

# “gain-of-function” studies ...

... their history, their utility and what they can tell us ...

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# location of my laboratory

the National Emerging Infectious Diseases Laboratories (NEIDL)

**BOSTON  
UNIVERSITY**



# research focus of my laboratory



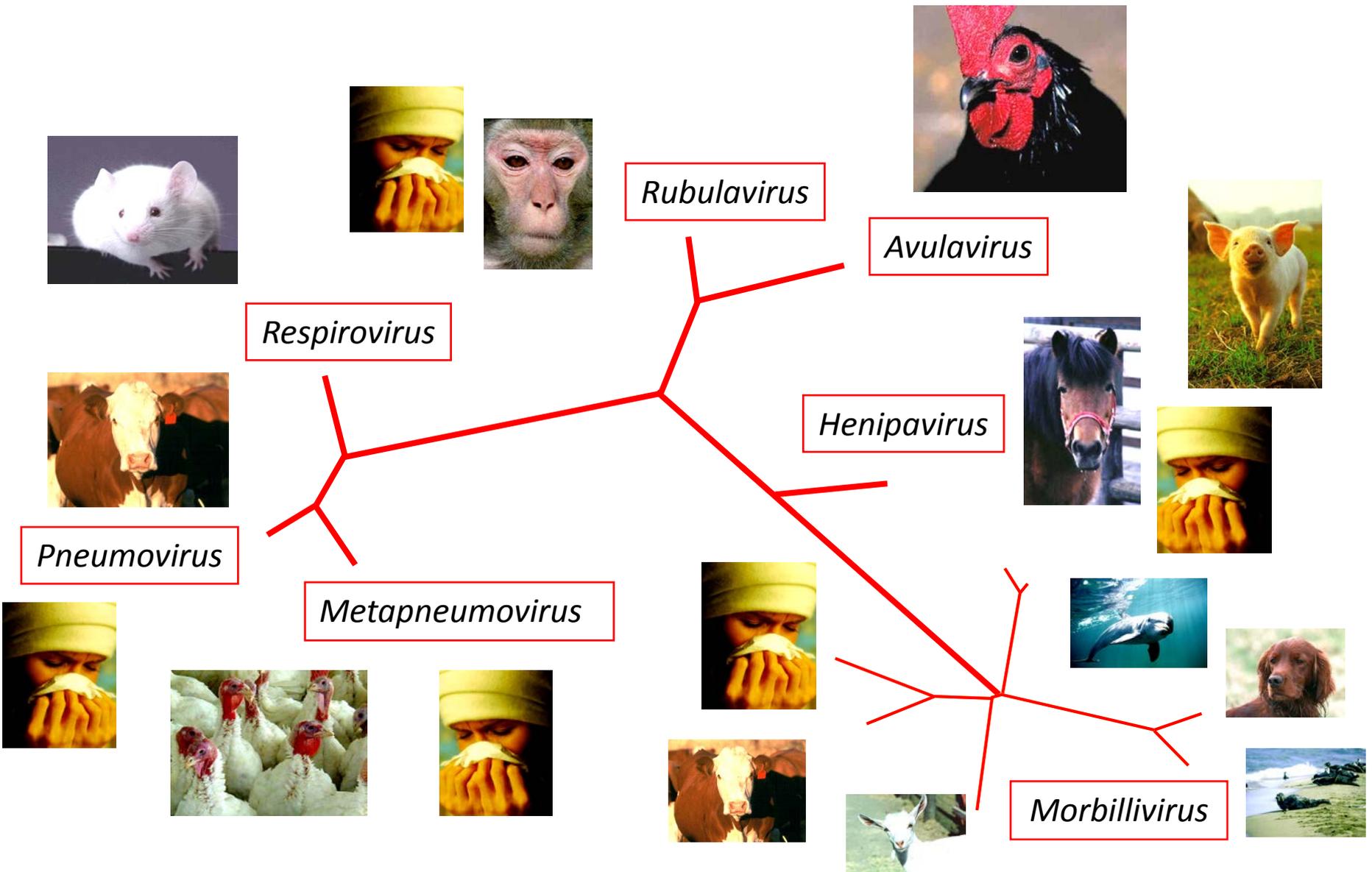
pathogenesis



attenuation

BASIC UNDERSTANDING OF THE MOLECULAR BIOLOGY OF THE VIRUSES

# a diverse family of human and animal viruses



# global eradication of rinderpest in 2011



## The Global Rinderpest Eradication Programme

Progress report on  
rinderpest eradication:  
Success stories and actions leading to  
the June 2011 Global Declaration

