TERMINATING SUPERBUGS: HOW NEW TECHNOLOGIES CAN FIGHT ANTIMICROBIAL RESISTANCE

Announcer 00:00

Thank you for joining us. Please welcome the panel to the stage.

Jomana Musmar 00:03

Opa! That's for good luck. Good morning, everyone. Thank you so much for joining us today. Everyone can hear me. We're all miked up. We're good. All right, excellent. My name is Jomana Musmar. I am the former executive director of the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria at the US Department of Health and Human Services and currently the CEO of the AMR Strategic Coalition. It's a new group of experts that serve in the same capacity of that as the PACCARB, but without the federal element to it. And so, I'm honored to be here with this group of panelists here. I'm honored to have this conversation to talk about antimicrobial resistance, which is a problem that we all know is not going away. It is an issue that is exponentially getting worse on the daily. The problem is, is that we're not connecting the dots. We need to be able to open our eyes and open our ears for us to see the progression of disease, the progression of resistance from the human health side of things, from the animal health side of things, and from the environmental side of things. And I am honored to be here with this lovely group of experts here that are going to discuss innovation and how all of the solutions that each of the different areas and expertise that are provided here are helping to contribute to the solutions to the problems that are exponentially growing. So, joining me here is Lord Ara Darzi. He is a professor and the co-director of the Institute of Global Health Innovation at Imperial College in London, and the executive chair of the Fleming Initiative, followed by Dr. Tom Frieden over there. He is the previous director of the CDC, the US Centers for Disease Control and Prevention, and the president and CEO of Resolve to Save Lives, and he just published a book on The Formula for Better Health, and you'll tell us the rest of the title, it's about saving millions and saving yourself as well. And of course, with me, the lovely Dr. Akhila Kosaraju, is the CEO and president of Phare Bio, and she's a biotech social venture pioneering the use of generative AI to discover novel antibiotics in partnership with the Collins Lab at MIT. And lastly, Dr. Andrew Hemmert is the senior VP of molecular research and development at bioMérieux. Thank you so much for joining us. So we're

going to have a conversation, folks. We're going to talk about things, anything that you would like to ask, I know that there's a QR code that's going to show up at the end. So please be sure to ask those questions, because we're going to build in a hefty amount of time for Q&A at the end, and there it is on the screen. All right, so we're going to start with Dr. Frieden. You're our CDC guy. You know everything about prevention. You know everything about infection control. Tell us about your personal experience, starting with antimicrobial resistance. Back in the day, you'd hear about it, a few stories here or there, incidences, highly resistant pathogen. Nightmare bacteria existed. But tell us about the incidence now, and how is the progression getting worse? And of course, elaborate a little bit on your 7-1-7 Alliance that is addressing surveillance and prevention overall.

Tom Frieden 03:25

Thanks so much, and it's great to be here with everyone. I look forward to learning from the other members of the panel. As you mentioned, I just published a book The Formula for Better Health: How to Save Millions of Lives—Including Your Own. All proceeds from the book go to support programs and organizations around the world fighting antimicrobial resistance and other leading health problems. The formula is an approach that has been proven to have saved millions of lives and to have stopped antimicrobial resistance, and can save millions more. And the approach is: 'See', 'Believe,' 'Create'—three steps. 'See' involves diagnostics, molecular diagnostics, figuring out trends. We need to look way past numbers of cases to see the molecular trends. When I was head of tuberculosis in New York City, we had the largest outbreak of MDR-TB the US has ever experienced. We did the first community-wide molecular epidemiologic study of the community. We found that there were actually 31 distinguishable outbreaks within the resurgence, and each of those needed to be stopped. So you need to see the invisible, which is the public health superpower. We could also see that they were being spread in hospitals. That was the 'Broad Street Pump,' and then believe progress can be possible, first by recognizing what's been done in the past, because there has been progress. We definitely need new drugs. But at the same time, we can do a lot with what we've got. When I was CDC director, Dr. Arjun Srinivasan, a wonderful CDC expert, came to my office and said "We have a problem. CRE is spreading. We don't have treatment for it. It may be the end of antibiotics in this country." We sounded the alarm, hospitals, with the help and mandate from the Center for Medicare and Medicaid Services, ensured that hospitals had much better comprehensive infection prevention and control, and CRE dramatically decreased. 'Believe' means phased progress to build optimism. And then, 'Creating' a healthier future means organizing, prioritizing, figuring out what's going to work best. Simplifying, because only simple approaches scale, and then communicating well and overcoming barriers, including the economic barriers to development and distribution of new antibiotics. So, there are definitely ways to reverse the spread of AMR, and it's going to require a balanced portfolio of prevention, including infection prevention and control in hospitals, which are often the main generators of drug resistance. It includes vaccination. You know—we think about some of the pathogens that were resistant, pathogens spreading, and now with vaccinations, they're much less of an issue. Antimicrobial stewardship, new antibiotics, and better diagnostics. You know, if you could know at a glance what a patient has, you could be much more specific with the antibiotics that you use. So I think not only is all not lost, but we have reasons both to sound the alarm about the possible loss of one of the greatest achievements of humankind, but also to be optimistic, and that's part of the 'Believe,' part of 'See,' Believe,' 'Create' because we have controlled drug-resistant infections, there are really exciting new ways to treat and diagnose that we're going to learn about, and I think we can look forward to a much healthier world.

Jomana Musmar 07:19

Thank you, Dr. Frieden. Fantastic level setting. So, I'm going to pivot over here. Andy, the 'See' component of what he's talking about. Personally, I believe that diagnostics are the cornerstone of being able to actually see and then also believe. Because, not only does it help the patient on an individual level, the 'do no harm' tenet that I always remember Dr. Sabiha Essack in KwaZulu University in South Africa. 'Do no harm,' is the foundation of, for every physician. But at the same time, diagnostics help promote that, because you're able to specify, and you're able to treat appropriately with that said, tell us a little bit about what bioMerieux is doing. How you work on things within that tenet, from the patient individual level, but also contributing to the population level, because that's when you get to the 'Believe,' when you see the data.

