

EPISODE 18: CELEBRATING 70 YEARS OF PROTECTING THE WORLD: COMBATING INFLUENZA NOW AND IN THE FUTURE

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Garry Aslanyan [00:00:08] Hello and welcome to Global Health Matters, the podcast where we discuss key issues and topics in global health, inclusive of the perspectives of low- and middle-income countries. As always, I'm your host, Garry Aslanyan. I'm excited to bring you this month's episode because it's produced in partnership with the World Health Organization's Global Influenza Surveillance and Response System, also known by its acronym, GISRS. GISRS is a global network of 150 laboratories across 127 countries. Annually, around a billion people get seasonal influenza, and the threat of a pandemic is always lurking on the horizon as viruses keep evolving. To safeguard and protect us from these public health threats, year round surveillance is being conducted by GISRS. This year, the network is celebrating 70 years of dedicated global scientific collaboration. So for today's episode, I'm joined by two stellar guests, Professor John McCauley, who is the Director of the Worldwide Influenza Centre at the Francis Crick Institute in the United Kingdom, and by Professor Mahmudur Rahman, who served previously as a Director of the Institute of Epidemiology, Disease Control and Research and the National Influenza Centre in Bangladesh. The Guardian newspaper referred to scientists like them as the flu hunters working to stop the next pandemic in its tracks. I must agree a very appropriate title for them indeed.

[00:01:54] Hi, John. Hi, Mahmudur. How are you today?

John McCauley [00:02:00] Very good, thanks.

Mahmudur Rahman [00:02:01] Thank you very much for that. Very fine and doing well. Thank you very much for this programme and inviting me here also.

Garry Aslanyan [00:02:09] Thanks for joining. So let's get started. John, let's rewind time. It's 1918 and a flu pandemic is sweeping through the world, eventually resulting in one third of the world's population being infected and 50 million people dying. Over the last couple of years, we had SARS-CoV-2. Seven million people dying out of that pandemic. If you could start by sharing with our audience what's been the difference and the features of the change that we've seen in the last hundred years observing these events?

John McCauley [00:02:43] Thanks very much, Garry. I think one of the things to bear in mind in 1918, is what the doctors could tell you; that you got flu and you were dying of flu. It wasn't very much at all that they could do about it; you could basically give palliative care. And really they didn't even know at that time in 1918 whether or not the virus, this influenza pandemic, was caused by a virus or a bacterium. We didn't know the nature of the agent. It wasn't until the middle thirties that people started successfully propagating this as now epidemic influenza viruses rather than pandemic viruses, and showing that they were actually a virus and they could be then studied. Once you can propagate something, you can analyse it.

John McCauley [00:03:25] One of the things that did happen once the virus was able to be propagated from the 1930s, relatively small numbers of laboratories could do this work. Initially, it required infection of ferrets and transmitting virus from ferret to ferret. But as technologies advanced, we had better ways to propagate the virus and we recognized the fact that influenza wasn't consistent around the world. We knew by the early 1940s that there were influenza A viruses and influenza B viruses in circulation. And after the Second World War, there were efforts to actually try and build up, not just counting

influenza deaths, but actually doing virological surveillance on the viruses that were out there to see if you can build up a global picture of what the virus is. Is the same virus circulating in Europe as in North America, as in Australia, as in the Far East? And so those kinds of advances were being made. And so this was taken up by, first of all under WHO support in 1947 and the first reports came to be published in season 1948-49. Subsequent to that, in 1952, this global influenza surveillance network was set up. So this formalizes this arrangement of collaboration between laboratories, and that's been really good so that at that time, when they first did reporting in 1948-49, there were about 20 or 30 laboratories around the world collaborating. And this has now built to close to 150 national influenza centres located around the world, all collaborating together to try and build up an even more detailed picture of what influenza viruses are out there, whether or not there are new viruses emerging, whether or not that's a zoonotic virus that may become a pandemic virus or a new epidemic virus. We do this in order that we know what's out there, know what's likely to happen, whether or not we're going to have a severe influenza season or not a severe influenza season, and also so that we can develop vaccines that are the most appropriate to use to minimize the impact of any influenza epidemic.