### PROGRESS TOWARDS RINDERPEST GLOBAL FREEDOM

	Last outbreak	<b>2001</b>
		2002
		2003
		<b>2004</b>
		<b>2005</b>
	Vaccination stopped and provisional freedom from rinderpest	<b>2006</b>
		2007
		2008
	Targeted surveillance exercise	2009
	End of the field operations	2010
	Global declaration	<b>2011</b>

# eradication of measles virus is also on the cards

it is the most infectious human pathogen on earth

*rinderpest*



*measles*



*BUT ... refusal to vaccinate is leading to a resurgence of the virus in Europe and the US*

# the problem of wild, unsubstantiated speculation

our job as scientists is to *inform* and *educate* not to entertain or scare



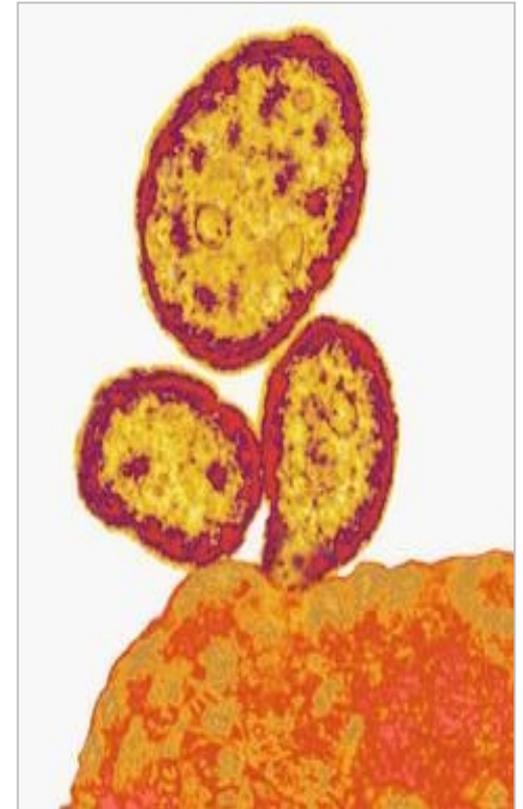
*we are not living in a Hollywood movie ... we all have to be responsible*

# what are the barriers to cross-species infection?



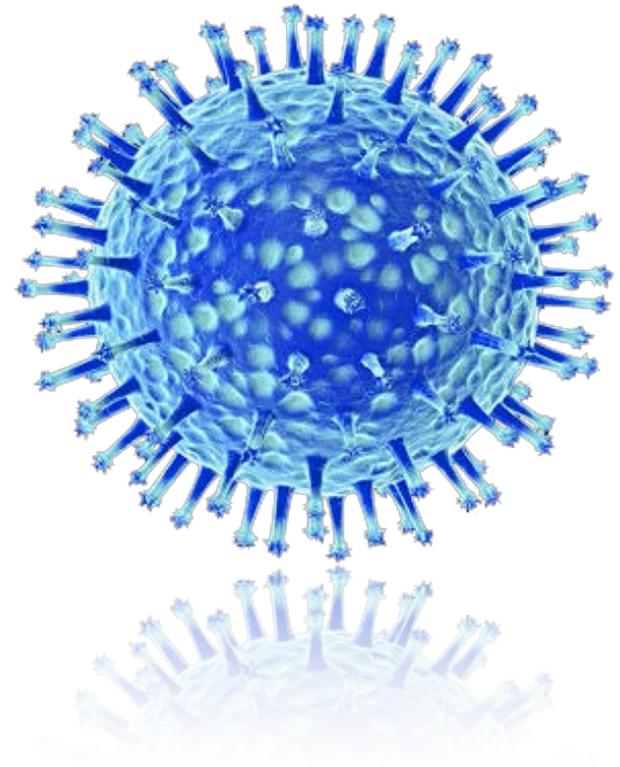
# outline

- *... understanding cross-species infections*
  - questions virologists ask
  - approaches virologists use
- *... working with dangerous pathogens*
  - influenza ... but ...
  - it's not all about influenza
- *... engaging constructively and being transparent*
  - articulating the benefits
  - mitigating the risks



