“An epidemic of novel viruses: how can we be protected?”

NIBI conferentie
13 januari 2012
“ochtendlezing“
Trends in infectious disease-related mortality rates in the United States

Deaths per year per 100,000 population

<table>
<thead>
<tr>
<th>Year</th>
<th>All diseases</th>
<th>Non-infectious diseases</th>
<th>Infectious diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data: CDC

WORLD HEALTH

smallpox is dead!

Data: CDC
Important achievements in the control of infectious diseases in the 20th century by:

- **Hygiene and sanitary measures** (clean drinking water, sewage systems…)
- **Veterinary control measures** for major **zoonoses** (TB, brucellosis, rabies…)
- **Implementation of vaccination** and elimination programs (smallpox, polio, measles, DTP, …)
- **Development and use of antibiotics and antivirals**

1970-1980`s: Influential scientists and policymakers stated:

“**Infectious diseases will no longer plague to humanity**”
The paradox:
Emerging virus infections in the past decade –
(source: WHO)
Daszak et al. 2000, Science
Animals are source of virtually all newly emerging infections of humans

Osterhaus, Philos. Trans. R. Soc., 2001
Kuiken et al. Science, 2005

Examples:

- **West Nile virus**: wild birds/mosquitoes
- **SARS-corona virus**: pteropid bats
- **Influenza A virus**: free-living ducks

Emerging diseases have a major impact on:

- **Public health**
- **Animal health/-welfare**
- **Food supply**
- **Economies**
- **Environment (biodiversity)**
The AIDS pandemic: started 30 years ago in a globalizing world!

>55 million infected, >20 million deaths, >2 million die each year!

- Animal contacts (bush meat consumption)
- Behaviour (changing taboos, mores, i.v. drug abuse)
- Demography (urbanisation...)
- Mobility (air travel, wars ...)
- Poverty (vs wealth)
- Medical practices (iatrogenic transmission)
- Virus adaptation (mutation, recombination)
Foodborne viral pandemics

- HIV 1 AIDS
- HIV 2
- Influenza
- BSE-vCJD
Since eradication smallpox: more animal poxvirus infections in humans?

Wolfs et al. E.I.D. 2002

monkeypox

cowpox


ProMED-mail 9 Jan 2003

Stittelaar et al., Nature, 2006
Morbilliviruses crossing species barriers

- PDV in European Harbour seals

- CDV in Baikal seals
  Nature 1988

- CDV in Caspian seals
  EID 2000

- CDV in Serengeti lions
  Vaccine 1994

- DMV in Med. monk seals
  Nature 1997

- CDV in macaques
  China, EID 2011

should we continue measles vaccination for ever?
**Rinderpest: morbillivirus disease of cattle**

**Animal husbandry catastrophes 17th Century Netherlands**

### PROGRESS TOWARDS RINDERPEST GLOBAL FREEDOM

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Last outbreak</td>
</tr>
<tr>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Vaccination stopped and provisional freedom from rinderpest</td>
</tr>
<tr>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Targeted surveillance exercise</td>
</tr>
<tr>
<td>2010</td>
<td>End of the field operations</td>
</tr>
<tr>
<td>2011</td>
<td>Global declaration</td>
</tr>
</tbody>
</table>

The Global Rinderpest Eradication Programme

Progress report on rinderpest eradication: Success stories and actions leading to the June 2011 Global Declaration.
Order Mononegavirales, family Paramyxoviridae

Morbiliviruses: a continuing story!!!

Morbiliviruses

Respirovirus

Henipavirus

Pneumovirinae

Pneumovirus

Metapneumovirus

DNA Maximum likelihood, Polymerase ORF

0.1
Identification of new viral pathogens

CDV as the cause of mass mortality in Serengeti lions

γ-herpesvirus in seals (phocid herpesvirus-2)

Monk seal morbilliviruses (MSMV-WA/G)

Influenza A (H5N1) virus in humans

Lentivirus from Talapoin monkeys (SIVtal)

Influenza B virus in seals

Human metapneumovirus (hMPV)

Re-emerging PDV in Europe

SARS CoV cause of SARS in humans (Koch`s postulates)

Influenza A (H7N7) virus in humans

Fourth human coronavirus (CoV NL)

