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Event

“Accelerating Innovation on Antimicrobial Resistance”

Panel II: Accelerating and Sustaining R&D of New Antibiotics and Technologies

DATE

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FEATURING

Malin Grape
Sweden AMR Ambassador

Christopher Houchens
Director, Division of CBRN Countermeasures
Biomedical Advanced Research and Development Authority (BARDA)

Wolfgang Philipp
Head of Unit
European Health Emergency Preparedness and Response Authority (HERA)

MODERATOR

Krishna Udayakumar
Founding Director, Duke Global Health Innovation Center;
Associate Professor of Global Health and Medicine, Duke University

CSIS EXPERTS

J. Stephen Morrison
Senior Vice President and Director,
Global Health Policy Center, CSIS

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All right. Well, thank you so much for that warm introduction. Pleasure to be here, and thanks also for such strong moderation of the last panel. I’ll invite my panelists up here as well.

Over the next hour or so, we’re going to continue the conversation and focus from what we just spent some time digging into, this transatlantic partnership, the policy perspectives. And of course, we’re going to now also think about how we accelerate research and development that’s so important to the field of antimicrobial resistance and how we think about the ways in which we can make this whole field more sustainable as well.

So it’s a pleasure to be joined here by Dr. Chris Houchens, who’s the director of the division of chemical, biological, radiological, and nuclear countermeasures at BARDA, the Biomedical Advanced Research and Development Authority in the U.S. government; and Ambassador and Dr. Malin Grape, who is the Swedish ambassador for antimicrobial resistance. And virtually we are also joined by Dr. Wolfgang Philipp, who is the head of unit for the European Health Emergency Preparedness and Response Authority, or HERA. So we have some eminent folks here to talk with us.

And to ground the conversation, let’s just get a sense of where we are in terms of the state of the science. We’ve talked about the challenges with the pipeline. We’ve talked about some recent advances that have been made. So, Chris, let me come to you first to help walk us through where we really are with the state of the science for antimicrobial resistance, and what, to you, have been the most important developments over the last several years?

Chris Houchens: Yeah, thank you very much. And, again really welcome – I really welcome the opportunity to be here today to talk about some of the things that we’ve been doing at BARDA, but also especially done on partnerships that have really be focusing on advancing the science within the AMR space.

I would say some of the greatest achievements or some of the greatest efforts and initiatives over the past several years within BARDA, but also amongst our partners, is really investing in novel technologies, novel antimicrobials, to address the issue of drug resistance. So really, you know, we’ve invested for many, many years in the development of small molecule antibacterials. But we really recognize that we have to invest in new modalities to address the emergence of antibiotic resistance by targeting new types of epitopes, new types of mechanisms of actions, and really developing, again, new types of innovative antimicrobial products.

We’ve worked very closely with our international partners over the past several years through the CARB-X accelerator, that is led by Boston University but includes partners at Welcome Trust, at the Gates Foundation,
at NIH, the German, the U.K. governments, and, most recently, the government of Canada. And really, that is focused on innovation. That is looking at new modalities, new approaches to address, you know, the rise of AMR. Not just doing the same thing over and over again, but really looking at new types of technologies.

You know, through that partnership, through that – through that platform, we've invested in new types of modalities, like microbiome-based approaches, phage-based approaches, looking at CRISPR-based approaches as well. But really looking at those types of, you know, interventions, and technologies, and innovations that really can overcome AMR rather than just continuing to invest in small molecules.

Obviously, small molecule antibacterials are always going to have a significant place in the total, the large global armamentarium of antimicrobials. But we really need to tackle this differently. You know, bacteria keep figuring out new ways to solve the solutions that we throw at them, so we need to keep figuring out new ways to counter their counteroffensive as well. So, you know, working through CARB-X we really have made significant investments in those novel types of technologies. We have partnerships, obviously, through our public-private partnerships with small biotechs and large global pharmaceutical companies through our advanced research and development portfolio, where we are also looking at the advanced development of these novel, innovative technologies.

We're looking at also working with our other international partners where we have a shared interest, a shared strategic interest. I'm joined, obviously, by my colleague Wolfgang, who we've had many, many conversations about tackling the issue of AMR and how we can work closely together in identifying those appropriate strategic partnerships. And I would say, you know, where we are well-aligned in terms of making co-investments in product development.

So, you know, it really is focused on the science. You know, again, developing new innovative modalities that counter, you know, the ability of bacteria to continue to evolve resistance amongst – to novel antibacterials. Really kind of advancing these products that are in earlier stage development through our advanced development portfolio. But really, we can't do this without our both federal and global partners.

Dr. Udayakumar: Great. Thank you so much. That’s a good grounding for us. Wolfgang, let me come to you next. From the perspective of HERA, how are you seeing the current pipeline? What are you most excited about in terms of recent developments? And, to build on this idea of partnerships, how has this transatlantic partnership really been valuable in advancing the science? Thanks for the invitation, first of all, and happy to see you all there.
Wolfgang Philipp:

About the pipeline, I mean, Chris mentioned a lot of – a lot of investments that are going on into basic research and development, but also, let’s say, late-stage research and development, which is great. On the other hand, if we look at antibiotics and innovation, in the field of antibiotics I think – and it’s not my personal opinion, but I think it’s widely shared – the evolution of the antibiotic innovation is, to a certain extent, varying. There has been a lack of innovation in the field of – talking about antibiotics. And that simply – that simply means we need to invest more and to re-incentivize research into new classes of compounds in particular. I think that is one point.

