Made in the Lab

New viruses and their implications for pandemic risk

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Investigating Future Mortality: Blending Medical & Actuarial Science for Life & Longevity Risk Management

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The Leading Actors in the Unfolding Drama

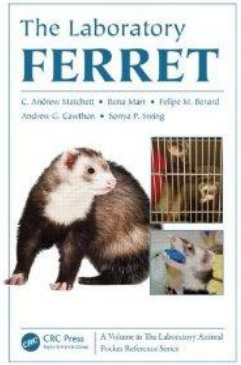
- **Prof. Yoshihiro Kawaoka**
  - Professor of virology, department of patho-biological sciences,

    University of Wisconsin, Madison

- **Dr. Ron Fouchier**
  - Leader of research group on the molecular biology of respiratory diseases,

    Erasmus Medical Centre, Rotterdam

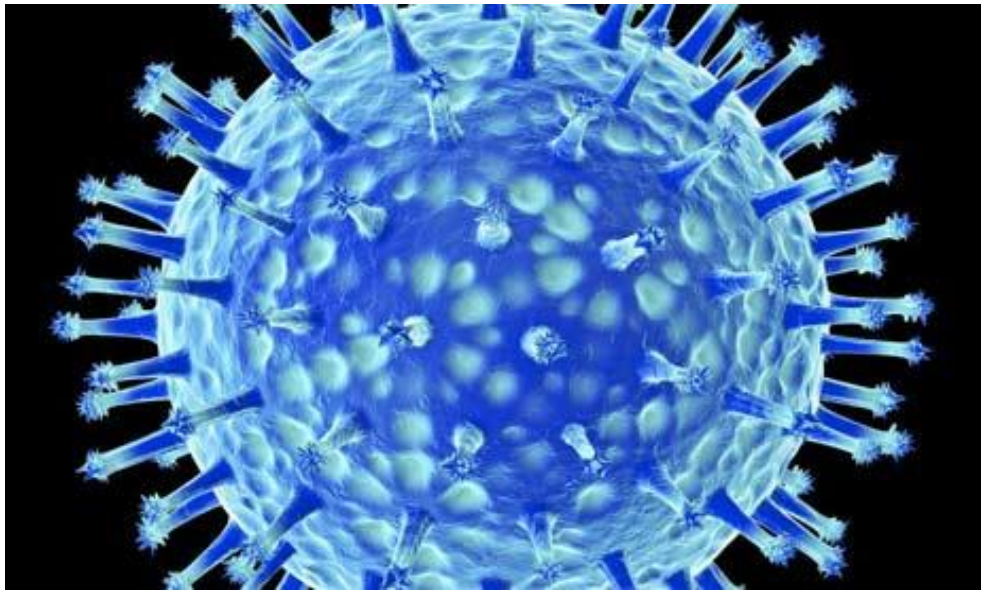
...plus a cast of extras



Part 1: Bio-Science

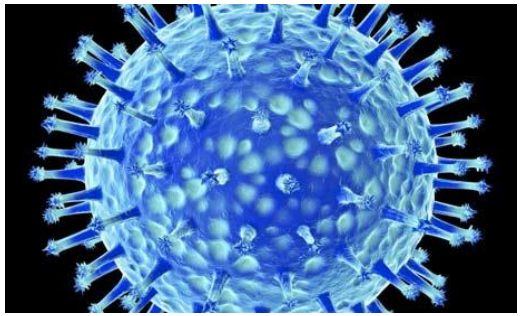
Structure of the Influenza Virus

- Strains are characterised by two proteins found on their surface: **Hemagglutinin** and **Neuraminidase**
- Approximately 80% of the spikes are hemagglutinin, which functions in the attachment of the virus to a host cell
- The remaining 20% or so of the spikes consist of neuraminidase, which is predominantly involved in facilitating the release of newly produced virus particles from the host cell