H16 influenza A viruses (new HA!) in black headed gulls

Dolphin herpesvirus

Deer astrovirus

Human astrovirus, human picobirnavirus

Ferret coronavirus, ferret HEV, porcine picobirnavirus, stone marten anellovirus

Influenza A (H1N1) virus in dog

Novel molecular techniques
Virus discovery
- expertise required -

- Clinical diagnosis
- Pathology
- Epidemiology
- Laboratory

Classical virology
Electron microscopy
Serology
Animal models

Novel molecular techniques
- Family specific degenerate PCR analyses
- Random PCR analyses
- "Pathogen chips"
- Metagenomic sequencing
Newly identified human respiratory viruses in last 15 years alone

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Species</th>
<th>Discovery Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>AIV`s</td>
<td>1997</td>
</tr>
<tr>
<td>Paramyxovirus</td>
<td>Hendra-/NipahV</td>
<td>2000</td>
</tr>
<tr>
<td>Paramyxovirus</td>
<td>hMPV</td>
<td>2001</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>SARS-CoV</td>
<td>2003</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>HCoV-NL63</td>
<td>2004</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>HCoV-HKU1</td>
<td>2005</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>HBoV</td>
<td>2005</td>
</tr>
<tr>
<td>Polyomavirus</td>
<td>KL/WU-PyV</td>
<td>2007</td>
</tr>
<tr>
<td>Orthoreovirus</td>
<td>MeIV (KamV)</td>
<td>2007 (2009)</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>H1N1v</td>
<td>2009</td>
</tr>
</tbody>
</table>

* ErasmusMC discovery / involvement
Order *Mononegavirales*, family *Paramyxoviridae*: “discovery of another human paramyxovirus”


(classical virology combined with random priming)

MRCA of APV and HMPV: about 200 years ago
Human metapneumovirus
- Rivers’ modified Koch’s postulates -

1. Virus isolation
2. Virus propagation
3. Filtration

4. Disease in macaques
5. Re-isolation & PCR of virus
6. Specific immune response

- O.D. 450 nm
- IgA
- IgM
- IgG

Days after infection:
0 7 14 22 88 113 127 161 240 254 260 273 289
Newly discovered human paramyxovirus hMPV
- Risk groups -

- (Young) children
  ~10% of children with RTI

- Immunocompromised individuals (fatal cases!)

- Elderly

- Normal individuals
  ~5% of RTI in community surveillance studies

  Osterhaus and Fouchier, The Lancet 2003
  v.d. Hoogen et al., JID 2003
  Williams, J. J Inf Dis 2006
Cloning of a human parovirus by molecular screening of respiratory tract samples

Tobias Allander*, Martti T. Tammi*, Margareta Eriksson, Annelie Bjerkmär, Annika Tiveljung-Lindell*, and Bjorn Andersson

*Department of Clinical Microbiology and Center for Molecular Medicine, Karolinska University Hospital, Department of Woman and Child Health, Astrid Lindgren Children’s Hospital, and Center for Genomics and Bioinformatics, Karolinska Institutet, SE-171 77 Stockholm, Sweden; and Departments of Biological Sciences and Biochemistry, National University of Singapore, 11 Science Drive 4, Singapore 117543, Singapore

Edited by Peter Palese, Mount Sinai School of Medicine, New York, NY, and approved July 15, 2005 (received for review June 5, 2005)

Table 1. Categorization by BLAST search of the sequenced clones derived from two pools of respiratory tract samples

<table>
<thead>
<tr>
<th>Category</th>
<th>Library 1 (%)</th>
<th>Library 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>84 (24)</td>
<td>110 (36)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>202 (59)</td>
<td>65 (21)</td>
</tr>
<tr>
<td>Phage</td>
<td>6 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (6)</td>
<td>33 (11)</td>
</tr>
<tr>
<td>Virus</td>
<td>29 (8)</td>
<td>99 (32)</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TT virus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Parovirus</td>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>Total</td>
<td>343</td>
<td>309</td>
</tr>
</tbody>
</table>

BPV; bovine parovirus
MVC; minute virus of canines: Human bocavirus

P.N.A.S. 102: 12891-6, 2005
Newly identified human respiratory viruses in last 15 years alone

- AIV`s * influenza virus 1997...
- Hendra-/NipahV paramyxovirus 2000...
- hMPV * paramyxovirus 2001
- SARS-CoV * coronavirus 2003
- HCoV-NL63 * coronavirus 2004
- HCoV-HKU1 coronavirus 2005
- HBoV parvovirus 2005
- KI/WU-PyV polyomavirus 2007
- MeIV (KamV) orthoreovirus 2007 (2009)
- H1N1v influenza virus 2009
- ...

