Anthony S. Fauci

Good afternoon ladies and gentlemen, and welcome to the 2016 John LaMontagne Memorial Lecture. Can I have the next slide please? Today we honor my dear friend and colleague Dr. John LaMontagne. John, as some of you know, joined NIAID in 1976 as the institute's first influenza program officer, and went on to serve for 11 years as director of NIAID's division of microbiology and infectious diseases. In 1998, I appointed John as my deputy director, a position he ably carried until his untimely death in 2004.

Anyone who had the pleasure of knowing John will remember his kindness, his quick wit, and his selflessness. He was a wonderful human being and a dear friend. In the scientific community, John may be best known for his work in influenza, but he also helped lead efforts at NIAID to address emerging and reemerging infectious diseases, including global diseases such as malaria, tuberculosis, and HIV, as well as the challenge of bio-defense. We are very fortunate today to have in the audience John's wife, Elaine, and members of John's family. Welcome Elaine, it's great to have you with us.

Can I have the next slide? Our speaker today, Dr. Ramanan Laxminarayan, shares a similar dedication to global health issues as did John Lamontagne. Dr. Laxminarayan is widely recognized as a leading authority on the growing problem of antibiotic resistance. In his current role as director and senior fellow at the Center for Disease Dynamics, Economics and Policy here in Washington, Dr. Laxminarayan is working to improve the understanding of antibiotic resistance and develop new ways to address the challenge of managing a shared global resource. An economist and epidemiologist by training, his research integrates the use of epidemiological methods of infectious diseases and drug resistance with economic analyses of public health problems.

Ramanan has worked with the World Health Organization and the World Bank on evaluating malaria treatment policy, vaccination strategies, the economic burden of tuberculosis, and control of non-communicable diseases. He has served on a number of advisory committees at WHO, CDC and IOM. From 2003 to 2004, Ramanan served as the IOM’s committee on the economics of antimalarial drugs, where he helped create the Affordable Medicines Facility for Malaria, which assists several developing countries. In 2012, he created the Immunization Technical Support Unit for the government of India's immunization program, which is credited with rapidly improving vaccination coverage and introducing new vaccines to that country. In 2014, he served on the United States President's Council of Advisors on Science and Technology Antimicrobial Resistance Working Group. He's also a voting member of the Presidential Advisory Council on combating antimicrobial resistance.

Dr. Laxminarayan’s contributions as both an economist and epidemiologist have earned him positions in several academic and scientific organizations. In addition to his current position here in DC, he is also a Senior Research Scholar and lecturer at Princeton, and a distinguished professor of Public Health at the Public Health Foundation of India. His talk will address the problem of antibiotic resistance, the current status of the global antibiotic pipeline, and the comprehensive approach needed to address this issue. Please join me in welcoming Dr. Ramanan Laxmanarayan.

Ramanan Laxminarayan

Thanks Dr. Fauci, both for inviting me to give this very prestigious lecture and for that introduction. Now, most of you may not know this, but actually coming into NIAID to give you a thought is sort of like, I don't know, it's like going to the Vatican to give a talk on Christianity. It's incredibly nerve-wracking, but I'll try to do it. I had the pleasure of meeting Dr. LaMontagne just once at the Institute of Medicine, I believe it was a forum of microbial threats, and it's always a fascinating time among the kinds of people that you see at the Institute of Medicine, and I certainly remember that it was a remarkable set of people including himself that really were giving shape to discussions that really shaped how I would think about antimicrobial resistance since then. So I'm really grateful to be able to give this talk today.

I'm just going to make five points. Now, our history with antibiotics is incredibly short and it's only about 70 or 75 years. But in that period of time, drug resistance has been rising, but particularly in the last 15 years, drug resistance is rising worldwide and it threatens gains that we've made in reducing the burden of infectious diseases.

So as you all know, we haven't had antibiotics that long just since 1929 and actually treat patients only since 1942. Antibiotics have saved lots of lives in the Second World War, more people were saved by the ability to not lose people to infectious disease than would have been saved from battle wounds directly, and since then, they've had an incredible role to play in global health. The first people to get antibiotics were incredibly lucky. This was a child that was treated in 1942 with antibiotics, and would have almost certainly died, but for the effect of penicillin, and by day six she is much better and this was truly a miracle drug.

Now, resistance to antibiotics is not just as old as treatment with antibiotics, it's in fact even older. The first paper to record resistance to penicillin is actually from 1940, two years before penicillin was used to treat the first patient and since then you can see, resistance to most antibiotic classes has arisen anywhere between five and 15 years after when they were first introduced all the way into the new antibiotics we have, linezolid and oxazolidinones. If you look at resistance over the 1990s, into the 2000s, resistance has been growing rapidly. As with most biological phenomena, you have a long period during which resistance was low, and then it suddenly takes off and this period of takeoff, particularly for the United States, but certainly globally as well, has happened during the 2000s.

Carbapenem resistance and third-generation cephalosporin resistance in Klebsiella started off being high on the East Coast, but by 2006 to 2010, have grown to be significant throughout. So if you look at carbapenem-resistant Acinetobacter baumannii, you'll see in 1999, nearly every region in the United States had less than 10% resistance. But moving forward from there you can see, going forward to 2000, that some resistance, you start going above 10%, then you get to the 20 to 40% range, 40 to 60%, nearly every region is affected. And by the time you get to 2009, 2010, 2011 and 2012, you'll see that in some

parts of the country we have more than 60% resistance, and certainly 40 to 60% resistance in most of the other parts. The parts that are in gray, we don't really have data for.

