Ralph Baric UN Public Health 2018

Thank you, Andy, that was really nice. And thank you all for being here. I really want to commend this morning's presentations.

I thought you all did a really excellent job. I'm now going to introduce the final speaker, Ralph Baric, who is a person I really admire at the school. He's one of the most accomplished and prolific scientists anywhere, and he's really brought tremendous creativity, persistence, and innovation to the study of viruses.

I've had the opportunity to tour his lab and on a couple of occasions, and it's just really impressive to see the way he and his team work together. And I'll just highlight a few of the things that are on the slide so we can get on to Ralph. He's a professor of epidemiology in our school and microbiology and immunology in the School of Medicine, like a number of the people who have spoken, you've crossed schools.

And I think that's really important. His lab specialises in coronaviruses and emerging infections like Zika viruses. I'll just mention that the first time I was introduced to Ralph was at my first faculty meeting when I came to the School of Public Health after being at the NIH.

And Bill Roper was dean at the time, and he talked about the fact that the NIH had just called Ralph and offered him a big grant to study SARS. And having just been at the NIH, I knew how unusual that was that somebody got called and offered a large grant. And that told me a lot about Ralph, and I decided I wanted to meet him.

And everything I've learned about him subsequently has shown how impressive he is, what a quick study, and the importance of the work that he does. So Ralph is going to talk about how bad it could be and what we can do about it. So Ralph, thank you so much.

Well, I have to admit I'm a little worried about giving this talk, partially because, as Yogi Berra said, it's tough to make predictions, especially about the future. So there's a good chance I could be wrong. I study coronaviruses, noroviruses, flaviviruses, and do some influenza virus research, just to give you some background of what I do.

The other reason that I'm a little bit worried is being labelled as a harbinger of doom. This is not me. I'm not one of the four horsemen of the apocalypse.

And I want to let you know that I'm really kind of a nice guy. So please come talk to me after this talk. I will mention that viruses are certainly in the pockets of all of the four horsemen.

And they can be used in all of these scenarios. So I'd like to start off by taking a step back and talk about how infectious diseases ranks or stacks up against other natural disasters that, in turn,

can be a threat in terms of frequency and relative risk. So if you step back, and every 300 to 400 million years or so, there's a danger of a gamma irradiation burst.

These occur when black holes and neutron stars collide. It shoots out this burst of gamma radiation, which can strip away the ozone layer, cause acid rain, result in high UV radiation levels to plant and animal life on the planet, can result in global warming. And this can occur as far as 6,500 light years away.

Fortunately, it doesn't happen so often. So don't really lose sleep about this at night. A little bit more likely to cause an issue is an asteroid strike.

The Earth runs into about 3,700 to about 7,800 tonnes of debris as it flows through space. Occasionally, some of these are big rocks. When a really big rock hits the planet, this can result in an extinction-level event, like what happened to the dinosaurs.

The good news is that mammals became dominant, and so we are here today. Otherwise, we'd probably be lunch. The US takes this threat fairly seriously.

So NASA has a near-Earth object programme that tracks satellites that are large enough to cause damage to the planet. One problem that they face is they can only track them for about 100 years, and then the accuracy falls off. But fortunately, Bruce Willis from Armageddon is here.

I just want to point out that he is also a Pennsgrove boy. We actually went to school together. It's a little town in New Jersey, 3,500 of us, a clear epicentre of planetary defence.

So remember that, please. Anyway, moving up on the list, we have supervolcanoes. These become a little more frequent.

They're about every million years. These are volcanoes that are large enough to coat the continent with about a half an inch of ash or more. The last big one that went off was Tabu, which was in Indonesia, resulted in an ice age and knocked the human population down to about 10,000 individuals.

There are about 20 of these of concern on the planet, and this is ours. It's Yellowstone, obviously. Please go to the caldera and spend some time at that hotel.

It's quite a treat. Finally, we have Carrington-level events, which probably some of you may have heard of. Most people have not.

These are geomagnetic storms. When solar flares throw off a lot of coronal mass, they can hit our electromagnetic waves that are around the Earth, and this can result in magnetic storms. The biggest one occurred in 1859.

There wasn't much electronics at the time, but it caused fires in telegraph offices. It shocked or

electrocuted telegraph workers. Much smaller ones occurred in the 60s and 70s.

