power comes great responsibility. So, similarly with Antibiotics, a boon of modern medicine, we must exercise caution and follow certain guidelines for their proper usage.

These guidelines, or ‘rules of the game’ are set up by various organizations, such as the World Health Organization, which sets these guidelines at an international level, considering the overall broad range effects of such antibiotics. At a more localized, national level, the country’s own government play this role, and shape policies to influence and control the use of antibiotics.

The main reasons for doing so are that antibiotic prescriptions need to be very precise (need to be given by an appropriate route, in adequate dosage, for an appropriate period of time etc.). Any small deviation from the appropriate path will lead to adverse consequences for the patient and also for the community in general.

In recent times, antibiotic resistance has come into prominence. As early as 1946, Sir Alexander Fleming, a pioneer in antibiotic research and development, pointed out the importance of acquired resistance, even though there was little of it at that time.

Another few concerns with respect to antibiotics are the publics irrational demands for antibiotics to treat unrelated diseases such as cancer, tuberculosis, rheumatoid arthritis, psoriasis etc. Moreover, though this isn’t the case with penicillin, excessive consumption of antibiotics may lead to toxicity in the body.

Another section of Fleming’s book discussed the comparative analysis of sulfonamides and penicillin for the prevention of infection in war wounds. The clinical trials, although not perfect, led to the abandonment of sulfonamides and their replacement by penicillin, a policy that was still in operation 40 years later. This might have been the first antibiotic policy!

Local Antibiotic Policies

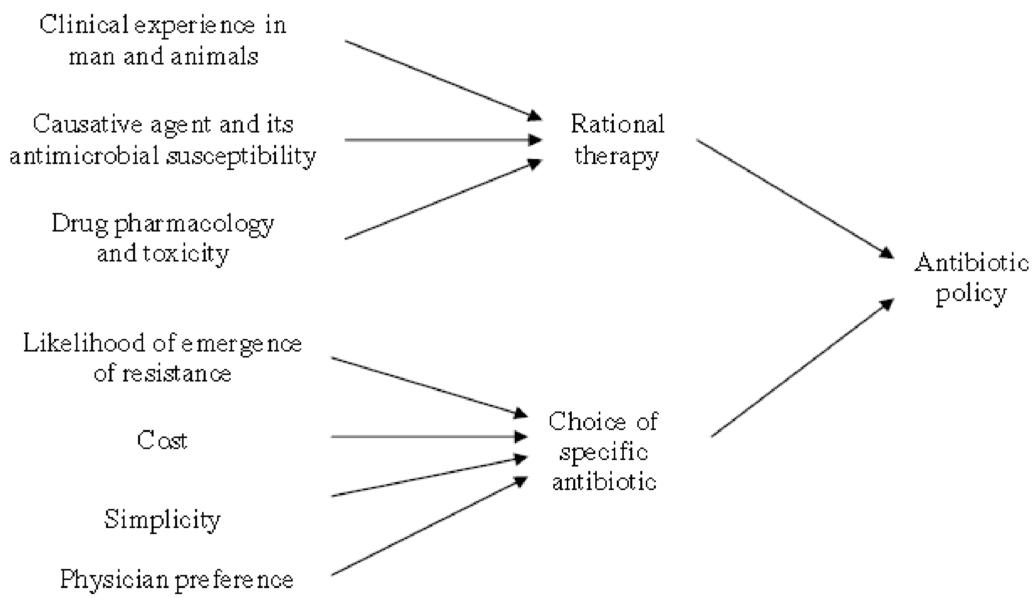


Figure 1. Components of an antibiotic policy (based on Phillips, 1979).

A policy is something superimposed on such rational use, taking into account the risk of development of resistance, cost, simplicity, and the personal preferences of the prescribing clinician. It depends on pragmatic consensus, but even that should not prevent a clinician ignoring it in what he believes to be the best interest of an individual patient. (Garrod and O'Grady, 1971; Phillips, 1979).

Initially, antibiotic polices were localized in the hospitals that they were created in. Most hospitals had their own Antibiotics Committee, to consider, continually review, recommend and give information on antibiotic policy in the hospital. (Phillips and Cooke, 1982). For example, the Antibiotics committee at St. Thomas' was set up in 1960, and continued its work for another 30 years, until it was taken over by a more general Use of Drugs Committee.

Towards National Policies

As predicted by Sir Alexander Fleming, antimicrobial resistance finally became a major problem, not just in hospitals, but in the community at large. As S. B. Levy said “the warnings were there long ago, but too few people heeded them. Thus an emerging problem has grown to a crisis” (Levy, 2001).

This flagging of antibiotic resistance would have happened years ago, but for the heavy lobbying by the manufacturers and providers to shift blame. It wasn’t until the late 1990s, that antibiotic abuse and resistance were definitively linked, although a completely quantifiable link still needs to be established. (Levy, 2001).

Finally, as the governments opened their eyes to the importance of restricting antibiotic use by implementing policies, to reverse the antimicrobial resistance. In fact, the principle aim of a policy is to bring about a change in prescribing, which will lead to reduced resistance, decreased costs, and improved quality (judicious, safe, and appropriate) of antibiotic prescribing (Nathwani, 1999).

