FEMS FOCUS
NEWSLETTER OF FEMS
FEDERATION OF EUROPEAN MICROBIOLOGICAL SOCIETIES
December 2009 No. 6

THE FLU PANDEMIC: Reason to get the chills?

This issue of FEMS Focus will zoom in on the Pandemic Flu, caused by the H1N1 virus. To address the subject efficiently, FEMS Focus interviewed two profiled experts in the field, Prof Dr Otto Haller of the University of Freiburg and President of the European Society of Virology and Prof Dr Hans Wolf of the University of Regensburg in Germany, who are frequently consulted on H1N1 issues. Here are their professional perspectives on central questions concerning the current pandemic.

Prof. Otto Haller

Prof. Hans Wolf

What is the nature of the virus causing the current pandemic flu?

Otto Haller: The current pandemic H1N1 strain is unique because it contains a novel composition of viral gene segments from swine, avian and human sources. Distinctive features of the new virus are high transmissibility, low pathogenicity with mostly mild disease, and the fact that the virus is less seasonal than normal flu.

An interesting property of the new H1N1 virus is how easily it is transmissible between host species. It was reintroduced from humans back to pigs, but also forwarded to cats, dogs, pet ferrets and reportedly turkeys. It remains to be seen whether this impressive capacity to jump between species is a unique trait of a rapidly evolving virus or a more common property also in non-pandemic strains but not usually recognized.

Hans Wolf: This is a mix of at least two gene segments generated by antigenic shift originating in Europe and/or Asia and unleashed in the outbreak in Mexico in March-April 2009. Additionally, antigenic drift in the form of two mutations in the hemagglutinin (HA) gene has been detected in Norway, without causing drug resistance or increased pathogenicity.

What are the differences of the current flu virus compared with other flu viruses, for example, the seasonal flu?

HW: H1N1 is only a little different from other flu viruses, with some preference for juveniles, inducing the founder effect originally seen when the epidemic first occurred during a festival in Mexico in March-April 2009.

From the Editorial Team

With the changing of the seasons, the influenza virus is, once again, just around the corner. Seasonal flu, that is. But before it reaches its peak this time, another kind of influenza virus already made waves the world over. The H1N1 virus was declared to be a pandemic on June 11, 2009 – the first influenza pandemic of the 21st century. The peak of the pandemic activity in Europe was reported in the period of November 13-20. The World Health Organization urged everyone to follow good respiratory and hand hygiene to control the number of pandemic flu victims.

Because of its importance and urgency, FEMS Focus will address the issue of the Flu Pandemic as broadly as possible. It's just not a regular flu after all!

Tone Tønjum, *Editor*
& Chared Verschuur,
Communications Assistant

Viral characteristics of the current Pandemic Flu strain

1. Some signatures of pathogenic strains in humans are missing. For example, the virus lacks the coding capacity for a protein called PB1-F2. This small viral protein is not strictly required for the viral life cycle but induces cellular apoptosis and promotes lung injury.
2. Certain virulence-associated mutations affecting the viral RNA polymerase or the hemagglutinin are not present.
3. In ferrets, pathogenicity of H1N1 is present and significant.

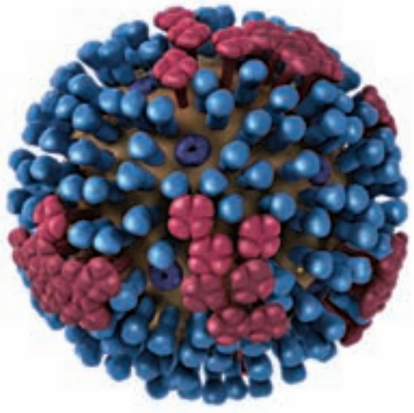
Otto Haller is Professor of Virology and acting Director of the Institute for Medical Microbiology and Hygiene of the University Medical Center Freiburg, Germany. He is also presently the Coordinator of the EU-Consortium FLUINNATE and President of the European Society for Virology.