Andrew Hemmert 08:08

Right, right. Thank you, and thank you. It's what an honor to share this stage with all of you. Thank you, Dr. Frieden, for your comments on diagnostics. I've been spending my whole career working on diagnostics, on creating novel diagnostics, for a variety of diseases. And so, I think at bioMerieux, as well as other companies in this space, we are in the process of making really comprehensive, sensitive, and specific diagnostics readily available in every health-care setting—whether it's in large hospitals to even the point of care. And as I think about how we're going to fight AMR and how we're going to fight the superbugs, there's multiple fronts. There's the fronts of the very difficult to treat [inaudible] bacteria, but there's also the fronts of that all of us experience annually, which is going to your care provider because you have a respiratory infection, right? The amount of antibiotics that are prescribed in that point-of-care setting, it's astronomical, most of which are not needed. So I think about when we have these tests, comprehensive, fast; I think these are some of the descriptions you had, very sensitive. They are becoming available. Just recently, bioMerieux launched what is called our SPOTFIRE system. It's a comprehensive molecular diagnostic test for up to 22 pathogens in 15 minutes. So by the time you've seen your care provider, they already know, certainty, what you have in terms of a respiratory disease. And what was interesting is in the sore throat data we saw—so these are patients who were enrolled because they met the criteria of having a suspicion of a sore throat or a pharyngitis—only about a quarter of those would have benefited from antibiotics. So with that information, you have rhinovirus, you have adenovirus, you have parainfluenza—maybe if you still need to give them something, give them a prescription for orange juice, right, so they could go home and rest. But as these kind of data now become available in the point-of-care space, more adoption of that data, it actually creates massive data sets. I think about—we have millions of tests that are run annually, all looking for a lot of pathogens and a lot of different diseases. Bringing these data together now starts to get into our surveillance aspect, and we have some really cool cloud-based applications in which we can look at the respiratory landscape across the United States and see the data in real time. So we're no longer weeks behind the ILI prediction. We're real time data. Here's what's trending. We can see the influenza start to come up. We can see parainfluenza start to go down, or RSV spikes. So these data are now becoming broadly available from all of the molecular tests available. So I think it's a really exciting time to be in diagnostics with the tests coming. I highlighted the point of care. There's, of course, equal to more tests available within the hospital setting. But I think all of these data that are emerging are going to

be really powerful, and I'm excited to see how we start applying AI to these data sets to give better prediction of what diseases do we need to be targeting, as all as well as what treatments are appropriate.

Jomana Musmar 11:05

Awesome, perfect transition. So now we're going to go to you, Akhila. Tell us about how all of this data helps your work and what you're doing and the innovations that you're doing at Phare Bio, because you guys are doing some pretty cool stuff. And so tell us how AI is contributing to all of this and analyzing what he's talking about, but also creating new ideas and partnerships.

Akhila Kosaraju 11:25

Well, thank you for including me that in this incredible panel. Just so admire everyone on this stage. So, in terms of the data, so that's absolutely essential to what we're doing at Phare Bio. And just to take a step back, at Phare we're using AI, and most recently generative AI, to design novel classes of antibiotics that address the most drug-resistant pathogens, like Acinetobacter, Pseudomonas, Klebsiella. And this really was launched off the backs of the first ever discovery of a novel antibiotic using AI in 2020. This came out of my brilliant colleague, Jim Collins's lab at MIT. And once we kind of caught wind of the potential of this. So, you know, kind of, you can think back to that period of time, which was, you know, very difficult time, of course, for everyone worldwide. It was also predating this entire cycle of AI, you know, videos talking about how it has changed every aspect of society. At that stage, we are really trying to address a problem with a solution that seemed to have efficiencies and scale and precision like never before. So in terms of the data aspect of it, our models are only as good as the data that we're using to train them. And not only that, we really feel that data is the entry point to lower the barriers to entry for other folks to start training their own models and start re-emerging in the antibiotic field. There's one statistic that I think has always really struck me, which is that there are only 3000 researchers worldwide that are conducting R&D on antibiotics. Now, with AI, we think we can really democratize more researchers entering the field. We're open accessing our data at Phare Bio. We expect by mid-next year, we'll have a portal that anyone can go on to interact, maybe even in a chat, interface, to start learning about and training their own models to really reinvigorate the antibiotic pipeline. So, I think this will take a collaborative approach, but one that also, we think, technology will have a really central part to play.

Jomana Musmar 13:33

Thank you, Akhila. And so, Lord Darzi, we're doing a lot in the US, okay, and so I know that we've always had a very strong alliance with the UK. Tell us a little bit about the current US-UK relationships, how all of the work that's being done here is contributing to the UK, and helping advance movement and mitigating the threat of AMR.

Ara Darzi 13:53

Thank you. Thank you for having me. I'm probably the only one on this panel who is not a microbiologist or, at least an interest, in infectious disease. I'm a surgical oncologist. Let me just take you back in my own personal history. The age of five, I went to see my general practitioner feeling unwell, and sent home and three days later, I was admitted to an intensive care unit in a lower and middle income country. Intubated, and I was ventilated for six weeks. And according to the records that my mum gave me, I had a blue leg, and they were thinking about amputation.

Jomana Musmar 14:34

Wow!