- animal origin * ErasmusMC involvement
Serological classification flaviviruses

**FIG. 2.** Evolutionary tree of flaviviruses drawn on the basis of their envelope (E) protein amino acid homologies. These were calculated as percentage identical residues after optimized alignment of compared sequences counting gaps as mismatches using the Beckman Microgenie software package, Version 4.0. DEN, dengue; WN, West Nile; KUN, Kunjin; MVE, Murray Valley encephalitis; JE, Japanese encephalitis; SLE, St. Louis encephalitis; YF, yellow fever; POW, Powassan; LGT, Langat; LI, loping ill; TBE, tick-borne encephalitis. Modified from Mandl et al. (342) and Heinz et al. (221).
Global Spread of Dengue: role of mosquito control

50-100 million infections/year

Countries with active dengue + *Aedes aegypti*
Dengue Virus Pathogenesis: an Integrated View

Martina et al.,
Clin Microbiol Rev. 2009
2001

West Nile Virus Activity

- Non-Human WNV Activity
- Human Disease Cases

National Center for Infectious Diseases

West Nile Virus Activity
Cumulative results for 2001 calendar year
WNV in Europe:

- First sero-detection:
  - Albania 1958

- Virus isolations:
  - France, Russia, Portugal, Slovakia, Moldavia, Ukraine, Hungary, Romania, Czech Rep., Italy

- Cases, outbreaks:
  - 1960s: France, Russia, Spain, Romania
  - 2000s: France, Italy, Hungary, Spain
  - 2010: Macedonia (Greece), Spain
  - 2011: continuing spread
Chikungunya outbreak Italy 2007

- human pathogen: fever, joint and muscle pains
- the virus was introduced into Italy in 2007
Chikungunya outbreak Italy 2007

• human pathogen: fever, joint and muscle pains
• the virus was introduced into Italy in 2007
TICK-BORNE ENCEPHALITIS
-geographical distribution-
SARS-CoV - Phylogeny -

Drosten et al., NEJM 2003
Rota et al., Science 2003
Fouchier et al., PNAS 2004
Woo et al., J.Virol., 2005

hMPV as the cause?
Emerging or newly identified respiratory viruses in last 13 years

- AIV`s * influenza virus 1997...
- Hendra-/NipahV paramyxovirus 2000...
- hMPV * paramyxovirus 2001
- SARS-CoV * coronavirus 2003
- HCoV-NL63 * coronavirus 2004
- HCoV-HKU1 coronavirus 2005
- HBoV parvovirus 2005
- KI/WU-PyV polyomavirus 2007
- MelV (KamV) orthoreovirus 2007 (2009)
- H1N1v influenza virus 2009

- animal origin
* ErasmusMC involvement
Cynomolgus macaques
*(Macaca fascicularis)*

“Koch postulates”

- **SARS-CoV**
- hMPV
- SARS-CoV followed by hMPV

Fouchier et al., *Nature* 2003
Kuiken et al., *Lancet* 2004
April 16, 2003
WHO Geneva

Press conference of
SARS etiology
network

Official declaration of
SARS-CoV as the
etiologic agent

**Short- and mid-term objectives:**
- clarification of transmission routes and natural history
- establishment and evaluation of diagnostic tools
Phylogenetic analysis of FRCov using partial nucleocapsid and spike sequences

Nucleocapsid

Spike

Provacia et al., EID 2011

FIP like disease in ferrets (FRCov)
IFN-α treatment macaques: SARS-CoV excretion from pharynx

Haagmans et al., Nature Med. 2004
Emergence of SARS coronavirus

(Haagmans et al., Plos Path 2009)
Bats as the origin of viruses lethal to humans

- Lyssa viruses (rabies!)
- Hendra/Nipah viruses
- Filoviruses (Ebola/Marburg)
- SARS-like coronaviruses
- Many others…!!!
Marburg (Ebola) virus infection in The Netherlands: “out of Africa”

- a Dutch woman died from Marburg virus infection in The Netherlands
- she had visited a bat cave in Uganda 2 weeks earlier

Timen et al., EID 2009

"Python cave" Maramagambo forest
Duvenhage (rabies) virus infection in The Netherlands: “out of Africa”

failure of treatment of a patient in The Netherlands!