Chris mentioned already a large number of areas where investments are going on and where innovation is really at high speed: alternatives to antimicrobials, nontraditional agents, promising technologies – phages, microbiome modulators; immune modulators; antibodies; and so on and so forth. Vaccines is also an area that’s coming up more and more as an alternative to the use of antibiotics for treatments.

But on the other hand, we have seen that great progress has been carried out also in the field of AMR diagnostics, which is supported, obviously, by the development of new technologies or rapid point-of-care diagnostics. That is an area where we certainly need to do a bit more. But on the other hand, it all comes together in the picture that we further need more innovation in the whole field – so not just antibiotics, also in the other fields – although modern technology allows us to make progress in some of these areas.

We need to do these things together. I mean, on the European, I can only talk for the commission, I mean, here. As it was mentioned already before, we have 27 member states. We have research programs that are usually investing into push incentives, so basic research and developments. Under the last research program, there was more than 700 million euros, so about $800 million, invested into AMR research and development. There were also public-private partnerships with industry carried out. There was a joint programming initiative on AMR. And now and in the future we are setting up and investing another up to 100 million euros into a One Health AMR partnership. So there’s a lot of things going on that all goes into the area of research and development.

And then we have a second possibility that is through what we call the health program. Here we can invest more the – into the incentivization of late-stage development of products. We are thinking about collaborations, and have discussed with BARDA about these things and also other international partners. So a lot of – a lot of these things are going on.

The international collaboration is important to avoid duplication, to avoid redundancy, and to drive a clear understanding which are the next areas that
need a fresh push. And that can be done through R&D, R&I, push incentives. And perhaps you can also talk a little bit later and a little bit more about pull incentives, where we see huge potential for – let’s say for triggering the AMR pipeline.

Dr. Udayakumar: Thank you. Great to hear about these new initiatives and the significant investments that are being made as well.

Malin, coming to you, we’ve heard a lot about specific innovations – whether that’s in the therapeutics, diagnostics, surveillance. In your role as an ambassador, you’re bridging the science, and the policy, and the politics. How do you think about all of these pieces fitting together into cohesive policy, and generating political will behind those policies?

Ambassador Malin Grape: Thank you. I think that’s a really important question, of course. Sometimes I get a little bit scared when we talk about all this progress and all these great initiatives that we have, that it might sound too good. Like, what is the problem here? We have so many promising molecules and projects going on, for example. But I would like to go back a little bit to where Julie started the first panel, why do we not see enough engagement in this? Why do we not see enough investment?

And I believe that we have to shift the perspective a little bit. We can’t get engagement despite – I mean, yes, we have these figures now. We have the 5 million associated deaths. We have the 1.27 deaths directly caused by resistance – which is more than AIDS and malaria. But still, it’s too vague. And, I mean, I can’t blame people for not being scared of an abbreviation. We talk about AMR. What is that? So I think this is a really important issue to start with.

I mean, the ultimate goal cannot be to fight AMR, right? The ultimate goal must be to make sure that we have a sustainable access to effective treatment. And this includes not only treatment of common infections, but antibiotics are also the basis for, you know, both the basic health services but also the modern medicine that we know today. So I think this is – I would like to kind of shift the language a little bit and talk much more about access to effective antibiotics.

And now, I mean, AMR is including all microorganisms, while antibiotics, of course, is just bacterial infections. But they do have certain – I think they have a certain place here where we have to focus much more on antibiotics specifically. Not saying that fungal infections, and viral, and parasitic infections are not also threatened by resistance development. But antibiotics are really important.
Dr. Udayakumar: Yeah. Well, thanks. Very important perspective that, as excited as we in this room might get about AMR, I suspect it doesn't quite hold the same interest in a community or a public level. So really, the way we frame this is going to be extremely important. And in that framing, I'm going to build from part of the conversation of the prior panel. We're in this post-emergency phase of the COVID-19 pandemic. We're starting to see a lot of conversations moving in one of two directions – one, around the broader pandemic prevention, preparedness, and response, PPR, and what needs to happen there, with we've heard about the negotiations with INB, the IHRs, and the like. The other place where really we're trying to move this conversation is really talking about resilient health systems and the role of primary care, and how to build those in. Clearly there's – both of those are very important to address some of these challenges that we have identified here around AMR. How do you see this? We heard a bit from the first panel about ways this might be part of the conversation, but it's not readily apparent. It's not clear that AMR surveillance is part of pandemic PPR surveillance, as one small example. How do we be sure that the current policy conversations and financing conversations are aligned between what traditionally may start to break down into verticals again?

So maybe I'll start with you, and ask anybody else to chime in.

