Jessica Manning
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Interviewed by Gabrielle Barr, Archivist, Office of NIH History and Stetten Museum

Barr: Good afternoon. Today is August 4, 2022. My name is Gabrielle Barr. I'm the Archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Jessica Manning. Dr. Manning is an Assistant Clinical Investigator in the Laboratory of Malaria and Vector Research, which is part of the National Institute of Allergy and Infectious Diseases [NIAID]. She's also the Science Attaché at the U.S. Embassy in Phnom Penh [Cambodia], and the NIAID ICER [International Center of Excellence in Research] in Cambodia. Thank you very much for being with me. [You've had some] really interesting positions.

Manning: Oh, thank you Gabrielle for the invitation.

Barr: My first question is, very early in the pandemic, like in January/February of 2020, your team used metagenomic next-generation sequencing on an iSeq100 Illumina platform paired with an open-source bioinformatics pipeline to quickly characterize Cambodia's first case of SARS-CoV-2. Will you please speak about the reasons you and your team chose this method and explain in lay terms how you all went about conducting this type of sequencing?

Manning: We were fortunate to have received a Bill & Melinda Gates Foundation award the previous year to establish a metagenomics platform. As part of that award, Illumina had partnered with the Gates Foundation, as well as with the Chan Zuckerberg Biohub, [to] provide to the low- to middle-income country that won the award an iSeq100 [Illumina] platform, because it is the smallest and least expensive platform that they have. We did this award because we were really curious about all of the pathogens that we did not know how to diagnose or identify. We wanted a metagenomics platform because we wanted to be able to have an agnostic approach. It allowed us to sequence everything within a clinical sample. So whether or not we're going to apply that to vectors, to humans, [or] to wildlife, we wanted to have this versatility. It was going to be a great tool for people like me who are interested in mosquito-borne diseases.

When the first cases [of SARS-CoV-2] began happening in late December in China, I partnered with the government in Cambodia as well as with our colleagues at the Institut Pasteur and agreed that if indeed we did see this novel virus, we would be willing to sequence it. That was how we ended up choosing the iSeq100 as our platform because in those early days, you needed sequencing to confirm the PCRs. The PCRs were all experimental in January 2020. You had to follow up with sequencing. We were the only ones in the country who had that capability at the time.

Barr: What were some of the challenges that you and your team experienced in going about doing the sequencing for COVID-19?

Manning: Well, I think, very similar to everyone, we were working within a vacuum. Nobody really knew what was happening. Nobody knew how well things worked. We were, at that time, always dealing with supply-chain issues, even before supply chains became a problem much later in 2020 and 2021. But our biggest problem was that when we first tried to sequence the virus, because the iSeq100 is such a small platform, we couldn't get full coverage of the genome. You needed to have above 95% of the genome covered in order to be able to submit it to a public database so other international researchers could see what was happening. With our first pass, we only got about 30% of the genome covered. We were a little devastated. [We were] happy that we could do it and confirm it, but [we] really wanted to go the extra mile to be able to publish the genome. We had just ordered primers that allowed us to sprinkle across the genome the different gaps that we needed to cover. Then that allowed us to achieve 100% coverage and be able to publish the genome. [Gestures with hands—open palms indicating breadth.]

So that was a couple of the first issues that we that we had in terms of trying to sequence. An iSeq100 gives you about 6 million reads compared to a NextSeq 2000 that gives you a billion reads. Our little 6 million reads were all going toward the N gene—now that everybody knows the different genes of the virus. They weren't necessarily going toward the 5-prime end. They weren't going on the spike [protein] quite as much. All the reads were going to the N gene. We had an RNA abundance issue, so we had to basically enrich the other parts of the genome.

Barr: Interesting. You detected your first case in Cambodia fairly quickly after you started this process.

Manning: In Cambodia, we were receiving direct flights from Wuhan until January 24 [2020]. [On] the last flight out of Wuhan, [there] was a tourist who arrived in Cambodia and then began to feel ill. He was there with three members of his family—his wife and two children. The government and [Institut] Pasteur obviously performed the PCR. Then we were given the sample to sequence. We were able to do that within 48 hours.

Barr: That's very interesting. Has this method been applied to other low-income countries throughout the world for detecting SARS-CoV-2 and have you all enhanced it? It's been it's been almost two years.