Ara Darzi 14:35

I had, in those days, meningococcal meningitis, which was missed. But, there was a miracle drug which is just coming into the system, and that was called penicillin, and that is what saved my life. Now, that was completely irrelevant to me as a six year old, because I was dumb, and you never look back as a child. Until about, move forward, nearly two and a half decades later, I was very fortunate to be appointed as—I was, I'm a cancer surgeon, by the way, surgical oncologist—and I was appointed at St. Mary's Hospital. And I was operating one afternoon in the first month, where someone told me next door to you, there was a chap many, many years ago in 1928 called Alexander Fleming, who discovered penicillin. So that hit me second time after my—and that's really how I got involved in this. And I think I don't have to rehearse to the audience here. We have a serious global health issue, and you have to remember antibiotics underpin any other innovation that you have heard of this morning or any other session in this room. It is a force amplifier. You cannot do transplantation without having a proper battery of antibiotics that are available in case of an infection. You cannot treat a cancer patient with immunotherapy for the same reasons. This is a serious global health issue. This is our defensive systems. We've gone fantastic, really well, on our offensive medications. We could do gene therapy now. We could do immunotherapy now, but our defensive investments, like antibiotics and the prevention of infection, has been sadly, left behind. And as a result of that, under the patronage of His Royal Highness, the Prince of Wales, and his father, by the way, King Charles, His Majesty, also had quite a big interest in AMR because of the association with Fleming. We've launched this global campaign. Our approach is slightly different. I'm a scientist. I'm a fellow of the Royal Society, and I believe in science. I wake up for breakfast for science, and go to sleep for science. The challenge we have, science alone is not going to address this problem. A significant part of it is behavioral. So we've combined the three pillars to go to war against AMR. First is the science, and I'm happy to share with you some of the work we're doing with Deep Mind in predicting evolution and the transformative impact on AI in this area. Diagnostics. You have to remember, 60 percent of antibiotics prescribed, we don't know what we're treating. Blindly. As a practicing physician, 60 percent of prescriptions, you don't actually know what you're treating. We have to do something about diagnostics. And the second is engaging the public in this debate. And it's not just in human health, by the way, it's in animal health. You probably know 80 percent of the meat you eat in this country is fed on antibiotics. If you go to other parts of the world, it's not dissimilar. So we have to do something about engaging, informing, and empowering the public. And finally, policy and regulation. You know, the regulation is the tail wagging the dog. We need to be a little bit more creative when it comes to that. And I think policy in

terms of funding diagnostics. My great friend bioMerieux, we just talked about it. You can't compare a $10-12 diagnostic test to pennies of buying antibiotics. You know, it's just illogical financially. So the Fleming is bringing it all together, making it global. Delighted that we have a center in the US. Johns Hopkins is going to lead the campaign in the US. We have a center in Hong Kong, entering into China through the back door, if I could use that word. India is one of the complete basket case, if I could call it. They take antibiotics for cleansing. It's not like just treating an illness. So we have to do something about that there. So a global initiative for a global health challenge.

Jomana Musmar 18:56

Thank you. And you know you touched on a lot of points in terms of how we face this. And I know we discussed focusing on solutions, but I think it's incredibly important that we discuss the problem and how we amplify how big of a problem this is. Because we have the solutions in hand, and the problem is that because we're not hearing it from the side that doesn't believe that the problem is there, the solutions aren't getting taken advantage of, and the solutions, unfortunately, need funding and they need support to be able to do that. So in terms of messaging and amplifying things, what has been successful in the UK in convincing leadership and decision-makers about how big of a problem this is. I mean, the WHO just released its surveillance data, just recently. One in six bloodstream infections is resistant to antibiotics. One in three UTIs is resistant. One in three! That's ridiculous! Do you have any idea how painful it is to have a UTI and then deal with it afterwards? It's fascinating! And these numbers are not going to go away. They're getting worse. And any physician or anyone that works in a hospital in general will tell you that resistant infections are a huge problem for them. This is not something that's an afterthought anymore. It is a day-to-day occurrence. And so what are we doing wrong in the US that we need to be able to connect the dots a little bit more, so that our messaging is stronger, to show that this is a problem that is loud enough that requires your innovation, your diagnostics, and your trifecta solution on how to do things.

Ara Darzi 20:35

Well, for me, this is a system problem. It has a demand and a supply issue, and people have focused on the supply end, we have to reduce the demand end. And the demand you can only do by engaging the public that every time you get a sniffle, you don't need antibiotics.

Jomana Musmar 20:52

100 percent.

Ara Darzi 20:53

You also need to reduce that from a clinical practitioner's perspective. You don't want to take a risk not to give an antibiotic, just in case something goes wrong. So the misuse of antibiotics is on both ends in

providing, because of that demand. So it's a demand issue. We need to do something about that. Animal health is a demand issue as well. You know, it's your livelihood as a farmer is dependent on that. How could you separate the two aspects? Is there another pipeline that we can use in animal health, rather than the supply side? Listen, we're living to through an unbelievable time in science. I've never been so excited. I'm just reaching a retirement age, and thank goodness, you know, I could stay for a few more years. It's transformative, absolutely transformative. You know, working with the likes of you know, just the idea of being able to predict resistance based on the genotype and phenotype of the infective organism and the host is transformational. It's going to be unbelievable. You know, intelligent prescribing by a doctor is supposed to be intelligent start off with but giving them with that those tools is is—

Jomana Musmar 22:12

An efficiency. You're adding to their efficiency.

Ara Darzi 22:15

Absolutely phenomenal. So, we it's—there's no better time to hit this, to hit the nail in the head in terms of AMR.