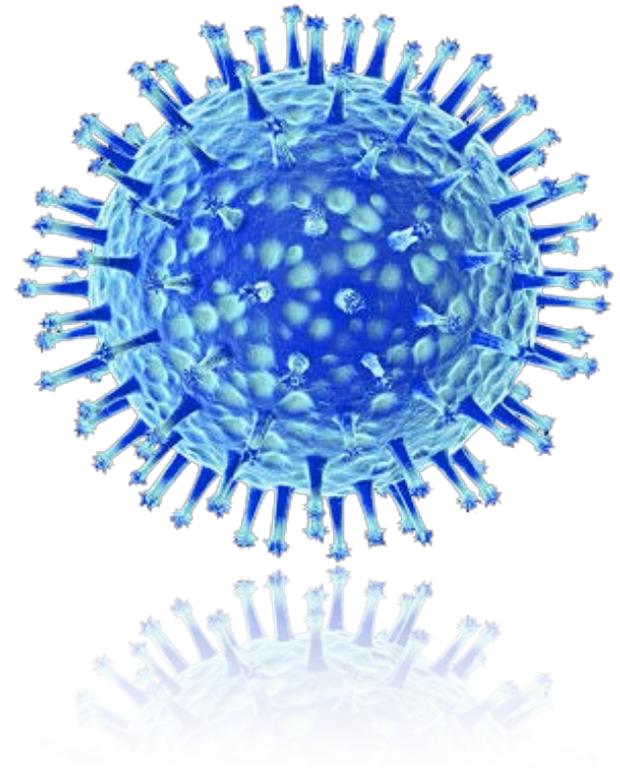
# questions virologists ask

- *why* does the virus infect and kill mammals?
- *do* antiviral drugs work and *how* does the virus become resistant?
- *do* current or developmental vaccines provide protection and *can* the virus escape?
- *how* does the virus spread within animals and other humans?
- *how* does the virus spread from animals to humans and from humans to humans?
- *could* the virus cause a pandemic?
- *what* is the likelihood of (re)emergence or, worse, *de novo* synthesis of a virus for malintent?



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definitions are key



# friend

*(noun)*

one of the  
many strangers  
on Facebook.

# approaches virologists use

two basic strategies: loss and gain of function



*many ways to destroy a phone but only a few ways to build one*

# reverse genetics

generating viruses using synthetic biology

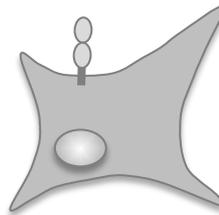
cDNA copy of genome



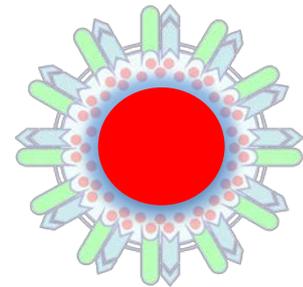
RNA



(+)



