Emerging Financial Models for Antibiotic Development (2000-2016)

Witness Seminar conducted by the DryAP project and in collaboration with the Global Health Centre, Geneva Graduate Institute

Geneva, 29 January 2024
13:00-18:00

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The Research Council of Norway

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GLOBAL HEALTH CENTRE

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Introduction

Antimicrobial resistance (AMR) is a major global health challenge caused by microbes' increasing ability to resist the antimicrobials we use to control them. The past thirty years have seen a surge of national and international governance frameworks designed to protect the ongoing efficacy of our antimicrobial infrastructures by improving stewardship of existing antimicrobials and boosting research and development (R&D) of new compounds. With international attention and investment in AMR steadily increasing between 2000 and 2016, decision-makers on both sides of the Atlantic experimented with a range of finance models to refill the 'empty antibiotic pipeline'.[1] The diversity of chosen models reflected varying innovation concepts, political contingency, as well as shifting problem diagnoses about where support was most needed. Although a limited number of novel therapies have resulted from increased public and non-profit support, current international reviews show that the overall level of antimicrobial innovation remains insufficient in the face of escalating AMR.[2]

Reconstructing the historical trajectory of these finance models is not only important when it comes to understanding why reinvigorating antimicrobial R&D has proven so complicated. It is also significant because models evolved during a critical transition period for Global Health marked by powerful new non-governmental entities, the securitisation of AMR and infectious disease threats, political preferences for private sector solutions, and the fragmentation and financialisation of pharmaceutical R&D.[3] The history of attempts to refill the 'empty pipeline' is thus a microcosm of the broader socio-cultural trends transforming Global Health from ca. 2000 onwards. While media, scientific, and policy reports provide insights into this dynamic world, much of the 'grey knowledge' about drivers of (in) action was never written down.

1 Kristen Overton, et al. "Waves of attention: patterns and themes of international antimicrobial resistance reports, 1945–2020." *BMJ global health* vol. 6, no. 11 (2021): e006909, https://doi.org/10.1136/bmjgh-2021-006909.

2 WHO. *2023 Antibacterial agents in clinical and preclinical development: an overview and analysis*. Geneva: World Health Organisation, 2024, https://iris.who.int/bitstream/handle/10665/376944/9789240094000-eng.pdf?sequence=1.

3 Fanny Chabrol and Jean-Paul Gaudillière. *Introduction à la santé globale*. Paris: La Découverte, 2023, https://www.editionsladecouverte.fr/introduction_a_la_sante_globale-9782348081019.

To preserve this tacit generational knowledge, we invited key decision-makers from across clinical medicine, industry, funders, and international health to participate in a witness seminar on *Emerging Financial Models for Antibiotic Development* in Geneva in January 2024. The seminar was jointly organised by researchers from the Norwegian Research Council-funded Dry-Antibiotic Pipeline (Dry-AP) project and the Geneva Graduate Institute's Global Health Centre. Following initial scene-setting by the project's principal investigators, the seminar consisted of four sessions focusing (1) on the emergence of concerns about the antimicrobial pipeline, (2) the conceptualisation of potential R&D solutions, and (3) emerging finance models between 2000 and 2016. This was followed by a final (4) session giving witnesses the opportunity to reflect in more detail on earlier or missed themes. Individual sessions were introduced and chaired by the three organising early career researchers. Witnesses were encouraged to comment on each other's responses and additional questions were asked by the organising team. Three witnesses participating online also posted comments in the chat. Ahead of the seminar, witnesses signed agreements for the seminar to be recorded and transcribed and were subsequently given opportunity to review their responses and provide additional comments. The resulting five-hour discussion provides unprecedented detail on the interconnected world of high-level decision-making on antimicrobial innovation and AMR during a dynamic period of change for Global Health. We are grateful to all witnesses for their time and generous intellectual contributions.

Claas Kirchhelle and Frédéric Vagneron, September 2024.

Speaker Key

MAP	Mirza Alas Portillo	PhD candidate at University College of Dublin, member of Dry AP Project.
JA	James Anderson	Executive Director, Global Health at IFPMA, former Head of Corporate Government Affairs at GlaxoSmithKline (GSK).
PB	Peter Beyer	Deputy Executive Director of GARDP, former Chair of the Expert Advisory Group of the Medicines Patent Pool, former Head of Unit at World Health Organisation.
OC	Otto Cars	Founder and Senior Advisor of ReACT, former leader of the Swedish Strategic Programme Against Antimicrobial Resistance (Strama).
SH	Stephan Harbarth	Professor at Université de Genève, Head of Infection Control Program, University of Geneva Hospitals and Faculty of Medicine, WHO Collaborating Center. Former participant of REVERSE, ECRAID, COMBACTE, and co-ordinator of DRIVE-AB projects.
MPK	Marie-Paule Kieny	Chair of the Board of DNDi and the Medicines Patent Pool Foundation | (In person & Online Participant).
CK	Claas Kirchhelle	INSERM Associate Research Professor (Chargé de Recherche), Unité CERMES3, École des Hautes Études en Sciences Sociales (EHESS)/Université Paris Cité, Principal Investigator Dry AP Project.
JO	Joe Larsen	Vice President, Clinical Development at Locus Biosciences, Former Deputy Director of Chemical, Biological, Radiological and Nuclear (CBRN) medical countermeasures at the Biomedical Advanced Research and Development Authority (BARDA) | (Online Participant).
JL	James Love	Director of Knowledge Ecology International (KEI) | (Online Participant).
KO	Kevin Outterson	Executive Director of CARB-X, Austin B. Fletcher Professor at Boston University School of Law, partner in DRIVE-AB. | (Online Participant).
ELP	Erin L. Paterson	PhD candidate at Université de Strasbourg, member of Dry AP Project.
FV	Frédéric Vagneron	Associate Professor (Maître de conférences) at Université de Strasbourg, Principal Investigator Dry AP Project.
NW	Nadya Wells	PhD candidate at University of Geneva, Senior Research Adviser, Global Health Centre Geneva Graduate Institute, member of SNF FINPHARM Project.

Setting the Scene

00:18:13

NW

Thank you so much for coming everybody. I am Nadya Wells, from the Global Health Centre at the Graduate Institute, and it is a great pleasure to have all of you here, thank you very much for joining us. It is a pleasure to co-host this event with the DryAP Project, who I've been collaborating with for a couple of years now.

Professor Moon, who's the director of our centre, will join us later in the afternoon for one of the sessions. So, thank you very much, and I'll hand over to my colleagues.

CK

Thank you very much everybody for joining. For those of you who don't know me, my name is Claas Kirchhelle, I am currently based at University College Dublin [Assistant Professor History of Medicine], but from July 2024 onwards will be moving over to INSERM [Institut National de la Santé et de la Recherche Médicale] in Paris, working for CERMES3 [Centre de Recherche Médecine, Sciences, Santé, Santé Mentale, Société].

I am delighted to welcome you here today to our oral-history witness seminar, which we are co-organizing with our colleagues from the University of Strasbourg, Fred Vagneron is here. This project is financed by the Norwegian Research Council's (NRC), as part of a broader collaboration, called "Why Did the Antibiotic Pipeline Run Dry?"[4]

00:19:29

So, what do we want to do, today? This is not about us talking to you. Instead, what we want to do with this oral-history seminar is to bring people together who were there during an absolutely critical period of antibiotic innovation from the 2000s onwards.

We want to really understand what happened during this time, specifically in the worlds of finance and innovation systems, which underwent radical shifts after a relative loss of attention for antibiotics during the 1990s. We want to draw on the collective expertise of this group because much of this story is not accessible in the archives or in the official policy reports.

4 The Dry AP Project, August 23, 2024, https://www.emptypipeline.org.

We want to work with you to reconstruct the evolving 'grey knowledge' in the antimicrobial space: what was happening outside of the formal institutional reports that were published? What conversations were happening, who was driving what? We hope that the collective knowledge of the group will allow us to get some insights into whose agendas were driving what during this period.

00:20:47

And also, which funding models got rejected, the castaways on the side of the road to the antibiotic-innovation models we have nowadays. And finally, our last aim is to analyse the intellectual and institutional backdrop of thinking about the dry innovation pipeline. Our central mission is to fill gaps in the historical narrative between 2000 and 2020. We believe that doing so will add an important new chapter to the ongoing history of antibiotics.

Ahead of handing over to our session chairs, let me start by setting the scene for this most recent chapter of antibiotic innovation. There are already great accounts of the early 'golden' era of antibiotic innovation, which many current initiatives seem to want to repeat. Most historical accounts of innovation have focused on iconic individuals or organisations ranging from Paul Ehrlich to the Oxford Penicillin Team as well as the nexus of Big Science, Big Industry and Big States coming together, from the 1930s onwards, to create the antimicrobial infrastructure we depend on nowadays for the functioning of health and agricultural systems.[5]

5 John E. Lesch. *The first miracle drugs: how the sulfa drugs transformed medicine*. Oxford: Oxford University Press, 2006, https://global.oup.com/academic/product/the-first-miracle-drugs-9780195187755?cc=fr&lang=en&;

Robert Bud. *Penicillin triumph and tragedy.* Oxford: Oxford University Press, 2007, https://global.oup.com/academic/product/penicillin-9780199541614;

Christoph Gradmann. "Re-inventing infectious disease: antibiotic resistance and drug development at the Bayer company 1945–80." *Medical History* vol. 60 no. 2 (2016): 155-180, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4847408/;

María Jesús Santesmases. *Circulation of Penicillin in Spain. Health, Wealth and Authority.* Cham: Palgrave Macmillan, 2018, https://link.springer.com/book/10.1007/978-3-319-69718-5.

Clare IR Chandler. "Current accounts of antimicrobial resistance: stabilisation, individualisation and antibiotics as infrastructure." *Palgrave communications* 5.1 (2019): 1-13, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6542671/;

Claas Kirchhelle, *Pyrrhic Progress: The History of Antibiotics in Anglo-American Food Production*. New Brunswick: Rutgers University Press, 2020, https://www.ncbi.nlm.nih.gov/books/NBK554200/;

For a detailed reading list on antibiotic innovation see "The Pipeline Reading List." *The Empty Pipeline,* accessed September 9, 2024, https://www.emptypipeline.org/the-pipeline-reading-list.

What is a really distinctive characteristic of this early phase [of innovation] is that it occurs at the intersection of the public and the private. What characterizes antimicrobials is that they result from big enterprise projects, an ecosystem that connects at many levels, states, industry actors and universities—albeit in different constellations and with varying recipes.

00:22:29

Another key characteristic, regardless of whether we look at salvarsan, the sulphonamides, or penicillin, is that these products emerge from research and development (R&D) ecosystems which are integrated, they are managed end-to-end. This integrated mode of development results in a wealth of new antimicrobial products coming to the market during the 1930s and 1940s, whose success drives further investment on the part of both states and industry.

Innovation and production are not only integrated in terms of managerial purview, but also in terms of geographical proximity. Examples include the large US antimicrobial production and research facilities at the Pearl River site of American Cyanamid, or Lederle as it was called in the 1950s and 1960s, Bayer's research facilities in Leverkusen in the 1930s,

00:23:50

As mentioned before, development within this integrated nexus is not necessarily solely private or solely public. In the US, the Army has a major public-development program for antimalarials for much of the 20th century but works with contractors for scale-up.[6] On the other side of the Iron Curtain, communist states also invest in antibiotic innovation, which results in products like gramicidin S, or nourseothricin, and have a big impact, for example, in the agricultural sector—but state-owned companies also have to compete for resources and income.[7]

6 Lynn W. Kitchen, David W. Vaughn, and Donald R. Skillman. "Role of US military research programs in the development of US Food and Drug Administration–approved antimalarial drugs." *Clinical Infectious Diseases* vol. 43, no. 1 (2006): 67-71, https://doi.org/10.1086/504873; Javier Lezaun. "The deferred promise of radical cure: pharmaceutical conjugations of malaria in the global health era." *Economy and Society* vol. 47, no. 4 (2018): 547-571, https://doi.org/10.1080/03085147.2018.1528075.

7 Claas Kirchhelle. "Pharming animals: a global history of antibiotics in food production (1935–2017)." *Palgrave Communications* vol. 4, no. 1 (2018), https://doi.org/10.1057/s41599-018-0152-2.

This big, aligned ecosystem starts experiencing problems from the 1970s onwards. And this has to do not only with a relative decline of attention for infectious-disease priorities, but also with changes in how companies work and how research agendas are set at the level of universities and states.

Within the sphere of companies, R&D managers start losing influence to marketing departments when it comes to internal decision-making. This shift of influence corresponds with a growing managerial focus on generating shareholder value rather than prioritising reinvestment in companies.

00:25:35

Another part of this entrepreneurial shift is the hope that new and exciting molecular recombinant technologies will replace the big integrated culture-based screening programs for naturally occurring antimicrobial compounds of the post-war era. From the 1990s onwards, this focus on targeted molecular innovation is complemented by the use of automated high-throughput screening of compound libraries to identify promising drugs and older microbiology-dominated R&D sections get shut down.[8]

The 'rationalisation' of drug research coincides with a time of rapid globalization, which sees companies outsource the production of resulting pharmaceuticals to middle-income countries with the help of new quality assurance systems such as Good Manufacturing Practice certification. It is no coincidence that it is in the late 1980s and 1990s when China and India start to emerge as major global antimicrobial suppliers.[9]

Another important factor in the turn away from integrated innovation-manufacturing campuses and old-school screening is the shift of international patent ecosystems, with an accelerating move away from process to product patents—which reward innovation at the molecular rather than manufacturing level. At the level of universities,

8 Belma Skender. "The demise of the antibiotic pipeline: the Bayer case." *Humanities and Social Sciences Communications* vol. 11, no. 1 (2024): 1-10, https://doi.org/10.1057/s41599-024-03584-3;

A. Daemmrich. "Synthesis by microbes or chemists? Pharmaceutical research and manufacturing in the antibiotic era." History and Technology vol. 25, no. 3 (2009), https://doi.org/10.1080/07341510903083237;

A. D. So et al. "Towards new business models for R&D for novel antibiotics," *Drug Resistance Updates* vol. 14, no. 2 (Apr 2011), https://doi.org/10.1016/j.drup.2011.01.006.

9 Mingyuan Zhang and Lise Bjerke. "Antibiotics "dumped": Negotiating pharmaceutical identities, properties, and interests in China–India trade disputes," *Medical Anthropology Quarterly* vol. 37, no. 2 (2023): 148-163, https://doi.org/10.1111/maq.12757.

research agendas are also reshaped by institutions' increasing focus on monetising innovation and generating intellectual property proceeds from on-campus research, which complicates knowledge flows.[10]

00:26:57

The final nail in the coffin of integrated post-war innovation ecosystems is the collapse of the Socialist Bloc and, with it, the dissolution of large-scale alternative public antimicrobial innovation systems in the communist sphere.

By the middle of the 1990s, the 20th century nexus of Big Science, Big Industry and the Big States, which had grown around antibiotic innovation, seems to have dissolved. And what we are left with is an increasing sense of crisis about antimicrobial-innovation in the face of AMR—and the rise of a new term to describe the problem— 'the empty pipeline'—which unifies fragmented earlier concerns about individual bug-drug combinations in public and policy discourse around 2000.[11]

Over the following two decades, the rediscovery of antimicrobial innovation through the lens of the 'empty pipeline' as an action field for public health and policy creates new alignments between actors from across industry, the state, and non-governmental organisations that are quite distinct from the post-war period of Big science, Big industry and the Big states.

00:29:06

And what we'd like you to do now is to tell us about this new era. Often, the Empty Pipeline narrative seems to imply that we will somehow bring back the golden era of plentiful antimicrobial innovation if only we fix current problems. But clearly the structures that were created after 2000 are very distinct from what came before and will lead to new kinds of innovation.

10 Victor Roy. *Capitalizing a Cure. How Finance Controls the Price and Value of Medicines.* Berkeley: University of California Press, 2023, https://www.ucpress.edu/books/capitalizing-a-cure/paper#about-book;

Kaushik Sunder Rajan. *Pharmocracy: Value, politics, and knowledge in global bio-medicine*. Durham: Duke University Press, 2017, https://www.dukeupress.edu/pharmocracy.

For a history of the origins of modern intellectual property rights in the US see Joseph M Gabriel. *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry.*. Chicago: University of Chicago Press, 2019, https://press.uchicago.edu/ucp/books/book/chicago/M/bo17212890.html.

11 Kristen Overton et al. "Waves of attention: patterns and themes of international antimicrobial resistance reports, 1945–2020." *BMJ Global Health* vol. 6, no. 11 (2021), https://doi.org/10.1136/bmjgh-2021-006909; see also forthcoming research by Mirza Alas Portillo.

FV

Thank you, Claas, for setting the scene for this afternoon of discussion. I am Frédéric Vagneron, I am a lecturer at the University of Strasbourg on the history of medicine and science, and I am part of the DryAP project.

Just briefly, a reminder of what a witness seminar is, and how we are going to work together this afternoon. Since the 90s, witness seminars are considered as a standard qualitative methodology in the history of medicine and science. In short, they are about bringing together people, selected because they are associated with a particular set of experiences, circumstances or events, to discuss and debate about their memories and 'shared' experience. As historians, we then work with this oral material produced together and triangulate it with other sources.[12]

What is our goal today? We would like to be guided by your experience in this field over the last two decades and, maybe, for you to let us know about subject matters and sources that we might be unaware of.

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We also want to decipher complex temporalities and find pivotal events. Of course, we are more than happy if you share your individual motivation, and also what happened with interpersonal dynamics. There is no goal to generate a perfect collective memory, of course. The idea is to explore areas of consensus and dissent that happened over the last two decades.

Of course, it is a selection of voices, and we are very happy with this set of people around the table. The idea is not simply to look for 'facts,' but we also want to delve into your vision of this history, and to enter the process of denaturalizing what happened over the last two decades.

We have organized the discussion in four sessions. Roughly, the first three sessions are chronological, and the last one is more about things that happened after 2016. Each session will be chaired by a moderator, and it will start with Mirza. Each moderator launches an introductory question for the session, and we will navigate together to explore the subject and go into greater depth according to your contributions.

As much as possible, please, state your name at the beginning of your contribution. Please take the liberty of completing each other, adding details, or creating different versions, and I guess the easiest way is just to wave your hand to take the floor.

12 The first Witness Seminar published by the team around E. M. Tansey was entitled: *Technology transfer in Britain: the case of monoclonal antibodies* (1993). Among the Witness Seminars initiated by the *History of Twentieth Century Medicine Group* (Queen Mary University of London) since 1993, and presented here (accessed September 9, 2024), we might mention the following: *Early heart transplant surgery in the UK* (1997), *Post penicillin antibiotics: from acceptance to resistance?* (1998); *Foot and Mouth Disease: the 1967 outbreak and its aftermath* (2001). These volumes are available here: https://histmodbiomed.history.qmul.ac.uk/article/wellcome-witnesses-volumes.html, accessed September 9, 2024.

00:32:43

Our meeting will be recorded, and the tapes will be transcribed. You will, of course, have the opportunity to add, and clarify, some of your comments if necessary. Since you all signed your consent form beforehand, this review process after the seminar aims at making minor, or editorial, changes.

To conclude, I would like to thank again all the participants here and online, and Nadya and the Graduate Institute for hosting us in Geneva. Mirza and Erin have been the key organizers of this event: thank you. Now, if you don't have any further questions, I think we can start with the first session...

Session One: Historical Origins of the Innovation Problem

MAP

Good afternoon, everyone, my name is Mirza Alas Portillo, I am a PhD student at University College Dublin. It is very nice to see you, I met some of you before in my previous role here [at the South Centre] in Geneva. As Claas was saying, another purpose of this meeting is to help us with our research, especially Erin, Nadya and I, as we are completing our PhDs.

This first part is about trying to think about the historical origins of the innovation problem. But to ground it a little in terms of your experience and your memories, I would like to know when you started becoming aware of the issue of the lack of new antibiotics. To start with, because I know we have some expertise here with many years of experience, I might direct the first question to Marie-Paule and Otto.

00:38:35

If you can recall, when was the moment that the lack of new antibiotics became a concern for you?

MPK

Well, thanks a lot. I suggest that Otto starts, because. I looked at my records, and printed a few materials, but it I would date it to the year 2014. But Otto has been there much longer than me, so I still suggest that you start Otto.

OC

Okay, thank you very much. There was no definite point in time, I will say. I was working in infectious diseases, also as the head of the department of infectious diseases at Uppsala University, and I was doing my research on microbiology and pharmacology of antibiotics.

But there was a sense of something wrong in the business model. There were all the time new antibiotics, macrolides, cephalosporins, and we could treat that and that. And there was another one on the shelf. And then, resistance developed and then came new antibiotics, marketing, and sales, and then the circle went round and round. So that vicious circle touched me somehow... I can't find the exact time. I've got that question very many times.

00:40:05

But still, that led to the Swedish program that we started in 1995, which is still alive, I am grateful to see.[13] The energy of young physicians is really driving this on behalf of the government. And then came Action on Antibiotic Resistance (ReAct),[14] and many activities around that that I am sure we will come back to, so I will not take the long story now, I will just only try to respond on the question.

But it wasn't easy to convince everyone that this was a problem. ReAct was also a bit criticized that we were taking too much of our time to deal with [the problem of antimicrobial innovation]. We went, of course, very much more broadly. But having said that there was discussion in many fora that, do we really need new antibiotics? Do we really need them, and why?

And just in memory of the 2001 Global Strategy, the World Health Organisation (WHO) strategy against AMR[15] R&D was a part of it, but not a very strong part. It was basic research, it was surveillance, but the issue of the need for new antibiotics wasn't there. In fact, I can read out one of the statements in that document, 'there are concerns within the industry that efforts to encourage the more appropriate use of antimicrobials may have a negative impact on sales.'

And that was what was stated. And there were no action-oriented recommendations around this problem, so it wasn't there at that time.

13 Swedish strategic programme against antibiotic resistance (Strama) https://www.reactgroup.org/toolbox/policy/examples-from-the-field/strama-swedish-model-for-work-against-antibiotic-resistance/.

14 Action on Antibiotic Resistance (ReAct), www.reactgroup.org.

15 WHO. *WHO global strategy for containment of antimicrobial resistance*, World Health Organisation. Geneva: World Health Organisation, 2001, https://apps.who.int/iris/handle/10665/66860.

Even before the WHO Global Strategy, two important processes took place, but neither of them contained strong recommendations on the development of novel antibiotics. These were a report from the Economic and Social Committee (ECOSOC) of the European Commission in 1998, and from the conference on The Microbial Threat, the same year.[16]

00:42:22

The opinion from the economic and social committee was the first formal statement on AMR from within the EU, and the need for new antibiotics was not featuring prominently, and challenged in fact. As the scientific expert for this process, I brought, of course, the industry into this, because we needed to have the dialogue. That was the first time that I had the opportunity to discuss directly with the industry. Because at that time, and maybe even today, the problem is the over-reliance of industry to produce new antibiotics is prevailing, and that was obvious at that time that industry should fix it, industry needed to be supported.

But in any case, an industry representative, in the first round of the discussions and negotiations even questioned the relation between antibiotic use and antibiotic resistance. So, there was strong power from the industry to defend their role and I think that was for many years to come also the reasoning within governments until the climate, and the discussions and the debate, changed towards more a public responsibility.

MPK

So my recollection is from 2014. It was in 2014 that WHO published a global report on surveillance on antimicrobial resistance.[17] They highlighted that there was high resistance in all regions, that is up everywhere. That this had a negative effect on patient outcome, and that treatment options were running out.