This is obviously an unusual phenomenon in the sense that after having known and talked about resistance for nearly the 50 years that we've had antibiotics, we started seeing this impatience and actually having a health burden associated with drug resistance in a significant fashion only in the 2000s and that has contributed in large part to the advocacy, to the policy action, at least the talk about policy action that we hear today.

We did a study on the State of the World's Antibiotics last year where we had data from a number of countries and there is good news. If you take Staphylococcus aureus, there's been a lot of attention on methicillin-resistant staph and if you look at resistance to methicillin-resistant staph, that's sort of plateaued over the course of that 2000s. It went up in the 1990s, all the way up to 30 or 40% but it hasn't gone past there. Largely also due to the fact that - a) there's been a lot of attention, but there's also been a lot of new antibiotics to deal with staph infections.

If you look at this picture by country, there are still some pockets where resistance is high between 80 and 100% and certainly above 60%, some are in Latin America and certainly India, Iran are also up there. But it is in the gram-negative infections that we have the biggest problem, so we start with extended spectrum beta-lactamase-producing E coli by country, significant challenges in China, in India and also in Vietnam. If you look at the carbapenem-resistant Klebsiella, again, India is a hotspot as are Vietnam and China again. If you look at CRE rates in children, we just published this last year, it went up from being pretty close to zero to about 5%. Now 5% is not high, but these are kids who are more vulnerable and this was the trajectory that we saw in the late 1990s for many other pathogens and there's no doubt this could also grow.

If you look at New Delhi metallo-beta-lactamase, it's a big concern which first started from 2006 to 2008 in patients from India and Pakistan who had been hospitalized and then were subsequently re-hospitalized in Sweden. This has now grown to being in more than 100 countries when last reported, so the spread has also been extremely rapid. And of course, we know this for other bacterial pathogens, Strep pneumonia 23F, possibly started from Spain, probably from France before that, but is now in most countries. We see this also when you look for unique beta-lactamase enzymes, which had been identified since the introduction of the first beta-lactam antibiotics, so if you see this as a marker of how well the bacteria are doing in terms of being resistant, the numbers have gone up. Certainly there's probably more detected because we're looking for them, but we have at least 900 and possibly more unique beta-lactamase enzymes, which have now been detected.

The use of antibiotics is very closely related to drug resistance, but we also have the problem with Clostridium difficile which is not drug resistant per se, but the fact that the use of antibiotics is clearing out ecological niches for C. diff to take hold. In fact, we published this paper which showed that oral vancomycin prescriptions were very good at predicting C. diff rates by county in Ohio, so it's not just the drug resistance, it's all of the other collateral damage that antibiotics do.

Now, we care about this for a number of reasons but if you had to summarize, the big burden of antibiotic resistance is already happening in newborns in developing countries, particularly in low-income countries with high rates of neonatal sepsis. And, of course, we know that mortality outcomes are worse in neonates with resistant infections. This is one study from Tanzania, we have a study which is soon to be out in The Lancet from India which shows even higher rates of mortality, but basically, if a culture is positive, there is about a 30% chance of dying, gram negative over 35% chance of dying, ESBL-producing organism found in the neonate over 50% mortality rates, and then MRSA again associated with high mortality rates, and you bump these up by another 10 or 15% and that's what we see in New Delhi hospitals. If you then extrapolate from this based on the numbers of neonatal sepsis deaths that we currently have with population-attributable fractions, in India, we estimate something like 58,000 neonatal deaths each year because of resistance to first-line antibiotics because for most of these kids, they don't really have a chance, they die before you can get them on anything else. Rates are high in Pakistan and Nigeria as well, but India is certainly an epicenter because you have all three things coming together. A lot of neonatal sepsis, certainly a lot of newborns as well, high levels of resistance, and that all comes together to produce this sort of a result. It's been recognized in the media, so again, the New York Times pitch on this is a "Superbugs Kill India's babies and Pose an Overseas Threat," but this is particularly important in India itself that it's an important cause of mortality.

The other age group that's bearing the brunt of drug resistance are the elderly. This is a study from the United States, the absolute risk reduction of infection with antibiotic prophylaxis was higher than what I thought it would be. We looked at a wide range of studies looking at what the reduction was in risk of infection across ten most common surgical procedures and blood cancer chemotherapy, and we reviewed these, and based on this, we estimated the number of additional infections per year, under the 30% decrease efficacy of antibiotic prophylaxis and it was about 120,000 additional infections, about 10,000 additional deaths. So, again, it's been said many times that antibiotics are sort of the backbone or the foundation of modern medicine.

The question is how much risk would be associated with hip replacements or transrectal prostate biopsies or with C-sections, if there was a higher risk of having a resistant infection, but what is worse and it's certainly not captured by this study or any other, is the fact that if people perceived a higher risk of infection or a higher risk of adverse outcome because of an infection, would they be more likely to not go in for procedures that they otherwise might have? So if that is deterring people from getting a hip replacement, then it's lowering their quality of life even if they didn't get an infection at all to begin with. So, the reality is important, but the perceptions that then drive whether people get these procedures are also important.