Tom Frieden 22:25

I totally agree. At the same time, if we see what's driving it, it to a great extent, it's misaligned incentives. And the 'tragedy of the commons,' right? The tragedy of the commons is that for any doctor patient interaction, you know, the path of least resistance. Prescription just takes a moment. Explaining why you don't need antibiotics, takes a long time. And the way we pay for health care, the way we pay for innovation, the way we pay for diagnostics and treatments, is leading to a situation where we are grinding through not just the past, but potentially, the future antibiotics that become available. It's not easy to correct tragedies of the commons, because it means trying to convey the importance of the public good, and that's not easy. So there are some creative economic models, but ultimately, many of these questions are political questions. There are things that can be resolved diagnostically. If we have a low-cost diagnostic that says it's viral, it's bacterial, that's going to help a lot. If we have low-cost diagnostics that say it's resistant, it's not resistant, that's going to help a lot. But we still can't lose sight of the economic drivers behind the crisis, because only by identifying who wins and who loses? Who can make decisions that change those drivers? What are the moments of possibility for those changes to be made, and who will be the most effective advocates, and what are the best partnerships to make that happen? We'll still be having the same conversation years from now.

Jomana Musmar 22:25

Go ahead, Dr. Frieden.

Jomana Musmar 24:19

So on that Dr. Frieden, though, and you mentioned something really critical, which is demand versus supply. The typical pharmaceutical model for any company to survive is high supply, high demand. I make money, I stay alive. You're talking about the inverse, right? Which is what our problem is when it comes to companies going through what's called the 'valley of death'—you have an innovative technology, you've got all this government support and subsidy, and then you get to the point of to commercialize things, and there's no buyer. And so how can we partner differently? What can we do? Because we have to shift the framework when it comes to being able to support these innovations that still need to put, you know, food on the table and make a profit to continue. What other models are there that we can talk about?

Ara Darzi 25:06

Well, there are many models. Let me give you an example how I engaged Big Pharma on this debate in relation to Fleming. I went, and I'm not going to name them, I went to couple of very senior players, the CEOs of these companies, and I just wanted to see the top three pipeline of new therapeutics coming through. And at the end of the conversation, I said, you do know none of these are going to work if you have a resistant infection and you are not investing in antibiotics. And that did catch the phrase, there is a lot of worry that the new pipeline of therapeutics in other areas may be compromised because you're not able to treat an infection in that pathway of care. So they're—they are listening. They're gently, gently listening. But you also need the public side, the public sector, meaning governments. This is a health security issue at the end of the day, I mean, my hat down to David Cameron, who brought this to the G20 nearly 20 years ago, and it was since then, there was the creation of the Fleming Fund in the UK. The recent government just dissolved the Fleming Fund, right? So we have to, you know this is, you have to frame this in a way, this is not just the private sector issue. This is the government's. This is a health security and public sector has to underwrite that risk.

Jomana Musmar 26:28

Right. And it goes back to telling our story and being able to connect those dots to show that we are talking about compromising modern medicine all together. This is not a single pathogen issue. It's not ugly like Ebola. It's not the sexiest thing in the world, but you're talking about an enterprise of pathogens, not a single issue. And I want to talk about diagnostics as one of the key solutions to that, though, Andy. Because, they help tell the story, right? And so like in a surgical procedure, in oncology treatment, there are some certain nightmare bacteria that we're concerned about, but we also need to be able to tailor what those antibiotics are for these immunocompromised patients. And so tell us a little bit about, I know you guys have these Antimicrobial Stewardship Centers for Excellence, right? Because you're able to further promote, teach, and address at least the messaging component to providers on what to do and what not to do.

Andrew Hemmert 27:26

Yeah. So you know, as I mentioned earlier, my career has been in the development of these rapid diagnostic tests, which is an integral part of antimicrobial stewardship—

Jomana Musmar 27:34

Huge—

Andrew Hemmert 27:35

But the diagnostic test alone, it's fine. Someone can run a test, that test results sit somewhere, someone, the physician maybe gets it at some point, maybe the next morning. Really, what we found, and this has been demonstrated in the literature, and there's a recent great meta-analysis showing that you have to pair it up with the Stewardship Committee. So an antimicrobial stewardship program combined with RDTs, or rapid diagnostic tests, is extremely powerful in terms of reducing length of stay, improving mortality, getting patients on the right drug as quickly as possible. So one thing we started to do at bioMerieux, is we have some centers of excellence throughout the world that are committed to antimicrobial stewardship, and so we partner with these centers in that we bring them together on an annual basis, and we let the groups work together to help teach each other on what is working well and what isn't working within their institution for stewardship programs. There's a lot of guidance everywhere. Great guidance from the CDC, great guidance from WHO on stewardship programs. But putting it into practice, all the different players that have to be on board with that stewardship program for it to be successful, it's extremely challenging. It's not just the laboratory, it's not just the pharmacist or the clinicians. You need all those folks, in addition to the payers, in addition to the administrative staff, all in alignment and believing that these stewardship programs are valuable. They have tremendous impact, but getting it working is very difficult. So we bring these teams together, we let them co-create, share best practices, and our hope is that by learning from each other at these different centers of excellence throughout the US and Europe and South America and Asia, that they're able to help each other solve the problems that they have in getting their stewardship programs off the ground and then making them sustainable. And so we we provide the venue to bring them together, we provide support. And then what we're seeing now is these—the outputs of these meetings, are being turned into publications, into posters, the information is getting out, and we want that shared more broadly. We believe it is such critical component to fighting AMR, not just the RDTs, but then how do the RDTs get used?

Jomana Musmar 29:44

No, that's tremendously important, and we have to be able to continue these conversations with everyone so that we could teach about appropriate use. Because even if we can have the newest antibiotics in the world, things evolve. It's not like it's a one slam dunk solution. And folks, please make sure that you put in your questions. We're about to reach the Q&A session, and I'd love for all of us to engage and talk a little bit more about this. Akhila, tell me a little bit about one of the biggest highlights that Phare Bio had done,

which is the three novel classes that were found by a partnership, by the partnership that you have with MIT. Because I know this was a great announcement earlier this year, so it was really fun to see that coming out of MIT. Tell us a little bit about that and how you contribute to that solution, because we still need—even though we can find out what the solution is, it's nice. You have this resistant bug, where's the antibiotic to go with it? Knowing about it is one thing, but treating it as an entirely different thing as well.