It knocked out power grids in the US and Canada. Lloyd's of London says that they can cause about $23 trillion in damage and potentially knock out the power grid for one to five years. So this is not insignificant.

And what's a little bit scary is that much larger flares are possible. So NASA has taken this pretty seriously, and the first solar probe that's going to go around the sun is going to be launched this summer, and they are going to take a look at this. But this can certainly knock out GPS, cell phone, internet, and the power grid for several years.

OK, so now we're back into infectious diseases. Here we are. It's the number one threat from my perspective.

So since I've been on the planet, there's been a epidemic virus every decade, starting with Asian flu in 1957, Hong Kong in 1967 or 68. H1N1 came back in the 70s, followed by HIV, followed by West Nile. And then we got to the 21st century.

And things sped up. SARS was the first epidemic virus of the 21st century, about 8,000 cases in 33 countries with a 10% mortality. Chicken Gunya virus emerged around 2005 and sort of slowly spread across Asian to Polynesian islands and then arrived in the Americas, where it caused a huge outbreak.

Millions of people were involved in 2015. It's still here today. The Mexican flu in 2009 caused 220,000 deaths worldwide.

MERS coronavirus emerged in 2012. It's still around today with a 36% mortality and about 2,200 cases. About the same time, H7N9 emerged in Southeast Asia with about 1,600 cases with 39% mortality.

It's still around today, followed by Ebola with about 30,000 cases and a 39% mortality. And then Zika virus sort of drifted across Asia, ended up in Polynesia, and then arrived in the New World to cause another huge epidemic, pandemic with the major complications being microcephaly and CNS development problems in infants and developing children. So if you look at virus families, clearly influenza and coronaviruses and flaviviruses are the three most predominant groups that are causing problems in the 21st century, followed by alphaviruses.

Because I predominantly study coronaviruses and hate being behind flu, I include swine. And so there's four more big pandemics of swine. So clearly the most dangerous viruses on the planet are coronaviruses.

I had to say that, Adolfo. That means outbreaks of flu also. Yeah, I know.

But I'm a coronavirologist, and so I'm not talking about flu. Did I mention I have high insecurity

levels about flu virology? I feel like a second-class citizen. So based on that data, I think it's clearly number one, if you don't believe me, you can believe Bill Gates.

He clearly thinks that 10 million people could easily be killed in the next decade or so from infectious diseases. So things like SARS disappeared after 2004. Ebola disappeared.

Zika virus has almost disappeared. So are these viruses actually extinct, or are they just hiding? We've actually asked that question with SARS. These are, again, between 2002, 2004.

These are the viruses associated with the expanding SARS epidemic. Most of them are gone. In fact, all of them are gone.

We can't find these viruses anymore. But when you sequence bats, these are horseshoe bats, and this is a bat that wants to bite whoever's handling it, you find all sorts of SARS-like viruses. In fact, these are up to 97% identical to these epidemic strains that caused human disease.

So do they have pre-pandemic potential? So that's the question that we were interested in. And so what we did was this spike, like a protein gene right here, mediates species specificity. You can actually remove that spike gene from these epidemic strains and put in these bat spike genes in place of them.

This was done by Vineet Menachery and other people in the lab. And of the five that we dropped in being almost identical to very, very different, three of these could actually replicate just fine and use human receptors for entry. If you took primary human airway epithelial cells, those are cells that are removed from the conducting airways from transplant recipients, the lung they gave up, not the lung they received.

So they take on the architecture of the human lung. SARS loves to replicate in these little cells that have cilia sticking out of them, and these viruses grow in those cells as well as the epidemic strains. And you can do a variety of experiments to try to get an idea of their pre-pandemic potential.

So they replicate in the right cells and they replicate exceptionally well. If this mouse, if the parental strain is virulent and you drop these bat genes in, they attenuate virulence, that's good news. But if you take a mouse that has the human receptor in it instead of the mouse receptor, these viruses are lethal.

So they certainly have the potential to cause lethal disease. If you take vaccines against SARS that work against SARS, they don't work against these variants that are sitting in the animal pools, zoonotic pools, and therapeutic antibodies that are present that work against SARS don't work as well against the more distant strains. So the answer is there's still lots of pre-epidemic viruses around.