Amb. Grape: Yeah. (Laughs.) Thank you. No, I think this is really important. But somehow it surprises me a little bit that when looking at preparing for new pandemics, we – of course, we need to learn from the past. But it's still a little bit narrow, isn't it? When we talk about medical countermeasures, for example, the focus seems to be so much on vaccines while, again, antibiotics are such important countermeasures. And that is – I mean, that goes for both a new viral pandemic, where most often you have a lot of secondary bacterial infection. You will need to have access to effective antibiotics.

But also, the – what we call sometimes the silent, I don't like this very much, but maybe the ongoing pandemic of AMR, or as my colleague Dame Sally Davies used to say the grand pandemic of AMR. (Laughs.) So to me, it's so clear that, yes, AMR is an obvious connection with PPR. And preparedness would include, as you say, surveillance. The one health perspective needs to be there, and it needs to be very well reflected. But also when it comes to access to countermeasures that it needs to be more highlighted, I believe, this conversation.

Dr. Udayakumar: Yeah. Chris.

Dr. Houchens: No, I think it's a wonderful question. You know, so BARDA was established, as many know, back in 2004-2005, to really focus on developing countermeasures to address CBRN threats, emerging infectious diseases, and
pandemic influenza. And really underlying all of that are the secondary bacterial infections that are driven by drug-resistant bacteria. And so, you know, as part of our ability to be able to, you know, effectively respond to any sort of pandemic in the future, we need to ensure that we have effective, novel, innovative antibiotics that are able to address, you know, those secondary bacterial infections.

As a result of COVID too, we also saw, as Julie pointed out, that, you know, many people were able to, you know, overcome or survive, you know, infection by SARS-CoV-2, but then succumbed to the secondary bacterial infection. So we need to make sure that, you know, effective drugs, effective antibiotics, you know, are part of that ability, part of our response capability and part of our response armamentarium to any sort of public health emergency, including pandemics.

One of the lessons learned out of COVID-19 is that, you know, we have to have not just products that are available to respond immediately to an event. We also need to ensure that we have capabilities that allow us to quickly evolve the development of new products, new medical countermeasures, to stay on top of or stay abreast of, or to continue to evolve with an emerging threat. So it could be a novel emerging threat or it could be – like SARS-CoV-2 was back in January 2020. Or, it could be the emergence of resistance against currently available therapeutics.

So we've made significant investments over the past several years – actually over the past decade or so on platform capabilities that allow us to rapidly respond by developing new vaccines and therapeutics to an emerging threat, and also to the emergence of resistance against currently available antibiotics, and currently available medical countermeasures. But I think we're going to – I know we're going to be taking those lessons learned, and a lot of those platform capabilities as well, and applying it to the AMR space going forward.

Because the – you know, the traditional timeline to develop a new antibiotics from discovery to licensure, you know, can be a decade or more. So that doesn't really bode well when you're trying to stay on top of, you know, the emergence of resistance in a bug that doubles – you know, has a lifespan of twenty minutes, and is able to, you know, generate resistance within a few years after a new drug is introduced to the market. So we need new ways, new platform capabilities that allow us to rapidly respond and develop new therapeutics, new antibiotics, new antimicrobials that are – that we are evolving, you know, those new – those new products along the evolution of resistance in the bacteria.
So I think those are, you know, two areas that, you know, we’re really focused on, is ensuring that we have, you know, effective products immediately on the shelf to be able to respond to the secondary bacterial infections that occur following any sort of public health emergency or pandemic. But also, ensuring that we have capabilities that allow us to quickly discover new types of antibiotics or antimicrobials to an emergent event. And, you know, kind of going back to what I was mentioning earlier; some of those new capabilities are things like, you know, CRISPR/Cas technology, ssRNA, you know, microbiome approaches could be another way as well. But really looking at innovative approaches, rather than just small molecules.

So the other thing that we’re doing also at BARDA is really making significant investments in new types of, you know, in-vitro approaches, like micro-physiological systems approaches that really help us to compress the timeline from discovery to development of a new, effective product. So really kind of taking an all-hands approach ensuring that we have these capabilities, these countermeasures available to be able to respond immediately. And, if we don’t, being able to compress the timelines in which we go from a new bug to an effective, safe therapeutic as quickly as possible.

Dr. Udayakumar: Yeah. Thanks. Great perspective. And thinking about platforms that are ready and then how quickly you can mobilize them towards specific threats.

Wolfgang, let me bring you into this conversation as well. Obviously at HERA you’re looking at health emergencies, broadly defined. And where do you see this intersection between AMR and pandemics and PPR more broadly there?

Dr. Philipp: I think – I think definitely what this pandemic has taught us is that we are able to react quickly and that we are also able – if we collaborate at a relevant international level, that we are able to develop countermeasures and also ways on how to react – how to prepare, first of all, and then to react to potential pandemics.

When it comes to AMR, it want to come back to what Malin said. Obviously, I mean, innovation and access, this is just one part of controlling, potentially, AMR. You mentioned awareness. You mentioned surveillance as a very important point, stewardship, IPC measures, and a couple of other policy pieces. And that is, obviously, something we should not forget.