Rising incomes around the world are a good thing and they are increasing access to antibiotics, which is also a good thing because it's saving lives. In spite of the numbers of children and possibly elderly dying of drug resistance, lack of access very likely still kills more people than antibiotic resistance does. And this is because we have lots of children who die of pneumococcal pneumonia in places without vaccines,

and where penicillin still works. But the fact is that we're using these as a substitute for public health and that's not a good thing.

If you look at bacterial diseases, they're still a big killer in many developing countries because of a lack of access to antibiotics. Take India or China, for instance, where there are low rates of pneumococcal deaths in children under five, but there are a lot of children and a lot of them who don't get treatment and both these countries don't have a pneumo vaccine yet, so there are still deaths. Now if you look at pneumococcal pneumonia deaths avertable with improved antibiotic access, so on the x-axis is the under-5 population with suspected pneumonia that's actually getting an antibiotic and you can see that, for many of these countries, those numbers are shockingly low. Less than 40% for Nigeria, just over 20% for Tanzania, and less than 20% for India. So that contributes a lot to the pneumococcal pneumonia deaths.

But it's important to step back and see what we're asking of antibiotics. So this is probably familiar to you, crude infection disease mortality rates in the United States in the previous century, and as you can see, that rate went down from about 800 per 100,000 per year, down to less than a 100, and that little bump up is likely HIV, it went down to 200 per 100,000 per year, a three-quarters decrease, not because of antibiotics, but even prior to the introduction of antibiotics in 1942. So in 1942, it was just about 200 but everything that happened prior to that was because of chlorination of water, having good public health departments, sanitation, and of course, we had the blip because of the flu influenza, but by and large rates are decreasing.

Now, if you look at where South Asia is at the moment that rate is twice what it was in the United States back in 1942 when antibiotics were introduced, which means that, if you look at again, Sub-Saharan Africa, that number is almost three times what it was in the United States in 1942, which means that in the West, antibiotics were used as a mop-up operation after we'd had public health reduce the burden of infectious disease. But in many other countries now, we're using antibiotics not as a complement to public health, but really as a substitute for public health. So if you don't have the water and sanitation, if you don't have the infection control, and then you're throwing a lot of antibiotics at the problem, it naturally results in huge amounts of selection pressure and resistance. So if you look at populations without access, improved sanitation, Southern Asia and Sub-Saharan Africa right up there and India and China account for a lot of this burden.

Now vaccines are possibly one of our best hopes, vaccines can be effective, but not used enough in the places where they can be so, they reduce both the penicillin-susceptible disease as well as resistant disease, and certainly, it's not beneficial just for the population that's vaccinated with, which are the kids, but also for the population above 65. So we do have tools and we need to apply public health as a major strategy to deal with antimicrobial resistance. And we've estimated what the averted antibiotic use would be if pneumococcal conjugate vaccine coverage were to be universal around the world, at least universal in the sense of every country adopting it, but adopted to the level of where the DPT3 coverage was, and it was about 11 million days of hospitalization that you can avoid by doing this.

Meanwhile, antibiotic consumption, as I mentioned, is increasing in developing countries. So you look across the board, per capita total antibiotic use in the retail sector has been increasing in places like Brazil, India, but it is flat and obviously higher in the United States. Now, it's flattening out in the United States for a number of reasons, but the introduction of Prevnar is possibly an important reason because kids under the age of five getting antibiotics is the single most important thing, they're biggest consumers of antibiotics, and reducing that burden has been important. But even so, on a per capita basis, the US is among the highest, if not the highest, per capita antibiotic usage in the world, at least among large countries.

Now, if you look at percentage change and antibiotic consumption per capita, and we did this for 72 countries for which we had data, what we saw was that over that period of time, global antibiotic consumption, as seen in these 72 countries, went up by 36% in just that 10-year period. Three-quarters of that increase was just in the five BRICS countries - Brazil, Russia, India, China, and South Africa. Of that three-quarters increase, most of the increase in the retail sector was in India, and most of the increase in the hospital sector was in China. Important incentive reasons for both of these, in China, a lot of hospitals do make money off of selling antibiotics and of diagnostic tests when they're not allowed to charge for hospital stays and it's common to give out antibiotics. In fact, a few studies done on this find that as much as a quarter of hospital revenues would come just from the sales of antibiotics. So obviously the incentives are completely perverse with respect to conserving the effectiveness of antibiotics. In India, lots of over-the-counter [antibiotic] use without a prescription and consequently huge amounts of use. If you look at consumption on the human side, this is not with animals, this is just for humans, India already led the world in 2000. Of course, when you stack the animals on top of it, then China is way ahead. The US is also high and you've got to account for the population difference.

This is very strongly correlated with income, so you can see that as countries get wealthier, there is going to be more antibiotic consumption. South Africa was an exception, because that's driven largely by cotrimoxazole use associated with HIV opportunistic pathogens. So if you take that out, then South Africa is right where the other countries are. If you look at carbapenem sales, I showed you all these pictures are on high levels of resistance to carbapenems, you can see that retail sales of carbapenems are very high in countries like India, Egypt, and Pakistan, and what's going on there is obviously some amount of retail sales without a prescription, but also the fact that hospitals don't necessarily sell antibiotics, so the patient's family might have to go around the corner to a retail pharmacy and bring it back and then give it to the doctor to give to the patient because they have to be given IV. Faropenem, a drug which is a rare oral carbapenem, not licensed for use in the EU or the United States, but certainly is seen as a very convenient drug, the use of that has really taken off in a significant way in India. It was only licensed for use in India in 2010 and it's gone up by 154% since then.

