Host

I would like to invite Ramanan to the podium. Thank you very much.

Ramanan Laxminarayan

Thank you very much for the kind introduction and for the invitation to be here. I don't think I have given a talk at a place as beautiful as this just yet, I'm unlikely to match something of this beauty and grandeur. So the subject is really on antibiotic resistance and this happens to be the World's Antibiotic Awareness Week celebrated, well not celebrated, sort of a week of concern both in Europe and in United States, for quite a few years now as Get Smart Week or Antibiotic Awareness Weekbut now it has spread to the rest of the world. I'm going to make just about six points and hopefully that gets us to the point of having a conversation about this and I'll try to leave some time at the end for that discussion.

The problem we face is that drug resistance is rising worldwide, and it is serious enough to threaten the significant gains that we've made in fighting infectious diseases. Now, we haven't had antibiotics for that long, just about seventy years, just a little over that, it was 1929 when Alexander Fleming discovers through quite an accident that the Penicillium mold is effective at killing bacteria, but it then takes another 12 years or 13 years for Howard Florey and his team to really figure out how to make the stuff again and then put it into a person. And, of course, it came out just in time in 1942 to be of use in the Second World War, a lot of people who would have otherwise died because of infections from wounds, their lives were saved. And during the First World War, far more people died of infections and actually did from actual battle injuries. Fortunately, that was greatly diminished during the Second World War, and since then life has not been the same.

Now this is a picture that's classically shown of a young girl treated sometime in 1943 or so with severe sepsis. That's on day 1, this is a small child, then day 2, day 3, she's on antibiotics. By day 4, 5, and 6, she's much better and you can see that this was something that had never been possible before, to literally bring someone back from the brink of death. And the idea that antibiotics are miracle drugs has been recognized ever since then, but even at that time, it was widely recognized, including by Alexander Fleming in his lecture to receive the Nobel Prize, that there would be a time when the overuse of antibiotics and the constant selection pressure imposed by the use of antibiotics would weed out the susceptible bacteria leaving only the resistant ones, which would then mean that progressively, the use of antibiotics to treat these bacterial colonies that are made up of resistant bacteria will be less and less effective. And we would have to deal with that in full course over some period of time.

Now, that was predicted back in the 1950s. In fact, if you look at this, this shows that the first reported cases of bacterial resistance against key antibiotics was only a few years after any antibiotics were introduced. So it never took very much time for bacterial resistance to be detected. In fact, if you look at penicillin, so I don't know if you can see this, at the very beginning, 1943, introduction of penicillin formally, but 1940, which is a full two and a half years

before penicillin was even used to treat the very first patient, there was already a paper published showing in-vitro resistance to penicillin, which means that the ability to be resistant has always existed except in very, very small concentrations, extremely rare amongst bacterial colonies, but once you impose a huge selection pressure that we have, that certainly becomes a predominant trait.

But I think one thing to remember is that resistance is inevitable to some extent, and we're always going to see it and the time to resistance is anywhere between two or three years to about 15 years if you're lucky. So you can see the maximum time that it's taken for resistance to be detected as in the case of erythromycin or vancomycin, it took about 15 years. Now, these are figures from US data showing carbapenem resistance and third-generation cephalosporin resistance in Klebsiella pneumonia, a particularly worrisome bug that is primarily in hospital settings and usually high along the East Coast, but prevalent across the country, so going from 1999, 2001, all the way to 2006, 2010, and you can see that this has been growing as an issue.

Most things in nature happen to be logistic, that's just the way in which nature works. And you can see that in many instances resistance has been at a low level for a long, long time. One thing that has characterized the 2000s or the new century, is that resistance is now taking off from the sub 5% range to get into the 30, 40, 50 or in some cases even 70% range. Now, I'll see if I can play this video, so this shows carbapenem resistance in Acinetobacter baumannii. Now carbapenem resistance is particularly worrisome because the carbapenem class of drugs are sort of our last resort drugs to deal with gram-negative bacteria, this entire class of bacteria that are particularly hard to treat and are quite common, particularly in the tropical countries, although that pattern is also changing. Iif you look at carbapenem resistance, it's usually an indicator of how bad things have come. And you can see in 1999, the percentage of isolates that were resistant to carbapenem was under 10%, but watch what happens when I play that video and you have the national rate for the US on the bottom right.

So it moves from 2000, starts going up on the East Coast, across the eastern seaboard crossing about 40% throughout the country, some places more than 60% now, and by the time you get to 2009, 2010, you have the entire picture, covered in orange, some in the darker red, which is over 60%. Now this is just over the space of 10 years, when we've seen resistance levels go progressively higher and higher from a sub 5 or 10% resistance rate to 40-60%, in some instances, a greater than 60% rate of resistance. Now, resistance doesn't map directly onto treatment failures, but it is correlated with treatment failures. In other words, if you have a lab test showing that bacterial colonies are resistant, it means that there's a higher probability that the patient will fail treatment.

Now, these are data that we just published last month in something called the State of the World's Antibiotics report, and you can see that there is some good news. Methicillin-resistant staph, which went as far as being an election issue in the UK, about 8 years ago, has been taken quite seriously and there are countries which are showing progressive improvement. But not all countries, the country in which I live, India, for instance, it's been high and it's going even

higher and it really wasn't such a big problem, I would say about 15 years ago, but now it really is. And some countries have managed to keep resistance quite low like Denmark, for instance.

