

Erta Kalanxhi

Hello, everyone, I think we are live. Yes. Sorry if you had to wait a couple of minutes, we just had to make sure that everyone could join in. So thank you, everyone for joining. Good morning, good afternoon, good evening. I know you might not see each other, but I have seen that you're from everywhere, including Asia, Africa and Europe. We have some from North America as well.

So hello everyone, and welcome to our conversation series on One Health. My name is Erta Kalanxhi. And it's my pleasure today to be able to facilitate this discussion. For those of you in the audience that have followed us over the years, it may be a bit confusing that now we are One Health Trust. You have been following us as CDDEP, but CDDEP is now the One Health Trust. This change came about to reflect the work that we're planning to do in the different sectors, and also to acknowledge the connection between human and animal health and the environment. So if you'd like to see the new developments with our work and our new website, we'll have the link available in the chat.

Today's webinar is organized in collaboration with the AMR Industry Alliance, and it's inspired by themes that we have encountered in a recent report that we launched this summer. The report revolved around regulatory innovations for antibiotics. And it highlights some of the topics that we will discuss today. If you're interested to know more details regarding some of the topics that we will discuss today, please check out our report. Today we will be discussing antimicrobials: our most important defense against bacteria, viruses, and fungi, a whole range of pathogens. Drugs such as antibiotics not only help us fight disease, but also help us prevent getting sick when we are most vulnerable, such as during surgeries or when we are having cancer therapy. Now, these drugs such as antibiotics have been available for decades, actually, soon it's going to be a century. And for some people, this may seem like a long time. But it's not such a long time when you consider their diminishing efficacy, this rampant use of these drugs all over the world for different conditions. So that's correct -- the more we use them, the more we drive these microbes to enhance their ability to survive them. Antimicrobials are vital for our health, and we undeniably are in need of new ones. We should do our best to preserve them. But there is no question that there is going to be a need for new antimicrobials in the future. The question is, why is it so difficult to develop new ones, given all the advances that we have today with technology and research? The answer for this is complex. Therefore I'm very, very happy to have with us today a fantastic group of people who have given a lot of contributions in their respective fields. And I'm very happy they're with us today. They're here to share their experiences and their insights and in some way, translate this complex issue into some take home messages that we can take home or at work today. So, we will have a brief discussion with each of our panelists, and then at the end, you will have the opportunity to ask questions directly. Please do not hesitate to use the Q&A section in your app and enter some questions now.

It's my pleasure today to welcome Dr. Anand Anandkumar from Bugworks, Dr. Christine Årdal from the Norwegian Institute of Public Health, Dr. Ralf Sudbrak from the Global AMR R&D Hub, and Dr. Marco Cavaleri from the European Medicines Agency.

I will start our session today with a couple of questions for Anand. Anand is the founder and the CEO of Bugworks. It's a company in Bengaluru, India, who is working to develop next-generation antibiotics. Thank you very much for joining us today, Anand, it's really a pleasure to have you here.

Anand Anandkumar

Thank you, Erta.

Erta Kalanxhi

Yeah, so I have been listening to one of our recent podcasts, where you spoke about the problem that we have with the antibiotic arsenal today. Could you please share with our audience some of the challenges surrounding this issue? And specifically, why are there so few companies doing what you're doing right now?

Anand Anandkumar

Thank you so much, Erta and the organizers. Can you hear me clearly?

Erta Kalanxhi

Yes, perfectly.

Anand Anandkumar

Great. Thank you. And it's wonderful to be on the same panel with these wonderful panelists. So, I'd like to first start by talking a little bit about Bugworks. We are a US, Bangalore, Australia-based company and we are inventing a new broad-spectrum antibiotic, a novel class, that can work on serious hospital infections as well as community infections. It's been a huge challenge, which is why we are here.

Just for the audience to understand, when we talk about AMR or antimicrobials are not just [for] bacteria, they're antibacterials, antivirals and antifungals. But one of the biggest issues we are faced with is in antibacterials. Companies like mine are working on antibacterials. So the word AMR sometimes gets associated heavily with antibacterial companies. That's okay. But I just want to let you know that antimicrobials include viruses, fungi, bacteria, as well as parasites.

So, Erta, the big issue here is, you know, you work for 10 to 12 years to come up with an antibiotic. It costs about \$1.5 billion dollars. It saves a ton of lives. Yet, the way in which we pay for antibiotics and

antivirus, etc, is based on fraud. So basically the standard pharmaceutical construct, that you sell more, you recoup money for R&D, you reinvest into a company. Completely broken, when it comes to AMR and antibacterials.

To be very, very specific, I went back and looked at the last five years, Erta. 207 oncology drugs -- approved, very happy about that. Less than four anti-infective drugs approved. One in five oncology deaths that happen, post chemotherapy, post human oncology, happens because of infection. So 20% of the oncology mortalities are because of infection, yet are 1:100, in terms of work going in the interest of normal assets, as a result of which our pipeline, Erta, is very, very poor to non-existent. Whatever is there in the pipeline is old BLBLIs, or beta lactam beta lactamase inhibitors, type of class going through it. It's very rare to see a novel class broad spectrum, novel Gram negatives going through. It's a very poor pipeline. And all of us know through the COVID experience that we have to be prepared.