It is a very broad approach that requires a lot of, let’s say, resistance to keep ongoing, no? So it is not just that huge investments into the – into the R&D or R&I side would potentially bring a major – the major breakthrough, but it is absolutely required. We in HERA, we are responsible for the development – like BARDA – for the development and availability of medical countermeasures to potential threats. And for us, AMR is one of the major – one of the three top – three top priorities on which we focused in the first
years – in the first two years of existence our investments when it comes to research and innovation, and also when it comes to development.

So it’s very important that we continue – that we continue on our side, ideally in a, let’s say, aligned approach with other funders and with other agencies or entities that support research and development or R&I into AMR, that we do this in an aligned way: First of all, to gain – to gain speed; secondly, to gain time; and, thirdly, hopefully to be, let’s say, more productive and more successful than we have been in the past 10 years.

Dr. Udayakumar: Mmm hmm. Thank you. Also very helpful to understand that broader perspective.

Let me perhaps now broaden the aperture a bit. We’ve been talking mostly about this transatlantic alliance, while recognizing that antimicrobial resistance is a global problem. And in fact, the greatest burden that we’re seeing in deaths, morbidity, are in low- and middle-income countries. Recognizing that the principles may look very similar, but the health system context, the populations that are affected, might look quite different based on geography, how do you see – Chris, let me start with you – the understanding more globally of the burden influencing priorities in terms of how you’re making decisions on R&D, on the science, what problems you’re taking on in this broad field? And also, how you’re designing new products and technologies to be fit for purpose where it might be most needed?

Dr. Houchens: No, it’s a wonderful question. And, you know, I would say that obviously through BARDA we have, you know, a perspective on developing and delivering, you know, effective medical countermeasures to address the U.S. population, but we understand that AMR is not a U.S. problem. It’s a global problem. And so we need to be able to ensure that we are – you know, we are developing products that are available across the globe, and effective across many populations across the globe, because, you know, being able to address, you know, AMR in other parts of the world are going to ensure our national health security preparedness here in the United States as well.

So we do take that – you know, keep that in mind in terms of, you know, developing products that are going to be effective across a range of populations. One of the things that we do with a lot of the partners that we develop antibiotics with is we support, you know, large, global phase three registrational clinical studies, so that these products are being evaluated in populations across the world. So that we want to ensure that we have products that are – you know, that are going to be able to meet our accessibility requirements as we get these products approved.

And that’s important for us for a number of reasons. One, again, because AMR is a global problem. You know, we’re not just concerned about the U.S.
population. We want to make sure that these, you know, products are effective, you know, to all different patient populations. But also, you know, products that have, you know, I would say, just a U.S.-centric focus for a U.S.-centric market really doesn’t do – really, I would say, hampers us, because, you know, as we understand, you know, the sales volume of antibiotics are so small. And even here in the United States, in which it is one of the – you know, it’s a large consumer – it is still a very small market for any drug development company or any company that’s developing antibiotics.

So we want to ensure that we are assisting companies to help to develop these products that are going – and get them into global markets so that we are able to, you know, ensure that there is global access and a global market for these products that these companies are going to be able to – be able to sell to a large market, generate the revenue that makes them – allows them to be sustainable.

One of the things that we’ve learned over the past, you know, several years, and I would say that we’ve been a bit chastened by this, is when we established our antimicrobials portfolio back in 2010, we had, you know, naively assumed that once we developed, you knew, new antibiotics that there was going to be an instant market for them, and that these products would be out in hospital formularies, and pharmacies, and in the hands of physicians, so that the products would be available if we ever needed them to address secondary bacterial infections or even biothreat infections. We learned after, you know, investment in, you know, numerous companies and hundreds of millions of dollars that after these companies got products approved, that the companies failed because there was no market for them.

So we are really looking at working with our international partners, partners like – you know, like HERA, like Wellcome Trust, like GARDP, like the Action Fund, SCARDA, which is the Japanese health agency, as well as with the European Commission, looking at how we can partner together to ensure that we are developing markets, looking at innovative approaches to develop markets or solutions that would allow us to have a global market for the accessibility of these newly approved antibiotics. So that, again, we’re not just focused on the U.S. market, we’re focused on the global market that allows these products, these companies, to be sustainable, you know, long after they get products approved by regulatory agencies.

Dr. Udayakumar: Yeah. That’s great. And something we learn over and over again, it seems, is that you actually have to design products from the beginning for where they might most be needed and where they’re used. And trying to translate from one context to another is often – sometimes more difficult than the science of developing the product themselves.
Malin, let me ask you, how do you see this transatlantic partnership really serving a global leadership role? How do you partner with more low- and middle-income countries to think about global solutions?

Amb. Grape: I think that’s extremely important, of course. And Sweden being part of the European Union, that in itself, of course, is a very important collaboration that we have. As you heard, we are currently the president of the Council of the European Union. This is coming to an end very soon, next week. But – and this was not the first time that we highlighted AMR on the agenda during our presidency. So I think this is – and the transatlantic collaboration and the global collaboration on AMR was also something that we highlighted during our presidency.

