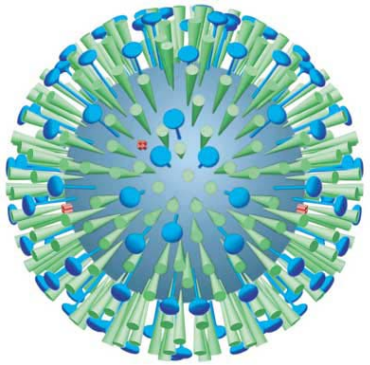
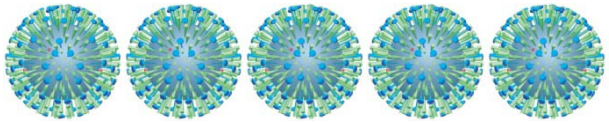


# Influenza: the scourge of the phantom menace




Narrator: Kin-Chow Chang

# Recent swine flu news coverage

**Doctors shocked by spread of swine flu – and its severity**

By Jeremy Laurance, Health Editor, Independent
Saturday, 11 December 2010

**Swine flu is back: Virus has killed 10 in the last six weeks and its spreading to Europe**

By Rob Cooper Daily Mail
Last updated at 1:18 PM on 11th December 2010

……There were 494 deaths from swine flu in Britain between the initial outbreak and April this year.

**Mother-of-two, 32, dies from swine flu two weeks before Christmas as the disease kills TEN**

By Daily Mail Reporter
Last updated at 2:58 PM on 15th December 2010

**Fighting for her life: Girl, 9, is latest victim of swine flu epidemic sweeping Britain**

By Daily Mail Reporter
Last updated at 12:26 PM on 17th December 2010


**Thursday 16 December 2010**

**Swine flu: half of worst afflicted were previously in good health**

By Laura Donnelly, Health Correspondent, The Telegraph 8:43PM GMT 18 Dec 2010

….Last night a pregnant woman was fighting for her life, after being put in a medical coma to save her and her unborn child. Fallon Devaney, 25, from Derbyshire, a mother of four who is five months pregnant, was in intensive care in **Nottingham Queen's Medical Centre**, after being admitted to hospital struggling to breathe. Recovered.

**Swine flu: three more deaths as 200 fight for life**

Doctors have warned they are seeing the worst flu outbreak in 10 years in some areas as fears grow that three more people may have died after contracting swine flu.

The Telegraph 10:31PM GMT 20 Dec 2010

**Sixty more deaths, but flu 'may be starting to plateau'**

Sixty-two people died with flu in the UK the last week, bringing the total to 112 since October 2010.

BBC News 13 January 2011 Last updated at 14:58

- **Pandemic 2009 H1N1 (swine flu), unlike conventional seasonal flu, appears to affect a disproportionate number of healthy and younger people (<65 years old), with no underlying conditions.**

**Parents release picture of their daughter, 3, just hours before swine flu killed her in bid to get All children to have vaccine** By Daily Mail Reporter Last updated at 11:41 AM on 12th January 2011

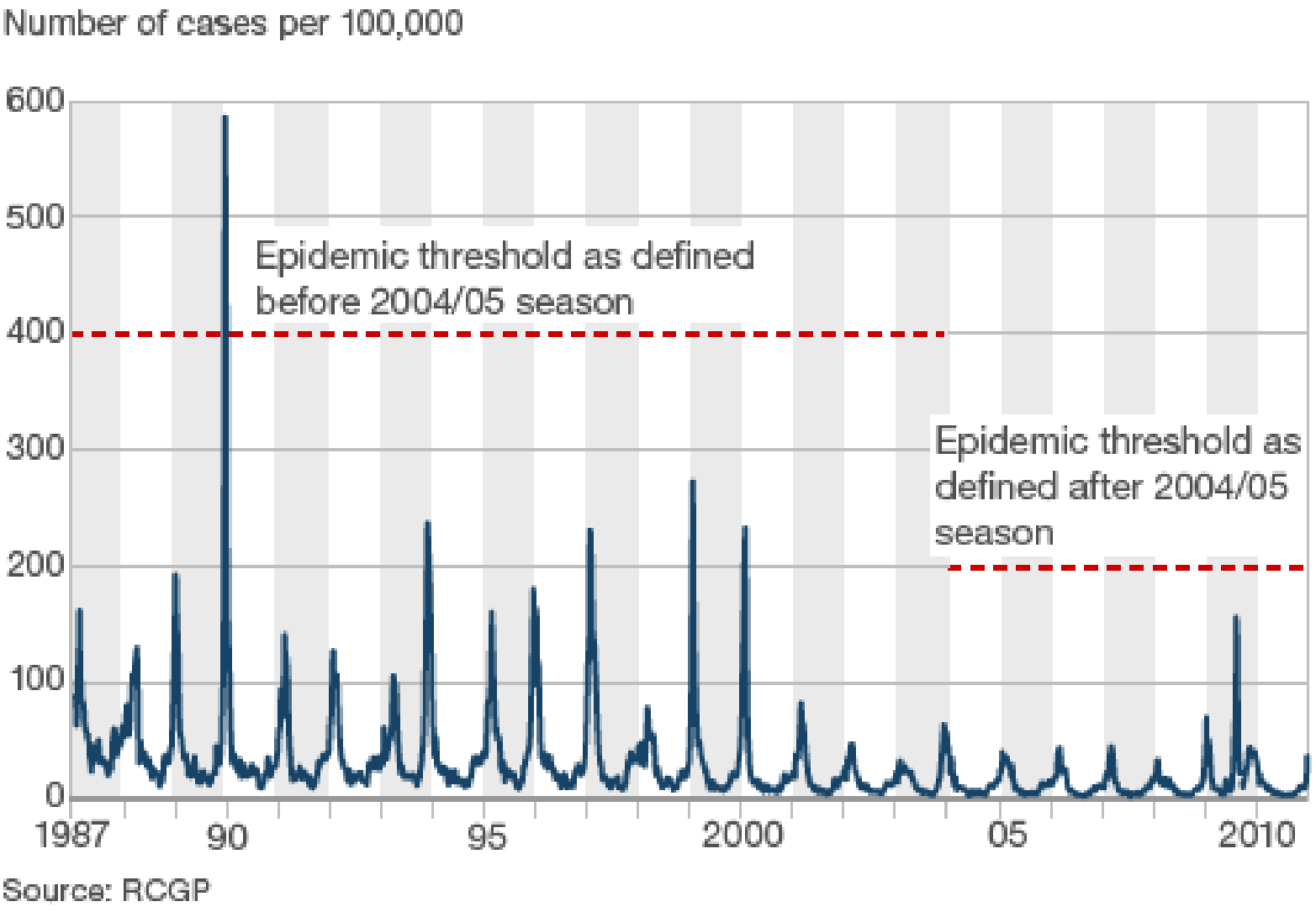
Lana fell ill with what appeared to be a cold on Christmas Eve but rapidly worsened and died just two days later.