Manning: Yeah. We published all of our protocols on open-source sites immediately. It was shared with other low- to middle-income countries who only had small sequencers like us [so they could] use this enrichment protocol that was developed in conjunction with the Chan Zuckerberg Biohub. I do know that it was used in other places like Madagascar and Nepal and even some reverse innovations flowing from the global south back to the global north when the virus hit. In the U.S., people were able to use this enrichment protocol in March of 2020—like in California—in order to increase the number of samples you could run at one time. Then in terms of building upon that, we don't really use it anymore because the next iteration of this was something called an ARTIC protocol, which was an amplicon-based protocol that became the standard later on in 2020.

Barr: Oh, so that's what you use now?

Manning: Yeah. Sometimes we use them both together, but for the most part, we just use ARTIC.

Barr: Do you use ARTIC for the other diseases that you look at now, too?

Manning: No, we don't. Actually, we typically go back to the enrichment method, which is not specific to SARS-CoV-2. But we have now developed the expertise [and] feel more comfortable enriching. [We] actually have some bat samples where we've been able to sequence Sarbecoviruses and are using it in this enrichment type of protocol to design primers to go back to see if we can fill in the gaps around the spike proteins of these closely related Sarbecoviruses we found in bats in Cambodia.

Barr: Really neat. Can you talk about the research that you're a part of looking at the interface of COVID-19, dengue, and malaria in Southeast Asia.

Manning: Along with my fellow Dr. [Christina] Yek, we collaborate with the national Dengue Control Program in Cambodia, as well as maintain professional relationships with other governments and surveillance systems within ASEAN, which is basically the Association of Southeast Asian Nations. In doing that, we've looked at national data trends of both malaria and dengue in order to better understand how COVID-related mobility restrictions have impacted those diseases. We don't necessarily have formal studies, but [we are] just looking at all of the national data together within the region. We can see that there has been an uptick of malaria. It seems like there has been a decrease in dengue, but it's really hard to say because there [are] natural waves of dengue epidemics. [Makes circular motion with her hands to indicate waves.] We had an unprecedented largest outbreak [of dengue] in Cambodian history in 2019. Actually, in the history of the world, there was more dengue cases than ever before. It's hard to say whether or not this is an artifact of COVID that we saw lower cases in 2020, or if it was more related to just the ebb and flow of the virus itself.

Barr: Yeah. Can you discuss the difficulty in detecting positive cases of COVID-19 in Southeastern Asian populations, due to the fact that some of these individuals have other diseases making it hard to see? You looked at the sera [samples] prepandemic. Can you talk a little bit about that and how you went about looking at that?

Manning : Yes. It actually doesn't affect the ability to diagnose when the virus is active in your blood, because we use a PCR test or a rapid test [antigen test] now—everybody's using a rapid test [with a] nasal swab. What muddies the picture is that when they take a serum sample and we're looking for antibodies. In the beginning, before everybody in the world had COVID—which is the case now, or had a vaccine, which is also hopefully the case now—that people were doing large-scale sera surveys to see how much SARS-CoV-2 had already circulated within a population to see how far we were from herd immunity. At that point in time, it would seem to be much more difficult to do those types of tests in Cambodia, because there are certain sugar moieties on the end of the spike protein that cross-react with Plasmodium falciparum [malaria-causing] antibodies. That is why we saw this mixed bag—we knew in this prepandemic population, nobody had ever seen COVID, yet there was almost 14% positivity. We're still doing follow-up studies on this, but we do think that is most of that is related to Plasmodium

falciparum cross-reactivity. However, we can't rule out the fact that there could be zoonotic exposures in Cambodia that are different than in Europe or in America, because [Cambodians] do work with bat guano and are a primarily agriculturally associated society.

Barr: Oh, that's very interesting. Can you talk a little bit about how COVID-19 has impacted countries in Southeast Asia in responding to endemic diseases, some of them that you've already mentioned? You said that you're very worried about the how that pandemic has …?

Manning: Well, I think the biggest point here is that there's a finite number of resources. In the U.S., we were very fortunate that we are able to expand and have emergency bills and the CARES Act and all sorts of funding that flows into our research and health care sectors. Whereas in Cambodia, or Malaysia, or Vietnam, there is not that type of cushion. It ultimately just gets pulled from other diseases. People who were normally working for the National Dengue Control Program, are now working on COVID; people who were working on the malaria control program, [are] now working on COVID. You just saw a shift of resources, and therefore, that certainly puts at risk the advances that we've made against those diseases.