Akhila Kosaraju 30:39

Absolutely, one of the areas I think, is most exciting is, as Lord Darzi mentioned, you know, this idea that now we're even aggregating data on resistance, you know, using genomic tools, all of that feeds into AI models. And so you start to see this force multiplier effect. And, you know, get to your question. So these three novel class of antibiotics that have been developed, it was really a fairly simple model And just to geek out on the technology for 30 seconds, the way we train our models is not the LLMs that you see, you know, are constantly probably interacting with at this stage. These are graph neural networks that learn from chemical scaffolds what chemical structures are best able to kill which particular bacteria. So initially, our partners in Phare Bio, we trained models that were a few thousand, 2,500 compounds or so, tested them against E coli, or tested these compounds to see how efficacious they were against that bug. Binarized our models, if they killed more than 80 percent of the bacteria in a petri dish, they scored a one. If not, it scored a zero. And then our models learned actively, and then were able to predict for previously unknown antibiotic properties across broad repurposing libraries. The reason I mentioned that is that alone, that predictive capability, led to these novel discoveries. And I think there's this sense that, oh, everything's already been discovered in antibiotics, and to some degree, we were recapitulating that because many of the compounds we were looking at had a lot of prior [inaudible]. There's difficulties working with it from an IP perspective and other reasons. But that also forced us to innovate even more. And so now we've moved from predictive to generative AI, and that's because somewhat, we weren't finding as many compounds as we wanted to push forward, capabilities were moving faster than the available data. So what did we do? We decoupled our discoveries from the available data. With generative AI we're now using a similar process to train our models, but instead of predicting for antibiotic properties, we're actually designing these compounds de novo, in silico, in these computational models. I think this is an extraordinary application of AI writ large, and I think this also unlocks an orders of magnitude more creativity. The last thing I'll say about it is, clearly, I'm very technophilic. I'm very optimistic that this can chart a new future for antibiotics. One of the reasons is that the creativity of generative AI is now we can now couple that with constraints. So we can take all of those liabilities that we were having in our early discovery work, incorporate those into parameters that we can now train our models on toxicology, oral bioavailability, pharmacokinetics, put those filters into the training of whether a compound actually kills a bug, and now basically ask our models to tell us, does—is it toxic? Will it actually be administrable in a non-hospital setting? That's going back to one more aspect of this panel—that's enabling partnerships. So what I think is unbelievably exciting is that our work lives and dies on partnerships. Partners are coming to the table with us now, way earlier than we ever expected, because they want to define what we're training our models on, because we're getting closer to this bespoke indication targeting capability that was entirely surprising to us. We now have multiple partners that we hope to announce some of those partnerships in the upcoming weeks, where we've defined that this is the unmet need that's also commercially viable. We will train our model together. If our team is able to hit certain criteria, our partners will take those compounds forward. That's unprecedented, and I think again, without the technology, we couldn't take

this end-to-end approach. Energize both the science and also energize the economics. So again, I'm probably too optimistic.

Jomana Musmar 34:29

No, I love that!

Akhila Kosaraju 34:30

Technology could be a really key part of the solution. But I also think, you know, it's a bright light across AI and impact.

Jomana Musmar 34:37

It really is because you talked about something really important, which is also the financial barrier part of things, right? That you're getting companies that are coming. You're talking about taking data, information, and discovery into now, hopefully development, so you're already transitioning into that second phase. Talk to me a little bit about how, and I don't know how you could frame it, but what are the finance barriers that you're actually saving companies on so that they're able to extend their life through development and hopefully get to commercialization?

Akhila Kosaraju 35:07

That's a great question. So I think the key thing that we are saving in these partnerships is building bridges to nowhere. So I think there's actually been tremendous science in antibiotics, but a lot of early stage assets sort of die on the vine, or they are taken forward. A lot of investment is pumped into them, and then ultimately the there's a, you know, an understanding that they actually weren't that commercially viable. So instead of another IV for MRSA, for example, we now are working with our partners to say, okay, if you develop an oral drug for MRSA that actually is both an unmet need and it's commercially viable, let's train our models on that. So instead of sort of—we're sort of flipping the narrative, flipping the science, instead of just seeing what's coming out of our pipeline and then trying to advance that, we're being very targeted about both what's an unmet need but also what's economically viable. I think that's incredibly important in AMR, not to pump hundreds of millions of dollars into programs that may ultimately not succeed, not because of the science, but also because of the economics.

Tom Frieden 36:09

On the economics issue, one of the real challenges is the medications that work well are the drug companies nightmare, because you only need a few doses. So that's a real economic challenge. A second

economic challenge is that the way they deal with that is to charge a very high amount per dose. But the groups that may need the most can't pay for that because they're in lower-income countries. At the same time, you don't want those antibiotics to fall prey, victim to overuse and rapidly get—engender the development of resistance. So if you had a tiered pricing model where you say at the outset, yes, we'll partner with this group, but you've got to sell it at cost in lower-income countries that meet certain requirements for stewardship. That might be a model that allows it. And remember, some of your funding comes from the taxpayers at ARPA-H, and so taxpayers end up paying twice, once they develop the drugs, and second, for the drugs themselves. And some of the hostility to the pharmaceutical industry, currently, is a resentment of the high prices. So you've got a nest of really complicated issues that a technophilic approach may have difficulty addressing. It's your word. I learned three words from you this today, binarize. It's a great word!

Akhila Kosaraju 37:48

Well, I think just a quick comment on that. You know, we're clearly addressing, or attempting to address, the early valley of death, the traditional valley of death in biotech discovery to clinical trials. The second valley of death, these complicated, sort of unintuitive economic dynamics. In some ways, we're almost using—we're so far away from that, that we're not able to sufficiently have these comprehensive approaches and solutions that we want to be a part of. But I think that probably we're not able to fully take on. So we hope to replenish the pipeline with novel antibiotics, with novel mechanisms, and rely, frankly, on folks like you all to carry the water beyond that.