**Super-fit dance teacher, 21, is killed by swine flu in just five days** By Andrew Levy Daily Mail Last updated at 8:42 AM on 1st Feb 11

…….within five days of being taken ill she died in hospital after suffering massive damage to her lungs.

**Why**

# Flu-like illness in England and Wales since 1987



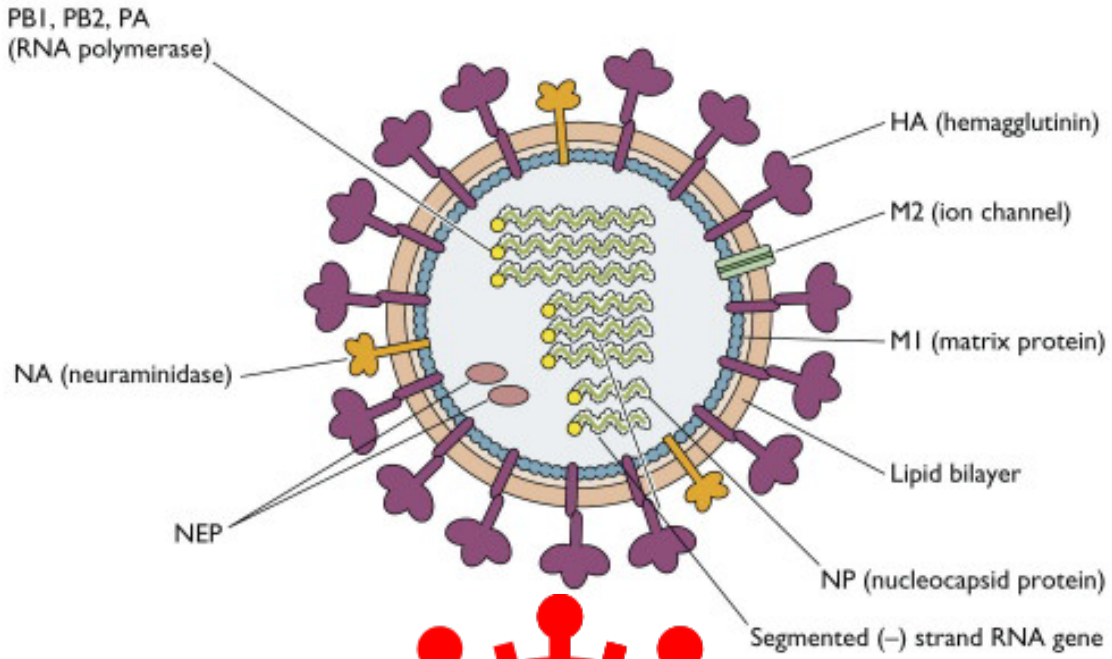

Source: RCGP

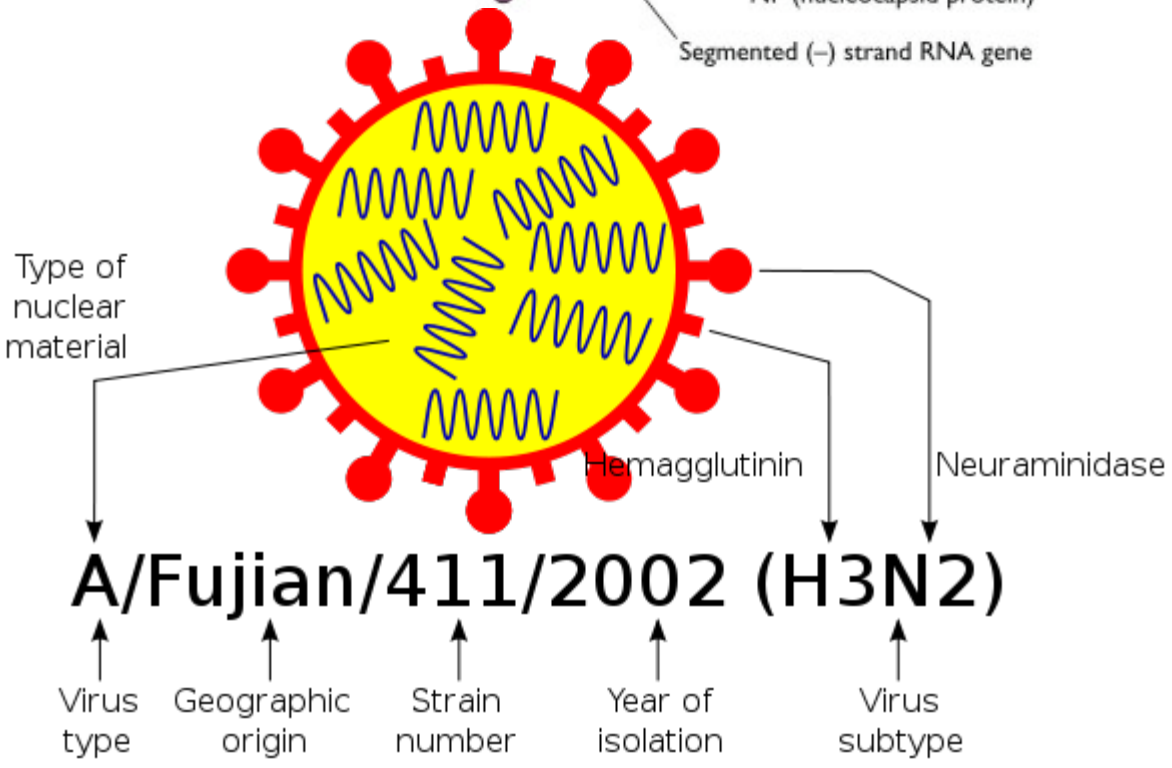
**Once every couple of decades, a new strain of influenza appears that is far more pathogenic, allowing it to spread rapidly. This happened at the end of World War I (Spanish flu), and the resultant pandemic* killed over 20 million people, more than twice the number of people that were killed in the war.**

| Human pandemics | Date | Deaths | Case fatality rate | Subtype involved |
|---|---|---|---|---|
| Asiatic (Russian) Flu | 1889–1890 | 1 million | 0.15% | possibly H3N8 |
| 1918 flu pandemic (Spanish flu) | 1918–1920 | 20 to 100 million | 2% | H1N1 |
| Asian Flu | 1957–1958 | 1 to 1.5 million | 0.13% | H2N2 |
| Hong Kong Flu | 1968–1969 | 0.75 to 1 million | <0.1% | H3N2 |
| 2009 flu pandemic | 2009–2010 (11.6.09 – 10.8.10, 14m) | 18,000 | 0.03% | H1N1 |