16 ECOSOC. *Draft Opinion of the Section for Protection of the Environment, Public Health and Consumer Affairs on the Resistance to antibiotics as a threat to public health.* Brussels: European Economic and Social Committee, 1998, https://strama.se/wp-content/uploads/2016/04/ECOSOC_1998.pdf;

Vibeke Thamdrup Rosdahl and Knud Børge Pedersen (eds.). *The Copenhagen Recommendations, Report from the Invitational EU Conference on The Microbial Threat.* Copenhagen, 1998, https://www.reactgroup.org/uploads/react/resources/430/The%20Copenhagen%20Recommendations.en.504.pdf;

D.J Mevius, J.W. Spronger, and H.C. Wegener. "EU conference 'The Microbial Threat'," *International Journal of Antimicrobial Agents* vol. 11, no. 2 (1999), https://doi.org/10.1016/S0924-8579(98)00093-4.

17 WHO. *Antimicrobial resistance: global report on surveillance.*

Geneva: World Health Organisation, 2014, https://iris.who.int/bitstream/handle/10665/112642/9789241564748_eng.pdf?sequence=1.

00:44:21

As a result of this report, the WHO member states requested that WHO develop a global action plan to combat AMR in the World Health Assembly of May 2014.[18] As Otto was saying, the plan, this global action plan, was not to focus on production of antibiotics in the pipeline. They wanted the guiding principles that were meant to be for this global action plan.

One, to have a whole-of-society engagement. Actions based on best available knowledge and evidence. Prevention first before treatment. There should be access and not excess. It needed to be sustainable. And also, they wanted to set incremental targets for implementation that recognised the different priorities and capacity of member states.

One of the reasons I think that the pipeline was not a first priority is that the pipeline, or the reconstruction of a pipeline, was not a global issue, it was a high-income countries issue. Because they were the ones working on a pipeline. And this global action plan wanted to take all the countries, whatever their level of wealth, into doing something together against antimicrobial resistance.

The report was requested in May 2014. So, there was a decision (which I think was in retrospect, not the best one), to put the AMR priority in an isolated, if I may say, in a new hierarchical position. So, there was the nomination of an AMR chief, and this was not integrated. It took out most of the focus from the infectious disease cluster.

00:46:52

And it was not integrated either into the cluster which I directed at that time, which was called health systems and innovation, where I was responsible for medicines and intellectual property. So, it was a little bit hanging alone, and not completely connected to what the rest of WHO was doing.

And I remember in this global action plan, and Peter may also remember, but we had to fight to have innovation and the pipeline recognised as a real priority. Because this was not the main interest of those who were responsible for AMR.

After this, I found another presentation which reminded me that the global action plan was indeed to be submitted to the World Health Assembly the year after, in 2015. And this is when [the plan] came to be an official document.[19] Setting official targets to all the regions and countries of the world. And it had five strategic objectives. The first one, it was to improve awareness and understanding through communication, education and training. Second was to strengthen

18 WHO. *Report by the Secretariat, Antimicrobial Drug Resistance, Provisional agenda item 16.5*. Geneva: World Health Organisation, 2014, https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_39-en.pdf.

19 World Health Assembly, *Global action plan on antimicrobial resistance*. Geneva: World Health Organisation, 2015, https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-sel-glass/a68-r7-en.pdf?sfvrsn=fa7f3dde_2.

the knowledge- and evidence-base for research and surveillance. The third was to reduce the incidence of infection through effective hygiene and infection-prevention measures.

The fourth was on optimizing the use of antimicrobial medicine in both human and animal health. And the fifth was to develop the business case for investment in new medicines, diagnostic tools, vaccines and interventions.

00:48:53

It was not only drugs, but it was also for the whole spectrum including diagnostics and vaccines. There was a lot of discussion about infection-prevention control, with Didier [Wernli] and your predecessors. What did we have on guidance, it is not that much. Then there was a discussion about the use of medicines, and a discussion about the fact that the antibiotic consumption in Europe was not uniform, and that some countries were better than others.

[There was also] a lot of discussion about how to achieve better use of antibiotics. Also, on the issue of quality of antimicrobial agents, because it was at the same time that there was a focus also of counterfeit medicines. And a recognition that in many countries actually what was sold as antibiotics was either substandard or counterfeit, and that this was fuelling resistance also. I don't know where the discussion on that was.

The objective also to enforce regulation, to eliminate irrational antibiotic combination, irrational pack sizes, to regulate, to have antibiotics only sold on prescription. To regulate the veterinary market, and to organize campaigns aimed at the public.

This is a time when I became more involved, also with Peter, in the development of health technologies. There was a setup of a global R&D observatory,[20] and some work on antibiotics and diagnostics for antibiotic resistance. At that time, we proposed a new model for innovation in the area of antibiotics.

00:51:06

This was from WHO, I remind you. Not everybody was in agreement, especially not industry. This would come completely under the stewardship and decision-making power of the public sector. The idea was to create a Public Development Partnership (PDP), but a huge PDP, where innovation was rewarded to academia in biotech with prizes and grants to fuel discovery.

20 WHO. *Global Observatory on Health Research and Development. Geneva: World Health Organisation*, 2024, https://www.who.int/observatories/global-observatory-on-health-research-and-development.

Then, the development would be done with biotech and pharma R&D, but under [collective] financing by the states through public financing. And the production and registration would be subcontracted by this huge PDP. And the idea was that all IP generated would be managed, not to provide, how would I say, optimisation of profit. Because this is what you, I will say, [talk about nicely as] giving value to shareholders, which is simply actually a maximisation of profits, private profits.

So, a lot of the IP, which was generated in academia, instead of staying a global public good, which was needed, was actually privatised. We proposed this to have this consortium, and we said at this time, to set it up, that it would request two to five billion US dollars, and that it should be funded by all WHO-member states.

And that this would allow financing the start of the pipeline again, and make sure that the market could be managed. Because the product would be provided to countries according to need, because the IP would be public and not private.

00:53:31

We had a lot of discussions about that, we had a lot of meetings with experts, member states, and all that. I am sure Otto remembers this model which was discussed at that moment. It never really took on because I think it was seen as needing too much money, and also because industry—although they didn't want to invest—they feared more than anything the idea that discovery and development of medicine and product could escape them and actually be managed under the stewardship of the public sector.

It was never the idea that the public sector becomes a producer, but the private sector would have a complete stewardship over the production and innovation, and subcontract the industry. Because they said there was no business for them, so if there's no business for them, well, they can as well do it under contract. But the contract needed to be, of course, extensive enough.

At that time, there was a decision, but as it was not, how they say, attractive enough, that there should be a pilot. And this is when the idea came between the Drugs for Neglected Diseases Initiative (DNDi)—a PDP-established foundation under Swiss law, established in Geneva, to produce and develop medicines against neglected tropical diseases—and the WHO to create a PDP that would be the only focused on the development of antibiotics. That each of DNDi and WHO would have a role. Together, we created a new foundation under Swiss law, which had to work on research and development, conservation, looking at policies that could improve conservation, and looking at equitable access.

00:55:49

So, this was the three-pronged approach. DNDi and WHO established the Global Antibiotic Research & Development Partnership (GARDP).[21] After a while it was necessary to see whether this would stay within DNDi or become a specific organisation. And the decision was that it should be a stand-alone organisation, and therefore GARDP was taken out of DNDi and became this organisation that we know, where Peter is now the, what are you, are you a deputy director? Deputy Executive Director.

So just to finish. From the WHO—I think it is still like that, on the contrary of what has been pushed by industry to say that the only, or the main, problem of antimicrobial resistance is the lack of the pipeline—WHO has always kept the view that it is not only the pipeline that you can have whatever pipeline and whatever new antibiotics. If there's not an effort made on preservation, and on stopping of misuse, and on conservation, we would never get anywhere.

Because otherwise any antibiotic that you develop will become [useless] after a few years. There are many forces that focus only on the pipeline, and I think that this is deceptive.

00:57:27

And of course, the pipeline is important, but the policies which are necessary to keep these new molecules active and useful is at least as important.

MAP

Otto? I don't know if anybody else wants to speak but I have a question. You mentioned that there was a fight to include innovation in the policy program, and I don't know if you can refer to why that was the case.

MPK

Well, at the beginning it wasn't seen as the first priority…

PB

In the AMR action plan.[22] Well, it was the guy, the English guy, Charles, running it, Charles Penn.

21 DNDi. "Global Antibiotic Research & Development Partnership (GARDP) garners key financial support for launch." *News Release*, 26 May 2016, https://dndi.org/press-releases/2016/gard-garners-key-support-for-launch/.

22 WHO, *Global Action Plan on Antimicrobial Resistance*. Geneva: World Health Organisation, 2015, https://iris.who.int/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.

OC

Yes.

PB

He was coming more from surveillance, disease burden, he was not an R&D person. He was rather leaving that and focusing on infection prevention and control (IPC), awareness raising, all the things where there was consensus and which avoided more contentious R&D politics.

00:58:43

MPK

In terms of structure it was not, innovation and R&D were not integrated into AMR, so this is why it was pushed back.

OC

I would like to fill the gap between 2001 and 2014 where you started this, if that's okay, because lots of things happened then. I mean, ReAct has all the way been taking this end-to-end approach, a holistic perspective not only development. I just have to say that as this meeting is concentrating more on R&D, we need to see this in a broader global perspective where stewardship and equitable access are important components.

The fact that nothing was included in the [WHO] global strategy in 2001 was probably because the global problem wasn't seen, we didn't have data from low- and middle-income countries, we didn't see the global burden. There were many other health challenges in those countries, and AMR was not sufficiently visible.

And then the WHO had difficulties to place this topic, and it moved around a bit in different parts of the organisation. We invited key people from the small AMR group at WHO to Uppsala, in 2002. And that led to future meetings, and then that was also the idea, incentive, to create ReAct.

01:00:08

So, WHO was with us from the very beginning on this journey. Now it is obvious that a lot of things happened after that. In 2004 there was something called Priority Medicines for Europe and the World,[23] and the person leading that from WHO was Richard Laing. And he was in Uppsala at the ReAct meeting in 2004 and said, 'We missed this, we missed this.'

So, in fact, we were offered to write the chapter on AMR, or antibiotic resistance, into that publication. It came first, I don't think just because it started with "A". I think maybe that it was seen as a priority. Also, simultaneously, the American side was, of course, also advocating 'bad bugs for no drugs,' and echoed this general advocacy…

23 Warren Kaplan and Richard Laing. *Priority Medicines for Europe and the World, Proposal*. Geneva: World Health Organisation, 2004, https://iris.who.int/handle/10665/68769.

SH

I thought it was New Drugs for Bad Bugs.[24]

OC

My mistake-Bad Bugs, No Drugs[25], it was called.

SH

Oh, yes.

MPK

The first one.

OC

Yes, so we continued to work with the European Medicines Agency (EMA), and we also saw the opportunity of a forthcoming presidency of the EU in 2009 in Sweden. And we worked together; I invited myself and talked to the heads of the EMA and the European Centres for Disease Control (ECDC) to see whether they couldn't put up a document or a process to get some figures on the [AMR] burden.

01:01:48

Secondly, to get the pipeline [on the agenda]. That emerged in a paper that was presented before the Swedish EU presidency in 2009.[26] And I say that was, at least from the European context, kicking off a lot of things, because then came the global conference in 2010,[27] where big pharma, notably Glaxo, was there, and others around the table. Not only on R&D but on the general problem, make it globally.

Then came in 2011 the first European action plan,[28] which was the result of negotiations after the Swedish EU presidency. That in turn

24 New Drugs for Bad Bugs or ND4BB is a later antibiotic research and development component of the Innovative Medicines Initiative (IMI).

25 IDSA, *Bad bugs, no drugs: as antibiotic discovery stagnates, a public health crisis brews*. Alexandria: Infectious Diseases Society of America, 2004, https://www.idsociety.org/globalassets/idsa/policy--advocacy/current_topics_and_issues/antimicrobial_resistance/10x20/statements/070104-as-antibiotic-discovery-stagnates-a-public-health-crisis-brews.pdf.

26 ECDC/EMEA. *Technical Report. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents*. Stockholm: European Centres for Disease Control/ European Medicines Agency, 2009, https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

27 O. Cars, A. Hedin, and A. Heddini. "The global need for effective antibiotics-Moving towards concerted action," *Drug Resistance Updates* vol. 14, no. 2 (2011), https://doi.org/10.1016/j.drup.2011.02.006.

28 Directorate General for Health & Consumers. *Communication from the Commission to the European Parliament and the Council: Action Plan against the Rising Threats from Antimicrobial Resistance*. Brussels: European Commission, 2011, https://health.ec.europa.eu/system/files/2020-01/communication_amr_2011_748_en_0.pdf.

challenged the EU Commission to come up with an action plan to include, a strong component on innovative incentives for effective antibiotics.[29]

I think all these things were the sequence of events that emerged into the creation of new collaborations -New Drugs for Bad Bugs, included in the already existing Public Private Partnership (PPP) Innovative Medicines Initiative (IMI)[30] I think this was a big success.

I recall that Richard Bergström, who was then the head of the European Federation of Pharmaceutical Industries and Associations (EFPIA), was personally meeting [José Manuel] Barroso who was the EU head, and also bringing CEOs from the big pharmaceutical industry to convince [Barroso] that this problem should be included in the IMI, and bending the mandate of that PPP a bit forward so that this could include, also, more competitive research and not only non-competitive research.

01:03:40

Sadly, IMI was closed, big mistake I would say, it had a lot of investments. Notably, the European Gram-negative Antibacterial Engine (ENABLE) which was really delivering support to academic groups and small pharma, including some advice from big pharma. And led to leads and also, I think even drugs, I don't know how far they have gone. But at least the pipeline was starting to be replenished, which was the intention.

The Swedish government supports a downsized ENABLE-2, but it is not on the scale it should be. And I think these early drug-discovery problems are still not seen as significant as I think they are.

There has been a debate over the years about what the real problem is. First of all, should the public intervene at all? Secondly, if so, what are the problems? Are they scientific or financial? Of course, there are both, but I think we are still struggling with major, major scientific challenges to get new molecules entering into the gram-negative bacteria as well as overcoming resistance mechanisms.

There is a great need in supporting small and big, small- and medium-sized enterprises (SMEs) with the technology and the support like ENABLE did. I think its' closure was unfortunate, to say the least. Almost around the time that you started your report, so maybe some other members might come all the way, thank you.

29 "Council Conclusions of 1 December 2009 on Innovative Incentives for Effective Antibiotics," *Official Journal of the European Union* C vol. 302, no. 05 (2009), https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:302:0010:0011:EN:PDF.

30 The Innovative Medicines Initiative (IMI) ran between 2008 and 2017 and has been replaced by a new European partnership for health called Innovative Health Initiative (IHI).

01:05:29

PB

You said you have three sessions, so I can tell you, a couple of things about what we did for GARDP, but I understand this session is focusing on the earlier part. So, when I was still in Switzerland, there was this commission on public health, innovation and intellectual property, chaired by Ruth Dreifuss.[31] They covered neglected diseases, but in 2006 they did not consider antibiotics neglected, they did not identify that there was an issue. They did a follow-on commission; it was the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) commission[32]

PB

Oh my God, you remember. This was... John-Arne Røttingen[33] was the chair. And they, for the first time to my memory, in WHO in 2012 said, well, there is actually low level of investment in R&D on antibiotics, and we actually need to do something. And that was the group that came up with the R&D treaty idea and some other recommendations. But that is where, I think, it was the first time in a WHO report I know, I mean, there may be others, I didn't follow the AMR reports. That this was identified as something, okay, we should actually...

MPK

...for R&D...

PB

...do something. And then as Marie-Paule said, the AMR people were different from those who would cover R&D issues, I can say a couple of words what we did then for GARDP.

31 WHO. *Intellectual Property Rights, Innovation and Public Health." Report by Secretariat. Provisional Agenda Item*. Geneva: World Health Organisation, 2005, https://apps.who.int/gb/ebwha/pdf_files/EB117/B117_9-en.pdf.

32 Refers to the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) that presented its report in May 2012.

33 John-Arne Røttingen (now chief executive of the Wellcome Trust) was CEWG co-chair.

01:07:07

The Germans had the G7 presidency in 2015,[34] and they came to us, and they asked WHO to do this priority-pathogen list of bacterial pathogens. Because Marie-Paule had done the blueprint, for the pathogens with pandemic potential.[35]

And so, Germany said, 'oh, we want you to do this for bacterial pathogens, and we are going to give you money. Also very interesting, why did it happen? Because they gave us money, not much but a little bit, so that's why we could do it. And with that money we also did the first pipeline report where Stephan [Harbarth] was involved. And then... But that's already, that's not history, that's contemporary.

MPK

No, but this was also interesting Peter, because there was this competition for attention. And so, when Peter and the group started to work on these priority pathogens for antimicrobial resistance, we had a huge fight with the tuberculosis people. Because it didn't include tuberculosis. But, of course, tuberculosis is a priority, but it is not the same kind of pathogen. So, it also means that ... one of the reasons that, maybe ... AMR didn't get all the attention at the beginning that it might have needed is also because there were so many different public-health priorities that were asking for attention.

01:08:47

And that AMR had a hard time raising over the bar.

MAP

I wanted to ask our two participants online if they wanted to add anything to these conversations. And perhaps since we are having, already, a conversation about how it was being framed, this lack of new antibiotics and whether it should be a priority or not, any reflections on that?

KO

Well, I mean, I have multiple comments, but your last comment asking me to respond as opposed to giving a little framing of the history as I saw it. So, I don't actually know how you want us online to participate today.

CK

I think, Kevin, if you want to give us a historical reflection first from your vantage point, from the other side of the Atlantic, I think that would be helpful.

34 German Federal Government. *G7 Summit on 7 and 8 June 2015* (29.05.2015), https://www.bundesregierung.de/breg-en/search/g7-summit-on-7-and-8-june-2015-399286.

35 WHO. *WHO R&D Blueprint*. Geneva: World Health Organisation, 2021, https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/who-r-d-blueprint/background.

KO

These are what I did to prepare for today[36], these are key things, we've talked about a lot of them already. I would say, on the pipeline issue, paper number two here, Steve Projan's paper, was really influential on the companies deciding to exit.[37]

01:10:43

It laid out their views and was like wildfire within the companies to make their decision to stop investing in antibiotics. I think Ramanan [Laxminarayan's] work, but also with Anup Malani in the Chicago Law School, and David Smith, who is an economist, along with a fair amount of the earlier papers on this topic. Funded by the Robert Johnson Foundation, 2007, I participated in that as well. That was early academic work that thought about what needs to be done in this pipeline. I had some papers in that period as well, but just focusing on major things, the Center for Global Development had a working group in 2010, Infectious Disease Society of America (IDSA)

So, the 'When Medicines Fail,'[38] I actually don't know who funded the CGD work, but somebody decided it was thoughtful to think about this. IDSA, we've talked about their advocacy campaign, starting in 2010, which led to the US Gain Act in 2012,[39] which most people think didn't do much.

I thought the Uppsala Conference, following the Swedish presidency in 2010, it was critical. It brought together all sorts of people. I was there physically, made a lot of connections there that were really useful. Dame Sally [Davies'] book,[40] but also just the emergence of Dame Sally as a force. And the US government, Joe Larsen will tell

36 In chat, KO: Presented a Slide image, see Appendix A for copy.

37 S. J. Projan. "Why is big Pharma getting out of antibacterial drug discovery?" *Curr Opin Microbiol* vol. 6, no. 5 (2003), https://doi.org/10.1016/j.mib.2003.08.003.

38 Rachel Nugent, Emma Back, and Alexandra Beith. *The Race Against Drug Resistance. Report of the Center for Global Development's Drug Resistance Working Group*. Washington DC: Center for Global Development, 2010, https://www.cgdev.org/sites/default/files/1424207_file_CGD_DRWG_FINAL.pdf.

39 Department of Health and Human Services. *Generating Antibiotic Incentives Now," Required by Section 805 of the Food and Drug Administration Safety and Innovation Act Public Law 112-144*. Washington DC: Department of Health and Human Services, 2012, https://www.fda.gov/files/about%20fda/published/Report-to-Congress-on-Generating-Antibiotic-Incentives-Now-%28GAIN%29.pdf.

40 Sally C. Davies, Jonathan Grant, and Mike Catchpole. *The drugs don't work: a global threat*. London: Penguin, 2013, https://www.penguin.co.uk/books/256685/the-drugs-dont-work-by-catchpole-professor-dame-sally-davies-dr-jonathan-grant-and-professor-mike/9780241969199.

you more about this probably. But David Cameron, the [UK] prime minister, had a personal conversation with Obama and Merkel at a G7 meeting, and that led to the US strategy in 2014-15, it finished with the US National Action Plan.[41]

01:12:36

You talked about John-Arne [Røttingen]'s report. All the things leading up to the United Nations General Assembly (UNGA) 2016. Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) and the New Drugs for Bad Bugs, which began in 2014 but final report in 2018. O'Neill['s AMR Review] in 2014 to 2016.[42] These were critical things in which groups of people came together, Sometimes academics, sometimes economists, sometimes multiple groups of academics plus industry, DRIVE-AB, to try to look at this problem.

There's a series of Chatham House papers which, I think, were the most aggressive in trying to advance de-linkage, so let's do R&D in which the price of the product is de-linked from the R&D recovery.[43] Which is the foundation, today, of the UK [Antimicrobial Products Subscription Model],[44] and the proposals in other G7 countries. And then all the partnerships which we'll talk about later in the day, all the partnerships.

And I just... If I had to think about which two physicians were really important globally, Otto and Stuart [Levy]. I read [Levy's] *The Antibiotic Paradox*[45] way back when, but his organisation, Alliance for the Prudent Use of Antibiotics—I think ReAct has been much more impactful—was an early attempt to organise folks in this area.

41 The White House. *National Action Plan for Combating Antibiotic-Resistant Bacteria*. Washington D.C.: The White House, March 2015, https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf.

42 Review on Antimicrobial Resistance. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. London: Wellcome Trust and Department of Health, 2016, https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf.

43 Chatham House Report. *Towards a New Global Business Model for Antibiotics. Delinking Revenues from Sales*. London: Chatham House, The Royal Institute of International Affairs, 2015, https://www.chathamhouse.org/sites/default/files/field/field_document/20151009NewBusinessModelAntibioticsCliftGopinathanMorelOutterson-RottingenSo.pdf.

44 NHS England. *Antimicrobial Products Subscription Model: Thematic Analysis Report*. London: NHS England, 2024, https://www.england.nhs.uk/long-read/antimicrobial-products-subscription-model-thematic-analysis-report/.

45 Levy, Stuart B. The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle. New York: Plenum, 1992, https://link.springer.com/book/10.1007/978-1-4899-6042-9.

Looking back on all that, a couple of the comments that I heard, just to comment a little bit on them. Things like I heard 'Industry is the only problem, it says the only problem is a lack of a pipeline.'

01:14:22

That has not been my experience, I've had lots of discussions with industry people in which they've had a broader view. Of course, the piece that they think they can fix is the pipeline, they don't see a way that they can fix WASH[46], or various other parts of the problem. And every report, really, that I've been a part of, or in most national action plans that I am aware of, they don't focus on only the pipeline.

I would agree, one of the speakers said that would be deceptive, I didn't actually see who was speaking. I agree, but I don't see people doing that. And every national action plan—they follow a script, a system, and infection prevention control, and stewardship and access are always higher. R&D is usually the fourth topic, and in some iterations the sixth topic.