Garry Aslanyan [00:05:46] Thanks for that great reflection and overview of how things have developed globally. Mahmudur I really want to learn more about measures that have been put in place in Bangladesh where you worked and you're working in this area, and what are the measures put in place for addressing the recurring threat of influenza?

Mahmudur Rahman [00:06:10] Actually, we started preparing for pandemic influenza since 2005, formally, rather, I should say. And then subsequently, we're building our strengths in that. And we actually became a member of the GISRS as National Influenza Centre in 2006, and we developed our laboratory so that we can also have a look into the circulating influenza virus, what is happening in this country. After that, we set up 12 centre sites across the country, in different parts covering, and we were collecting data on a regular basis to understand what was happening. And for the first time, we could learn from that our influenza season is different from some other countries. Our influenza season actually starts in April and ends in September, and July-August is the peak time what was happening. So that is the first learning we got from setting up of the influenza surveillance in this country. And not only that, over the years we have developed our capacity with the support of business and CDC also supported us in building our strengths and building our laboratory capacity, and also understanding more on that. Also, when COVID came in, we could easily and quickly diagnose COVID also in this country very quickly in our laboratory. We didn't have to transport it elsewhere to understand that. So these sort of arrangements were made and we could understand very well about the circulation of the influenza virus. This also helped our policy-makers to understand a bit more on this. We are doing this since 2007, along with the GISRS network, and we are trying to share all this data with the GISRS collaborating centre so that they can take care of what type of vaccine is to be developed there. So these are the things in Bangladesh we were doing and we are very much getting help and understanding about the influenza separation in this country from this network.

Garry Aslanyan [00:08:24] So you've been linked to the network and it's quite instrumental in the work that you're doing. So John, can I continue with that and ask you, as the director of the Worldwide Influenza Centre. At your institute, you've been the director for the past 13 years there, and it's one of the seven WHO collaborating centres for influenza, which form part of this network, the Global Influenza Surveillance and Response Assistance Network. Maybe you could add a bit more for our listeners to better understand how this network of scientists is actually working, what is its primary function; it would be great if you could share that.

John McCauley [00:09:04] GISRS is now in its 70th year of existence as a recognized network within WHO, and what it really does is it joins like-minded people from around the world, like Professor Rahman and others. From now what are there, 148 national influenza centres in something like 115 UN Member States. What we've tried to build up together, through the collaborating centres so that with the national influenza centres assessing what's going on locally at their level, and some of these are very highly populous countries, such as Bangladesh, which we've just been hearing about, and others, the smaller countries. We put together a jigsaw to get the impression of what viruses are out there. Are there new viruses? And so this is the thing; we're looking at, it's a global threat, and so that what we need to do is build up a global picture. It's not isolated events, these events are linked because flu spreads really quickly. And so that when you get a flu virus establishing in one place, basically, we've seen it time and again, within a year that virus has gone all around the world. It's been less than a year quite frequently. And so what we're trying to do, so if we have a virus in one place, that if the picture is better, it overcomes population immunity better, then other centres need to know about it because it's going to hit them next. So how does it work? We work by the national influenza centres doing their local surveillance and doing analysis of the samples that they receive, and if they see something unusual, then they need to share that virus with the collaborating centres who can apply a wider range of techniques and a wider range of anti-sera to be able to analyse the virus in somewhat more depth than the national influenza centres can. And they also need to share not only the unusual viruses, but representative viruses. We can then build up a picture, region by region, continent by continent, of what's happening where. Then what we can do is look and see whether or not there is, in fact, a consistent global pattern of the emergence of any new virus. But of course, what we're also able to do, because we can build a picture for epidemic flu, we can also look at zoonotic influenza viruses, we can see whether or not the animal viruses are infecting humans on a consistent basis, not one individual country, but is it being seen in one country and not in another? And so we're looking at preparedness as well as intelligence. So intelligence is what's out there. Preparedness is getting ready to find out what's out there. And then thirdly what it is, is vaccines. So that with all of this information, we can find viruses that will be most suitable for intervention through vaccination.