Now, antibiotic resistance has both a local and a global nature. If countries use antibiotics appropriately and have policies to keep infections in check, it is possible to have low rates of resistance within a country. But resistance does spread from one country to the other as well, so both of these are simultaneously true. If you look at the percentage of methicillin-resistant staph for the most recent years, 2011-2014, you can see that this is a problem throughout the world but particularly concentrated in pockets of Latin America and Russia, Russia being a country where antibiotics are actually quite freely available without too many restrictions, and then of course India and Iran as well.

If you look at extended-spectrum beta-lactamase-producing E. coli again, a good marker, these are sort of canaries in coal mines for where things might be going bad. You can see that it's really a problem in India, and we don't have data here from Bangladesh, but it's pretty bad in Bangladesh as well, you can see in East Africa and then also in Latin America. Carbapenem-resistant Klebsiella, growing problem again, the country I live in tops the list and if you can look at New Delhi, metallo-beta-lactamase-1, which is a particular class, so, this particular strain, which was first detected in an Indian patient in Sweden back in 2007, is now endemic in the subcontinent and in China, and has been detected in over 110 countries around the world. As you can see, in the US, it was detected quite early, so things can get created in one place and go to other places.

Now, I'm just showing you an Indian example, but there is a strain of community-acquired methicillin-resistant staph, that is called USA 300 and it's called so because it was first detected in the US. Many of these strains of vancomycin resistance have been detected in Japan, so all countries bear some culpability, it might arise from anywhere, but the whole idea that resistance can arise anywhere and spread everywhere. This is clonal spread of S. pneumoniae 23F, possibly started in France, although they blame the Spanish for it, and it probably spread from there to most of the countries that we see it and 23F is now a predominant strain of Strep pneumoniae.

If you look at another marker, unique beta-lactamase enzymes identified since the first introduction of beta-lactam antibiotics, that's also going up. Obviously some of it has to do with scientific discovery of these enzymes, but the fact is that the tools that bacteria now possess to evade, avoid and thwart the antibiotics that we have is growing at a constant pace, so there's no avoiding this, they have this information, they're able to share this quite easily and they share this through horizontal gene transfer through plasmids. So in other words, it's quite similar to when we're in a library, if you've written a book and it's on the shelf on how to be resistant, I don't have to go through the same process to learn how to be resistant, I can be an unrelated bacteria and go check that book out of the library and learn how to be resistant. And I can use that book and the information just when I need it and not use it when I don't need it. Bacteria have this amazing ability to be able to transfer information to each other and this is a collective

action for them, and they are certainly far more united in purpose than we are, although, we're just one species and they are multiple species.

Now you can see again daptomycin, linezolid, these were the drugs that were introduced in the early 2000s and were touted as, this is really how we're going to deal with MRSA and gram positive infections, and even here you are seeing resistance actually go up. Now why is this of concern? Simply because people get sicker and they die as a consequence. The one age group that is more susceptible to the lack of availability of prompt and effective treatment are neonates, simply because they really lack the immune defenses that we would have as adults and we don't have two shots at them if we happen to have sepsis, for instance. So if the first line drug fails for a neonate with sepsis, there isn't the time to go back and give them a second line drug that might actually work, even with sepsis they're very likely to die.

So the fact you can see in this one study done in Tanzania, if that child is culture positive, that's a 30% chance of dying, pretty high. If the gram-negative infection, which means bacteria are classified into gram-positive and negative depending on whether depending on the Gram stain, and if they are gram-negative infection, then they are more than 35% likely to die. If they have the extended spectrum beta-lactamase, then that's a much higher probability of dying and similarly with MRSA, much higher probability of dying.

Now, these are not all that we would wish for ourselves. Imagine if I were to tell you that there is a condition in the world where if you had that condition, you had a 30% chance of dying, that would just be unacceptably high, but those are the odds that neonates with sepsis have because a lot of them don't necessarily have access to the high-end health care facilities, they have to go with the antibiotics that they can get in the community. So just yesterday, we published a special series in The Lancet which is a collection of five papers laying out what the world we could be doing about the problem, it's all online as well, I just have one hard copy, and this was the first paper in the series laying out the problem of access to effective antibiotics. And here we estimated that there were probably about 215,000 deaths every year because of neonatal sepsis that is untreatable because of the prevailing levels of resistance. Of that, 58,000 are just in India alone, and then Pakistan, Nigeria, Congo and China. And these are all countries with high rates of neonatal sepsis. You know some has to do with population, these are all large countries to be sure, but they also have rates of resistance that lead to the sorts of outcomes that would then produce these kinds of deaths.

Now, the other age group that is particularly affected by antibiotic resistance are the elderly, because they tend to go in the hospitals a lot and hospitals are not places that you would want to go to casually because of the high risk of getting an infection that was untreatable, high as in the US, it's about a one in 20 chance that you'd get an infection but I think a one in 20 chance of getting an infection is pretty high, and some of those will be untreatable. When we looked at the effect of antibiotic prophylaxis that was not going to be effective because of drug resistance, and we looked in just about 10 categories, if someone who's going to go through colorectal surgery, or hysterectomy, appendectomy, C section, all things that most of us will need at some point in

our life, hip replacement, spinal surgery and so forth, we're all gonna need these at some point, and if we have parents or grandparents, they probably are going through these right now.

There are enough studies that have shown that less effective antibiotic prophylaxis leads to worse outcomes for folks going through these kinds of procedures. And if you look at two scenarios of decreased efficacy, a 10% or a 70% reduction in efficacy, that you do have increased infections, and we did this just for the United States and this was published a few months ago in The Lancet Infectious Disease. So with a baseline of about a 30% reduction in efficacy of antibiotic prophylaxis, we would expect about 6500 additional deaths in the US and about 120,000 additional infections. So again, these are not millions of deaths, but I would say, some reporter asked me, 6500 deaths, is that a lot? I said, well, that's a lot, if your parent happens to be one of the 6500 deaths.