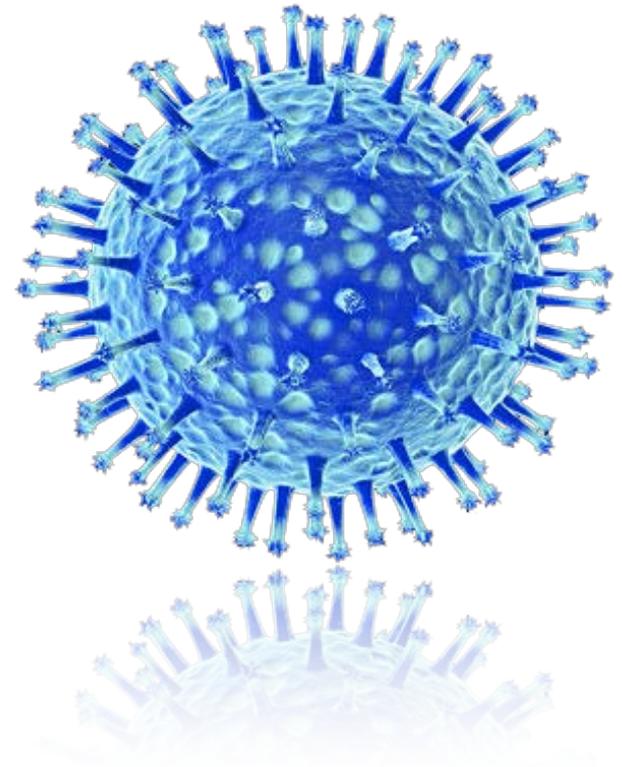
introduce into cells



recombinant  
virus

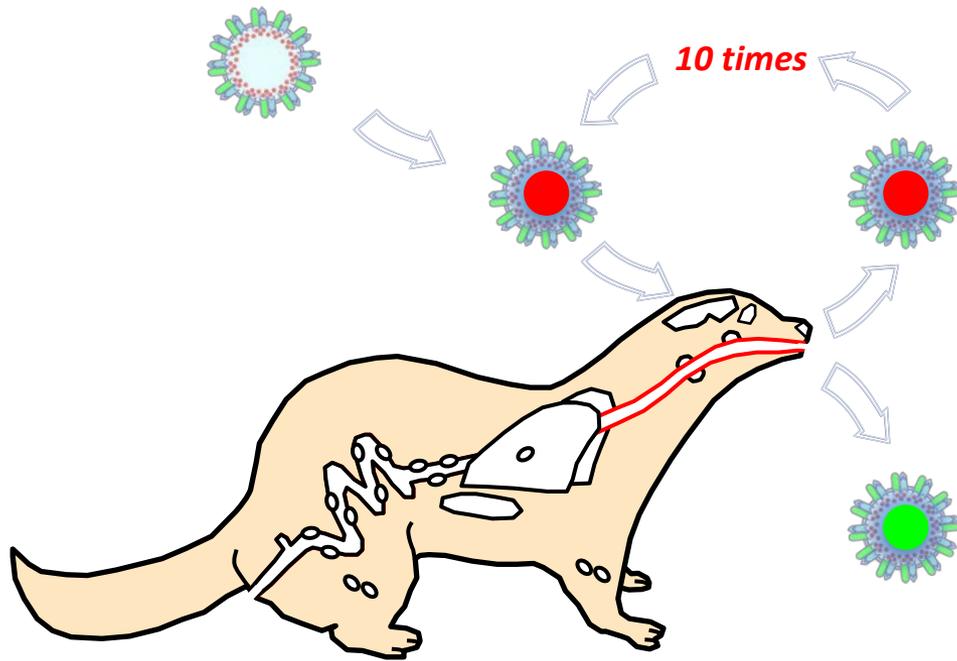
# working with dangerous pathogens

the strange case of the tail wagging the dog

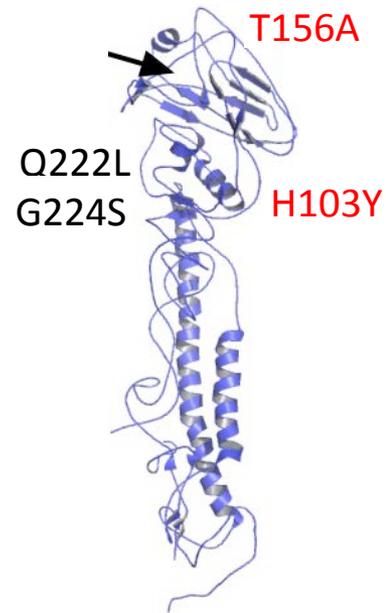


# reverse and forward genetics: virus evolution/adaptation

Indonesian H5N1 strain: Ron Fouchier (2012)