Garry Aslanyan [00:12:03] John and Mahmudur, as you have explained so far, the scientific progress made to curb the threat of influenza and the country capacity built by this network is very impressive. Next, let's talk more about the influenza surveillance; how it happens at country level, and also how the GISRS network identifies viruses for vaccine development. Mahmudur, could you tell our listeners how you first detected the H1N1 influenza virus in Bangladesh and how the GISRS network supported you at the time?

Mahmudur Rahman [00:12:38] Actually, if I go to tell you the history. We set up our influenza centres in the country, which I mentioned in 2006-2007, and then it goes onwards, but at the same time, we also had to set up even better surveillance in our country to detect any outbreaks happening anywhere. And that was also very supplementing each other actually to understand if a new virus is emerging. So when you ask about the first case, what we had detected, we detected through our event based surveillance in 2009, 18th of June precisely. This was like a group of tourists who were travelling back home, and from them we identified one of them first and then subsequently we could trace back all the 28 students who came to the country and of them, we could find out six of them found to be positive of H1N1 and we immediately isolated them and kept them confined and also followed them up. So what we were doing at that period, I would bring up here the requirement for international regulation also because we as part of the requirement also we reported to WHO within 24 hours the first case detected and subsequently the first hundred cases were also reported to WHO in the system. That helped to understand also what is happening, how it is being spread. This is one issue about the first few cases what we have identified and from our country, what we were doing actually, we set up teams in our

country so that we could send them for the contact tracing and to find out that how many cases are coming from one case and contact tracing was working very well. And as you know, that we cannot stop the pandemic, but we can slow down it as much as possible to get prepared so that we can also combat that. And from there, I would like to bring here that this system we had in place, the 12 centre sites, we could clearly see that first appeared in the event based surveillance. Subsequently, it came in the capital Dhakka city in one of the sites, and we had actually Eid celebration in between, and we could clearly see that how the virus spreading from Dhakka to outside Dhakka sites and it was happening and we could follow them up very well that where it was going. And subsequently we had one also community site for influenza in our capital city and we could detect in the community site also the virus. So the conclusion what I want to say that initially we were undertaking containment basis when the cases were in the sentinel sites. But when we got it in the community site, we concluded that there is no more containment measures necessary and we went to go for mitigation measures and subsequently we went accordingly for the mitigation measures. This was also necessary as a policy decision-making. So this GISRS network, the NIC and the surveillance network that we had, helped us making policy decision-making also in the country because we didn't have the capacity to go and testing every individual for influenza. So when we were getting the symptoms, it was understood that it was H1N1, so we advised all our physicians, all our health centres, to go for treating with antivirals as early as possible because these were distributed to all of them. So this network really helped us in understanding this is a reality, understand and identify the first human case of H1N1 and also to follow them up and to take appropriate measures accordingly so that we can contain it well and also we can reduce the spread and reduce the death. That was the history. I want to bring it up and how it helped us to understand more about the influenza and the first human case identification.

Garry Aslanyan [00:16:51] Thanks Mahmudur for that background on the state of play in Bangladesh, how that particular event has played out and how you are linked through the network. John, quickly, something occurred to me. You mentioned the importance of sharing of data and viral samples between various partners of the network; I'm sure our listeners will be curious to know and how do the centres determine which seasonal flu viruses they need to develop a vaccine for, or how does that happen?