Basics of Influenza Virus Infection

- Influenza virus particles enter the respiratory system
- Hemagglutinin (HA) is a molecular machine that targets and attacks cells, and is the major virulence factor associated with the virus
- HA latches onto host cells in throat and upper lungs. It binds only to matched receptors in host cells. The structure of HA is very similar between strains, but differs in the specificity of its binding regions
- The virus enters the nucleus of the host cell, and hijacks the cell's own reproductive machinery to replicate itself numerous times



H1N1 Pandemic 2009

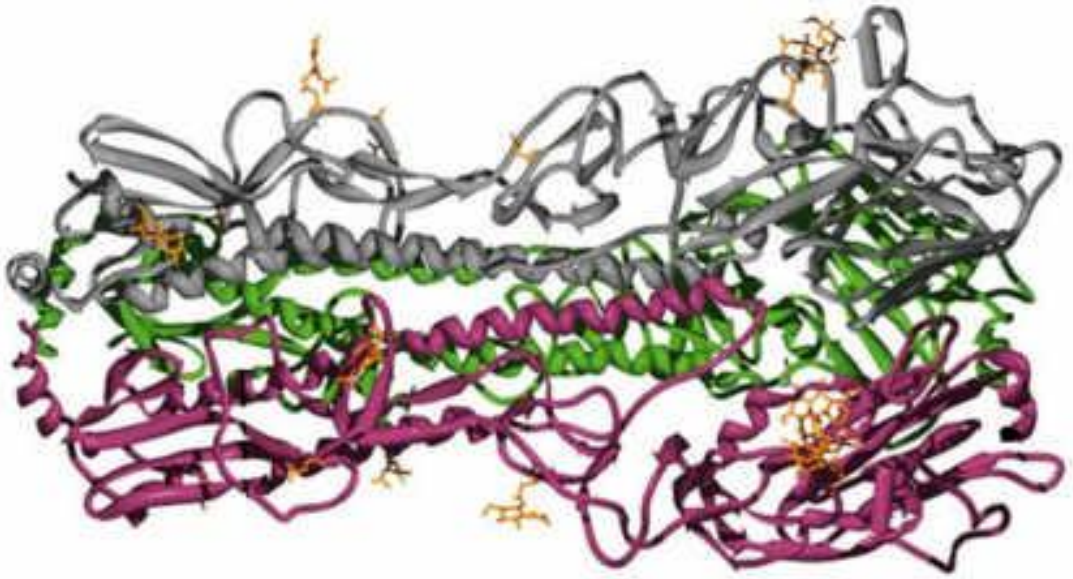
- During the spring of 2009, a novel H1N1 virus of swine origin caused human infection and acute respiratory illness in Mexico. After initially spreading among persons in North America, the virus spread globally, resulting in the first influenza pandemic since 1968
- Most illnesses caused by the 2009 H1N1 virus were acute and self-limited, with the highest attack rates reported among children and young adults. But the virus was not particularly lethal: the overall case fatality rate < 0.5%
- Studies of hemagglutinin-receptor binding indicated that the 2009 H1N1 virus was well adapted to mammalian hosts

H5N1 Avian Flu

- Since 2003, there have been around 600 confirmed cases of H5N1 virus infection – about 60% died
- However, the true mortality rate will be lower because there are probably some milder, unrecorded infections of H5N1. Even so, it seems likely that this virus has a greater mortality rate than either ordinary seasonal flu or possibly the 1918 pandemic H1N1 strain
- But so far, H5N1 has failed to spark a pandemic because it cannot effectively spread between people. It is caught from infected birds
- Wild H5N1 viruses cannot latch on to the cells in a person's nose and throat

The Hemagglutinin Molecule

- The hemagglutinin (HA) molecule is actually a combination of three identical parts (shown here as grey, green, and purple) that are bound together to form an elongated cylindrical shape
- A mutation that changes just one of hundreds of amino acids in the protein structure can alter the viral properties significantly



Cracking the Combinatorial Problem

- Creating a dangerous virus in a lab is a vast combinatorial search challenge
- There are thousands of possible combinations of genetic changes that might potentially lead to dangerous characteristics
- However, the probability distribution for such changes is very high dimensional, and remains poorly known and weakly constrained

