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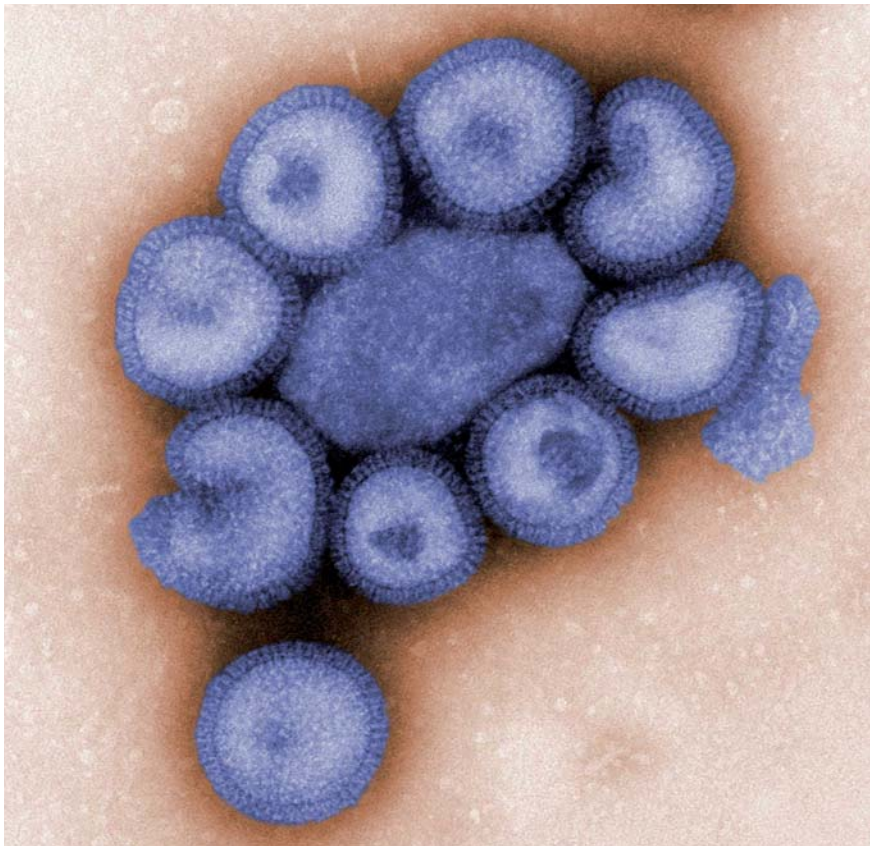
Virus on Trial

Here we address the controversy unleashed when Dr. Ron Fouchier and colleagues submitted a manuscript describing aerosol transmission of the H5N1 influenza virus between birds and ferrets. Professor Hugues Tolou has more restrictive views on the potential dangers that this work poses.

FEMS Focus: ***Why are the H5N1 studies on transmission between hosts important?***
Ron Fouchier (RF): All pandemic viruses have caused pandemics because they were transmitted by aerosols and we know that many of the animal viruses cannot be transmitted by aerosols between mammals. So knowing what it takes for influenza viruses to become airborne between mammals will potentially allow us to predict which viruses will cause the next pandemics. It's a very fundamental research project: to understand what it takes for an animal-influenza virus that is non-airborne to change it into an animal-influenza virus that is airborne. With H5N1, it's a very practical question. Since 1997, these viruses have been around in poultry in Southeast Asia and Africa, the Middle East and Europe and since 1997, the question has been: "can this virus cause the next pandemic?" Nobody knows because nobody knows what it will take for such a virus to go airborne. Therefore, we and other groups have investigated whether this was a possibility, whether this virus will ever acquire the ability to go airborne between mammals. That question was actually put high on the research agenda by many international organizations – the FAO, the WHO, the NIH, the EU. It's a very important question to answer. We are now the first to have an answer for H5N1 and then we find out that the world did not want to know that answer. A question they were asking themselves.