Since this problem was a global one, affecting most countries, this led to the involvement of international organizations, like the European Union, in the battle against resistance.

But, the involvement of a national or global organization to solve local issues is not without problems. Primarily each pocket would require its own independent solution and strategy to tackle this issue. Secondly, due to social, political, geological and economic differences, there would have to be heavy tailoring of solutions to fit and apply to all the various locations under the European Union.

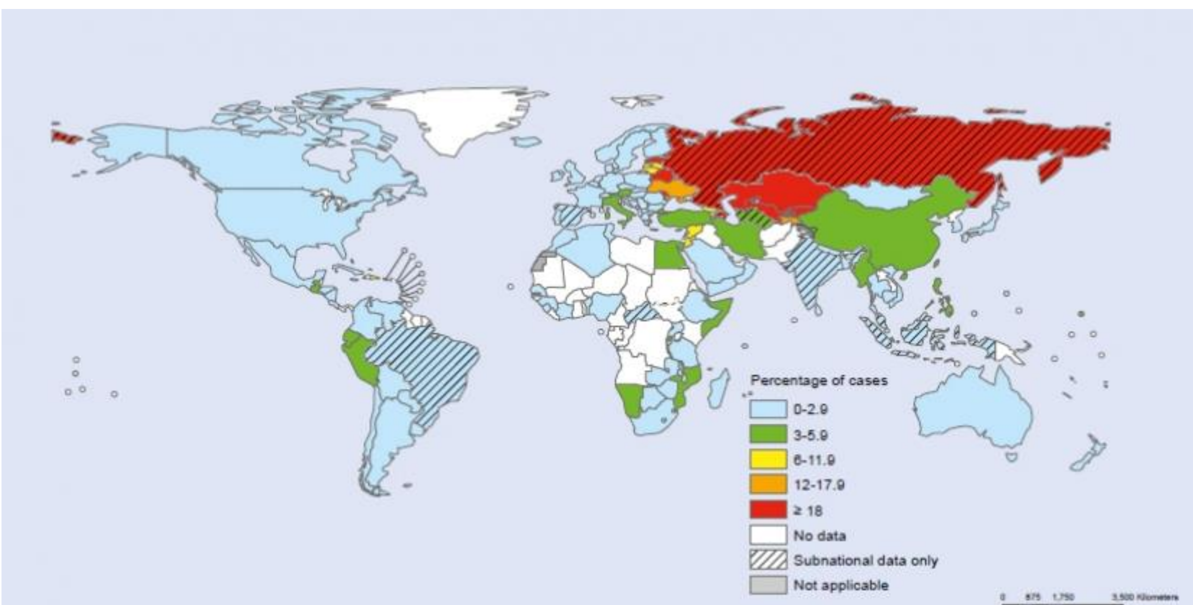
Nevertheless, the minimum standards for a European Antibiotic Policy have been proposed (Keuleyan and Gould, 2001):

- Establishment of a European antimicrobial resistance surveillance system to provide data about antibiotic usage, resistance, and linked clinical information
- Establishment of European guidelines for good clinical practice
- Support of educational programs for practitioners and consumers
- Establishment of an infection prevention and control policy
- Support of research in the field
- Supply of funds for developing countries, for example, from WHO and the World Bank.

National Antibiotic Polices

A National Policy should address all relevant issues for antibiotic use, both in the community and the hospital, including veterinary and agricultural use. A national expert committee should be established in each country for that purpose (Keuleyan and Gould, 2001).
Some important issues to be included in the policy are (Keuleyan and Gould, 2001):

- Existing laws should be enforced to prevent non-prescription, over the counter sale of antibiotics
- Guidelines for antibiotic treatment and prophylaxis should be prepared and adapted institutionally at a local level
- Consumption of antibiotics should be monitored to estimate the national consumption of antibiotics
- A national antimicrobial resistance surveillance system should be established and coordinated with international systems
- A national control of infections program should be implemented
- Educational programs should be elaborated for both healthcare workers and the public
- Collaboration with international organizations (WHO, APUA, ESGAP, etc.) should be established
- Appropriate funding should be made available by government or any other organization.



A world perspective of the number of cases of reported drug resistance microbes - showing the immediate need for national and global antibiotic policies.

A perspective on Policies implemented by some European Countries

1. Spain

In Spain, a Task Force was set up by the Ministry of Health to tackle the problem of antimicrobial resistance among community acquired bacterial resistance. They implemented various extensive measures, which resulted in a general decrease in the antibiotic consumption, which can be seen over three distinct periods. The first period (1985 – 1989) was characterized by a minor decrease, whereas the second period (1989-1996) showed an increase in consumption. Only after this is there a sustained decrease of antibiotics, attributed to the government campaigns, to promote awareness about the appropriate use of these medicines. (Bengoa et al., 2002).

2. UK

Around 1994, after a survey among microbiologists and pharmacists, resulting the formulation of the first set of policies to restrict and curb antibiotic consumption. Despite this, there were still reports of increasing antibiotic prescription both in hospitals and the community (Gould, 1996). In the northeastern part of Scotland despite the implementation of a very strict antibiotic policy, a significant increase in antibiotic consumption was recorded between 1992–3 and 1996–7 (Gould and Jappy, 2000). Finally, in 1998, the government implemented a comprehensive strategy to tackle the problem of resistance.