So the fact is that these are deaths that we think are avertable if we used antibiotics appropriately and we also had better infection control. So in that sense, it's just a problem that can be solved, can be addressed and really should be addressed. This again is the counterpart of that. So I already showed you the number of infections, and this is a 30% decrease in the efficacy of antibiotic prophylaxis and again C-section, a lot of folks will go through C-sections, but this is a pretty high risk of infection. And typically, when someone went to the hospital and then they died of multiorgan failure, or something completely different, that typically is a marker that they got an infection, which was not treatable, and that's why they really died.

Now, the second point is that there's good news, rising incomes and increasing access to antibiotics are saving lives and one of the main points of this Lancet series which is about access and sustainable effectiveness. It's really this fact that lack of access, although the talk was about drug resistance, lack of access to effective antibiotics still kills more people than antibiotic resistance does. So there are lots of children that are dying of pneumonia, that are easily treatable, those who die simply because their parent was not able to get them a penicillin or, whatever the appropriate first line antibiotic in that place would be, in a timely fashion. But at the same time, we're using antibiotics as a substitute for public health. How's that the case?

So this is a report I talked about and that was the embargo that was lifted yesterday. And here in that Lancet paper, we estimated the pneumococcal pneumonia deaths that were avertable with improved antibiotic access. So if we have universal antibiotic access, which means every child who needs an antibiotic was able to get one, in the same way that we have vastly ramped up access to antimalarials, we would in total avert 430-440,000 deaths every year.

Why is that number so high? It's because a lot of children die of bacterial pneumonia, which is really quite easily treatable. And you can see the largest numbers are really in India and also in Nigeria and DRC, China also has some proportion of these deaths.

So, on the x-axis is the under-5 population with suspected pneumonia receiving antibiotics and the reason why India has far more of the deaths is because, say compared to China, a far lower proportion of the under-5 population with suspected pneumonia actually gets the antibiotics in

India relative to in China. And of course, the y-axis is pneumonia deaths because of S. pneumo and Haemophilus influenzae type B per 1000 children aged younger than 5 years. So, the point is that bacterial diseases are still the major killers in developing countries and that's because of the lack of access to antibiotics.

Now, what are we asking of antibiotics? If you look at crude infectious disease mortality rates in the United States over the previous centuries, from 1900 to just about 2000, you see that they were declining all the time, so they've gone all the way down. The first use of penicillin was in 1941, 1943, by which time crude infectious disease mortality rates have dropped by 75% from 800 per 100,000 per year to 200 per 100,000 per year. Much of what we count as our success against infectious disease had nothing to do with antibiotics or very little to do with antibiotics. It had to do with improved water and sanitation, improved hygiene, vaccines to some extent, availability of public health departments, chlorination of water, all of these were what made a difference and then we got the antibiotics to deliver the knockout punch.

Now, what are we doing with antibiotics today in some other countries? In South Asia today, the crude infectious disease mortality rate is 400 per 100,000 per year, it's twice the rate it was in the US back in 1942. So we're not using the antibiotics as a mop up operation, we're using it as a substitute for water and sanitation, as a substitute for public health, and antibiotics are not designed for that sort of heavy duty use. They can come in if you've done everything else. But if you use them as a first line of defense against infectious diseases, then the risk of resistance is much greater.

In Sub-Saharan Africa, rates are much higher than that, two and a half to four times what it was back in 1942 in the United States and in fact I just showed you these two, if you look at Afghanistan for instance, the rates are even higher than this. So, an urgent need is to not use antibiotics as a substitute for common sense infection control, water sanitation, but really to put in place measures to get those. Now if you look at the population without access to improved sanitation, and you can look at it by the MDG region in 2012, Southern Asia, largest amount, about a billion people without access to improved sanitation, India obviously has the largest population so that accounts for a lot of it. But China as well has lots of people without access to improved sanitation. So this is why you have a lot of diarrheal disease, a lot of people take antibiotics inappropriately for diarrheal disease ergo you have resistance.

Vaccines can be effective. Invasive disease caused by pneumococci in children under 2 declined, and this is just one study from the United States, there are similar studies from the Netherlands, South Africa from Latin America, all of which show that once you introduce a pneumococcal vaccine, the prevalence of disease goes down, it goes down both for the strains that are susceptible to penicillin as well as strains that are not susceptible to penicillin. So you can actually get rid of resistance to some extent by introducing a pneumococcal vaccine.

Now, you also have benefits, so you introduce the vaccine for the under-2s and certainly their rates go down, but you also have benefits for the elderly, the over-65 population, because the kids are the ones that are transmitting the disease to the elderly. So you're helping the old folks

by getting the vaccine to the young ones. So here is an obvious thing to really do, which is to scale up using this vaccine.

Again, in the paper that we published yesterday, we looked at the number of antibiotic treatment days that you could avoid by scaling up the pneumococcal vaccine which is now available in many countries around the world, but many countries in Asia still don't have the vaccine. And we estimated about 11.4 million days on antibiotics that could be averted if we improve the pneumococcal conjugate vaccine coverage.

Now meanwhile, as I said, there is good news in the fact that antibiotic consumption is increasing in developing countries, although some of it is inappropriate use, so that's a concern. Brazil, India, Norway and the US it's leveling off or going down, in the US use is going down primarily because of the introduction of Prevnar, the pneumococcal vaccine, because children under the age of five are the single most important reason for antibiotics being given out.