Making the 2009 H1N1 Virus More Dangerous

- Researchers working in a high security lab in Beijing demonstrated that a single amino acid substitution in the HA protein would change the pathogenicity of the 2009 H1N1 virus (Xu L. et al., Virology: Vol. 7, 2010)
- When the 2009 pandemic A (H1N1) influenza virus was propagated in chicken eggs, this substitution in the HA protein was prone to occur under positive selection pressures
- The laboratory potential for generating new flu viruses is illustrated by these experiments. Animal tests of pathogenicity were done using mice, which are readily available at low cost

How to Make a Dangerous Virus

- Virologists have for years been experimenting on influenza viruses to see if it is possible to create artificially a lethal and transmissible virus in a laboratory
- Virologists can use heuristics to guess some plausible exploratory changes to the HA structure. They can then tweak virus genes using enzymes to mutate certain sites
- But such directed laboratory experiments are time-consuming; virus alterations can be made by infecting animals with the virus, and harnessing the power of evolution
- A composite approach of Man working with Nature offers the best prospects of making rapid progress on the combinatorial challenge of creating a dangerous virus in a laboratory

The Ferret as an Animal Model for Influenza

- The ferret has been a highly reliable – but not perfect model for human influenza. The virulence and transmissibility of a wide range of influenza viruses are found to be similar between ferrets and humans
- Human seasonal strains cause mild disease in ferrets and transmit very well between ferrets. Wild H5N1 strains cause severe disease and do not transmit readily
- Low pathogenic avian influenza strains do not, in general, transmit either among ferrets or humans
- The ferret is the most reliable animal model for human influenza, (better for transmission studies than macaque monkeys), so lab experiments are done mainly using ferrets

Kawaoka's Experiments in Wisconsin, USA

- Yoshihiro Kawaoka introduced random alterations into the H5N1 hemagglutinin protein. From the resulting library of mutants, he isolated viruses with two mutations that could stick to receptors in human tracheal cells - something H5N1 viruses cannot usually do
- Kawaoka then created a hybrid virus by combining this with the 2009 H1N1 pandemic virus
- This mirrors the natural reassortment process through which wild viruses swap genes
- But this *chimeric* virus still would NOT go airborne

Further Mutations are Left to the Ferrets

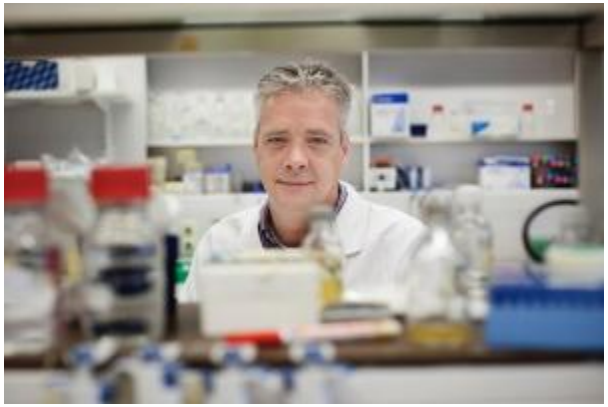
- However, Kawaoka noticed that one of the ferrets he infected had especially high levels of virus in its nose. These viruses had picked up a third HA mutation, and could now spread between neighbouring ferrets
- Kawaoka found that two of six healthy animals picked up infections from neighbours they had no contact with. Along the way, the virus acquired a fourth mutation
- *With all four mutations*, the virus spread even more easily. Kawaoka exposed six more uninfected ferrets to sick peers in adjacent cages. Within a week, he had found signs of the virus in all of them
- However, this mutant virus did NOT kill any of the animals, and it spread more slowly than the 2009 H1N1 strain

