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Keynote Address

Christopher Chyba, Introduction of Dr. Joshua Lederberg

With this audience I hardly need to introduce Joshua Lederberg.

I think that many of you know that Josh won the Nobel prize for physiology and medicine at the age of 33. He is a Professor Emeritus at Rockefeller University, but in addition to being a research geneticist, he consistently played a major role in advancing various areas of science in a policy sense. He single-handedly invented the field of exobiology, but for decades he had been the prime mover with respect to thinking about biological terrorism and the threat of emerging infectious diseases.

Josh, its an honor for you to speak to us tonight. Josh will be speaking for about a half hour and we'll spend some time for discussion.

Joshua Lederberg

Thanks Chris.

Well you've been hearing all day, and I've joined you for a large part of that, about emerging infections; and so there is a lot of background material that you are thoroughly familiar with, that I'll rely on what's been presented before. In fact I'm going to give you a preview of what I'm going to talk about. I am not a very dramatic personality. I like to telegraph my punches. I like to say things first in very general terms and then more specific ones and then nail them in a third time. So l do like you to know what the message is that I try to carry over. I guess the bottom line is the bottom line.

I'm trying to reflect what I have to say, which is an ecological view of our relationships with microbes, which occasionally flare up in frank disease. What does that have to do with surveillance? I guess one short answer is that most of the outbreaks that you have been hearing about are, in fact, zoonoses.

And why is that important to our consideration of them? They are events that are out of the ordinary-evolved equilibrium between parasites and hosts that reflect the great majority of our interaction with microbes. Most of those interactions are reasonably silent—they are a few sniffles or they are the occupation of our gut space with enormous masses of microbes. We suffer when this process is interrupted. There are ecological interactions between different members of what I call our microbiome. The microbiome is the sum of all the other genomes that occupy the same body space that we do. They're all microbes of one kind or another, an infinite variety.

I was sorry to miss David Relman, who has played such an important role in exposing a number of those that have not even been cultivated for the present time. And the role of that microbiome in regulating health and disease has only begun to be appreciated.

The natural lifecycle of most microbes is not the exacerbation of disease and the lethality that we are so accustomed to focus on. Of course we should focus on lethal events, but we ought to understand a broader biological background to the extent to which those are the aberrations—they're not the norm in our relationship with that world. So I will elaborate that somewhat as we move forward.

Now there is one surveillance that I have been following for the last fifty years or so and that's this wonderful chart; probably the most important statistical chart that you have ever seen, and this is life expectancy in the United States throughout the 20th century. I think you're all familiar with the general outlines of it. I've been adding a point to that every year that they've been public and thanks to the extraordinary efforts of our bureaus of vital statistics and the CDC for providing that information.

About half the gap is infant mortality. So if we erased the infant mortality from those curves, you'd start out with something that looks something like that. Infant mortality today plays a negligible role in overall life expectancy, but a major factor in life expectancy at the turn of the century. There are, of course, differences between males and females; there are differences among racial groups, among economic sectors and so on, but they are relatively small, in fact, compared to the overall trend of improvement of health and of life expectancy during that century.

The ordinary person today, the average person, lives in a luxuriant condition compared to the monarchs of 200 years ago with respect to the exposure to disease, the expectation of life, the comfort of life, and so forth—a point we don't always realize when we talk about the good old days.

One could spend hours in the particularities of what is reflected in this slide; of course, this is a summary of our vital experience throughout that history, but the main features I want to stress besides the discrepancy between what we have on a national basis. India today is about where we were around 1950. The overseas are generally just about were we were at the turn of the century. There are the real disaster cases of Uganda and Sierra Leone, where a combination of HIV and civil disorder and conspiring infections diseases have rendered those the real hellholes of contemporary existence.

We don't fare quite as well as a number of other countries. We don't know what the ultimate asymptotic limits will be, although it will obviously be difficult to achieve further progress as we remove the major causes that are ameliorable. Mortality and infectious disease—they're still there but they're nothing in the dimensions of what they were at the early part of the century.