So what we did – I mean, we were fortunate enough to have started really early. Just as a very brief background, Sweden banned the use of antibiotics for growth promotion in animals in 1986. Twenty years later, we convinced also the members of the European Union to do the same. Our national stewardship program, which is named Strama, has been quite famous for its success. That started in ‘94. Since then we have had an uninterrupted decrease of antibiotic consumption in humans. So of course, we’re lucky enough we started earlier and we do have lots of experiences in this.

But what we wanted to highlight now during this presidency is antibiotics also affects and is affected by what is happening in the world around us. But I would also like a little bit to come back to the interconnectedness between the development and the access. Because – and we also wanted to illustrated this, because, you know, this is not a linear process. It’s not like you start with research and development, and we make sure that this candidates come all the way through the pipeline, and in the end we have them on the market, hopefully accessible to everyone.

But as long as we use antibiotics, we will also have a development of new resistance. So we wanted to illustrate this in a circular way, that this – you know, we will never be rid – we will never have the drugs that we need. And this goes very much together with the access to existing antibiotics because, I mean, to save the ones that eventually will become developed and put on the market, we will have to have access to all the existing and still effective ones.

And Sweden, U.S., the EU are not the only ones suffering from, you know, stockouts. The weak production supply chains affects us all. But we also suffer, and especially, I think, small markets like Sweden, with successful stewardship. We are not interesting markets. We also suffer from market withdrawal. Still affect the antibiotics that we would need to keep in the toolbox. So and this, of course, goes together with the use and the surveillance.
So this circle, and the weaknesses, and the possible solutions of this entire circular chain, this was something that we make it an expert meeting also during the presidency, where we really digged into many of these weaknesses and the possible solutions. So I mean, this is a lot of experiences that we have now. We have a lot of options already on the table. We don’t need to invent so many new things. But I’m convinced, and this was one of the conclusions from this meeting, that we need a comprehensive package of different solutions. One pull incentive will never be enough. It’s not going to be strong enough. But we have to really look at the weaknesses and see what to do along this chain. So end-to-end approaches is what we’re looking for here.

Dr. Udayakumar: Yeah. Thank you. Really important to understand this idea of sustainable access, right? And love the idea that it’s not a linear approach, it’s much more circular than that.

Wolfgang, let me ask you in this idea of sort of global perspectives, how have you thought about a portfolio approach? And what you’re prioritizing, what you’re trying to look at investments into, to try to understand how you can support global, equitable access more effectively.

Dr. Philipp: A portfolio approach is certainly a possibility. Guaranteeing or contributing to support global access more effectively, that requires, certainly, leadership role of certain countries. It requires also – we have heard about TATFAR earlier. That is not enough. It goes beyond. It is also about Asian countries, where a lot of – a lot of activities are going on – Southeast Asia, Japan, and so on and so forth. So there is a lot that can be done, but the implementation needs a good level of coordination. That’s one thing, coordination.

And second point is, obviously, financing, because at the end of the day, when it comes to access, we are talking about – when it comes to access, we are talking about funding and we are talking about also pull incentives to get, let’s say, better our new products through the pipeline and to make them available to all countries across the globe, including low- and middle-income countries. So what HERA is doing – I mean, Chris mentioned already a couple of points that would apply to us at the European Commission. What we are doing more specifically is we’re supporting, for example, CARB-X that was mentioned, but also another initiative which is called SECURE, and both initiatives are contributing to improve access to antibiotics in low- and middle-income countries.

And when we then go down in analyzing a little bit better what these initiatives are doing – these and other initiatives are doing – it’s very interesting to see how the details are sorted out, that – like, for example, licensing; like, for example, tech-transfer agreements which – (inaudible) – and certain antibiotic producers.
So what we need to have, at the end of the day, is funding. We need coordination. And we need political leadership that trickles down to operational leadership.

Dr. Udayakumar: Thanks. Very important points there, including this idea of pull incentives being really important.

And let's maybe dig into that a bit more. We've talked a lot about how do you create the science, how do you push the science through the R&D pathways? And of course, when we talk about pull incentives a lot of times in other aspects of health we talk about demand generation. And we've talked already about many of these products, especially antibiotics, being different. In that, we're not trying to increase volume. We're trying to make sure that there's access and stewardship at the same time. How have you seen – are there effective models to try to make sure that there are pull incentives, that there is creation of a functional market, or at least addressing market failures in ways that are able to balance access and stewardship?

Malin, would you like to get us started?

Amb. Grape: Yeah, I can start. No, as I said, I think it's really important to have a package and a comprehensive approach. But you also have to try something out, right? We've been talking and talking about all those different models. We do know that we somehow would benefit from delinking volumes, say, from revenue. Obviously, from what you say, that we need to use as – we need to lose not as little as possible, but as appropriate as possible, I would say. So what we have done in Sweden is to pilot a partially delink model, which is a revenue guarantee model for reimbursement of access to antibiotics now.