infection in the respiratory tract

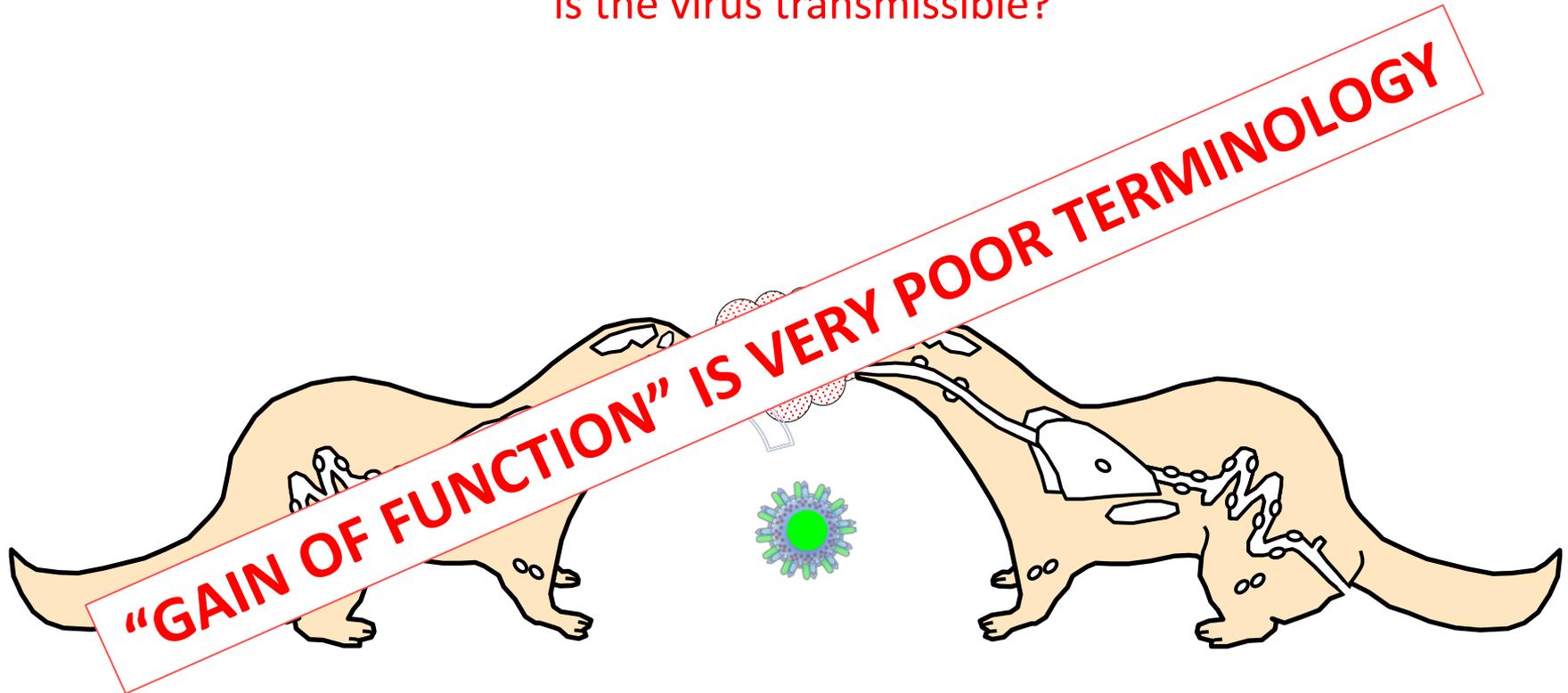


mutations in 7 segments, 2 new changes (red) in HA

*is the virus transmissible?*

# reverse and forward genetics: virus evolution/adaptation

is the virus transmissible?