So let's look a little bit more closely at that. This is a kind of "mise-en-scène"—for my major message I borrowed very heavily from Bob and his associates at the CDC. This comes straight out of the publication in the JAMA a couple years ago and this is a reflection of the same curve we saw before. This is total, this is the crude mortality from all causes. Here again I remind you infant mortality was about half of the picture at the beginning of the century. This is the infectious disease component; this is the total crude mortality. And that's gone on very strikingly for the first half of the last century with this enormous peak in 1918—the influenza epidemic which was commented on several times

As an acute plague, this is an outstanding event in recent history. It will be eventually overshadowed by AIDS, but that's spread over a number of years and of course much more so in countries other than the United States

The other features to notice are that there's been an uptick relative to previous history of fairly small dimensions, but roughly a doubling of infectious disease-related mortality in the last two decades. About 50 percent of that is accountable by the AIDS epidemic, the rest of it from antibiotic resistant infection and circonial infection and a variety of other aspiratory disease. So were falling back in some of those very special areas. Again, small in absolute dimensions, small in dimensions relative to what we had from infectious disease earlier in history, but alarming in terms of the vector that's being reflected here.

One of the consequences of this very sharp trend which asymptoted around 1950 was the complacency that went along with it

And of course one recites things like this galore. One of my favorites, because it come from Yale, my Ph.D. ala mater, was Charles Edward Emery Winslow: that our wonderful intellectual accomplishments has forever banned from the earth the major plagues and pestilences of the past.

How that could have been justified even in terms of those days is quite baffling. But you see you're on the bottom end of that sharp decline, you had occasion to be fairly optimistic. It's HIV that woke us up that we were hardly in a position to dispose of infectious disease generally. And we're here to talk about how to deal with what's going on.

So there was some reaction to that complacency, but maybe not many more people than myself. And I have to say I don't deny those headlines, but I didn't write them. I was writing a regular column for the Washington Post in those days and it was a rude shock for me to discover that I might write a title, but that's not what appeared in the paper – it was a headline writer who did that.

("The Infamous Black Death May Return to Haunt US")
("Mankind Had a Near Miss From a Mystery Pandemic")

(OK in this case never mind that is alright) But there are not too many folks who were really focused on the hazards of recurrent plagues that might arise-guess what-out of Africa. Africa is a combination of exposure to the widest variety of zoonoses, still undeveloped, very limited economic and social development for dealing with disease, and so its no surprise that we have seen so many of those.

I had never dreamed of an AIDS, or something as clever that, that gets into our psyche, into political mechanisms to its advantage to a degree that Ebola, Lassa fever, Marberg—those were the things that we were talking about in those days.

Whatever complacency we might have felt justified of in the United States, of course, has never been true of the world as a whole. These are again statistics very familiar to you all, of the disease picture, globally speaking, this is a adding everybody together—developed and undeveloped world. I don't think the numbers have changed significantly in the last 5 years; infectious and parasitic disease still playing a role for one-third of our total mortality. And some idea of where these things might come from. I also am a very fond reader, *(I have not contributed, maybe I did once, I don't remember)* to Promed. This is simply a list of the conditions that you can find in the index, widowed out to reduce some of the duplications, just to give an idea of the enormous range of different conditions. So my, my what the biospheric world has in store for us. And I'm not done yet—this is the rest of the alphabet. And the great majority of these are outbreaks, and they are outbreaks of zoonoic conditions, not all.

What's left out, and with very good reason, and Dr. Woodall explained all that, doesn't attempt to cover everything, the very prevalent diseases that are there all along, are like HIV, staph and streptococcus

infections, which are the routine grist of the mill in hospital treated infections, aren't even mentioned at all in that list. We have a lot to worry about. But OK there's been some reaction to all this: we've had the IOM report, we've had the CDC responses, we've had public health being reawaked to some degree to try to make its fair claim and we have a pretty good idea of what to do, and the very first line of what to do is concerted global and domestic surveillance. There's hardly a question there.

I suppose if there is one failing in our surveillance system, it's that given how much of our outbreak concerns have zoonotic sources, we should be looking at the zoonotic reservoirs much more intently because that's where so much of the new disease is going to come from. We see a little bit of that, we have sample of the avian population to see where the new flues are going to come along; we now look at the birds again for West Nile, to see what is likely to be in the offing.

But I think it's a major hole in our program of global surveillance not to be looking much more intently at the zoonoses.

There's also an issue of what I might call "zoo-anosis", in that, one of the places to find infection in exotic animals is in the zoos themselves. And people who want to wake up the world about this are really being persecuted—but that's a no-no to even talk about; that the animals we're are so fond of seeing in the zoos really do have to be scrutinized very, very carefully for what they in turn transmit to human populations.

