Erta Kalanxhi

Okay, I think we're ready to start. All right. Hello, everyone. Thank you for joining us today. My name is Erta Kalanxhi. I'm a researcher at CDDEP and I'll be moderating the webinar today.

This is the third webinar in our conversations series on global health, which we have launched to celebrate our 10-year anniversary. Today's webinar has been organized in collaboration with the World Health Organization, as well as the support of the speakers that have joined us today.

In today's discussion, we'll explore the critical interplay between vaccines and antimicrobial resistance. And in order to get a full, comprehensive picture on the tissue, we have experts from different fields of research and policymaking here with us today. We are honored to have with us:

- Dr. Hanan Balkhy, Assistant Director General for antimicrobial resistance at the World Health Organization.
- Dr. Deepali Patel, acting head of policy at GAVI.
- Dr. Padmini Srikantiah, a senior program officer and AMR strategy lead at Bill and Melinda Gates Foundation.
- Dr. Mateusz Hasso, Technical Officer at the World Health Organization
- Dr. Joseph Lewnard, assistant professor at UC Berkeley.

Now, we will start our discussion today with a brief introduction to this topic by the director of CDDEP, Dr. Ramanan Laxminarayan. So thank you for joining us today, and over to your Ramanan.

Ramanan Laxminarayan

Thank you, Erta, and thank you all for being here. It's exciting to celebrate CDDEP's 10th anniversary this way. Now, AMR, as you know, is a topic that's very close to the work that CDDEP does, and particularly the area of vaccines is one which hasn't received as much attention until recent times.

We know anecdotally, and obviously from published evidence, that for instance, the introduction of the pneumococcal vaccine in many countries has been instrumental in reducing childhood antibiotic use. In fact, in the US, where it has been measured quite well, the introduction of the seven Valent vaccine around 2000 was instrumental in both reducing pneumococcal strains that were sensitive to antibiotics, but also ones that were resistant to antibiotics. Now, we haven't had much evidence on the role of vaccines on AMR apart from the pneumococcal vaccine.

In a project that was supported by the Gates Foundation and in a partnership with the World Health Organization and also the Wellcome Trust, we have done some work to look at what the effect would be of introducing vaccines or scaling up vaccines for rotavirus, Shigella, and tuberculosis. Obviously, in some cases, the vaccines exist and need to be scaled up. And in other instances, the vaccines don't really exist and they deserve to be produced. We've done this across a range of diseases. I think you'll hear that from some of the speakers today.

But what's interesting is that this also comes at a time when global support for vaccines is very high, thanks to COVID. So people are aware of vaccines and have a lot of respect for what vaccines can do. There's also a need for this kind of evidence to inform the kinds of vaccines that will be supported in national programs, and also financially by entities like Gavi, to make sure that the value of the vaccines and reducing AMR is recognized as part of that vaccine introduction decision. So that's really the focus of our discussion today on how vaccines can address AMR.

And as we all know, behavior change is one of the major ways in which we try to deal with AMR, with reducing the use of antibiotics. But if we can reduce the need for antibiotics by using vaccines and also reduce the prevalence of resistant infections by using vaccines — these are the two mechanisms that you'll hear from our first speaker, Joe Lewnard — then we can go a long way in using vaccines as being a primary tool in addressing AMR.

And what I'd love to hear from the speakers and what I'm most curious about is: Can the improvements in vaccinology that have happened over the last decade or so, and which continue to accelerate with investments in COVID vaccines, help us solve a large part of the AMR problem with vaccines?

Obviously, we'll have to do infection control and we'll have to do, you know, water and sanitation, all the other things. But could vaccines help us take a big bite out of this problem as it has helped us with many other issues? So with that, I'll hand it back to Erta and, again, welcome and thank you all for being here.

Erta Kalanxhi

Thank you, Ramanan. It's our pleasure to have here today Dr. Balkhy, who is going to share with us the World Health Organization's perspective on vaccines and AMR. So thank you for joining us, Dr. Balkhy. Over to you.

Hanan Balkhy

Thank you, Erta. And good evening, good afternoon, good morning to everybody and good afternoon from Geneva. Thank you for inviting me to be part of this very exciting event. And congratulations to CDDEP and Ramanan and all your leadership and partners in your organization for 10 years, and for doing some really amazing work that has opened the world's eyes on the major burden of AMR. So thank you for all the work that you do.

As you probably know, the COVID pandemic has created an unprecedented collaboration among the global players in health, economics, politics and in many, many areas that we have never found them. They've never thought that we would even live through such a pandemic that, even for me, for the past 20 years, I kept preaching about the next pandemic and we need to be prepared and aware, but I don't think that I ever thought that we would actually live through it.

And I think that the viral infections, such as Ebola, the viral hemorrhagic ones, the novel influenza, the coronaviruses, they were lucky enough to get enough attention. What we're facing with the MDRs and with the Gram-negative bacteria and AMR is that they will never, in my humble opinion, reach the attention that some of these other viruses have reached. And the evidence to that is that we've been facing and dealing with one emerging pathogen after the other. And then we become, I like to say, a bit numb or used to having that pathogen lurking around in our institutions and in organizations.