Hugues Tolou (HT): Highly pathogenic influenza viruses (H5N1-HPAI) is today a very dangerous pathogen for several species of birds. It can also infect mammals and humans, but only rarely, when the mammals or humans come in close contact with infected birds or their carcasses. Transmission of this natural virus from human to human is inefficient, a situation very different from the one we know for other influenza viruses. Clearly, the question of what makes the transmission between particular hosts possible is an important one. Knowing



This colorized negative-stained transmission electron micrograph (TEM) depicts the ultrastructural details of a number of influenza virus particles, or "virions". A member of the taxonomic family Orthomyxoviridae, the influenza virus is a single-stranded RNA organism.
Photo: Dr. F. A. Murphy

From the Editors,

Once again, the H5N1 virus defines the name of the game! We interviewed two scientific capacities with key expertise, firstly Dr. Ron Fouchier who tried to publish findings on how the H5N1 virus could be transmitted from birds to ferrets, and Professor Hugues Tolou who has an opposing view on how and why this work should not be published. This topic has engendered ample discussions in the public and scientific arenas alike and among policy makers on microbiology and bioterrorism. Here we get unique insight from the points of view of Dr. Fouchier and Prof. Tolou directly. Please join us in this balancing act!

Tone Tonjum
& Chared Verschuur-Ballo,
Editors

the answer, we could conceive, maybe, new strategies for prevention.

Has the work on the H5N1 mutation demonstrated that H5N1 will evolve and spread without further human intervention?

RF: Several of the mutations that we find in our airborne virus are already occurring in the field. We even see viruses with dual viral mutations, thus, the chance that these viruses like ours is going to evolve in the field are always present. That chance is not nil. I do not know exactly how big the chance is but I do know that the consequences might be fairly large. So the chance of this happening is very hard to calculate but you know that if it happens, we might be in trouble. Therefore, we have to be prepared for that.

HT: Clearly not. The process used remains artificial; it has "forced" the evolution of the virus in a particular condition. No one can certify that the virus will evolve the same way if the experiment is done again (except if it has already been done!), and no one can certify that the virus will evolve that way in nature.

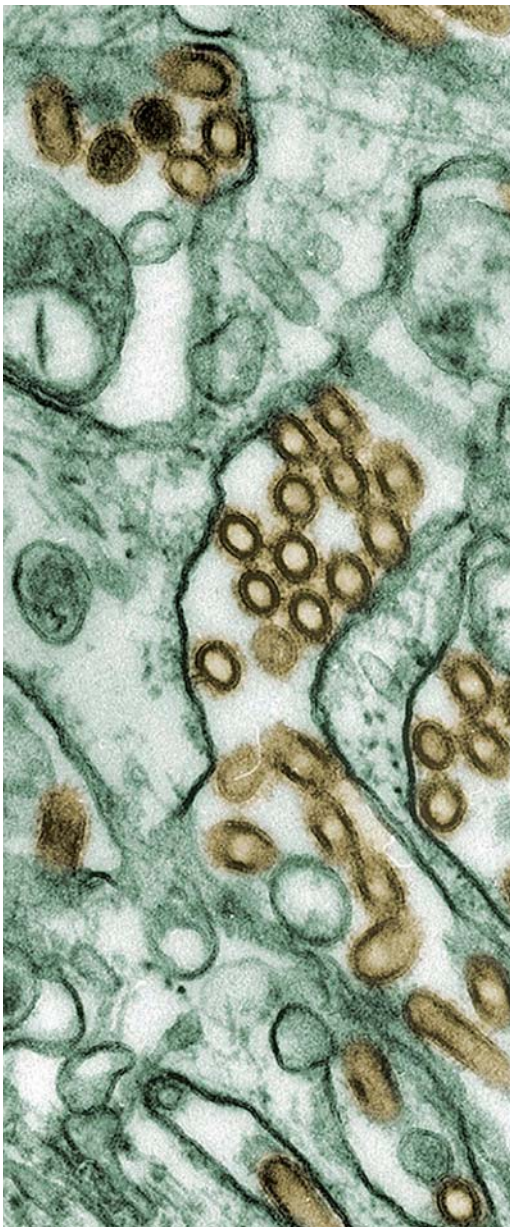
Why were methodological details from papers submitted to Science and Nature describing research that genetically modified the H5N1 virus to increase its aerosol transmissibility among mammals retracted? What about scientific freedom?

RF: The US National Science Advisory Board for Biosecurity (NSABB) was afraid that people with bad intentions would misuse our information. At the same time, they recognize that the work was important and needed to be shared with the scientific field and so they recommended to the US government that some mechanism would be put in place to share the detailed information with people with the legitimate need to know on a confidential basis. That was the advice of the NSABB and the NSABB advised the US government and the US government took over their advice. Then, the US government asked us, the authors, and the journals to do what the NSABB had asked. Now, we were not agreeing with what the NSABB had said. We did not agree with the risks, we did not agree with the limited benefits that the NSABB had identified. We think the benefits of publishing will be far, far bigger.