Unfortunately, we are terribly underprepared. And AMR is a very silent pandemic, it's a slow burn. It's like the forest fire that starts quietly in the west, and then spreads and then it's too late to contain it. And it takes away tens of thousands of hectares. So you spend so much money, 5% success rate, because the science is so hard, you're dealing with a live organism, getting into the organism, getting a novel target, escaping the resistance mechanisms of the organisms, yet the average income of a novel antibiotic is \$45 million. Why is this the case? Antibacterials, or antimicrobials, are the only pharmaceutical class, for your audience, where you don't want to use too much, because the more you use, the more you show your bullets to your enemy. It's a natural selection process, natural evolutionary intelligence, that microorganisms will figure out ways to destroy. So if you overuse it, you abuse it, you sell too much of a novel antibacterial, resistance that kicks in in 20 years may start coming in 10 years, may start coming in five years, right. So it's very important to appreciate that this is the only class where the more you use and overuse and misuse, you very quickly lose it to resistance.

Then look at the conundrum: 5% success rate, 10 to 12 years, \$1.5 billion, no revenue, and you want to keep our drugs under lock and key, as the last resort to save that patient that's dear to all of us. Huge value to society, but no money. Hence high bankruptcies, even after you get approvals in FDA or EMA.

I also went back in and looked at the last 18 antibacterials. I was surprised and shocked to find out that most of them are available only in three countries: UK, United States, and Sweden. So even the high income countries, including Europe, don't have access to some of the new antibacterials coming because there is no market or no commercial partner. Big pharmaceutical companies have fled. The small folks who are barely alive on low oxygen are trying to push.

But now let's look forward, before I finish my opening comments: what needs to happen, what is happening? The most important thing that needs to happen is we fix the broken market. And that's called pull incentives. That means, pay for antimicrobials like defense equipment. You never look at how many times you file an F16. Or how many times you're going to launch from a warship; yet you pay for it and keep it there for a bad day. So something like the Pasteur Act or transferable exclusivity vouchers or the UK model. Excellent start. We need to fix the business model. Two: regulatory harmonization.

Antimicrobials do not give us the luxury of time and money to do regulatory paradigm shifts in every different region and in different countries. EMA is a leader, and Marco and team have done a phenomenal job in trying to work on data harmonization, but we know sitting in the trenches that a lot more needs to happen in many parts of the world. We can't afford to do harmonization everywhere. Number 3: 85% of the disease load, Erta, is coming from low to medium income countries, 160 countries. Revenue is 85-15 reversed. 15% of AMR problem [countries] generate 85% revenue. 85% AMR problem countries generate less than 15% revenue. It's completely lopsided. So if I do all this innovation, and if our asset is not available in those 160 countries, what is the point of innovation? And then some resistance picking up in India or Ghana or Timbuktu is going to show up in Boston or the Bay Area or worse. And the last point is the ecosystem has to make this sustainable.

So it's good to see GARDP, CARB-X, AMR Action Fund, slowly things are happening in the ecosystem. I'm still positive. So I wanted to finish up on a positive note that there are many wheels in motion. But if the business model is not fixed, it's game over, whatever else happens. So the biggest issue is economics at the backend, to treat antimicrobials like a war chest, like medical infrastructure, like military infrastructure. If we don't do that, we're going to be in big trouble. But some of us will continue fighting. Thank you.

Erta Kalanxhi

Thank you, Anand, thank you, that was very well explained. Thank you so much. It's always a pleasure listening to you. But we're not done yet because I still have a couple of questions. I have another question, which is related to something you said [in] your opening statement, which is that antimicrobials do not only include antibiotics. So my question is, these challenges that you just described, do they also apply to antifungals, antiparasitic agents, antivirals?

Anand Anandkumar

Okay, Erta, it's very simple, right? Most of the diseases happen in low to medium income countries. I want to be brutally honest. There clearly is, you know, there's clearly a divide, right, between the haves and the have nots. And you see that in infection. It's called neglected tropical disease. The word is part of the nomenclature. Would you believe it? Neglected tropical diseases, and "tropical" because they used to happen mainly in tropical climates. So if you look at antifungals, less than 1.5% of pharmaceutical budgets go into antifungals. We have a huge problem with azole resistance, Aspergillus, etc. I'm hoping that we'll have new drugs in the pipeline.

I look at malaria: resistance to chloroquine, mefloquine, artemisinin. And please pray and hope that the WHO or MMB will step up and continue to fund it. There are no private dollars, the issue is private money. Antivirals, we all know, before COVID, at least, it was very hard to get money out of antivirals. The only exception, Erta, is hepatitis C. Hep C is a \$7.5 billion market per year. And great work done by

Gilead and other companies. Because the predominance of patients happens in rich countries, right? And I'm happy that there is a solution. And we should all be proud and happy about it. But if we don't fix the business end of antivirals, antifungals, antiparasitics, and antibacterials, this problem is common. You solve a huge human problem, but you're solving it mainly in areas where there's not big money to be made. Who's going to pay for it? Why should they pay for it? Private dollars don't flow in. Private dollars will flow in when we have pull incentives, which is why we all pray that exclusivity vouchers or Pasteur or the UK model work, because, Erta, they set the pathway for a new paradigm to think about infectious diseases. Thank you.