So with WHO, we will be paying a lot of attention to this. In 2019, the AMR division was established to enhance the collaboration and communication among the different entities that deal with AMR. And this unit, specifically the Vaccine Unit within the WHO, is one of the extremely relevant pillars of the 2015 AMR Global Action Plan that was released by the WHO, which is the major roadmap or assistance for the member states to develop their AMR national action plans. And I think coming here today to discuss specifically vaccines is extremely important.

Again, the COVID pandemic might help us enhance and give better attention to adult vaccine programs, which the Global Action Plan for AMR talks about, but really does not have that strong of a political stick to make sure that countries do implement adult vaccine programs. I think that COVID might be our way into that, also enhancing many of the epi programs for children. We still have a lot of work in dealing with the anti-vaxxers and the doubters on that -- that's a lot of work, and as Ramanan was saying, it's the behavioral attitude towards vaccines.

But what I would like to emphasize today, there's so much to talk about what WHO has done in 2020. We launched our newsletter earlier this quarter if you want to take a closer look at what we've been doing. But we're successful with one of the three global governance mechanisms with the establishment of the Global Leaders Group to provide the better political enhancement for AMR in general.

But what the Vaccine Unit has done is, they have published the action framework for vaccines against AMR. And it focuses on three very common sense issues that need to be done. Number one is that it calls for making sure that we expand the usage license and accessibility to the vaccines that already exist, such as influenza, pneumococcal, and many of the other vaccines. And the vaccines that are not just respiratory, but actually all of the vaccines that reduce the burden of infections so the need for antibiotics goes down.

The second one is to work more on R&D and establish more of the vaccine development for some of the vaccines that might be endemic in hospitals. We're going to figure out how we need to use them, how we can use them.

And the third one is trying to be innovative in R&D and modeling to try to understand the benefits of vaccines in driving AMR down. And I think the last one is extremely critical and it can maybe be one of the first things that needs to be done so we can convince our partners, politicians, economists about the value of vaccinating populations when it comes to the cost to health and also the cost of antimicrobial use and the side effects that we also don't talk enough about, as well as reducing the drive to more and more multidrug-resistant pathogens.

So there's a lot to talk about for AMR. But I'd like to stop here and say that this is an excellent event. And I'd like to thank my colleague from the WHO, Dr. Mateusz Hasso, for engaging me also on this event and back to you, Erta.

Erta Kalanxhi

Thank you. Thank you very much. We're now going to direct some questions to our speakers to get different perspectives on this issue. And we'll start with research. Dr. Joseph Lewnard is here with us today and we have some questions. What does the evidence suggest on the impact of vaccines on resistant infections and antibiotic consumption?

Joseph Lewnard

Thank you for this. I'm going to share my screen to walk through a few slides to go through recent studies of this nature in various pathogens and for various vaccines. So bear with me for a second while I open this.

The question of how vaccination might impact both antibiotic use and ultimately the burden of resistant disease is a complex one, which I think can be tackled from multiple angles, some of which were nicely laid out in a recent or now several years old review article by colleagues Katie Hopkins, Mark Jarrett, and others at the London School of Hygiene and Tropical Medicine.

Broadly speaking, the effects of vaccines might comprise several things that result from directly preventing infection or carriage of an organism. If that is an organism that is resistant to disease, then obviously that is resistant to drug treatment and preventing disease involving a resistant organism, that's the immediate benefit of a vaccine. However, other considerations might include that there is a reduced risk of disease that would trigger antibiotic use and therefore resistant selection.

When we use a vaccine to prevent infections involving a particular organism, we also reduce exposure of that pathogen to selective pressure from drug treatment when we prevent it from causing infection in a host. So this is another kind of broad benefit of vaccination beyond just preventing drug resistant infections to begin with.

And then maybe at a sort of higher level or at a more societal or clinical practice level, we might also consider how preventing infections involving particular organisms might impact the behavior of clinicians or the behavior of patients. For instance, if we can change the fundamental etiology of conditions that are common causes of antibiotic use, there might be less sort of justification for antibiotic treatment for particular common conditions that right now account for a whole lot of the outpatient antibiotic exposure, for instance, that happens in general clinical practice.

One of the challenges that we encounter is that to date, not all of these effects have been all that well measured or all that well quantified. Although with increasing attention to the subject, this is rapidly

changing. Emerging evidence suggests substantial effects of vaccines, or potential effects of vaccines in several scenarios, even for several pathogens.

So one of the kinds of studies that we've worked on here in recent years (on this topic) was addressing antibiotic treatment for the two most common conditions among children that results in antibiotic treatment, which are acute respiratory infections and diarrhea. And so in this work, focusing on low and middle-income countries globally, we use data to quantify the direct effects of pneumococcal conjugate vaccines and rotavirus vaccines, certainly after they were implemented in various low and middle-income countries in a large case-control study to look at their effect on antibiotic-treated acute respiratory infection and diarrhea endpoints.

