Human Respiratory Viruses: ‘new kids on the block’

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The importance of understanding the human-animal interface: from early hominins to global citizens

Past decades: zoonoses at the origin of major human disease outbreaks

The importance of understanding the human-animal interface: from early hominins to global citizens
Clinical Study

Epidemiology of Human Respiratory Viruses in Children with Acute Respiratory Tract Infections in Jinan, China

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Figure 1: Number of recruited patients and the numbers of positive samples for viral infections.

Figure 2: Number of positive results for various viruses in patients with acute upper respiratory tract infections.

Figure 3: Number of positive results for various viruses in patients with acute lower respiratory tract infections.
Identification of viral pathogens based on surveillance activities: ErasmusMC / RIZ TiHo

1995 CDV as the cause of mass mortality in Serengeti lions
1996 γ-herpesvirus in seals (phocid herpesvirus-2)
1997 monk seal morbilliviruses (MSMV-WA/G)
1997 influenza A (H5N1) virus in humans
1998 lentivirus from Talapoin monkeys (SIVtal)
1999 influenza B virus in seals
2000 human metapneumovirus (hMPV)
2002 re-emerging PDV in Europe
2003 SARS CoV cause of SARS in humans (Koch`s postulates)
2003 influenza A (H7N7) virus in humans
2004 fourth human coronavirus (CoV NL63)
2005 H16 influenza A viruses (new HA!) in black headed gulls
2008 dolphin herpesvirus
2009 deer astrovirus
2010 human astrovirus, human picobirnavirus
2011 ferret coronavirus, ferret HEV, porcine picobirnavirus, stone marten anellovirus.
influenza A (H1N1) virus in dogs
2012 human calicivirus, MERS CoV, boa arenaviruses
2013 seal parvovirus, seal anelloviruses, deer papillomavirus, fox hepevirus, fox parvovirus, turtle herpesvirus
2014 canine bocavirus, porcine bocavirus, python nidovirus, camel circovirus, phocid herpes virus-7
2015 influenza A (H10N7) virus seals
2017... morbillivirus fin whale, hepadnavirus Tinamou, rec.canine circovirus, rec.canine bocavirus, herpesvirus sperm whale, Batai virus seal, avian metapneumovirus, novel pestivirus...

novel molecular techniques

Funding:
EU: EMPERIE; ANTIGONE; PREPARE; COMPARE...
NL: VIRGO-FES...
DFG: N-RENNT; VIPER

XXX human respiratory
Parvoviruses: wide spectrum of disease in humans and animals alike

- Asymptomatic
- Erythema infectiosum (Human B19)
- Fetal hydrops (Human B19, Porcine parvoviruses)
- Gastro-enteritis (Canine parvovirus, Human bocavirus, Bufavirus)
- Anemia (Human B19, non-human primate erythroviruses)
- Respiratory disease (Human bocavirus, Canine bocavirus)
- Immune disorders (Aleutian mink disease, Human B19)
- Hepatitis, myocarditis (Canine parvovirus, Goose parvovirus, B19)
- Brain involvement

Image of parvovirus particles and illustrations of disease symptoms.
Virus discovery in pigs, dogs and seals with encephalitis (comparative virology)

**Novel (recombinant) canine bocaviruses**

**Novel porcine bocavirus**

**novel seal parvovirus**

Piewbang et al., Vet Pathol. 2018
**FIG. 2.** Comparison between median Ct-values of human bocavirus (HBoV) RT-PCR-positive respiratory tract samples of paediatric patient admitted to the Erasmus MC-Sophia from 2007 to 2012; all hospital-admitted paediatric patients versus patients admitted to the paediatric intensive care unit (PICU) with HBoV and viral co-detection versus PICU-admitted patients with a single HBoV infection. Horizontal bars represent group medians.
Rinderpest eradication: lessons for measles eradication?
de Swart RL, Duprex WP, Osterhaus AD. *Curr Opin Virol*. 2012
Morbilloviruses crossing species barriers a pandemic risk after measles eradication?