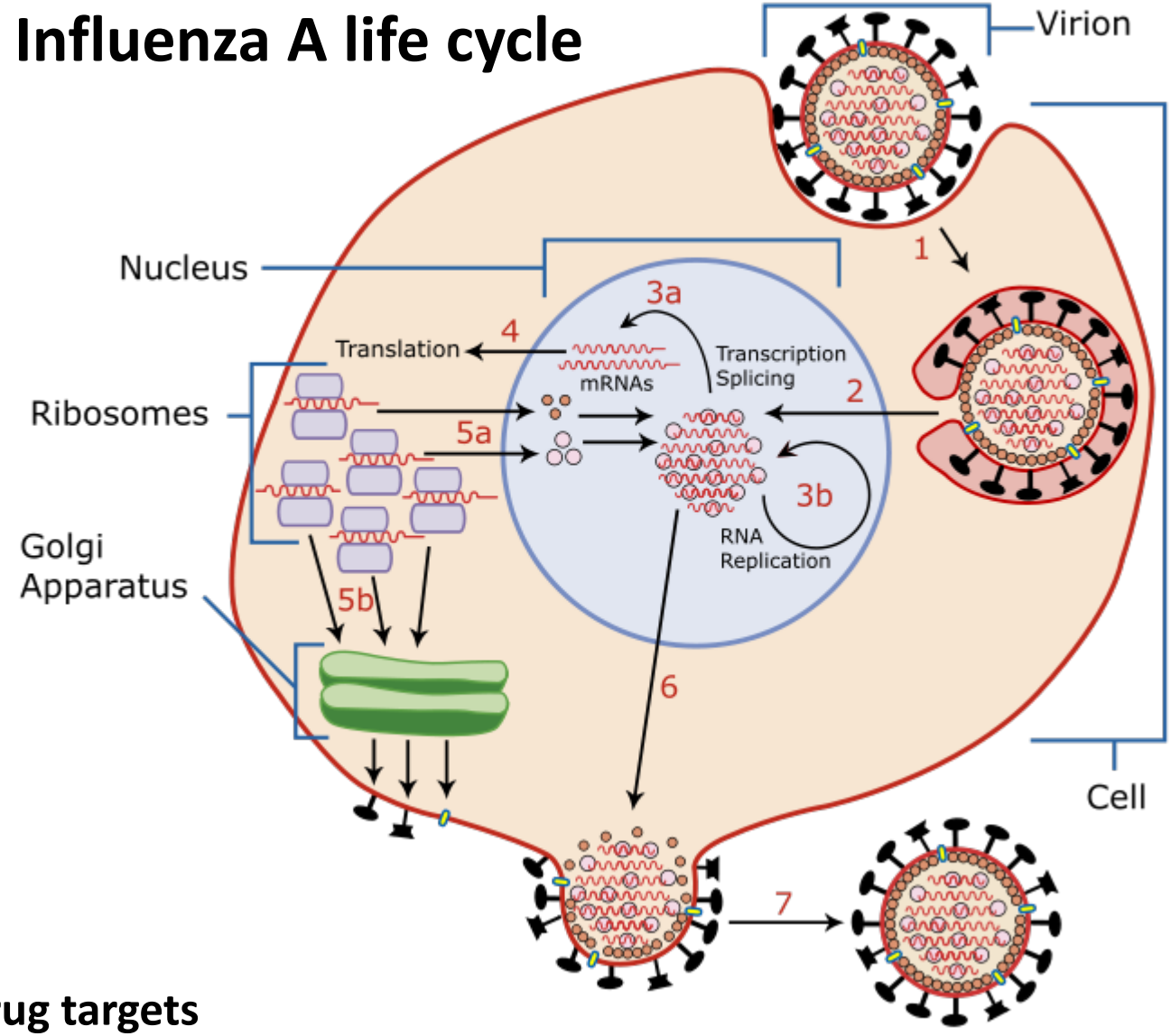
* Pandemic = global epidemic

# Influenza: negative stranded RNA virus



# Influenza A life cycle

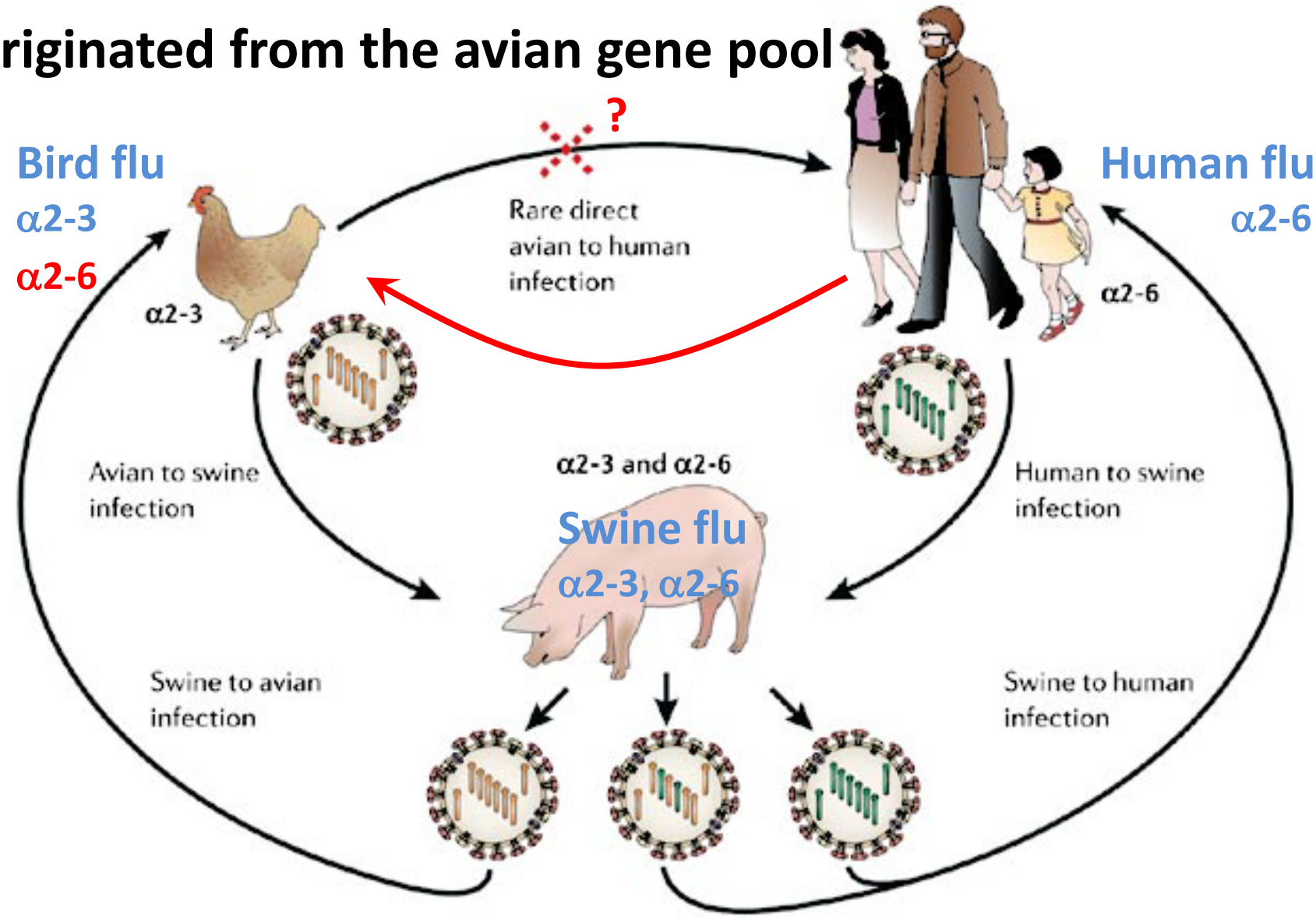


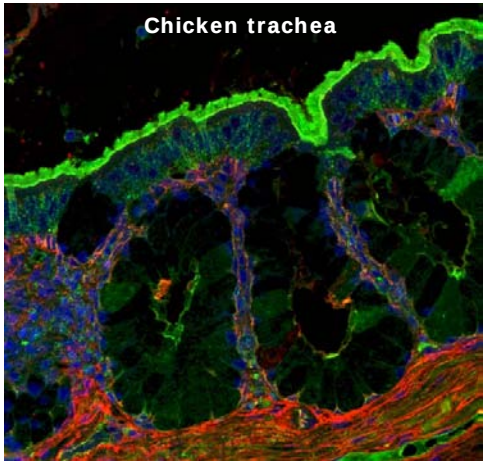

**Drug targets**

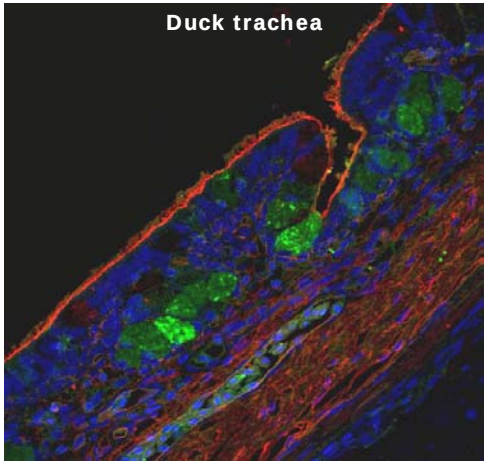
The M2 ion channel is blocked by amantadine, preventing infection.

Drugs that inhibit neuraminidase, such as oseltamivir (Tamiflu), prevent the release of new infectious viruses.

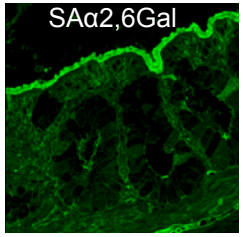
# All influenza A viruses of mammalian sources had originated from the avian gene pool