This is the SARS story, but you can go to flu or any other virus that has emerging potential that

pops up, causes an outbreak, and then disappears. It's still here. They don't go extinct.

They are waning to return. In fact, people that live around the caves where these bats hang out with these viruses actually are seropositive, and several of them have, many of them who are seropositive have neutralising antibodies. So they're being exposed.

The virus is spilling over. It will happen again. So we can go to our panic-o-metre.

This is an important thing. What kind of person will you see on the news that will raise your tension level and cause panic? This is by field, so clearly these guys don't cause much panic. But down at this end, as you can tell, astronomers, volcanologists, and virologists are the ones that cause all the panic on TV.

So I think the virologists can probably do better. I think the astronomers are doing a better job of scaring people than the virologists are doing. But virologists actually, there is a real threat.

So can we learn anything about past and current pandemics in terms of their severity to give us an idea of how bad the next one can be? Let's look historically. Well, we have the Black Death, 75 million people in Europe over about a 300, 400 year period of time. The Spanish Flu that we're talking about today with 50 to 100 million deaths.

HIV AIDS in 37 years has killed a million people plus a year. 35 million are infected, devastating disease. Smallpox during the Antonian Plague, I think this was during the Byzantine Empire, 20 to 30% mortality.

In adults, 80% of the children died. In fact, although it's rarely mentioned, smallpox killed more people in the 20th century than any other pathogen, 300 to 500 million before it was eradicated. One of the greatest public health success stories in the history of the planet.

TB, 1.3 to 1.7 million deaths per year. Asian Flu, 2 million deaths. Typhus, this is right after World War I in Russia, 3 million deaths.

This is just one example, there are more. You can go to malaria, which kills about a half a million people per year. And then there's the gastrointestinal viruses.

I usually try to show a video of Victoria Falls. Imagine the water flowing over that for 30 to 45 seconds and you have an idea of how much diarrhoea is on the planet. Yeah, but this is a little squeamish before lunch.

But in reality, one out of nine children die from diarrhoeal disease, and this is a tragedy. When naive populations come into contact with new pathogens, the results can be devastating. In the New World, when Columbus and Cortez came, they brought smallpox, flu, and measles.

For example, there were about 250,000 natives in Hispaniola when Columbus first arrived. Within

about 50 years, 95% of them were dead. In general, 90%, some argue as much as 90% of the native Indian populations on the North and South American continents in Central America died from the 30 plus pathogens that came over with colonists.

That's pretty tragic. Let's not just think about humans when you think about the potential for catastrophic events. Food production is critical.

Fungal pathogens, largely ignored, have caused about 70% of the global and regional extinctions. The best one in my mind is the chestnut tree blight, which killed two billion chestnut trees. Food crops, there's lots of food crop pathogens that attack potato, rice, corn, wheat, and soybean.

In fact, the blight on the potato crop in Ireland resulted in about a million deaths from starvation. It's a little bit of a concern that this wheat stem rust super strain called UG-99, which emerged in Uganda, has been slowly making its way into the Middle East, approaching these big wheat growing areas. This strain will kill 80 to 100% of the 90% types of wheat that are grown on the planet.

Of the 700 million tonnes of product that are used to feed four and a half billion, and making up 20 to 30% of their diet, we could lose 90% of that. GMO is most likely the solution, and that irritates people. Sorry.

And then there's swine pathogens, because I wanted to document that coronaviruses like to kill pigs. It's just not fair. Porcine epidemic, the diarrhoea virus in about 20 years has killed over a billion pigs on the planet.

So pathogens can cause a tremendous amount of disease, despite the best farming practises that exist. This swept across the US and killed a dozen, not tens of millions of pigs. Okay, and so rather than having trucks or trainloads of human bodies, you get the idea.

Okay, this is the idea. This can happen. What are the pandemic drivers? EcoHealth has mapped the hotspots for virus emergence.

These are shown here. As it gets more inflamed, there is more evidence of virus spread into human populations. This is supported by human growth, in terms of population growth.

But really, probably the most important thing is population density, which is shown here. And you can overlay these population density maps right on top of these grids, which are associated with pandemic outbreaks. So it's not only the interface between humans and wildlife, population density allows for increased and more efficient transmission that leads to increased virulence.