So if you look at the period between 2000-2010 for the 72 countries for which we have data, global antibiotic consumption went up by 36% over just that 10-year period. So the current consumption is somewhere about 37,000 tonnes in these 72 countries. Of that 36% increase, 75%, three-quarters, are just in the BRICS countries - Brazil, Russia, India, China, and South Africa. Now, within the BRICS countries about two-thirds of the sales in the retail sector, which is pharmacies outside of hospitals, two-thirds of that increase is just in India, and two-thirds of the increase in sales in hospitals is just in China. Now, obviously, these are large countries again, but this is really where much of the increase is happening. Now, South Africa, as you can see, also had high rates of increase between that period, but that was mostly of just one kind of antibiotic, cotrimoxazole, which is used to deal with secondary bacterial infections if someone has HIV and they have a big HIV burden, so they used a lot of cotrimoxazole.

But you can see that across the board, we're seeing a pattern here. Brazil, Peru, you have a lot of countries where antibiotic consumption is going up. Some of it is good because they previously were dying without the antibiotics, are no longer dying and that's great. But there are people in urban areas who have access to very powerful antibiotics and that is not so great.

So again if you look at the leaders in consumptions – I wish the Olympic tally looked lke this but this is not the Olympic tally, this is antibiotic consumption – India's on top and China is number 2 and the US is number 3. These are totals, not per capita rates. But you can also see the increase of rates over time. France has actually gone down, they've had very successful campaigns against antibiotic overuse. The UK, very marginal increase, South Africa, for the reasons I explained, a significant increase, and Brazil as well.

Now if you look at countries by per-capita income on the x-axis and then how much antibiotics are being consumed on a per-capita basis on the y-axis, it gives you some sense of the idea that incomes do matter. When countries are wealthier, they do use more antibiotics on a per-capita basis. So, even though I showed you India and China as having very large amounts of consumption, they are nowhere close to what the US is when it comes to per-capita

consumption. So the US still leads by far and most other countries, even the UK, will be much higher on a per-capita basis.

The broad-spectrum penicillins lead, and then cephalosporins, macrolides and so forth. So we are reliant on just about five or six classes of antibiotics to do much of our heavy-lifting on infectious diseases. If you look at carbapenem sales, and I have mentioned to you earlier, carbapenem is a marker of a drug that is a last-line drug, retail sales means its available in the pharmacy somewhere, possibly without a prescription, and this is of particular concern, again, the growth there in India has been tremendous, in Pakistan it has been quite significant and Egypt as well. These are just countries that I happen to have data for and there's possibly other countries for which it looks even worse and these are per-capita figures, so it looks pretty bad. But there are countries that don't do it, like Vietnam and Indonesia and there is something to learn from them.

Now, carbapenem consumption is also a marker for the fact that other drugs are not working and if you look at the hospital sector across Europe, you can see by and large it's been going up over time, you'd probably look for the UK and I don't have it in here. But overall, carbapenem consumption, measured as defined daily doses per thousand inhabitants, has been going up over time. Globally, hospital use of carbapenems is growing, it's really an indicator of the fact that we have a resistance problem that's quite serious and you can see that the per capita rates of the US are much higher than in China or Vietnam although the growth rates are higher in those two countries.

Macrolides are also growing quite rapidly, again look at per-capita rates, India might be growing, Brazil might be growing, but the US is still the king when it comes to per-capita consumption. The US really leads in per-capita consumption of antibiotics, the one other country that I suspect has more but for which we don't have very good data is Japan, so Japan and South Korea also use a lot of antibiotics per person.

Now, colistin is, any clinician will tell you is a horrible drug with terrible side effects, not a drug that one would want to use, except if the patient was really going to die and when someone has carbapenem resistance, then colistin is really what one might think of using. The global availability of colistin is a marker of how bad the resistance problem is. 10 years ago you wouldn't have seen this breadth of availability of colistin. In fact, in Vietnam it was only available in the veterinary sector, so if the doctors needed it they would go and take it from the vets because it was not approved for human use. Colistin is now widely available and that is really a problem, so all the greens are where colistin is actually available. And today the first instance of plasmid-mediated colistin resistance was reported from China and again, if you use enough of it, the resistance will arrive.

Why this picture? Not because we're in Scotland and you guys are familiar with oil, but really the fact that there are two things that one could do in terms of managing the antibiotics that we have. We can either make better use of the existing antibiotics that we have so we can engage with conservation, or we can go out and find new antibiotics.

Now that's really the only two options and the fact is that if we make better use of our existing antibiotics, then we will have to certainly invest less in finding new antibiotics. But if we invest a lot in finding new antibiotics, so let's say we subsidize oil drilling, what's that gonna do for incentives for conservation? It's going to go down. So if I know that, as a doctor, the government has put in billions of dollars into finding new antibiotics, I'm not really gonna care about conservation as much because I know that someone's gonna come up with a new antibiotic. So the incentives here for how one uses antibiotics are really, really important and at the end of the day, we cannot just innovate our way out of the problem, I'll talk more about that towards the end of my talk, but really, these are the main opportunities that we have and much of our policy responses fall into one of these categories.

This is really a co-evolution game between us and the bacterias. These are Thompson's gazelles and cheetahs and they have sort of co-evolved so that if the gazelle wasn't fast enough, it would be eaten by the cheetah, and if the cheetah didn't run fast enough, it wouldn't get any lunch. Now we're playing that same game against the bacteria. We of course are not the cheetahs, we're the gazelles and the cheetahs are staying ahead, obviously, by the time I finish this talk, they would have probably had kids and grandkids so they're doing this repeated experiment and figuring out how to be resistant and we have a very slow drug approval, drug innovation process that is simply not going to be enough to keep up with the bacteria. So the idea that we can out compete the bacteria but being smarter with new drugs is not really likely to work out, at least if you believe what evolutionary biologists have learned over a very long time.