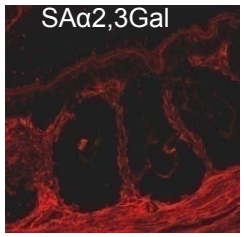


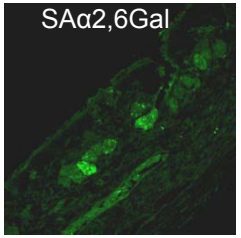


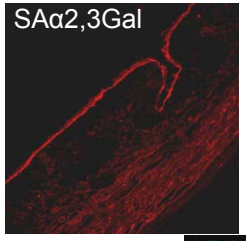




## Avian and human receptors for influenza virus are both differentially present in chickens and ducks

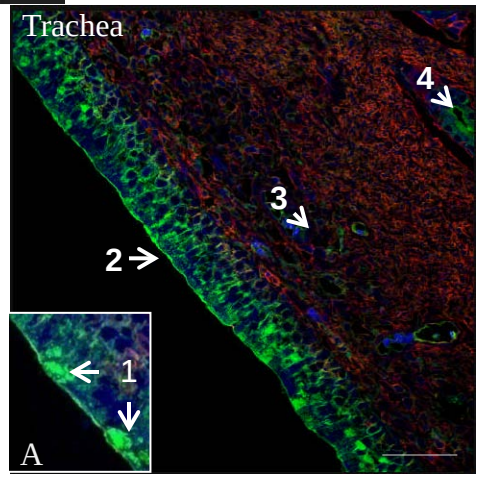


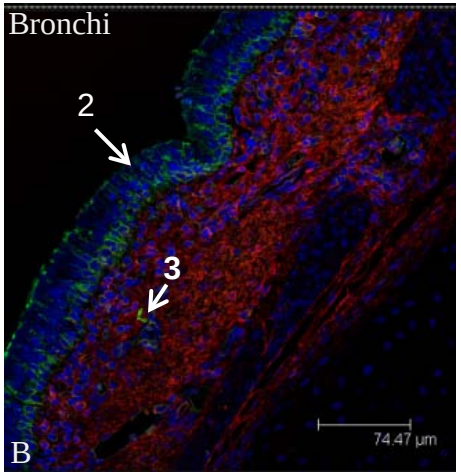



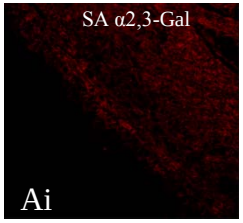



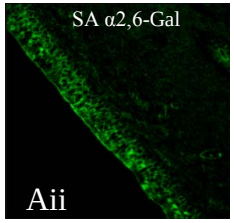



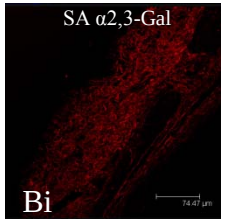

## Avian and human receptors for influenza virus are both present in the pig

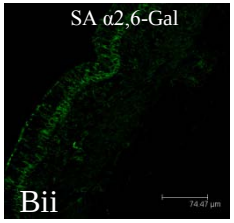