PDV: European Harbour seals

CDV: Baikal seals
Nature 1988

CDV: Caspian seals
EID 2000

DMV: Med. monk seals
Nature 1997

CDV: Serengeti lions
Vaccine 1994

DMV: Fin Whale Denmark
JWD 2016

CDV: Rhesus macaques
China, EID 2011

Should we continue measles vaccination for ever?
CD150 is the primary morbillivirus entry receptor

PVRL4 is the morbillivirus receptor on epithelial cells

**Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality**

Michael J. Mina, C. Jessica E. Metcalf, Rik L. de Swart, A. D. M. E. Osterhaus, Bryan T. Grenfell

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**Measles immune suppression; lessons from the macaque model.**

**CD45RA(-) memory T-lymphocytes and follicular B-lymphocytes killed**
Significant changes in the frequencies of different lymphocyte subsets after measles. Frequency ratios of a naive or memory lymphocyte subsets or b functionally distinct T and B cell subsets \((n = 42\) paired samples). The ratio was calculated as the frequency of a subset after measles divided by the frequency of the same subset before measles. Horizontal dashed line indicates no changes (‘ratio = 1’) in frequency after measles. Ratio ‘>1’ indicates increase and ratio ‘<1’ indicates decrease in lymphocyte subset frequency after measles. Vertical dashed lines separate different lymphocyte subsets. TH1/17: TH1TH17 cells. CD27+IgM+IgD− B cells are also known as IgM-only memory B cells. CD27+IgM+IgD+ B cells are also known as natural effector cells. TC: transitional B cells. Green box represents significant decrease. Orange box represents significant increase. Statistical differences in frequencies of lymphocyte subsets before and after measles were analysed by two-tailed paired t-test or Wilcoxon signed-rank test. Centre lines of the box plots represent medians. Lower and upper boundaries of the boxes represent first and third quartiles, respectively. Lower and upper whiskers represent the 10th and 90th percentiles of the data, respectively. Dots represent outliers. \(*P < 0.05; **P < 0.01; ***P \leq 0.001\)
A newly discovered human pneumovirus isolated from young children with respiratory tract disease

Bernadette G. van den Hoogen, Jan C. de Jong, Jan Groen, Thijs Kuiken, Ronald de Groot, Ron A.M. Fouchier & Albert D.M.E. Osterhaus

DNA Maximum likelihood, Polymerase ORF

**Paramyxovirinae**

**Pneumovirinae**

**Metapneumovirinae**
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?
Press conference of SARS etiology network

Official declaration of SARS-CoV as the etiologic agent

April 16, 2003
WHO Geneva

Short- and mid-term objectives:
- clarification of transmission routes and natural history
- establishment and evaluation of diagnostic tools

Fouchier et al., Nature 2003
Kuiken et al., Lancet 2004
To date: estimated >2260 cases in 27 countries with >800 deaths

Saudi Arabia, Malaysia, Jordan, Qatar, Egypt, the United Arab Emirates, Kuwait, Oman, Algeria, Bangladesh, the Philippines, Indonesia (none confirmed), UK, and USA
Antibodies in dromedary camels
(Reusken et al. Lancet ID 2013)

Dromedary camels: carriers of MERS-CoV
(Haagmans et al., Lancet ID 2013)

Identification of the CD 26 MERS-CoV receptor
(Raj et al., Nature 2013)
MVA expressing the MERS-CoV spike protein;

PREVENTION AT THE SOURCE?

A ONE HEALTH APPROACH

Fei Song et al. JV 2013

Haagmans et al., Science 2016
MERS-CoV MVA vaccination: ‘one stone - two birds’ approach

PREVENTION AT THE SOURCE?

A ONE HEALTH APPROACH

MVA MERS-S vaccine now in human trials (HCW’s, camel handlers, immune-compromised)

Fei Song et al. JV 2013

Haagmans et al., Science 2016
Chimeric camel/human heavy-chain antibodies protect against MERS-CoV infection


Schematic overview of VHH identification by direct cloning using bone marrow from immunized dromedary camels.
Last four pandemics

1918
“Spanish Flu”
>40 million deaths
A(H1N1)

1957
“Asian Flu”
1-4 million deaths
A(H2N2)

1968
“Hong Kong Flu”
1-4 million deaths
A(H3N2)