The first result of this strategy was a public education campaign advising patients not to pressure their doctors to give them antibiotics for colds and flu and recommended 3 days' treatment for simple urinary tract infections (Gould, 2001). With the evidence of reduced expectations by patients, there has been

downturn in community prescribing but this had already started before 1998.

Lastly, a favorable impact on antibiotic prescribing is expected after the last reforms of the National Health Service, with its drive to improve quality and ensure better education of and performance by doctors. This includes the introduction of Clinical Governance, which intends to make doctors responsible

for the quality of their antibiotic prescribing and empower their employers to ensure that this quality is achieved (Gould, 2001).

3. France

In France, in an effort to control ambulatory care costs, regulatory practice guidelines, known as" references medicales opposables" (RMOs) or regulatory medical references, were introduced by law in 1993 (Durieux et al., 2000). According to the law, physicians who do not comply with RMOs can be fined. In terms of antibiotic prescribing, the aim of this strategy was not to decrease the number of prescriptions, but to reduce the total cost of antibiotics and reduce especially the prescription of broad-spectrum, expensive agents (Chahwakilian, 2000). Moreover, they were not planned to promote good antibiotic prescribing practice. The RMO policy was questioned in 1997, when the reform of the French Health System changed the rules (Colin et al., 1997). According to the reform, French physicians having private practice could be collectively fined at the end of each year if they overspent the budget prescribed by the French parliament. On the contrary they could receive a bonus if they stayed within this budget. This regulation resulted in

protest on the part of physicians as being unethical and it created an intense conflict. In a survey done in 1998 among French family physicians, it was quite obvious that despite financial penalties French physicians' knowledge of RMOs was poor (Durieux et al., 2000).
The introduction of RMOs did not decrease the overall volume of outpatient antibiotic use and had only a modest economic impact. However, the prescription patterns changed with this policy, leading to a decrease in the use of fluoroquinolones and oral cephalosporins and to a substantial increase in macrolide use (Choutet, 2001).

Conclusion

Finally understanding the threat of antimicrobial resistance, many countries woke up and started taking action. However, their involvement varies from loosely drafting policies, to implementing and enforcing an all-encompassing system of rules for the same. Most countries keep in mind their specific socio-economic and geographical factors while deciding how to tackle this ever growing problem of antibiotic resistance. There has been quite the variation in responses to these policies, some were successful, some were not, and others are still in their infancy, so we still cannot definitively conclude. However, the effects of many national policies may not be optimal from a global perspective if countries fail to take account of the cross-border effect of their actions (Smith and Coast, 2002). Therefore, besides national policies, international cooperation is a factor that can play a significant role in the battle against antimicrobial resistance. Apart from these, another major policy sector is reducing the very need for antibiotics by improving water, sanitation and immunization. Specifically, for Europe, as discussed in this section, they should use the existing framework of the European Union to formulate generic policies, with region specific flexibility. The policies have to incorporate the social and economic differences of these regions in addition to the antibiotic pattern.

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Antibiotic Use

Antibiotic misuse (both overuse and underuse) is a very key factor in driving increased antimicrobial resistance. Tracking and keeping data on antibiotic use is necessary to understand how the technology interacts with society. Moreover, it is an essential step towards understanding the nature and extent of antibiotic resistance, and taking the requisite mitigatory steps to control it. However, lack of comprehensive data on antibiotic use is not available for many countries, and this has been a plaguing problem for many years. In recent years, the amount of publically available data on antibiotic consumption has increased, however it is far from satisfactory, especially for developing nations, like India.

There is a lack of consensus of choice of unit of measurement of antibiotic use, and this makes comparison across hospitals and communities complicated. However, there is growing acceptance of DDD (Defined Daily Use) as the preferred unit, which is the average adult dosage of the drug as standardized by WHO. We use numbers of DDDs per 1000 inhabitants per day (DID), to make comparisons across countries and geographical areas. These don't take into account the antibiotic consumption by children, for which no of antibiotic prescriptions per 1000 inhabitants.

Consumption

There are significant variations in antibiotic use, among the developed nations too. A study by the Institute of Medical Statistics (IMS) from 1997 suggested that France (36.5 DID), Spain (32.4 DID), Portugal (28.8 DID) & Belgium (26.7 DID) had greater consumption rates than the average for Europe (20 DID). Germany (13.6 DID), Denmark (11.6 DID), Sweden (13.5 DID), and the Netherlands (8.9 DID) were the lowest consumers. The range is large, with France consuming nearly 4 times that what Netherlands consumes. In the Nordic nations (Sweden, Finland, Norway, Denmark, Iceland), the antibiotics are distributed through a national network of pharmacies, which allows for precise and extensive statistics on consumption, and also allow for prompt action to be taken against increased consumption. This leads to lower average consumptions in the Nordic countries.