The outstanding related example that I can think of was the herpes-b infection that the laboratory worker experienced-was that was in Atlanta? San Diego? Which should be a matter of very serious concern, but well this is for another day.

Ok, this is our traditional picture, we have our military metaphors for dealing with it: we are trying to mobilize ourselves, there is the enemy, it is very clear-cut, we have a pretty clear idea of what to get after.

There's plainly a "but" coming along. Lots to worry about. Vive the microbe hunters, I adore them, I adored them in the past, I adore them today, as well they bring us notice of these adventures. I wish I could have played a more active role myself in those front lines. Instead, I've been a bench scientist and I've worked on genetic mechanisms by which microbes could alter like some kind of deeper understanding of what's actually going on in their evolution.

But do we really have the right search agenda and that is what I'm going to be talking about.

Now, I could have extracted any number and when I give this talk at somewhat greater length, I pull out the Promed descriptions of these kinds of events. I took a sample, five of the last couple of hundred titles, of very real scares that we've had over the last few years of out breaks that had every potential of indeed breaking out and becoming a matter of great epidemic importance in the human population. Influenza A/H5N1, was probably the best managed incident in recent history. It was in a political and organizational context that allowed for efficient public health administration. I don't know that any city in the United States would have been able to match that. I think the behavior of the Hong Kong authorities in invoking international assistance and in publishing the information that they had in the necessary measures for control are really absolutely exemplary and I never tire of an occasion to give credit for that as an example.

We had our own scare with the Hantavirus. We had no way when it started of having any notion of how far it would spread. It must have been very scary in the early stages to realize how deeply (infected) infested the rodent populations were with viruses at least closely related to these, that give rise to the pulmonary syndrome. We still don't have a clue as to what fraction of the actual viral entities that are endemic in the rodents would

actually be that harmful in humans, we don't understand at all. I don't think we have a shred of insight about the sporadic occurrence of human disease against the background of pervasive presence of these viruses or at least related viruses in the environment.

But anyhow, I guess FMD in cattle is not really a scare as far as human populations are concerned—I should erase that from the situation. Yet none of them did end of conflagrating, none of them ended up threatening the species. And you could say that about a hundred other incidences, the 1918 flu and HIV are the two out of the hundreds if not thousands of latent outbreaks that have had that further consequence.

Should that be a surprise on one hand or should we ask the question, why are we still here when the word is so full of booby traps, so full of land mines, so full of potentials for major catastrophe? Is it just pure luck? Well, in part it is. But I think there's a logic to it as well.

I think about this more particularly in the framework of my own studies of microbial genetics and evolutions and think of this as an evolutionary race—we have adaptations to disease, we have the disease organisms' adaptation to our defenses. So there's an armed conflict going on all the time. But let's look a little more at the particularities about at first order all the advantage should be on the side of the bugs. And as you'll see, I do argue they really are driving the bus. But to a different destination that you might have though of in the first instance.

So these are the great truncation of all the molecular biology of microbial species. So I'll just give you a few lines here and there. The most important are the population size, the cycle time, the size of organisms. The human carryomes are chromosomal. The part of our body space which are our own genomes, if you like, are manifested. Who ever said the human population size was limited, but it's a mere less than ten billion people? It'll reach there. I say mere because as you all very well know, a cupful of broth inoculated last night with a bacterial seed would have ten or a hundred times that population size if I incubated in that tiny vessel. A single infested human with a highly proliferative virus could easily have as many as 10 to 15 infectious particles within that body size and multiply that by the number of individuals who might be inflicted, not all 10 billion of us at once, and you see we're talking about 6-8-10 orders of magnitude of difference in population size of the microbial world—our competitors compared to ourselves.

There's also a nearly million-to-one ratio of tempo of reproduction. So it works out that evolutionary pace in any microbial species you care to mention, even neglecting the much greater ferocity of natural selection operating on these huge populations. Inflating, deflating, inflating on an almost daily basis would amplify this even further. So we're talking to something like a million-to-one of evolutionary tempo. So that in two years in the world of microbes is a million measured in mammalian evolutionary time.

When considered that mammals only differentiated about a hundred million years ago, you see how far back in our own vertebraen evolution we have to be to talk about what, say a century's worth of what microbial evolution would have to consist of.