And what we can see here is that in particular, at ages of roughly 24 to 59 months, we can see an almost 20% effect of pneumococcal conjugate vaccines in preventing antibiotic-treated acute respiratory infections. In particular, in the first two years of life when rotavirus is a very common cause of diarrhea, we can see a roughly 10% effect of rotavirus vaccines in preventing antibiotic-treated diarrhea episodes. And so this, I think, was sort of an important endpoint to quantify. We have always evaluated and licensed vaccines predominantly on their effects on severe disease involving a particular pathogen, but knowing that vaccines such as these can have a fairly large effect beyond what we can achieve through antimicrobial stewardship alone in preventing antibiotic use is an encouraging additional sign of their potential public health benefit.

This view also gives us a sense of just how much antibiotic use is caused by some of these vaccine-preventable pathogens. So having probed the amount of antibiotic-treated illness that's prevented by these two vaccines, we can see that just over 20% of both antibiotic-treated acute respiratory infections and just over 20% of antibiotic-treated diarrheal infections in children in low and middle-income countries are attributable to vaccine-targeted Streptococcus pneumoniae and rotavirus. So another measure that's worth considering, as we talk about which vaccines merit consideration for their potential effects on antibiotic use and antibiotic resistance, is what is the etiology of infections that are ultimately receiving antibiotic treatment.

This is an especially interesting consideration for rotavirus because, in its own right, rotavirus does not merit antibiotic treatment -- that is a viral infection. However, treatment of diarrhea in the community, and particularly in low and middle-income countries, is common. And so a lot of the resistance selection that this exposes pathogens to is potentially preventable and is being prevented by rotavirus vaccination.

So for what other vaccines, or for what other pathogens, might this be a worthwhile consideration? In addition to the study we just showed, we also revisited etiologic studies of diarrhea in the community and, looking at the subset of cases that were antibiotic-treated in low and middle-income countries, were able to quantify attributable fractions of diarrhea cases that were antibiotic-treated and associated with various pathogens. And so we can see rotavirus individually was in fact the leading etiology of antibiotic-treated diarrhea cases; they’ve been underscoring the benefits of rotavirus vaccines for reducing antibiotic consumption.

But then the next several pathogens down the list have some important lessons for us as well. So Shigella, of course, is another very prominent cause of severe diarrhea, potentially associated with very adverse clinical outcomes and the rapidly growing burden of resistance. And Shigella, including multi-drug resistance and potentially, in the not too distant future, untreatable infections, absolutely warrants consideration of vaccines against this pathogen.

However, others that come high up on this list in terms of their attributable fraction to low and middle-income countries were surprises. For instance, adenovirus and sapovirus are not necessarily infections that are associated with the greatest burden of fatal or very severe diarrhea cases. However, because they are common causes of diarrhea they are, in fact, associated with a substantial proportion of all antibiotic-treated diarrhea episodes.

So, you know, for pathogens like this that have not necessarily always been prioritized at the top of the list for vaccine development because they're not causing fatal disease, there might be a substantial impact of vaccines that result in significant effects on antibiotic treatment of common conditions like diarrhea. Similar arguments to this have been raised, for instance, for streptococcal pharyngitis and some in the case of acute respiratory infections and pharyngitis. In particular, this is a very common cause of antibiotic treatment, and changing the etiology of a condition might reduce the clinical justification or patient expectations for antibiotic treatment.

We can also look at least in several instances where reductions have been achieved in resistant disease or within the proportion of circulating lineages that are resistant for a particular pathogen. So in recent work in Streptococcus pneumoniae, looking at changes in antimicrobial resistance globally, following the introduction of pneumococcal conjugate vaccines, for instance, we were able to see reductions in most drugs including, importantly, penicillin, which remains the first-line treatment for pneumonia in children globally. And we were able to see reductions in both the proportion of isolates that were non-susceptible to antibiotics and fully resistant and potentially associated with treatment failure.

In macrolides, this is a little bit less clear, which is of concern as macrolide use grows around the world. However, for other drugs including trimethoprim and third-generation cephalosporins, which are sort of a second-line recommended treatment for pneumonia in low and middle-income countries for children, we were able to see clear reductions in resistance that have, in this instance, real meaning for preventing treatment failure and ensuring that children who receive antibiotics appropriately for pneumonia have a better chance of survival.

Another interesting line of work has surrounded what the future might hold for tuberculosis vaccines. And as many on this call will know, in recent years, clinical trials are demonstrating considerable efficacy of anti-tuberculosis vaccines given post-exposure to prevent progression to active disease.

Recent work by colleagues Han Fu and Nim Pathy at Imperial College London showed additional reductions that can be achieved through a vaccine with this kind of efficacy profile in reducing the burden of resistant tuberculosis cases relative to the status quo continuation of what's going on right now, in terms of treatment and management of TB infections, but also as an additional strategy to

reduce disease burden in conjunction with and sort of supplemental to improvements in the management of tuberculosis infections using the tools that we currently have to reduce the burden of resistant disease.

And what we can see here, looking at the sort of dark red areas on these plots, is that this could be a substantial improvement for many different countries that are listed on the kind of x-axis here beyond what we currently have at our disposal, for ways of containing the burden of resistant disease. So I will stop my screen share there and go back to the panel for questions.