In Stratchounski et. al. (1998), they compared antibiotic consumption in Eastern European countries, and found that countries 'more east' consumed much less antibiotics (Russia – 11.2 DID, Belarus – 8 DID), than the countries closer to Western Europe (Slovakia – 25.8 DID, Poland – 22.5 DID, Hungary – 21.1 DID). This stark contrast can mainly be attributed to the fact that Russia and Belarus were a part of USSR, where they didn't solely rely on antibiotics to treat infectious diseases; there was a significant development of bacteriophage technology, where you viruses instead of chemicals to kill harmful bacteria.

There also exist vast differences in the kind of antibiotics consumed across nations. In European countries, the most common antibiotic is the broad spectrum penicillin, with usage varying from as much as 56% in Spain, to 20% in Germany. The Nordic countries have different preferences, with Sweden and Denmark using narrow spectrum penicillins (40%, 36%) and Finland using tetracylines (28%).

Australia has had a very steady consumption of antibiotics, with an estimated 24.7 DID in 1990, to 24.8 DID in 1995. However, it is one of the world’s largest importers of antibiotics, importing nearly 700 tons of antibiotics every year, with more than 2/3rd of it being used for animals. It is also has the highest number of users per capita of oral antibiotics in the world.

Prescriptions

Interestingly, Greece, which doesn’t fare that highly in antibiotic consumption, has the highest number of prescriptions per 1000 inhabitants – 1350. It is closely followed by Spain (1320), and Belgium (1070). The lowest number of prescriptions are found in Netherlands (390), Sweden (460), and Austria (480).

In the United States, from 1992 to 2000, there was a significant decrease in antibiotic consumption and prescriptions. The number of prescriptions declined by 23% (from 599 to 461 prescriptions/1000 inhabitants), and the number of prescriptions per visit also declined by 25%. There was a starker decline of 32% in antibiotic prescription for children. This is largely due to widespread awareness on the consequences of unnecessary antibiotic use. Canada, Australia, and UK all also showed decreasing signs of antibiotic usage

Antibiotics Usage in France

France has got one of the highest antibiotic consumptions in the world. In 2002, the national expenditure on health was estimated to be around 186 billion euros, representing 9.5% of the GND. A large part of this was on drug consumption. There are more than an estimated 1.2 antibiotic purchases per person per year in France. A large part of this high consumption is due to an upsurge that happened in the 1980s. There was a severe increase in antimicrobial prescription for viral respiratory tract infections (acute nasopharyngitis, acute tracheitis, acute bronchitis, influenza), where antibiotics are of no effect. The frequency of such diagnoses increased by 115% for children, and 86% for adults. There is an estimated more than 50% unjustified use of antibiotics this scenario.

There is high overdependence on antibiotics in France. The French recommended daily doses are usually greater than those set by WHO – France recommends 3 times the dose for Amoxicillin, than what WHO does. The people of France, consider antibiotics to be very powerful drugs – with no side effects. The French national health insurance organization performed a survey, where 39% of the respondents said that antibiotics are effective against viral infections. This unnecessary and excessive usage of antibiotics has far reaching consequences on the French society, with France very frequently facing highly resistant strains of microbes.

Conclusion

Comparisons of antibiotic usage across countries is always a complicated process. There are many differences in the national guidelines in several variables across countries, such as preferred class of antibiotics, recommended dosage, length of treatment, degree of conservation in prescribing antibiotics, pricing, etc. Additionally, there are various socio-economic, and cultural differences, which significantly impact consumption policy. This makes it a bit difficult to associate causality with change.

However, a general trend that is noticed across countries in the 1980-2000 period is an irrationality in consumption. There has been an increased usage of these drugs since the 1980s, as is seen in France, Greece, Spain, Belgium, and Australia. A lot of it attributed to unnecessary prescriptions. There is a marked increase in prescription of broad-spectrum antibiotics for viral respiratory tract infections, which is worrisome for the medical community. Antibiotic resistance is a real threat to society, especially in this time of increased globalization, and it is imperative for countries as a whole to be very prudent about their consumptions.

Another key point is the lack of comprehensive data. There was very little statistics on consumption before the 1980s. Though things are a bit better now, there is still a need for a more robust and extensive data collection. This is especially true for developing nations such as India, where there is dearth of reliable data on consumption, and where there is not a rigid prescription based system, and it is relatively easy to procure drugs OTC.

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Antibiotics in Developing Countries

Developing nations, due to financial constraints, are plagued with several issues that cumulatively severely increase the national burden of disease. This leads to higher morbidity, mortality, and also makes these nations thriving centers for resistant strains.

In many developing countries, due to various competing needs, and financial constraints, the healthcare budget represents only 2-5% of the total annual budget. In comparison, developed nations spend 7-14% of their GDP on health care. This creates a very vulnerable public health infrastructure.

Developing nations many times face a dearth of diagnostic facilities and laboratories. The ones that exist are overloaded with jobs, making them hardly robust. In such circumstances, doctors are compelled to prescribe antibiotics to acute infections without the test results. This leads to high instances of overdosage, than what is recommended.

Widespread availability of antibiotics without a prescription is one of the biggest problems that developing nations face. A survey of drugstore sales of antibiotics in Mexico revealed that only 57% of antibiotic purchases were made with a prescription, and that the person selling the drug gave instructions on its proper use in only 15% of observed transactions (Calva, 1996). Unregulated sale of antibiotics is a breeding ground for strong resistant strains to emerge. One study in Bolivia tested healthy children from urban areas and found that 97% carried Escherichia coli insensitive to ampicillin (Bartoloni et al., 1998).