Surveillance Benefit of Tracking Mutations

- Three of the four Kawaoka mutations are new, at least in public databases
- One of the four mutations has been documented in wild birds. It was found in several samples collected in recent years from Egypt, and seems to be common among viruses that jumped into humans
- Because there already has been a serious H5N1 outbreak in Egypt, this mutation is clearly one to study and watch for appearing in human H5N1 cases
- It also illustrates some potential surveillance benefits. Data about this mutation were already in published flu sequences, but as Kawaoka says, *"Unless you knew what to look for, you wouldn't have found it."*

Fouchier's Experiments in Rotterdam, Netherlands

- Initially, Ron Fouchier used reverse genetics to attempt to render the H5N1 virus more transmissible by making specific changes to the genome. This was not successful
- However, with just a few genetic substitutions, the H5N1 virus was able to affix to human nose and trachea cells in lab cultures (Seasonal flu strains are readily transferable among people by coughing and sneezing, because they are adept at attaching to the upper respiratory tract).
- Performing tests on ferrets, there was still no airborne virus transmission



‘Mutating the Hell Out of H5N1’

- Following an assistant’s radical but enterprising suggestion, Fouchier then used a low-tech method of making a pathogen adapt to a new host
- He passed the virus from one ferret to another:
  - The mutated H5N1 virus was put into the nose of one ferret
  - Then a sample of nasal fluid from this ferret was put into the nose of another ferret
  - After ten ferrets, the virus finally began spreading from one ferret to another via air

Fouchier's Experiments Clarified

- Fouchier claimed that the virus he worked a decade to create is *'one of the most dangerous viruses'*
- Yet, contrary to original press reports, the ferrets did **not** die when infected through aerosol transmission, or if ferrets start coughing and sneezing on one another
- Only when the virus was physically implanted into the trachea or nasal passages of ferrets did the infected animals die
- The genome of the airborne strain differed from the original one by just five mutations, which have all been spotted individually in wild viruses

Part 2: Bio-Security

Bio-Security Risk Pathways

1. Pathogens may be released accidentally from labs, even those with high Bio Safety Level (BSL) status 3 or 4
2. Pathogens may be removed intentionally from labs, and transported illegally. Dr. Thomas Butler, a Texas Tech University professor transported plague bacteria into the United States through VIP air travel – Vials In Pocket. The vials also eventually went missing
3. Pathogens may be maliciously released

Fouchier has said he was prepared to defy the Dutch government in publishing his work without seeking an official export permit.

The Risk Analyst's Perspective of Man-Made Flu

- Whereas scientists are focused on absolute evidence-based statements of scientific reality, risk analysts are focused on the tail risk of what might happen
- The prospect remains of future man-made flu experiments generating a dangerous outcome
- Accordingly, biosecurity professionals take a different view from the virologists themselves on the importance of developing new flu strains in a laboratory

> *We would like to assure the public that these experiments have been conducted with appropriate regulatory oversight in secure containment facilities by highly trained and responsible personnel to minimize any risk of accidental release.'*
>
> Fouchier, Kawaoka et al., Science express, 20 January 2012

Man-Made Influenza Risk-Benefit Dilemma

Scientific discovery is prioritized

Laboratory virologists

e.g. Fouchier & Kawaoka

World Health Organization:
'This work is important for global surveillance'

Center for Biosecurity: *'We need new approaches for the rapid development of large quantities of medicines or vaccines to protect us against new emerging viruses.*

Biosafety analysts

But engineering highly transmissible strains of avian flu is not the way to get us there'.

Precautionary approach

Precedent for Accidental Flu Virus Release

- A major swine flu epidemic occurred in 1977
- A study published in the New England Journal of Medicine showed that the 1977 virus was closely related to a 1950 strain, but dissimilar to the H1N1 strains of 1947 and 1957
- This suggests that the 1977 outbreak strain had been preserved since 1950
- This re-emergence was probably an accidental release from a laboratory source. This might have arisen after a laboratory worker became infected accidentally, and then infected family and friends