I think the reason why some people come in and say, let's focus on this or this. And partially it is a competition for money, for resources, obviously. But partially, it is that that's what this group can do, if you are a hammer you are looking for nails, right? And so, the groups that are excellent at stewardship focus on stewardship, and those that do surveillance, on surveillance, and those that do R&D, etc.

And what I wish [is that] the world had a better way. The Independent Panel on Evidence for Action is one iteration of this.[47] But a better way to make trade-offs between these various types of responses, so that we, as a planet, could have a thoughtful, integrated response to it.

01:16:16

JO

I think the question, right, was 'When did we notice that this was a problem?' Kevin pointed out a lot of events and publications that I think are of value. A couple that stand out in my mind, as I was beginning to start to finance antibiotics in the US government in 2010, were publications in the early 2000s from large pharma. Showing that their genetic screens and work looking to identify essential genes in bacteria and then trying to screen those for drugs came up largely empty-handed.

And then second, I think one of the key events that occurred, particularly

46 Water, Sanitation and Hygiene (WASH).

47 Refers to a proposal by the UN Inter-Agency Coordination Group: Interagency Coordination Group on Antimicrobial Resistance. *No Time to Wait: Securing the Future From Drug-Resistant Infections. Report to the Secretary General of the United Nations. Interagency Coordination Group on Antimicrobial Resistance*. New York: United Nations, 2019, https://www.who.int/publications/i/item/no-time-to-wait-securing-the-future-from-drug-resistant-infections.

in the US market, was the approval and subsequent withdrawal of Ketek from the marketplace due to severe hepatotoxicity in 2006-2007.[48] No value comment on that decision, obviously, but it did have a significant ripple effect.

There was a significant amount of political fallout, and congressional investigations of the FDA as a result of that withdrawal. That resulted in significantly increased regulatory requirements, particularly for clinical development of new antibiotics in that timeframe. And so, there was the precipitation of an already-moving train of large pharma withdrawing from developing new antibiotics.

I think that regulatory decision, or just the fallout from the regulatory decision, I should say, further hastened that exit. And when I began financing these antibiotics at the Biomedical Advanced Research and Development Authority (BARDA) in 2010, the things that I was hearing from small companies was that they could not raise money for clinical development.

01:18:19

And so that, I think, is where I noted, putting the resistance rates aside for a moment, that there was an actual problem with companies developing these products. Because, namely, it got much, much harder and more expensive to do so.

During this timeframe that we are covering today, many of those regulatory decisions made in the wake of the Ketek decision have seemingly not, I wouldn't say been reversed. There's been injections of, obviously, increased regulatory flexibility along the way, I think to facilitate and encourage the development of new antibiotics.

And if I were to just speak from my perspective about starting programs, because that's where I see other people have gone. When I helped BARDA to start their antibiotic program it was in a weird place because BARDA was formed in the wake of the Amerithrax [anthrax] attacks that occurred shortly after 9/11, and was largely envisioned to be a chemical, biological, radiological, nuclear preparedness and response organisation. Infectious diseases like AMR, or emerging infectious disease, was not part of the remit of the organisation.

01:19:46

I can certainly get much more into this, but there was a significant amount of political headwind from Congress, depending upon who was in political authority in the US administrations, about BARDA's role in supporting the development of new products to address antimicrobial resistance.

In fact, we initially had to only support products that had applicability in both [bioterrorism/AMR]. And the flexibility for us to operate established programs like CARB-X oftentimes were really dictated by who, again, was in political power. Which ultimately, I think, did a

48 David B. Ross. "The FDA and the Case of Ketek," *New England Journal of Medicine* vol. 356, no. 16 (2007), https://doi.org/doi:10.1056/NEJMp078032.

disservice to directly addressing the problem.

And happy to discuss more about different political events that occurred along the way, like the release of the Combating Antibiotic-Resistant Bacteria (National Strategy),[49] and National Action Plan[50], that really catalysed a lot of efforts politically for us, as well as headwinds that were encountered as a result of that.

SH

Yes, lots of things have been said, especially I really like the statements by our senior statesmen, women, here because—and it is an extremely useful endeavour to try to keep this memory, so I can only congratulate you for this attempt. So, I think I can add a little bit for the period between 1995 and 2010, because I remember we had some pretty harsh discussions about R&D pipelines before 2010, and I just found an editorial I wrote in 2007 going against the need for investing more in antibiotics, so I also changed my mind, but it is true.

Let's start. First, you have to look when was the problem really discovered? When was the clinical impact seen?

01:22:08

Not speaking about public awareness, it is just first you have clinicians who see treatment failures, I mean, that's the driver. It started in the '90s because you had the problem of Extended-Spectrum Beta-Lactamases (ESBL), when suddenly some of these third-generation cephalosporins didn't work, that was in the 1990s.

Then you had Methicillin-Resistant *Staphylococcus aureus* (MRSA) in some places, but still we had enough MRSA-active drugs, it was not completely desperate. But I can remember in the 1995 period then, we started to have discussions about improved infection control and about antibiotic stewardship.

There was a famous quote by a famous Intensive Care Unit (ICU) physician in the US, Dennis Maki, who said in 1997, at the most important conference in the world, that it doesn't make sense to develop new antibiotics without ensuring their appropriate use. Otherwise, it is like providing a finer brandy to your alcoholic patients.[51]

49 White House, *National Strategy for Combating Antibiotic Resistant Bacteria*. Washington D.C: The White House, September 2014, https://obamawhitehouse.archives.gov/sites/default/files/docs/carb_national_strategy.pdf.

50 White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria*. Washington D.C.: The White House, March 2015, https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf.

51 Dennis Maki (IDSA meeting 1998) cited in Stephan Harbarth. "Should the development of new antibiotics be a public health priority?" *Current Opinion in Critical Care* vol. 13, no. 5 (2007): 554-556, https://doi.org/10.1186%2Fs13756-015-0091-2.

So, it was clear, at that time, the clinicians thought that we have to make sure that, the new drugs that were still coming, they should be used properly. It was not our mindset at that time to say, we have a problem with the pipeline, it was not.

And then there was this momentum where stewardship got more traction, there was even a WHO guideline book,[52] that got completely forgotten, that was my moment of glory at WHO in 2015. When I said, hey, we were talking about a new antibiotic booklet, how to use it. And all the WHO colleagues in the room, they had forgotten that Hoggarth in the late 1990s had developed that, and nobody knew that there was this document.

01:24:06

And then there was, like described before, in 2001 there was this big statement, the first WHO document which was released on September 11, which didn't help at all.[53] I would say that the overall AMR-control momentum got a lot of damage for almost ten years because of the, like Joe [Larsen] just mentioned, the bioterrorism issues. Which had only one positive byproduct, the huge investment into diagnostics which was really helpful.

So, it didn't go into developing new antibiotics, but the momentum and the increase in investment in rapid diagnostics because of the bioterrorist threat. But there was so much spillover that, for us, it was extremely helpful for clinicians, there were lots of very positive things.

To close this gap until 2010, it was only in the mid 2005-08, period that we start to realize, yes, there is a problem. Because that was when the MRSA problem was at its peak, the first carbapenemase producers made huge outbreaks in Israel and the United States. And then suddenly some of our super guns, the 'super-penems', (carbapenems), they failed to treat patients.

So, there was this awareness among clinicians plus stakeholders that, yes, there is now going to be a new threat beyond MRSA. So, you have to look, if you look into the history and the memory of the last 20-25 years, you always have to look a little bit also at the epidemiology of multi-resistant organisms.

01:26:00

And this delay when clinicians, first they see, and then there is this delay, staggered awareness, of policymakers. There are some voices like Otto and others saying, 'Woo, there is something happening.' It takes time, so there is this lag time. And I think you could probably do even a nice time-series analysis between the moment when an antibiotic resistance is first described, discovered, like carbapenemase producers. Then the first opinion leaders saying, oh, there is a

52 WHO. *WHO Model Prescribing Information: Drugs Used in Bacterial Infections*. Geneva: World Health Organisation, 2001, https://iris.who.int/handle/10665/42372.

53 WHO. *WHO global strategy for containment of antimicrobial resistance*. Geneva: World Health Organisation, 2001, https://apps.who.int/iris/handle/10665/66860.

problem, the first outbreaks. And then it takes, sometimes, ten to fifteen years that everybody understands we have a problem. And so, therefore, during this period I can only say that lots of colleagues, including myself, we changed our opinion, we said, okay, yes, now we understand the pipeline is a problem. But if you had asked in 2003 whether we needed to really take care of the pipeline, I would have said, no, we have to invest [in stewardship and infection control].

I have this paper, I said it is not a public-health priority, we should invest in infection control, stewardship, vaccines like the pneumococcal vaccine. We should invest in better diagnostics, and the pipeline is not a problem.[54] So that was at least during the period until 2005, 2007, that was a prevailing opinion among many people in charge of AMR, they said it is not a priority.

01:27:37

CK

Just to have a conversation here between Joe and Stephan on these points. I mean, was there alignment here between views on this side of the Atlantic, in Europe, and the North American side, about the problem and the solution? BARDA was set up to produce things, it was set up to stockpile things. Whereas Stephan just said he was all about vaccines, diagnostics, during this time.

Do you have, retrospectively, the impression that there's been a different emphasis on both sides of the Atlantic when it comes to infection prevention and control versus drug innovation? Are there different cultures at play here? Stephan's shaking his head. Joe, do you want to come in first?

JO

Yes, infection control and prevention was not an area under my remit, that's more other components of the federal government. I would say that in terms of the bioterrorism implications, I mean, we were able to thread the needle and support these programs by a couple of talking points.

The first one being that much of the things that were in the preparedness stockpile, and that are still in the preparedness stockpile, are antibiotics that were purchased on the basis of low cost. And the volumes that you would need to protect the American public from an enormous mass-casualty situation. Much of these products were of the 1950s and 1960s variety. These products potentially needed to be updated to counter what we were observing, gravitated. But also, there was the continued notion that we still needed products for these agents, these bioterrorism pathogens.

54 Harbarth, Stephan. "Should the development of new antibiotics be a public health priority?." *Current Opinion in Critical Care* vol. 13, no. 5 (2007): 554-556, https://doi.org/10.1186%2Fs13756-015-0091-2.

01:29:41

By supporting a next-generation cephalosporin that had activity against hospital-acquired infections and developing it for that purpose but then also doing these tests for bioterrorism agents, left the people who are our detractors with nothing much to say back to us. Because we were still doing what they were giving BARDA money for, in Congress, to accomplish that mission. It just so happened that we were also addressing this arguably more pressing public-health concern.

It only really became more problematic the more we began to broaden the aperture of that. And it became the most problematic when you would have one administration who was supportive, who wanted to issue a national strategy and national action plan, who issued an executive order giving us that authority. And then that administration changed, and then the Houses of Congress switch from one party to another, and those parties tend to be less supportive of these public-health issues, and more hawkish on the biodefence ones.

And that set up dynamics where we were having to counter that we were moving away from BARDA's core mission. Unfortunately, you still see this dynamic play out today in the way that BARDA messages about its antibiotics program.

01:31:19

It is still about protecting and ensuring Americans survive secondary infections related to these mass-casualty events. It is not really about just dealing with the threat of AMR explicitly. There have been new stockpiling contracts for antibiotics that have been issued since 2018, to begin to refresh the stockpile. Those again are under the auspices of protecting against bioterrorism agents.

You may want to easily argue that they are really about trying to provide a minimum guarantee of revenue to companies that have developed some of these new antibiotics, small biotechs. To make sure that they have some minimal guarantee of revenue to keep them commercially viable.

MAP

James, you wanted to add something?

JA

Just a brief from my side because I think you want me to more come in on the second session, right? So, a couple of observations from [the perspective of industry]. So, first of all, I studied molecular pathology in the early '90s and I don't remember AMR being mentioned at all, so my history doesn't go back long. But this was in a top university, joint programs with the medical course, etc. If it did I was more focused on emerging exciting things like genetics and so on.

Anyway, so then at Glaxo Smith Kline (GSK) I joined in 2005, and a few years in there was a fascinating debate between the R&D antibiotics team and the commercial antibiotics team. The debate was about every time we try and in-licence an antibiotic to develop, the deal falls apart. And the R&D team were saying, the commercial team is not ambitious enough about what this is worth, what you can sell of it, and the commercial team would point to the R&D team, and say, yes, but you are not finding us any nice products to do this.

01:33:19

So, my first thing was to do a modelling exercise, started in 2008, with the Office of Health Economics, on the economics of investing into developing an antibiotic, and then what you would expect normally to make, to sell.[55] And that's the exact process that companies do when they decide any in-licencing, or pretty much any R&D investment.

And it was clear that the numbers by and large just didn't work, which then led into the recognition of a number of different things. One was the need for incentives as a way to make the numbers, the economics, work. The second was a bit broader, was that, I would say, companies have to make sure that the products they produce are valued by society appropriately.

This was almost the poster child of where that was going wrong. There were all sorts of debates in other disease areas that were saying, look the model's broken, it doesn't even work there.

01:34:54

And yet the company wanted to carry on investing. GSK had been investing into antibiotics since the Second World War, some of those earliest points that [Claas] made at the beginning.

The second issue was we also had some older antibiotics that were still on the market and were still significantly big-selling products. And there were also difficult decisions around how to set the sales targets for those, whilst making sure that the promotion was done appropriately and was not excessive or leading to poor use.

So, both of those were really quite fundamental to the business of any pharmaceutical company. And then what really started to tie it all together was the 2010 ReAct conference, I did meet Kevin there, potentially some others.

And also, what I felt was starting there, and then definitely played out through many of the events in that decade, was what I describe as the shift from a very public health, internally-focussed discussion to a much

55 Priya Sharma and Adrian Towse. *New Drugs To Tackle Antimicrobial Resistance. Analysis of EU Policy Options*. London: Office of Health Economics, 2011, https://www.ohe.org/wp-content/uploads/2014/07/352-NewDrugsToTackle_April2011.pdf.

broader [debate with] policy-makers, economics, lawyers, academics, outside the public-health and the private sector. And certainly, that opened up a lot of the other actions that, then, I've been involved with the private sector, which I think I will talk about in the next session, right?

01:36:52

OC

I just wanted to get back to the fight we had. I remember sitting in the hotel lobby with Stephan Harbarth and Herman Goossens, and I was provoked by your [JA] counterargument. And looking at the STOA, the science and technology panel on the European Parliament, they stated the following in 2006 : 'We cannot wait any longer for the discovery of new antibiotics. The research and development of these drugs is a long, expensive and arduous process, which most large pharmaceutical companies no longer find profitable, and hence they are pulling out of the market. Even if profit could be assured, it is still by no means certain that new drug leads could be found and developed into useable antibiotics by the time they are needed. Containment of the development and spread of resistance must therefore be given first priority.[56]

PB

It was when?

OC

2006. And even if profit could be shown, it is still by no means certain that new drugs could be found and developed. So, the conclusion was not to prioritize innovation and then go for prevention. For sure we need both. And now I think what is happening, in the preparatory documents that are circulating now ahead of the high-level meeting, prevention is absolutely coming up front. So, I mean, that's like going into the car station filling up the gas with a hole in the tank. I mean, sure but we need to plug the tank not to waste the fuel. And also, some comment on institutional memory, I think that is a real problem for everyone, not only that governments and administrations come and go.

56 Policy Department Economic and Scientific Policy. *Antibiotic Resistance*. Brussels: European Parliament Directorate General for Internal Policies of the Union, 2006, https://www.itas.kit.edu/downloads/etag_hoho06a.pdf.

01:38:22

At WHO, colleagues come and go, and where is the institutional memory, where does it lie? It is really... How does this problem keep living ahead timewise? Last thing, the CEWG defined de-linkage, wasn't that the first time it came up?[57]

MPK

It was the EWG just before.[58]

OC

I think it was important though, that that was then picked up in the political declaration in 2016.[59]

PB

Yes, it came up in the global strategy for intellectual property and so on, because I remember that...

MPK

It was the global strategy and plan of action on public-health innovation in intellectual property.[60]

PB

I, as the Swiss delegate, questioned using the term de-linkage, because we were suspicious of what it would mean in the end, it sounded socialist.

CK

Kevin, do you want to come in on that?

KO

Yes, I want to say that the first written description of de-linkage in the antibiotic space I think was Jamie Love's short, very short piece

57 World Health Assembly. *Consultative Expert Working Group on Research and Development: Financing and Coordination. Corrigendum, Provisional Agenda Item 13.14*. Geneva: World Health Organisation, 2012, https://iris.who.int/handle/10665/79197.

58 Refers to the Expert Working Group (EWG) convened ahead of CEWG and its report.

59 United Nations General Assembly. *Draft Resolution Submitted by the President of the General Assembly," Seventy-first session: Agenda item 127, Global Health and Foreign Policy*. New York: United Nations, 2016, https://digitallibrary.un.org/record/842813/files/A_71_L-2-EN.pdf.

60 World Health Assembly. *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, Agenda Item 17.5*. Geneva: World Health Organisation, 2015, https://iris.who.int/bitstream/handle/10665/253247/A68_R18-en.pdf?sequence=1.

on prizes not prices for antibiotic R&D.[61] But there was a fair amount of academic work, and then it finally broke into the international organisations as we've just said. But go back and read Jamie's first little, short piece, that was the genesis.[62]

01:39:49

CK

One final question from me just to round it up, and I am aware of the time factor here. I mean, it's very interesting to see all of these different strands emerging. So, we've got the WHO perspective, we've had the perspective of the Swiss-German government, we've had industry, we've had BARDA.

For me one of the really interesting questions here is whether there was learning also from other areas, we've only talked about AMR as a problem in and of itself. But I assume all of you here in the room were also dealing with other infectious-disease challenges.

Was there one area from which, at this very early stage of the AMR debate, there were learnings being brought in? Was there a model area where everybody thought, oh, we should learn from this in order to solve AMR? Or did it emerge *sui generis*, in and of itself?

PB

There is this area of neglected tropical diseases, where we knew for ages already that the patent system doesn't work because there is no market. Either the countries are poor, or the patients are poor, or both are poor. That's why nobody is investing because you will never earn any money with that.

01:41:09

MPK

Make enough [money].

61 James Love. "Prizes, Not Prices, to Stimulate Antibiotic R&D," *SciDevNet*, March 18, 2008, https://www.scidev.net/global/opinions/prizes-not-prices-to-stimulate-antibiotic-r-d/.

62 Outterson first discussed the tension between R&D & stewardship (conservation) in 2005: Kevin Outterson. "The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law," *University of Pittsburgh Law Review* vol. 67, no. 1 (2005), https://doi.org/10.5195/lawreview.2005.70;

Aaron S. Kesselheim and Kevin Outterson. "Fighting Antibiotic Resistance: Marrying New Financial Incentives To Meeting Public Health Goals," *Health Affairs* vol. 29, no. 9 (2010): 1689–96, https://doi.org/10.1377/hlthaff.2009.0439;

Aaron S. Kesselheim and Kevin Outterson. "Improving Antibiotic Markets for Long-Term Sustainability," *Yale Journal of Health Policy, Law, and Ethics* vol. 11, no. 1 (2011): 101–67, https://scholarship.law.bu.edu/cgi/viewcontent.cgi?article=1694&context=faculty_scholarship.

PB

And that is where we knew, also, what you can do as DNDi was set up about 20 years ago and has since then successfully developed treatments.

I think that was one area where the knowledge transfer was better than TB, because TB was the other area where there was also more experience with resistance, and it was a bacterial infection. Even in WHO it was a very specific area where there was not a lot of interaction as I experienced. At least we never had some people from the TB coming while from neglected tropical diseases, there was a much better interaction.

MPK

But this was why GARDP was created by WHO and DNDi, because of proximity of what was expected to be needed for a non-profit product-development initiative.

PB

We could have asked the MMV [Medicines for Malaria Venture] as well.

MPK

Absolutely, and also malaria, HIV/AIDS and there was an issue of resistance.

PB

Yes.

MPK

So yes, the model of PDP was something that looked like a structure, we could address the issue of a pipeline.

CK

Joe, you had your hand raised.

01:42:38

JO

One of the biggest areas we drew inspiration and knowledge from was the bioterrorism area itself. I mean, in the wake of Amerithrax 9/11, the public was very concerned, there was a high demand for products that addressed those concerns. But there was no market, and there was no incentive to make those, because there was no guarantee that there would be any revenue on the back side.

And so, a lot of the way we modelled things, in terms of supporting companies, supporting industry, was born out of that experience. Unfortunately, we only listened to 50% of the best practice. With the bioterrorism support, there was both R&D support to make the products and de-risk them, and push incentives. And then there was actually a pull incentive on the back end, to actually begin to stockpile and purchase products, and guarantee company's revenues for successful development.

We only took the first part, which was the R&D support to develop the products. That helped address the acute need at the time, that these companies couldn't raise money for clinical development due to the frozen investor sentiment at that time. But then, what we observed from 2010 basically through 2018 to 2020 was successful clinical development of multiple products, and then subsequent commercial failures or bankruptcies that resulted because we were missing a holistic ecosystem of support.

01:44:27

FV

One last question, if I may. I am just wondering if these bioterrorism and preparedness incentives had gained any traction in Europe or at the global level? Or was it something only related to the American context?

JO

In my experience, certainly, maybe the R&D support but not the stockpiling at that level. But I think... I haven't followed what the European Health Emergency Response Authority (HERA) is doing, but it looks like at least there's been some sort of infrastructure setup recently to maybe rectify that, but I don't know if they are stockpiling products or not.

JA

Not that I am aware of either. Europe focused more on the IMI, previously mentioned as R&D.

JO

Yes, and we worked with IMI, or attempted to, at least coordinated with them during their existence.

MPK

I think it is interesting that the two models that we just discussed, the PDP model for neglected tropical diseases and the model of what you did for stockpiling for bioterrorism. Actually, neither of them addressed the issue of the need for stewardship for AMR, for antibiotics.

Because for neglected tropical diseases, it is not a question that if there's too much produced, there's too much used, then so what, nobody was worried about that. The issue was more having access of sufficient material. For you, in the bioterrorism there was then stockpiling, but also in your experience, actually, you found enough incentive to have industry work on these new products for stockpiling them. Instead, also, of not having any market at the end because you only wanted to stockpile.

But yes, surprisingly enough I think neither of these two experiences were put together to shape something that might have been, I don't know, interesting for the private sector. Well, you tried a lot actually, there was a lot of incentive, and prizes, and all this, but it never worked.

MAP

With this, we are moving, anyway, toward the second session that will go deeper into this. So, I'll pass onto Erin.

Session Two: Shaping & Conceptualizing Solutions

ELP

I think we are following the natural flow of the conversation, so it is a good time to transition anyway. So, just as a recap, our first session was very much about discussing how AMR became a problem, and how people became aware of it, and what their initial reactions to it were.

This second part of the seminar today is going to be about shaping solutions. How did the solutions or the funding models actually develop from those initial ideas that were coming out? So, the initial questions to keep in mind throughout this conversation would be: why and how did specific funding models get chosen as solutions? Why were others not considered or rejected off the table as not valid? And then also, how did those models change over time, were they always static or did they evolve in some way? So why don't we start with James, and then we can go over to our online participants afterwards.

01:47:59

JA

Sure, I'll have a go. So, when we talk about funding models there's what we now call push funding, which is simply funding that comes from somewhere, usually a government in one way or another, or set of governments or foundations, to the researchers directly, and usually it is purely just to advance the research, but rarely will it enable the research to go all the way through the particularly expensive later stages.