So in all of vertebraen evolution, there really hasn't been that much time for much differentiation in adaptation, differentiation in functions, evolution of new ways of coping with microbial disease, compared to the versatility that the bugs themselves have to offer.

Now there must have been some and we tend to pay very little attention to it. It is inevitable that even in the very limited number of generations that's reflected in the say 50 million years of divergent evolution, that rodents and primates should have had differentiated components of their immune responses.

But the world of immunology has only barely begun to think about comparative biology. We're so preoccupied in the historical development of the subject of the universals of the immune response, and those fundamentals haven't changed very much in two hundred or three hundred million years since it first appeared on the scene, where we first begin to see the adaptive immune system as we see it today. But we may be exploiting very important opportunities in which individual species have, in fact, been able to develop specific responses to the infectious environment that they had to experience and everything is swept under the rug of the universals of immune response. So we tend to regard the mouse as equivalent to the rabbit as equivalent to the guinea pig as equivalent to the primate as equivalent to the human.

Now there's another way in which evolution is greatly enhanced in the microbial world compared to our world of multicellulars, and that's in breeding speciation once a medillion breeding group has so differentiated. That it no longer hybridizes with the rest of the world, it's a closed box as far as further innovation is concerned. So that they're whatever the rodents have developed since their divergence from the primates roughly 50 million years ago. There's no sharing of that information from one group to the other, there are no cross-breeding mechanisms to allow for that, whereas the microbial world are quite promiscuous—there's exchanging of plasmas and genetic information across all the taxa of the microbes and some penetration even in the higher forms. The first reading of the human genome pointed to three or four hundred DNA sequences that are almost certainly of microbial origin in and of themselves and are later intrusions. But we see almost none of that cross-talk between species in higher forms, which is habitual among the microbes.

So we're kind of locked into a given style of evolution to infection in a way that our adversaries are not. They can exchange information. Like drug resistance, this is the outstanding example relevant to our concerns today that we have very much information about.

As of five years ago that situation has changed—a real turning point in human evolution because we can begin to overtake that barrier of speciation. We can begin to use our knowledge of what has evolved in, let's say, the rodent world to our advantage that purely biological mechanisms have not allowed through our culture, through our knowledge, through our insight, and so forth.

So, given all of this disparity, why are we still here? And there's only one possible answer. The evolutionary drive of the microbes is not for our elimination. And of course not. Because with the exception of so few not worth mentioning, the death of the host is the death of the parasite. And all ordered, well-behaved, well-adapted microbial systems will have domesticated us rather that wiped us out, and that's were we see most of our microbiome living in a reasonable degree of cohabitation with us. They give us the sniffles. In many respects, they're totally asymptomatic. They, in many ways, protect us from intercurrent disease, as we learn to our dismay when we sterilize ourselves with antibiotics and have grave intercurrent infections as a result of that sterilization when we break up that competition of that microbiomial world within our own bodies.

Is this pure speculation? Almost, but there's a lot of clues about microbes and their self-restraint being a part of their usual natural history. Now they sometimes make mistakes. They sometimes say "oops, sorry, we're both gone." And that's what we focus on. And as well we might. That's where our tragedies come from. But we don't I think spend enough of our research agenda on the normal natural history of our relationship with infectious organisms. But we don't really have a clue about how we just carry streptococcus, staph and minioxide (?) in our noses and our phenyl system. And we're able to sustain that delicate balance of enough immunity that they almost never, in statistical terms, overwhelm us. But we almost never overwhelm them. And we can maintain some degree of stable balance. If we understood that better, I think we'd understand better how to deal with more virulent disease.

So here are the clues that I operate on. Mostly the zoonotic adaptations, and these are legion. I mean almost every example of zoonoses that you've heard about are nearly asymptomatic in their zoonotic hosts. There are exceptions to that, as there are in almost all of my statements. But there must be 50 arina viruses in rodent populations with no known pathology in the host organism. They break into the human, it's a new ballgame. There's been no time for the evolution of the adaptations on the part of the organism to protect the host, to make them more efficient parasites in dealing with us.

We're certainly in a transitional stage when dealing with HIV. But it's so clever it has adopted a latent period where it really doesn't matter very much to the ecology of the HIV if its host lives ten years or lives fifty years—it will make very little difference in the transmitability of HIV. The fact that it's gotten to as long as 10 is a major factor in it's capability of we being stuck with it for a very long time and having to suffer the consequences.