And then the ageing population. We're getting a lot older. I'm happy about that.

However, several pathogens like flu, coronas, noras, flavies, RSV, et cetera, cause much more

increased pathogenesis and are much more virulent in the age population. I don't wanna stigmatise any group, especially a group that I'm now in, but I wanna show you an example of this using mice as models. And so imagine each transmission wave going from one person to the next.

You can mimic that in the laboratory by having young mice and having old mice and comparing the effect of virus transmission, a non-pathogenic virus, being transmitted in these animals. After about 15 to 20 passages, these mice will be dead. The virus will become lethal in a young animal.

In an old animal, it takes five to six passages. When you sequence these viruses, six to 10 mutations are critical for disease emergence in the young animals. One to two mutations in the old animals.

There are patterns of change that you can see in the young animals that have to occur. In the older animals, and these are six different replicates here, there's no pattern. There are many pathways to increased virulence in a immunocompromised population.

If you attenuate this virus even further, so it should be harder, the virus figures out the strategy. It deletes the gene and it becomes more virulent. So viruses have many tricks up their sleeve to enhance virulence.

Now the good news is that these viruses that are killing the older animals, if you put them back in the young animals, they don't kill them. So it's population control, I guess, at its worst. And so these factors all merge together to produce maps like this.

We've all seen it. There are emerging viruses that are occurring all over the planet, in addition to flu. And this scenario is likely not to change anytime soon in the 21st century.

Okay, so I wanted to give one other example about the effect of travel. Imagine an outbreak occurring in Hong Kong or Southeast Asia. It takes about two months to arrive in rural North Carolina.

David Weber, I actually got these slides from David. And I saw that he showed them. This was SARS in June, where we were setting up a triage unit to look at individuals who had been exposed to the SARS case.

But this is not an isolated story. When MERS emerged, this occurred at Indiana University. We have Ebola case occurring at Dallas.

And so there are really no places to hide from emerging pathogens. And they're basically about 24 hours away. And so we have to think globally rather than locally.

Okay, so how much worse could it be? Well, I like this quote. This is from a U.S. Army physician. It's one of the most powerful letters I've ever read.

It's in the National Academy, a report about pandemic flu. He's writing his father about treating cases during the flu pandemic. I don't have time to read it.

But I will say this, the data suggests that it can be a lot worse. So if you were going to pressure me to say which flu strain was the worst, and I wasn't allowed to say coronaviruses, my best guess would be an H2 virus or an H7 virus, or like H7N9. I'll talk about H2 first.

H2 has been in the human population in 1859 and then again in 1957. It has caused high mortality rates. It disappeared in 1968.

This is a hemagglutinin gene that can function well in humans. Anyone under the age of 51 has never seen it, so there's very little herd immunity. In essence, the same scenario now exists that existed in 1981 with H2 virus instead of H1 virus.

If you're old, you're gonna do well. If you're young, you're in trouble. So yay for the age people.

Finally. However, H7N9 is a much different story. None of us have any preexisting immunity.

We are all at risk. So what does the data suggest? Well, the numbers can be pretty horrifying in the absence of any intervention. So if you look at an attack rate during a flu pandemic, which ranges from about 20 to 38%, some people say 10%, others say 50%, that's sort of the range that can occur in terms of the attack rate.

If you look at the mortality rate, 0.1 to 60%, this is generous in my opinion, but that's what has been reported in the literature so you can use it as the top rate. And the reason I mention it's generous is because asymptomatic infections probably don't get calculated in this H5N1 mortality rate. And there's this other factor which there is an inverse relationship in general between transmission efficiency and virulence.

In other words, if you have someone who's infected and dies quickly, they don't transmit. Having said that, HIV figured out a way around that, didn't it? It kills slowly, allowing for a longer transmission window. So it's not necessarily true that this will occur, and it's also influenced by population density.

So when you start doing the math using the lower numbers, you end up with 1.68 million deaths out of 7 billion individuals who use the higher numbers, it's 1.6 billion. That's the range you're looking at. Let's take a 1918 flu-like virus with about a 4% mortality, you're looking at about 106 million deaths.