- van Thiel et al., Euro surveill., 2008

Presence of Rabies

Annual number of rabies deaths between 50,000 and 60,000

- Presence of rabies
- “rabies free” in terrestrial animals
- “rabies free” in terrestrial animals and bats

Annual number of rabies deaths between 50,000 and 60,000
Order *Mononegavirales*, family *Paramyxoviridae*

- Henipavirus
- Paramyxovirinae
  - Pneumovirinae
    - Pneumovirus
      - hRSV
      - bRSV
    - Metapneumovirus
      - APV
      - hMPV
  - Morbillivirus
    - TuV
    - CDV
    - PDV
    - RPV
    - MV
    - hPIV3
    - bPIV3
    - SeV
    - hPIV1
  - Respirovirus
    - NDV
    - Avulavirus
      - LPMV
      - MuV
      - SV41
      - SV5
      - hPIV2
      - SV5hPIV2
      - hMPV
      - hRSV
      - bRSV
- Avulavirus
- Rubulavirus
Geographical range of henipaviruses

Henipavirus Outbreaks (1997-2008)
- Fruit bats collection site positive for Henipavirus
- Home range of Pteropus genus of fruit bats
- Home range of Pteropodidae family of fruit bats
- Countries at risk (serological evidence)
- Countries with reported outbreaks

Map highlights:
- Nipah 1998
- Bangladesh 2001
- Hendra 1997

Conditions:
- ARDS
- Vasculitis
- Encephalitis
Human-to-human transmission
(Luby et al. 2009, Emerg Infect Dis)

- 23 zoonotic events, 2001-2007
  - 13 isolated cases
  - 10 clusters (mean: 10, range: 2-35 cases)

- Human-to-human (h2h) transmission
  - 62 of 122 (51%) involved h2h transmission
  - 5 of 10 clusters involved h2h transmission
  - Generations of transmission: 2 to 5
  - $R_0 = 0.48$

- Unlikely to become pandemic?
Human influenza:
three appearances

Seasonal influenza
(A: H3N2, H1N1; B)

Avian influenza
(A: H7N7, H5N1…)

Pandemic influenza
(A: H1N1, H2N2, H3N2, H1N1…?)
Aquatic wild birds
Influenza A virus reservoir
# INFLUENZA A VIRUS

Recent zoonotic transmissions

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Country</th>
<th>Year</th>
<th># Cases</th>
<th># Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>H7N7</td>
<td>UK</td>
<td>1996</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>H5N1</td>
<td>Hongkong</td>
<td>1997</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>H9N2</td>
<td>SE-Asia</td>
<td>1999</td>
<td>&gt;2</td>
<td>0</td>
</tr>
<tr>
<td>H5N1</td>
<td>Hongkong</td>
<td>2003</td>
<td>2?</td>
<td>1</td>
</tr>
<tr>
<td>H7N7</td>
<td>Netherlands</td>
<td>2003</td>
<td>89</td>
<td>1</td>
</tr>
<tr>
<td>H7N2</td>
<td>USA</td>
<td>2003</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>H7N3</td>
<td>Canada</td>
<td>2004</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>H5N1</td>
<td>SE-Asia/M-East/ Europe/W-Africa</td>
<td>2003-11</td>
<td>&gt;550</td>
<td>&gt;320*</td>
</tr>
</tbody>
</table>

*CFR ~ 60%
Avian influenza H5N1, Eastern hemisphere - H5N1 human - 2003-2011 - 

Case fatality rate ~ 60 % ??