Now the drivers of how antibiotic use actually plays out in the real world relates to incentives, so, this is not fundamentally a medical problem. If I take aspirin, that has no implications for whether that aspirin will work for you or not, absolutely none, except for if you are psychologically influenced by it that it's not working for me or something. But it really has no other connection with whether it would work for you.

However, if I were to misuse antibiotics or overuse antibiotics, that both has implications for myself, in that the antibiotics will not work as well for me in the future, but it also has implications for the rest of you because we all share bacteria, we have 10 times the number of bacterial cells in our bodies as we do have human cells, and it means that the antibiotics won't work for you. In that sense, the whole problem of resistance is one that is not very common in medicine. It's really a global commons problem, has far more to do with climate change and carbon emissions and living on a shared planet than it really does with most other problems that we deal with in medicine.

Incentives are really the same way. Physicians really try to satisfy patient expectations and usually the frequency of antibiotic prescribing relates to whether the patient expects an antibiotic because at the end of the day, it's a provider-customer relationship, and if the customer wants something that the provider provides it. We find that in areas where there's a high concentration of GPs that are competing with each other, in Taiwan, for instance, that when you have a high concentration, they tend to prescribe more antibiotics because they're competing on the basis of

whether you get a prescription or not. Now health insurance actually increases prescribing, again because it makes antibiotics cheaper. I'm not saying that you shouldn't have health insurance, but just to say that we have to be mindful of the drivers of prescribing and this is one of them. This is from the RAND health insurance experiment that showed that oral antibiotics were more likely to prescribed when it was a free program compared to when it had some cost sharing involved.

Now this is a study that we did in the United States, based on an experiment when antibiotics were provided free, that was not an experiment by the way. About seven years ago, a whole bunch of grocery chains, Amaya, Giant, all these grocery chains started providing some antibiotics as loss leaders to get people to come into their grocery store. They would get the antibiotic for free and maybe they would buy their milk and vegetables and whatever else from there, and this was widespread until the CDC shut it down.

But during that period, what we found was that the prescription of all antibiotics actually went up, so it's not as if physicians are prescribing antibiotics completely agnostic to what the external environment is out there, if it's cheaper for the patients to buy it, they prescribe more of it. In this particular instance, they also prescribe more of the antibiotics that were covered under the free program and less of the antibiotics that were not covered under the free program. So it's not as if this entire prescription decision is written in this completely scientific, do you need the antibiotic or not, way. It's a complex human-to-human interaction and fundamentally the solution to the problem of resistance will be found, not under a microscope, but really in our understanding of how people relate to each other and really do with incentives.

And so there's also hospital incentives where antibiotics are really a substitute for infection control. Imagine a world where the doctor knew that, if you were to get an infection they had no antibiotics and you would almost certainly die or would be very sick, they would take infection control a lot more seriously in that world compared to if they knew that, I can always treat the patient even if they had an infection. And particularly so when antibiotics are reimbursed and infection control is not – and infection control is often not reimbursed. So in fact, there is a very nice study from Harvard two years ago, which looked at how hospitals view infections and what they found was something that cynical economists might have always guessed, but I was shocked to find out, which is that hospitals don't mind their patients having complications, at least in the US system, because it fills beds. So if you have extra beds, nice to have them filled, and in fact, compared to an absence of complications, this is published in the JAMA by the way, complications were associated with $39,000 higher contribution margin per patient with private insurance, and about $1700 more with Medicare. It's not like the hospital manager saying, yeah, I've got to give my patients complications, but let's just say that they're not dying to get their patients out in the fastest way possible, because that's not what's making their money.

Fourth and very important – antibiotic use in the animal sector is increasing rapidly because the demand for animal protein is increasing as well. Now, this is one of the defining sort of changes that I think we're seeing over our lifetime which is that the demand for animal protein, what people eat is really shifting dramatically across much of the developing world. You know, where

meat used to be this once in a year luxury is becoming something that people eat every week perhaps even every day. Just for full disclosure, I'm vegetarian but I remember being in China 15 years ago and people saw that I was vegetarian and they assumed I was poor because why would you not eat meat if you had the money, you must be poor if you don't eat meat. So conversely as people get wealthier, people are actually eating more meat and that's true in India and China.

If you look at the increase in demand for poultry in India and China, you could see that already per capita consumption was high in China, it's gonna go up even further and of course the population's up there as well. Now India's got a much bigger increase in per capita consumption that's been projected by the Food and Agriculture Organization between 2000 and 2030 and then of course a larger population increase as well and the total increase, that's a lot more poultry that has to be produced. Now, how are you gonna produce that kind of poultry?

We use antibiotics for growth promotion and disease prevention because you gotta keep a lot of animals stuck close to each other. Two-thirds of the tonnage of antibiotics sold every year, about a 100,000 tonnes roughly of antibiotics are manufactured and sold, two-thirds of that is just in the animal sector and they are used primarily for disease prevention and growth promotion. So essentially for pigs, if you want to get them to feed faster you've got to wean them away from their mothers faster, you do that fast too soon, they'll lack the maternal antibodies that come with the milk and therefore you're going to substitute that with the antibiotics and you get them out and you get to save three days of production time on getting that pig on your plate compared to if you didn't give it the antibiotics. Is it worth the three days faster to come to your plate? The animal industry certainly thinks so. You also have to remember, the number of hogs in China is six times the number of hogs raised in the United States. So all these sorts of huge effects are no longer from the West, much of the production has really shifted.