The one data that led me to this kind of thinking was reflections about disturdium botulinum and knowing how easy it would be with artificial genetic engineering to get constructs of infectious agents that would contain this most toxic of all known bacterial toxins—one or two orders of magnitude more efficient at killing you than other toxins. And unlike most other toxins, irrelevant to knocking down local tissue defenses against invasion. It doesn't really do the bot toxin organism any good whatsoever in terms of invading an organism, but by killing its host it has an unique attitude. The attribate anaerobic parasitia feed on their dead hosts like no other pathogen (we have) we know about does. So they have a totally different lifestyle, they accommodate it totally differently. There's no such neurotoxin of that potency in any systemic pathogen that relies on the survival of the host and of course that makes this an oxymoron.

We also have very specific examples today of pathogens or quasi-commensals secreting antibiotic against other organisms. Normark in Stockholm has shown anti-Cholera peptides being secreted by Helicobacter makes perfect evolutionary sense. Helicobacter, which is probably in the stomachs of half of us around the room here, will suffer no benefit from having Cholera invade its turf and cause any degree of severe morbidity and mortality to it. So it's an active participant in our mutual defense against those other third parties.

We have particular examples in other parasites. I don't know of any that I can be sure of because things aren't looked at in that way in viral or bacterial infections where the role of immunity has been co-opted by the parasite to it's own advantage in inhibiting super-infection with other related parasitic organisms. The case in question is gystasoma. The mature worm living in your liver will evoke antibodies, which are no benefit whatsoever attacking the worm itself. What will prevent super-infection, we'll have the little larvae trying to compete with the space that the big worm already occupies. So it's a clear example of the parasite exploiting the immune machinery of the host for its own ecological advantage. I suspect there are many other examples of this. But we've called host defense instead of understanding whose really driving the bus in many of these encounters.

And then something that's puzzled me all of my life since I've done most of my genetic work on bacteria using their nutritional traits. The most interesting organisms are the most fastidious. Tuberculosis grows so slowly it's about the slowest growing bug that's ever been cultivated. It probably never would be if not for the necessity of doing so. Staph and Streph have such complicated nutritional requirements nobody ever grows them in any practical sense on a chemically well-defined medium. You find again and again even within salmonella some of the main types are auxo-autotrophic; tryptophane requirements keep creeping in all the time and so forth. It's as if there's a general trend toward nutritional dependency in systemic pathogenic organisms. Maybe it's enough that they're permitted to do so by living in very rich media. But I think there's a further message to be gotten from the slow-down in their functions that they can then operate, which is

paradoxically to their advantage if they want to be around form a long time, they have to learn how to restrain themselves. You could give other arguments for that.

So I have a rhetorical question here: are we too host-centered? Obviously I'm arguing for the converse, that if we spent a little more time from the worm's eye view or the bug eye view of the world we might have a little different picture of our relationships. There would be the oops, the exceptions. The evolution of microbes in a given host is quite paradoxical. In a competition of one bug cell to another bug cell, rapid proliferation, by implication virulence, is an advantage. From the point of view of the tribe it's a gross disadvantage because if it knocks out the host, not only that mutant bug but all of its cousins and sisters and brothers and aunts go down with the host as well. And I am certain that there must be mechanisms to control the mutability of parasites in order to preserve the integrity of the tribe, which is almost the inverse of what's been argued in terms of drives toward virulence. But theses are diversion operations going on at the same time. Tribal advantage is to moderation, individual advantage within the tribe is to lack of restraint—but with ultimate disaster in that case for the host and for the parasite as well. And both are going on all the time.

So you might think a little more clearly if we understood that the ultimate competition is not between them and us. It's between them and them. If the parasites don't get us, the saprophytes will. Or let's turn that around—that's a certainty, that's biblically enshrined. And there is that competition going on but we pay very little attention to it. And it astonishes me how little in light of the fact that the entire antibiotic industry has been founded on our insight into the competition of bugs and soil and none of it so far have been based on the competition of bugs within us. So I think there's ripe territory for further exploitation in that direction.

So I'm suggesting this, not as a given datum, but as a broadening of our research agenda we should investigate how parasites moderate their attack, how chronic infection is sustained. That's against the paradigm of every animal model worth mentioning that anybody ever uses. The ideal animal model: Inject 2 bugs into the peraium and the mouse goes belly up the next day. That's ideal. Totally artificial demonstration, resembles nothing that we see by way of natural disease. There are good reasons for that animal model but there are no good reasons for its being the only one and it's given us a totally misleading view of what disease consists of in our relationship to our microbial neighbors.