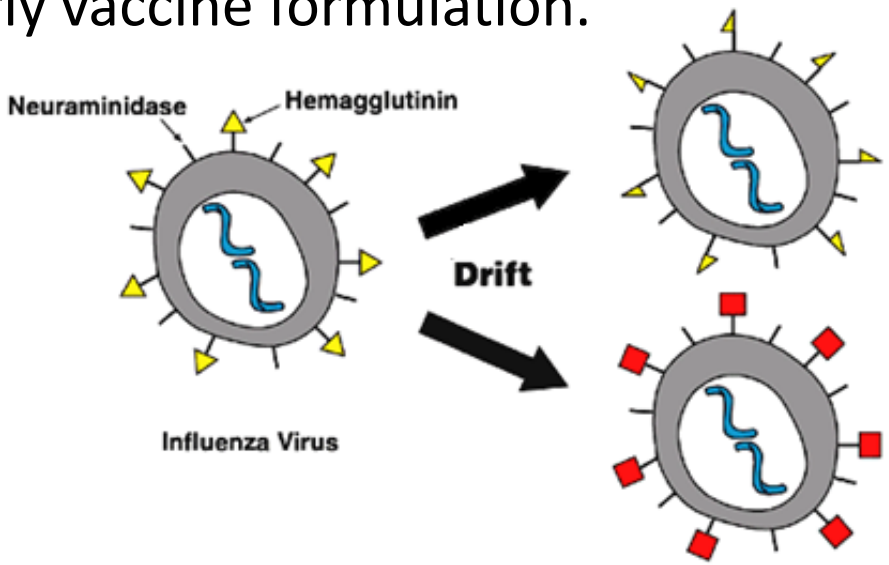



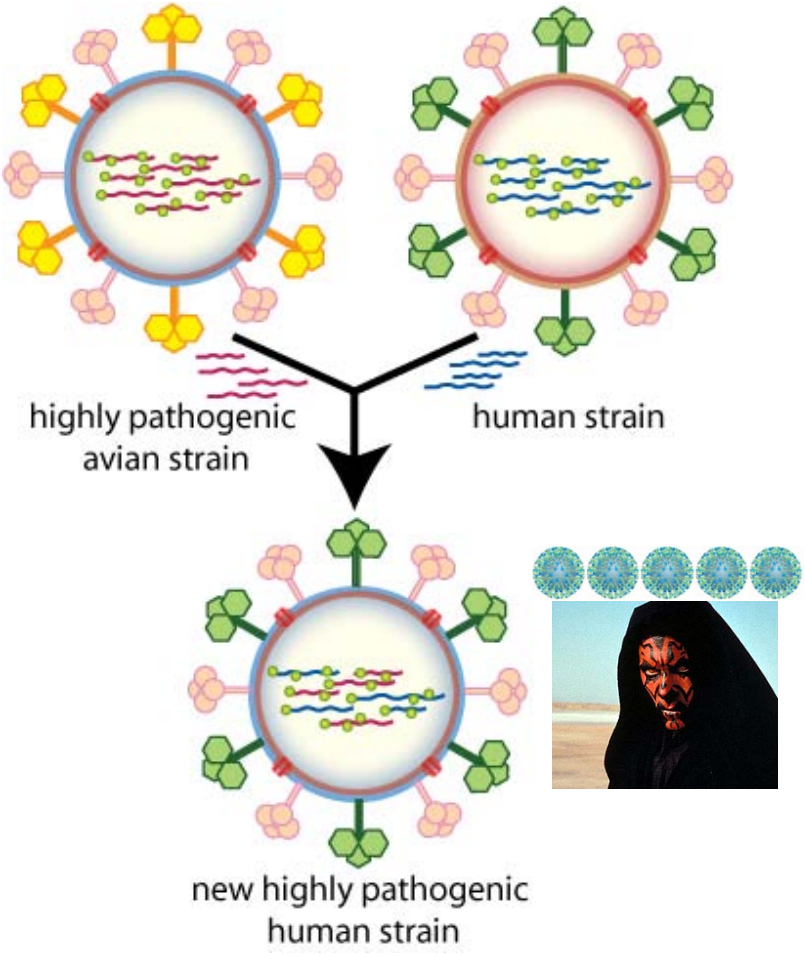
# Dangerous features of influenza virus

- Negative RNA virus
  - Wide range of susceptible avian and **mammalian** hosts.
  - Because of the absence of RNA proof reading enzymes, the RNA-dependent RNA polymerase that copies the viral genome makes an error roughly every 10 thousand nucleotides, which is the approximate length of the influenza vRNA. This causes **antigenic drift**, hence need for yearly vaccine formulation.