Erta Kalanxhi

Thank you, Anand. For those of you who are wondering about pull incentives, this conversation will also reappear or reemerge in our discussion a bit later today. I would like to ask a question to Dr. Ralf Sudbrak, who is interim secretary and co-lead for the Global AMR R&D Hub. Thank you so much, Ralf, for joining us.

Ralf Sudbrak

Thank you for inviting me.

Erta Kalanxhi

My question is actually around discovery research and knowledge because we're talking about developing these new drugs, and we're talking about the challenges with financing them. But drug development starts with discovery. And so my question is, given the lack of development potential, which is not good for research, where are we right now? Is research and knowledge keeping up with the developments in resistance and the need for these new drugs?

Ralf Sudbrak

Thank you. So I'll also take a quick turn first. So if you listen to Anand, it seems that it's very frustrating to work in the AMR field. Why are we motivated, all of us working in the field? This is because antibiotics, I say antibiotics, but I mean antimicrobials, including all antifungals and so on in order to make it easier, antibiotics are fantastic. They are the best, most successful drug class humankind has had, ever. So if you have a deadly infection, we take antibiotics and those illnesses revert to health within one week and this does not happen in other diseases. So this is the most successful drug class we have in hand as Anand said. So it's not only fighting infection -- we need antibiotics for all kinds of modern medicine, this is really the foundation of modern medicine. That's the motivation, why we are still in the business, even if the market is broken, and you can't earn anything, and we lose all our talents.

Now coming to the Global AMR R&D Hub. We are a G20-initiated initiative. And our aim is to really enhance coordination and improve collaboration on the policy level by making recommendations on gaps and opportunities in AMR R&D. So we are advising and supporting G7 and G20. So this is really our aim, our vision, our mission.

One of the first things we did is we established and developed a dynamic dashboard, where we collect all information about funding happening globally in AMR R&D. And what we see is that 40% of all funding by public funders and philanthropic funders goes to so-called product-related research. This consists of preventives, including vaccines, diagnostics, and therapeutics. And the majority of this 40% goes really to these early drug discovery phases; in our definition, it includes preclinical phases, but also the discovery phase, which happens more or less in the academics and in the very small micro SMEs, companies, which only have one to ten employees.

So according to Erin Duffy from CARB-X -- I was on a panel last week with her -- she said that we have enough innovation within this space. If you see it as the entire, let's say, value chain, everything is very well covered. So we have, from the basic research going to early discovery, we have JPIAMR in Europe. This is a consortium of funders aligned in the aim of combating AMR. Then we have CARB-X and then we have GARDP and later on, we have in the later clinical phases, the AMR Action Fund now and BARDA. So we have a lot of players.

But if you look in more detail, you'll see that we have only one player per region. If CARB-X, for example, is not funded anymore, the entire system will collapse because no one is there. So the IMI, the Innovative Medicine Initiative, stopped last year, so there's no funding in this phase. The REPAIR Impact Fund is really pausing the investments, they're waiting for market incentive, so no new investment is coming from the REPAIR Impact Fund at the moment. So CARB-X is the lonely kid in this playground at the moment, and there is no sustainable funding for existing partnerships. The entire system will collapse.

We've made a lot of progress. We got the second funding round from CARB-X. Last week, Germany announced another 50 million for GARDP, the AMR Action Fund is now live and funding the first project. So there is a lot of good news. But you have to keep in mind [that] the entire system is very fragile. And we have of course, the problem is, as Anand really laid out brilliantly, that we have no pull. Even if the companies are bringing drugs to the market, I think the majority of companies even go bankrupt after they have successfully launched an antibiotic to the market. What we need is probably also regulatory incentives and I'm sure Marco will refer to it. We are in good shape, but you have to keep in mind that everything is very fragile and can collapse very quickly if one of the existing players is not there anymore in the future.

Erta Kalanxhi

Thank you so much for explaining this. It appears that we are okay, but it's a fine balance going forward and we need additional investment to continue. My next question is also something that we touched upon earlier in the conversation, that AMR is a One Health issue. It really is complex and it affects the environment, animals, and us humans. A lot of work has been focused on looking at the AMR problem in human health. But given the complexity, and it being a One Health issue, I just wanted to know how the Global AMR R&D Hub, that is doing amazing work at collating this information, how are they promoting this One Health approach to looking at AMR and finding solutions for it?

Ralf Sudbrak

We were set up, I think, in 2018. And this One Health aspect was already implemented at the very beginning. Not as many of the other organizations have this One Health aspect on top now, so it was implemented directly from the beginning. And in our dashboard, we collect the product information, not only for human health, but also for animal health, environmental health, and even agriculture. And I think our dashboard is One Health, if you want, since April 2021, when we have all the other vectors included.