From the perspective of industry, many of the PDPs work in that way, and work very well, particularly in the earlier stages where there's a scale that works. But it gets much harder as you go through, and in particular in the big Phase-2, Phase-3 studies, where sometimes the budgets just still don't work.

And that's often where, in other disease areas, the industry will come in and will be able to raise the money from investors based on the commercial return. To put the big hundreds of millions of dollar investments into those later-stage studies.

Now that works in many disease areas, but as we've just been talking here, it doesn't work in antibiotics and, actually, in some other areas, including some other infectious-disease areas. And that is because the return, as I said in my opening remarks, that the sales forecasts don't make the economic sense that companies, or the investors behind companies, need to justify that investment.

01:50:19

In order to think about solving that economic problem, it is not one or the other (push or pull funding) because there's two bits that you need, that actually do achieve a different purpose. And I think that's broadly accepted, and a number of the papers and discussions that Kevin listed really landed on that.[63] I would say that the work Stephan led, and DRIVE-AB, very much got to that place.[64] The Jim O'Neill review certainly did.[65]

There was the one, Kevin, you didn't mention in the US quite early on, and I did a presentation at Brookings that you invited me to at about 2012.[66] I forget the name of that project, but they did the modelling as well, and it is exactly the same. In order to make the economics work some sort of additional pull incentive is needed.

To Marie-Paule's point, and what I've always pushed here, and I think again is now very well accepted, is that that additional incentive should be not linked to the amount of the product that gets used.

63 See Appendix A.

64 Drive AB. *Driving Re-Investment in R&D for Antibiotics and Advocating Their Responsible Use* (2014), https://drive-ab.eu/.

65 Review on Antimicrobial Resistance. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. London: Wellcome Trust and Department of Health, 2016, https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf.

66 Beginning in 2012, the non-profit organisation, Brookings Institute, held a series of events on Antibacterial Drug Development. The referenced event likely refers to the meeting: Incentives for Change: Addressing the Challenges in Antibacterial Drug Development held on 27 February 2013, Brookings Institute. "Incentives for Change: Addressing the Challenges in Antibacterial Drug Development Meeting Summary." Washington DC: Brookings Institute, 2013, https://www.brookings.edu/wp-content/uploads/2013/02/meeting-summary-20130925-FINAL.pdf.

I am not using the term de-linkage, because that actually means a number of different things to a number of different people.[67]

In the context of antibiotics, I think it is very clear that—and Otto said this right up front—the more that any antibiotic gets used the greater the chance that resistance will develop.

01:52:04

Therefore, any new antibiotic should be looked after, which means used as little as possible, but the patients that need it should get it. So that in itself is a very difficult balance to achieve. However, what we have said for many years from the side of industry is that the economic incentives should be as aligned as possible with that goal. And that's why a pull incentive that's not connected, or not dependent, to the amount of the volume of the product that gets used, is what we've been calling for.

And indeed, when you look at today – I know we are looking backwards – but where we are today, there are I would say most of what we think are quite promising, pilots or proposals or discussions are all focused on this separation. None of them are proposing a volume-based incentive.

So again, from my perspective, jumping back to 2012, Kevin had put forward this concept in a number of papers he referred to earlier than that, including at Uppsala in 2010. I think the response from industry initially was, not very sure about that, frankly. It sounds like it's setting a precedent that could become problematic in the future.

But then after we'd thought about it more, and recognised that the antibiotics market, and others where resistance is a critical factor, are actually unique. There's no other part of medicine, really, where if you come up with the best product it shouldn't be used very much, right, that's pretty unique.[68]

67 In a separate oral history interview, dated 9 May 2024 with Erin L. Paterson, James Anderson elaborated that "delinkage" is a term used to denote the idea that a financial reward should be delinked from the amount of the product that gets used. In the case of antibiotics, this would negate a desire to overuse or prescribe a product as such use would not lead to material gain. However, some critics of the pharmaceutical industry use the word "delinkage" to indicate that the cost of R&D should be delinked from the price of the medicines. "That's more like an ideological argument about how pricing is done rather than anything related to public health or specific to the antibiotics case."

68 In chat, KO: The move for industry to accept value instead of volume is a significant one. This idea was in the academic wilderness for years before widespread adoption. It is now the core principle in the UK program.

01:54:05

Anything else, heart disease, oncology, mental health, if you come up with the best treatment, it should be used as much as possible pretty much. So, once we'd got over that concern then… And in my Brookings presentation, I think, was the first time that I was aware of that industry was publicly saying, yes, we like the idea of this separation.

It has to be done in the right way because it is solving a very specific problem here, it is nothing to do with IP or even price. This is about incentivising R&D in a way that aligns with the public-health need of conservation. So, let me pause there. There are more places we could go but I'd say Otto can continue the conversation.

ELP

I believe it was Peter first, unless there was something online quickly, Kevin I think had something, and then we'll go to Peter after.

KO

I'll let Peter go first.

PB

Yes, I looked up a couple of documents, because now that you are asking, it is quite interesting. And you asked whether we learned from other disease areas. I mean, with Marie-Paule, we were responsible for this.

I was still working for Switzerland when this global strategy on intellectual property was negotiated, and it was really focusing on neglected diseases. And it was Type-I, Type-II, Type-III. Type-III were diseases only prevalent in low-income countries. Type-II was mostly. And Type-I was specific needs of developed countries for diseases like cancer.

01:55:48

And that is where we had identified this lack of R&D because of no money to be made. And that is where, then, we systematically looked at, through these two commissions in WHO, EWG, and CEWG, what are the instruments?

And we looked at a new indirect tax, voluntary contributions from business and consumers, taxation of repatriated pharma-industry profits. New donor funds for health research, open-source patent pools, health-impact fund,[69] Thomas Pogge's priority-review voucher, orphan-drug legislation, transferrable IP rights, green intellectual

69 In chat, KO: Pogge was also a champion of the Health Impact Fund. For more information, see: Kevin Outterson, Thomas Pogge, and Aidan Hollis. "Combating Antibiotic Resistance Through the Health Impact Fund." *Boston Univ. School of Law and Economics* vol. 11, no. 30 (2011): 36, https://scholarship.law.bu.edu/cgi/viewcontent.cgi?article=1387&context=faculty_scholarship.

property, removal of data exclusivity, biomedical research and development treaty. And so, I mean, we looked at everything. From moving back exclusivity towards giving more exclusivity, everything.

Two expert groups, in the end they came up with this R&D treaty.[70] And this was really not at all linked to AMR or antibiotics. And only when it came up that, 'oh my God, antibiotics is a similar area.' That is when in Marie-Paule's cluster, we worked on IP and innovation – not at all responsible for AMR in WHO – we thought, 'well, then why don't we actually use what we explored for neglected tropical diseases, for antibiotics.' And from these debates we knew exactly which ones would be politically feasible and which ones not: 'No way.' I mean, either industry would never support them, and related, governments that would likely be more R&D-based.

01:57:29

And that is when we started working with groups, and I remember the meeting where James [Anderson], you presented the GSK proposal[71]. There was the Novartis Health Impact Fund proposal. There was Kevin with Thomas Pogge and Aidan Hollis.[72] This was Health Impact Fund. Then there was a DNDi model, Jamie Love came with something else.

So, we really went through it, and in the end I remember I sat there with Manica [Balasegaram] and Jean-Pierre Paccaud, and we said, 'well, the R&D treaty, we will never get it. Removing data exclusivity, well...' So, we thought the product-development partnership, we knew it is something that is feasible, it works, it is not going to solve everything, but at least it would mean that in a relatively short-term we could be operational and do something, versus writing more reports.

And that is where also, I mean, James Anderson supported us. Joe, you were with BARDA, you supported us. And we had the really good coalition which was spanning from Manica being at Médecins Sans Frontières (MSF), South Centre was also fairly sympathetic. And companies... Paul Shaper was there for Merck Sharp & Dohme (MSD). You were there, Petra Laux for Novartis.

70 Information on the unratified treaty can be found here: Knowledge Ecology International. *Views on the Report of the WHO Consultative Expert Working Group on Research and Development (CEWG).* (2012), https://www.keionline.org/21832;

S. Moon. "WHO's role in the global health system: what can be learned from global R&D debates?" *Public Health* vol. 128, no. 2 (2014), https://doi.org/10.1016/j.puhe.2013.08.014.

71 Finnegan, Gary. "We Need a New Way to Pay for Antibiotics – Dr David Payne." *Horizon: The EU Research and Innovation Magazine,* November 23, 2017, https://projects.research-and-innovation.ec.europa.eu/en/horizon-magazine/we-need-new-way-pay-antibiotics-dr-david-payne.

72 Kevin Outterson, Thomas Pogge, and Aidan Hollis, "Combating Antibiotic Resistance Through the Health Impact Fund".

JA

Paul Stoffels [overtalking], yes.

PB

Paul Stoffels from Novartis. They all said, 'it is okay if you do what we as industry will not do because it is not commercially interesting, it is a good idea.'

01:59:06

And that is also why it was a bit the coalition of the willing, for something which we knew is feasible without having a political fight. And we also avoided asking the member-states approval of all WHO member states because we would never get an agreement on anything. And then so we actually engineered this separately, with enough support from all parties not to get into trouble, but not to ask everybody. And so, I think that is... And we had reviewed, extensively, all these models, but we knew that ... at WHO there are things we can do and others we can't.

ELP

Just to follow up on what you had said, you had said you knew that the PPP model worked, were there specific public-private partnerships that you'd used as proof of saying, these have worked in the past. And what would those have been in your discussions?

PB

Yes. DNDi, MMV, TB Alliance, I mean, there were different...

MPK

It was mainly... I think it was mainly the DNDi-model work.

PB

And in hindsight, maybe we should have looked at MMV more closely. It is also a bit about ideology, MMV was always considered to be too closely modelled as a non-profit pharma company. While DNDi was a bit more MSF, activist, this is about access...

02:00:46

MPK

Advocacy, yes.

PB

What appeals to people.

MPK

No, it is true. But also, we... I think we wanted a model which was not dependent on one single public-health funder, like the Gates Foundation, which was the main funder of MMV, which tied their hands.

PB

And DNDi put resources into it, after others were not interested.

ELP

Kevin, I believe you were next.

KO

Thanks. I am thinking, I've been writing in this area maybe for 25 years at this point, and at the beginning I and other researchers, academics writing at the time looked for models, and the only models out there were DNDi. And that was for neglected diseases.

The thing that drove me to differentiate was my article first published in 2005, which recognised just the difference, this wasn't just an innovation-versus-access question based on patents. This was actually a stewardship, let's not waste the drugs, let's preserve them for the long haul, and how patents were an inadequate way to manage that.

And so that was 2005. I spent a lot of time with Jamie Love the next two years, he published his thing in 2007,[73] and we began...

02:02:15

I began publishing about de-linkage over the next few years, what James Anderson refuses to call de-linkage. But separating the R&D recovery from the cost, the price of the product, the unit price of the product. He's right, industry was, I would say, more than sceptical the first years of that process. And I think an important change over the past 20 years is that because of stewardship, because of the need to preserve these drugs, industry has embraced a different reimbursement model. But it was based on academic work that goes back to 2005.

PB

As a funny anecdote, just the wording which is... Looking at incentive models that de-link the volume for the sales: the US was the only ones that opposed this. It was a consensus pending on US, actually, in the final document. I mean, at the end they agreed....

KO

Sorry, one other thing, and sorry for jumping right back in. But part of the fruit of all those discussions—academic literature, and then conferences, and then lots of side discussions, and what Peter just described—is that people eventually moved towards consensus on this issue.

In 2016, when I received the award from BARDA to lead the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), and BARDA and Wellcome Trust was their co-founding

73 James Love. "Measures to Enhance Access to Medical Technologies, and New Methods of Stimulating Medical R & D." *UC Davis Law Review*, Symposium, vol. 40, no. 3 (2007), https://lawreview.law.ucdavis.edu/archives/40/3.

partner. I insisted, based on my academic work, that we include stewardship and access requirements in every CARB-X contract from the beginning.

02:04:08

The companies were initially... Joe, you can say more, they were very sceptical or opposed to this idea. Over time, over a one-year process, we came to the public-transparent stewardship access requirements that's applied to every single recipient of every CARB-X award from the beginning.

And that was with the US government's blessing, and obviously with Wellcome's enthusiasm and support. But also based on work going back, at that point, more than a decade, showing that because the antibiotics have resistance, and that resistance is transmissible you have a global collective-action problem that requires careful thought on use.

And plus, the fact that we also acknowledged that, based on Ramanan's papers,[74] and just everyone else's observations that more people were dying presently of lack of access to existing, typically unpatented, generic antibiotics. Then there were, today, from the multi-drug-resistant bacteria, so we needed to prioritise stewardship and access. And the only reason it was done the way that we got it done in 2016 was because of all the discussions that had occurred, based on academic literature, conferences and meetings prior decade.

CK

So this... I don't know if you want to quickly introduce James Love.

ELP

Yes, just to let everyone know, James Love has just joined the meeting, he is from Knowledge Ecology International (KEI), I am sure everyone is already familiar.

02:05:50

But where we are right now is discussing how funding models have been created, and how different perspectives have added into that creation process or differed over time.

74 In chat, KO: Ramanan Laxminarayan has written many papers in this field, but these two may be of most relevance here: Ramanan Laxminarayan, Adriano Duse, Chand Wattal, Anita K M Zaidi, Heiman F L Wertheim, Nithima Sumpradit, Erika Vlieghe, et al. "Antibiotic Resistance—the Need for Global Solutions." *The Lancet Infectious Diseases* vol. 13, no. 12 (2013): 1057–98, https://doi.org/10.1016/S1473-3099(13)70318-9.
and: Ramanan Laxminarayan, Precious Matsoso, Suraj Pant, Charles Brower, John-Arne Røttingen, Keith Klugman, and Sally Davies. "Access to Effective Antimicrobials: A Worldwide Challenge," *The Lancet* vol. 387, no. 10014 (2016): 168–75, https://doi.org/10.1016/S0140-6736(15)00474-2.

MPK

And there was a lot of discussion of you Jamie. And very positive, how you managed to actually push this field. Too bad that you were not with us when we had that.

KO

It is all recorded.

JL

I am embarrassed that I am late, I am sorry about joining the call late.

CK

No problem at all. So just to continue the discussion that we had just had. It is quite remarkable when we compare it to where we started out earlier today: limited awareness of AMR, clinicians are raising awareness, some people are listening, but innovation isn't very high on the agenda. And then suddenly around, I think we are all talking about the period between 2010-2015, suddenly there seems to be this consensus on the need for more innovation forming. Now in history we always like to zoom out and also look for structural factors that enabled this consensus to form. What do you think it was, at this moment in time that had changed? Why was AMR suddenly able to make these inroads, why was there consensus forming? Were there any new actors who were joining the table? Was the group of discussions widening? Or as a collective here, what was it about this time that was different?

02:07:05

SH

As I said before there was now a real threat of the superbugs. We cannot just talk about the political arena. It is before we had MRSA, which was already making headlines, especially in Europe. And you remember in the UK it was on the political agenda during the elections of Tony Blair.

Then there was a VRE, the vancomycin-resistant enterococcus, which was a huge problem in the United States. But still the clinicians, they didn't really believe in the large threat. Because they said, it is mostly colonisation. Yes, we have trouble sometimes with transplant patients, a very specific one.

But when we started to see the gram-negative superbugs all over the world, it was like a catalyst of change, this kind of thing. And then of course all the other players, and things, started to get together.

02:08:42

But I would say, without having this huge threat of the gram-negative superbugs we would not have had the right momentum. And there would have been, still, this kind of dissonance, or you said discrepancy, between some visionary mostly Europeans, very proactive like Otto in

the mid-90s. Holistic thinking, which is not always the case in the United States I have to say.

Because Claas, you asked before, the Europeans tend to be a little bit more pessimistic in general, and so they are more into very proactive prevention compared to some opinion leaders in the US. We'll say, 'okay, let's see what is happening, and if there is a problem we will fix it.' So therefore, I think that's very important to state, the superbugs helped us a lot.

MPK

And I think there was also more recognition that infectious disease could create havoc, I think. Because before [the perception] was: 'Infectious diseases? That's the old time.' And [now] the world had gone through, in 2006-2007, through a scare of H5N1. And there was the H1N1 pandemic in 2010. And there was, although it was not infectious, it was the 9/11, but all this craze about bioterrorism and anthrax.

And all this brought also to the politicians the reality of threats by infectious diseases. And I don't know when they started calling the AMR threat 'the silent pandemic,' but I think, all this together was also something that moved the politicians to think a little bit more seriously about it. I would say it is not one single event, but it is the synthesis of all that.

02:10:42

KO

I typed in the comment[75] that in my mind it was the clinical societies that began talking about this, in the US IDSA but also in Europe. In the late 2008, 2009, 2010, and that's what motivated a lot of energy from my perspective.

OC

I agree, I think it is what Stephan was saying. I mean, we saw the problem. And I think what really triggered it was the data, the burden data that came out from the EU first, and then from the US, and then continuously moving into the media, making it clear that people are dying. And now late, too late, but in 2022, the GRAM study on the global mortality.

02:11:48

So, I think that we saw the problem but it did not translate into political action because we had been covering it up in very technical expressions. Language is a crisis, language around this problem is really one of the major problems we have. We don't talk about the patients, we don't talk about diseases, we talk about a technical concept, and we understand it, but no one else does.

75 In chat, KO: The clinicians spoke up, especially in US and Europe. There was the rising awareness of the problem, and a separate discussion of the way of funding R&D.

CK

One of the things I was just really curious about, nobody here mentioned the Obama election, the change in the White House administration. In the UK David Cameron's government gets elected shortly afterwards. So, you think this was something that was rising organically out of the community or whether people were also becoming more receptive in the policy sphere because of other factors outside of the science so to speak.

JA

I agree with what Marie-Paule said really, that it was a snowballing effect. I think, certainly in the UK, that Jim O'Neill's work was pretty significant, and I think worldwide as well. I think Dame Sally is an incredible leader in this space worldwide, and she kicked off, and pushed, and pulled, and promoted a tremendous amount of all of these different things.

And then the UNGA in 2016 actually... Although sometimes it is not clear exactly what an UNGA does achieve. I think in this case it came at the right time; it meant that many heads of state were then talking about this otherwise rather public health topic. And we are all looking forwards to later this year, and also looking back to eight years ago and saying, what has happened? Well, actually a lot has happened since then, right?

02:13:51

Certainly, it helped the industry, or helped encourage the industry come together and make the two declarations that we did. The Davos Declaration at the beginning of 2016, which was a set of commitments from the industry and 100 companies signed it.[76] I mean, that was pretty much unprecedented at the time on anything. Companies rarely all get together and commit in public to a number of things like that.

Of course, we were asking for others to do what we felt was needed there as well. That did mean that at the UN in September 2016, again the industry was pretty prominent taking some of those commitments forwards, and that led into the formation of the AMR Industry Alliance, which was in 2017.[77] Then a few years later on the AMR Action Fund as well.[78]

76 AMR Industry Alliance. *Declaration by the Pharmaceutical, Biotechnology and Diagnostics on Combating Resistance*. January 2016, https://www.amrindustryalliance.org/wp-content/uploads/2017/12/AMR-Industry-Declaration.pdf.

77 The AMR Industry Alliance is a coalition of about one hundred pharmaceutical companies, who aim to curb antimicrobial resistance in four different areas: research & science, appropriate use, access, and manufacturing, https://www.amrindustryalliance.org/.

78 The AMR Action Fund is a public private partnership (PPP) that invests in companies developing antimicrobial therapeutics for priority pathogens and advocate for market reforms to change how society values these drugs, https://www.amractionfund.com/about.

And I think all of that came about because we recognised there was a big public-health need, that was increasingly clear. We did want to be part of it, we did feel that we could contribute, that we had a role to play, and we wanted to be on the front foot. And there was the right leadership in enough of the companies to make that happen.

The final piece I will say, which Otto also referred to in his opening remarks, the data. AMR is a bit amorphous compared to HIV or TB, right, and that's still something we wrestle with today.

02:15:34

Combined with that the data was poor, was really poor. The EMA study that you did, that number, I think it was 25,000 deaths, right?[79] And that number was used for about a whole decade until the Institute for Health Metrics and Evaluation (IHME) came along and said, actually it is a lot higher than that, right? And that was because there wasn't really any other good measure of how big the problem really was. And I think that made it harder as well, to attract attention a more macro level.

PB

You asked about the governments, I remember. I mean, you are looking for witnesses. When Germany had the G7 presidency starting in 2015, and also 2014, I went to the chancellery for WHO to see the German sherpa [personal representative of a head of state who prepares an international summit], and we pitched the idea of doing a global R&D fund for antibiotic research.

And it was funny because we gave this data, so many people are dying, and then the reaction was: 'we just had the climate-change guys, and they said more people would even die. And then there's the ocean-protection people, they also told us we could all die by I don't know when.' So, they were absolutely not impressed by how many people would die, because everybody is actually saying that everybody...

MPK

We will all die.

02:17:06

PB

We all die. But then they picked up this thing, and I believe it is because of what Stephan said, because they got this also from the Robert Koch Institute, and from clinicians in Germany, that said that it is a problem.

79 ECDC/EMEA Joint Working Group. *The Bacterial Challenge: Time to React. A call to narrow the gap between the multidrug-resistant bacteria in the EU and the development of new antibacterial agents. Technical Report*. Stockholm: European Centres for Disease Control/ European Medicines Agency: 2009, https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

It was not us who actually convinced them; they had heard this in Germany from people actually working at the front. But then one reason why the AMR R&D fund did not make it onto the G7 policy agenda at the time was because the British were waiting for the Jim O'Neill report.

JA

Those Brits.

PB

Because they wanted to wait for next year when the Jim O'Neill report [AMR Review] comes. Well, maybe, let's say, maybe also they had a better idea than just putting up a global R&D fund. But it was interesting that you had two super-committed governments, and since then the two most committed European governments mostly could not agree on what they would actually do. Political ownership matters. I mean, maybe I am biased. I am German.

JA

Where's your pull incentives in Germany?

02:18:29

PB

Yes, this is it, yes. It is a different philosophy also, the Germans wanted to put public money into something which is real, and they can touch. And the UK wanted to incentivise, and then industry is going to do it.[80]

ELP

I'd like to re-frame this moving on because we have a very similar question that I'd like to ask: Who were these national drivers, or non-governmental factors, which were within this international sphere, and who really did want to own this issue? As you said, it bounced back and forth between different governments, but were there other people who stood up and were trying to be louder voices in the room?

80 In chat, JL: If you had a ven diagram about who thought it was a big problem, and who thought it needed innovative financing, you could split that into who wanted more traditional incentives like tradeable patent extensions and who wanted delinkage. I think the R&D incentives reforms conversation in some ways began earlier, and antibiotic drugs seemed like a problem to fit a solution. One of my accounts of the debate on financing incentives for antibiotic drugs is ANNEX 1 to this 2014 WIPO document, WIPO. *Committee on Development and Intellectual Property (CDIP). Fourteenth Session. Geneva, November 10 to 14, 2014*. Geneva: World Intellectual Property Organization, 2014, https://www.wipo.int/edocs/mdocs/mdocs/en/cdip_14/cdip_14_inf_12.pdf and ANNEX C: APPROACHES TO SIMULATING INNOVATION FOR THE DEVELOPMENT OF NEW ANTIBIOTIC DRUGS' https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-gcp-irc-website/meetingdocuments-technicalconsultationantibioticinnovation-2014-05-13.pdf?sfvrsn=df6f077f_4.