Jomana Musmar 38:31

Go ahead.

Ara Darzi 38:32

This is brilliant work. No question, identifying new assets, new drugs. I think there's another transformative role on the AI side, is understanding the evolutionary pressures. And, you know, we tried that during COVID. Could you predict the next mutations that are coming through, the next variants? Remember the variants question? Could you do that in and you can, there's no question you can. And the ability to start, then, reprogramming whatever the word might be, or redesigning your therapeutic pipeline based on the evolutionary pressures that you might anticipate if you have again, back to the genotype and the phenotype of the infective organisms. That's the piece of work that potentially could even lead, a piece of work doing with Flagship Pioneering, is there such thing as a resistible antibiotics? Should we have an aspiration like that? Well, why not?

Jomana Musmar 39:28

Yeah, no, I think the possibilities are endless, but it brings up a point. We are a society that is reactive, not proactive, right? And so Dr. Frieden probably be the first person to tell you that you're constantly putting out fires and doing your best to make sure that the fires don't start to begin with. So based on your experience, Dr. Frieden, and what you've done, and also the successes in the UK, because you all were one of the first to actually apply a pilot a program on incentives, the delinkage model, that's able to promote these companies and not let them die in that secondary valley of death, to get them over the line. What can we do to make that message louder for decision-makers again, to show that if we can, we have a hard time saying it's a problem now, as opposed to us telling them it's a problem 10 years from now. So how can we bundle that message in a way that actually resonates? And what do decision-makers need to say? All right, we need to pump the brakes, because we already have data that shows that it's going to cost trillions of dollars. We have data that shows that millions of people are going to die. And so what are we missing from our messaging to be able to show that cancer, childbirth, any surgery, immunocompromised patients are all suffering and going to suffer even further. So what's the secret sauce? Solve it now!

Tom Frieden 40:57

I'm sorry to say this, but chapter eight of my book, in specific detail. This is not a unique problem for AMR. This is a general problem for public health. Public health is structurally the underdog, because what we do is good for everybody a little bit, and will cost some people a lot, and that's an economic model of concentrated costs and distributed benefits. The political scientists talk about that all the time. And to address that, you identify four things, who are the winners and losers, who are the deciders and influencers, who are the advocates and the organizations that can advocate, and what is the timing and the pragmatic path to progress. And with that, you can figure out, you know, where are there wins and when. And those wins sometimes are, or the window of opportunity for progress can open in a day and shut in a day, even within the same political party. But there are ways to activate the groups that will win from a change in the status quo and to mitigate the opposition of those who will lose from a change in the status quo. Now that's a very theoretical answer, but I think the practical details will depend on the country, the time, the politics. But there are lots of opportunities to make progress, but we don't make progress just by saying, oh, there isn't enough political will. You know, it's that same rigor that we apply to detection and to treatment and to epidemiology, that same rigor we need to apply to the political economy and the barriers behind progress on public health issues, including AMR.

Jomana Musmar 42:57

No, I'm so glad you mentioned that, because really, and let's just talk about the elephant in the room in the country, that our messaging needs to change. We have to adapt strategies. You have to think differently. It is not business as usual, and so partnerships are a huge part of that. And part of what we're doing as part of our AMR Strategic Coalition, is tweaking our messaging surrounding antimicrobial resistance to be able to adapt to the administration's priorities today. That's a window of opportunity. Look at what those priorities are, looking at what the administration's main points are, and being being able to adapt your message and tailor what you can provide and add value to what their priorities are.

Tom Frieden 43:40

One thing to add about messaging, I think in health and in public health, we're often very reluctant to talk about progress, because if we talk about progress, it sounds like we're saying, "mission accomplished, enough, done, foot off the accelerator." But I think actually the opposite is possible, that by showing progress, we can show that more progress is possible. I haven't seen, though it may well exist, some analysis of the benefits of—there have been some recent antibiotics, and the counterfactual of what would have happened if those had not been discovered. Certainly, we can talk about control of antimicrobial resistance and what might have happened if that hadn't been accomplished. So I think, I think part of this messaging is not just the "sky is falling," but there are ways that we not only can make progress, but have already, and we can make more.

Jomana Musmar 44:32

Yes, we're definitely in a "sky is falling" fatigue mode, so we need to be able to kind of transition. Go ahead.

Ara Darzi 44:37

But just don't underestimate industry's role here. I have raised $200 million in the last two years.

Jomana Musmar 44:43

You're really good.

Ara Darzi 44:44

Yeah, well, I'm not good, and I have zero credibility in the subject matter. I'm a counselor. There is a desire to come, as long as it's structured, it has outputs. It has clear sets of metrics and how you're going to measure the performance. And they include industry have come in, philanthropists have come in, and government has come in as well. And the end of the day is the market pressures who will drive this. But if you can take it as a global initiative, the tragic fact is, the big global conveners are weaker than they used to be, so you have to find another way of addressing or at least filling the gap.

Jomana Musmar 45:29

But you mentioned an important point, which is these lateral partnerships, right? Government's a component, and in the absence of as much government support, we have to think very differently about a) how we approach them, but more so, how we hold hands together to be able to advance what we're

doing. Talk about doing different things, and look beyond the sectors and the domains that you typically approach. We all have a common thread, particularly as it relates to antimicrobial resistance, right? It doesn't it's not just strictly human health. There's a huge animal health component. There's a huge environmental and agricultural component, and we all have the same concerns. So we're a little bit—please put in your questions. We're about to get to Q&A. This iPad's empty. Please fill it up. But I do want to, and I want to prepare our panel here, because I want our audience to have a takeaway. So please think of a call to action, either on an individual level or on a community level that we can have people take. So let's, let's see what's in here. So I don't know if I'm doing this wrong, but this iPad isn't populating. Can anybody here help me? But if anybody here have a question? Yeah, okay, go ahead, because I don't see anything.

