Introduction: a quick tour of the virosphere
Prof Dr Marion Koopmans, public health virology

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Virosphere 2005

International Committee on Taxonomy of Viruses
Expanding virosphere

Virus discovery, disease focus
Focus on etiology of common diseases
Metagenomics, focus on ecosystem balance in health and disease

Figure 1. Different Ways to Explore the Virosphere
A tree is used to represent the total phylogenetic diversity of RNA viruses. The colored circles illustrate the extent of this diversity that can be discovered using three common approaches for virus discovery: cell culture, consensus PCR, and metagenomics.

Zhang et al., 2018
- $10^7$ viruses / ml of ocean water
- $10^8$–$10^9$ viruses per gram in nearshore surface sediments
- $4^{32}$ viruses

- Viruses are everywhere
- Important part of biomass
- Controlling balance in ecosystems (phages, infections)
- Every living creature is infected / can be infected with viruses

*Suttle, Genome sequences from the sea. Nature 2003*
Shi et al., 2018
Multiple (> 200) new virus species through RNA metatranscriptomics

“Vertebrate: viruses in a range of hosts

Similar tissue tropisms across host species

Shi et al., 2018
So what do we know now?

- Our knowledge of virology is often oversimplified and biased
- Virome is part of macro-and micro-ecosystems
- Viruses are “regulators of health” in ecosystems
- Understanding the interactions between viruses and hosts should take these factors into account
- The complexity of these interactions requires input from new disciplines (data science), and new ways of doing research

_The trouble with facts is that there are so many of them_

Anonymous
Strategic goals:

increasing our understanding of the interactions between viruses and their hosts at the molecular, host and population level,

improving patient level prevention and intervention strategies against virus infections of particular concern to patients at risk of (developing) severe virus infections;

improving population level prevention and intervention strategies against virus infections of particular public health concern, with a focus on zoonotic viruses with epidemic or pandemic potential;

Providing state-of-the-art diagnostics and advise for known and emerging diseases
ABSL3 facility
Negative pressure, filtered air

-45 Pa

-30 Pa

-210 Pa

-60 Pa

0 Pa

-15 Pa
Structure ⇔ Function
Virus problems in changing demographics

Childhood mortality
Diseases associated with sanitation
Bloodborne diseases
Lack of resources

Immune senescence
Higher impact of common diseases
Increased severity
Chronic infections, reactivations
Health care settings as amplifiers

Changing patient population

Huttunen et al., 2014
Petrignani et al., 2014

Bigger (norovirus) outbreaks with increasing dependency
(GII4) Noroviruses persist in the population through evolution

Effects of mutations:
Escape mutants (drift) > No protective immunity
Differences in host cell binding > New host range

Siebenga et al., 2008; Allen et al., 2008; Parra et al., 2012; Tan et al., 2003
Lindesmith et al., 2008; Bok et al., 2009; Siebenga et al. 2010, de raaf 2016; van Beek 2017
New expressions of known diseases > immunocompromised patients as reservoir for evolution?

Van Beek et al., 2017

Chronic evolving norovirus in immunocompromised patients
Our systemic virome may affect our response to other exposures
De Vlaminck et al., 2013
The more we know, the less we know.
THE HEALTH OF INDIVIDUALS IS HIGHLY DEPENDENT ON GROUP HEALTH, BEHAVIOR, ENVIRONMENTAL EXPOSURES, HABITATS, ECOSYSTEM

Viruses (and microorganisms) share these habitats, outnumber us, and evolve much faster.
Drivers of **EID emergence**

- CHANGE in demographics of humans and animals (size, age, health status)
- CHANGE in political landscape (civil unrest, wars, discovery of new mineral resources, migration)
- CHANGE in behavior (sexual behavior, tourism, food habits)
- CHANGE in pathogen behavior (new viruses, antimicrobial resistance, evolution)
- CHANGE in technology (inplants, increased survival, transplantation)
- CHANGE in climate
Global changes that will inevitably impact on infectious disease dynamics, and our ability to control them.