Source: www.who.int (August, 2011)
Confirmed H5N1 avian influenza virus endemic areas (poultry and wild birds) since 2003

Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003
Clinical disease in diving ducks only
*(Keawcharoen et al. 2008 Emerg Infect Dis)*

<table>
<thead>
<tr>
<th>Species</th>
<th>No. inoculated</th>
<th>Mild signs</th>
<th>Severe signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tufted duck</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pochard</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mallard</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Teal</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wigeon</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gadwall</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

IHC H&E spreading? no spreading?
Pathology
"naturally" and experimentally
HPAI-H5N1 infected cats

Severe necrosis and inflammation in:
- Lung
- Brain
- Heart
- Kidney
- Liver
- Small intestine
- Adrenal gland

Kuiken et al., Nature 2006
A/H5N1 virus
- Genetic variation -

Source: www.who.int

WHO/OIE/FAO H5N1 Evolution Working Group
In preparation (2011)
Avian influenza A virus
Adaptation:
Based on data
Spanish flu (H1N1), H7N7 and H5N1 viruses
E. De Wit et al., J.Virol 2010

1. Virus binding, fusion and entry
2. Transcription and replication
PB1, PB2, PA, NP
3. Modulation of innate immune responses
NS1
4. Virion release
HA
NA

IFN-α/β
IFN-inducible genes
+cRNA
-vRNA
+mRNA
proteins
Attachment to upper or lower respiratory tract

<table>
<thead>
<tr>
<th></th>
<th>Seasonal H3N2</th>
<th>Pandemic H1N1</th>
<th>HPAIV H5N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Riel et al., Science 2006</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>van Riel et al., Am J Pathol 2007</td>
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<tr>
<td>van Riel et al., Am J Pathol 2009</td>
<td></td>
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</tr>
<tr>
<td>van Riel et al., Am J Pathol 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Riel et al., PLoS Path. 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

transmission

HPAIV H5N1
<table>
<thead>
<tr>
<th>Year</th>
<th>Epidemic</th>
<th>Deaths</th>
<th>Virus Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>“Spanish Flu”</td>
<td>&gt;40 million</td>
<td>A(H1N1)</td>
</tr>
<tr>
<td>1957</td>
<td>“Asian Flu”</td>
<td>1-4 million</td>
<td>A(H2N2)</td>
</tr>
<tr>
<td>1968</td>
<td>“Hong Kong Flu”</td>
<td>1-4 million</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td>2009</td>
<td>”Swine Flu”</td>
<td>???</td>
<td>A(H1N1)</td>
</tr>
</tbody>
</table>

Credit: US National Museum of Health and Medicine
In a few weeks, the 2009 H1N1v pandemic spread around the world affecting all countries.

* Date of last report for July 2009

Air traffic from Mexico
Origin of the H1N1v pandemic virus

Neumann et al, 2009

PB2 - North American avian
PB1 - Human H3N2
PA - North American avian
H1 - Classical swine
NP - Classical swine
N1 - Eurasian avian-like swine
M - Eurasian avian-like swine
NS - Classical swine
Children in the Alaskan village of Nushagak survived the Spanish flu

1918 Spanish flu
The Flu Orphans

2009 Mexican flu
fatal cases USA

Alaska State Library
Successful treatment of H1N1 pneumonia with oseltamivir on ECMO support
Wildschut, Fraaij et al., PLoS One 2010

Rapid progression:
intubation and
12 hr later ECMO

After start ECMO day 1, 3 and 5: full recovery and discharge 24 days after first signs and symptoms
2009 influenza A (H1N1) virus: relevant mutations

**Virulence** associated substitution in HA: **D222G**
(Herfst et al., J.Virol. 2010)

**Oseltamivir** resistance substitution in NA: **H275Y**
(de Vries et al., J.Clin Microbiol. 2010)

**Zanamivir** resistance substitution in NA: **I223R**
(de Vries et al. NEJM 2010)
Rethinking Influenza


Today, we are better prepared to face the H1N1 influenza A 2009 virus than we were for any other previous pandemic. Although the present manufacturing capacity is unlikely to have all the vaccines needed before the peak of the next wave of cases, the potential output of vaccine manufacturing has increased from 400 to 900 million (1). A vaccine will be produced in Europe with modern cell culture technology instead of eggs. A large facility for cell culture production construction in the United States is to improve the current limited capacity. Although vaccines against avian not highly immunogenic, this shc can be overcome by using adjuvants using whole-virus vaccines (2–5).