And since April 2022, we have a special report in our dashboard, which is only covering projects where at least two sectors are included, so it's mainly human and animal health, but also it could be human and environmental health. That does not mean that these projects are One Health but at least they cover more than one section. And what we see is that in our dashboard, 12% of investment goes into animal health, and around probably 6% of investment goes to projects [that] cover more than one sector.

We are doing a lot of reports externally. We also did a report with EU-JAMRAI together with Christine, but this was on pull incentives. We are also doing reports on, let's say, animal health topics like veterinary vaccines to reduce the use of antimicrobials. There's other reports we are doing externally, a couple of them are relevant to AMR, and we're also doing now some collaborations internally within the board members and the first working group was on pull incentives, but already the second topic was chosen by the board members as One Health so it was really appreciated, the importance of One Health within our board.

So our board consists of 17 countries, Wellcome Trust, Bill and Melinda Gates Foundation, WHO, FAO, WOA, and OECD, and all agreed that the second most urgent topic is really One Health. I'll probably stop here before I go too long. We are, for example, observers of the WHO Roadmap on One Health. We are invited to the meeting in Oman next month, which will be more or less entirely on One Health and the main call will be reducing the antibiotics in livestock, which has to be reduced by 30% to 50% by 2030. So, we are doing a lot and we're promoting a lot of One Health topics directly to the G7 or to the G20. We are in contact with Lav Agarwal from India who represents India in the health communities within the G20. So we reached out to G7, to the Japan delegation, and tried to make this topic a priority.

Erta Kalanxhi

Thank you, Ralf, that's good news from your side. My next set of questions will be directed to Dr. Christine Årdal from the Norwegian Institute of Public Health. Christine has done a lot of work with a focus on access to medicines and policy innovation.

The question I have for you today, Christine, is regarding measures that could tackle or address this issue with the failing markets that Anand described earlier. The problem with developing new antimicrobials right now seems to be pure economics, but there are mechanisms in place that have been mentioned during our talk that could address this issue. Could you share with our audience what they are? And does it look better for us that they are here?

Christine Årdal

Thanks, Erta. Thanks for having me. It's really a pleasure to be here. So I guess, you know, I come from the public health side of it. And so I don't have a lot of investment dollars and am watching the clock to know how much money I have left by the end of the year. Actually, from a public health perspective, we're going pretty quickly. The O'Neill report was launched in 2017, the DRIVE-AB in 2018. We see significant investment by CARB-X and GARDP and the preclinical pipeline looks stronger than it has done in decades because of them. We see that France and Germany have implemented models to pay higher prices for important antibiotics, we see delinked pull incentives from England and Sweden. Pasteur is being discussed in Congress. I know for Anand and other innovators that feels terribly slow. But actually, I mean, five years, it's pretty quick actually, when you think about government policy. Things are going, progressing further.

I think there's general agreement. The work that we did through the EU Joint Action on AMR, we found out that countries basically know that they need to pay for antibiotics differently. They know that they need to pay for access rather than consumption. And that's very important. And that's why the conversations about the delinked pull incentives...probably some people were pretty surprised to hear that Sweden has the third best access in the world to new antibiotics, seems a bit odd for a country that has very low antibiotic resistance levels. And that's because Sweden implemented a delinked incentive for access. Now, they were very explicit, they implemented it only for access, not to stimulate innovation. So it's a modest award, but they pay a guaranteed revenue in order to have access to important antibiotics.

Through the EU Joint Action, and through the work that we did with the hub, we think that this model could be easily ramped up to a European level. And there are discussions going on about that right now. The European Commission through HERA is evaluating this possibility. So we're hoping that there can be progress. We believe that it can be implemented through the Joint Procurement Agreement.

Anand mentioned the transferable exclusivity voucher, which is something that is contemplating being approved through the pharmaceutical legislation right now. I must say that I think that's a terrible idea.

Because it is very expensive. The transferable exclusivity voucher does not ensure access to the antibiotic, and it's unpredictably expensive. But I do think that Europe is poised to act quickly in this area, and we need them to act quickly, absolutely, because innovators need to have predictable and higher rewards.

As a part of the work that I've been doing, just because I know that there's a lot of people on this call from low and middle income countries, I think it's important to say that there is a general recognition as well that high income countries need to pay these delinked pull incentives. We need to be the ones to spur on and pay for that innovation. It doesn't make a lot of sense to talk about delinked pull incentives in countries that don't have a national health care system. In exchange for spurring on innovation, it's really looking to low and middle income countries to invest their scarce funds in infection prevention and control. We see through the results of the Graham study with the antibiotic resistance levels that low income countries have people who are dying from antibiotic-resistant infections to which they do not have antibiotics. They're dying from carbapenem-resistant infections but don't have access to carbapenems. So we have to make sure that, really, the most cost-effective investment is being placed in the right countries.