- Environmental degradation
- Climate change
- Urbanization
- Rising geographic mobility
- Rise of chronic diseases
- Weakening international organisations
- Rise of hyperconnectivity
- Nationalism
- Increasing polarization
- Shifts in power
- Raising income disparity
- Ageing populations
- Raising income disparity
- Growing middle class Low SES
- Weakening of finance
- Profound social instability
- Interstate conflict
- Unemployment or underemployment
- Status collapse or crisis
- Economic risk
- Geopolitical risks
- Societal risks
- Technological risks
- Trends

1 human replication event > 1-3 offspring

1 virus particle > around \((10^4)^{8760}\) mutant offspring

Bonhoeffer et al., 2002; Holmes, 2011
Virus quasispecies - evolution via “bottlenecks” -
Co-phylogeny shows: species cross-over is seen in almost all known virus families.

Can involve adaptation through mutations or gene reassortment/recombination or both.

Geoghegan and Holmes, 2017
Zoonotic disease adaptation concerns \( \text{H7N9, Nipah, Monkeypox} \)

- Most EID come from animals, opportunity for contact increases, but probably not so much
- Once introduced in people, many opportunities for transmission:

\[\text{Stage 1: agent only in animals} \quad \text{Rabies, Ebola, Dengue, HIV-1 M} \]

\[\text{Stage 2: primary infection} \quad \text{None} \]

\[\text{Stage 3: limited outbreak} \quad \text{From animals or (few cycles) humans} \]

\[\text{Stage 4: long outbreak} \quad \text{From animals or (many cycles) humans} \]

\[\text{Stage 5: exclusive human agent} \quad \text{Only from humans} \]

\[\text{Transmission to humans} \]

\[\text{Wolfe et al., 2007; http://rambaut.github.io/EBOV_Visualization/Makona_1561_D3/; Gytis et al., 2017}\]
urban amplification concerns
Ebola, MERS CoV, Lassa, Nipah…

- Most EID come from animals, opportunity for contact increases, but probably not so much

- Once introduced in people, many opportunities for transmission:
- WHEN it occurs, things can move extremely fast: high density cities

Wolfe et al., 2007; http://rambaut.github.io/EBOV_Visualization/Makona_1561_D3/; Gytis et al., 2017
Healthcare settings as amplifiers of infection

Around 50% nosocomial?
VECTORBORNE DISEASE AMPLIFICATION EVENTS (Zika, dengue, chikungunya, yellow fever, ....)
## Ongoing threats

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<td>ZIKA</td>
<td>French Polynesia</td>
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<td>Brasil&gt;Americas</td>
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<td>EBOLA</td>
<td>West Africa</td>
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<td>DRC</td>
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<td>CHIKUNGUNYA</td>
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<td>MERS COV</td>
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<td>YFV</td>
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<td>LASSA</td>
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<td>Nigeria</td>
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<td>NIPAH</td>
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<td>India</td>
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<td>China</td>
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<td>H7N9</td>
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<td>MONKEYPOX</td>
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**Vectorborne**

**Zoonotic, amplified**

**Zoonotic, adaptation, pandemic Threat**
Zika virus history

- First isolation 1947, rhesus blood, Uganda
- First human case 1952, Nigeria

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**Transactions of the Royal Society of Tropical Medicine and Hygiene.**


**Communications**

**Zika Virus**

(1) Isolations and serological specificity

By

G. W. A. Dick,

*The National Institute for Medical Research, London*

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**Zika Virus: A Report on Three Cases of Human Infection During an Epidemic of Jaundice in Nigeria**

By

F. N. Macnamara*

*Acting Director, Virus Research Institute, Yaba, Nigeria*

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*Transactions of the Royal Society of Tropical Medicine and Hygiene.*

*Vol. 46, No. 5. September, 1952.*
Since 2007 several outbreaks on islands in the Pacific Ocean
2007: outbreak with 186 cases in Yap island (Micronesia)
2013-14: approx. 30,000 cases in French Polynesia
Arrived in the America’s (Easter Island) in 2014
Historic timeline of Zika virus (WHO)