JO

Well, I think it is off topic now. But there was a question about the Obama administration's involvement. And I do think they played quite a key role. I think they took action based upon the bringing about of public awareness of others over several years. But they played a key role in establishing the national strategy and setting up presidential advisory committees.[81]

They approached us [at BARDA] and said that they wanted to see a bold partnership that would demonstrate that the US government was taking tangible action in this area. That direction led to the establishment of CARB-X. They more than doubled the amount of money, and funding, which was going to BARDA to support antimicrobials. And then they explicitly issued an executive order that directed us to support these products as a function of addressing antimicrobial resistance and not just bioterrorism.

So, I think they played a catalytic role in expanding what we were doing in terms of public-private partnerships in this space.

JL

From our perspective there were separate conversations about antibiotic drugs from a threat and a public health thing with a pretty significant constituency. Around the same time there was a separate discussion about reforms of how you finance R&D, both globally and what kind of incentive mechanisms, what kind of subsidies are necessary.

02:21:23

And I was noting that for some of the people working on the reforms for the incentive systems, and the intellectual-property systems, antibiotics initially seemed like a convenient problem to fit a solution. I mean, people thought, well, we have a solution, we would like to see implemented, maybe antibiotic drugs, maybe we should look at those because those are a good example of why you might want to do this reform.

But separately there were people that really mobilised around the threat of antibiotic-resistant diseases that really would do anything to move the ball. And so there was this conversation about, on the funding side, about things like patent extensions, and big collaborative efforts to fund R&D, and big advance-purchase funds and things like that on the one hand.

81 In chat, JL: These committees include the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (launched in 2014) and also the September 2014 report: Executive Office of the President and PCAST Antibiotic Resistance Working Group. *Report to the President on Combating Antibiotic Resistance* (Washington DC: President's Council of Advisors on Science and Technology, Sept. 2014), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast_amr_jan2015.pdf.

And both those conversations were happening at the same time, but they involved different people who were more prominent in these different zones at the time. And some people, like I think Joe and Kevin, were really familiar with what was happening in both conversations.

02:23:14

MPK

It is interesting, to follow up on what was said about the rivalry. But competition between nation states to do something like that. Many of those who are the funders want to be seen as driving it, but at the same time they don't want to be alone, because if you are alone it means that maybe it is an error. So, they want to have others joining in, and co-fund. But the others also have other horses or fires or other parties or other items that they have decided to fund.

So, it is difficult to bring it together. So, when you look at CARB-X, this was a unique coming together of something for which at BARDA there was an executive order, so this was a fact. And then Jeremy Farrar [Director of the Wellcome Trust], as an individual, I think was powerful enough to convince Wellcome Trust to go with it. So, people matter, and it was Jeremy… Of course, he had to convince his board … he had enough convincing power to work with together with BARDA to create CARB-X.

But we look at the same time at GARDP, which was founded about the same time, and also looking at having support by member states. And here, although as was discussed by Peter this was a proposal which was not contentious. Everybody nodded, including industry, that it was the thing to do. But then the difficulty was to find somebody who wanted to fund it.

02:25:05

So of course, the Germans, who hadn't been able to create these R&D funds, were willing to fund this. But the UK, because of the Jim O'Neill report, Sally Davies, which was a very powerful person on the international scene at that time, wanted to follow the O'Neill report conclusion and was not at all interested. And we tried a lot to interest Sally into doing anything positive for GARDP, there was no way.

So, we ended up with insufficient funding for GARDP. It could have been a little bit better and there is a contrast with certain enthusiasm, or an agreement of all the international community in terms of funding potential. I am still surprised by the absence, apart from the Germans, of very high-level and substantial funding that has come to this initiative. I don't know whether anybody can add on that.

PB

I just wanted to draw a parallel to neglected tropical diseases, where we had the consensus that there is a need, there is a lack of research, there are instruments, and Jamie was essential in driving all these discussions. And then there was the Commission on Intellectual Property Rights, Innovation and Public Health, there was the first commission in 2006,[82] then we had this action plan, then we had the CEWG which was already the third commission, 2012.[83] They said, do the R&D treaty. Member-states of course didn't agree to the R&D treaty. Then they said, yes, but you can do pilot projects. We had these six pilot projects[84] for which we had to raise money, which went nowhere, we silently let them die at one point in time.

02:27:07

MPK

You killed them.

PB

But then the member-states were keeping doing resolutions, then they asked the secretary, 'yes, we want to have a better concept.' So, TDR came up with the concept – a really-sophisticated concept – for a 100-million R&D fund for neglected tropical diseases. Even that one, member states did not agree to it. And we didn't say, put it in WHO. We had said, you can put it wherever you want, I mean, whichever institution you trust.

So basically, as a WHO person, having worked on this for a long time and doing these reports, I was tired of this attitude where you pretend you want to do something, but in the end the people die in Africa and not in high-income areas, and when it comes to money, there is none. And that's why still, for neglected tropical diseases, we have zero pull mechanisms. All right, priority-review boards, but this is a US thing.

And that is why you could move stuff on antibiotics, because actually it is also a German problem, a Swiss problem, and a US problem.

02:28:28

82 WHO. *Report of the Commission on Intellectual Property Rights, Innovation and Public Health, Technical document*. Geneva: World Health Organisation, 2006, https://www.who.int/publications/i/item/9241563230.

83 Details on the CEWG's financial concerns and continuing actions can be found here: World Health Assembly. *Consultative Expert Working Group on Research and Development: Financing and Coordination. Corrigendum, Provisional Agenda Item 13.14*. Geneva: World Health Organisation, 2012, https://iris.who.int/handle/10665/79197.

84 In chat, KO: the projects were a follow-up from the CEWG report; DNDi. *Demonstration Projects in the Framework of the Follow-up of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG)*. Geneva: Drugs for Neglected Diseases Initiative, 2013, https://dndi.org/wp-content/uploads/2009/03/DNDi_Briefing_CEWG_Demonstration_project.pdf.

OC

Well, it is certainly a collective-action problem in its core. But it is interesting to listen here, we seem to come to an agreement that after 2010, or beyond a few years, there is an agreement that we can't continue with the sales-driven model, okay.

So, governments need to intervene, they need to take more responsibility for this global public good. But I think that the options are diffuse, and too complex, and too many. I mean, if we are a government, I don't have the full control of the landscape, and it is difficult to read everything that's happening, so this is my sense only.

But where to put the money? And why should we go there, and there, or there? And what options are there? I mean, we are not really playing out this yet for the governments, I think, in a good way. So that's one of my points. I also want to get back to the start of this meeting, and the development of penicillin. I mean, it all started with an academic public-private. And where are the academics today? Where is the real innovation, and where is the breakthrough innovation, and who is funding that? I think that many countries, like Sweden, have put a lot of money into AMR research lately, but it was faded out but then it came back. But that funding is for basic research, it is surveillance, it is mechanism action, it is resistance mechanism. Sometimes it also comes forward to something that could be a potential drug. And then over the years these researchers would call me up, 'oh, can you… Where is the money?

02:30:15

Can you guide me, where is the next steps? We have something interesting here.' For what? No, money. So, the early stages and also for academics of course the career is driven by papers, so there is a risk-aversion also here in terms of going safe, and not trying to go the real bold ways.

So, my point here is that the early stages, including academics and also, primarily maybe, SMEs, that bottleneck needs funding. And I think that is in fact, coming back to the end-to-end approach we have published on for over ten years, we need to see the whole spectrum. And governments might be lost here, and can we somewhere, at some time, agree upon how to advocate in a concerted way.

ELP

As we are coming to the end of this particular session, I think Claas will have a last few words, or comments.

CK

I think Peter's observation is an interesting one. Antibiotic innovation is one problem, but actually there are sometimes too many knights trying to solve the quest. Historically, movement is often a question of political ownership. If we look, for example, at HIV/AIDS before the Bush administration's PEPFAR program, there wasn't a lot of movement in terms of drug availability despite many actors in the field. Why hasn't something similar occurred in the case of AMR?

02:31:51

$500 million from the US government is obviously a big commitment from the perspective of an individual, but in terms of state commitment, in terms of driving R&D, it is not that much. The US has invested more historically in other health-priority programs.

In the context of the UK, we've seen the enactment of the Antimicrobial Products Subscription Model. It is a lot of money for the UK, but then again they have invested much more money in other health priorities. Germany has also invested a bit in the R&D hub, and a bit in these R&D plans.[85]

But it really seems curious that, given the scale of the monster that is to come, given these warnings of global calamity etc., that no government has truly wanted to own the innovation topic.[86]

85 In chat, KO: Germany has invested more than 100M Euros, fairly evenly split between GARDP and CARB-X.

86 In chat, KO: I see progress in G7 on owning antibacterial R&D.

Session Three: Fixing the Pipeline

02:50:37

NW

So Kevin, do you want to kick us off? And then I'll talk about the next session.

KO

It is just a shame that Marie-Paule is gone because some of it was in response to some of her comments. I remember having a conversation with Manica [Balasegaram], the executive director of GARDP in, I don't know, 2015. And I think we were in China. And he drew on a napkin, literally, what he thought could happen with the thing that eventually became GARDP. He had no title at that point, he was just thinking out loud about what the world needed.

02:51:19

It was prior to the call for proposal from BARDA, so CARB-X was not in my mind yet. I also remember John-Arne [Røttingen] having a conversation with me about the thing that eventually became Coalition for Epidemic Preparedness Innovations (CEPI). We haven't talked about CEPI, but in terms of resources, viruses attracted a lot of resources. And part of it is because of the world's experience with some bacterial pandemics like MERS and SARS, and now COVID.

But the data was really visible to people, and of course CEPI has collected billions of dollars, not hundreds of millions. But I think that's because of the salience of the problem that they are addressing in their mission, not because the world is making a mistake in giving money to CEPI.

Between CARB-X and GARDP there was a report under the Swedish presidency of the European Council this last time, not the one in 2009 but last year, which laid out the fact that there's inadequate funding for all the push incentives in this antibacterial space right now.[87]

And our efforts at CARB-X are really complementary to GARDP's, [we focus on earlier stages of the pipeline and they focus on later stages]. I think it goes back to the core of, let's focus on articulating the mission and the problem with data, so that we can attract new money, like CEPI successfully did, to address a pressing problem.

NW

Thank you, and Jamie, you had your hand up as well.

02:53:05

JL

Yes, thank you, I wanted to comment on some of the developments like financing in terms of an international mechanism. Right now, internationally, the primary mechanism to fund R&D is intellectual property rights agreements.

The idea that even developing countries have to, except for Least Developed Countries (LDCs), have to have patents on pharmaceuticals, and there's big trade pressure. And there's a full-court press, by Europe and the United States and other high-income countries, to push out really strong intellectual property (IP). And there's nothing like that on the government-funded or subsidy side that you see on the intellectual property rights (IPR) side, it is kind of an unbalanced thing.

Where you look domestically, like in the United States, everyone thinks the National Institutes of Health (NIH) is really important, and BARDA's role, and the Defence Department role in developing things, and it is more of a balanced approach. Not completely balanced, but there's quite a bit going on regarding these things. So, the idea is that, internationally, the trade framework should be more balanced, or look at more than just monopolies and high drug prices you get from patents and things like that.

87 General Secretariat of the Council. *Council Recommendation on Stepping up EU Actions to Combat Antimicrobial Resistance in a One Health Approach. Proposal for a Council Recommendation*. Brussels: Council of the European Union, 2023, https://data.consilium.europa.eu/doc/document/ST-9581-2023-INIT/en/pdf.

It really started early, it started really before the, in terms of my involvement, before the 1995 Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreements. And I put this link in the chat,[88] it is an older link that we put up on some of the early negotiations in R&D funding, but I'll just mention a couple of events.

02:54:55

Around 1999, I'll skip some of the earlier things, but around 1999 there was a World Trade Organisation (WTO) agreement in Seattle, and at the same time MSF is organizing this working group on R&D. And I think the MSF working group on R&D was the first thing I've ever seen that was a big NGO, well it is not the NGOs because MSF was dealing with everyone, I mean, they were bringing governments in, they were bringing the industry in, they had the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), they had lots of different people there.

But they were clearly the leader in this conversation, and James Orbinski was the president internationally, and Bernard Pécoul was leading the access campaign. And I was really keen for them to put forward the idea of an international treaty on R&D, because we had been saying for some time already, back in '99, that you can't really solve the problem of high prices in developing countries if you don't look at how you fund R&D, and what the international framework for funding R&D is.

And if it is only about IP, if you just have one tool like patents, that's all you are going to look at, and anything that weakens patents is going to weaken the innovation. And that's not going to work, not going to play out well for people. So, we wanted people to look at alternative funding mechanisms.

And MSF was really back and forth, they liked the neglected-disease effort they were doing, but the idea of an R&D treaty was something that they weren't completely sold on. But the day that this meeting was held in Paris, in the lead up to the WTO meeting, it turned out that they won the Nobel prize in the middle of the meeting. And then James Orbinski went out and gave a press conference.

02:56:41

I'd been pounding on him at the time, and then he made this speech where he said they were going to use the money, in part from their Nobel prize, to push for the R&D treaty, and they got that going. And

88 In chat, JL: Some links to older negotiations on R&D funding. "Negotiations on R&D funding agreements", *Knowledge Ecology International,* accessed September 08, 2024, https://www.keionline.org/global-norms-rnd-funding.

then there was this 1999 statement, this Amsterdam Statement.[89] But it was always like, is the R&D agreement, would it be just about areas of well-known market failures like antibiotic drugs or tropical diseases? Or would it be more general for even non-communicable diseases and across the board?

Well, the fact that some of us wanted the reform efforts to be more thorough, and you saw this as the AMR debate played out. Some of us wanted, and still do, want really deep, substantial reforms in the way you fund R&D, that de-link the incentive system as much as possible from the grant or the monopoly. And that's a scary thing for pharma companies.

And because antibiotics were always part of that conversation—and a really strong case for de-linkage, or a really strong case for global agreements on funding, raising global commitments on funding even basic research or R&D subsidies in different ways—it was always problematic, because we would lean on the antibiotics story, it was a legitimate story, as a strong argument for the other reforms.

02:58:18

And the industry would be very nervous about that because they hated it. They were open to the idea that you'd do something different in antibiotics, but they didn't want that to contaminate the political support for strong IP, and they hated compulsory licence, stuff like that.

So, there was this situation where the ability to get international agreement on how you fund R&D, in the areas where it was not so controversial—like antibiotic drugs, like neglected diseases—was always running in parallel with the debate about, do you extend these reforms more generally to areas where there's inequality of access in things like cancer drugs and things like that. So, I just wanted to bring that up.

Now, not all the people that were working on antimicrobial resistance were really paying much attention to this other conversation, but it spilled over. I mean—and I think Kevin could probably confirm that, that it was... and Marie-Paule, Peter and other people that were following this—that the attitudes about how deep you go on the reforms, or how ambitious you are in an international agreement, always has a backdrop of the fear that the industry has that you might run the table, and reform more than just tropical diseases or antimicrobial drugs. You see that even today in the Pandemic Treaty negotiations, where there's a big effort by people to man the ramparts and say, the system works great, you don't really have to change very much.

And that's just where we are, I don't know if Peter, or Marie-Paule, or Kevin agree with me, but I mean, I think they do, but maybe not.

89 James Love, "Amsterdam Statement to WTO Member States on Access to Medicine," *Knowledge Ecology International* (blog), November 26, 1999, https://www.keionline.org/25089.

03:00:15

NW

Marie-Paule has joined again online, and Suerie Moon's just joined us in the room. So, before we go on, I'll just frame the third section.

We started touching on some of these topics in the second part, in Erin's area of discussion just before. We are going to talk now about solutions, incentives, so thank you Jamie for teeing that up very nicely, de-linkage, and accelerating and fixing the pipeline.

And there are three big areas that we want to touch on, so one is government, which Claas mentioned at the end of the remarks of the last session. Another one is funding, and then of course there's the access piece, which you've also just touched on Jamie.

Peter, would you like to make some comments about that? At some point in your remarks, Jamie, you were talking about AMR being used as a tool because it was less controversial than other areas.

03:01:30

But in other places it also was a challenge that made people raise the ramparts as we discussed in the first section this morning. And you talked about policy interaction with the German government, or the Swiss government, in terms of fears of the kind of language that was used.

PB

Yes. I mean, first I totally agree with what Jamie just said. And as I said, I never again wanted to be more involved into the neglected-tropical-disease issue, because it is like if you do environmental protection and you do nature protection. Nobody cares except NGOs, because you don't make any money, I mean, there are no players.

So, AMR, yes, the Germans were interested, the US were interested. They would eventually put in money, they might agree to some instruments, not a treaty though which didn't get a lot of traction from them.[90] But there was more room to do something, and the companies were agreeable, and supportive, so actually there was more space for

90 The Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) was set up by the World Health Assembly at WHO and presented its findings in a 2012 report. CEWG suggested improvements to R&D coordination and financing including a framework for negotiation of an R&D convention based on Article 19 of the WHO Constitution. WHO. *SEA/RC65/17-Key issues and challenges arising out of the Sixty-fifth World Health Assembly and the 130th and 131st sessions of the WHO Executive Board* no. SEA/RC65/17. Yogyakarta: WHO Regional Office for South-East Asia, 2012, https://iris.who.int/handle/10665/128310;

John-Arne Røttingen and Claudia Chamas. "A new deal for global health R&D? The recommendations of the Consultative Expert Working Group on Research and Development (CEWG)," *PLoS medicine* vol. 9, no. 5 (2012): e1001219, https://doi.org/10.1371/journal.pmed.1001219.

actually creating something, and it was less ideologically poisoned, it was less stuck into, as Jamie said, compulsory licencing, for high price drugs for cancer.

If you do the same thing on cancer, I mean, you are doomed, you will never go anywhere, the companies will kill any threatening initiative because it is their cash-cow. So, I mean, go somewhere where the companies are a bit more open...

And you asked why governments do something. I think in the UK, Sally Davies, she convinced David Cameron. In Germany, we had in the ministry, Dagmar Reitenbach who did a lot.

03:03:32

I think it always hinges on the individuals. It is not that because you have a problem that that translates into action necessarily. I think that is also, let's say, disappointing, but it is a fact.

The other issue is some governments... I mean, the US had BARDA, they had an instrument that works that they could use. Germany created something in the Ministry of Research which allows them to fund product-development partnerships like MMV, like GARDP.[91]

In Switzerland for example, they did this under development cooperation, but that didn't work for antibiotics. And so, whenever we talk to Switzerland they always say, yes, but we can't do it because The Ministry of Health has no budget line, research is only doing university research.

And so, it is also that sometimes the government's setup makes it more difficult for them to do something, because they would have to do something new, and then they have to go to the parliament, and that is of course more complicated.

03:05:20

So, I think it depends on the individual setup, also, of the administration, do they have an instrument they can use? Which is much easier than creating a new instrument.

OC

Yes. Why are governments doing things? Some listen to science. I think it comes from the bottom up really, seldom from the top, at least in my experience in my limited part of the world. It is coming from the scientists and from healthcare, data showing the problem. But then we are facing, again, the institutional-memory problem.

I've been meeting with health ministers, I don't know how many, and I try to get them on the first week where their calendar is not blocked.

91 In chat, KO: Switzerland is in a multi-year process to update its law to permit support for activities like CEPI, GARDP, and CARB-X. The same instrument in BMBF funds CARB-X, at similar levels to GARDP.

And then just continue to 'educate' them. Influence them and educate them. But I think the continuity often lies with bright, interested civil servants in the government, providing the continued momentum. That's the why.

Then the how is an even bigger problem. And what can they do? The easy way is to support more research in their national research agenda, which has happened as I've said before.

But then going globally, I think the real problem we have is that we need to translate the fact that this is a common problem, and what we are doing, what is happening in that country, affects all, and I think we don't have that narrative clear right now. We know that this is a pandemic, or pandemics, we probably should not use that language because it is pandemic fatigue, and it doesn't fit into the virus pandemics. But still we need to really convince government that this is a common problem, and we are not there yet, I am sorry.

03:07:19

CK

If I could just jump in there with a question. I really like the point about continuity within governments, and especially the mid-tier civil service level as being an important area of push. What about push continuity from outside government? So far in this conversation, we've talked about activists, we've talked about clinicians, scientists, and governments, and international organisations. We haven't talked a lot about the funders. And I'd like at this point, perhaps, to push the group also to reflect on the role that organisations like the Wellcome Trust, Jeremy Farrar was already mentioned, but also perhaps the absent role of the Gates Foundation in this.

OC

Yes.

CK

For me this has always been one of the most remarkable things about the AMR field. Around 2000 Gates, GAVI, we also mentioned CEPI later on, coming in. All of these funders make massive differences in the fields that they enter.

03:08:21

What is it about AMR that, perhaps, didn't so much attract the Gates, and how has the Wellcome Trust shaped the landscape around AMR? I don't know if anybody wants to come in on this. Yes, Jamie, please come in.

PB

What is the comment[92] Jamie? I want to hear it.

92 In chat, JL: The Gates Foundation is ideological about the IP issues, even more than many companies.

JL

Oh, from me? Oh, well, yes, I think the Gates Foundation is more ideological about the IP issues than even the drug companies. I mean, I talked to a lawyer once from Microsoft, the software company, once, about their position on patents, because Microsoft was being sued all the time for infringing patents. Because you can't make a hundreds-of-millions-of-lines-of-code piece of software without violating a lot of patents, and they regularly got sued.

And I said, 'well, why doesn't Microsoft see patents as more of a problem?' And they said, 'well, we can pay for it in the litigation, but Bill (it wasn't the lawyers' decision, it was Bill personally,) was like a maniac on strong IP.' And he always was.

He was following very closely a lot of the negotiations on the IP reforms, and if there was something going to WHO, Gates would fund an alternative initiative that he controlled, with groups that he funded, that went in a completely different way. And he would lean on the secretariat of the WHO to undermine, stop, slow down, slow walk, do whatever he could to steer the conversation around anything that threatened strong IP rights.

And that even at some of these WHO negotiations, there was one of them where you had people that could be in the room with the governments that were doing the negotiating, and people that couldn't.

03:10:36

So, groups like MSF would have to be on the outside, Oxfam, different groups like that. And there'd be these closed-doors sessions. But for some reason Microsoft, I mean, I am not even talking about the Gates Foundation, Microsoft, Dick Wilder, would be on the inside as some advisor, and that's because they were the biggest private funder, and they were bigger than most governments in funding the WHO.

So, the role of the Gates Foundation has always been, in our opinion, the biggest problem we've had in making progress on the medical R&D treaty, because the industry thing you can manage. Because the industry was perceived to have conflicts of interest, and commercial biases and things like that. But Gates was perceived as a do-gooder, a philanthropist. And he was giving more money to journalists, NGOs, academics, UN agencies, everywhere in the public-health field.

And so, his opposition to the reforms in this area were really problematic. And then we were really disappointed that, when Farrar was running the Wellcome Trust, that they took the Gates Foundation and leaned on these things. They submitted a paper against the R&D

treaty for example at one point, just out of the blue it came from the Wellcome Trust, and so there was that problem as well.[93]

03:12:05

KO

Okay, just going back about continuity, what is the average tenure of a health minister within the G20? I think it is less than two years, it is short. And so, we've seen a lot of turnover even recently of people that had key AMR mid-level positions within governments.[94] Not at the ministerial level, but lifelong employees at senior levels. So, it is important that this be a career path for some people in that sector.

And where we see the continuity is where we've also described, in the funders, the director of Wellcome is typically two terms of five years. And Gates is for the rest of his life. And for other academics, it is for as long as we choose to follow this topic. But for a lot of the people, we are trying to convince in governments, it is a rotating cast of individuals who have to be reintroduced again to the things that were written back a decade or two ago.