If you look at the amount in milligrams of veterinary antibiotics sold per kilogram of pig meat or poultry meat, that varies widely. That's about 180 milligrams per kilogram of meat that we're producing in the Netherlands or France, compared to less than 20 in Norway. Norway and Sweden show that it's possible to do it with far less, but in order to do it in Norway and Sweden, they have to maintain very high levels of farm hygiene and nutrition for the animals. So it's not like it can't be done, it just requires paying attention to other inputs. If you look at meat production and sales of antibiotic feed additives for a very long time in the United States that's been going up steadily over time.

Now, what we did was we computed like we did in that other paper how much antibiotics would be sold within the animal sector. We use data from the EU which has very good data and also we had some decent data from Thailand as well. And so we published this last year on "Global Trends in Antimicrobial Use in Food Animals." This is a map which shows where the global antibiotic consumption is in livestock, and you can see that's generally correlated with where people tend to live – China, India, Europe, around Brazil, and the Eastern seaboard of the United States. Global consumption was estimated at 63,000 tons in 2010, projected to rise by

67% to 105,000 tons and there's going to be hotspots like India, where there are areas of high consumption, expected to grow by 312%.

Now, of the top 10 countries, China is by far the big leader, followed by the US and Brazil and then Germany. So, this is where a lot of the antibiotics are really going, far more than in the human sector. Some countries have tried to ban veterinary sales or profits from drug sales. That's what you see, this red shows the growth promotion here, this blue is for treatment. There is some offsetting of the disease prevention by an increase in the antibiotics that are used in disease treatments but not enough to completely offset it.

So, we've gotten down from 200 down to an average of about 100 metric tonnes in Denmark just by following that sort of a procedure and there's no reason why other countries couldn't do it as well. An interesting fact is that the value of antibiotics in terms of average daily growth of pigs, for instance, fed antibiotics, in the 1960s, the effect sizes were quite large, by the time you got to the 2000s, the effect sizes were much smaller.

Now why is that? It's simply because modern farming is actually a lot more modern than what it was 50 years ago. 50 years ago, you had animals being grown in fairly unhealthy conditions, they didn't get great nutrition, they didn't have genetic potential, as in these were not animals that have been reared for doing really well. All that has changed. So the added value of antibiotics is actually much less today than it was in the past. and in fact, if you look at a pig, a single pig, and what it would cost to remove the antibiotic growth promoters, or AGPs, you're going to lose about 44 cents in excess mortality, 30 cents in excess feeding days, some increased medications, and some increased workload. But at the end of the day, you're gonna lose about $1.34 for removing the antibiotics per pig. Is that a lot of money? I think it's well worth it.

And if you scale that up to the world and this was a report from the OECD, you'll see the potential loss in meat production in percentage terms at its highest, it's about 2.5%, not big at all. And if you put it down in actual numbers, it will cost China about $3 billion in what they gain from the AGPs to remove them entirely. So I think this is an area for immediate action and certainly other countries, US, Brazil, India could all be doing the same thing. Now the countries that actually regulate antimicrobial growth promotion are very very few. The European Union is the exception, the US has voluntary guidance so far, and much of the world has nothing at all.

So two slides on who pays the price of resistance, so this is going to certainly be hitting someone, turns out that the price of second and third-line drugs is going to increase significantly and this is the bottom line. You and I, if resistance were to go up, we'll simply pay £100-200 for the next course of antibiotics. But for someone who is making an average of $20 or $50 a month, they would pay for it with their lives, because if you look at the developing world, the cost of the antibiotics that were used there is far lower than what we tend to use in the developed world. So it's a problem of costs in the West, it's going to be a problem of lives in Sub-Saharan Africa and across much of Asia.

Now can we innovate our way out of the problem? I've already put up the slide to show that resistance is in some sense inevitable. So to some extent, we're going to have to constantly innovate to come up with new antibiotics. However, this figure is often shown to show that the rate of new drug development is actually declining. But this is really what the right figure is, which is, between 1980 and 2004, there is actually no discernible trend in the development of new antibiotics. There are new antibiotics that are coming to market. It is not whether antibiotics come to market, it is whether they satisfy your public health need, whether they are affordable, whether you're doing something of value.

Of 61 new antibiotics that were approved between 1980 and 2009, 43% were withdrawn either because of toxicity or lack of market, compared to 13% for other therapeutic categories, which just means that what we don't need is just another antibiotic, because a lot of antibiotics come on board and about half of them leave. What we need are, very specifically, good antibiotics. Governments may not be very good at picking which ones those are, but we do need those very specific antibiotics that are going to still have to compete with all the existing antibiotics.

So, although I've given you some bit of a bad news story, by and large, you have to remember that the antibiotics we have still work, they work a lot of the time but they don't work all of the time. And the way to fix our problem is to try to conserve the ones that we have. It's like saying the road is really bad and my car breaks down every year and I have to buy a new car, that's a really dumb solution. If the road is bad then, we want to fix the road and not buy a new car. In the same way, if our process for how we use antibiotics is bad, we want to fix that rather than just investing in new antibiotics all the time. So if you look at systemic new molecular entities (NME) antibiotics marketed in the US by period of introduction, there's no particular trend, it's about five, six drugs every year that have been produced except for 2005 and 2010. So for my part, I don't doubt that the industry will come back with new antibiotics. The problem is that most drugs will be far more expensive than the ones we have right now and that will drive up overall healthcare costs for us.