2009
“Mexican flu”
0.2-0.3 million deaths
A(H1N1)

Credit: US National Museum of Health and Medicine
Aquatic wild birds: Influenza A virus reservoir

Short et al. 2015 One Health 2015
Recent zoonotic transmissions from birds -confirmed human cases-

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Country</th>
<th>Year</th>
<th># Cases</th>
<th># Deaths</th>
</tr>
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<tbody>
<tr>
<td>H7N7</td>
<td>UK</td>
<td>1996</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>H5N1</strong></td>
<td>Hong Kong</td>
<td>1997</td>
<td><strong>18</strong></td>
<td><strong>6</strong></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>Hong Kong</td>
<td>2003</td>
<td>2?</td>
<td>1</td>
</tr>
<tr>
<td>H7N7</td>
<td>Netherlands</td>
<td>2003</td>
<td><strong>89</strong></td>
<td><strong>1</strong></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><strong>H5N1</strong></td>
<td>SE-Asia/M-East/</td>
<td>2003-18*</td>
<td>&gt;840</td>
<td>&gt;450*</td>
</tr>
<tr>
<td>Europe/W-Africa</td>
<td></td>
<td></td>
<td></td>
<td>(increasing)</td>
</tr>
<tr>
<td>H7N9</td>
<td>PR China</td>
<td>2013-18*</td>
<td>&gt;1500</td>
<td>&gt;600*</td>
</tr>
</tbody>
</table>

H9, H10, H6.. Asia...

*CFR ~ 55% (increasing)
Avian Influenza: Asia ‘live bird markets’
Virus passaging in ferrets (P1 to P10, passages 1 to 10).

Sander Herfst et al. Science 2012

Munster et al., Science 2009
Russel et al., Science 2012
Linster et al., Cell 2014
High and low pathogenic avian influenza A viruses H7N9

Laboratory confirmed: 1584  
Deaths: 612  
Recoveries: 972

Source: FAO
Novel avian-origin influenza A (H7N9) virus attaches to epithelium in both upper and lower respiratory tract of humans.

*D van Riel et al. Am J Pathol. 2013*

Limited human-to-human transmission: Small clusters!

*Chen Z, et al., Emerg Infect Dis. 2014*

Limited airborne transmission of H7N9 influenza A virus between ferrets.

Crucial preparedness elements for emerging viruses to be developed in ‘peace time’:

- **Disease surveillance** in humans & animals
- **Virus surveillance / genetic characterization** for humans & animals
- **Diagnostics development and distribution platforms**
- **Mathematical modeling** capacity
- **Animal model** capacity (BSL3/4)
- **Pathogenesis and transmission platforms**
- **Preventive intervention platforms** (societal, vaccination, antiviral)
- **Therapeutics discovery platforms** (antivirals, antibodies, BRM’s...)
- **Healthcare preparedness**
- **Communication and distribution strategies**

Of key importance for their control:
- International collaboration and coordination
- Using all available technology and information
Acknowledgements

Respiratory Viruses Erasmus MC and TiHo

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Mol. Virology
Pathology
Epidemiology
Antiviral research
Clinical / Pediatrics
Viro-Immunology
Virology
Virus discovery studies

SARS collaborations
Drosten C.
Lim W
Peiris M
Guan Y
Tam JS
Rottier PJ
Rota PA
Stöhr K
Tashiro M
v.d. Werf S
Zambon MC

Bonn University Germany
QM Hospital Hongkong
University of Hongkong
University of Hongkong
Hongkong Polytech. University
Utrecht University Netherlands
CDC Atlanta
WHO Geneva
NIC Tokyo
Pasteur Paris
PHE London

MERS and Flu collaborations
Drosten C.
Farag E
Bosch BJ
Sutter G
Segalis Q
Zambon MC
Neubert A

Bonn University Germany
Supreme Health Council Qatar
Utrecht University Netherlands
Max. Univ. München Germany
CRESA Barcelona Spain
PHE London
IDT
Forthcoming conferences dealing with outbreak preparedness

See you in Edinburgh, Scotland, UK!

SAVE THE DATE
15-18 June 2020

Organized by European Scientific Working group on Influenza

www.worldonehealthcongress.com