Developing nations may not end up having strong & powerful drug regulatory bodies. The pharmaceutical industry requires strict control of quality, and extensive regulation before a drug is released in the market, and the lack of strong regulatory body can lead to a significant perforation of substandard, and even counterfeit drugs.

Developing nations usually end up having lower medical densities (number of general practitioners per 100,000 inhabitants), than the developed nations. This leads to a lot of doctors being overworked, and also inadequate attention for many patients.

In certain cases, the doctors may be under pressures to unnecessarily overprescribe, and this contributes to increasing antibiotic resistance. . In a study by Paredes et al., of 36 physicians surveyed in Lima, Peru, who, despite agreeing to the fact that the majority of diarrhoeal disease is of viral origin, 35 unnecessarily prescribed antibiotics for this condition.

Another key point is that developing nations lack comprehensive data. The majority of transactions are unregulated (without prescriptions), and thus, it’s very hard to keep a track of the consumption in the nation. The data that already exists, is also very unreliable. This makes tracking the consumption of antibiotics, the national burden of disease, and the nature of antibiotic resistance in the country a difficult challenge.

All the above mentioned problems are present in nations to varying degrees, and to counter them, it is imperative to have a robust government, with a dynamic and effective policy to systematically address the issues. Without a national policy that aims at mitigating these problems and relieving the national burden of disease becomes an enormous challenge.

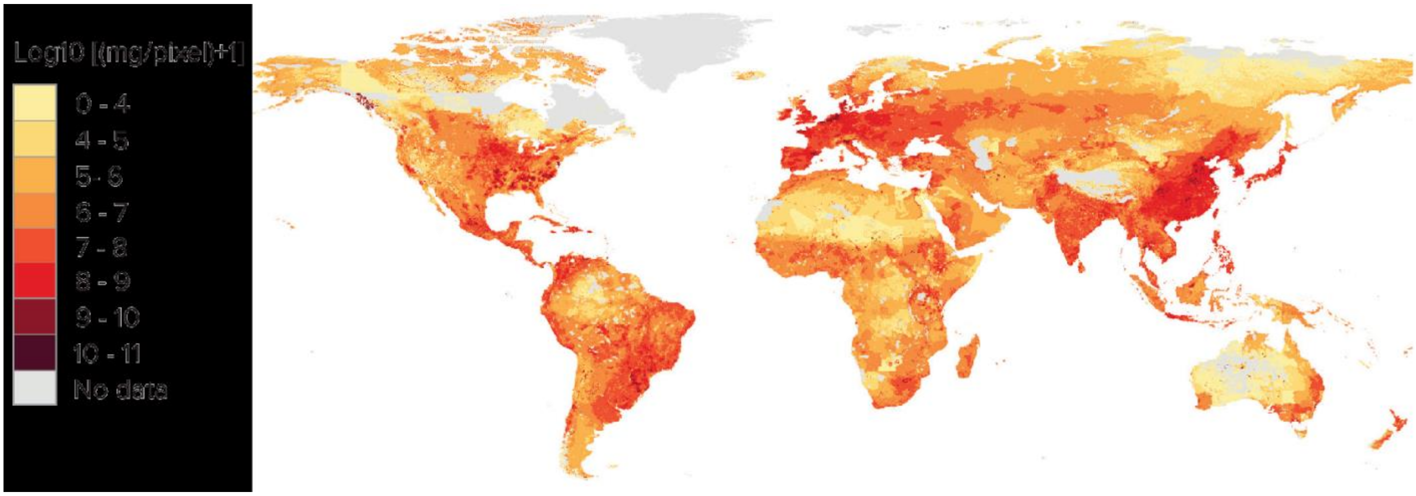
Antibiotics in agriculture and environment

Antibiotics have been used to treat animals for as long as they have been used on humans. The main reasons for antibiotic use in animals are to prevent and treat bacterial infections and to promote their growth. Currently, use of antibiotics in farm animals and food animals is more than the consumption of entire human population. Almost 80% of antibiotics consumed in the US are for food animals. Chickens and pigs consume the most antibiotics among all animals. These numbers are constantly growing as demand for meat increases due to rising incomes of people of the low and mid income countries. According to United Nations Food and Agriculture Organisation (FAO), in the next 35 years the demand for meat will rise by 73% and 58% for dairy products. This will increase the use of antibiotics in animals a large portion of which is to increase their growth.

The use of antibiotics in animals gives rise to antibiotic resistance in them which can be transferred very easily to humans and the environment. If other inputs like food and water quality, sanitation, breeding etc. are improved growth antibiotics would contribute very little. Thus this is the area of focus of the regulations on use of antibiotics in animals.

The antibiotic use in aquaculture is also significant. China is the main exporter of shrimp and other carnivorous fish with 80-90% of the world. Chile is major producer of salmon which is raised with a lot of antibiotics. This not only helps the growth of resistant bacteria in farmed fish but it also transfers to other wild fish and marine life.