HT: Freedom is not tolerable when it consists in producing hazards and threats. Of course, defining what is hazardous or risky and what is potential benefit, is not so easy. Maybe we would never have had to face a transmissible-highly pathogenic H5N1 virus, but now, we know it is possible. Maybe the virus could escape from the laboratory, or somebody, somewhere, is working to produce another one, now being sure he can succeed.

Why is there a controversy related to the H5N1 mutants and scientific freedom? (i.e., why did the USA government attempt to restrict publication of sensitive data in Nature, Science, and elsewhere)

RF: We did not agree with the advice of the NSABB. The WHO also recommended that it is important to publish but it's also important to recognize the controversy that has arisen. They recommended a strong communications strategy as well as some additional review of the biosafety and biosecurity issues again but now with the manu-

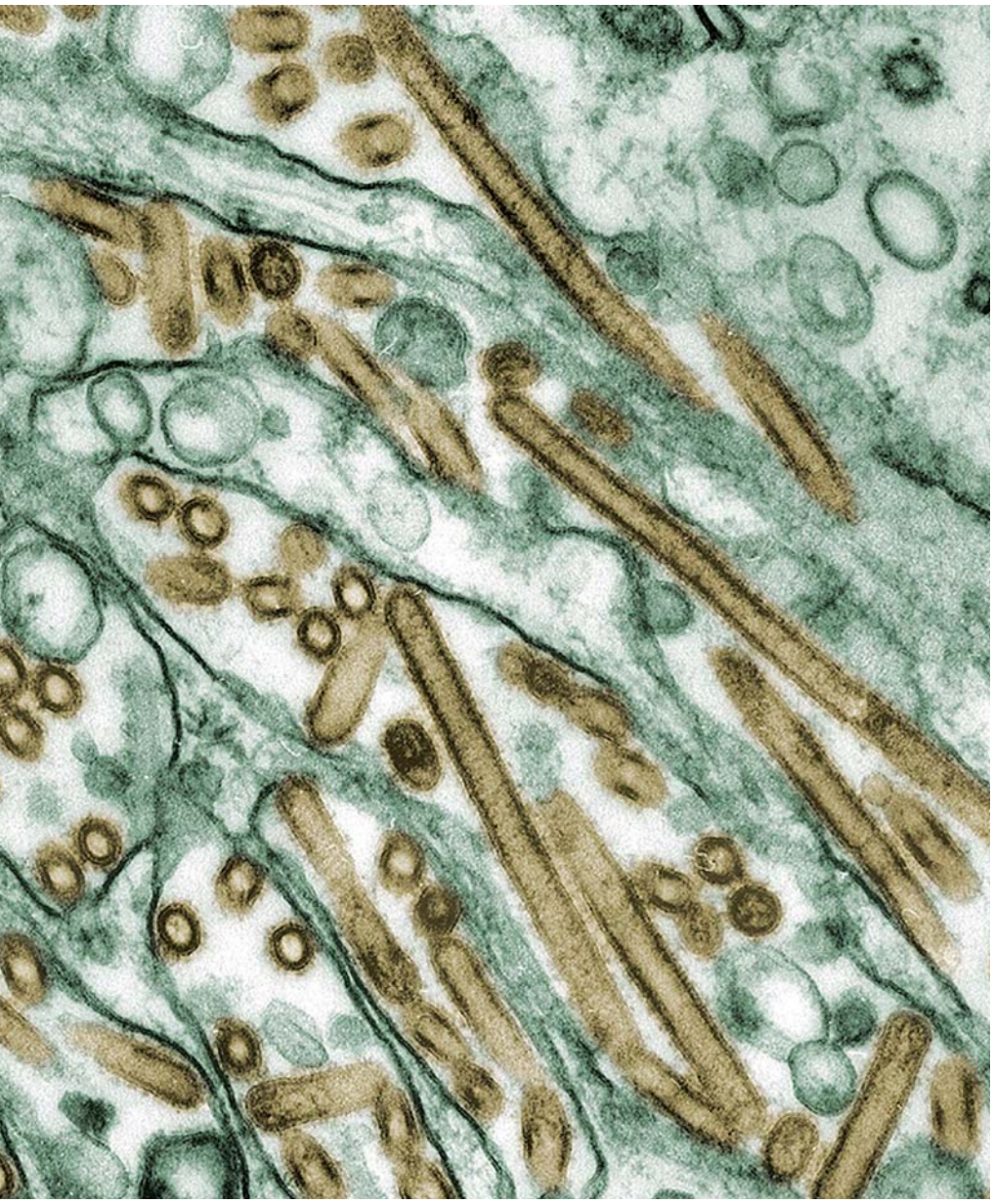


Source: Chared Verschuur-Ballo

***Ron Fouchier** received a PhD in Medicine from the University of Amsterdam in 1995, for his studies on molecular determinants of HIV-1 phenotype variability at the Department of Clinical Viro-immunology, Sanquin Research. He was a post-doctoral fellow at the Howard Hughes Medical Institute, University of Pennsylvania School of Medicine in Philadelphia, from 1995-1998, where he studied the function of the HIV-1 Vif protein, and nuclear transport of HIV-1 pre-integration complexes. He subsequently joined the Department of Virology at Erasmus MC to start a new group studying the molecular biology of respiratory viruses, in particular influenza A virus. As a KNAW fellow, he studied influenza virus zoonoses and pathogenicity. Recent achievements of his team include the identification and characterization of several "new" viruses; the human metapneumovirus (hMPV), a human coronavirus (hCoV-NL), the SARS coronavirus (SARS-CoV), and a new influenza A virus subtype (H16). Currently, his research is focused on the evolution and molecular biology of respiratory viruses in humans and animals, with special emphasis on influenza virus zoonoses and pandemics, and hMPV. Ron Fouchier is a member of the "Jonge Akademie" of the KNAW. (source: Erasmus MC website)*

Source: Prof. Hugues Tolou