So this is not – it's not designed as a pull incentive. It's designed as an incentive for access. And again, because, you know, we have to do something to get hold of these new important antibiotics in Sweden. We will not have them on the market unless we do something differently. So we tried this model. We just concluded this pilot. It was reported two weeks ago. There is a report published. Unfortunately, in Swedish, but there is a summary in English you may find interesting reading that. (Laughter.) And, I mean, these experiences, even though this was for access, I think they could be really valuable when we go together and look at how to expand and how to move on.

So we are also looking to work closely together with the EU Commission, and especially here, of course, on this revenue guarantee model, and together with other countries. We are also fortunate enough to being connected now with the Canadian initiative and the pilot there. So we very much look forward also to follow this and to learn more from their experiences.
Dr. Udayakumar: That’s great. Chris, you’ve talked a bit about public-private partnership. That’s a good bit of what you do. We all know there’s never going to be enough money to do everything we hope, and we can really only substantially address this problem if there’s private capital. And there has to be some sustainability related to that. What are the ways that you’ve been able to source in private capital to help support this field?

Dr. Houchens: Well, the funding for the – for the most part, the funding that BARDA to product developers is non-dilutive funding. I mean, we do have another arm of BARDA called Ventures, which provides, you know, equity-based investments in a companies’ developing countermeasures, or technologies that address BARDA’s mission space. But, you know, as kind of focusing on the AMR field, you know, all the funding that we provided over the past 15 or 16 years has been non-dilutive funding.

And what that does, it – you know, whether it’s through our advanced development portfolio, whether it’s through our – I would say, our post-licensure portfolio, in which we use a different pot of money called Project BioShield money, or even if it’s in our earlier pre-clinical development portfolio, which is really largely supported by CARB-X, or managed by CARB-X. Every dollar that we invest into a company to develop a new product often results in private equity coming off the sidelines and investing in those companies as well.

You know, I’m not sure exactly what the metric is right now, but a few years ago when we ran the analysis of the CARB-X portfolio, we saw that, you know, for every dollar that BARDA – or, that every dollar that BARDA invested into CARB-X, there was about eight dollars that was pulled in, you know, from the private sector to support the development of those antibiotics. We haven’t seen an eight to one match necessarily in our advanced development portfolio, but we do see that often when we are working with a small biotech company and making an investment into that company, that does open up additional capital or access to capital for those small companies.

Also for large pharmaceutical companies, they’re often looking for private investment. But when we invested the development of a candidate with a – you know, that’s being developed by a large pharmaceutical company, that company will then often provide additional resources because they see that they are getting non-dilutive funding as part of this partnership – this private-public partnership.

And so, you know, it really has – I would say that the public financing, the public funding of AMR research and development has really, you know, served as a – you know, I would say, a mechanism to allow other private
investors and other private equity to start coming into the development of AMR. So we see that as a positive. Obviously, we haven't addressed the failed market. You know, not enough capitalists coming in off the sidelines – private capitalists coming in off the sidelines to really sustain, you know, this area. But with the companies that we work with, it has been hugely beneficial.

Dr. Udayakumar: That's very good to hear.

And, Wolfgang, how have you thought about the financing innovation that has to match the innovation in the science to make this more sustainable over time?

Dr. Philipp: We are a young organization. I would just like to remind us of this. We are thinking about possibilities apart from push incentives – so apart from investments into research and development – but to look more on the pull incentive side. So that's one possibility.

First thing we have done is to run a study, basically to explore various options for implementing pull incentives for antimicrobials through different procurement mechanisms, such as revenue guarantees, market entry rewards, milestone-based rewards, or a combination of revenue guarantee and market entry reward. So there is a lot of – a lot of different possibilities here.

I think it was mentioned already reports, data, and proposals are available – largely available. But what we found is that, based on a revenue pulling effect of each mechanism, depending on the size of the report would be ranging from 700 million euros to 3 billion (euros) per antimicrobial developed. So these are big triggers, and that's certainly something that, let's say, one entity could hardly support. So what we are doing now is with EU member states to see how far we could establish a network to support HERA for the interpretation for one or for some of these chosen schemes.

We're also thinking about – and that is part of a recently revised pharmaceutical regulations in the EU – about transferable exclusivity extension vouchers. Sorry for that, long name. Basically, what it says, it's to provide a higher reward to developers of novel antimicrobials that could be used to protect – to protect the – to incentivize access and to protect other products than the antibiotic when buying such a voucher. So that's another idea.

So there's many elements out there. We heard something from Sweden. We know about many of these things. But at the end of the day, it comes with investments. And we have to see what is the – what is the – let's say the most effective way in pulling some of the good products which are currently also
in the pipeline and with a higher technological readiness to see what is the – what is the most appropriate way of doing it. There will be not the usual one-size-fits-all, but probably adapted models that we need to use.

Something else that HERA is also setting up now is a way of providing loans to companies that work also in that area. That’s what we call HERA Invest. That is going to be a top-up to an existing program run by the European Investment Bank. And we hope also to attract additional donor funding to that scheme and not just incentivize development of further vaccines or other medical countermeasures, but also of novel antimicrobials.

Dr. Udayakumar: Fantastic. Great to hear about the breadth of options being pursued or experimented with there. Thank you.