So, it is an interesting issue. But I don't know if it is the same issue for people that work in HIV/AIDS in governments, or in tuberculosis in governments, do they have a more stable career path within that field? It seems like an open question to me.

JL

Can I just add that one of the problems that you have with government people are, like you say, established. Sometimes the next job isn't with the government, it is with the private sector, with the for-profit drug makers. And because of that, if you brand yourself as someone pushing policies that they don't like, that's going to narrow your job prospects when you leave, or it might.

93 The WHO Consultative Expert Working Group on Research and Development Financing and Coordination (CEWG) met 26-28 November 2012. Bolivia, Colombia and Thailand expressed support for a binding R&D Treaty. The Wellcome Trust did not attend the meeting but sent a 6-page floor document criticising CEWG's delinkage advocacy stating that this approach risked disrupting engagement with the pharmaceutical industry; Thiru Balasubramaniam. "Wellcome Trust tells WHO it opposes R&D Treaty and the de-linkage of R&D costs from drug prices," *Knowledge Ecology International* (blog), November 26, 2012, https://www.keionline.org/22073.

94 In chat, JL: Turnover on the Congressional staff level too.

03:14:15

PB

I would like to make two points. One thing that I saw made a big impact in Germany was the 2014 Ebola outbreak. For the first time the general public and politicians understood, 'oh my God, what happens in Africa may actually come to us and really be devastating.'

So that is when for the first time, the Minister of Health started to come to the World Health Assembly, because before the German minister never, came to Geneva and WHO issues were not a priority.

Then suddenly they realised, 'oh my God, this is actually important, and we cannot solve it on our own, we need to work together, and it is infectious diseases.' And so, this was real. And that helped when then people came, yes, and also AMR is also a problem which is a bit similar, it was better, it was much more a thing.

On the Wellcome Trust, I mean, you should of course ask Tim Jinks or Jeremy Knox.[95] But I agree with Jamie, I mean, the Wellcome Trust is very industry-friendly in their way of functioning, even still today. They finance CARB-X and early research, and they think that if they only lobby enough for pull mechanisms the industry is going to fix the problem.

03:15:55

Because they believe in private-sector-driven solutions, if you only give them enough carrots so that they will actually do what you want them to do.

KO

So Peter, I am sorry, CARB-X is non-profit, GARDP also works with private industry. Maybe you are talking about Wellcome, but...

PB

Yes, I'm talking about Wellcome, not about CARB-X. No, no, it is not about the way... Because Claas asked the question. I mean, when we did the AMR, the initial concept paper for an impact fund, which I developed at WHO, we did the economic model with the European Investment Bank, and we looked for supporters.[96]

95 The Wellcome Trust were invited to participate in the seminar.

96 WHO. *A Financial Model for an Impact Investment Fund for the Development of Antibacterial Treatments and Diagnostics, Technical Document*. Geneva: World Health Organisation, 2020, https://www.who.int/publications/i/item/a-financial-model-for-an-impact-investment-fund-for-the-development-of-antibacterial-treatments-and-diagnostics-a-user-guide.

The Wellcome Trust was against it.[97] Only when then the industry came onboard, and the industry picked up the concept, and the industry were in the driver's seat, then Wellcome Trust came onboard.

So, it is also a bit like, I mean, whether it is a great idea or not a great idea, well, we'll see what comes out of it. But I mean, again it is not that one agenda, at the end whether one agenda, one idea, is better than the other. But there were differences in ideas, the same as whether you believe more in providing incentives so that the industry would then do what you want the industry to do. Or whether you put public money into institutions who maybe do it themselves in collaboration with industry. It is a different philosophy and that is what you can see, and what functions better is ... let's see.

03:17:50

But you can see that in organisations. I think interesting also if you look at CEPI, why did CEPI happen? Because the vaccine industry said, we can do it on a no-loss no-profit basis. And it was Andrew Witty, and it was Paul Stoffels from Johnson & Johnson (J&J), and it was John-Arne [Røttingen] from Norway, and it was Jeremy [Farrar] for Wellcome Trust.

And we were in this, they convened this meeting in Oslo, John-Arne, I was there with Marie-Paule. We argued that they should include therapeutics and diagnostics, because it seemed to make sense from the WHO's perspective. But it was clear you could only make it on vaccines because you had the vaccine-industry buy-in, which was amazing.

And that, is what made it happen, it was unique, and it was based on individuals also in companies. I think it is another argument for, yes, that with somebody else than Paul Stoffels and Andrew Witty, CEPI would maybe have been not even half as successful as they've been.

NW

Professor Harbarth, I'd like to ask you, please, about how you navigated through some of these different stakeholders during the DRIVE-AB[98] work, and the focus on the financing piece and the incentives piece that came out of all that work.

97 See Footnote 93.

98 DRIVE-AB stands for "Driving reinvestment in research and development and responsible antibiotic use." The project is composed of 15 public and 7 private partners from 12 countries and was funded by the Innovative Medicines Initiative (IMI), which was a joint undertaking between the European Union and the European Pharmaceutical Industry Association (EFPIA). DRIVE-AB was tasked with defining responsible use of antibiotics, identifying antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, and developing and costing new economic models to promote antibiotic innovation as well as the sustainable use of novel antibiotics, see DRIVE-AB. *About DRIVE-AB*. Accessed May 16, 2024, https://drive-ab.eu/about/.

SH

Yes, we were in a real struggle. It is true that it was the early times when public academic leaders tried to match their perspectives and wish lists with the private sector. So, I think that we were, DRIVE-AB was a little bit a catalyst, it was...

03:19:43

I think, Kevin or John Rex[99] who mentioned that we were the catalyst of change, not only when it came to the ideas, the desires, but also the way how these different sectors interact. And I think that was probably one of the most important heritages of DRIVE-AB, that we learned to respect and to talk to each other in a very direct and unbiased way. Where everybody was clearly communicating what they thought.

And Otto was a little bit, also, a victim of DRIVE-AB because at some point you stepped out with ReAct,[100] and I was a little bit the fool on the hill because I tried to finalise the project, and make sure that we were able to disseminate and finalise the final report, which was really painful. Because at some point, when you have 25 US-company lawyers reading each single word of this kind of document, it was painful.[101]

So, I cannot say that now, personally, I am completely enthusiastic about this experience, but I think the legacy of DRIVE-AB, if you hear many people around this field say, 'yes, it was important, it was a catalyst.' Of course, we had a wide spectrum of voices and opinions, from the Che Guevara approach to what should be done to the very market-driven approach, where the philosophy was that, 'oh, the market still should solve...is able to solve everything.'

So, to reconcile the whole spectrum of voices and arguments, it was a difficult undertaking. But maybe, Otto, you can complement it.

99 Dr John Rex, Chief Medical Officer for F2G Ltd., Operating Partner at Advent Life Sciences, and Adjunct Professor of Medicine at McGovern Medical School.

100 ReAct was created in 2005 as one of the first international independent networks to articulate the complex nature of antibiotic resistance and its drivers. The goal was to be a global catalyst using advocacy, engagement and multi-stakeholder collaboration. Action on Antibiotic Resistance (ReAct), Accessed on May 16, 2024, https://www.reactgroup.org/.

101 Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John Rex. *Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access, Final Report, DRIVE-AB*. Brussels: Innovative Medicines Initiative, 2018, https://www.imi.europa.eu/sites/default/files/projects/documents/DriveAB_Report_FINAL.pdf.

03:21:42

OC

No, thank you for bringing up this. I mean, it is...

SH

And Kevin was also onboard, yes, so I think both of you should...

OC

As you know, I was not so much personally involved in the project really, but we were in fact asking the [EU] Commission, and IMI, and EFPIA quite early on, that there is something missing in the New Drugs for Bad Bugs initiative. Namely what we call the controlled distribution and use, and access. And we sent in a proposal for an additional component of the IMI, but it was sitting still for some time. And then the call for what became DRIVE-AB came up. So obviously we might have been preparing the thoughts on this.

I agree with your analysis, I think it was in that way a success, it was really a difficult situation. But it was a conversation between parties. And the reason for my colleagues advising us to pull out at the end was the fact that there was not full transparency about how the partial de-linkage concept was born and promoted. And the strong industry voices around that, I think that was the real, major issue. But I think that it has really done it. I mean, we can see now what has happened, I think it was a catalyst.

SH

Yes, yes, so maybe Kevin, also...

KO

Yes.

03:23:24

SH

You were also part of the family of DRIVE-AB

KO

Yes, like every family it has some dysfunction, right? But the ReAct position that caused them to depart, the discussion over a partial de-linkage and the transparency over it, or lack thereof. It is interesting that today, really, the industry for antibiotics is more aligned with the position that ReAct was trying to make, the primary position in that report,[102] so we have moved on.

102 In chat, KO: The DRIVE-AB report from which ReACT withdrew; see also: Årdal, Christine, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John Rex. *Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access. Final Report Drive-AB.* Brussels: DRIVE-AB/ Innovative Medicines Initiative, 2018, https://www.imi.europa.eu/sites/default/files/projects/documents/DriveAB_Report_FINAL.pdf.

My personal biggest frustration in DRIVE-AB was lack of continuity. That I felt we had agreed on some things on the first year, and then here comes year three and the industry, some of the industry people are different, and now the documents are being reviewed by teams back at the home office who've never participated in all the discussions. And so, we had consensus in a room on year one that was then not understood, remembered, respected, or something, when more people became part of the process.

So that was structural and reflects the lack of the same people communicating in a way that they can't change their mind without new data in year two or year three.

NW

Yes, Jamie, did you raise your hand?

JL

Yes, Kevin brings up this point where I've seen this before. You are working with a group of people from industry, they start out as hardliners but after a while the conversation proceeds, and you see some flexibility, and you make some accommodations, I've seen this in a variety of negotiations. Like when we worked on the Treaty for the Blind for example, the publishers were the super-hardliners, but eventually they completely came on.

03:25:24

They became much more flexible as it went on. But then you'd have people that were not part of five years of talks on this, who would come in toward the end, and they would go ballistic when they see things coming up that we thought had been fixed.

And that is a problem, you have turnover throughout the food chain, and the value chain, and sometimes the progress, if you are trying to get a consensus of, not even a consensus but enough, knocking down enough resistance to move forward, it is a problem.

Often if you talk to people that were former leaders of R&D organisations... I talked to Jeff Kindler last year at a meeting, and he was the former CEO of Pfizer. And I think he felt that the industry position was pretty hardline I think, more than he was personally maybe. And so that's a challenge when you work, and I think Kevin described a really important point there.

NW

Thank you. And Joe, you talked earlier about government changes, but you do get to a point, in this period of history that we are looking at, where we have BARDA, and we have CARB-X starting to be funded, coming into the end of the time period that we are looking at.

03:27:01

So, could you talk a bit about what was the impetus for finally getting some money on the table? What were the challenges, what were the great pushes, what was the balance between the push and pull that we talk about in relation to the pipeline. And how did it finally get over the line?

JL

Yes, I mean, there was, as I mentioned, a huge amount of resource expansion from the Obama administration that led to CARB-X. That led to a doubling of the budget of the antimicrobials program at BARDA, and that allowed multiple additional partnerships to be formed.

What was missing, despite efforts that were endorsed to try to coordinate some agreement within the federal government on a framework for a pull incentive. We were, despite months of trying, and Kevin can comment a little bit about this too, really unable, particularly with some economists[103] that were in the group, for them to recognise that there was really a problem with the market.

And one that actually would warrant intervention in some way through a de-linkage, or partial de-linkage, or any—insert pull incentive there. And so, what at the time seemed that there was an administration willing to take action, had there been a definitive and consensus position within the government to move forward, quickly, quickly fell apart.

And then in 2016 of course the administration changed, there was zero interest in pursuing any sort of meaningful pull incentive, the questions resumed about why we were supporting antimicrobials at all.

03:29:11

Some of the concerns, also, about having international partnerships were raised in relation to CARB-X. And so those efforts really went nowhere. With pull incentives particularly, BARDA has done a few, done two stockpiling contracts with antibiotic companies, under the auspices of refreshing the antibiotic holdings in the stockpile.[104]

But no one is raising money on the prospect of getting a BARDA [stockpiling] proposal. And so, the impact to the overall ecosystem of small biotechs in this space has been negligible as a result of those.

103 In chat, JL: Which economists?; KO later response: One career economist in the Treasury, now retired.

104 US Department of Health and Human Services. Administration for Strategic Preparedness and Response. "Under Project BioShield Contract, BARDA Procures Additional Doses of Antibiotic NUZYRA from Paratek Pharmaceuticals," *Government News, Medical Countermeasures*, March 5, 2024, https://medicalcountermeasures.gov/newsroom/2024/nuzyra/.

And then the political dialogue here in the US about legislation related to the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act,[105] I am not optimistic on the passage of that bill. I just don't see the political will to support the level of resources that it is asking, despite it being similar in scale to what was done for bioterrorism preparedness in the wake of 9/11, with the passage of the Project Bioshield Act.[106]

And so, where we are left is we keep putting money behind these companies, whether it is early-stage through CARB-X or clinical development through BARDA. And then expecting some sort of different outcome when they launch their products onto the market. And then we've continually seen how that goes. And so, in the absence of any other progress on the pull-incentive front, I don't, at least in the near-term, envision that situation substantially altering.

03:31:02

JL

Joe, which economist?

JO

You are really making me go back here Jamie. Jason Brown was one, they were all from the Treasury department. Randy Brimmer? Kevin, do you...

KO

No, Marenger.

JO

Right, Randy Marenger.

NW

Would you like to continue Kevin?

105 Pioneering Antimicrobial Subscriptions To End Upsurging Resistance Act of 2023 or the PASTEUR Act of 2023, *Congress.Gov,* accessed September 8, 2024, https://www.congress.gov/bill/118th-congress/senate-bill/1355.

106 White House. "President Bush signs Project Bioshield Act of 2004," *News Release*, July 21, 2004, http://georgewbush-whitehouse.archives.gov/news/releases/2004/07/20040721-2.html.

United States Congress. "Public Law 108-276". *108th Congress.* 118 STAT. 835. July 21, 2004, https://www.govinfo.gov/content/pkg/PLAW-108publ276/pdf/PLAW-108publ276.pdf.

Joseph C. Larsen and Gary L. Disbrow. "Project BioShield and the Biomedical Advanced Research Development Authority: A 10-Year Progress Report on Meeting US Preparedness Objectives for Threat Agents." *Clinical Infectious Diseases* vol. 64, no. 10 (2017), https://doi.org/10.1093/cid/cix097.

KO

No, I was just providing the name of the person Joe was talking about. The Treasury folks just weren't convinced that a pull incentive was needed, they thought the market might be able to right itself. If enough people were dying, then the market would respond was their short answer.

PB

Yes, the dead are a market.

NW

Wow. And if we think about the pipeline, albeit we discussed at the beginning whether that's the appropriate way to think about it. But if we think about it, and we think about the money that has come together, whether it is through different initiatives in Europe, or in the US, or I mean, we are at a later stage now with some of the more recent ones. As that money's been brought together, there's also been drugs coming through this pipeline, with the catastrophic outcomes for access and availability that Joe just alluded to, for drugs coming out of the SME space.

03:32:42

Stephan, you talked about lags, the lag in reaction to the clinical need. And there's the lag in reaction to the financial need as well, to fix the financial part of the pipeline. And I don't know to what extent anyone would like to comment on trying to get through those challenges, or successes, or failures, failed initiatives, to try to deal with that lag issue.

Do you feel that there were moments when there were financial initiatives that were put on the table that just couldn't make it through? If you look back with hindsight maybe they would have made a difference.

JO

Well, certainly one of my biggest regrets was that we weren't able to get consensus amongst that group. And in fact, if you would have just taken those economists off of the panel, off of the group, I think consensus would have been achieved. And there was a gravitation to a partial de-linkage model that I think would have been workable, and much akin to what is being proposed in the PASTEUR Act.[107]

03:34:50

But the way government consensus works, at least in the US, is that you can have 30 people in a group, but if two people, or one people disagree, then nothing moves forward. Despite the flaws in the rationale for those people's disagreements.

107 Pioneering Antimicrobial Subscriptions To End Upsurging Resistance Act of 2023 or the PASTEUR Act of 2023.

OC

I think obviously the subscription models in Sweden and UK are a success, I mean, it comes from, again, the facts, and the danger, and the clinical need. So, I mean, that's something that has really worked, although I don't think that, even if it is going to be pooled in a larger subscription model, will it really drive innovation? Will there be sufficient market there? I am not an expert, but I think it may not be sufficient as a pull.

These are late-stage antibiotics, even launched, that we secure the access for because we want it not to be put on the shelf but used really clearly strategically for only those in need. So that is a question we have. We need major pooled pull mechanisms that really make the break. But it is something new, it is something that some governments have understood the need for.

CK

And if I may also ask, obviously it is dependent on who we've invited, we've had the international perspective, US perspective, European perspective. What we haven't really had is the perspective of middle-income countries (MICs).

03:36:52

From the 1980s onwards, nearly all of the world's antibiotics get produced outside of the countries we are talking about, right. And I am well aware of the market pull of the US and of European drug markets. But I wonder, based on your interactions here in the policy sphere, in this grey space, whether you are aware of innovation initiatives from MICs. So, I am thinking of countries like China, countries like India. Whether that role has shifted, whether this, what seems from the outside like a remarkably European, North American discussion, has broadened over time?

JL

One of the issues about how you fund the pull incentives, I mean, the idea that you have transferrable patent extensions and things like that. They are all just different ways you might fund market entry rewards for example. Or acts like a market entry reward in a way, like a priority review voucher or something like that, it is off-budget things.

We thought that, and people who are closer to the data might correct me on this, but we thought that low taxes on the agricultural use of antibiotic drugs for fish farmers, for farming—I have a brother that once showed me that he bought tetracycline in 55-gallon drums—and so I have the impression that was a pretty significant market, and a fairly low levy on agricultural use would be justified from the point of view of the externality of increased resistance from the use of the antibiotic drugs.[108]

108 In chat, JL: On funding of new pull incentives. Why is there not more focus on fees on agricultural use?

03:39:00

And I also thought that low fees on prescriptions in the United States, for antibiotic drugs, would be a problem. I know that at one point I said, well, you could have a three or four, maybe even a dollar per fee on a US prescription of an antibiotic drug in the US, in addition to the agriculture.[109] And someone from, I think, DNDi had the point, or MSF said, 'oh, you don't want to do that because that will raise the price of the drugs in the US.'

And I said, well, you can. That's a cup of coffee at Starbucks, I mean, it is really $1,000 for an antibiotic drug is going to be a problem, but an extra three or four dollars on a prescription for an antibiotic which is not like something you take every day anyhow for the rest of your life. I said, 'of course you can do that.' But there's been a weak will to go where you get the money to pay for incentives that are not based on some patent extension or something like that, or some off-budget things like the priority review voucher. And it has been frustrating for us because we go, well, if you don't like the grants of monopolies, if you don't like high prices, if you don't like a priority review voucher, if you don't like patent extensions. You have to like something that involves money, right? And it has to come from somewhere.

And I find in my fellow travelers, in my anarchist, left-wing, anti-corporate world that I reside in currently, it is a constant source of frustration for me.

03:40:44

Because I think that if you can't solve how you finance the R&D and the incentive structure, not just the grants but the incentives as well, you are going to fall back on the current system. Because at least they are willing to do it, right, so you have to do it some way.

So, I've talked to people once about market entry rewards versus getting rid of monopolies on HIV drugs, once. And people said, well, let's focus on the access part, but we don't want to agree to the financing mechanisms or how you finance the incentive to openly licence your patents. Because we don't want to give any more money to the drug companies. And I said, 'yes, well, of course I understand how that looks to you, but how do you think it looks to them?'

So, it is almost like not an adult conversation about how you approach this thing, and I must say it has been a constant. I blame myself because I feel like somehow, we haven't found the right metaphors, or PR strategy, or we just don't know how to solve the problem politically, within our own community, because I come out of the NGO community.

109 In chat, KO: Aiden Hollis at University of Calgary has written several times on these Pigovian / tax ideas. Barrier includes opposition from the agriculture industry.

NW

Marie-Paule, would you like to comment on GARDP's creation in the context of this conversation?

03:42:14

MPK

I think it was seen as a pretty innocuous creation, so this is why there was an agreement by everybody, because PDP was a model which invested. And the money that was invested at the beginning was quite small, so it was taken up as another push mechanism, but not resolving the issue of the pull.

But as Jamie's just said, we discussed quite a lot, when I was still at WHO on this, with industry lobbies and industry themselves. That if you want a pull you, what is it that you want? And there was no answer to that.

So, I don't know how much this has progressed, but we want more, we want different, but there was never something that would be seen as important enough so that they would say, yes, we go for it. And in this discussion that is, again as Jamie said, it is very difficult to make progress, because you don't know what you are looking for.

PB

I think, picking up on what Jamie said, I mean, for a national or even regional legislator like Europe, intellectual-property-driven incentives are much easier, because you don't need to put up the budget. I mean, look at the transferrable IP voucher that they are discussing, it is budget-neutral for the European budget, because it would be health insurances actually paying for it.

So, it is much easier to convince than—imagine, all this money, they would have to find it in the European Union budget, put it up in a new budget for a new instrument, the opposition you will have.

03:44:16

Versus creating something where you just, you actually do a law which gives some intellectual property right to somebody, and that creates a market position which allows them to actually recoup it somehow, and the budget impact is actually with other people. So, you have different opposition, you have Jamie opposing. But that is why, for example, in the orphan-drug legislation—I mean, it is providing incentives—you had the industry massively invested, because they found these incentives attractive, they can earn, they had high returns that they earned with that. And it remained always, let's say, there is no budget that the Commission has to pay out to companies.

And the other thing which I see also is if you ask the government, the parliament, to come up with an incentive, and then they have to put the money in a pot, and then they have to pay it out somehow, whether it is milestones, or market entry reward, or something. It is also, okay, so we give money to industry, how can we be sure that they don't screw us? Because we give money to industry, so what do we get back?

So, then we get back the patents, but what is the government doing with the patents? They don't know what to do with it because they actually don't sell drugs, because this is not their job.

03:45:48

So actually, what they pay for they don't even want to own it, because they wouldn't know what to do with it. So, it is also something which is, for an administration, very difficult to handle. What is the Federal Office of Public Health doing with IP on drugs?

And then if you give out money incentives without getting something back, yes, that also feels not right. So, I think that is why the intellectual-property system is somehow so elegant, because it is actually just a law you pass in the parliament, and then things happen.

MPK

But it is mainly also because nobody really analyses the downstream cost. Because as you say, there's no money to be put on the table immediately...

PB

Yes

MPK

...but the cost of the reimbursement by the public, health systems are huge, and this is where we have an issue.[110]

CK

It would be interesting to have Kevin's opinion on the market entry reward discussion. Kevin, you said earlier that you were quite vocal in arguing for access provisions when CARB-X was being set up. And I am sure you've been privy to many conversations on market entry rewards, be they IP, or transferrable exclusivity vouchers, or you name them. How do you have the feeling that this discussion has been handled in the US context?

KO

Well, I'll say in the United Kingdom the subscription does not currently have any global access or stewardship conditionalities on the contracts.

110 In chat, JL: The cost of extending the patent of a Keytruda? [Pembrolizumab – a humanized antibody used in cancer immunotherapy].