Hans Wolf is Professor of Virology and Director of the Institute for Medical Microbiology and Hygiene of the University of Regensburg, Germany. The institute in Regensburg, Germany is frequently consulted on H1N1 topics due to their range of services and skills from infection biology and pathogenesis to rapid diagnostics and cultivation and clinical expertise. They identified and sequenced the first German isolate and specialized on vaccine development and evaluation.

HIN1 timeline

1918: The 1918 H1N1 flu strain of avian origin appears and causes the "Spanish" flu pandemic in the non-immune human population. Four decades of circulating seasonal H1N1 leads to increasing immunity in the human population.
1957: Genetic reassortment with avian strain results in the H2N2 strain causing the Asian flu pandemic. H1N1 disappears.
1968: Genetic reassortment with avian strain produces theH3N2 strain of the Hong-Kong flu pandemic. H3N2 circulates as seasonal strain in the human population until today. H2N2 disappears.
1977: H1N1 reappeared without signs of drift since 1957, presumably released from frozen reserve. It co-circulated with H3N2 as seasonal flu until today.
2009: New H1N1 pandemic strain appears.

Why is the H1N1 strain so successful even though it is not very virulent? Is it due to optimal transmissibility?
HW: The flu virus normally exists in the oral cavity for 1-3 days, where it replicates without causing clinical symptoms, as long as it is not in the bloodstream, providing a very efficient means of spread without giving away where it comes from. It might be that the phase of oral viremia lasts longer than for other flu variants in the absence of clinical symptoms but with the potential to infect contact persons. When it breaks through to the bloodstream, all danger signals (cytokines, chemokines) are shed and are responsible for the rapid onset of clinical symptoms. This usually leads to reduced activity and reduces the spread of the virus.



A 3D graphical representation of a generic influenza virion's ultrastructure.
Credits: CDC/ Douglas Jordan

OH: The 2009 H1N1 pandemic is a big surprise. We feared that an avian H5 or H7 strain would emerge in the human population having no pre-existing immunity, but H1N1 from pigs appeared instead and caused an unexpected pandemic. With the rate of infections currently seen, we are fortunate that the new virus is not a killer strain.
Transmissibility is an issue. The big scientific question is: how does an animal virus gain the capacity to rapidly spread among humans? Which viral factors are responsible for successful man- to- man transmission? For example, the avian H5N1 strain is zoonotic, but is so far unable to transmit from man to man. A likely reason is that H5N1 preferentially replicates deep in the lung tissue and can not be efficiently excreted and transmitted through the upper respiratory tract.