John McCauley [00:17:20] Well, I think we keep trying to build up a global picture of what's circulating where and are there viruses that are new. But what we do is we keep an eye on the characteristics of these viruses, the genetic characteristics, much more now easily determined than was the case, say, ten years ago. But we also are focused as well, hugely important is the antigenic analysis, so that what we can see is not just whether or not the virus has genetically moved on, it's really whether or not the new viruses are antigenically different from those that were in circulation before, because it's these new antigenic variants that are likely to be the epidemic virus. And so what we're doing is we go through data from as many countries as we can that are sharing viruses, we go through this in absolute real detail, looking at the antigenic and the genetic data to indicate where the viruses are; are they different from those that have been seen before; are they likely to spread? And if they are antigenically different and we think they're likely to spread, then that says, is the vaccine that we've got at present the best it can be? I think when we've seen new antigenic variants and its likely spread, the answer is always no. At that stage it comes down to: have we got a virus that we can get to the manufacturers for production? Because if we can't get a virus to the manufacturers for production, then we need to say that well, we're going to have to do with the second best. We don't want to ever do with the second best. The whole point about this global surveillance network is that it works together to produce the best for the world. We want to be comprehensive, to get the best global picture we can, and that's the way that this all works together. With centres like Professor Rahman's centre in Bangladesh and those that are still becoming national influenza centres, like, for example, the laboratory I was visiting just last month in Mozambique. They're not yet approved as the national influenza centre. They will be approved as the

national influenza centre. But they've been contributing to the Global Influenza Surveillance and Response System for eight or nine years now, so they're playing their role. The likelihood is that if we can pick up viruses and then we can feed back what other countries, adjacent countries have seen, what we've seen elsewhere. For example, I can give the national influenza in Mozambique. They have a lot of tourists coming in. What are they bringing in with them? Are they going to bring new epidemic viruses in from the airplane? You know, the speed of spread of flu is as fast as the plane can cross oceans.

Mahmudur Rahman [00:19:54] I would like to add one more issue about how GISRS also helped in the virus sharing and benefit sharing. The virus is shared by the countries and now it is just supporting to bring together the industries so that they share also their benefits. And also the virus is also traced of where it is going from one to the other, so that there is a mechanism which has been set up which is helping actually to get some money from the industries, to build capacities of the GISRS network and also prepare for the next pandemic. So this is also an important, I should say achievement, from the GISRS which has happened, and then the history behind how it came up. But I myself was involved in the process with this discussion since 2006, and finally in 2013 it happened and that it became a framework with all the countries I've been following and also the industries are now together sharing their profit, but so that the capacities can be built up.

Garry Aslanyan [00:21:03] John and Mahmudur, that is very informative overview of how decisions are made and the actions that are taken to support vaccine development. Mahmudur, I'm curious, how well is flu vaccine taken up in Bangladesh and what factors influence this?

Mahmudur Rahman [00:21:22] In Bangladesh it was not considered that much as a very serious disease. The reason for which I always say that because we can't diagnose it well, because we don't have capacity. I am talking about previously before COVID with the PCR to diagnose it and PCR was the only method to diagnose influenza. So there was evidence but we were not very sensitive based on which the diagnosis could be made. Not only that, the antivirals are not very common and it's quite expensive also. So that's the reason actually and there are competing priorities also within the country. So all of this was actually vaccinating the young children and that is very much established in the country and Bangladesh had good achievement in terms of coverage of immunization and within the region compared with the other countries in the world also. So we had an effort of vaccinating the children, but we didn't have the capacity to vaccinate the adults and this COVID period also when it came up, we used that network, that whole structure, to convert it to the adult vaccination and also brought in other sectors, the private sectors also in it so that the diagnosis could be made and also the vaccination can be given. So that is how we have changed a little bit on that part. Not only that, for COVID also, we have set up a very good system of registration and also followed them up that a lot of countries did and also we also started from the very beginning. So that is how the change has taken place, the COVID and also I would like to add here that the influenza platform helped us to diagnose COVID in this country first. Not only that and also expanding this capacity within the whole country, now we have more than 200 sites where we can do PCR within the country. Initially it was two. But during the COVID period it has expanded so much that we have to keep it running so that in future we can also use this strength for any emerging infectious diseases if it is coming.

Garry Aslanyan [00:23:41] John, Mahmudur, thank you for giving us such a detailed understanding of the practicalities of the network. I imagine many of our listeners may be wondering, what's the secret ingredient that has made this global network of scientists so effective, and what opportunity is there for surveillance of other diseases as well? John, could you reflect on what has made it so successful and also tell our listeners about the exciting future of the network as it expands into GISRS Plus.