If you look at the hospital sector again, this is not just a developing country phenomenon, carbapenem consumption is going up even in hospitals, particularly in European countries where there's a perception that higher rates of resistant gram negative organisms have to be dealt with more actively. Now, non-prescription use of antimicrobials is common, these come from published studies possibly understating what the levels are but you see them in many countries around the world. India, I can

guarantee, is almost certainly higher than 18%, it's probably closer to 90%, but this is the best published data out there. But the problem is that the workforce of doctors and nurses is simply not adequate, so even if one were to want prescription-only antibiotics in these countries, there are simply not enough doctors or even trained nurse practitioners to hand out the antibiotics. So for many people living in rural areas, that's not a solution. India proposed that as a regulatory solution, but that's not really going to happen because it would prevent a lot of people who legitimately needed antibiotics from getting them.

The flu season is the key driver of antibiotic consumption, as you may already know, so if you look at peak month consumption that we published with that other paper on global consumption of antibiotics, January, February, peak months for the United States, and if you look at the southern hemisphere, it's their wintertime which is June, July. In fact, in the United States, you can predict the influenza season or the ILI, influenza-like illnesses, almost perfectly with antibiotic sales data. So with about a two-week time lag, it does extremely well, which also goes to say that maybe the seasonal influenza vaccine is one measure, but also educating the public that they don't need antibiotics in the case of a flu, and not to pressure the doctor for it, is an important one.

Carbapenem used in the hospital sector, as I mentioned, in China is a growing phenomenon, actually in the United States as well. Extended-spectrum macrolide use is also highly prevalent in the US and increasing in many developing countries. This is a particularly troubling phenomenon – the global availability of colistin. Colistin as we all know, has high levels of toxicity and therefore is not really widely used or licensed in many countries. But in places like Vietnam, it's not licensed for use in the human sector, but the doctors will go get it from the veterinarians to give it to their patients, because there are no alternatives. But now, of course we have the MCR-1 plasmid-mediated colistin resistance mechanism, and this has now been reported in more than 10 countries, possibly because colistin is very widely used in animals for growth promotion in China.

We're also losing some of the last line drugs, which are not even the desirable last line drugs that we do have. From an economics hat, this is a problem much like using other resources – we can either make better use of our existing antibiotics, just like we can conserve energy or oil, or we can find new antibiotics and both these are related to each other, because if we spend a lot of money on trying to find new antibiotics, we are effectively disincentivizing people from using existing antibiotics appropriately. So there is a cost to be paid there and certainly if we use our existing antibiotics appropriately, then maybe we don't have to spend as much on finding the new antibiotics. So the incentives are very tied to each other and they're not independent.

The drivers of antibiotic use relate to incentives and the behavior of patients, so although it's a medical problem, it's got a lot more to do with behaviors. A lot of physicians want to satisfy patient expectations. In fact, hundreds of studies show that if the patient expects an antibiotic, or even if the clinician believes that the patient expects an antibiotic, there's an over 75% chance that an antibiotic will actually get prescribed. And even if there's a perception that it helped in the past, there is a high chance that the antibiotic will get prescribed.

Things like decision fatigue increases inappropriate prescribing, so in this particular study, relative to the first hour of a session, the adjusted odds of prescribing an antibiotic inappropriately in the fourth hour was about 1.26. So you can see during the course of the day and the three lines, the top line is antibiotics sometimes, second is overall, and the third is never indicated, and the never indicated goes from about 27 to about 35%. So obviously a lot of human elements are involved, so it's not as if the prescriber, the doctor standing between you and the prescription is necessarily going to make sure that the antibiotic is indicated. Health insurance does increase prescribing. It shouldn't be a surprise because when you make something cheaper, than typically people tend to consume more of it. And these are data from the very well-known RAND health insurance experiment.

We did this study based on grocery chains deciding to give antibiotics for free, and they did this a few years ago until CDC asked them to stop and what we found was very interesting. You would think that doctors' prescriptions of antibiotics were completely uncorrelated with whether the grocery chain next to them had free antibiotics or not. Not the case. It turns out that there was an increase overall in prescribing in the zip codes where the program was introduced, and in fact, a 7% increase in the specific antibiotics that were actually covered under these free prescribing programs, and what was most interesting was that the effect size was largest when the patients were of the lowest income quintile. And the effect almost goes away when the patients are wealthy, so it means that the doctors don't care about the affordability question. So all these are problems that one has to deal with.

Hospitals are another place where there's a lot of room for action. And to put it very simply, antibiotics as simply a substitute for infection control, if you think about it, if as a clinician, you knew that your patient was absolutely going to die because there weren't effective antibiotics, if there wasn't sufficient infection control, the emphasis on infection control naturally is going to be a lot higher. But the fact that there is a backup option available certainly means that infection control is seen as one of the tools rather than something that hospitals are able or willing to put a huge amount of resources into, also because it's not often compensated. So, in fact, some of you may have seen this study by Atul Gawande's group on the relationship between occurrence of surgical complications and hospital finances and in fact, compared to absence of complications, having surgical complications, including particularly infections, provides a $39,000 higher contribution margin per patient with private insurance and about $1700 for patients with Medicare.