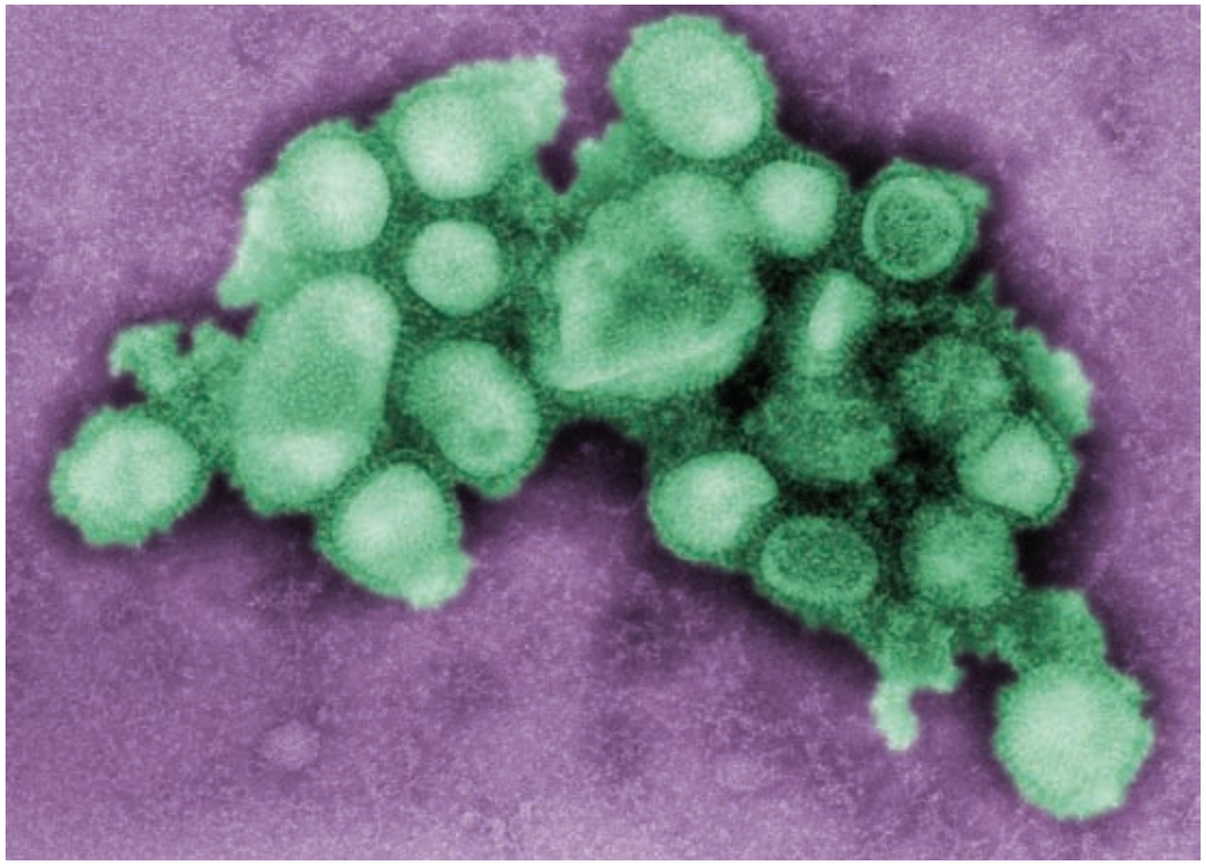
Why do people die from the flu?
OH: There have been 60 deaths in Germany and around 900 in the EU so far (end of November 2009). All severe cases belonged to the known risk groups with underlying medical conditions. The high morbidity and mortality in other parts of the world are presumably due to a late start of antiviral and intensive care treatment and strong host inflammatory reactions, but specific mutations in the infecting virus can presently not be excluded. In any case, the majority of deaths were caused by severe viral pneumonia and acute respiratory distress.

Timeline for the spring 2009 H1N1-studies at the Institute for Medical Microbiology, Regensburg

April 28, 2009 – First request for viral diagnosis
April 29, 2009 – First viral genome directly sequenced and inoculated onto kidney cells
May 1, 2009 – First viral genome synthesized and handed over to Roche for vaccine development

HW: Flu symptoms are normally fever >38oC, chills and poor general condition due to dissemination of virus from the oral cavity to the blood stream. However, if there is lung infection, this variant of the disease can be aggravated by the concurrent presence of bacteria. Therefore, any flu lung infection deserves prime alert in terms of intensive care. The viral HA must be unfolded and activated or "cut" by a protease for the virus to be infectious. When exposed to bacteria, their proteases can unfold HA very efficiently, boosting the infection. This is why influenza lung infections coinciding with bacterial infections can be so serious with such high death tolls.

Is the virus still sensitive to Tamiflu? What mutations are occurring? Are the two mutations detected in Norway associated with resistance development or enhanced virulence or transmissibility?
HW: Tamiflu (oseltamivir) works by inhibiting the neuraminidase (NA) by mimicking the target. Drugs must enter into the cell to reach its intracellular target. No Tamiflu resistance is detected so far. However, psychological side-effects in the form of suicidal activity have been noted in juvenile males/ young men in Japan and long-term preventive/prophylactic Tamiflu treatment is not recommended.
OH: A small number of oseltamivir-resistant viruses have been identified worldwide. Resistant strains carry the known H275Y mutation in the NA protein. These mutations do not seem to confer an advantage over the wildtype and do not appear to be more transmissible.