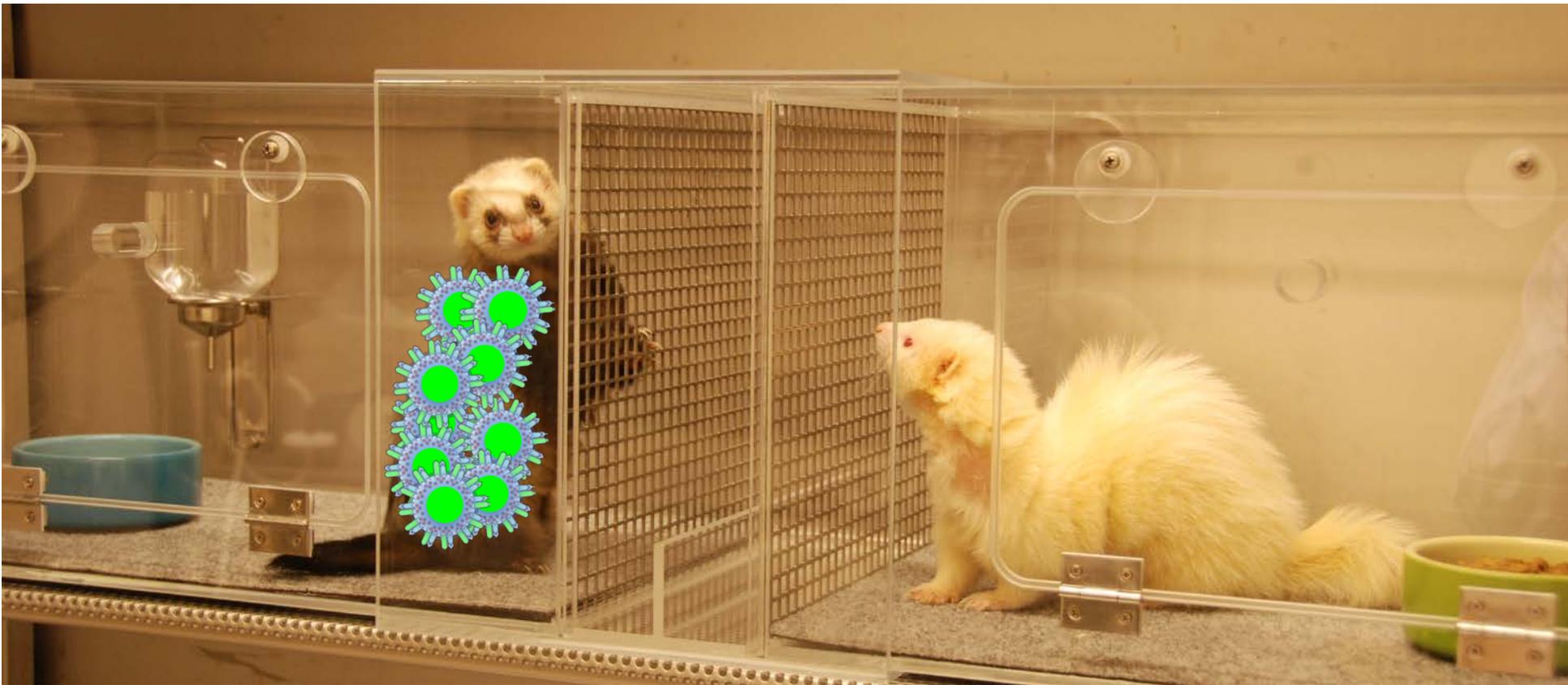


infection in the respiratory tract

*the virus transmissible: THIS IS A "GAIN OF FUNCTION" EXPERIMENT*

these studies must have a controlled *in vivo* dimension

prove mechanistically what is needed to make an avian influenza transmit



*the animals did not die from the infection*

# uncontrolled transmission “experiments”

what is needed to make an avian influenza transmit



*does not provide mechanistic data*