Below is a map of estimated antibiotic use in animals in 2010:



The top five countries in animal antibiotics consumption are: China, US, Brazil, Germany and India. The rise in income and of the developing countries will significantly change this map. The BRICS countries will require double the amount they are consuming today in 2030 assuming just 13% growth in population. Mexico is expected to replace Germany in the top 5 consumers.
Antibiotic resistance issue has led to some regulatory measures to be applied on the use of antibiotics in food animals. In 1986, Sweden became the first country to ban use of growth promoting antibiotics for food animals. Denmark banned vets from selling particular antibiotics to farmers and later producers in Denmark voluntarily stopped the production of growth promoters. The EU in 2006 banned use of most of the growth promoters and since then sales of antibiotics have declined and have remained low.

Antibiotic residue has been found in significant amounts in the environment and enters it through the waste of pharma companies, flushing of unused drugs by humans and through human and animal excreta. This increases the antibiotic content of the environment to as much as or even more than levels of someone who is undergoing the treatment. This increases the levels of resistant bacteria in the environment which can enter our bodies through various ways which can prove very harmful to us.

Future of Antibiotics

Introduction

We currently stand at the threshold of what could be the post- antibiotic era. Almost a century after their discovery and unparalleled contribution to medicine and healthcare, the efficacy of antibiotics is in danger. Bacterial strains resistant to many of the existing in-use antibiotics have started emerging in many parts of the world.[1-2] And in these days of globalisation and rapid transport their reach would not remain localised for long. Even though a natural process of evolution, the sheer rapidity of the resistance emergence is startling. This has been attributed primarily to the overuse and misuse of the medicines, supplemented by lack of development of new antibiotics by the pharmaceutical industries due to reduced economic incentives.[3] Many of these emergent strains have already become a serious economic and healthcare burden to general public in even developed countries like the U.S., where competent agencies have described some of the outbreak situations as "urgent".[5] In densely populated delevoping nations such as India , the problem is taking even more gigantic proportions.[6] Hence, there is a dire need to renew research efforts, make and implement policy changes and pursue steps to curb the possible crisis.

History and Benefits

Historically, there is evidence of antimicrobial fungal treatment being given to wounds in many ancient civilisations, especially China. The modern era of antibiotics began with the revolutionary discovery of penicillin by Sir Alexander Fleming (1928), almost by an accident. It found wide scale application during the WW2 in treating the wounded soldiers. Since then modern antibiotics have helped save millions of lives all over the world, lives which would have had been lost due to infections by simple wounds such as even a scratch by a thorn. However, this wasn't achieved by any one miracle drug. Shortly after its application started, wide-scale resistant to penicillin emerged (1950s). In response to that, a new class of antibiotics called the beta-lactum antibiotics (containing a beta-lactum four sided ring , inhibiting the cell wall development) were developed. However, the bacterial evolution caught up again, and resistance to these, in the form of methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in the following decade. And this had been a continuous trend until the 1980s; a new drug was discovered and wide-scale resistance to it followed in a decade (or earlier). Unfortunately, after that period, the supply of novel antibiotics began drying up; fewer and fewer antibiotics were being synthesised by pharmaceutical companies, both as any new drug had fewer bacterial functions to target for inhibition, and the economic incentives for companies were not as high in this area. Rapid emergence of resistant strains followed, rendering many antibiotics useless.

Antibiotics are credited with changing the expected life spans of people worldwide , curbing majority of deaths happening due to bacterial infections both in the developed and the developing world. For example, from 1920(s) to now the average life span for a U.S. citizen has increased from 56.4 to 80 years (although this can be attributed to many other factors and developments too, such as better access nutrition , etc).Also, antibiotics have not only helped in direct targeting of bacterial infections, but have also enabled in the development of many other healthcare methods, including containing potential infections through chemotherapy administration , joint replacement surgeries , cardiac surgeries, etc. Absence of antibiotics can make all these procedures unsafe and therefore take our healthcare system backwards by many decades.

Causes of Crisis

Bacteria compete for nutrition and habitat. As an antibiotic is administered, it clears of all the bacteria *except* the ones having resistance to it. Hence, the resistant strains now have relatively negligible competition and can now thrive. Excessive usage and misuse of antibiotics are both believed to have played a major part in the *rapid* emergence of antibiotic resistance. Epidemiological studies concluded with a clear demonstration of relation between antibiotic consumption rates and emergence and spread of resistant bacteria.

Bacterias are a highly flexible and adept class of organisms. The most abundant domain of organisms on earth, most of them have a reproduction time of about 20 min. And its an exponential growth , meaning their no. double every 20 mins. Now, gene transfer in them can occur either through vertical transfer (From parent to offspring) or through horizontal transfer (HGT) though vector DNA elements such as plasmids. Often the resistance genes are located on the plasmid, which means that the transfer of such a gene can take place from species to species. This makes the fight more uneven and graver for us. For any new antibiotic we find, they will find a way through and catch up. Hence here , prevention is better than cure. And despite issuing of many warnings, even by organisations such as the UN , antibiotics overuse remains a global problem.

These problems are even starker in developing countries such as India , where huge population , lack of hygiene and sanitation , congested environments , and poor regulation of drug delivery systems all multiply the problem many times over.