# Dangerous features of influenza virus

- Segmented genome (8 separate segments of vRNA)
  - Allows mixing or reassortment of vRNAs if more than one type of influenza virus infects a single cell. Leads to sudden changes in viral genetics and to susceptibility in hosts: **antigenic shift**.
  - Pandemic H1N1 2009 (swine flu 2009) virus is a previous triple reassortment of bird, pig and human flu viruses further combined with a Eurasian pig flu virus.

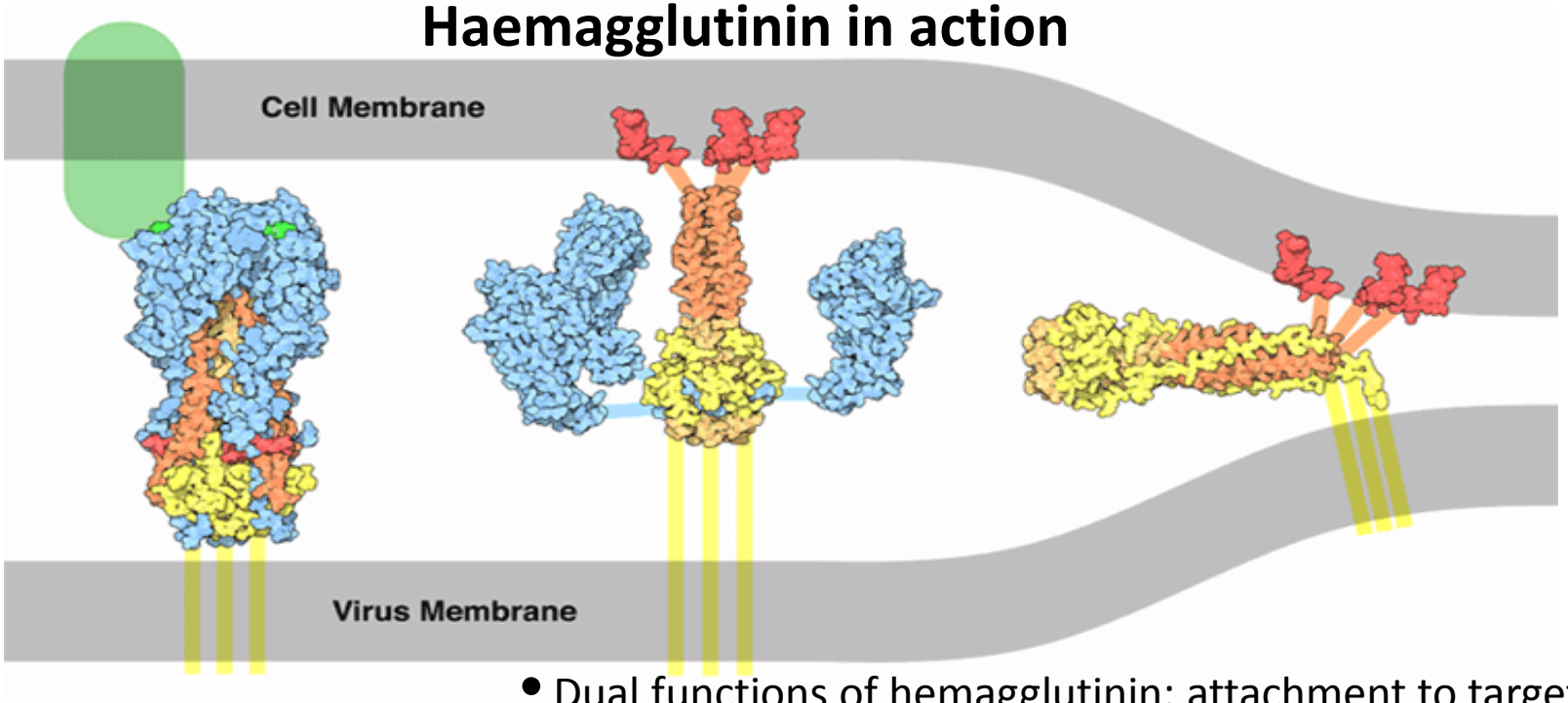



**WHO avian H5N1 mortality rate in humans: 59% (303 deaths in 510 confirmed cases, Dec 2010)**

# Specific virulence feature: haemagglutinin activation

Cleavage of the HA precursor molecule HA0 (to HA1 and HA2) is required to activate virus infectivity (virus cell-entry [endocytosis], and fusion of endosomal and virus membranes). The HAs of mammalian and non-pathogenic avian viruses are cleaved extracellularly, which limits their spread in hosts to tissues where the appropriate proteases are present. On the other hand, the HAs of pathogenic viruses are cleaved intracellularly by ubiquitously occurring proteases and therefore can readily cause widespread systemic infections.