Reconstruction of the 1918 Virus

- At the time that the 1918 virus was reconstructed in 2005, it was believed that there was a high level of population immunity to the 1918 H1N1. The full and unrestricted release of the 1918 virus manuscript was authorized based on this belief
- According to the CDC director, *'If the virus escaped into the population today it's unlikely to cause a global pandemic, because most people have some built-in immunity to it from exposure to related viruses.'*
- However, the 2009 H1N1 swine flu pandemic showed this to be optimistic

SARS Laboratory Security Failures

- Over the past decade, SARS has accidentally infected staff at high-containment labs in China, Taiwan and Singapore

A: At the National Institute of Virology in Beijing, a graduate student developed SARS, a few weeks after starting work

B:The Taiwan case happened in a BSL-4 lab when a military scientist failed to follow procedures in cleaning up a spill of SARS-containing fluid

C: In Singapore, a sample of West Nile virus contaminated with SARS virus infected a lab worker in a BSL-3 lab at the Environmental Health Institute

Malicious Release: Extremist Sects

- Extreme millenarian sects espousing an apocalyptic vision of the world's future may strive to create a global catastrophe
- One such sect, Aum Shinrikyo, had its own scientific laboratory, which was used to produce the sarin for the deadly chemical terrorist attack on the Tokyo subway on 20th March 1995

Malicious Release: Rogue Scientists

- Much more likely a source of malicious release than an extremist sect is a disgruntled or disturbed virologist
- An individual may commit a criminal act of bioterror as a self-empowered way of protesting against grievances
- This scenario played out tragically with the anthrax letters mailed in the US after 9/11
- The FBI claims these were distributed by Bruce Ivins, a microbiologist at Fort Detrick's bioweapons defense research institute USAMRIID. Before he could be charged, Ivins committed suicide on 29th July, 2008

Bruce Ivins: Psychotic Microbiologist

- Bruce Ivins had a secret double life, plagued by mental health problems. He had a fixation about a sorority (ΚΚΓ), and mailed the anthrax letters from near their office in Princeton
- His emails describe episodes of anxiety, paranoia, and depression, for which he was medicated
- A clinical psychologist has found evidence of psychoses, yet he was able to withstand FBI screening for years

09-11-01
THIS IS NEX**T**
TAKE PEN**A**CILIN NOW
DE**A**TH **T**O AMERICA
DEATH **T**O ISRAEL
ALLAH IS GREA**T**

Malicious Release: Rogue Scientist Risk

- The more labs that have access to the technical information about a dangerous man-made virus, the greater the risk of malicious release by a rogue scientist
- Fouchier has compiled a sharing list of 100 organizations around the globe, and around 1000 experts. There may be a proliferation of this kind of research in future
- Given the typical population prevalence of psychosis, it might be expected that one of these 1000 experts has the mental problems that plagued Bruce Ivins
- Annualizing the rogue risk over a career, recognizing the limits of personal psychological vetting at biosecure labs, the likelihood of a malicious release per year might be around 1%

Accidental and Malicious Release Frequency

- Human factors govern both the chance of accidental and malicious release. Experience across the spectrum of catastrophe risks tends to indicate that human errors, mis-judgements, regulation violations etc. are underestimated
- Based on the SARS experience of three releases in 300 lab-years, a risk of estimate of ~ 1% per lab-year has been suggested by members of the National Science Advisory Board for Biosecurity. A benchmark of 1% per year for accidental release does not seem excessive
- The aggregate annual chance of release from accidental and malicious causes may be estimated to be about 2%

Implications for Pandemic Risk Assessment

- Scientists do not have control over the dangerousness of the viruses which are created in their labs.
- It was fortunate that neither Kawaoka nor Fouchier created dangerous viruses
- **RMS is not proposing to change its view of pandemic risk at this time, as result of these laboratory experiments**
- Laboratory production of lethal and transmissible flu viruses raises the risk from the background natural level
- Further use of ferrets as forced mutation machines may well lead in future to a dangerous man-made pandemic virus
- **RMS will continue to monitor and advise clients of new developments**

RMS LifeRisks Whitepaper

- Coming soon
- Available on rms.com/liferisks