This colorized negative stained transmission electron micrograph (TEM) depicted some of the ultrastructural morphology of the A/CA/4/09 swine flu virus.
Credit: CDC/C. S. Goldsmith and A. Balish

Important scientific words of this issue

Antigenic Shift
The recombination process by which at least two different strains of a virus (or different viruses), especially influenza, combine to form a new subtype having a mixture of the surface antigens of the two original strains.
Antigenic Drift
Random point mutations that cause subtle differences in the flu genome.
Apopotosis
The process of programmed cell death that may occur in multicellular organisms.
Epitopes
The part of a macromolecule that is recognized by the immune system, specifically by antibodies, B cells, or T cells
Hemagglutinin (HA)
a substance that causes red blood cells to agglutinate.
Neuraminidase (NA)
are glycoside hydrolase enzymes (EC 3.2.1.18) which cleave the glycosidic linkages of neuraminic acids. Neuraminidase enzymes are a large family, found in a range of organisms. The most commonly known neuraminidase is the viral neuraminidase, a drug target for the prevention of influenza infection.
Pathogenicity
The ability of a pathogen to produce an infectious disease in an organism. It is often used interchangeably with the term "virulence".
Polymerase
An enzyme whose central function is associated with polymers of nucleic acids such as RNA and DNA. The primary function of a polymerase is the polymerization of new DNA or RNA against an existing DNA or RNA template in the processes of replication and transcription.
Protease
Breaks down proteins.
Viremia
A medical condition where viruses enter the bloodstream and hence have access to the rest of the body.
Virulence
The ability of an organism to cause disease.
Zoonotic
Any infectious disease that can be transmitted (in some instances, by a vector) from non-human animals, both wild and domestic, to humans or from humans to non-human animals.

Why should we take the vaccine? Is the flu vaccine dangerous?
HW: This vaccine is very safe and should be taken by all when possible. The H1N1 vaccine is a good vaccine. It incapacitates the virus by mimicking it, and should be taken by all, even by small children – and even when they have a cold. When the vaccine is given, during the first 2-3 days, it provides transient protection, beyond that time-point it stimulates life-long memory cells and is fully active after 2 weeks. The H1N1 epitope already occurred 60+ years ago, so many of those who were infected with the flu then are naturally protected against the current flu.
The vaccine prevents 1) viral replication in the oral cavity and 2) entry of virus into the bloodstream. In summary, the vaccine prevents silent carriers.
OH: The vaccine works and should be taken, also by children and juveniles, in particular also by pregnant women. In pregnancy, the vaccine version without the adjuvant is preferable.

What is the impact of other preventive measures?
HW: In addition to vaccination, avoidance of hand-shaking is most important (as this is a most common vehicle for exchange of microbes including viruses). However, mouth protection as used in large parts of Asia is not useful, since it only consists of one layer which is not very protective and it keeps bacteria unnecessarily close to the mouth. Furthermore, alcohol for skin washing is not beneficial as it makes the skin dry and cracky – just use normal soap!

When will the pandemic be over? What happens to the new virus?
HW: Probably in March-April 2010, depending on the vaccine coverage.
OH: There are three possible scenarios. The best scenario would be that the current pandemic virus simply disappears again. However, this is unlikely. A more likely scenario is that the new H1N1 strain becomes seasonal and may even replace the present seasonal H1N1 virus. Finally, a less favourable outcome would be the emergence of a more virulent variant with high pathogenicity. Unfortunately, this is still a real possibility given the high mutation rates and adaptive skills of flu viruses. It is too early for complacency.