John McCauley [00:24:18] I think that the success of GISRS as it started off as, and that's now 70 years on, has actually been the same throughout. It's like-minded people collaborating actively together. Everybody's treated absolutely equally. We're working together to achieve the goal of trying to understand and mitigate the population from influenza, whether that be epidemic influenza, zoonotic influenza or even the influenza pandemic. We're all working together with no side, if you understand what I mean. I write reports to all of the national influenza centres that share viruses with us, telling them absolutely everything that I know about the viruses that they've shared. So that I'm actually saying: you know as much as I do about what has been shared. And I take this as the open collaboration that has been established over this 70 year period, and I hope that this will continue into the future. Actually, one of the things that's also helped that is, we haven't been plagued by paperwork in this. One of the things, it's this free and open sharing. We understand it's taken for read what we do, what we don't do. We're not into exploiting this or that, it's all together for the same goal. We're all working towards the same goal and trying to do it as efficiently as possible. So we're not plagued by a lot of bureaucracy on this sharing. And I think this has been something that's been really successful within this GISRS thing, it's an old fashioned network. Whether or not it could be set up in the same kind of way again is a big question. But we don't have to go there because it works, it exists and it works through just this open collaboration of like-minded individuals around the world and so that's why it works. It's just an open, honest collaboration.

John McCauley [00:26:28] You asked about GISRS Plus. This is an idea in which I'm not really clear how it's actually going to be borne out, but it does make common sense that we shouldn't have... If we're going to have people turning up at their practitioners or into their hospitals with respiratory infections, we shouldn't be putting people: oh that's flu, that goes down this way. That's SARS-CoV-2, that goes down there. This is RSV. We need to have an integrated approach for respiratory infections. The first signs as such that it will be; I'm sure Professor Rahman will be able to sort it out better than I would, but he would be able to see a child coming in is more likely to have a respiratory syncytial virus than influenza. If it's a sick old person coming into the hospital, would be more likely to have influenza than an RSV. Over the last two years, most people probably the most likely have SARS-CoV-2. But you do want to differentiate, and you do want to know who's got what, because the interventions are liable to be different. So this is the point about surveillance, integrating the surveillance. We have a system that works for flu. If we can have that system and efficiently expand it, for example, to simply say, alright, we're going to use the same system for SARS-CoV-2, its value for money. And we can do the same with paediatrics in the paediatric population. You might well say, well actually we should be looking at RSV. How much effect we've got?? for RSV in the paediatric population. And that's ignoring the effect of RSV in the older population, but focus on where the problem is. So GISRS Plus is trying to make better use of the system where you have the flu that's worked so well and try and expand it to include, be inclusive of SARS-CoV-2, RSV and of course any virus that is liable to come up. One of the features about all of this sharing is the fantastic sharing that has happened of gene sequence data during the SARS-CoV-2 pandemic. So I think there are something like 13 million virus samples that have been sequenced and shared openly. This open sharing has actually largely been built upon the system that was developed for pandemic and seasonal influenza viruses. And this is GISAID. This has been fantastic. And this is another system which can be used; they have a component for RSV in GISAID they have a component for SARS-CoV-2 in there, and of course they've got their original influenza compartment in there. So again, this is another way to expand the surveillance and this plan to expand the sharing of gene sequence data. And so that's the extension of the very successful global influenza surveillance and response system, to just build upon it, to encompass a broader approach.

Mahmudur Rahman [00:29:31] Can I add with John that what we are doing in GISRS Plus in our country, we have 19 central sites now running in the country and we are testing both influenza and COVID, along with that, we are using multiplex PCR and doing it on a regular basis. This is one of the components of the GISRS Plus which has come up. And subsequently, also as John has mentioned, there are other viruses which will also be added there. But obviously in our country, we look for other viruses also using this platform. And this platform helped in developing, as you have heard, the GISAID which helped tremendously which was for influenza, but this pandemic period, it helped tremendously to understand what variant is circulating. Even now this is being monitored and in which part of the country, what or which type, which variant is circulating. And taking precaution for that is also very important, and countries are openly sharing their findings to that platform. So those are also, the component are benefits which came out of this GISRS network.