In 2010, India was the world's largest consumer of antibiotics for human health, consuming 12.9 x 10^9 units (10.7 units per person). The next largest consumers were China at 10.0 x10^9 units (7.5 units per person) and the US at 6.8 x10^9 units (22.0 units per person). These no. had taken a jump between the years from 2000-2010, with India contributing to about 17.6 % of the increase in the retail antibiotic sales volume worldwide. This scale-up in antibiotic use in India was enabled by rapid economic growth and rising incomes in many regions , which have not translated into improvements in water, sanitation, and public health (There isn't even enough reliable evidence to predict the exact figures , and these are based on rough estimates).

The biggest contributor in India though is that India lags on basic public health measures:

- Immunization rates (as measured by diphtheria-tetanus-pertussis [DPT3]) coverage in India (72%) lag behind those in Brazil (95%), China (99%), and Indonesia (85%). Often we tend to think of immunity being individual specific, that the immune system of an individual determines his chances of being infected by a disease. This however is just one piece of the puzzle. The concept of herd immunity, often used by advocates for vaccinations is applicable here too. Ones chances for infection are highly dependent on the immune systems strength (which can be modified by vaccinations) of his/her community, as his associates may become channels through which the infections can pass to him/her.

- Doctors in India routinely receive compensation from pharmaceutical companies and pharmacists in exchange for antibiotic prescriptions. These often lead to inappropriate prescription (though this is also attributed to lack of expertise) of antibiotics, for diseases such as diarrhoea where these are minimally efficacious and better alternatives exist.

- Infection control in hospitals is poorly monitored and can be improved. A point prevalence study in a large tertiary care hospital in India found an overall health-care-associated infection prevalence of 7%, with a third of these being surgical site infections.

Another major concern is easy , over-the-counter access to antibiotics in India. Many argue that this is a major cause of overuse and hence should be tightly regulated or even stopped. However , these views are contested by others ,who claim that though this is a problem, the regulations to restrict access have to be balanced against the need to maintain access for the significant proportion of the population that lacks access to doctors. This is as lack of access to effective and affordable antibiotics still kills more children in India than does drug resistance.

Extensive Agricultural Use

Healthcare usage though significant pales in comparison with antibiotics usage for livestock . An estimated 80% of antibiotics sold in the U.S. are used on animals, primarily to promote growth and to prevent infection. Treating livestock with antibiotics is believed to improve the overall health of the animals, producing larger yields and a higher-quality product. Again, these are not being used to cure sick animals, rather used for general improvement in yield, which essentially translates to saving a few pennies per farm animal.

These antibiotics used in livestock are ingested by humans when they consume food. This transfer of resistant organisms through farm animals to humans was first noted more than 35 years ago, when high rates of antibiotic resistance were found in the intestinal flora of both farm animals and farmers. More recently, molecular detection methods have demonstrated that resistant bacteria in farm animals reach consumers through meat products.

Following is the sequence of events that leads to this :

1) antibiotic use in food-producing animals kills or suppresses susceptible bacteria, promoting resistant bacteria growth and development.

2) resistant bacteria are then transmitted to humans through the food supply (meat products essentially);

3) these bacteria can (if pathogenic) cause infections in humans that may lead to adverse health consequences.

Declining innovation and development in this field

Due to economic and regulatory obstacles, development of new antibiotics did not remain a very lucrative area of research for pharmaceutical companies. Usually, the investments that go into R&D are huge, if the results do not correspond, it may lead to slow death of the company. Also , in case of medical innovation , the lag period between innovation and its coming to market is huge, often 20 years , through the slow process of first researching , lab testing , trials on animals, clinical trials , etc. Hence pharmaceutical companies often shy away from areas where returns are not huge. In case of antibiotics , most treatments last not more than a few days. Also , even the per course cost of most expensive antibiotics is between 2000-3000 ; this pales in comparison with cancer drugs for example , where the per course cost of medicine may reach above 100000$ and the medicine is administered often years at length. In addition to this, microbiologists and doctors , aware of possibility of microbial resistance development often do not prescribe newly developed drugs to keep them as last resort. This further declines the market demand for these companies.

Also, the newly developed drugs usually have to go through gruelling phase of regulation to be passed to the market. Many changes have been suggested in this , including limited-population antibiotic drug (LPAD) regulatory approval pathway , which should make the whole process faster and efficient.

RESISTANT BACTERIAL INFECTIONS

Antibiotic-resistant infections are already widespread across the globe. A 2011 national (U.S.) survey of infectious disease specialists, conducted by the IDSA Emerging Infections Network, found that more than 60% of participants had seen a pan-resistant, untreatable bacterial infection within the prior year. The rapid emergence of resistant bacteria has been described as a “crisis” or “nightmare scenario” that could have “catastrophic consequences” by various public health. The CDC (Centre for Disease Control and Prevention) had declared in 2013 that the human race is now in the “post-antibiotic era,” and in 2014, the World Health Organization (WHO) warned that the antibiotic resistance crisis is becoming dire.