As I mentioned earlier, for people living in other countries, who can't afford them, then they will pay with their lives or with ill health. So, you can see new antibiotic launches since 1994, we've had a lot of drugs, some useful, some not so useful. The other part is really around our expectation of what price an antibiotic is really ought to be. I'm not suggesting that we should pay tens and thousands of dollars for antibiotics, but if you really think about it, a course of antibiotics, when you have an infection that could kill you, essentially saves your life until your natural lifespan. And today we expect to get that drug at $1, $5, $10.

Penicillin is about 10 cents a course, linezolid is about $155, daptomycin about $181. Now we tend to think that $181 is a lot of money for an antibiotic, because that's how we are conditioned, because we say we have penicillin 10 cents a dose. But we're perfectly happy to pay $31,000 for a drug that will help us extend the life of someone with prostate cancer by three or four months. That's just a huge mismatch. I'm not saying we need to pay $31,000 for a new antibiotic, but we need to recognize that antibiotics are really powerful, really valuable drugs and

if you hold the price down, it sends a signal that somehow these are not worth very much, and that's a signal that most people get wrong around the world.

It's 10 cents, big deal, I'll just use this, so what if I treat another 300 patients with it, no big deal. I don't think we globally recognize the value of what these drugs really mean to us because no one has really come up with a good substitute for antibiotics. If truly the antibiotics run out, we don't really have anything else to turn to, we always will need antibiotics. So we have other technologies, bacteriophages, probiotics, quorum sensing, I won't get into those but there are other technologies that are being explored, and there's a lot of work that's going on. So this is The Lancet Infectious Disease Commission, this was an article that was done in the New York Times on "Superbugs' Kill India's Babies and Pose an Overseas Threat," this is all over the news, obviously and I guess in the last 18 years or so that I've spent working on this problem, I've never seen the level of awareness or the media attention that this problem has had as it does today.

But it's really important for us to take this time to step back and to translate this into something meaningful. 30 years ago, you guys could have just pulled out a cigarette and be smoking in this room, perhaps right? None of you can imagine doing something like that right now. That's a remarkable shift in behavior that has happened not even over one generation perhaps with the half of generation, really, really brief in terms of that kind of change in behavior.

Now we need to do the same things for antibiotics. We just have to take it along with that same seriousness so that people don't demand antibiotics from their doctors, that doctors don't prescribe antibiotics inappropriately, and that we fundamentally shift our attitudes with antibiotics not just in one country but globally.

The Scandinavians have shown that It's possible. But the same behavior change, as I was mentioning at the previous talk, in India we have a festival called Diwali, big festival of lights, biggest festival of the year. When I was a kid, the thing you would do is set off fireworks and you do it all day for two days, lots of pollution, lots of smoke, but that's what you did. Now, my kids won't celebrate Diwali with fireworks, they do it with a lamp. And none of the kids will do it because they've learnt in school that it causes pollution and it scares little animals. That's a remarkable behavior change, that kids won't set off fireworks, it's just a dumb thing to do. It was always a thing to do. And I'm hopeful if that sort of shift can be achieved in a population as large as India's over the last 10 years, maybe even five years, certainly we can change attitudes about antibiotics there as well.

Much of what I've shown you is some work that we do in about 8 countries for the Global Antibiotic Resistance Partnership and what needs to work at the country level, very well laid out, not rocket science, we can certainly do it. WHO is pushing for this, other organizations are pushing for it, and significant political leadership. And last to say, I'm not suggesting that we're gonna return to this world where a blade of grass is responsible for the loss of a foot – it was just as simple as that, for someone to just get a small cut and die of it, because they didn't have

antibiotics. This is something from 1899, I think in North Carolina or somewhere, maybe Georgia, Athens, Clarke County.

But for many people around the world, not necessarily in this room, this is becoming more and more of a reality. You don't see these people but 15 years ago, I didn't know someone who had died of a resistant infection. Now I know lots of people who have died of a resistant infection. So this whole thing is shifting into a very, very serious area, which is why it really justifies the kind of response that is now being called for and it really is that commons problem that we all need to work on together. So all the slides are online and thanks again to Edinburgh Infectious Diseases for inviting me, it's been a pleasure.

Other Speaker

Instead of the world eating as much meat, which we use in so many antibiotics, whether or not trying to adopt a plant-based diet would be an effective way to help this issue in any way?

Ramanan Laxminarayan

I always hesitate to speak on this. You're absolutely right. For multiple reasons, antibiotics being only one and climate being another, a fifth of our carbon emission comes from livestock emissions, meat does impose consequences. However there are cultural issues dealing with people's preference for eating meat, so people don't have to be vegetarian but certainly eating less meat has strong environmental benefits including for antibiotics, there's no question about that.

Other Speaker

Thank you very much Ramanan. It was a wonderful talk. I agree for the most for the most part with your analysis of the role of antibiotic usage in livestock, in farming, which the previous question was interested in. But I would like to see your thoughts about taking it to the final step and my argument on this issue because as you well know the medics are very, very keen to ban antibiotics in animals is, to what extent would that work as a measure taken in isolation from reducing antibiotic usage in humans.

My sense of it is that most resistance in human patients stems from the use of antibiotics in humans. There is not a huge amount of evidence for the direct transmission of antibiotic resistance from farm animals, except in the foodborne bacteria of course, but actually that's a relatively minor public health problem, compared with the sorts of issues you were talking about with Klebsiella and other pathogens. So, what's your view about that last one? My sense is that they have to be done in parallel, doing it simply in the veterinary field by itself I suspect won't have much impact.