I guess I am positive. I think we are going forward with pull incentives. The whole idea with pull incentives is to try to get the private industry back to investing in antibiotics especially in the late stage. And, you know, we can hope that Pasteur will be passed quite quickly but the other G7 countries are also making progress. So I think within 2023, we can be quite hopeful. Thank you.

Erta Kalanxhi

Thank you. You sort of touched upon my next question, but I'd like for us to elaborate a little bit more. And you mentioned the issue with low and middle income countries that are expected to suffer the greatest burden given the level of resistance and the lack of access to basic drugs. So how can we ensure access to these new antibiotics in the future? Is there a role for the Global Fund here in this conversation?

Christine Årdal

I wouldn't say that there's a role for the Global Fund. But I think GARDP is leading the way. GARDP is the Global Antibiotic Research and Development Partnership. One of the innovative initiatives that GARDP has just taken up is that they have got a license for Cefiderocol from Shionogi. Cefiderocol is one of their newest antibiotics, it's considered active against critical priority pathogens. It's the focus of the English pilot, the Swedish pilot, [and] the German higher prices. So this is an important new antibiotic. And GARDP has just partnered and has the license to distribute Cefiderocol in 135 low and middle income countries. That means that a low income country or middle income country will likely have access to Cefiderocol before Norway does, where I sit. And that's exactly the way it should be. We should see that antibiotics are available in countries where the demand and the need is the greatest. There's a lot of

things that need to be worked out with this, you know, how do we steward these important antibiotics? This is a hospital antibiotic, how do we ensure distribution? What kind of surveillance is necessary? So I'm just so pleased that GARDP is really leading the way and we'll have so many learnings from this. I think that's probably the best way forward that I see right now.

Erta Kalanxhi

Thank you, that sounds amazing. Interesting point you made about Norway, but it is true and that's the reality. Before I continue with the next set of questions, I would like to just remind the audience that now is the time for you to start writing up any burning questions you may have.

With that, I will move on and speak with Dr. Cavaleri, who is the Head of Biological Threats and Vaccines at the EMA. Dr. Cavaleri has been at the forefront of the COVID response with all the vaccine work that he has done and I think you are the right person to ask with regards to the impact that the COVID-19 pandemic has had on antimicrobial use, the need for new antimicrobials. I know that the focus will primarily be on antibiotics, but there were a lot of other drugs used in an unregulated way during the pandemic. So my question is, how has the pandemic impacted the need for new antimicrobials? Where are we now as compared to two or three years ago?

Marco Cavaleri

Yeah, I think that the pandemic, of course, required that we put a lot of the work dedicated to antimicrobial resistance into the acute problem of COVID-19. But I think, you know, at the same time, there has been a lot of learning about how to handle this silent crisis [of] antimicrobial resistance and what we can do more as regulators in order to facilitate the development of new products that could tackle the issue of antimicrobial resistance in the long run.

At the same time, of course, we have also seen an abuse of antibiotics during the COVID period, and also it emphasized the need that we always need good evidence from rigorous clinical research in order to draw conclusions about what is effective or what can be harmful, and really defining the benefit-risk of medicinal products. For example, azithromycin being overused, you know, with the claims that it would have been helpful in the context of COVID-19, when in actuality, it was not. So there has been a massive misuse of antibiotics related to macrolides to start with, which is something that reminds us that we need to find streamlined regulatory processes for rapid approval of new antibiotics or new molecules that could tackle the issue of AMR. But we also need good evidence, we need to be sure that the products will be effective and safe. And that's what really this pandemic was telling us.

At the same time, clearly, there were a lot of people hospitalized that were really frail, and co-infections occurred, either with fungi or bacteria, so it reiterates the fact that now it's time to go back full steam, and really think about what else we can do to tackle the problem of antimicrobial resistance, and really working with the scientific community, with the government. I think you've heard from Christine and Ralf

and Anand a clear call for having something more done with respect to return on investment and all the economics in this area. This really is a priority.

But of course, for us as regulators, we need to think of what else we can do. And maybe the last point that I will mention that is being really incredibly helpful during this pandemic is the international collaborations among regulators. We had a fantastic way of working together, like through the International Coalition of Medicines Regulatory Authorities that brings together regulatory agencies from all the continents in the world. I think we should build on that in order to ensure that the work that we started doing in terms of harmonization or requirements with some agencies, like FDA, PMDA, and Health Canada, can now be expanded to other countries so that we have a more consistent approach across the globe on how we regulate these products for the sake of making them available to patients in need as soon as possible.

Erta Kalanxhi

Thank you, Marco. Is it possible to elaborate a bit more on these roadmaps or these opportunities for harmonization from the regulatory perspective?

Marco Cavaleri

Yeah, as you know, we reached quite a good level of harmonization of the requirements with the US FDA, the Japanese PMDA, and Health Canada. Even there, there are still some areas that are not fully aligned, and that's something that we have not forgotten about. We will come back to see if we can work the extra mile and really try to have a complete and consistent alignment on the requirements.