03:47:56

Having said that though, one of the two companies with such a contract, Shionogi, has signed an extraordinary licence with GARDP. Which in almost anybody's imaginations, giving the IP to GARDP the way that Shionogi did, should satisfy most of our concerns about global access and stewardship in those countries. I would hope that everyone is [there], tell me if you disagree Peter. And so no formal conditions, but one of the two companies who really did an extraordinary voluntary thing.

In the US the PASTEUR Act, which Joe is pessimistic on it passing before the next election, and depending on the next election we'll have different ideas. But in the PASTEUR Act, there is an actual provision which at least lays down a marker in the legislation for having these considerations. My view is that, if you pay enough to the company in the subscription, across the whole G7, so the company really has been rewarded for its sunk R&D cost, then they should be willing to do what Shionogi did voluntarily.

NW

Joe, do you have any comments on that? You alluded to the collapse of the SME-led pipeline in the US. And whether such new initiatives, considering the comments that Kevin made, if those models could be extended would it have helped?

03:49:41

JO

In terms of access or just the financial models? I mean, small-and-medium-enterprise companies licence off global rights. So, it is my view, I don't know that they perhaps have any direct control over access, they sell those rights off to other companies that then distribute in those geographies. In terms of the incentives themselves, I mean, these companies are just looking for an offramp for their R&D, for their investment, so that they can be a sustainable model.

JL

On the issue of willingness to pay, Peter was saying how easy it is to pass legislation that just pushes cost down the road, that Marie-Paule correctly noted is not free down the road.

PB

Not free.

JL

But I've had pretty serious conversations with health insurers in both Europe and the United States, in the private sector, and at one point with NICE.[111] And we posed this question, would you be willing to

111 NICE: The National Institute for Health and Care Excellence, UK.

make contributions to a fund for market entry rewards.[112] If the deal was that you put up a lot of money into market entry rewards, but the price of the products was lower than it would be without the market entry rewards.

So, if you just say, do you want to put money into incentives, as a complementary thing, and nothing else changes, so you don't get any savings anywhere, you are just putting in more money from you. No, they don't want to do that, they hate that. But if you say, there's two different ways you can pay for this, you can either put money into market-entry rewards are you can pay for the monopoly. Would you consider the market entry reward approach as an alternative to the monopoly? And they go, 'yes.'

03:51:52

And a lot of reasons why they like the market entry rewards, one of which is that it is predictable, the obligations are not completely random going forward. And also, they don't have to impose really unpopular formularies on patients, where they say, you can't get something that maybe you feel like you want. And I've had these conversations with private insurers from the UK where there's a small private-insurance market, from the Netherlands where it is a much bigger part of the market, and certainly in the United States. And so, I think that's the conversation.

I think the people that are the biggest constituency for market entry reward reform of the monopoly would be the payers, not the consumers who often don't even see the price in the United States, or in France, or a lot of places. But the entities whose job it is to write the cheque.

NW

But both in the funding of the pipeline, and in the purchasing of what comes out of it, there is this public-private money question that you just alluded to. How do you feel? I guess across the Atlantic these questions are different, and the payers and the systems that support, or don't. So, maybe we come back to Europe to try to think about that, this debate between public and private funding of R&D. And then the end stage when we think about these de-linkages, when we think about the incentives.

03:53:35

OC

Well, first of all, I am not an economist I think this is difficult, We are maybe seeing the light of the new pharma legislation in Europe, where this transferrable patent extension is one of the proposals on the table.

My concern is that, I mean, if there is a company promising to develop a drug with a certain target-product profile and provide also stewardship and access provisions of some type. Where does this

112 In chat, JL: Our conversations with health insurers have suggested there is willingness to pay for [Market Entry Rewards] if there is a savings on the IP side.

[incentive] really kick in? Because the pipeline is so fragile, and we need to have something to pull.

So, all the time coming back to this chain of the events. I think that during the Swedish EU presidency in 2023 there was a long discussion on this topic. And again, the European Health Observatory published a major report like they did already in 2009[113] So another document on moving beyond the previous one, and also elaborating on different PPP, public-private partnerships and models and all that.

But although the governments that were sitting around this table, and their delegations, were then equipped with something, it is a very complex picture of the whole chain from early discovery to marketing and access. And it should probably scare away any government from this because it is too complex, and where do they put the money, and how can they understand the complexity.

03:55:54

OC

I think, after listening to this debate, and the discussions, I think one proposal that came to the table is milestone payments. To see whether something comes up, potentially from the SME—because the pre-clinical pipeline according to the WHO pipeline analysis, 80% is coming from very small SMEs and academia, so that's where the innovative capacity lies—and we need to secure that those drugs don't die. So, I think that stepwise milestone payments would be, in that respect at least, a better way of securing what is coming along, yes.

CK

Just to pose a question here. I think one of the interesting things here, and Otto's really just put his finger on it, is that much of the initial research capacity is essentially public. A lot of this research is going on in the university space. A lot of it is financed indirectly via public funds, be they from BARDA and then via CARB-X, or via other funding bodies that finance early-stage development. What I would really like this group to focus on is where, for you, this boundary between the public and the private actually lies in the antibiotic space?

03:57:21

Because I think for nearly all of this witness seminar we've spoken about industry, with the big I. And we've had one industry representative here who has been very helpful in terms of presenting the GSK perspective, and the British perspective, on it. But I think what is quite remarkable, with how the funding mechanisms have evolved, is that when I actually analyse where the public stops and where the private starts it gets more and more difficult the longer this story goes on. So,

113 Elias Mossialos, Chantal M Morel, Suzanne Edwards, Julia Berenson, Marin Gemmill-Toyama, and David Brogan. *Policies and incentives for promoting innovation in antibiotic research*. Copenhagen: European Observatory on Health Systems and Policies/ WHO Regional Office for Europe, 2010, https://iris.who.int/bitstream/handle/10665/326376/9789289042130-eng.pdf?sequence=1.

what I'd like the group to reflect on is whether you've also experienced this in your own work, is it that the more you engage in the antibiotic-innovation space, the more these boundaries between what is public and private blur?

And when we talk about market entry rewards, and we have this, as Peter said, difficulty of defining what it actually is that we are trying to incentivise here, what are the rewards for the different people. And Marie-Paule has also said this. I mean, how does this relate to the increasing role of the public in just keeping the entire space alive?

MPK

Thanks. Well, I think that this idea of having milestone payments was one of the ideas that we had put into this global PDP if I may say.[114] But the issue is that in order to do it, which I think would be very helpful to keep the very-early pipeline alive, you need to have access to unrestricted funds to start with, and with a serious amount of funds.[115]

03:58:54

And this has never, ever been available. [Most] big chunks of money have always been targeted, except for some of the money coming from GARDP. [However, these targeted] strategies have never been really tested, so we are not sure whether they would work or not, but I think it is worth trying.

Now about blurring of public and private, I don't quite agree with you. Because there is still a difference of purpose and engagement, and the private sector and the industry, the large industry, but even the SME. I think we all must recognise that what is their motivation is mainly profit, and for the small one it is to be purchased by the large one. And these are not the same motivations as for the public.

So, I think, yes, they need to work together, and everybody needs to understand that you can have divergent interests mixed with common interests. But I don't think it is true that they are blurred.

KO

To respond to Claas's call here, I think there has been some blurring, but it is a little different, or some moving towards the centre. CARB-X, I mean, when BARDA started its initiatives in 2014 it was clearly to protect US citizens.

114 Referring to earlier discussion of the potential to set up a global Public Development Partnership at 00:51:06 within the transcript.

115 In chat, JL: This proposal in a WHO negotiation, included the user fee on agricultural use. *Antibiotics Innovation Funding Mechanism* (AIFM) [WHO Candidate Demonstration Project, undated], https://web.archive.org/web/20220119231958/http://www.who.int/phi/implementation/7.pdf.

04:00:36

BARDA represents a minority of the CARB-X funding now, we are mainly a G7 project plus foundations. And the focus of everything that is happening between those funders, and their discussions, is really about focusing on things that are global priorities. And it turns out that the top four bacteria killing people in low-income countries are the same four, in a different order, that kill people in Europe and North America. So that's a blurring I do see, or a convergence I see.

On the public-private balance, in some neglected-disease spaces, I don't know, Dengue perhaps, you don't see a lot of private companies operating because there's just really not a path for them. For antibiotics, as the large companies left, there's still a lot of small, private companies. The WHO pipeline report describing the companies, more than 200 companies in the pre-clinical space.[116] At CARB-X we are aware of maybe another 100 of them globally.

So, we still have a lot of small companies, the big ones are largely gone, but a lot of small companies that are trying to work in this space. And so, the question is, do we give up on that and go to Dengue or the neglected tropical disease sort of model, in which there is no private enterprise. Or do we try to work with them, and make it into a system in which their private interest and the public-health pulls are better aligned? So that's how I would frame it, instead of it being a shift from a purely private model to a purely-public model.

CK

Any reflections from the European side, Peter? Oh yes, sorry.

ELP

Jamie has just raised his hand.

04:02:40

JL

Okay, well, one thing that has come up, and in our conversation with companies is they complain about market entry rewards because they feel like, well, we do things, they work, they don't work, but we want to work on the next project. And they feel like they are too episodic, they like the idea that if you have a drug on the market, this is mostly from bigger companies, you have a steady stream of revenue so you can maintain your R&D staff and things like that, and you don't have to fire everyone once a product gets through the door or something like that. The idea that building a team and maintaining a team over time requires not big spikes and valleys in terms of when the incentive money comes through.

116 Valeria Gigante, Mark Butler, Richard Alm, Pilar Garcia-Vello, and Hatim Sati. *2021 Antibacterial Agents in Clinical and Preclinical Development. Overview and Analysis*. Geneva: World Health Organisation, 2022. https://iris.who.int/bitstream/handle/10665/354545/9789240047655-eng.pdf?sequence=1.

So, if you have a drug on the market, and you are making money every single year for 15 years, or 14 years when you have an effective monopoly, that allows you to build an institution that has continuity, and memory, and all those good things, and stuff like that.

And if you just have big market entry rewards, the idea is that somehow that works against the idea that you have this team that you maintain over time. I just bring that up, because I think that's one of the more persuasive arguments, I've heard against things I am working on.

04:04:28

PB

Yes. You asked for a European perspective. I mean, and I think that's also important on the Wellcome Trust, they did the Jim O'Neill report which was a really a big milestone.[117] And probably back then we had the—what was it?—one billion per new drug, and the ballpark figure was six new antibiotics in ten years. Which is reasonable, six billion among the G7 countries over ten years is not that much.

And still we were never nowhere near any consensus that they would get their act together and do something jointly. I mean, nowhere even close. And Joe says that PASTEUR Act is rather unlikely, which would be the biggest single one. Let's see what Europe, whether there will be something. So, I mean, if you said at the beginning in your introduction, Claas, that we look back, and we want to draw back the clock and make that it as it was before. I think even today it is much different than 2015, I think today, one billion, probably the companies may not even actually do much, because now they want obesity drugs which give them 20 billion per year.

So, I mean, the expectations of shareholders may have actually also evolved, that they don't even think that this is actually even that interesting. So, I think we tend to want to, as you said, do something and then it is as it was before. Maybe that is actually never going to happen, I mean maybe we have to be more future-looking and say, well, maybe we create something very different. But also, if then they have these examples, yes, but they managed to do the Global Fund, they managed to setup GAVI.

04:06:39

Yes, that's a while ago, I've not seen so many big initiatives coming out of these organisations. I mean, WHO, the Pandemic Treaty,[118] I am not super-optimistic that there is going to be a strong instrument coming out of these negotiations. It is more difficult than ten years ago; it is even more difficult than 2015. And both in terms of getting an agreement as well as in terms of finding the money.

117 Review on Antimicrobial Resistance. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations.*

118 Negotiations for the 2024 *Pandemic Prevention, Preparedness and Response Accord* were still ongoing at the time of the witness seminar.

So yes, and I am not even sure you said we get more public money and less private, I am not sure we get enough public money through whatever instrument, whether it is push versus pull. So, I think it is a very different environment we are in than in 2015, if you think about multilateralism and what these organisations can do.

What was the last big initiative the G7 succeeded on? What is the last thing you remember G7 did on public health? I mean really [done], not a declaration. G7, G20, I mean, now you can see how it functions, they have health working groups, they meet, they agree with difficulties on a text. Yes, and so what?

NW

Maybe if we go back in time.

04:08:43

We've talked about the clinical need that emerged, and then the need for specific agents, the antimicrobial resistance that was building. The emergence of the superbugs that drove some of the decision-making I am on the scientific side within the pipeline. And then initiatives like GARDP and CARB-X that emerged to deal with trying to push some of that scientific work through the pipeline. And now we are at the stage that you just alluded to Peter, on the 'we need some really big pull incentives to fix the other end.' As we see some of these drugs coming through the pipeline, you've written on it a lot Kevin,[119] we've seen drugs, during the timeline that we are looking at, we've seen drugs approved, we've seen most of them approved in the US, we've seen many of them not accessible anywhere in the world today.

And so, there's this gap between the creation of the push incentives and the difficulties of the pull incentives and multilateralism that we talk about now. What conversations have you had in that time period, with policymakers or with funders that have tried to get over those barriers. Because there's this hole that we've alluded to in the conversations today. Marie-Paule, you had your hand up so...

MPK

Yes, you are now talking about what is needed to make a scale difference. I was always looking at the difference between Global Fund funding, and what is requested for AMR. And what you see with Global Fund with many countries, at least in Europe, it starts with a president, it is not a question.

04:10:35

So, we've been in many opportunities, many other projects, trying to convince the French government that they should move their funding, not to abandon the Global Fund, but some of the funding might be

119 Kevin Outterson, Ebiowei S F Orubu, John Rex, Christine Årdal, and Muhammad H Zaman. "Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020," *Clinical Infectious Diseases* vol. 74, no. 7 (2022), https://doi.org/10.1093/cid/ciab612.

used differently whatsoever. And even say that they don't have a lot of clout for what they owe, the billions that they put in the Global Fund. But it doesn't work because it is the president who decides. And then nobody says anything against it.

So, when I see the need for funding for AMR, I think we haven't been able, the community hasn't been able to reach to this level of advocate, and this is what is needed if we want this to come on a reasonable-competition level, with, I don't know, with climate change or whatsoever. We are too low, we are the Minister of Health, the Minister of Agriculture, and they have to justify and fight with the other ministers about the funding. And this is why it is still a relatively low profile. But how is it possible to go one step higher is something that I quite don't know.

04:12:06

JL

It took really a long time for the patent system to become a global system, I mean, it wasn't until 1995 that it even imposed requirements to have developing countries give patents on pharmaceuticals.

And so, one of the problems in funding incentives, or funding R&D in general, is the free-rider problem. I mean, why if the UK has a subscription model and no one else does, that's a big burden on the UK. And people want BARDA to fund everything, but we are only a quarter of world GDP, and so it is really difficult to get from where we are right now to where the patent system has evolved over the last 150 years of agreements on patents.

And that's why some of these conversations about putting R&D into trade agreements, or into WHO agreements, or G7 agreements and things like that is so important. It is how do you share the cost of, whether it is direct funding or incentives, I mean, basically how do you get people to participate?

And one thing that we've noticed that some countries like Germany are really negative, for example, on some of these things. They trust themselves; they think if Germany promises to do something, they are going to follow, they think some countries, they don't trust that much. And you have changes in political leadership. Even the US right now countries don't know if NATO will be around if Trump gets re-elected.

So, it is a little risky for people to enter into long-term commitments if they don't think their partners are in it for the long-haul. And if you've ever been to a restaurant where people leave the restaurant before the bill comes, and then you start with 12 people, and then you have seven people, and the bill comes and they didn't pay, that's an unpleasant experience.

04:14:26

So that's what funders think about for R&D funding, they don't want to be the last person at the table when the bill comes. And that's a Global Fund problem right now, right, because Global Fund has been around. The initial politicians that got all the glory for doing the Global Fund are gone, right, so the new guys, you don't get any glory for continuing the policies of your predecessor.

And so, we've thought a fair amount about this issue. One thing that we've proposed, that we think we've had a good reaction from rich, hard-line countries, is the idea of introducing to the WTO, an agreement on the supply of public goods.[120] Where it'd be a voluntary, opt-in commitment you could make to do something, so you wouldn't have to do anything but if you did agree to do something like fund an antibiotic-drug development, or paying for refugees, or whatever it was that you wanted to fund. Even though it was entirely voluntary to make the commitment, once you made the commitment then you would be bound and subject to dispute-resolution penalties from the WTO cross-sector if you didn't follow through. And the model for that is the WTO Service Agreement.

04:15:48

And we've had conversations with the director general, we are supposed to submit a paper on this, a new paper on this to her. She's tentatively agreed to chair a meeting of maybe a dozen countries, east, west, north, south, to see if there's buy-in on this idea. And there's been some interest even at USTR (Office of the United States Trade Representative) on this idea, and some people within the European Commission find this an appealing idea.

But what I am getting to is this idea of how you get durable commitments for something that doesn't happen in 12 months, it is going to take years to do, and it is going to be expensive. It is not a trivial, unimportant issue, and it is a barrier to building some of the funding models that are really important in this area.

NW

Kevin?

KO

I was going to take the conversation in a slightly different direction, we've barely talked, I think I heard one comment, maybe it was during coffee or something, about really, we say AMR, but everything's really B [bacterial]. And so, this thing about silos, right, CEPI raised a lot of money, and lots of money and pull incentives effectively for COVID, a virus, right, pandemic virus.

120 James Love. "Proposal for a WTO Agreement on the Supply of Global Public Goods," *Lecture at WTO Public Forum*, September 21, 2011, https://www.wto.org/english/forums_e/public_forum11_e/wto_supply_of_public_goods_kei_2011_e.pdf.

And Global Fund, it is a different infectious-disease-organism silo, and almost all the policy work and the discussions that have led to where we are today have been bacteria. And I am not aware of deep, enduring partnerships, linkages, working together with the antifungal, the other M, microbiological, groups. So, it is worth noting at least, right, that we all still remain relatively siloed by where our pathogens of interest fall on the tree of life.

04:17:36

NW

So our big three topics for this part were governments, finance and access. Is there anything else that anybody else wants to put into the conversation on those three broad topics before I hand over to Claas and Fred to carry on with the next section?

Session Four: Reflections & Stocktake

CK

Thank you everybody for some really stimulating reflections on 20 years of antibiotic innovation. What Fred and I have decided to do in the last session is to give you the opportunity to reflect on the period from 2015 to the present day. I think we've all already been doing this in lots of the comments. I would also like to give you the opportunity to highlight what we've missed.

To kickstart this final session, let's start with the COVID-19 experience. I mean, in many ways the AMR space had its glory time in 2015, and regardless of how we tracked it in terms of reports published or money committed, this period between 2014 and 2017 seems to have been a real high point of global attention for AMR. And this high point precedes the COVID-19 pandemic where discussions about global access, innovation, etc., have all been re-triggered.

04:19:28

Given the expertise that we have here, virtually and also in the room, now is the opportunity to reflect a bit on how COVID has changed the space again for AMR. Kevin has already alluded to the fact that viruses have their own interest groups, and their own lobby. But how has COVID influenced your thinking about AMR?

And the second thing I'd like to interlink with this question is that in parallel to COVID, one of the big things that did come up for the antibiotic space were discussions about re-onshoring production. In my historical introduction, I mentioned that one of the big differences that we have between us now and this golden era that we are constantly evoking, is that Europe and North America no longer produce the drugs themselves in their geographic territories. And there is a certain impulse now to re-onshore production. Based on your expertise, what difference would that make, could that make, for the R&D space, to actually have production expertise back where all of these innovation debates are taking place? So COVID-19 and onshoring, if anybody wants to comment.

OC

I can start commenting on COVID. I mean, just broadly of course. COVID made Global Health, and the interest in health and health systems absolutely boom. I mean, people around the world understood how critical it is to have access, prevention, treatment, diagnostics. So that has possibly also helped AMR, although the overuse of antibiotics in healthcare settings was obvious.

04:21:18

And also, the lack of access to effective antibiotics in the poor countries in the community, also very obvious. But having said that, the comparison between a slow, non-visible threat, and a fast-travelling, very visible threat is our enemy here. I mean, this is where we are, it is again about the narrative.

We wouldn't have been able to cope with COVID that rapidly without diagnostics, which was number one, diagnostics. And then came vaccines, and then also treatments. I mean, we haven't been mentioning diagnostics until now, and that is another problem that is becoming more and more critical for antibiotics, and antibiotic resistance, because of the need to pinpoint the type of bacteria and a resistant pattern.

If you should be able to conserve the lost resource tracks, and we don't have that, we are far off. We have technology from the 1800s, cultures, smelling plates, looking at bacteria and all. It's too slow, and that is another business model that needs to be ramped up. So, I mean, the urgency that came with COVID, in terms of the technology development, should at least improve in the antibiotic sector, yes.

KO

A couple of things that worked well on COVID, on the response.

04:23:09

One is that we got lucky and had phase-2-ready vaccine candidates. So, somebody had been supporting all that work prior, and it didn't have to start at the basic level. The world deployed billions of dollars in push incentives, and billions of dollars, essentially, in pull incentives on guaranteed supply contracts. But still most of the projects that were supported by push incentives failed. You have to remember that that it is just an ordinary attrition. That's just natural science. But you have to fund a bunch of things in order to get the one or two that you want.

The most prominent, just terrible, failures are of course the vaccine nationalism and lack of any concern when these contracts are being awarded for the global health needs. And some of that was driven just by all of the problems that we all are very familiar with, on each country just looking out for itself at the time.

In bacteria some of these learnings from COVID are applicable and some aren't. The first one: it is nice to have things that are along in the pipeline, ready to advance, I think that's still equally applicable. On the fact that push and pull incentives can work to get an articulated target-product profile across the finish line, I think that's right.

On vaccine nationalism, I don't think the constraint on access for bacteria, for antibiotics and whatnot, will be an unimaginable increase in demand, and production facilities unable to keep up. As Peter could speak to more authoritatively on SECURE at GARDP for cefiderocol.[121] It is the predictions on volume of use, or within tighter bands than what we had in COVID, and the question's [about creating] a sustainable market that can function for decades, not just meeting the demand for the next quarter.

04:25:11

So, on that last piece, how to do access, I think we have to distinguish the differences between a viral outbreak or pandemic and a bacterial evolutionary change over time. And plan appropriately for that. So, learn lessons, but not every lesson is directly applicable from COVID.

CK

Peter, do you want to come in on the access issues? And I think also in view of the ongoing shortages of antibiotics across Europe.

PB

I mean, you spoke about the onshoring. I don't think that we are going to see this. I mean, you saw in the US, Pfizer, which is I think the biggest pharmaceutical company globally, doesn't produce enough benzathine penicillin. [The Americans] now have to import benzathine penicillin from a miniscule French company, Delbert, which is a really small laboratory. And it is not that Pfizer is lacking money.

But I think I am more optimistic about the US because the home market is really big. But in Europe? In particular antibiotics? So complicated to manufacture, high investment, and then no guarantee that buyers will buy from you.

04:26:49

And it is not easy for government to do it. I mean, look at Switzerland, I mean, there is no state-run manufacturing. The hospitals buy from wherever they want to buy from. It is very complicated. In centralised systems, so like the UK, it is easier. But Germany, for example: it is hospitals procuring most of the antibiotics, or insurance is paying for them, they don't buy Germany-made antibiotics. It is not in line with their procurement systems. I mean, maybe we'll get into it, that they will prioritise environmentally-sound production, maybe they will come up with stuff like, buy European first. I mean, the onshoring agenda, it is not a straightforward thing to just do.