The bacterial community can be divided into two parts using Gram’s test : gram positive and gram negative. Among gram-positive pathogens, a global pandemic of resistant S. aureus and Enterococcus species currently poses the biggest threat. For example , MRSA kills more Americans each year than HIV/AIDS, Parkinson’s disease, emphysema, and homicide combined. The global spread of drug resistance among common respiratory pathogens : Streptococcus pneumoniae and Mycobacterium tuberculosis, has taken epidemic proportions.

The gram-negative pathogens are pose a more severe threat developing resistance to nearly all the antibiotic drug options available (Pan-Resitance), creating situations reminiscent of the pre-antibiotic era. Also , these are not isolated occurrences ; the emergence of MDR (and increasingly pan-resistant) gram-negative bacilli has adversely affected practice in every field of medicine. The most serious gram-negative infections occur in health care settings and are most commonly caused by Enterobacteriaceae (mostly Klebsiella pneumoniae), Pseudomonas aeruginosa, and Acinetobacter.

Suggested Solutions

- **Development of new antibiotics :**

Providing incentives to the pharmaceutical companies , perhaps through PPPs or “pull” approaches (rewarding the solution finder) , to invest in the development of novel antibiotics is one of the most obvious ways to tackle this problem. Some of the newly developed available drugs include : Tigecycline , Doripenem , Telavenicin , etc.

- **Switching away from antibiotics , creating novel ways to kill pathogenic microbes :**

Antibiotics are not the only solution to infections . Many next gen technologies are under development. For example , Nobel Prize winning Biochemist Karry Mullis and his team have found a novel method , to tag the infecting bacteria with a molecule , so that our own natural immune system digests it. This might be available to the general public within a few years. Also , bacteriophages , viral agent which eat bacteria can also be used as vectors to carry bacteria killing chemicals and disrupting their machinery have been studied and developed to suit these needs. Technologies such as these can be promoted in part through increased investments in such R&D.

- **Prevention through Policy framing and Regulation :**

Along with creating new solutions, we must make efforts to slow the rate of resistant bacteria emergence. This is likely to become a loosing race if we don’t do that. For example , policy changes to strengthen antibiotic dissemination regulations be imposed , especially in developing countries. Laws can be passed to ban the use of antibiotics in agriculture and animal rearing where this can be easily avoided. And prescriptions can be checked through some regulatory framework to avoid incorrect and overdose of antibiotics.

Conclusions

As mentioned before , prevention is better than cure (in this case atleast), as bacteria are highly diverse and adapt quickly. No matter what solution we find , the bacteria are likely to outrun it in a span of few years or decades at max. Hence , our efforts to find new solutions ,though indispensable, should be complemented by changing the policy frameworks and its implementation .Overuse and misuse of the antibiotics should be stalled , especially in areas such as animal husbandry where metaphorically a gun is being used to cut a ribbon. In countries like India, hygiene and sanitation conditions , and the general “health” of the healthcare system itself needs to improve , which is the underlying problem. Regulations must be put in place to stop antibiotics remaining over-the counter drugs, however, this should be done keeping in mind that access to the really needy is not compromised ,and simultaneously the reach of these medicines must increase. These are hard and difficult tasks , but still nothing compared to the difficulty which might arise out of complacency now.

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Antibiotic Resistance in India

Antibiotic resistance is a global public health threat, but it is particularly stark in India. The infectious disease mortality rate in India today is 416.75 per 100,000 persons and is twice the rate that existed in the United States when antibiotics were introduced (roughly 200 per 100,000 persons). There are multiple causes for this.

Antibiotic use is a major driver of resistance. In 2010, India was the world's largest consumer of antibiotics for human health at 12.9 x 109 units (10.7 units per person). The next largest consumers were China at 10.0 x109 units (7.5 units per person) and the US at 6.8 x109 units (22.0 units per person).

The scale-up in antibiotic use in India has been enabled by rapid economic growth and rising incomes, which have not translated into improvements in water, sanitation, and public health. Antibiotics continue to be prescribed or sold for diarrheal diseases and upper respiratory infections for which they have limited value.

The main problem is that India lags on basic public health measures. Immunization rates coverage in India (72%) lag behind those in Brazil (95%), China (99%), and Indonesia (85%). The percentage of the population with access to improved sanitation facilities in India (36%) was far lower than the percentage in Brazil (81.3%), China (65.3%), and Indonesia (58.8%).

Over-the-counter access to antibiotics is a huge problem, but regulations to restrict access have to be balanced against the need to maintain access for the significant proportion of the population that lacks access to doctors. Indeed, lack of access to effective and affordable antibiotics still kills more children in India than does drug resistance.

Improved capacity of drug regulatory bodies is essential to safeguard against powerful antibiotics being sold over the counter and to phase out the use of antimicrobial growth promoters in livestock.

Behavior change is needed among physicians and patients. India has achieved remarkable reductions in smoking in buildings and workplaces through regulation and behavior change communication. Similar campaigns could work to educate the public and physicians about the dangers of uncontrolled antibiotic use.

There is very little data on the extent of resistance, with the exception of a few single-hospital reports. There is a desperate need for robust national data in order to drive policy.

To counter a problem of such scale, it is necessary for the government to acknowledge its vast scale and need to mitigate it. It necessary for robust, data driven, and effective policy to be implemented nationwide. Without interest from the government, it becomes a very big challenge to curb the epidemic of antibiotic resistance.

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