So the incentives are simply not there in the system, either in the United States or in many other countries for using infection control, instead of turning to the antibiotics, and antibiotics are seen as just a substitute there. We did this study in about six hospitals, six of the best facilities in the United States, well not the best because this one wasn't part of it, but what we found was that in about 10% of cases that wasn't a documented diagnosis for starting an index antibiotic and if you looked at fever and high white blood cell count and also radiology reports, we found that in a third of the patients, we followed about 2000 patients who were on antibiotics to see whether there was anything in their charts that indicated whether they should have gotten an antibiotic in the first place, and a little less than a third of them had nothing, they didn't have the fever or the high white blood cell count, and if you see that there is a breakdown of infection sites for the "no" patients. But what was more interesting was the fact that

about 60% of the patients actually had a blood culture done, but in half the patients who had a negative blood culture, there was no de-escalation of the antibiotic. So the blood culture itself did not change what antibiotics they were on. Now, obviously when you're looking at charts, it's hard to read everything out of it, but we had ID docs to see whether it made sense or not. So this was that slide. 50% on one antibiotic and 48% on more than one antibiotic.

Antibiotic use in the animal sector is increasing, so moving from humans to animals, but it's not just animals, its animals and the environment and just like there's this phenomenon of increasing incomes, there's a phenomenon that the increasing incomes are also leading to a huge increase in the demand for animal protein.

So these are FAO estimates. China's increase in consumption is going to be driven both by a near doubling or 70% increase in per capita consumption, but also an increase in the population. So both those are going to result in this growth for 2030 in China. In India, the population growth is certainly there, but there's also a huge increase in per capita consumption of animal protein. So what this means is that these animals, these chickens, these hogs have to come from somewhere. Already, China produces six times the number of hogs that the United States does, and nearly all of them are on antibiotics. So if we think that the consumption now is high, we haven't seen anything yet.

Antibiotics are used for growth promotion and for disease prevention. Two-thirds of the tonnage of antibiotics sold worldwide are used in agriculture, and if you look at consumption, in China, for instance, about 92,000 tonnes in 2013, about 54,000 tonnes [of antibiotics] excreted by humans and animals, and much of this entering these river basins in China, so huge concentrations, both modeled and actual estimates, that have been published. And the consequence of that is that you see these diverse and abundant antibiotic resistance genes in Chinese swine farms, huge numbers of these, about 20,000-fold compared to their respective antibiotic-free manure or soil controls, and they cover all of the ranges of mechanisms that we would be worried about antibiotic deactivation, efflux pumps, cellular protection, et cetera. We suddenly have this huge environmental experiment going on as to how much we can pump antibiotics into animals and have them come out the other end and what that might do to the environment.

Now, this is also in countries which have used antibiotics in the past, both for agricultural use and for environmental use. This study from the Netherlands showed a huge increase in antibiotic resistance genes collected among soils in five sites between 1940 and 2008. I can't review all the studies that have linked antibiotic consumption in livestock and poultry to resistance either in animals or in humans, but there's certainly quite a few of these. And you can see that most of these are usually temporal correlations, because most of these will have to be ecological studies. So fluoroquinolones were licensed for poultry and livestock in 1990 and resistance, or prevalence of fluoroquinolone resistance in Campylobacter, which is one of the species where we know reliably that antibiotic use and animal studies does result in resistance in humans. This was a well known study where there was a voluntary withdrawal of ceftiofur in chicken and basically that resulted in a huge reduction in ceftiofur-resistant Salmonella strains in humans, so if you want a really compelling study, this is the one.

The question is, we know this well for salmonella and a few other pathogens, which cause foodborne infections, how well do we know this across the board? So for instance, for gram negative infections, how important is use in animals for resistance in humans? The honest answer is we don't really know, so we know this for some pathogens, but not for others.

It does turn out that there's a huge variation in the quantity of antibiotics that is used per pound of meat produced, per kilogram of meat produced, across different countries. So you can see the Netherlands use much higher levels and this is back in 2007, it's gone down since then, compared to Norway and Sweden, Sweden banned the use of antibiotics for growth promotion about 25 years ago, so it is theoretically possible to produce meat with lower levels of antibiotics. You look at the US, you can see that we've had increases in meat production, but also a huge amount of increase in sales of antibiotic feed additives. And antimicrobial use per unit of meat has increased every year for the last five years for which we have data. In fact, the use of tetracycline, which is right there in the middle, is the most important antibiotic that's used in the animal sector for growth promotion. And all of the ones which are on the left side here, the pink side, all the medically important ones, and the ionophores are not considered medically important, and then you've got the ones on the right, but you can see that a lot of these are also used in humans, the penicillins, the macrolides, the aminoglycosides, and so forth.

Global antibiotic consumption in livestock, we have now these new estimates that have been based on models, and this is obviously seems smaller than what was just in China but based on this study, we found about 63,000 tonnes of antibiotics used in animals in 2010 and this is projected to rise by 67% by 2030, so over just the next 20 years from 2010. And there are hotspots like in India where there's gonna be areas of very high consumption, where industrial poultry consumption is expected to grow. Now, what's driving this is two things - one is the sheer increase in the amount of meat that we're going to need, that's two-thirds of it, and then one-thirds of it is because the farming practices will have to move to more intensive forms of agriculture, which will, by definition, need lots of antibiotics if you don't have good herd hygiene, if you don't have good sanitation, good genetic potential of stock, and so forth. So again, China is going to be certainly the world's highest consumer of antibiotics in livestock in 2030, it already is. You add this to human use, and certainly animal use is most of where the antibiotics are going.