***H. Tolou, MD, PhD**, first worked as a physician in the French navy. In 1987, he joined the Institute of Tropical Medicine of the French Armed Forces Health Service (IMTSSA, "Le Pharo"), in Marseilles. From 1991 to 2011, he was the chief of the laboratory of tropical virology in this institute. His research focused on arboviruses, particularly yellow fever, dengue and chikungunya. His main fields of research were molecular biology and epidemiology, viruses' evolution, antivirals and physiopathology of severe infections. Diagnosis was also developed, including identification of new emerging viruses, making the laboratory a French National Centre of Reference (CNR) for arboviruses. During this period, H. Tolou worked as an expert for both military and civilian authorities for questions relative to tropical and emerging viruses and infections, public health impact of expanding arboviruses. He is now the scientific director of the new Institute of Biomedical Research of the French Armed Forces (IRBA) in Bretigny sur Orge. He authored or co-authored more than 70 publications.*



Colorized transmission electron micrograph of Avian influenza A H5N1 viruses (seen in gold) grown in MDCK cells (seen in green). Photo: Cynthia Goldsmith

scripts. So this is going to happen and the NSABB has been asked by the US government to re-convene and have a discussion again about this issue. The Dutch government will be doing that on the short term too. They will assemble a group of experts to look at these issues. Hopefully, by that time, after international governments will look at the publication, we can also publish. The journals, Science and Nature, as well as the authors were very pleased with the outcome of the WHO meeting because we finally got support for what we've been doing all these years and also we receive support for our intention to publish.

HT: Since the publication of the modification of ectromelia virus (Jackson et al., J. Virol. 2001, 75:1205-10), and maybe for other reasons, USA authorities (and many people in the world) consider that some "dual use" researches and results create new threats for populations or environment that go beyond the potential benefits. However, it is disturbing to observe that the work on H5N1-HPAI has been largely financed on US funds (as far as I know). It has been proposed to control the publication of such works in such a manner to limit diffusion and misuse of specific methodologies and results. I am not sure it is an efficient strategy. Once manufactured, there are many ways for a dangerous pathogen to "leak" from a laboratory, as it was the case for Bacillus anthracis spores in 2001. Like Professor Luc Montagnier (last issue of "Science et Avenir"), I would prefer that such research is not done at all.