Predicted habitats of the main mosquito that transmits the Zika virus

Aedes aegypti
Primary carrier of the virus

Areas that are
- Highly suitable
- Moderately suitable
- Unsuitable

Sources: Kraemer MUG et al., eLife Sciences, University of Oxford; photo by Marvin Recinos/Agence France-Presse/Getty Images
1 February 2016: WHO declared 4th PHEIC
“the increasing cases of neonatal and neurological disorders, amid the growing Zika outbreak in the Americas”

Mirando-Filho et al., 2016; Vandereijk et al., 2016
Primary infection

Dengue virus

Secondary infection

Dengue virus

Zika virus

ADE

In vitro

Yes

Yes

In vivo

Yes

Yes

Yes

No

Yes

No

NA

Langerak, Mumtaz, Rockx et al
Figure 1. Cumulative number of countries and territories by WHO region\(^1\) reporting mosquito-borne Zika virus transmission for the first time by year (2007–2014), and by month from 1 January 2015 to 16 November 2016.
Current ZIKV risk map

International areas and US territories

- Areas with risk of Zika infection (below 6,500 feet)*
- Areas with low likelihood of Zika infection (above 6,500 feet)*
- Areas with no known risk of Zika infection

*Mosquitoes that can spread Zika usually live in places below 6,500 feet. The chances of getting Zika from mosquitoes living above that altitude are very low.
A massive outbreak of neuroinvasive mosquito-borne disease in birds detected through hotspot surveillance

Zoonotic, transmitted by the same mosquitoes as West Nile virus, heralding change in ecology of these viruses in northern Europe?

Een beklemmende stilte zonder de merels

Het usuto-virus zorgt voor massale merelsterfte. Frans van der Helm mist zijn tuingenoten.
Several lineages, what does that mean for human health risk?

Blue = Owl
Red = Blackbird
Green = Mosquito
Light blue = Pigeon

Africa 3 lineage

Europe 3 lineage

Reusken, Oude Munnink et al
Ebolavirus West Africa: historical perspective

Cumulative number Ebolavirus cases 1976-2016
Start outbreak EBOV

- March 10, 2014 notification unknown disease characterized by fever, severe diarrhea, vomiting and high fatality rate in Guéckédou and Macenta in Guinea.
- March 22, EVD reported by Guinea to WHO.
- March 27, EVD suspected cases in Liberia and Sierra Leone related to outbreak in Guinea.
District data for July not available
Source: WHO, national health ministries and HDX
Democratic Republic of the Congo
Ebola cases per Health Zone in Equateur province as of May 19, 2018

Map date: 21 May 2018

Data Source: World Health Organization
GSM: GICO
Map Production: WHO Health Emergencies Programme

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Ebola in the DRC

The research response timeline

08 May
WHO notified by the DRC MoH of confirmed cases of EVD

09 May
First deployments of teams to Bikoro

10 May
Distribution of Notes for the Record and circulation of draft research response plan
WHO, MoH DRC, MSF and Merck prepare for implementation of ring vaccination, pending support of DRC authorities

13 May
DRC formally asks to use experimental Merck vaccine

13 May
WHO forms expert working group to prioritize candidate investigational Ebola therapeutics for MEURI

15 May
NIH support to vaccinate deployed frontline workers from NIH

16-17 May
TCs on use of investigational therapeutic agents (INFR)

18 May
TC with GCM & SAG

Partner contributions
Wellcome Trust pledged 2M GBP and is engaging with other funding partners through GloPID-R. DFID has pledged 1M GBP, Gavi has pledged 1M USD.

ECDC has 2 networks (ALERRT/PANDORA) ready to provide support

GOARN research will support definition of the non-product R&D, including research to assess acceptability of experimental interventions.

Planned activities
Ring vaccination
TC to discuss interpretation of lab results, EVD diagnostic tools, and laboratory capacity
TC on clinical management to discuss the standard of care, clinical core variables, and clinical evaluation
Recommendations on MEURI for therapeutic agents

09 May
R&D Blueprint Ebola Roadmap online for public consultation

09 May
TC between WHO, R&D Blueprint GCM and SAG, and the DRC MoH

10 May
Merck offers support to facilitate access of experimental vaccine under the framework of an FDA Expanded Use.

10-14 May
WHO approaches Sponsors of investigational therapeutics to access data for scientific assessment under WHO ethical framework.