I’m going to come to the floor in just a minute, so if anybody has questions please do let us know. And there’s a microphone in the back. But first, Malin, I want to come to you. We’ve heard a couple of times now about some recent progress in the EU with leadership from Sweden, including this transferable data exclusivity voucher as part of council recommendations more broadly. Tell us a bit more about how that came together and what that package actually looks like.

Amb. Grape: Yeah, thank you. And just to be very clear, the transferable voucher is not concluded yet. So that’s part of the pharmaceutical legislation that will be negotiated probably for quite some time, because it’s a huge package, the revision of this legislation. But what came with this former package but also, as Ingrid mentioned, this legal instrument which is called council recommendation. And this is what we were really happy to be able to conclude during our presidency. So even though we have a really short time, thanks to the constructiveness and the cooperation with all the 27 member states, we managed to conclude these negotiations. So this was agreed by the health ministers in the council last week. So we’re really happy for this.

And this legal instrument, it reflects, as Ingrid touched upon, the broad spectrum of AMR work, including surveillance, stewardship, infection prevention and control, but also some of these elements of access and pull incentives that HERA would take lead on. So we’re really happy that what was discussed during this high-level meeting in Stockholm is also very much reflected in this council recommendation, including the work on international collaboration on the global level. But what really – what I’m really happy about also in this, and which I think is really promising also for the high-level meeting in the U.N. General Assembly next year, is that the 27 member states actually came to an agreement on specific and measurable targets on antibiotic consumption and on resistance.
So I think this is really promising. And to me, this is also what we will need some kind of measurable targets, concrete and tangible targets, to work for – in the political declaration of the high-level meeting of ’24. So I think this was promising. Of course, I do understand that the 27 EU member states is just one small part of the entire world. But also when we talk about targets, we should think very carefully about how to design these. And, I mean, the focus of this panel has been access to new antibiotics and development. So why not put a target, for example, on the number of new and really novel antibiotics meeting the public health needs on the market within a certain time period, for example?

So I think it’s promising. I look forward to – both through the EU, but also as Sweden collaborate with the U.S. and globally partnering with both institutions and countries to really strive for ambitious commitments in the political declaration of next year.

Dr. Udayakumar: Wonderful. We certainly need that. Thanks.

We have a question. Please introduce yourself and direct your question if it’s to –

Q: Is it live? Yes, OK. Hi. My name is Erin Duffy and I’m with CARB-X. We’re a global implementing partner of BARDA in the early development space for antimicrobial products.

And I just wanted to touch on two topics that I’ve heard throughout this and give a little perspective that we’ve seen. And the first is the number of products in the development pipeline today. So since 2017, from CARB-X, we’ve put 13 treatment and prevention products into human clinical trials. And nine remain active. And while that number may sound large, in fact there’s almost no overlap among them in terms of the syndromes and the pathogens that cause them that they target. And I think that’s really important, because as we move these and we understand attrition, it’d be great if they make it through to a point where we have them on the market, but I think it would be foolish to think that they alone are enough. So I think that’s comment number one.

Related to that is that only one of those products of the nine that are active can be considered a traditional small molecule antibiotic. And so we’ve talked a lot about, you know, innovation and novelty. And those are wonderful, and certainly we need those for resistance. But one thing that we haven’t talked about today is what is needed to take them through to approval by a regulatory body. And this is an area of serious global interaction and collaboration that is just starting to happen. I see our colleague, Michael Craig here from the CDC. Michael took a leadership position last year, in concert with the FDA, to encourage a conversation, a
global conversation, around meaningful endpoints. And I think we need to do this if we’re going to see these novel products really come through.

The second thing, and this is a more positive thing, I think, that I’d like to end on. And this goes back to the earlier conversation about what we may take away and enhance in lessons from COVID. So this year we had an omnibus solicitation with three distinct funding themes, all meant to bring products focused on the global need. I’d like to say that in those three themes – which are actually pretty narrow in their focus – we had about 240 unique global expressions of interest to these calls.

And so the innovation is out there. And of those, importantly nearly 100 of these were diagnostic developers who brought COVID products from every level of the health care system, from reflex tests at the highest level down to, you know, true point of care tests, and everything in between. And I think we need to capitalize on these before we lose them. They’re out there, and we need to work with them. So thank you.

Dr. Udayakumar: Great. Thank you so much. Fantastic to hear about some of the work that partners here have also supported. It sounds like we’ve got a growing early-stage pipeline, which is fantastic to hear about. Some questions, of course, of how do you push that through to late-stage development, regulatory review, and authorization. Anybody want to take that perspective? How should we look – how should we think about regulation in the context of access and accelerating R&D?

Dr. Houchens: Yeah, I mean, I can take that too. I mean, we work very closely with the FDA in really mostly, I would say, a product-agnostic manner, in which we talk about regulatory challenges for the development of new innovative technologies that really don’t have a well-worn path towards regulatory approval. So we try to identify what are going to be the significant challenges or even, I would say, the opportunities in the development of these novel, innovative, new types of technologies that are being developed by organizations like CARB-X, that are going to advance into the clinical development pipeline of BARDA, for example.