If you look at Denmark, for instance, they did have a ban on veterinary profits from drug sales that resulted in a decrease in total antibiotic consumption, then they banned all antibiotic growth promoters and the use did go up because the use of therapeutic antibiotics went up some but overall the levels would come down from where it was in 1994 to where it is in the 2000s. So there are indications that this sort of strategy would work.

The rationale for using antibiotics for growth promotion, which is giving small amounts to them every day, day after day, was based on the fact that observationally, we found that the animals got fatter faster, so it had economic value, but that's not true anymore. If you put all the studies together since the 1950s, on average, daily growth of pigs fed antibiotics over time, that's a clearly declining figure. So because

animals are produced in highly optimized systems today, they have good sanitation, they have a veterinarian on call, they have good nutrition, the role of antibiotics has decreased significantly. In fact, in this report, we estimated that the total cost of withdrawing antibiotics for growth promotion per pig was only about $1.30 for some excess mortality, some excess feeding days, some increased medication and some increased workload, certainly, but then the choice is would we want to take the antibiotics out of the pigs if it cost us $1.34 more per pig, and that's a choice for public policy to make.

The last point is on what the role is of innovation, which again, we're in the center of the innovation world here at NIAID, and innovation takes many forms. The innovation we need is not necessarily just in terms of new antibiotics. I showed the slide at the very beginning to show that resistance does come up to every antibiotic a year or a few years after it's introduced, so clearly the next few antibiotics is not going to solve the problem for the foreseeable future, we're always going to need that investment in new antibiotics.

However, we have to keep in mind that a lot of people may not be able to afford those new antibiotics. So the loss of first line drugs always increases drug costs regardless of whether it's gonorrhea or malaria or pneumonia. In fact, if you look at antibiotic consumption, price and consumption of selected antibiotics in the US by year of FDA approval, the size of the circles is the consumption in standard units. You see that much of the antibiotics that we use today, even in the United States, are the ones that were approved prior to 1980. And if you look at the ones that were approved after 1980, we use less of them, but also their prices are extremely high compared to the ones that we had before.

We've sort of anchored our mental model of how expensive it should be to being $1 to $5, and the newer ones can be really close to $100 and the newest ones maybe even more expensive than that. If you look at India, for instance, that number, all those big circles are obviously bigger because of more consumption, they're all anchored to the ones that were before 1980 and the prices are in general much, much lower because much of the older antibiotics are being used, and that for this reason – simply the fact that the developed world can afford antibiotics that the developing world simply cannot, so the burden of antimicrobial resistance will be in terms of increased spending on health in high income countries. In low income countries, the poor pay every day with their lives because they won't be able to afford these drugs, the drugs on the top category, the ones below are the ones that they can afford right now.

Now, is the rate of new drug development declining? IDSA had published this study which strangely picked year intervals, like '80 to '87 and so forth, and this was reproduced widely to show that perhaps new drug development was actually declining. I don't think that's necessarily the case. Now, first of all, if you take that out for 2013 to the present, for the next four years, that's started picking up again, but new drug development is a tricky business. If you look at trends in development of new antibiotics, you can see that if you include the drugs including the ones that are still in the market, versus the ones that were developed then withdrawn from the market, there's not really a steady trend if you do it by year. In fact, you see the 61 new antibiotics that were approved between 1980 and 2009, 43% were withdrawn because of toxicity or lack of market compared to a 13% withdrawal rate for other therapeutic

categories. So it is still not a great business to produce new antibiotics, but that's primarily because, the good news is that in many cases a lot of the existing antibiotics still work.

The reason why it is this problem that we have all this response to is because even if that proportion where the drugs are not working is small, the burden of bacterial infections is large enough that that small number is still important from a health burden perspective. Now, if you look at systemic new molecular entities that are still marketed in the US by period of introduction, we still have a lot of these and this has been anywhere between 5 and 8, so a lot of the old antibiotics are still very much in use.

So, if you look at new product launches since 1994, a lot of drugs, particularly ones that may be familiar to you – moxifloxacin, meropenem, linezolid, telithromycin, the ones that came after that, these have been all the new antibiotics that have been launched that are still working and still are clinically relevant. So it's not just a pipeline issue, it is a problem of how we solve the problem of drug resistance for the longer term and in fact, there have been many incentive programs for new antibiotics, as proposed by BARDA and EU, they all encourage new drug development but they don't really change the fundamental problem which is that they don't affect the incentive for using drugs appropriately.

Now the last point is really around other innovations, so in addition to a pipeline for new antibiotics, what else? Diagnostics, now rapid diagnostics have been talked about forever. The challenge with diagnostics is not just in terms of innovation, but also in terms of coming up with a market model where someone would want to use a diagnostic that maybe cost $20 to get a result back in one hour, to not use an antibiotic that also possibly cost $10-20 dollars. And you take it to a developing country scale, someone will either have a choice between buying an antibiotic for $1 or you say I'll sell you a rapid diagnostic for $2. Why would they want to buy a rapid diagnostic? They would just use the antibiotic. The diagnostics business model has not really been worked out yet, so it's both science and the business.