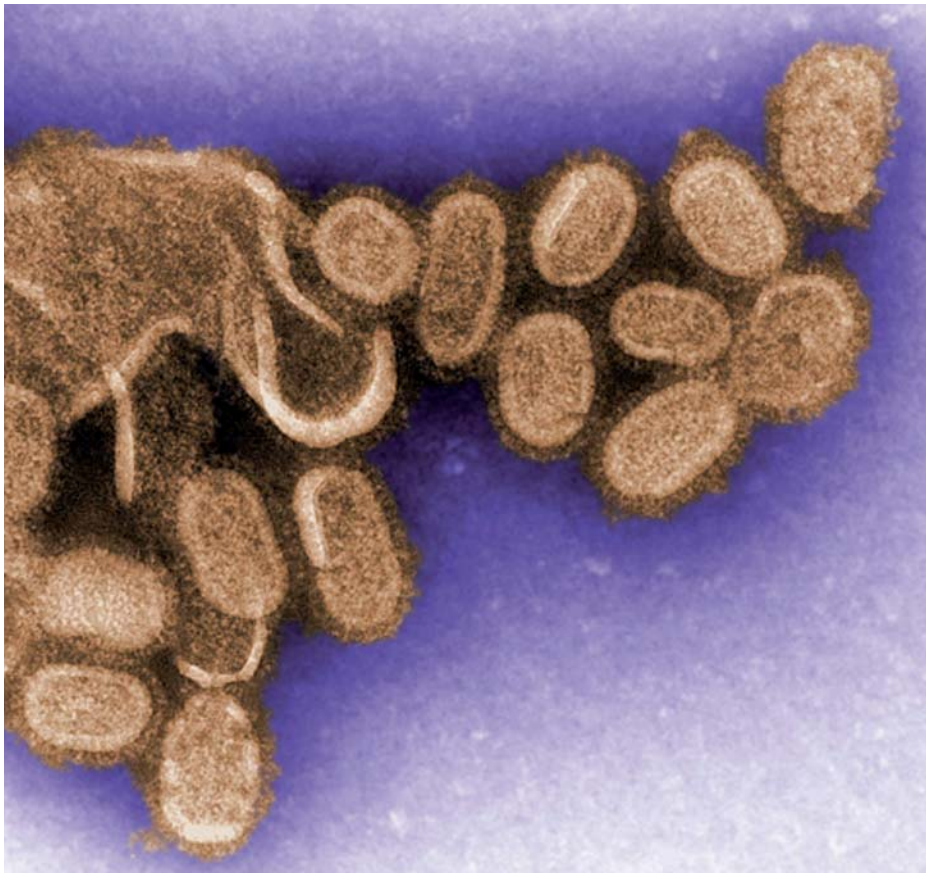
Why/How do such studies have so strong ethical aspects and public interest? What is the potential of these studies in the context of bioterrorism?

RF: The ethics is a hard thing. In my opinion, the infectious disease community should determine what needs to be analyzed, what needs to be investigated and then biosafety and biosecurity experts can help determine under what conditions you do the research. That's the normal procedure in any type of research and that is also how it went in this case. The entire flu community decided what needed to be done. Biosafety and biosecurity experts decided how it should be done and we explain what we do and how we do it to the public.

HT: Manufacturing (potentially) "the more dangerous virus for mankind that has ever existed" obviously create a risk, not for the scientists that did the job (they know how to protect themselves), but for populations. It is not surprising that such an activity has ethical aspects and gives rise to public interest! In fact, I consider it deserves even more interest, included from politicians. In our "small village", infectious, highly transmissible diseases have proven to be a global problem.

H5N1 TIMELINE

2007 – 2011	Ron Fouchier and his team conducted research on aerosol transmissibility of the H5N1 virus in a laboratory in Rotterdam, The Netherlands
July 2011	Fouchier stepped into his boss's office and reports that H5N1 can go airborne (http://nyti.ms/xlf454)
September 2011	Fouchier presented the group's findings in a scientific meeting on flu in Malta
September 2011	New Scientist reported Fouchier's report (http://bit.ly/pLMqag)
November 17, 2011	Dr. Thomas Inglesby, a bioterrorism expert and director of the Center for Biosecurity of the University of Pittsburgh Medical Center comments on Fouchier's research and rattles bioterrorism field (http://n.pr/tYMPeK). More stories followed.
December 20, 2011	US National Science Advisory Board for Biosecurity (NSABB) advised the government to put a stop on the publication of Fouchier's work (http://1.usa.gov/vm8GPQ)
December 23, 2011	Al-Jazeera produced a video report on the NSABB decision. (http://youtu.be/NUOTBPZ25RM) Other news stories and speculations followed.
December 30, 2011	WHO expressed concerns that new H5N1 influenza research could undermine the 2011 Pandemic Influenza Preparedness Framework (http://bit.ly/rYX6ei)
January 2012	The controversy on the H5N1 research heightens. Several newspapers and magazines have produced several stories and interviews. The public asked why this kind of research was done. Some scientists are surprised and asserted scientific freedom.
January 20, 2012	Scientists related to the research agree to a 60-day moratorium on the controversial H5N1 research.
February 16-17, 2012	WHO holds a meeting to talk about H5N1 controversy, concludes that it is an important research and supports full publication.
March 20, 2012	60-day moratorium expired. Scientists expect to resume work.
March 30, 2012	NSABB reverses decision. H5N1 research safe to publish.