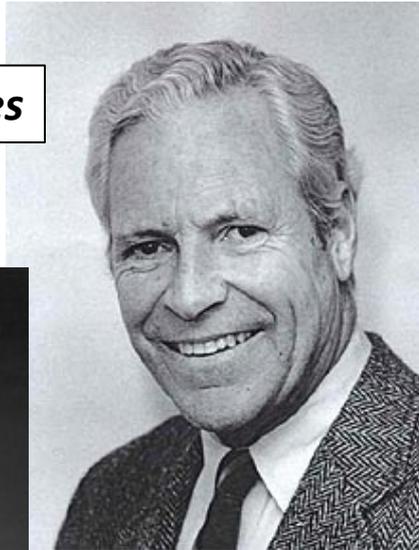
it's not all about influenza



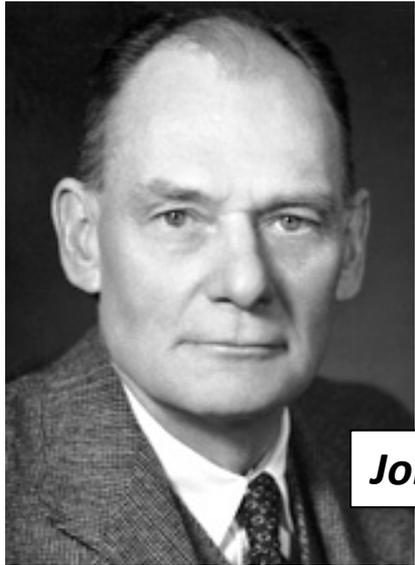
# working with dangerous pathogens

8 million people were dying of measles per annum

***Thomas Peebles***



***John Enders***



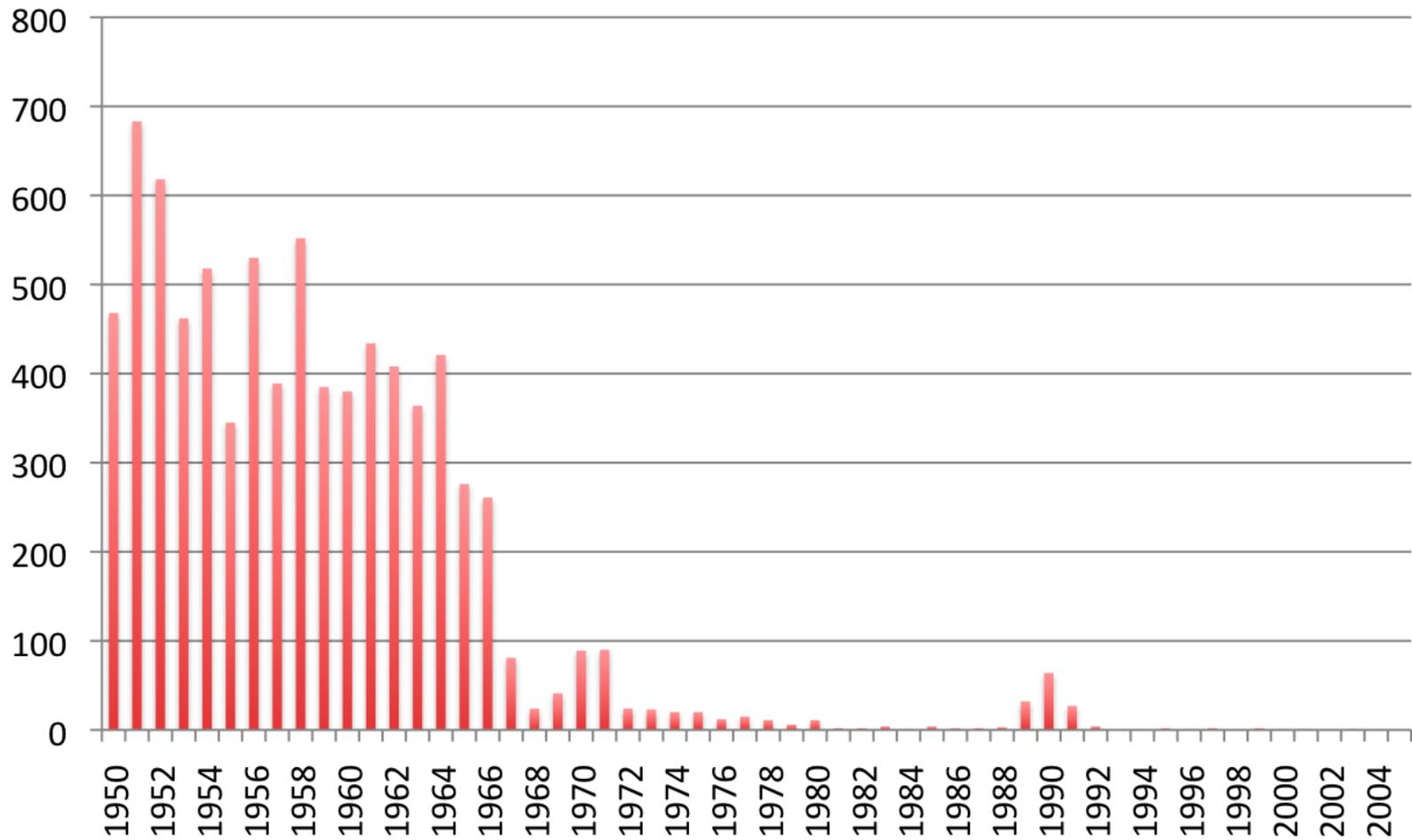
***measles***



*so they decided to try and isolate and culture it*

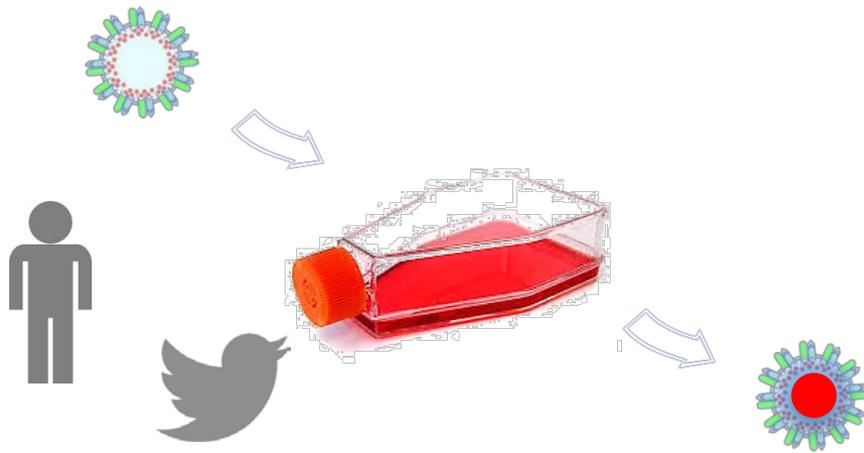
# how virologists study dangerous pathogens