Erta Kalanxhi

Thank you. Thank you, Joe, for that. Very nice presentation and very thorough examples. What do you see as challenges when it comes to addressing these questions at large scale?

Joseph Lewnard

I think at a large scale, one of the fundamental challenges that we have is that we have done very little research on the non-severe spectrum of disease that accounts for the greatest burden of antibiotic use or the greatest fraction of antibiotic use. We, for good reason, focus a whole lot on very severe disease and on the effects of vaccines against various severe disease endpoints.

For instance, for pneumococcal vaccines, most trials have looked at the prevention of invasive infections. For rotavirus vaccines, trials have looked at the prevention of very severe rotavirus gastroenteritis while we have a good understanding of vaccine impacts on these endpoints.

We don't have as good of an understanding of just what pathogens out there in the community are accounting for the less severe disease cases that are very prevalent, very common causes of antibiotic use. So if we want to achieve reductions in antibiotic use, including through vaccination, or other strategies that are really targeted to particular pathogens, we're kind of working from very little previous evidence on identifying what pathogens should be prevented and what the efficacy profile of vaccines might be on very non-severe or even non-specific outcomes such as acute respiratory infection or diarrhea of lower severity.

Erta Kalanxhi

Thank you. Thank you very much for that. Okay. So we'll move along with our next speaker, Dr. Padmini Srikantiah and we have some questions. The Gates Foundation has been a strong advocate of vaccines as a key way to address child mortality. How are you starting to think about vaccines in the context of AMR?

Padmini Srikantiah

Well, thanks, Erta, for the question. And thanks to the organizers for inviting me to join the panel. Congratulations to CDDEP for 10 years of work, advocacy, and research. It's great to have an entire webinar that is solely devoted to vaccines and AMR.

You're right that the foundation has been working on vaccines and vaccines form a central pillar of what the foundation does in terms of its focus on the prevention of infectious diseases and related deaths. In fact, I would say that in our AMR strategy, vaccines are really at the center of it. Prevention of infectious diseases and related deaths are the center of our overall global health strategy and form the basis of our antimicrobial resistance strategy.

I think we heard some really nice examples of what vaccines can do for both antimicrobial resistance and antibiotic use from Joe. And in our work, even over the last several years, much of the work that we've been focusing on in terms of increasing vaccine rollout and vaccine use. Whether it is with pneumococcus, which has actually, as Ramanan pointed out, very early on made a significant impact in not only antibiotic use for invasive pneumococcal disease, but actually reduction in resistant strains. Or for other pathogens, like more recently typhoid, where the typhoid conjugate vaccine actually gained WHO prequalification with a specific indication and a prompt because of rising multidrug-resistant strains in South and Southeast Asia and other parts of the world.

And our enteric and diarrheal diseases team, and our pneumonia team, and other global health teams have been focusing on ensuring that these vaccines are scaled up, rolled up, and delivered to the communities that need them with both impacts in disease reduction and related deaths, as the most central, but also reduction in resistant strains for pneumococcus and typhoid and the potential reduction in antibiotic use that we have seen an increase in data in and a data need that we hope that groups like CDDEP and WHO continue to address.

Regarding antimicrobial resistance strategy, we have now taken that approach and applied it also to some of these WHO priority pathogens. But we also looked beyond just WHO priority bacterial pathogens to include, what are the impacts of vaccines on additional pathogens, including viral pathogens where, as Joe pointed out, there may not be a role for antibiotic use directly. But the addition of a vaccine to prevent a viral illness can make a clear impact on antibiotic use for that syndrome.

One of the examples that Joe mentioned was rotavirus and Ramanan mentioned influenza, which I think is probably the most striking example for which there has been a lot of data for a number of years. There's a great paper from 12-13 years ago now from Ontario where the seasonal influenza vaccination was actually free and given to the entire province over a given year. And they compared antibiotic use in that province to other provinces in Canada and there was approximately 60-65% reduction in antibiotic use just in this observational study. So you can imagine that there's great promise.

One of the other pathogens which is a clear priority for the pneumonia team at the Gates Foundation is respiratory syncytial virus, or RSV, which is a major cause of pneumonia in young infants. And there have been a few different papers recently that show that not only the RSV vaccine had an impact on RSV disease in young infants and related deaths, but also may have an impact on preventing future episodes of lower respiratory tract infections, as well as the incumbent antibiotic use.

Within the AMR strategy, our priority focus is on neonatal sepsis, which we believe this population is at greatest risk for poor outcomes and death related to antimicrobial resistance in these WHO priority pathogens. So, you know, vaccines have always been a central part of our work at the foundation, and now it forms the central pillar of our AMR strategy as well.

Erta Kalanxhi

Thank you for that. You've just touched upon the priority areas, but would you like to add something more?