But I think the next step is that these four agencies were able to agree quite largely on the requirements, but now we need to speak to the other agencies in the world. And you know, within ICMRA, we have, for example, authorities from other Asian countries like India, China, Singapore, authorities from South America, like Brazil and Argentina, Australia is also represented, and importantly, authorities from Africa, like Nigeria and South Africa. So it might be a good starting point to try to build a consensus or try to get an alignment with the requirements that will not be only for those agencies in high income countries, but more spread across the globe so that we all are looking at the data in the same way, we are all looking into the requirements in a more consistent way.

I believe this will help a lot with the call for having these products made available to low and medium income countries as soon as possible, because as has been rightly said by Anand, the burden of disease of AMR is mainly there.

Erta Kalanxhi

Thank you so much, Marco. That sounds great. I think Anand has another comment.

Anand Anandkumar

Yes, I just want to come in: excellent comments from everyone. I want to take off from something that Dr. Christine said. It's very important for the audience to understand: as innovators in the trench, we could not have survived, had it not been for the support of CARB-X, GARDP, Department of Biotechnology in India, etc., more than 65 companies. The preclinical pipeline has never been as robust as it has been in the last three years. I just want to accentuate that point. So these are very positive things, including phage, including peptides, that's one.

Two, the work done by Dr. Marco and team has to be really appreciated. And now, I just heard today that the Africans are going to follow a similar model, Dr. Marco, the AMA, they call it, that has 55 countries across eight regions looking at a block for data harmonization. These are big, big changes, these are interactive changes in harmonization that may come up.

Number three, GARDP, the point that Dr. Christine made: never before, Erta, never before has there been the WHO on the table along with a pharmaceutical company like Shionogi along with an agency, the Clinton Health Foundation, figuring out methods to take a drug and make it available in 136 countries. [It's] very hard to do something like that. So someone is putting effort, money, resources, to figure out how to make the supply chain available, the regulatory mechanisms, the local foot soldiers who go to distribute this, it will take three, four years to play out. But I expect that we're going to have a template for other neglected tropical diseases.

The pipeline looks good for a template to make such new drugs, antimicrobial drugs available in hard-to-reach countries that have a very high load of the disease. And the fact that there are folks like CARB-X and GARDP and others coming to the rescue and creating 60 to 70 companies in the clinical pipeline. These are plausibly inflective moments for the space.

Erta Kalanxhi

Ralf, I believe you have a comment.

Ralf Sudbrak

Yeah, I only want to add that there is a new project by CARB-X enabled by GARDP and the WHO that is called SECURE. And last week during the World Health Summit, there were announcements that the first countries' funding is now secured. So Canada stood up, Monaco stood up, and the Wellcome Trust, so there is only moderate funding at the moment. But that's at least a sign that these countries and

foundations think that this new initiative is very important. And this is really focusing on access to drugs in low and middle income countries. I only wanted to mention it because it was just announced last week here in Berlin.

Anand Anandkumar

And Ralf, the fact that we have an AMR Action Fund to help late-stage development is also very positive. This didn't exist before 2020.

Erta Kalanxhi

While we are actually talking about new developments, I think it is really noteworthy to mention the latest launch from the WHO, the list of the fungal priority pathogens. We did touch upon this topic today that antimicrobials include antifungals as well. And this move is just another indication that things are going forward. Yes, Christine.

Christine Årdal

I just saw a question in the chat, and the question is, is the quality of water sanitation and hygiene related to AMR? I'm probably the least credentialed person to answer this question, so for those of you who are doctors and microbiologists, please correct anything that I say wrong here. But my understanding is that when you're exposed, and when you have exposure to poor sanitation systems, or do not have access to clean drinking water, this creates the environment where resistance pressure is exerted.

Bacteria, of course, are living organisms, and they evolve, the same as us. And as they're exerting more and more resistance pressure, they can change. This is the reason why WASH is really so important in low and middle income countries, and it's really such a cost-effective intervention because it's not only against AMR, but it also will be helpful against a host of other infectious diseases. Thank you.

Erta Kalanxhi

I couldn't agree more, Christine, I think you answered it perfectly. Anand, I think you have raised your hand.

Anand Anandkumar

There were two questions addressed to me in the chat box on diagnostics. I think it's very, very important to, again, let everyone know here that AMR is not just about therapeutics. It's about

prevention, which is WASH, that Christine spoke about, diagnosis, diagnostics, and I think diagnostics and therapeutics are two sides of the same coin. And we realize that if you only talk about therapies without prevention and diagnosis, we will lose a lot because you need the right drug to be used in the right patient for the right bug. And you can't do that with the diagnostics.

Good news again, there are many mechanisms like CARB-X, Longitudinal Prize, Wellcome Trust Prize, Bill and Melinda Gates putting money, etc., to promote diagnostics. So I think in the next two years, we're going to see a fantastic, major leapfrogging, generational change, in diagnosis, where within two hours, while the patient is having fever and possibly going down with sepsis, within two hours, you should be able to know whether it's a bacterial infection or not, which bacteria, what the susceptibility pattern is, with high accuracy. So I think this is very important that new therapeutics creating a vibrant pipeline, Erta, has to go hand in hand with these new diagnosis methods, because diagnosis is the cornerstone of allowing us to treat correctly and preserve what we have.