At BARDA, we have a significant number of subject-matter experts who have spent, you know, most of their career in drug development in the industry, and then they come to BARDA and they share their expertise with us, and also with the companies that they work with. And, you know, they participate in all the conversations that we have with the FDA. They are looking at lots of different – and sitting on the development programs for lots of different products, and lots of different innovative products. They are hearing what the FDA is saying across the board with regard to challenges, regulatory challenges for the development of these products. And they can use that collective wisdom to be able to, you know, inform our product
developers. You know, again, not about any specific product, but just in general.

These are the things that the FDA’s been looking for. These are the data sets that the FDA is going to need. These are the clinical end points that the FDA is going to want. And being able to communicate that back and articulate that back to our developers helps to kind, I would say, minimize the risk. It doesn’t reduce the risk to zero, but it – I would say, it reduces the risk of technical and scientific failure, because we’re working in concert as – you know, between us, BARDA, as a funder, our industry partners, the developers, and then the regulatory agency. So we’re all talking together, we’re all working together to ensure that we are, you know, identifying risks as early as possible and trying to mitigate those risks before they become, you know, issues that just can’t be solved. So that’s one of the ways that we do it.

Dr. Udayakumar: Please.

Amb. Grape Can I have a very short comment? Look, I think – I really agree that the regulatory aspects are so important, and maybe a bit invisible in this. So I would also just like to mention that during the last week of the Swedish EU presidency, the Swedish Medical Products Agency will actually hold a meeting inviting regulatory agencies from around the world for a best practice sharing and experience sharing. And this is aimed to also launch a network – a global network of regulatory agencies. FDA is, of course, invited, and I hope they will participate. So this could be one way. And I do think that there is also probably a need to increase the engagement of many of these regulatory agencies in different parts of the world. So this is something that might contribute a little bit to this also.

Dr. Udayakumar: Sure.

Wolfgang, anything you’d like to add to that?

Mr. Philipp: Yeah, just one point. I mean, we have seen now in the COVID – in the COVID pandemic it’s possible that regulatory agencies work together very closely and also discuss what the colleagues said, for example endpoints, and agree on certain schemes. So why should – why should it not be possible for novel antimicrobials or antibiotics?

We talk to many, many companies that come to us and say: We have something good in the pipeline. We don’t know how to go through – into clinical trials. Normally, they would talk also to the European Medicines Agency. But at the end of the day, I think it’s very important that the leading – the leading regulatory agencies sit down and develop a concept on how to do that, in particular when you’re talking about very scarce products that
might not end up anywhere – very far in the clinical trials. So a big plea for that.

Dr. Udayakumar: Excellent. There’s much more we could delve into. Unfortunately, we’ve run out of time. I’d love to thank our speakers in the second panel, Dr. Chris Houchens from BARDA, Dr. Wolfgang Philipp from HERA, and Ambassador and Dr. Malin Grape from the Swedish ambassador for AMR. Thanks for your wonderful insights. I think I leave here certainly optimistic in terms of the state of the science, the ability that we can continue to invest.

Clearly, we are increasing the tools we have in our arsenal, whether it’s on the technical side with the early pipeline or on the collaborative side, and testing out new models of public-private partnership, as well as really thinking about the financial innovation that’s really going to be necessary to create sustainable markets and global access. It’s also quite clear that for us to make real progress we’re going to need much more coordinated, comprehensive approaches that really look from R&D all the way to access and stewardship. So I’d thank all of you for participating, and really for your leadership in moving this important field forward.

With that, I’ll thank everybody for joining us, and hand back over to Steve Morrison to close the overall session. Thank you. (Applause.)

J. Stephen Morrison: Thanks, everyone. It’s been a rich morning. I think Krishna did a terrific job of summarizing what we heard today. We came together with the thought that the transatlantic alliance provides a very important mechanism and a lens for looking at this problem. And I think we’ve confirmed that. There’s a lot of common purpose, a lot of muscle and capacity, common frameworks. And we know the trick now is really to try and get higher level political leadership committed to this, to reach publics better through communications, to have a much stronger coordination and metrics and accountability for performance, and to reach beyond the transatlantic alliance to the broader community of states.

I was very encouraged by what we said about thinking bigger in terms of R&D to platforms, reaching beyond small molecules, taking the lessons from COVID and applying those here. And I think we’re going to have a lot more to think about as we look downstream 14-15 months to the 2024 AMR high-level meeting which, I would assume, many of the ideas and challenges we talked about this morning are going to figure in the deliberations leading up to that, and the preparations, and trying to set goals as we look forward.

So thank you all for being with us here in person, remote. And special thanks to all of the presenters on the two panels, and to Julie Gerberding and Krishna Udayakumar. And we’re really grateful. We’ll be posting the video shortly with a transcript. And so please look for that. The Director General
for Health and Food Safety Sandra Gallina has recorded a message for us, which we will incorporate into that product, which you’ll see as we post it. So thank you. And we’re adjourned. (Applause.)

(END)