Audience Member 46:39

What is the role of telehealth in AMR where not 60 perecnt but 100 perecent of prescriptions are written without the test results that would typically care?

Tom Frieden 46:58

Yeah, well. First, I think it's a question for more than just me. The telehealth is one of the few positive things to come out of the COVID pandemic. The advance in telehealth, and it is dramatically changing the practice of medicine, and it should change it even more, because we want to make things easy for patients. There are some video diagnostics that are pretty impressive. I mean, we're not there yet, but, but we're getting close, so at least you could say yeah, you need to come in, or yeah, you need to go to your local diagnostic facility for this. I think, more broadly than AMR, the biggest single challenge and opportunity going forward is strengthening primary health care. It's a disaster in the US, 100 million Americans don't have a primary care provider. It's a disaster globally—50 years after Alma-Ata, most people in the world don't have a primary care clinician, and that would deliver most of the benefits of modern medical care. And I know in the UK, you've had some issues with the NHS, which was formerly the national religion I understood it, relating to primary care, and I think telemedicine and AI have the potential to dramatically improve both the efficiency and quality. But in terms of AMR, there are, as with many things, both risks and opportunities. But any thoughts from your standpoint?

Andrew Hemmert 48:35

You know, I think telehealth is incredible, right? Not everyone lives in densely populated areas to where they could see a primary care provider. But that does need to be combined with rapid diagnostics, and so having more accessible solutions to either bring the diagnostics into your home or to have a sample be picked up and delivered to a rapid testing center. I mean, it sounds fanciful, but the drone comes to your house and picks up your nasal swab and takes it for a testing center, right? It's not inconceivable that we're at a future to where maybe Amazon is doing this. So I think it needs to be combined together, and those rapid diagnostics comprehensive are available and they are fast. So it should be combined together. And when you get that approach, I think we'd really change what you actually do with your primary care provider, if you could have that kind of interaction be more easily accessible.

Jomana Musmar 49:24

And I will also comment, so within the Council, we had a presentation from CVS Minute Clinic and a lot of other providers that provide the telehealth feature—their stewardship practices are on point. They are very, very meticulous when it relates to antibiotic prescribing. They want to make sure that they have the right guidelines in place, because they don't want to be able to contribute to an ongoing problem. And like you said, the delivery of rapid diagnostics right now, the evolution with AI and being able to analyze the data faster, whatever that looks like, and also but deliver it, like you mentioned, with all these new. Technologies we're getting there, we just need to push a little bit faster before these bugs get us. But in any case.

Audience Member 50:08

The challenge is really market access. So we built a platform for doing rapid diagnostics in conjunction with telehealth with Mayo Clinic. And Lee Fleischer, who's here on one of your panels, actually helped us identify that there was a labeling issue, that the OTC tests didn't support use of the results for clinical decision making, and that same device approved or cleared with labeling for point of care allowed the exact opposite. So you could use the results for clinical decision making, but not self collection outside of point of care.

Jomana Musmar 50:40

Yeah, go for it.

Ara Darzi 50:41

Yeah. One area might be worth to look at is sexual health. For some reason, that's worked, certainly in the UK, it's worked. Why did it work? What are the incentives there? The privacy issue drives that. So there might be other lessons learned.

Tom Frieden 50:56

Yeah. You know, in one low-income country where they used an extensive telehealth service, 40 percent of all visits were sexual health visits, and you know you can understand it. You don't want to go to the health center where your sister-in-law is the nurse.

Jomana Musmar 51:15

So apparently, I do have questions. My apologies if you sent it. It didn't refresh in time. But now I have it, so I'll just there's one question here about culture data. So in the hospital, culture data with antibiotic sensitivity studies take days to result, leaving the patient on on broad coverage. How do we speed up this process to ensure narrow, targeted antibiotic use occurs earlier?

Andrew Hemmert 51:37

Yeah, so there's some—you're right, culturing does take a long time, and there are still many diagnostic methods that require culture confirmation. However, there are a number of new technologies coming out that once the culture is either completed, it's say a blood culture is ringed positive. You can run it on a MALDI you can run it on a rapid AST platform. You could run it on a genotyping platform that gives a profile of the AMR targets. So there's a number of new technologies. And then as we look further ahead in the future, with next generation sequencing, we're going to be able to get the full profile, and not just what's under the street lights that we have today. So it does still take time. I appreciate that, but I can see in the future, and even today, there are more rapid methods post culturing that will allow for the change in antibiotic, hopefully, at that second dose. That would be the point to where you're in the hospital. They're on empirics. You get to that second dose, you have the profile by that point to then get them on the right antibiotic.

Tom Frieden 52:35

There's a flip side of that, which is that as we get the culture independent diagnostic techniques, we're losing some of the genotyping. So until we get the whole genome from the specimen itself, we have a real risk of losing sight of some fundamental epidemiologic issues. You're right.

Jomana Musmar 52:50

So I want to ask a quick question, though, can we bring the price down on rapid diagnostic tests so that they're used more? And what can we do to bring them down?

Andrew Hemmert 52:58

It's a great question. I get asked that all the time. You know, working in research and development, my career has been developing these diagnostic tests, and we certainly develop them to be as sensitive and as specific and as reliable as possible. I would say what I see happening in the industry is that there's more competition in the space, and competition is good. It will continue to drive down price, however, manufacturing costs and all the regulatory burden associated with it. It's not cheap.

Jomana Musmar 53:24

Regulatory burden that may be part of the areas?