Erta Kalanxhi

Yes, Ralf.

Ralf Sudbrak

Yeah, I totally agree with Anand, this importance of diagnostics. But I also wanted to mention vaccines as a really important tool for prevention. So we need to really prevent a disease, we need prudent use, and we need new therapeutics. We need all three, so, vaccines, diagnostics, and therapeutics.

Erta Kalanxhi

Yes, and again, I know this is a recurring theme, but promoting vaccination in regions that have the highest infectious disease burden would make the greatest impact with regards to prevention of antibiotic use, the need for these advanced antibiotics, and to slow down the emergence of resistance. So that's a very good point. Ralf, thank you for reminding us of that. There are some other questions that are unanswered here. Christine? You're doing a great job, because I don't even need to see the questions. This is the best panel ever.

Christine Årdal

I see a question from Louis, how would you judge the effectiveness of antibiotic reduction policies on farms in Denmark, the Netherlands, other European countries? What lessons could be learned to inform a similar effort in other countries? And I think this is really important because Europe has done very well in reducing antibiotic use for veterinary use. 30% in the last 10 years, which is fabulous. And I think this

has to do with more awareness on behalf of consumers. People don't want to have a lot of antibiotics in their meat. And also, of course, a huge amount of awareness in veterinarians.

Europe, of course, has [it] regulated so that it's not allowed to use antibiotics for growth promotion. But we see here in Norway, for example, we have large salmon fisheries. And the industry itself saw that they were using much too much antibiotics with the salmon production in the 1980s. And so it worked with a company, I believe it was Merck, to develop a vaccine for the salmon and now every salmon is vaccinated as a young salmon in Norway. So there's a great video on YouTube if you want to watch vaccinating salmon, please check it out. But because of this, we've completely switched now. In Norway, most of our antibiotic use is actually in people as opposed to animals. Thank you.

Erta Kalanxhi

Thank you, Christine. Yes, Marco.

Marco Cavaleri

Yeah, I'm keeping the same line of a proactive panel here.

Erta Kalanxhi

Thank you so much.

Marco Cavaleri

Question on bacteriophages. And I have to say that, you know, it's [been] more than a decade actually, since we have opened up to discuss with developers what could be the regulatory pathway for bacteriophages. Because we understand there is an intrinsic complexity there that requires a special way of handling this type of product from a regulatory perspective. And we have always been, you know, very clear in saying that if this product turns out or shows that they are really efficacious, then we will be very much open to see what we can do in order to solve all the potential regulatory bottlenecks that this type of approach could entail.

The problem has been that we have not seen that large of an amount of clinical trials really demonstrating what is really the efficacy of this type of intervention. And as you know, there are a lot of problems associated with the use of these products if they are given systemically and how, you know, they could be handled together with antibiotics. And of course, that's the reason why many of the developers start looking at bacteriophage products that can be given topically to treat recalcitrant infections.

Again, we are very open to discussing how to design these clinical trials and development plans in this area, but we really need efforts put in this area because unfortunately, we have not seen as much progress as we may have wanted to see in terms of having a real good understanding of how this type of treatment approach could be promising to tackle AMR.

Erta Kalanxhi

That's a great answer. Anand, yes?

Anand Anandkumar

Yes. There are a couple of questions on what are pull incentives, just for the audience to keep it simple. Any type of grants or mechanisms or incentives that allow your product to go through preclinical and clinical development are called push incentives -- they push you through. CARB-X, REPAIR, GARDP, etc., even AMR Action Fund, right? Pull simply says, "After I do all this and spend a billion dollars and build these bridges, am I building a bridge to somewhere or a bridge to nowhere?" as Kevin Outterson of CARB-X says. So pull incentives are mechanisms used by different countries, G7, G20, and others, thinking about how to pay some kind of deterministic amount for an antibiotic so that a small company doesn't go bankrupt trying to sell it aggressively. Because you don't want a new antibiotic sold aggressively to be used, misused, with resistance developed.

At the same time, we need to keep our lights on. So the amount of money that can keep the lights on and allow companies to recoup some amount of the R&D is a pull incentive. In the United States, it's called the Pasteur Act, which we hope will come for discussion before this Congress goes into recess. That says, if you crack an important problem, for example, gram negatives, novel chemistry, novel mechanism, IV to oral step down, you can be assured of a certain amount of payment over a 10 year period. So you amortize, say, a billion over 10 years, or one and a half billion over 10 years. That's Pasteur.

The UK has taken a fantastic role and created a Netflix subscription model, as Christine said, where I think they're giving up to £10 million per year per drug to the drugs Avycaz and Cefiderocol, \$100 million over 10 years, whether those assets are used or not, and the NHS and NICE will basically take it, will basically stockpile it.

So pull incentives simply means keep the lights on, put some money back into the companies that are developing at risk, so that private investors will then say, "Aha, governments are going to back this company if they crack the science. So we are going to back this company to see, you know, if there can be business potential." At the end of the day, small companies are not dependent on the government for handouts and for long term sustenance. We just need this bridge support before private dollars and private dynamics kick in. So that's a quick 101 on pull incentives.