Padmini Srikantiah

So I think actually in terms of antimicrobial resistance, we are most concerned about the potential excess mortality that would be borne by the most vulnerable populations. This, particularly in low and middle-income countries, surveillance work that the foundation has supported over the last several years suggests that neonatal sepsis or invasive bloodstream infections in neonates in the first month of life are increasingly caused by Gram-negative organisms that are multidrug-resistant, as well as sometimes also Staph(ylococcus) aureus, a Gram-positive organism. Resistant Staph aureus plays an important role and is the most common pathogen and most important pathogen that we see across multiple geographies.

That is, time and again, a leading etiology of neonatal sepsis in low and middle-income country settings: this is Klebsiella pneumonia, which as Hanan referred to earlier, Klebsiella and these other MDR organisms are central to WHO priority pathogens and priority pathogens for the CDC as well as other organizations. For Klebsiella, the data that we have supported to generate, we see that Klebsiella is an important pathogen that is in the causal chain of neonatal deaths and approximately 30 to 40% of neonatal infectious deaths across multiple geographies.

And this is from data that have been generated from the Child Health and Mortality Prevention Surveillance platform, or CHAMPS platform, along with other platforms, including the very important and multi-country study done by the neonatal observational cohort study by GARDP. So our focus now is actually on the development of Klebsiella, particularly the development of a Klebsiella maternal, vaccine. We're at the very early stages of this.

There is, as Hanan also suggested, a potential for a dual market because Klebsiella, as folks probably know, is a very important nosocomial pathogen for adult populations in multiple countries, in low, high, and middle-income country settings. So in the situation of neonates, we believe that the development of

a maternal vaccine given to pregnant women in their third trimester of pregnancy could generate protective antibodies to the responsible Klebsiella strains that are causing sepsis and death. Those would then be passively transferred to the infant through the placenta, and that infant would be protected in that most vulnerable period of time.

So we hope that with, and this is, as I mentioned, something that we're at the very early stages of and a pathway that we're embarking on now, but we do believe that this vaccine approach will have relevance certainly for Klebsiella, for neonates, and potentially for other populations as well.

Erta Kalanxhi

Thank you, thank you so much. Thank you so much for your insights. And we're now going to go back to the World Health Organization perspective. And we have here Mateusz Hasso today, so could you please elaborate a bit on the World Health Organization's strategy on how to understand, articulate, and communicate the value of vaccines against AMR?

Mateusz Hasso

Great, thank you so much, Erta, for the question. And thanks to Ramanan and congratulations to CDDEP for organizing this great webinar. We, over the past few years, are seeing more and more focus on vaccines and antimicrobial resistance. So it's really nice to see and be able to participate in such an event.

And also I would like to extend my thanks to Hanan for describing the environment of AMR and what is taking place at WHO. I'm hoping that maybe I'll be able to give you a bit more perspective as to what it is that we're doing in terms of workstreams. Who is it that we are engaging with? And what is it that we are trying to achieve in the immunization department and WHO?

I think that our work has started a few years ago when there was a clear need from a number of experts, even experts in the vaccine and AMR fields, when the role of vaccines against antimicrobial resistance was not really well understood and articulated and communicated, whether it's within the experts or even to the outside community. And I think there was a call for WHO that yes, this is something that you should probably take an active role in to fulfill these activities, and think of it in a strategic way.

But I think before we embarked on this journey, we sort of asked ourselves, why do we actually need to understand the role of vaccines against antimicrobial resistance? I think in line with WHO's mandate and the mandate of our immunization department, we help to identify what are the diseases out there for which we need to develop vaccines? Then if needed, we facilitate the development, and then once developed, we work with countries to introduce them and help inform them how they could use these potential vaccines.

And I think antimicrobial resistance sort of spans across all of these aspects. So if a stakeholder would understand, what the role of a vaccine is against antimicrobial resistance, for example, a funding agency that would help them to decide which vaccines they should invest their money in, if there is a funding agency that specifically is interested in averting the AMR problem, using vaccines is one of the tools. Understanding the

value would help them to sort of make the decision as to which vaccines they should be developing. Similarly, for a country of origin, they know that they have an AMR problem in the region. They then can look at the available tools to them and say, okay, maybe vaccines could also be one of the tools that we could use to combat antimicrobial resistance.

And then also there was a question of how, for example, if this is just a regional prevalence of antimicrobial resistance, the country or region would know here, we probably need to put emphasis on a vaccine. In other regions, we can continue to use antibiotics that continue to work. So it's really about making decisions about development and making decisions about vaccine introduction and about vaccine use.

So having that in mind, we sort of thought, okay, we need to develop some sort of coherent strategy as to how to best do this. And Hanan has alluded to this -- we had published a document that we call an action framework. What it really is, are sort of guiding principles for us and also for stakeholders outside of WHO to [understand] what sort of actions do we really need to take for this understanding and articulation and communication of the value of vaccines against AMR to be really understood and well-heard.

And we decided to strategize our activity around three areas: expansion of licensed vaccines, development of new vaccines that could have potential impact on antimicrobial resistance, and thinking of data generation facilitating research and producing estimates that could inform us about the value of vaccines against antimicrobial resistance. And I think in line with the strategy going forward, we have a number of workstreams that we are engaging in.