In the U.S., that would equate to about 12 million deaths. A flu strain that had a 10% mortality rate, that's about what SARS had, and it was fairly efficiently transmitted, so it's likely. You'd be looking at about 266 million deaths.

In the U.S., it would be 30 million deaths. An H7N9 virus with a 39% mortality is a billion

individuals. Again, this is unlikely to keep this high rate, but it could be 10 to 20% or less.

H5N1 would be 1.6 billion, so those are pretty horrible numbers. You can modify that a little bit if you think about treatment with drugs that would reduce both the attack rate and the mortality rate. I'm guessing at these numbers, I gave it a half reduction in the disease mortality rate by half each, so this would reduce these numbers by about a quarter, 400,000 to about 400 million deaths.

Surprisingly, and I might be wrong about this, but everything that I read in the literature said that treatment of secondary bacterial infections really show very little improvement in flu-infected individuals, and so it really has very little impact on the overall mortality rates. I'll show you a reason why that might be the case, so that's not really gonna help. I didn't talk about other barriers to infection.

That's certainly going to help, but those are the numbers you're looking at. In terms of our stockpile, I think we've passed somewhere between 50 and 100 million doses of Tamiflu. That certainly will help quite a bit in the first wave.

Okay, what about the efficacy of antiviral drugs? Well, these emerging coronaviruses and flu viruses cause this disease called acute respiratory distress syndrome, so this is your alveoli. You're transmitting oxygen very efficiently to the red blood cells in the capillary bed that surround it. What do these viruses do? They love this cell right here.

They kill it. This cell supports these two cells. Some of these viruses, like MERS, also infects these cells, these are called type 1 cells, and this barrier that prevents fluid from coming across this capillary bed into the alveoli is broken down.

In addition, inflammatory cells come in and dump lots of pro-inflammatory cytokines, which cause more damage, and so these alveoli fill up with fluid. So when you think about the description of the story of Ben and Thomas Wolfe's novel, you're now looking inside to see what exactly happened to his lung. He was drowning in his own fluid.

Now, if this is bad enough, you have haemorrhage, lots of red blood cells pouring into here as well. What happens when you haemorrhage? You try to clot and wall off that bleeding, and that's exactly what you do in your lung, and you lay down these big clots, which look like they're called hyaline membranes. They have lots of clotting factors in them and cellular debris, so you're building a wall to prevent this fluid coming out, and then you have efflux pumps that pump the fluid back out, opening up the airway.

Problem is that is a thick, gooey barrier. Oxygen can't transfer across, so now you're suffocating. This is a devastating end-stage lung disease.

It's been difficult to clinically manage for many, many years, and there are no real treatments

besides NIH spending millions of dollars. So what happens, so I wanted to mention that this is both a virus and an host immunopathologic disease, and so you have to treat both, but all of our antivirals only attack the virus, not the host response, so you're only getting half of the disease. So this is what happens in flu, also in coronaviruses.

If you have mock-treated animals with no drug, okay, they all die, they get sick or die. If you treat with a drug that works against a virus like MERS or SARS and you give it before infection or one day after infection, these guys get mild disease and do well, but at day two or beyond, they die. That means the virus has already hit its peak titer.

The programme leading to an immunopathologic-mediated death has been set, and you can't stop it even if you knock down virus. So a highly pathogenic flu virus that limits that therapeutic window is gonna result in more death. Less pathogenic one that opens that window up will make drugs more effective.

So it's hard to predict what will happen. Vaccine availability, if we don't, if Barney doesn't make the universal flu, which his data looks great, we're limited to traditional methods that's four to eight months. Seed stocks will be ready in a few days if we use reverse genetics, if we use reassortment.

That was developed in the 50s and the 60s. It takes a little bit longer, but we can develop the seed stocks incredibly quickly. The bottlenecks are egg production, and then you have to put the surface proteins of the virus into a backbone that grows well in eggs, and sometimes that match doesn't work.

Like during the 2009 pandemic, it doesn't grow as well. You make less vaccine, and so now the vaccine is in limited quantities. So you miss the epidemic wave for most people.

The other problem that can occur is egg adaptation. The virus could adapt to the egg, and the mutation from growing in the egg could actually be the juicy epitope that your immune system responds to. So you don't make a good immune response against the pathogen, so that's the other problem.

Then you have the anti-vaccine.