Erta Kalanxhi

That's a great one, Anand, thank you so much. Maybe, I don't know, Christine, if you could or Anand, this is open to everybody. But there's a question about how to bring more high income countries into GARDP. It's open to anyone.

Christine Årdal

Well, I would imagine that as GARDP continues to demonstrate all of the excellence that's happening, they will be able to raise more funds. I think GARDP is really using their funds so effectively and demonstrating with Cefiderocol how they can improve access. They're partnering with Entasis on a new gonorrhea drug. I think that their success is probably the way forward for future partnerships. But maybe Ralf has better thoughts there.

Erta Kalanxhi

Yes, Ralf.

Ralf Sudbrak

No, it's not a better thought, of course not. But I think the countries first make sure that CARB-X was funded sustainably. So that was the first announcement a couple of months ago. And I think now they also are funding GARDP more sustainably. And I think the announcement from Germany last week for the 50 million was only the first country and Germany is setting an example and I'm sure many countries will follow and increase investment in GARDP so I'm quite hopeful that we will see a lot more investment in GARDP in the next month.

Anand Anandkumar

And, Erta, just to add on to this, right? GARDP, CARB-X, all these mechanisms that are primarily government or quasi-government, PDP-funded, they can't solve the entire problem. They can create the infrastructure, the edifice for innovation to make it to patients who need it. Private dollars and private capital markets have to step in to fund companies to keep them alive to move forward. And I think they are waiting, quietly watching to see if any of those pull incentives we spoke about go through in [20]23, 24. If any combination of these pull incentives go through, big pharmaceuticals will start getting more excited, as will private investors. And that's the prayer.

Ralf Sudbrak

I probably mentioned it before, I think this webinar is co-sponsored by the AMR Industry Alliance, so we are really recognizing the input from industry by the AMR Action Fund. This is what's really needed to take up or to fund this late stage development project. In addition to the pull, which comes after the AMR Action Fund, the industry already gave a signal by investing via the AMR Action Fund, together with the Wellcome Trust and some other philanthropic foundations.

Erta Kalanxhi

Marco?

Marco Cavaleri

Yeah, I see there are a couple of questions remaining. One is about the QIDP from the FDA. I have to admit that this tool has been helpful, but not really a game changer. So we should keep in mind, really, what we can achieve with all these different tools.

But it gives me the opportunity to say that, you know, this question is about a more global approach towards incentives or how they can be looked at. And I think the difficulty is that, of course, here, we're talking about legislation that each country will develop on its own. But I do believe that, when we talk about incentives, it would be good if there is convergence across different countries and regions because it will give more strength to that. I think even if it might not be possible, because of obvious reasons, to have similar legislation in place, and because each country has a different way of working and operating and being governed; nevertheless, this international dialogue on incentives is important, because the more they get aligned, the more they can be impactful. I think this is an important point.

And then very rapidly, I see this question about cationic polymers. Yeah, we're seeing interesting data about this and nanoparticles. By all means, we are very open to discuss any new approach that, at the end of the day, was proven to be effective and safe. If there are new ideas, coming up with a strong pharmacological rationale and data, we'll be very happy to discuss that and see how we can advance that.

Erta Kalanxhi

On that line, there's two last questions, and I think maybe one of them, we can answer quickly. And it's about extracting novel antimicrobials from plant products. I don't know if any of you have any knowledge on that?

Marco Cavaleri

Well, probably because in my previous professional life, I was working in a research center that was extracting antibiotics from fungi and microorganisms and had successes such as discovering rifampicin, teicoplanin, or dalbavancin, just to quote a few. So clearly, this has paid off tremendously in the past. Then, there was the era of synthetic products, proteomics, and all these approaches that have been abandoned.

But I think we should go back to natural products. Nature itself gives us a lot of opportunity to find diversity and really to find potentially new molecules that could be important in this area. So I do believe that it's important that we go back to that and think about setting up a good platform for discovery and looking into this type of product. The problem that we've seen in the past is that all the expertise that has been growing over the decades has been completely destroyed when the industry turned their back on this area, and this is a pity and we should avoid that this happens again.

Erta Kalanxhi

Thank you, Marco, so much. I think that we are over our time. I think we have to close our webinar here. The questions keep coming and I'm sorry that we are not able to answer all of them, but it shows that you were engaged and we'd like to thank you for your participation and giving us these questions because it gives us an idea of the themes that are evolving around these topics we have discussed today.

So with that, I'd like to thank everybody for joining us. And I'd like to thank our speakers who took time from their busy schedules. I don't know about you, but I think it was a sort of uplifting conversation with a lot of good progress for the future. And again, I'd like to thank you again to everybody that tuned in, and hope to see you again in our next webinar.

Anand Anandkumar

Thank you very much for the opportunity. Hello to everyone. Bye bye.

Erta Kalanxhi

Thank you all. Thank you so much. Have a great day.