Adjuvants based on oil-in-water emulsions, such as MF59 and AS03, are licensed in Europe and, although their approval in the United States is still a work in progress, they can be used under the Emergency Use Application legislation. MF59 has already been used in vaccination of more than 45 million people. Although yields may be lower than those of seasonal vaccines, preliminary data to be vaccinated in order to see whether changes in rates occur after vaccination.

The current approach of responding to influenza outbreaks in a reactive rather than anticipatory mode is not optimal, but because most of our knowledge of influenza virus is based on data accumulated in developed countries, we have an incomplete, and sometimes inaccurate, view of virus spread and its global impacts. For example, in many low-income and middle-income countries, influenza viruses among infants and children (9, 10). Therefore, improved influenza surveillance in developing countries is needed, and it seems appropriate to add influenza to the vaccines recommended by the Expanded Program for Immunization (EPI). Potential sources for funding could derive from one of the existing models such as the Advanced Market Commitment. The increase in vaccination would be based on the excess manufacturing capacity for humans, their livestock, and wild animals to be able to map the diversity and circulation of the virus.

Until H1N1, the scientific community believed that a pandemic strain could only arise from a strain that had not previously been widely disseminated in humans. However, the H1N1 virus has shown that human varieties characterized by different hemagglutinin (HA) molecules may follow separate modes of evolution and may generate pandemic strains within an existing HA type. Hence, it is essential to methods for estimating how many ally different subtypes may reside within a type.

Public-Private Collaboration to develop intervention strategies against pdv H1N1 2009

Research toward development of a universal vaccine should be accelerated by testing adjuvants to increase cross-protection, conserved antigens (such as M2 and NP), or different vaccine platforms (such as the live attenuated vaccines) (11), and alternative approaches to vaccine delivery. In conclusion, although the H1N1 pandemic has the potential to cause a social and economic emergency, it also provides an opportunity to...
Seasonal H1N1  
Seasonal H1N1  

pH1N1 2009  
Munster et al., Science 2009  
Del Giudice et al., Science TM 2009  
Chutinimitkul et al., J. Virol 2010  
Herfst et al., Vet.Pathol. 2010  
Bosch et al., J.Virol. 2010  
Kreijtz et al., J.Gen.Virol. 2010  
v.d.Brand et al., JID 2010  
v.d.Brand et al., J.Virol 2010  
Bodewes et al. ,Am J Pathol. 2011

HPAI H5N1  

Lung Weight

Temperature

Virus Load

Clinical & Virological Parameters
Pandemic H1N1 (2009)-induced lung lesions as measured by CT and histopathology

“used for testing antiviral and vaccine candidates”
Viral load in the lungs by culture
Day 4 post-challenge (A/The Netherlands/602/09)

Lower virus load observed in animals immunized with AS03-adjuvanted vaccines compared to ferrets receiving the non-adjuvanted vaccine (or PBS).
Seasonal vaccine provides priming against A/H1N1 pandemic influenza

**Vaccines**
- = PBS
A = seasonal H1N1
F = seasonal H1N1 + MF59
C = pdm H1N1
C+ = pdm H1N1 + MF59

*Del Guidice et al. Science TM 2009*
*v.d.Brand et al J.Virol. 2010*
You tube et al.,: “pandemic vaccines 2009 are unsafe”

Nothing new!!!
Edward Jenner
“father of vaccination”

1796: first vaccination

Public outrage!!!
CONCLUSIONS:

EMERGING VIRUSES

- identified with increasing frequency in animals and humans
- due to a complex mix of predisposing factors and
- due to more advanced molecular techniques
- in our changing and globalizing society
- most “new” human viruses come from the animal world
CONCLUSIONS:

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International collaboration and coordination
- using all available technology (classical and novel!!!)
- are of key importance for their future control !!!
Emerging virus research
- The team leaders -

Prof. Dr. R.A.M. Fouchier  |  Virology
Prof. Dr. T. Kuiken       |  Pathology
Prof. Dr. M. Koopmans    |  Epidemiology
Prof. Dr. C.A.B. Boucher  |  Antiviral research
Dr. A. van der Eijk / Dr. P. Fraaij / Dr. E. van Gorp |  Clinical research
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Dr. M. Schutten           |  Diagnostics
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