WHO is working with MSF and DRC MoH to prepare to use those investigational therapeutics.

16 May
First shipment of vaccine arrives in DRC

18-19 May
Cold chain set up
Guinean team arrives, begins vaccination training with MOH

A DEPARTMENT OF Erasmus MC
Countries reporting monkeypox cases in humans and animals

- Country reporting human monkeypox cases
- Country reporting monkeypox in animals

2000-2009

2010-2017

Rimoin et al., 2010
Rimoin et al., 2010
Rimoin et al., 2010
Infectious disease dynamics need to be studied in context of this ecosystem

*Anthropocentric*  

*Ecocentric / One Health*
Relevant parameters collected in the four past influenza pandemics for the study on pandemic influenza scenarios in Europe:

<table>
<thead>
<tr>
<th>Season</th>
<th>Clinical attack rate (%)</th>
<th>Complication rate (%)</th>
<th>Hospital admission rate (%)</th>
<th>Case fatality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918/19</td>
<td>25</td>
<td>20</td>
<td>4</td>
<td>2-3</td>
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<tr>
<td>1957/58</td>
<td>30</td>
<td>2.7</td>
<td>&lt;0.6</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>1968/69–1969/70</td>
<td>35</td>
<td>2.7</td>
<td>&lt;0.6</td>
<td>&lt;0.2</td>
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<tr>
<td>2009/10</td>
<td>5</td>
<td>5–16 in at-risk groups</td>
<td>&lt;0.02–1</td>
<td>&lt;0.0048 (influenza-like illness rate)</td>
</tr>
</tbody>
</table>

Napoli et al., 2015
Lycett et al., 2016
A(H7N9) activity - humans

Wave 1
Wave 2
Wave 3
Wave 4
Wave 5

1521 total cases

WHO human animal interface update
## Tool for Influenza Pandemic Risk Assessment

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Element</th>
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<tbody>
<tr>
<td>Public Health</td>
<td>Human infection</td>
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<tr>
<td></td>
<td>Disease severity</td>
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<tr>
<td></td>
<td>Population immunity</td>
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<tr>
<td>Animal Health</td>
<td>Geographic distribution in animals</td>
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<tr>
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<td>Infections in animals</td>
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<tr>
<td>Virology</td>
<td>Receptor binding properties</td>
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<td></td>
<td>Transmission in animal models</td>
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<tr>
<td></td>
<td>Susceptibility to antiviral treatment</td>
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<tr>
<td></td>
<td>Genomic characteristics</td>
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</table>

### H7N9

* *** CFR 40%  
  *** low  
  *** Increasing  

** mixed avian-human  
** mixed, increasing?  
* susceptible

Assessing H7N9 transmissibility in ferrets

Ancestral 
First wave

2nd wave 
3d wave

Airborne Tx experiment

Direct contact Tx experiment

Belser et al., 2016
So what do we know now?

- Our knowledge of virology is often oversimplified and biased.
- Virome is part of macro- and micro-ecosystems.
- Viruses are “regulators of health” in ecosystems.
- Understanding the interactions between viruses and hosts should take these factors into account.
- The complexity of these interactions requires input from new disciplines (data science), and new ways of doing research.

*The trouble with facts is that there are so many of them*

Anonymous
Changing paradigms in EID research

Karesh et al., 2012

Past & current paradigm
reactive outbreak research agenda

Future paradigm
pro-active preparedness research agenda
Prof Dick Heederik, UU, chair
Prof Marc Bonten, UMCU, Director antimicrobial resistance
Prof Marion Koopmans, EMC, Director emerging infections
Dr Annemarie Rebel, WUR: Director Smart and healthy farming
Prof Andrea Groehne, UU DGK: Director Healthy wildlife and ecosystems
We aim to convene scientists from across the Virosphere, ranging from basic to applied virology, mixing medical, veterinary, wildlife, invertebrate and plant virology.

There will be plenary sessions on themes that are informative and inspiring to virologists from all these areas, as well as sessions for a more specialized audience.