The main vaccines against H1N1

Influenza A (H1N1) 2009 Monovalent Vaccine (CSL Limited, ID Biomedical Corporation of Quebec, Novartis Vaccines and Diagnostics Limited, Sanofi Pasteur, Inc.and more)

Pandemrix (GSK)/ (Sanofi-Pasteur): virus amplified/cultivated in kidney cells

Roche: vaccine based on the synthetic genome

What is an influenza pandemic?

An influenza pandemic is an epidemic of an influenza virus that spreads on a worldwide scale and infects a large proportion of the human population.
Influenza pandemics occur when a new strain of the influenza virus is transmitted to humans from another animal species. Species that are thought to be important in the emergence of new human strains are pigs, chickens and ducks. These novel strains are unaffected by any immunity people may have to older strains of human influenza and can therefore spread extremely rapidly and infect very large numbers of people.
In contrast to an epidemic which occurs when the incidence rate of a certain disease substantially exceeds what is "expected," based on recent experience, a pandemic is an epidemic of an infectious disease that spreads through human populations across a large region, such as a continent.

Source: wikipedia

News from the European Commission

The EU strategy against the Pandemic Flu

EU health ministers discussed the commission's proposals at a special meeting on the flu in October.

Three months after it was declared pandemic, the new H1N1 virus continues to be the main flu strain circulating worldwide. Most cases have been mild, but there are fears of a more virulent wave of the virus in the months ahead. While vaccines are now hitting the market, demand far exceeds production capacity in the short term, and costs could be prohibitive for some countries.

The EU strategy addresses these issues, as well as the possible economic impact of a more severe epidemic. Stressing close co-operation between EU governments, it presents a range of options for joint action. In particular, it calls for a clear and coherent approach to vaccination and other preventive measures.

For more information on the EU strategy on the Pandemic Flu, please visit the European Commission's website: http://ec.europa.eu/news/environment/090915_en.htm.

The newest cutting edge

Steel J, Staeheli P, Mubareka S, García-Sastre A, Palese P, Lowen AC. **Transmission of pandemic H1N1 influenza virus and impact of prior exposure to seasonal strains or interferon treatment.** J Virol. 2009 Oct 14. PMID: 19828604

Zhirnov OP, Klenk HD. **Alterations in caspase cleavage motifs of NP and M2 proteins attenuate virulence of a highly pathogenic avian influenza virus.** Virology. 2009 Nov 10;394(1):57-63.

Gabriel G, Klingel K, Planz O, Bier K, Herwig A, Sauter M, Klenk HD. **Spread of infection and lymphocyte depletion in mice depends on polymerase of influenza virus.** Am J Pathol. 2009 Sep;175(3):1178-86.

Matrosovich M, Stech J, Klenk HD. **Influenza receptors, polymerase and host range.** Rev Sci Tech. 2009 Apr;28(1):203-17.

Pandemic Flu Links and Resources

http://www.euro.who.int/influenza/ah1n1
http://ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx
http://www.emea.europa.eu/influenza/home.htm
http://www.cdc.gov/h1n1flu/
http://www.flu.gov/
http://ec.europa.eu/health/ph_threats/com/Influenza/h1n1_en.htm
http://www.who.int/csr/disease/swineflu/en/index.html
http://www.direct.gov.uk/en/groups/dg_digitalassets/@dg/@en/documents/digitalasset/dg_178842.htm
http://www.dh.gov.uk/en/Publichealth/flu/PandemicFlu/index.htm
http://www.phac-aspc.gc.ca/alert-alerte/h1n1/index-eng.php
http://www.who.int/csr/disease/influenza/pandemic/en/
https://www.pandemicflu.direct.gov.uk/
http://www.redcross.org/pandemicflu
http://www.nhs.uk/conditions/pandemic-flu/Pages/Introduction.aspx
http://www.google.org/flutrends/intl/nl/

The FEMS Focus is published by the FEMS Central Office.

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FEMS is a registered charity (no. 1072117) and also a company limited by guarantee (no. 3565643).

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