121 GARDP, *Access to Antibiotics*, October 4, 2022. https://gardp.org/access-to-antibiotics/.

OC

I would say it is a really complex ecosystem. We had one of the first meetings on this, with shortages of generic drugs.[122] And there is a commission to the Swedish public-health agency to come up with some ideas about how Nordic collaboration on production, or at least access, and potentially production of generic antibiotics will look. So that's on the table.[123]

NW

Joe and Jamie have their hands up.

JO

Yes, I'll jump in. So, this may be a little bit more of a cynical view. But yes, I think COVID actually sucked the air out of the room with what we were trying to accomplish, particularly related to market reforms for [antibiotics]. Policy makers that were involved in this, during that period of time, their attention was solely focused on COVID, understandably so.

04:29:01

The government funding agencies similarly were all hands-on deck, focused on COVID, appropriately so. In some initial conversations in the wake of COVID that we had with policymakers, they said, show us that there was increased AMR as a result of COVID.

So, they [told us] to wait until there was actually definitive studies that came out, and then once we had that data we went back to them. And they said, 'oh, well, that's interesting.' And by the time that had occurred, I think there was a little bit of a tiring on the part of the policymakers of dealing with infectious disease. And there was a continuing loss of appetite to support additional resources going to a potential infectious-disease threat.

So, I think COVID, in a way, burned away three or four years. And actually, I think, at least the experience in the US, with a segment of policy-makers there's a significant undermining of their views on the [value of the] public health sector as a result of COVID. And that has made our jobs exceedingly more difficult than it was before COVID.

122 WHO. *Antibiotic Shortages: Magnitude, Causes and Possible Solutions, Meeting Report, Norwegian Directorate of Health, Oslo, Norway 10-11 December 2018*, Geneva: World Health Organisation, 2019, https://iris.who.int/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf?sequence=1.

123 Charlotta Edlund. *Mapping the Antibiotic Market in Denmark, Finland, Norway and Sweden – Focus on Clinically Important Antibiotic with a Risk of Insufficient Availability.* Uppsala: Platinea, 2024, https://www.uu.se/download/18.372739df18d8724e32efbba/1707745814389/240212_Mappingtheantibioticmarket_PLATINEA.pdf.

So, I think we all agree that COVID's really important, and it highlighted a lot of successes, but I think to the average person involved in making policy, I think we've got a lot of work to do.

CK

James, if you want to come in.

04:30:35

JL

Yes, there are lessons from COVID, we've covered a lot of ground. The other people have done a good job of highlighting a lot of the challenges. I want to mention a couple of things. One, of course, the fact it was considered a national-security issue for a lot of countries really changed things. You had the US sending armed members of the military into the factories where countermeasures were being made, and these interdictions of countermeasures.

There was a report recently in *The Guardian* that the UK considered sending the army into the Netherlands, in a military mission to get some COVID vaccine or something like that. And that led to a secrecy and a lot of lack of cooperation. I think that's sad.

The speed at which the virus was spreading. I mean, HIV didn't spread that fast, and so [viruses] are not all the same. But that was a special characteristic, it was really pronounced in COVID, yet nothing was [attempted]. We tried to get CEPI to engage with Cuba on its vaccine development, and CEPI initially said they had a rule they couldn't deal with sanctioned countries like Iran, Venezuela, North Korea, and Cuba. And we said, 'well, but you are a Norwegian. The sanctions are American sanctions, and you are a Norwegian NGO, why do you care?' And the reality is lots of people cared because, if you get on a Treasury Department sanctions list, it is pretty bad for you no matter who you are. And in order to avoid that you have to have specialised lawyers that know how to sort through the sanctions. We wrote to the Treasury; we asked them to have some of the things that are well known you could do in these cases.

04:32:53

You could whitelist suppliers, whitelist products, you can make things simpler. But the sanctions go not just to the products, they go to anyone that provides a loan, financing, transportation, Federal Express, anything, and that's something that rarely gets mentioned, but I just wanted to bring it up.

Another thing was the regulatory issues. The pandemic agreement negotiations, one of the things you are talking about, which is pretty good, is can they make it easier to register products in multiple countries. Because the regulatory process is protectionist all over the

place. I mean, why is it that we'll have a shortage of a generic drug for cancer in the United States, that's widely available as a generic in Europe.

And that's because the local generic companies also benefit from protection from competition from other countries, not just the brand-name companies, and they have vaccines. So that's one issue that came up as a regulatory barrier. It could be a great incentive for people developing a drug if there's something that has a fast-track regulatory approval in lots of countries, that also becomes a huge financial incentive for the developer of the vaccine or the drug.

Another thing that we were frustrated by was the lack of head-to-head trials. And if the funding for the development of the drug put... Or the advanced-purchase drug...

04:34:26

Or the procurement process, if they would put obligations onto the supply products for head-to-head trials,[124] independently designed by third parties. I mean, we never really knew how the protein vaccines stacked up against the messenger-RNA vaccines. I thought that the NIH was all over the messenger-RNA vaccines because they were excited about the technology, about a new platform.

And you had the older recombinant-protein vaccines that were really cheap to make, and the beta-vaccine not subject to any IP at all. And there wasn't much of an interest in seeing was there much difference in the efficacy and safety, or the durability, of vaccines. And some of these things are in the interests of the developers, like a bigger regulatory footprint, if you can get things registered in lots of countries.

And some things are in the interest of the consumers of the products, if you have head-to-head trials and funding of independent trials to test products. But this could be, and should be, integrated in the process of public subsidies. There should be obligations to make your products available [for trials]. And also, you might find some way to figure out how to finance the independent trials, so you don't have to depend on the companies evaluating their own products all that time.

CK

Thank you. Fred, do you have questions?

04:35:57

FV

Well, it is not really a question rather a comment. First of all, I have been really struck by the question of continuity and memory, which has been raised again and again this afternoon. It is quite impressive, and a little counter-intuitive for the historian, to see the extent to which you collectively present a retrospective view of a period and point out the importance of history for the actors.

124 A clinical trial where an intervention is not compared against a placebo but against another intervention that has previously been shown to be effective.

If you look at all the reports, conferences, and everything that has been published, all the statements of the last two decades, your word, as a group, so to speak, of veterans on this subject, pointing out the difficulty of making the problem of innovation in the field of antibiotics exist, seems to me to be something important and which contrasts with this avalanche of reports.

In fact, this discontinuity and the lack of memories are quite impressive to me. The lack of institutional memory, as you said, and the lack of continuity in the careers of those involved, which is very important. The lack of political commitment, too. James talked about market-entry incentives that were not really favourable for the pharmaceutical industry because of the lack of long-term commitment they might imply.

The COVID-19 crisis, which Joe mentioned, too, was the last straw with yet another discontinuity and lack of memory, even within institutions. That's what makes this group of people, this witness seminar, quite interesting because we have brought together people from different sectors who have this memory and share this perception of the fluctuation of attention and commitment.

To me it is really impressive: it is maybe something that you want to comment on? Something else I would like to ask the group:

04:37:37

in the field of global health, and the history of global health, something that is coming up in the 70s is the role of new institutions. We haven't talked at all about institutions such as the World Bank. In terms of funding, the World Bank has been a key player since the 70s, and I was just wondering if the World Bank, for instance, is totally out of the picture?

On the economic implications of the burden of AMR: I think it's quite important. I remember Marie-Paule mentioned that to reach the top level of the government, the health minister or the agriculture minister, you need to come with figures and numbers about the cost of the AMR. Not only the burden in terms of mortality, but economics and figures.

Last question! You talked a lot about competing emergencies, and the difficulty for AMR to get attention when there have been other pressing emergencies. I was wondering if, in Western countries in particular, the issue of a shortage of antibiotics, which is a growing public problem, is not something that might lead to some changes in the attention to the innovation in this field.

04:39:28

CK

Survivor bias.

FV

Yes. To sum up: continuity and memory, new institutions such as the World Bank, and shortage of drugs in the North. I don't know if anyone wants to react?

JA

I can jump in. I was on another call also on AMR this last couple of hours, so apologies for the clash. So, a couple of thoughts. Just to pick up on the question of what can we apply from what we learned in COVID into AMR. I actually think quite a lot, right. The main thing is, when it comes to R&D, it is all about what you do in advance. If you wait for an outbreak, it can be too late. Which means, and I think that's what we've been talking about in antibiotics for many years, that we need to get ahead of the bugs developing resistance.

I was in Rome last week for the 100 Days Mission launch event,[125] which was looking at the pipeline for antivirals against future viral-pandemic pathogens. It is exactly the same, it is basically bare, which means nobody's really investing much against the viruses that are expected to be pandemics in the future.

04:41:06

It is a very similar issue, that then we need to look at push funding there to kick off the early stage, and to support academic spinouts, and biotechs. And then we do need to think about pull funding, or something, to bring it through the expensive late-stage trials, really the same. For me that's part of the institutional memory thing. Because this is what was said after previous viral outbreaks, and yet really nothing much happened. It didn't change the situation we were in when SARS-CoV-2 broke out, and where we still are frankly, right.

Fully agree on the regulatory point, which is one that I think everyone sees. Which is that it doesn't actually cost that much but can really make a difference to developing and launching any drug around the world. Actually, there were comments from the CEO of Shionogi today, I think in the FT [Financial Times] or Politico, from an interview where he's saying that's the single thing that would make the biggest

125 International Pandemic Preparedness Secretariat. *Warnings of Bare R&D Pipeline for Top Pathogens with Pandemic Potential, as Latest 100 Days Mission Report Launched*, January 23, 2024, https://ippsecretariat.org/news/warnings-of-bare-rd-pipeline-for-top-pathogens-with-pandemic-potential-as-latest-100-days-mission-report-launched/.

difference to him.[126] He does talk about pull incentives as well, but making it much easier to register a product which is then accepted everywhere.[127]

And I know WHO is moving on this, but we are really not there yet, and there's not the urgency. And that again was shown up as a problem during COVID. So that's one that doesn't cost much, but does require sustained push, political push actually. And so surely, if nothing else, that's one that we [can act on].

04:43:03

In terms of the World Bank, it is another big, complicated institution. My sense, two steps removed there, is that they've never really taken on AMR as a priority, to follow on from when they did do the report you mentioned.[128] It was really good, and as you'd expect sound economically based. But there didn't seem to be any intention from within the institution to take it forward, or to take something forward.

My belief is that the role they are best playing is when they are building the infrastructure on the ground, health-focused infrastructure on the ground. Helping to support governments to create additional financial headroom to invest in primary healthcare. And a lot of the things that would really help detecting, and diagnosing, and treating bacterial infections.

So, for me there is certainly a bigger role there. It is probably less about AMR and more about Universal Healthcare (UHC) more broadly, which definitely will help with AMR, and future pandemics, and non-communicable diseases (NCDs). That's a little bit how I think about that one.

And then briefly the third issue was shortages. Another big, very complex one. The short version is that most of the shortages, in volume terms, are for off-patent products, which if the market was working properly, would be supplied by many different companies: there's no reason that they can't be.

04:44:50

So, it does mean that the economic drivers of the market on generics companies are causing this big consolidation. Companies are choosing which products they want to do and which ones they don't, which then results in a shortage if there's only one or two suppliers and for some reason they have a problem. Or the demand changes too quickly and they can't react.

126 In chat: JA: Andrew Jack. "How pharma economics hold back antibiotic development." *Financial Times* (07.03.2022), https://www.ft.com/content/29292a3c-321d-4187-9ff0-59d70eb796f4.

127 In chat, JL: The regulatory pathway is quite a useful point of leverage.

128 Jonas, Olga B., Alec Irwin, Franck Cesar Jean Berthe, François G. Le Gall, and Patricio V. Marquez. *Drug-Resistant Infections : A Threat To Our Economic Future (Vol. 2) : Final Report*. Washington, DC: World Bank Group, 2017, http://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf.

I think changing the economics of that is something that we probably maybe need a second Jim O'Neill report. I don't think there's a clear consensus on what can be done there. A much better way would be to think about improved global forecasts, or at least regionally consolidated forecasts. It would help if there was any kind of medium-term forecast that showed companies there was a demand for their product - companies will try to meet that demand. And so, for me there is a lack of any kind of forecast, and it needs to be one to two years out, because that's how long it often takes to set up a factory, and change it over, and then produce a whole batch of stuff.

Certainly, when we look at Europe, that should be doable, and I know there are some discussions underway there. If you look globally, it is harder and we also saw the same lack of demand forecasts with the Access to COVID-19 Tools Accelerator (Act-A) for Therapeutics, that didn't really happen, and was a problem therefore in supplying COVID therapeutics into lower- and middle-income countries. So that for me is a gap that should be seriously worked on, to really help on the shortages front.

04:46:41

CK

Does anybody else want to come in on the World Bank or, I guess, what we might term survivor bias also within this group here?

KO

I was going to say, the World Bank report around UNGA 2016 was thoughtful and influential, it was a good report.[129] But it hasn't been followed up by dramatic other actions since then, but that report was solid. It is one of the things that keeps getting cited affirmatively.

FV

Any hypothesis about why the World Bank would not follow up on this topic?

KO

I don't know.

CK

Interesting. I think that's another witness seminar, to think about the relations between WHO, FAO, OIE, World Bank, etc., in this space. I think we'd probably need another day to disentangle that.

04:48:11

For me the final interesting question here is that we obviously have a big bias in the group of experts we've assembled here—a survivor bias, right? We have the people here who have survived multiple

129 Jonas et al., *Drug-Resistant Infections. A Threat To Our Economic Future.*

turnarounds of institutions, multiple changes in funding structures, etc. And as a consequence, these are also the survivors who have formulated the strategies we are living through at the moment—the architects of lots of the thinking of the reports.

PB

But we also changed. I mean, James from GSK to IFPMA. I switched; I moved several times in WHO. Joe is not where he used to be. So, I mean, we survived but not in the same institutions.

CK

You make my point for me.

ELP

Evolution.

CK

This is one of the most remarkable things that has popped up in our research. We haven't quantified it yet. But I think if we were to do a bibliometric analysis of who has published, we will see institutions shifting but we will also see a remarkable, perhaps generational, effect of certain people coming in at a certain point and making it to the present through the system, and then generating certain ideas about how to do things. I was wondering whether, in this group, you think that there was this generational aspect of the 2000-2020 period that we are analysing. So as a historian I am asking you to really zoom out here.

04:49:40

We have an early golden era of antibiotic innovation and then we've got an era of fragmentation. How would you, as a generation, label this moment between 2000 and 2020? You encounter each other all around the world at the same conferences, and I've also had the privilege of being at some of them. But is there this awareness of a cohort, of a network, that's been forged around specific events?

JA

I mean, I would say pretty much, yes. And I think again, well, as you've heard, actually there's a pretty strong consensus from all different parts of that network on the main things that need to be done. I mean, there are no easy answers. I think everyone has the same things on the list, there may be different prioritisation, or there's certainly debate about that. And there may be what I see as peripheral differences on the details, some of the details, of how to implement the changes that are needed. But I think, in terms of what needs to be done, I think there's a pretty strong alignment in all the sectors that you have represented here.

OC

I can agree on that, although my fear is that the regrowth of champions is not there. The regrowth of people that can move out, like myself, have the luxury to do the move out of healthcare and almost create a position, and also create a new organisation, which could deal with this—it has been a luxury and a privilege really.

04:51:26

But it is not easy. My colleagues are fighting every day to make their daily duties on healthcare. And how could they move out and also become an advocate?

So, I mean, we have something we called an AMR community, it has been growing, there are more organisations and constituencies around this, but it is still extremely small. We are all friends, we preach to the already converted, we don't reach out. We haven't become a movement, and moreover we haven't been able to engage civil society like for example the HIV community, and TB community, no way. And that is also, again, because of the lack of narrative and the language. So, we have a lot ahead of us to really make a case, maybe making a bottom-up movement to challenge governments. So, we are too few, yes.

PB

You know what, it reminds me, Jamie. It was *The Guardian* who had this long article about you? It was called Pharma's Biggest Nightmare.[130] And I don't think that you have a good successor, I mean, we have to ask pharma whether they have somebody.

But I mean, the access, MSF Access, campaign is a shadow of what it used to be.[131] I mean, you said it, Sally Davies, I don't see anybody replacing Sally when she finally will stop actually pushing AMR. I mean, it is a bit sad, but I see less, maybe... Hopefully they will come out of the next generation.

04:53:22

OC

Yes, hopefully, but...

JL

Well, the leadership has changed from when I first started getting involved. You had people, I think Bernard Pécoul was really an important person in the beginning.[132] Because Bernard Pécoul, I first met him in 1998.

130 Sarah Boseley. "Big Pharma's worst nightmare." *The Guardian* (26.01.2016), https://www.theguardian.com/society/2016/jan/26/big-pharmas-worst-nightmare.

131 MSF announced the closure of its access campaign in June 2024.

132 Founder of DNDi and executive director from 2003 to 2022 and before that executive director of the MSF Access to Essential Medicines campaign.

PB

Yes.

JL

He had this attitude of getting out the best of everyone. I mean, he started talking to Harvey Bale, who was running the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). And he talked to the companies, he talked to the NGOs, he talked to the governments. And he'd get you all in the same room together, and he'd... You'd get to know each other, and people would start cooperating more. And he was not very idealised, he was very pragmatic, and really a problem-solving kind of a guy.

And his whole campaign he built around that was very entrepreneurial, action-oriented, but very focused on trying to solve problems all the time. I think what we have today, and the access to medicine, is a massive amount of ideology, and just reactionary anti-corporate stuff. And the industry thinks that's me, right, I mean, that's the reputation I have, but I've always been... I am not...

04:54:55

I always tell people I am right wing of my movement because I am more pro-market, probably, than most people are, or open. I come out of the consulting world. But it doesn't make any difference, if they think that you challenge the status quo you are all the same, you are all Karl Marx basically.

But Bernard wasn't... Bernard was able to make everyone understand that that wasn't him, and that wasn't his movement, and that wasn't the objective, and I think that was a beautiful period. And of course he went onto DNDi, and he built that up into a very significant institution. And you've got people in the room that are off the Bernard Pécoul tree one way or the other, which is great.

But I will express some frustration. As much as I am a constant critic of companies, and business practice, and practically everyone else, everything else, as well. But I still think that a change in business model is different than just getting rid of businesses, or something like that, and I think that that's been a hard conversation to have in my community.

It is to get people to think [that talking] about changes of business models means there's a business involved. And I think for a lot of people I work with they just want to get off the for-profit sector altogether, and I think that's going nowhere.

CK

Any final reflections from you Kevin, or Joe?

KO

Well, I do worry what happens when people like Dame Sally retire. I think we have a window, and if we don't make significant progress within a window with X number of years, and X is less than five or whatever, right, then we have a reset, and it'll have to be a new generation that carries it forward.

04:57:13

KO

I think I am a little more optimistic than Joe, just because I'll say that there's a lot of things in climate change, in public health, and global issues, which are hard to fix. This one we've hammered out a lot of the solution sets, and there's actually remarkable consensus between companies and many academics that the barrier is really 'let's fund the damn thing,' which I know is an important barrier, but we are not arguing over fundamentals like we did a decade ago.

JO

I agree. Yes, I think we are half done. I've heard golden age referred to in this call today, but I don't know if it was a golden age. I think we got half the work done, and we need to use the next short time frame to get the rest completed.

CK

I think that's a perfect final comment. Thank you everybody for making the time, and for bearing with us through lots of gruelling questions.

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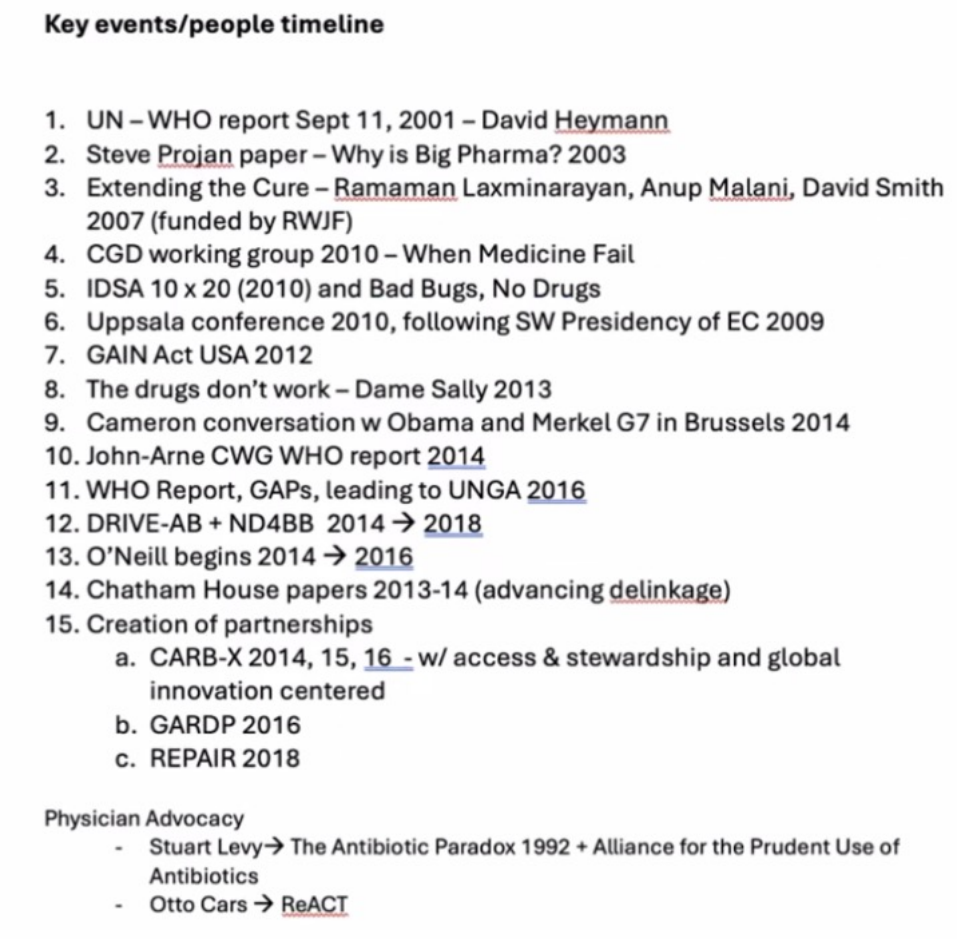
Slide offered by Kevin Outterson during discussion:



Key events/people timeline

1. UN – WHO report Sept 11, 2001 – David Heymann
2. Steve Projan paper – Why is Big Pharma? 2003
3. Extending the Cure – Ramaman Laxminarayan, Anup Malani, David Smith 2007 (funded by RWJF)
4. CGD working group 2010 – When Medicine Fail
5. IDSA 10 x 20 (2010) and Bad Bugs, No Drugs
6. Uppsala conference 2010, following SW Presidency of EC 2009
7. GAIN Act USA 2012
8. The drugs don't work – Dame Sally 2013
9. Cameron conversation w Obama and Merkel G7 in Brussels 2014
10. John-Arne CWG WHO report 2014
11. WHO Report, GAPs, leading to UNGA 2016
12. DRIVE-AB + ND4BB 2014 → 2018
13. O'Neill begins 2014 → 2016
14. Chatham House papers 2013-14 (advancing delinkage)
15. Creation of partnerships
    a. CARB-X 2014, 15, 16 - w/ access & stewardship and global innovation centered
    b. GARDP 2016
    c. REPAIR 2018

Physician Advocacy

- Stuart Levy→ The Antibiotic Paradox 1992 + Alliance for the Prudent Use of Antibiotics
- Otto Cars → ReACT