Barr: Yeah, definitely. Can you talk a little bit about how COVID-19 has impacted Cambodia as a whole? It's very different than the U.S. and Europe to some degree.

Manning: For the most part, our mortality is much lower. Cambodia, I think, also has, I don't want to call it a shadow economy, but an informal economy. In America, we have a cushion and resources and bills to protect people. In Cambodia, [where] many of those people were working in a fringe economy or an informal economy—and there were no more tourists—the economic devastation was profound.

Barr: Have you been involved or plan to be involved in any other COVID-19 research initiatives or studies?

Manning: We are following up our cross-reactivity [studies] between SARS-CoV-2 and malaria and also exploring the zoonotic exposures through wildlife sampling. But in terms of setting up new COVID-19 studies, I'm using this opportunity now to migrate back to what I normally do in terms of mosquito-borne diseases. We'll be wrapping up those COVID-19 [studies]. But we still help as much as we can with the ongoing sequencing efforts by the national government to improve and increase the amount of reporting of SARS-CoV-2 genomes.

Barr: You have very unique jobs. Can you talk a little bit about how you divide your time between your work in the United States and in Cambodia, and how you work with both the U.S. government and the Cambodian government?

Manning: Yes, but I don't think that I have it all figured out yet. For the most part, I'm based in Cambodia. I've lived there for the last five years. Because it's summertime and my kids are out of school, we're here in the U.S. for a few weeks. I work across 12 time zones with my team. We have a pretty big

group in Cambodia that works in our lab and our field sites and our hospitals. There's a core group of us here at the Rockville laboratory of the National Institute of Allergy and Infectious Diseases, about five of us—[including] students and fellows and a staff scientist. What we really want to do is make sure that we're always learning from each other, because what we can do in the U.S. is different than what we can do in Cambodia. We have our lab meeting at 8:30 p.m. on Wednesday nights—which is 7:30 a.m. in Cambodia—to try to create that bridge, because not everybody [can or will] travel. We want to be able to increase the level of education and the pedagogy that our Cambodian staff are exposed to. [We also want to] make sure that our staff that's predominantly here in the U.S. understand what it's like to work in Cambodia. That is how I manage our time here, but I feel really fortunate that, as a NIAID physician-scientist, I get to be posted within an embassy and have the privilege to live full time in Cambodia but still have access to all the cutting-edge resources that we have here at the NIH.

Barr: What is it like to work in Cambodia?

Manning : It is very hot and humid. The pace of life is definitely slower. It is a Buddhist country, so there are inflections from that in terms of how things work and how people perceive their lives and their connection to the land. Everybody feels very strongly about their home province. Most people, if given the opportunity, try to not be in the city and [want] to go back to their home provinces. But I think it's also difficult working in Cambodia because [of] the genocide in the late 1970s that killed 25% of the population—it targeted doctors and teachers and lawyers and educators. That generation would be the leaders right now. The pedagogy that currently exists in Cambodia is very weak. You cannot get a Ph.D. in the country. They really only just started a master's in biomedical science very recently. I think that those higher levels of education, that you cannot attain, impact to some degree the way the country is run [and] also make the biomedical enterprise that we represent more of a very fledgling sector of the community.

Barr: What have been some personal challenges and opportunities for you that the pandemic has presented?

Manning: Well, I think we would all say that SARS-CoV-2 has been both a challenge and an opportunity because it let us expand into respiratory viruses, zoonotic reservoirs, many, many things that we probably wouldn't have focused on as arbovirus researchers. I think it also helped us at the same time while we're expanding [to] understand what was most important for us to focus on within our core specialties. There wasn't time to do all of these surplus projects because [we] were dealing with COVID. Then you needed to maintain what your focus was. I think it helped refocus our research agenda at the same time. It helped strengthen our bond even more in our collaboration with the Cambodian Ministry of Health—not so that we were working outside the National Center for Entomology, Parasitology, and Malaria [in Cambodia] as well as outside of the National AIDS Control Program. [We were] working with the Cambodia CDC [Council for the Development of Cambodia] and with other parts of the ministry we hadn't before.

Barr: Thank you so much for all the research and all the efforts that you've put into the situation. I wish you and your family a lovely last few weeks in the U.S. before the school year.

Manning: Great. Thanks so much, Gabrielle. I appreciate the invitation.

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