Garry Aslanyan [00:30:50] Thanks for that. We're coming to the end of our discussion. In ending today, maybe I could just ask you to tell me what continues to make you passionate and excited about your work. Maybe we'll start with John.

John McCauley [00:31:05] Thanks, Garry. What a way to finish! I think what it is, it's the same in the flu community; when you've seen one influenza season, you've seen one influenza season. And what you then do is the next influenza season is different and they are always different. Something somewhere causes a problem and something goes wrong and you got to solve those problems urgently.

Garry Aslanyan [00:31:29] Okay, Mahmudur.

Mahmudur Rahman [00:31:31] Actually, this is very interesting, like as John has mentioned. And I can also tell you that during the pandemic, the COVID pandemic, influenza was almost nil. In a lot of countries we were not detecting influenza virus. And still now we see variation of the season also; something pushing back, something early onset. So these sort of things which actually would encourage us to understand and get involved. And this is the ownership actually, which is also very important. And you have heard that John was mentioning several times that like-minded people and people who are working in influenza, even when they are responsible but; well I was in the government for 32 years. Even after my retirement, I'm still supporting the influenza network. From a different tact, not from the government's side, but advising them what to do at what stage.

Garry Aslanyan [00:32:30] Mahmudur and John, thanks for joining me today and for this insightful discussion. All of the best in your future work.

John McCauley [00:32:39] Thanks very much Garry, and thanks for the questions. Thank you, Garry, and also John. We are working together for long. I don't remember how many years, but still now we are together and also we discuss all the time and also work for that. So thank you very much also for bringing this important topic for discussion with us. Thank you very much.

Garry Aslanyan [00:33:03] Achieving public health progress is not the effort of lone heroes. Rather, as illustrated by John, Mahmudur and all their collaborating colleagues from across the world, it is combined actions and shared leadership which result in tremendous progress for humanity. Launched seven years ago, GISRS is a remarkable example of a successful, peer-led network based on deep trust and a unifying common vision. Before we end this episode, let's listen to a short reflection from Dr Wenqing Zhang, from WHO's Global Influenza Programme.

EPISODE 18: CELEBRATING 70 YEARS OF PROTECTING THE WORLD: COMBATING INFLUENZA NOW AND IN THE FUTURE

Wenqing Zhang [00:33:44] Hi. I'm Wenqing Zhang, head of the Global Influenza Programme in WHO. I want to thank TDR for collaborating with us to produce this episode in commemoration of the seventieth anniversary of the WHO Global Influenza Surveillance and Response System (GISRS). It was really encouraging to hear from John and Mahmudur both sharing their experience of the network. The success of the network has been based on several generations of committed collaborators like them.

Garry Aslanyan [00:34:19] I want to thank Dr Zhang and our colleagues at WHO who partnered with us to produce this episode. For more information about GISRS and the 70th anniversary, visit our podcast web page. Don't forget to get in touch with us via social media, email or by sharing a voice message with your reflections about today's episode. See you next month for yet another thought provoking discussion on a complex global health topic.

Elisabetta Dessi [00:34:49] Global Health Matters is produced by TDR, an infectious diseases research programme based at the World Health Organization. Garry Aslanyan, Lindi Van Niekerk and Maki Kitamura are the content producers and Obadiah George is the technical producer. This podcast was also made possible with the support of Chris Coze, Elizabeth Dessi, Izabela Suder-Dayao, Noreen O'Gallagher and Chembe Collaborative. The goal of Global Health Matters is to produce a forum for sharing perspectives on key issues affecting global health research. Send us your comments and suggestions by email or voice message to TDRpod@who.int, and be sure to download and subscribe wherever you get your podcasts. Thank you for listening.