We were recently in close collaboration with the AMR department. We want to understand, firstly, what are the available vaccines out there? The WHO has published a list of pathogens for which we urgently need to produce antimicrobials, we call it WHO-PPL list. We also want to understand what are the available vaccines for these pathogens. So we are conducting a pipeline analysis to be able firstly to understand what it is that we are working with; what are the vaccines that will be coming to the market in the next couple of years. Knowing what the licensed vaccines are and what vaccines will be coming to the market in the next couple of years, we want to understand their value.

So how could we put a numerical value on a vaccine? When we talk about the value here, we have a number of criteria in mind. It's not just a version of antimicrobial resistance, but it's all of the things that are secondary to that. When we think of averting the health burden, so if we have a vaccine for Shigella for example, how many AMR deaths would that vaccine prevent, or what was the economic burden that will be associated with that pathogen that is resistant to a certain strain? And would the vaccine for that pathogen be able to avert a proportion of this economic burden? What will be the antibiotic use that is associated with these pathogens? And again, would the vaccine be able to avert a proportion of this antibiotic use?

So we tried to come up with some modeling estimates and we work very closely with collaborators who are also on this call with CDDEP, with Joe closely collaborating with the Gates Foundation, etc., to be able to put this together in a standardized way to inform decisions about vaccine development, introduction, and use. And I think, all in all, where we want to go with this, to make sure that we are strategic, is we want to make sure that we are reaching some sort of impact.

So when we think about this value and action framework, when we think about this analysis of what vaccines are available and of the strategy that we have developed, we want to link it to impact, so we work closely with the AMR department at WHO to make sure that our work reaches the country level.

With Hanan and her team, we are developing national action plans to combat antimicrobial resistance and access immunization. Folks who want to make sure that vaccines feature prominently -- yes, they can be one of the tools to prevent antimicrobial resistance and we want countries to consider that as one of the tools to combat AMR. We are also engaging with Gavi to make sure that, if possible, the work that we're doing in understanding their value would inform their decisions around which vaccines to invest in and which country should these vaccines go to, taking this AMR perspective into account?

So I think, all in all, we are looking at lots of different angles. We want to make sure that we are encouraging the use of licensed vaccines by understanding their value and we're facilitating generation of data to understand the potential impact of future vaccines that will come to the market. And I think there is a real need to work in collaboration that would never happen if you would have worked in isolation.

So we're working closely with the Gates Foundation, CDDEP, and a lot of modeling consortia. We are aiming to involve Gavi in our work. We're also understanding that it's not just about human AMR. We are also considering other international organizations such as FAO and the International Organization for Animal Health. So we work closely in collaboration to hopefully achieve this long-term impact, which is reducing AMR and the burden that is associated with that.

Erta Kalanxhi

Thank you. Thank you very much, Mateusz. We are moving along well with our questions. So for time purposes, I'm going to merge the two questions I had for our next speaker, Deepali Patel, into one and I think that's going to be okay.

So the question for you, Deepali, is: How has Gavi incorporated the value of vaccines into its decision-making for supporting new vaccines? And how will the new evidence that is accumulating influence your decisions?

Deepali Patel

Thanks, Erta. And thanks everyone at CDDEP and happy anniversary as well. Thanks for this question and hosting this webinar. So I would say Gavi, prior to 2018, I don't think we really thought that much about AMR vis-a-vis vaccine decisions, largely because I think in the global space, the priority was emerging for many stakeholders.

But in our last vaccine investment strategy, we did include, for the first time, a specific indicator that we referred to as impact on AMR in our assessment process. And I think this actually serves as a good signal that we were starting to place more importance on this topic. So let me just take a quick step back, because I'm not sure everybody would be familiar with the vaccine investment strategy of Gavi overall.

Let me just describe that VIS is a process that we use to determine which new vaccines we add to our portfolio of support. So it is our sort of hallmark vaccine decision-making process. We run it every five years and essentially, it's a comparative assessment.

So first, we take a scan of the landscape and identify a list of candidate vaccines. And these would be vaccines for diseases which are of high public health priority and in Gavi-supported countries, which are low and middle-income countries. We then develop an evaluation framework, which consists of a standard set of criteria and indicators, and we'll use that framework to assess the candidates. And then this allows us to see how the candidates measure up against each other, and in some cases, some of the criteria might allow for some ranking.

Usually the criteria that we use, and this has sort of been consistent through VIS cycles, include things like value for money, health impact, economic impact, etc. But as I mentioned, in 2018, we included a new indicator impact on AMR, which we included as part of a larger criteria on global health security. We were really facing a challenge on how we measure this indicator, so for many candidate vaccines, even just generally for other indicators, we often have difficulty in getting good, basic data on disease burden or economic burden per vaccine and per country.

And so you can imagine that, at the time, the AMR burden was particularly hard to identify as well, this made it hard to do a quantitative assessment. We, in the end, did a qualitative one, where we reached out to key experts in the field and we asked them to rank the candidates in the VIS as well as the current portfolio that we supported at the time in terms of what they saw as being the impact on various dimensions of AMR.