This negative stained transmission electron micrograph (TEM) shows recreated 1918 influenza virions that were collected from supernatants of 1918-infected Madin-Darby Canine Kidney (MDCK) cells cultures 18 hours after infection.
Photo: Cynthia Goldsmith

What is the potential of these studies in the context of bioterrorism?

RF: I think the bioterrorism threat is negligible. There are many pathogens which you can pick out of nature that are very dangerous with which you can really create terror and with which you can kill a lot of people. We already know that those viruses or bacteria or fungi would be effective because we know what they are. In my case, this virus, first of all is very hard to make, you need experts to do it. A bioterrorist cannot repeat what we have done, it's too technical. Secondly, our virus would probably make a pretty lousy bioweapon. It spreads in ferrets but there is no guarantee that it also spreads in humans. Well, we know that the H5N1 can kill humans but we do not know how fatal it really is. So far we have 600 people reported in hospitals and 300 of those have died but it's very well possible that there have been thousands and thousands who just never ended up in the hospital and just had mild symptoms and so the true case fatality rate of this virus is unknown. Now why would you want to make a bioweapon for which you do not know how well it will transmit and you would not know how many people it would actually kill? It makes no sense at all.

HT: Terrorists try to find the simplest and most efficient way to provoke terror. That's not so easy, and, like everybody, they have no time or money to lose. We must not do the job for them. Now, they know that a super virus exists; they could envisage to obtain it, or to reproduce the experiment, knowing they have good chance of succeeding.

If it was another institution, a European institution for example, that's funding your work, do you think there will be a controversy like this?

RF: I think not. I find it very unlikely that the European NSABB-like group would come up with the same conclusion.

Why?

RF: In Europe, there's less of a fear-dominated discussion than in the US. And of course, this is triggered in part by the anthrax letters in the US, in part by 9-11. If I look at the press here and the European scientists who commented on our work, I haven't seen a single scientist whom I respect that was negative about this publication. We have a different sense of fear and we have a different sense of threat of bioterrorism attacks. That's what I think.

Is the work of sufficient scientific or technical originality, quality and/or interest to deserve publication in prestigious journals? Or can media impact influence the main criteria for good research?

RF: I and the editors and reviewers think so. This is the first time that we start to understand what makes an influenza virus aerosol transmissible and I think that's a major breakthrough from a fundamental perspective. We now start to understand what makes a virus airborne. Why is Ebola not airborne? Why are some respiratory viruses only transmitted by direct contact – via doorknobs, taps, toilets, handshaking – while others go via the aerosol route? This is the first time that we're starting to get some clues. Fundamentally, I think this is tremendously important. But on top of that, there is direct application because it is helping us to predict the next pandemics.

HT: Adapting viruses to new hosts, making them evolve toward new properties has been done for a long time, using empirical or more directed techniques. I am not sure that technical originality is the hallmark of the work. Probably, evoking a "super virus" did much more for publication acceptance.

Is there an efficient cure against H5N1 transmitted between different classes of hosts?

RF: The antiviral drugs that we already have, they seem to work, they work in vitro but we still have to evaluate it with animals. Also, the vaccines that we currently have seem to be close enough to our virus that they probably will also work. Again, we need to properly evaluate it, but probably, the answer is yes.

HT: Drugs active against naturally occurring influenza viruses, like oseltamivir, have proven efficient against H5N1, until resistances appeared, like it is regularly the case with viruses. We need to develop new drugs, targeting multiple different steps that are critical for virus replication and pathogenicity, without focusing on transmissibility.

Which precautions should be taken now, if any?

RF: The reason of our research is to try to prevent a pandemic. If we are successful in preventing a pandemic, then we do not need to take further precautions. If we can eradicate the viruses with pandemic potential, we're done. We should not go any further than doing good pandemic preparation by doing everything ahead of time. Secondly, do good surveillance in animals so we know which pandemic is going to hit us next. That is all the preparation we need.

HT: Turning back to the previous situation, where the super virus was only hypothetical, is not feasible. There were many viruses we had to work on, in order to protect people, now there is another one!

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