Ramanan Laxminarayan

So you are absolutely right in that we've already created a lot of the resistance genes on the veterinary side and it's almost like closing the door to the barn after these genes have already left, that's absolutely correct. It's probably quite likely that no new antibiotic will ever be used in the veterinary sector given where we are, so that is also true. People often ask about the relative contribution. How much is it off the human use and how much is it of the animal use? That's sort of like saying well how much of a forest fire is because of the dead wood and how much is it because of someone you know throwing a cigarette butt: both are important. I mean if you didn't have a cigarette butt, the dead wood is not going to do much damage and vice versa. So I think it's the same thing and I fully agree with you, both have to go hand in hand.

Many years ago at the Institute of Medicine, I remember a two day meeting on AMR where all the scientists gathered and they said well this is what the problem is and they concluded that the problem is really because of those guys in Nigeria who are using antibiotics over the counter and these other guys in the animal sector who are using too many antibiotics and it's always been used for that purpose to point the finger somewhere else, and I think that is no longer the case. I think now there's quite good recognition that we're going to have to change things very much on the human side, so I fully agree with you.

Other Speaker

I was really struck by the comment about the price of antibiotics and do you want to extrapolate a bit further in terms of how that could work sort of globally? I mean I get the idea that perhaps within developed countries we could set a much higher price for the use of antibiotics, and how would that work across the globe, to therefore have the treatments that are required whether they're not even getting antibiotics yet, because I think it's critical that we do pay more, but how could it actually work?

Ramanan Laxminarayan

You know there are antibiotics that don't have to be first-line drugs that someone can just go pick up at the pharmacy, like carbapenems for instance. So a higher price is always a signal that what you're consuming is of value and therefore you need to conserve it, so you don't have to go from five cents to five hundred dollars, but certainly making them a little more expensive at least signals the importance of those drugs relative to everything else. So I think there is some room for play there and if you look at the overuse of antibiotics in Kenya and South Africa, Pakistan, Bangladesh, India, Nepal, it's not the poor folks living in the countryside, they barely have access to penicillin. It's the wealthy folks living in the cities who just walk into pharmacies and say give me the most recent antibiotic and are willing to pay for it. So those are the folks for whom a higher price would not be a bad idea at all.

Other Speaker

Hi, thanks very much for your talk. I was just wondering a lot of the countries you spoke about which have the biggest problems with antibiotic resistance are developing countries. How do you incentivize antibiotic stewardship and countries like this where the economy is obviously an issue with funding?

Ramanan Laxminarayan

So let me clarify to say that although I said the future of the problem was very much in the developing world, a lot of the past is really in the developed world, which still has rates of resistance that are high so it is a common issue in that sense in both places. Now stewardship operates at different levels – there's hospital level stewardship, there's infection control. I think the first thing for developing countries to do is do the things that reduce the need for antibiotics in the first place – water sanitation, infection control, vaccinations. Those three things will dramatically reduce the need for antibiotics. After we've done that, then we can reduce the use of antibiotics, but I wouldn't go after the use of antibiotics as my first cut measure, it's really the need that needs to be cut out first, which, just a pneumococcal vaccine, I showed you in that one figure can do a lot.

Host

You did mention it's a problem of people not finishing their course of antibiotics or whether that's more common when people self medicate or are trying to economize, does that contribute?

Ramanan Laxminarayan

That’s an interesting question, I know that the message I’m supposed to give is that you should really finish your course of antibiotics, but let me put this in the way that I think about it and don't take away too much from it. If I were to tell you that 50% of the antibiotics that are getting inappropriate because you didn't have a bacterial infection to begin with, why in the world should I be asking you to finish your course of treatment which is inappropriate to begin with. It just is imposing more selection pressure, so I have never found a really good answer to that particular question because that's valid only if antibiotic prescriptions were appropriate at all and I think in many instances you know what we count as the “course of treatment” doesn't come from randomized trials. It comes from the fact that, I didn't tell you, the story of that first person who was treated with antibiotics back in 1941, Albert Alexander, that policeman in Oxford who dies after five days because they ran out of antibiotics and the next time they treated someone they made sure it was a child so that they had enough antibiotics to treat the person with fully. So the whole idea of a 10-day course of treatment of antibiotics didn't come from a trial, it just came from an overabundance of caution to say I don't want this person to die so i'll keep treating them until I think I've completely gotten rid of the problem.

So what we might consider a 3-day treatment, or “I haven't completed my course of treatment,” could well be the correct duration of treatment. Don't say that you heard this at a lecture on antibiotic resistance but you know this is a university and it's important to have these conversations, but I think this is something we need to think about a little more.

Other Speaker

Thank you, it's a question about the place for vaccines in this. I can see where it works in transmissible infections. The data that you showed in terms of the hospital situation looked as if it was commensals that we're getting into an inappropriate anatomical site because of surgery and so on, and I'm just wondering what your views are on the likelihood of vaccination in those situations.

Ramanan Laxminarayan

So you’re talking about vaccinations for when it's commensals that are actually causing…no you're right, I mean that's not going to make a huge difference in those particular instances. I think with commensals, selection pressure because if people using antibiotics is really going to be the main driver of what's going on. But there's a lot of invasive disease that can be prevented with antibiotics and one thing I forgot to mention is that, regardless of country, the biggest predictor of antibiotic consumption is the strength of the flu season for the entire year. If you have a bad flu season, that really drives consumption. That’s like saying if I had a seasonal influenza vaccine, though influenza is a virus it has nothing to do with the bacteria, but because that triggers the antibiotic prescription, I care about people having a seasonal flu vaccine.

So it's a lot of things coming together and not always in the ways that would be “rational,” but again everything about use of antibiotics is a bit crazy and irrational, so that's the problem.

Host

I want to thank Ramanan very, very warmly. Fantastic presentation. So, thank you.