So this included mortality and morbidity. In fact, the dimensions aligned quite closely to my case I was just referring to in the value attribution framework. So it was a really valuable and insightful exercise, quite limited by its qualitative nature, which made it quite subjective as well. As conducted, I'm not sure that it lent itself to a sort of make-or-break decision for our process, but I think it really did raise the profile of AMR as an important dimension and then add some important strategic considerations as well for decision making.

And then particularly, I think, not just for Gavi, for our decision making, but also for the financing decisions that countries make as well when it comes to introducing vaccines, in terms of how new evidence might inform our future decision making, I think I see two critical shifts here. The first is that it's not actually just new evidence, but it's also increasing sophistication and the methodology and the ways in which we assess issues like AMR. And so as I mentioned, we face data challenges with our evaluation framework.

In essence, the question that we tried to answer in the vaccine investment strategy is really, what is the value of Gavi investments in any given vaccine, in any of the candidates? The best way for us to answer that question would be, quite directly, identifying the impact in the Gavi countries that we support. This requires having baseline data available on the burden in those countries. It would then also require having an understanding of AMR dynamics by disease, and then being able to model the impact in every country, so, of course, for future investments.

The second best way would be an assessment using global burden metrics, which would be less precise for our purposes, but still helpful for comparative assessment. But you can imagine that it could be confounded a bit by, for example, if the impact is driven by a non-Gavi supported country. So the third way would then be

what I just described that we did in 2018, which is the most subjective assessment. I think we're in a place where when we get to the next VIS, we would be a lot closer to having that global impact understood. And then some cases, also country and regional levels, don't really lend themselves to a more robust indicator much like I just described.

And then the second shift that I see is, I find vaccines currently include quite a few diseases where AMR is already being seen as a concern, where these diseases are driving, or AMR is even driving mortality and morbidity. We look at our current portfolio at Gavi, of course, and we also see these diseases with high AMR burden, but we didn't really recognize that at the time we made the decision to include those vaccines five years ago, 10 years ago, etc. But we're seeing it now that we already have that sort of forward view, so I think that's really critical. We've already seen TB, Shigella, RSV, maybe we'll see a vaccine for group A strep sometime soon as well. So these are the kinds of things that we're seeing in the pipeline, and that's really important.

But I also just wanted to flag that it's not just investments in new vaccines that matter for Gavi; we also invest in increasing the coverage of the vaccines already in our portfolio. And as I said, many of them are also important for the fight against AMR; pneumococcal vaccines, meningococcal vaccines, even as we've already seen, vaccines for rotavirus and other diseases with a sort of broader set of symptoms that result in unnecessary antibiotic use, like diarrhea and pneumonia.

So I think this is a really important consideration as well for us which is the other types of investments and health systems, strengthening immunization programs, strengthening investments that increase coverage. It's sort of at the global level, but also at a country level, because countries also need to make those investments as well. And so I think in general, a better awareness of how AMR costs lives and money is really important and really helpful for building the case for greater investment all around. We really can make sure that it's all children, all people being reached with all of the vaccines that we need. So it's not just Gavi decision-making, but also other donors as well as countries as well.

Erta Kalanxhi

Thank you so much, Deepali. Thank you so much. Now, we actually have about 10 minutes to answer some questions from the audience. And I have one over here that perhaps Padmini could address. The question is: Could the K. pneumoniae vaccine potentially be given as prophylaxis for healthcare-associated infections when there is invasive surgery or high risk of SSI?

Padmini Srikantiah

Yeah, that's a great question. So I think the answer is potentially yes. As others have also pointed out, Gram-negative organisms are an incredibly important etiology that causes a significant number of infections, increased duration of hospitalization, and deaths among those who are hospitalized with healthcare-associated infections across the world, including in low and middle-income countries, but also in higher-income countries.

So a vaccine that targets Klebsiella pneumoniae, for neonates, which would be a maternal vaccine given to pregnant women, has the potential to also be applicable in other settings given in target populations — such as those coming in for elective surgery, or those being discharged from the hospital to long term care facilities, where there are greater risks of Klebsiella pneumonia as an etiology for healthcare-associated infections. I think the evidence that we need to better understand is the strains of Klebsiella and the serotypes of Klebsiella that are the causative agents of sepsis in neonates, and how well that overlaps with the strains and serotypes that are causing these healthcare-associated infections.

And that's an area where the foundation certainly, at least in the neonatal sepsis sphere, is helping to generate data. The data that we have thus far suggests that there is a reason to be hopeful and that there's a reasonable overlap in serotypes, but it's still a road ahead.

And I think, one thing I'll just take this opportunity to add is, in addition to the vaccine development work that we're working on for Klebsiella, the other area that we're also supporting vaccine development for AMR is through our partnership with CARB-X. CARB-X is Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. It's funded jointly by Wellcome Trust, BARDA, Gates Foundation, the German government Department of Research, as well as the UK Government.

While CARB-X has a broad ambition, including therapeutics as its mainstay as well as diagnostics, vaccines do form an important part of the complex portfolio and, in fact, the Gates Foundation support is entirely focused on vaccines. So in that sphere, it is not necessarily focused specifically on neonates in the global sphere, even if our interest is there. I think that there is growing recognition in the product development field as well of the need for support and funding for vaccines for AMR, and a perhaps small but growing number of companies who are working to develop these products.