Andrew Hemmert 53:26

Yeah, so yes. Certainly, I think costs will continue to come down. Will they come down dramatically? I don't think as fast as everyone would like. I can also appreciate that they need to come down to get broader adoption. So it's finding that balance of, how do we balance the cost of development, the burden with manufacturing, the burden with regulatory versus the opportunity.

Jomana Musmar 53:46

Well, speaking of prevention and also treatment, and I'm going to pick your brain on this, since you're from the outside looking in also, how do you see current lack of us support for global mechanisms like Gavi, CEPI and the Global Fund affecting the global AMR crisis in both the near and long term.

Ara Darzi 54:03

Well, I'm a member of Parliament. So the idea I'm going to sit down and say how the US is doing is beyond my—bilateral relationships are very important. So you probably know the answer.

Jomana Musmar 54:16

I do. I do know the answer. And I didn't mean to put you on the spot. I was trying to, I was trying to tease a little bit. Okay, let's see. Akhila, how can AI and tech be used against AMR resulting from conflict, like Ukraine? And how can we get the US administration to care more about AMR and the potential impact to US forces? Is there a way that we can get more data to help you turn the C to 'believe.'

Akhila Kosaraju 54:42

It's a great question. So we are already we have a few MOUs with some of the research institutes, some of the DoD collaborations in Thailand and Africa and other places. That data is absolutely invaluable. So some of the drug-resistant bugs you're seeing in the Ukraine are samples that frankly, we don't have here. And of course, that should accelerate with AI. We should be able to quickly have an end-to-end approach, take that data, feed it into our models, have some candidates to then work with the government on. With our ARPA work, we're generating 15 novel antibiotics, pushing those into our pre-clinical pipeline, again, relying on partnerships to take those forward. But we very much hope that of those 15, we can address, you know, particular pathogens of relevance to our troops, and also for biosecurity. So plague and other

biodefense, you know, pathogens are addressing pathogens with biodefense. And also, I want to comment on the biosecurity aspect of AI and the models themselves. So we get asked this question frequently of, you know, if you can train a model to produce a compound that's not toxic, how do you prevent the opposite? And I think that's an approach that we are being very deliberate about, learning from partners like Google and others on how to ensure that we can audit who's using our models, and also get ahead of any kind of unusual activity. So that's an area where, you know, again, bringing in partners who have experience in other areas, like tech, who've contended with these challenges, expanding the tent. I think one, you know, one comment I wanted to make about, how do we get these messages to resonate is you have to bring in other players who traditionally haven't been in AMR. I think everyone on this panel has done an exceptional job of that. And I think that needs to continue. You need to have unusual, you know, folks like NVIDIA and, you know, Anthromorphic and others—*Anthropic*, sorry, and others that think that this is the next example of AI for good. So I just want to put that out there that I think is a key part of this, to have new voices in this field.

Jomana Musmar 56:47

Thank you. And Ara, tell us, what would you like to see even more so, between the bilateral UK-US relationship that we currently have? What would you envision more collaboration looks like, and how to further advance things?

Ara Darzi 57:01

Well—let me start by saying penicillin would not have happened without the US involvement. The discovery happened in the UK. Actual fact, it was Fleming, an immigrant who escaped Nazi Germany, who was Ernest Chain, a distinguished scientist who actually made penicillin. And we had Howard Florey from Australia, who was doing a fellowship in Oxford, who did the trial.

Jomana Musmar 57:24

Which people don't know.

Ara Darzi 57:25

And we made a small amount of it, and that was it. And this was the heyday of the Empire. So then Chain and Florey got on a boat, crossed the Atlantic and knocked the door of Rockefeller to get some money to help him develop this. Rockefeller apparently listened to them—I have all the MOD papers. Listened to them, didn't say much, and at the end, he said, I'll fund this. And they left. Then he contacted, guess who? Roosevelt. Told him there's a miraculous drug here, potentially. Both sensitized that there might be a second world war, and Roosevelt is the person who put pressure on Lilly, Pfizer and Merck to start making, to clear their pipeline, start making antibiotics Just before the Second World War. The lovely idea about all

of this, bioMerieux being here, they kept that very secret from the French for whatever reason. And that's the story behind it. So without US, we would have not had antibiotics. It was the US leadership. It was the political leadership, philanthropic leadership that turned the clock and made antibiotics available during the Second World War.

Jomana Musmar 58:47

I love that story, and so that is such a great reflection of collaboration before and how we can continue to move things along. We have one minute left. The screen is yelling at me in red. Tell us one, one takeaway for the audience, please.

Jomana Musmar 58:47

One takeaway for the audience is that each of us have a responsibility for antibiotic stewardship. You will get to make that decision this fall, this winter, you and your family. You are at the front line. So please remember that.

Tom Frieden 59:14

There's a way to stop AMR, reverse it. See the problems, believe they can change, create a healthier future with a comprehensive approach to preventing, treating, diagnosing, treating and controlling AMR.

Akhila Kosaraju 59:29

Mine would be innovation and antibiotics can be in the same sentence again, and we have an incredible opportunity here to be at the forefront of so many aspects of AI for good and generative AI, using antibiotics as the case study to again expand that tent of interested and resourcing stakeholders to take these antibiotics actually to patients.

Ara Darzi 59:57

They're precious drugs, whichever way we discover them. They will lose their potency and effectiveness if we misuse them and overuse them. Think twice before you take antibiotics.

Jomana Musmar 1:00:07

Thank you. And I'll close with teach your kids, teach your kids, teach your kids. Tell them the difference between a virus and a bacteria, and it's okay to get sick. If it's a virus, you don't have to take something for it, just ride it out. Thank you so much for being with us. Appreciate it, and apologies if that we didn't get to all the questions. It's my technical SNAFU. Have a great day and feel free to engage with everyone else on the panel here. Thank you for joining.