We need vaccines, we don't have a vaccine for staph or gram-negative infections. Certainly here, the population to be vaccinated is really small, it's people who might be going to a hospital, you might want to give them the vaccine. But here again the price point would have to be not much higher in order for a pharma company to want to come up with those vaccines. There are other things we can talk about, license, bacteriophages, probiotics, antibodies, quorum sensing, all these are areas of new science, but there is the challenge of the regulatory pathway, there are challenges with an understanding of how they fit in to how we deal with that infections in a way that we've done now for the last 70 years, which has been a fairly simple model. You try to prevent the patient's infection through a vaccine or through infection control, they get sick, then they get an antibiotic, it's a fairly linear pathway in that way. And some of these ideas, including innovations to slow down resistance or reverse resistance, are not necessarily operating at the patient level. So the benefits may be at the patient level.

If you look at penicillin in 1941, it's about 10 cents a dose, linezolid at about $155, and daptomycin at about $181, it was much more expensive, the price has come down. Any of these would treat a bacterial infection, and arguably that person could live to the rest of their natural life as they would have. So essentially the life gain is tremendous for antibiotics.

When you look at the willingness to pay, say, for the newest cancer drug, that's about $31,000 for a three to four month extension of life. So again, we've mentally anchored ourselves to very low prices. I am not arguing that we should pay higher prices for antibiotics, but what I am saying is that this is similar to the oil analogy, right? If we overuse oil, or we don't conserve the oil that we have, we should expect to pay more for the oil that we know that our kids have, or our grandkids would have, because that oil is going to come out of a small hole in Texas, it's going to have to come out of some deep well of the North Pole, and it's the same thing with antibiotics as well. If we don't conserve the antibiotics we have, by extension, the new antibiotics will have to be more expensive to produce, the regulations more tight now in terms of what it takes to bring a new drug to market, and the newer antibiotics will actually be more expensive.

Now, what the cost of the new antibiotics is also doing is acting as a price signal to tell you, conserve the antibiotics that you have because you're not going to have these 10 cent antibiotics forever unless you do something to really conserve them. So that's really what's going on here, and I don't think that we can expect that without action on conservation, stewardship, infection control, prevention, that we can expect to have cheap antibiotics forever and forever, that just might not happen.

A lot of this work is based on many colleagues in many countries through the Global Antibiotic Resistance Partnership. We've put a lot of these slides together, I think there might be a couple of copies of the State Of The World's Antibiotics report that was put out last year. And lastly, we wrote this Lancet series to focus on this idea that this is not just a problem of antibiotic resistance, this is a problem of effective access or access to effective antibiotics, which many of us here take for granted. But many people around the world still don't have access to effective antibiotics, and the real tragedy will be that when those folks who currently don't have access finally are able to afford an antibiotic, that antibiotic will not work for them, not because they overused the antibiotic but because the rest of us did.

That's really where we stand and I don't think we'll go back to this blade of grass responsible for the loss of foot story, but we'll certainly hear a few more of these as things slide down. So a lot of the data that I presented is at this website, resistancemap.org, and the slides are on this website. Thank you again for the opportunity to speak with you and thank you, Dr. Fauci.

Anthony S. Fauci

So we have time for some questions, if anyone has any questions, let me know.

Audience Member

Hi. So you talk a lot about incentives for new drug development, and I was just reading the other day that drug companies are disincentivized from developing new drugs because of the rapid emergence of

resistance. So is that really an important factor in the development of these new drugs? Will that actually slow down the development of antibiotics?

And then, also, you mentioned that [buy-ins] can incentivize development by providing these surprises. But, is that sufficient to incentivize development when we could turn elsewhere and find some other drugs that they can sell for greater revenues?

Ramanan Laxminarayan

So that's a good point about what disincentivizes drug development. In the case of antibiotics, the single biggest disincentive is really the fact that any new antibiotic will still have to compete with many other antibiotics that are out there in the market. That is really the biggest disincentive.

And the second part is of course, that the cost is as high as bringing any new drug to market. So everyone's looking for that one blockbuster drug that is a great broad-spectrum drug that we sold for all gram positives, all gram negatives and those are obviously hard to find. So the challenge is not any in any way particular to antibiotics.

Resistance has not necessarily been a break on sales, at least for the existing antibiotics so far. It could be in the future, but it hasn't been till date. So I don't know if that's necessarily an important issue, but it is a challenging market to bring a drug, particularly through the regulatory process where you have to show that your drug is at least as good or better than all the existing drugs and to do a trial for resistant infections is extremely high, because it's not like doing a trial for someone with cancer, you have more time; here, it's an acute infection and trials for acute infections are more challenging to deal with.

Audience Member

One thing about costs that you didn't talk about is the cost of a resistant infection can be quite high at least in the US. Are those costs hidden, or they don't really seem to be discussed too often, are those costs hidden in how we account for the cost of medical care or is that really just something that's written off the books?

Ramanan Laxminarayan

So the primary cost of resistant infection is in longer hospital stays and, of course, worse outcomes. Now longer hospital stays, in many instances, the hospital will just bill for the longer hospital stays, so they don't necessarily have an incentive from that perspective to reduce resistance. Now, obviously, the mortality-morbidity cost is borne by the patient which they might not necessarily recognize. Since we don't actually know that someone died of a resistant pathogen, right, we know that they had an infection, or they went in for hip replacement, they got an infection and then they died, because we

don't keep track of this as carefully as we would say for HIV or for other diseases, we don't attribute costs to resistant infections as well as we do for other infections.