This has had consequences. The normal flora ecology is notoriously neglected. I would say one I don't have on the chart here: the way we've approached HIV has been 99% let's get rid of this virus. Almost none of it to how can we live with it, when we have examples of co-habitation if we see HIV in the chimpanzee. We have effective co-habitation. I'm not suggesting we turn ourselves into chimpanzees, but if we spend more effort investigating how that equilibrium can be established in one species, maybe we'd be a leg up in the management of AIDS even if we tolerate it because we have no way to avoid tolerating the persistence of HIV in an individual once infected, once it's lodged in the chromosomes of infected cells. So these attitudes really have made a difference.

Another place that I've been very deeply stuck at, this military model of toxins as weapons. From the day that Robert Cope discovered the cholerae vibrio in 1882 or 1883, there was a search on for the toxin by which the cholera killed its host. One of the most serious epidemic diseases known at that time. And almost all of the research on cholera was thoroughly contaminated with this idea of a hyper-toxic compound secreted by the vibrio, and guess what? It's a hormone that promotes the secretion of water into the gut. And it's not until they caught onto that and developed the different animal model — and demonstrating secretion of water into the gut as the main action of cholera toxin, that we had the kind of insight that led to the appropriate management of cholera.

Cholera is no longer a note of doom—it can be very well managed by re-hydration to where its mortality should be driven back practically back to zero if well-managed. But this was obscured for 70 years by the attitudes that we had in how we were going to cope with bacteria and bacterial toxins.

So I want just one more possible instantiation about other things to look for in the surveillance mode. I'm not going to go through this entire chart, I'm just going to focus on the top one. I've been puzzled many years and maybe some of you can illuminate me about the epidemiology of this infection. It's universally carried yet it occurs in outbreaks where it does seem to be infectious on a broader scale. It's been presumed that I would have been one of the first to hypothesize that OK, maybe now and then there's a more virulent mutant of the carried meningitis who proliferates more broadly, gets across into the cerebral spinal fluid and gives us more lethal meningitis. It's a little puzzling how that happens in outbreaks. I've known about cross-reacting polysaccharides for a long time, but stop and put two & two together. Maybe epidemic meningitis is an epidemic of the non-occurrence of e-coli K100 in certain groups that other e-coli have taken over and do not provide the cross-reactive stimulus that would allow for a more usual, less virulent equilibrium, of the kind that we see in most of our hosts. So that says maybe surveillance should also be looking for the things that are not there that are habitually there, if we should account for these kind of epidemics. Well I know that's not going to happen, but I wanted to suggest at least a research approach that we have to give some thought to.

So what's the bottom line here? I'm not sure. I don't know how far to take this line of reasoning. It's not novel. I could have learned it from Theogold Smith, I could have learned it from Ronnie Dubose. But I don't think they ever carry these notions to the level of trying to make an explicit research agenda out of it. And that's my plea today, that let's think a little more deeply about molecular "solutogenesis".—the opposite of pathogenesis. How do we maintain health-sustaining equilibrium with the very same bugs that in other circumstances will do us in. And maybe that will allow us new insights and new avenues into the control of infectious diseases. Thank you very much.

Q&A/Remarks

Audience remark: I think the classic example of the adaptation of the pathogen to reduced virulence is the case of the myxoma virus in Australia. When the myxoma virus was introduced for rabbit population control, the introduced stain killed 90% of infected rabbits. More than 90% of infected rabbits. About 3 years later, wild myxoma virus isolated from Australian rabbits was killing something on the order of 2%. Myxoma virus is an insect transmitted virus from rabbit to rabbit and presumably what happened was simply that those viruses that killed rabbits with the very high infectedness of the initial isolate had much less opportunity to transmit, and so within a few years myxoma virus was no longer an effective biological killer.

Q: (Chris Chyba) Perhaps I'll just close the evening with a last question. Josh, you called for an effective research agenda, a research program. But what does the model you've laid out apply to what we should be doing currently differently in public health?

A: Well, I did give a few hints of it. I think probably most importantly looking from zoonoses, since so many of the outbreaks where you have severe disease are of zoonoic origin. I think reaching back further to what's happening in the animal reservoir just makes simple sense.