Erta Kalanxhi

Thank you so much. Here we have another question directed to Joe. The question is about the choice of pathogens, talking about E. Coli. and S. aureus, as both could be very important as they may be a way of entry for resistance mechanisms, especially E. coli with respect to ESBL.

Joseph Lewnard

That's a good point. I think we need to know sort of how the overall impact on the burden of resistant disease is changed by any particular vaccine, including one that could reduce antibiotic use and exposure for commensal organisms that could be harbors of resistance that can be transferred to others, as well as the impact that can be achieved for a more TB-like vaccine, for instance, by just preventing the resistant disease associated with the targeted organism in particular. So I think this is an exciting area for exploration for a lot of different pathogens and vaccines.

Erta Kalanxhi

Thank you. We'll move on to the question. The question is: How do we work closer with FAO and others to approach vaccination for both humans and animals in a One Health perspective?

Mateusz Hasso

I think that's a very good question. And this is very much at the forefront of the agenda of WHO and how we are working closely with other organizations. I think we realize we all know that AMR is not an isolated human problem and we can only address it if we have consolidated action between all the different aspects of health.

We call it One Health and to work in this One Health framework, we have a tripartite agreement between these three organizations. What it means is that WHO works closely with international agencies on animal health and also the UN Food Agency. And when we discuss AMR, we make sure that this is reflected not just in the WHO's mandate but also in the mandate of these other organizations.

That's what's happening at that high level, at a more granular level. I could give you some examples. I know that OIE, which is the International Organization for Animal Health, also considered how vaccines could prevent AMR in the animal world and they were developing a framework to also prioritize vaccine use for animal work. I don't want to speak on their behalf, but I remember there was a report that they had issued from a Paris meeting in 2018, where they actually prioritized which vaccines should be used to prevent antimicrobial resistance in the animal world.

And I think a good example of the impact of this is if we have certain pathogens for which resistance could spread independently of who they infect, whether they infect a human or whether they infect an animal. And any sort of reduction of first of all, the incidence and prevalence and secondly, the transmission between different hosts actually reduces the chance of developing antimicrobial resistance. So this is why a concerted action between animal health, agriculture, and human health is really needed to be able to address that.

And OIE and FAO, they do put a lot of input into the work that we are doing, into the action framework they are partners on. They had reviewed the framework that we had put together. But also in the exercise of estimating the value of vaccines…when we consider the value of vaccines, we presented very much against other considerations such as the context of One Health, so what is happening in the animal world and also what is happening in agriculture to be able to really draw this overall picture of One Health and highlight that this One Health approach is really needed to combat AMR.

Erta Kalanxhi

Thank you. I think we have time for one last question and this one is for Deepali and it's on adult vaccines. So how is Gavi thinking about routine adult vaccines that would be needed to address AMR?

Deepali Patel

Okay, that's a really good and very timely question as we start rolling out COVID vaccines which is sort of our first foray into adult vaccination. Gavi's model is primarily a setup for childhood vaccination and until we introduced the HPV vaccine, we hadn't progressed beyond childhood in terms of our support. So I think this is demonstrating how we're shifting towards more of a course of vaccination. I think there are a lot of lessons we're going to learn about vaccination through the COVID vaccine.

I think the jury's still a little bit out in terms of how we approach this. I think there are probably two aspects that we need to consider, and we would work closely with WHO on this one, which is in terms of existing vaccines, there are certain vaccines for which you need boosters and you would provide boosters through adulthood. For Gavi's support, I think it's something worth thinking about.

And then the second area, which I think is being highlighted with COVID, would be flu vaccination and the seasonal approach for flu vaccination, as well as any sort of pandemic preparedness around that. In 2018, we did approve what we call a learning agenda, which are sort of targeted investments that look at how we can support countries to introduce seasonal flu vaccination for healthcare workers and help to identify barriers to uptake and usability in that sense. So we haven't actually had a chance to roll that learning agenda out yet, largely because of COVID, but we are looking to leverage some of the common vaccinations.

And then similarly, we have seen in some ways, some of the outbreak response for Ebola also includes vaccinating adults, so it's very piecemeal and very opportunistic now. But as and when a vaccine comes to us, we need to think about what is primarily indicated and recommended for adult use. I think these questions around what feasibility looks like will come out of it.

It's probably going to be maternal immunization. First, we have to answer these questions. We would indeed support, particularly thinking of RSV, early immunization. Relevant for this context, we would need to look into the feasibility questions in terms of extending our portfolios.

Erta Kalanxhi

Thank you. I see that now we are a little bit over time. This has been a great session. I would like to thank the speakers for participating in this discussion and like many other organizations, including the ones that are present in this webinar, we're trying to bring attention to antimicrobial resistance.

And I think that today has been a good day for that, so we would like to thank you for attending. Thank you for taking your time, and I also would like to bring to your attention that we have another webinar in this series next month, and that is going to be on the long-term economic consequences of nutrition. So with that, have a great day, and see you next time. Thank you.