Audience Member

Thank you for entering this talk, Dr. Laxminarayan, I hope I pronounced your name correctly. I wanted to ask, so in the beginning you showed the maps of how resistant pathogens spread. I was wondering, have you ever studied a case where, say, one region completely did the right procedures, right dosage, and just eliminated their targeted pathogen, but let's say some other region didn't do so and then, while this region A did everything correctly and has eliminated their problem, region B didn't and then their now resistant pathogen came back. So the implication I was wondering is that even if one single area completely did everything correctly and applied their procedures, what is the chance that they're still going to get a pathogen because some other area has it?

Ramanan Laxminarayan

I think that's a great question and maybe Dr. Fauci wants to talk about how that happened in the clinical center, it's a very real world example. But I'll let him talk to that. You know, that's a really good point.

To some extent, resistance is local and to some extent it’s global. So if you take the Netherlands for instance, they had a policy where after the rates of MRSA went up to about 20%, they had a search and destroy policy where any case of MRSA would result in that ward being shut down, total disinfection, and they would not reopen the ward till they got rid of all the MRSA and they managed to bring MRSA rates down to less than 2%. Now, obviously a very expensive policy, that policy also requires that if someone comes in from a country with higher levels of MRSA colonization, such as the one we happen to be in right now, then that person would be isolated and decolonized before they were allowed to be part of the system.

So it is possible to create these closed systems but it then incurs a cost in terms of being closed. And it's possible to do for a small country like the Netherlands. I just can't imagine how we would do it to the United States with 6000-7000 facilities. And you might want to talk about the clinical center example where it comes in from the outside.

Anthony S. Fauci

Well, the person to talk about the clinical center examples is right by your foot. But we have a very special system here in the United States, in the NIH, in the sense that we do things that I'm not sure would be economically feasible in other another hospitals, where we screen everyone that comes in and then we have a routine screening on a periodic basis, doing screening of perianal and rectal cultures. And when we find that they’re resistant, we isolate them and we learned that from less than that here in

this building, that as I was mentioning to Ramanan before we came here, when we had the big outbreak here, not that big, but it was at least a notable outbreak, here in this hospital. The word was out because it reached the press that there must be something wrong with the NIH hospital because we had these infections with resistant organisms and the fact is, it's going on everywhere, all the time, more than it is here, except that we just took the time and the money to look for it.

But I think that as you have mentioned correctly, Ramanan, I don't think that the hospitals in the United States are going to do the kinds of things we do here, because it is really essentially hospital control, and hospital control is a very expensive thing.

Audience Member

So would it be prudent to have a sort of consortium or association where a large number of countries or hospitals participate, where they agree to push out the same procedures and check that everyone is performing to a certain dosage or an application standard?

Ramanan Laxminarayan

So actually, that's a great point. We wrote about this almost 10 years ago about how regional collaborations were the right way to do infection control and that sort. And in fact, about six months ago, the CDC had put out a Vital Signs Report and an advisory to do exactly that, which is to have infection control, not at the individual hospital level and to look for AMR and resistant infections in clusters of hospitals that were exchanging patients quite a bit.

In fact, there was an epidemic of vancomycin-resistant Enterococci, that was in an area of Sioux lands, which basically encompasses parts of the Dakotas and some of the Western states, but they've managed to do it precisely with the strategy. So the correct takeaway is that the hospital is not necessarily the appropriate unit at which one could control resistance.

Audience Member

Could you comment on poor quality drugs and antimicrobials, and their contributions in development of antimicrobial resistance, both the fakes and the substandards. You yourself have shown that the under-5 mortality due to malaria in Africa, about a quarter of those deaths are due to fake antimalarial drugs.

Ramanan Laxminarayan

Yeah, Joe I knew you'd ask that question. So, the problem of drugs with no active ingredient, by definition, to some extent, it doesn't create resistance at all, there is no active ingredient. It's the ones

with lower levels of active ingredient that potentially create resistance because you're putting patients on a suboptimal dose of an antibiotic.

The data we have, as you know, is strong for Africa, but we don't necessarily have that same level of problem in India or China, where much of the antibiotic consumption is really happening. So India, China, and Brazil don't have the same rates, at least based on data that we have, of the substandard, suboptimal drugs, as Africa does. So I suspect it's a smaller problem in this particular instance. Malaria, of course, it's all in Africa and that's where the drug problem also is.

Audience Member

If the mosquito picks up a resistant strain from a patient who receives a drug without an antimalarial, wouldn't that be spreading resistant organisms?

Ramanan Laxminarayan

So certainly for patients with malaria, you certainly want to treat them with an effective antimalarial. But we also know that there's a huge amount of overtreatment of people with antimalarials, even when they actually didn't have malaria. So we've got to square those two somehow, that we use them appropriately, but then we also use the appropriate drugs.

But the answer is simply that, you know, in many countries, we just don't have the data to be able to answer that question. We just don't have the population-level service that we have for the antimalarials for the antibiotics as well.

Anthony S. Fauci

Are there any other questions? Thank you very much Ramanan, great job.