## measles deaths in the US



# evolution and adaption of a virus to non-human cells

a common approach in virology

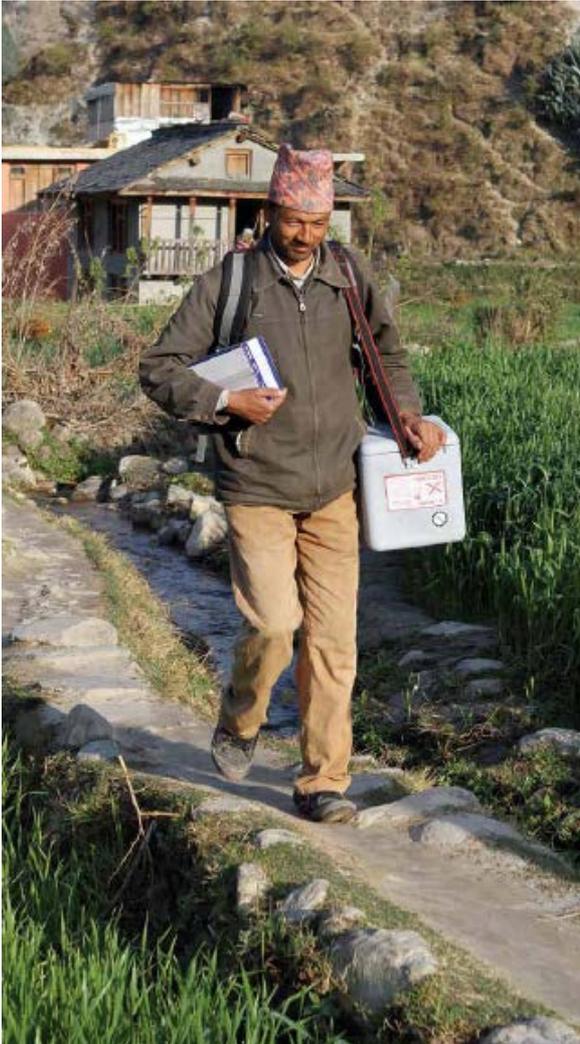


*infects immune, epithelial and neural cells (tri-tropic)*

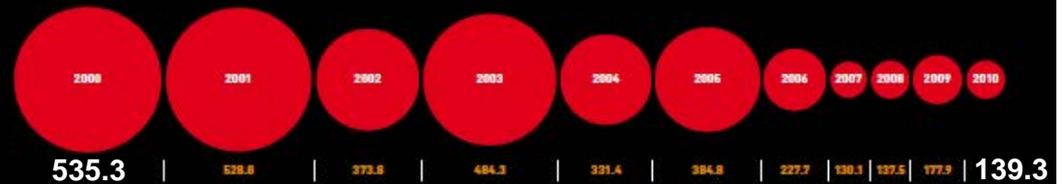
*infects every human cell type due to a major alteration of receptor usage (pantropic)*

*tropism was expanded: THIS IS A "GAIN OF FUNCTION" EXPERIMENT*

# towards measles eradication



number of estimated measles deaths (in thousands) globally 2000-2010



# unforeseen risks

forward genetics + gain of function = vaccine

*rinderpest*



*measles*



*should vaccination be discontinued in a measles-free world when zoonosis occurs?*

# unforeseen benefits

reverse genetics + gain of function = oncolytic virotherapy

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Breaking News: Measles Vaccine Cures Woman Of Cancer

## Breaking News: Measles Vaccine Cures Woman Of Cancer

A radical new treatment wiped out a Minnesota woman's blood cancer  
By Markham Heid



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# CNN Health

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## Measles virus used to put woman's cancer into remission

By Jacque Wilson and William Hudson, CNN  
updated 3:21 PM EDT, Sun May 18, 2014

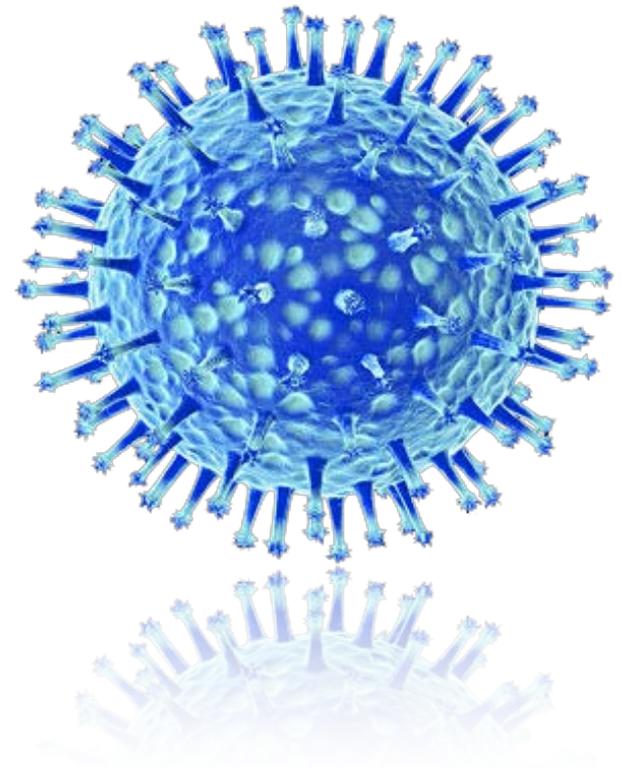


NEWS ROOM CANCER-FREE AFTER MEASLES TREATMENT LIVE CNN

*it is unlikely Enders would have predicted such a use for the vaccine*

# biosafety is bigger than influenza

the strange case of the tail wagging the dog



# what they tell us, their utility and what we should realize

specifically based on influenza virus “gain of function” studies

- transmissible virus is more stable at lower pH and higher temperatures than poultry adapted viruses
- avian viruses are transmissible from mammal to mammal
- experiments can be performed safely at BSL3+
- biopharmaceutical industry is taking notice
- public health policy makers are being informed
- the end of the world has not arrived
- we need to continue to think globally

*mechanism*

*transmission*

*biosafety*

*vaccinology*

*surveillance*

*apocalyptic*

*international*

# virologists are responsible scientists

we understand and mitigate risk for ourselves, our staff and our communities



*"With great power comes  
great responsibility"  
~Voltaire*

good communication and transparency is critical



# Scientists for Science

Scientists for Science are confident that biomedical *research on potentially dangerous pathogens can be performed safely and is essential* for a comprehensive understanding of microbial disease pathogenesis, prevention and treatment.

The *results of such research are often unanticipated* and accrue over time; therefore, risk-benefit analyses are difficult to assess accurately.

*...only by engaging in open constructive debate can we learn from one another's experience.* Most importantly, we are united as experts committed to ensuring public health is not compromised and the reputation of science in general, and microbiology in particular, is defended.

*“gain of function” studies are only one element of this wider debate*

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