## Haemagglutinin in action

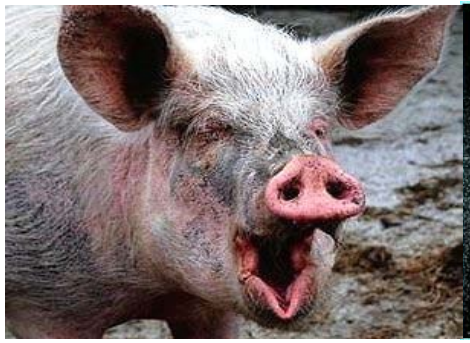



- Dual functions of hemagglutinin: attachment to target cells, and membranes fusion (cytoplasmic release).

http://www.pdb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb76_2.html

# Severity of influenza viruses

- Pathogenicity varies between subtypes from low morbidity to 100% mortality.
- Death, in particular from HPAI H5N1 infection, is often associated with a hyperacute pro-inflammatory response (cytokine storm) which is self-destructive and self-perpetuating.
  - Incorrect claim made that suggests high virus replication is the cause of cytokine storm. Antiviral Res. **78** (1): 91–102.




# How to control influenza infections?

- **Target the virus**
  - Anti-virus treatment (amantadine, zanamivir, oseltamivir).
    - Limited efficacy; rapid virus resistance.


- **Target the host**
  - Subtype-specific vaccination.
    - Regular antigen update. Vaccine effective and safe.
      - Guillain-Barre syndrome  rare.
    - 6 months period from identification to distribution is too long in a pandemic. Universal vaccine in the future?
- **Prognosis** of a future highly pathogenic influenza pandemic is **poor**
  - Estimate of 30 to 300 million deaths.

# Is there a “New Hope”?


- **Restoration/maintenance of an appropriate host innate response to the virus. Prevention of cytokine storm.**
  - Broad applications: different subtypes and other viruses.

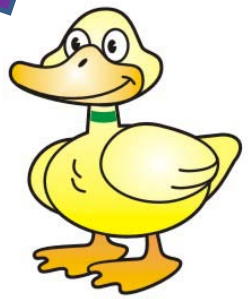
# Contrasting outcomes of highly pathogenic avian influenza infection in birds

**Rapidly fatal infection**

**24-48 h post-infection**

**No or little clinical signs**

?

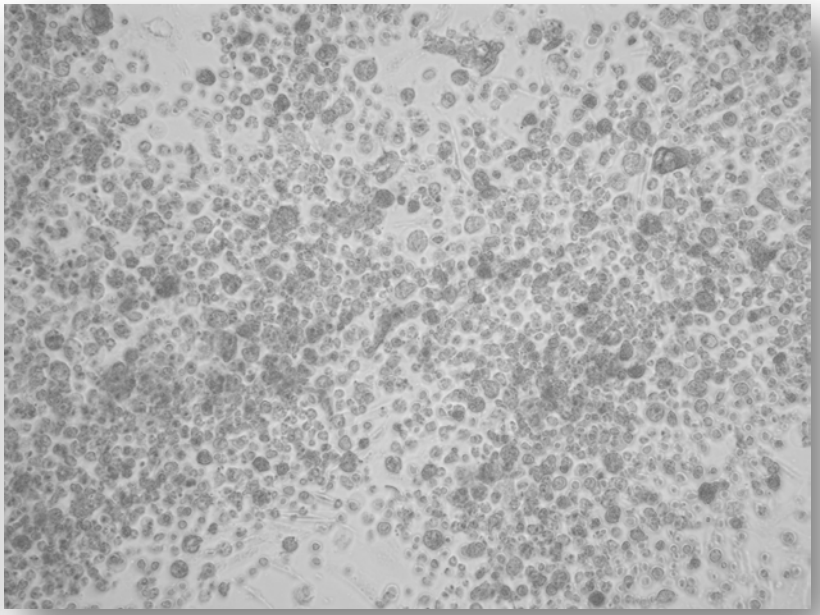


# Duck cells exhibited rapid cell death following influenza virus infection

**After 24 hours of infection with low pathogenic avian influenza virus**

**Chicken Lung cells**

**Duck Lung cells**

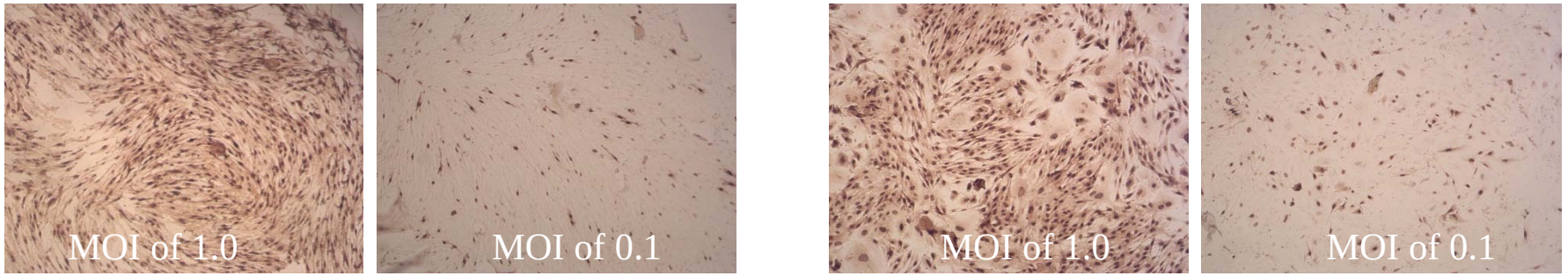


## Contrasting cellular response to infection

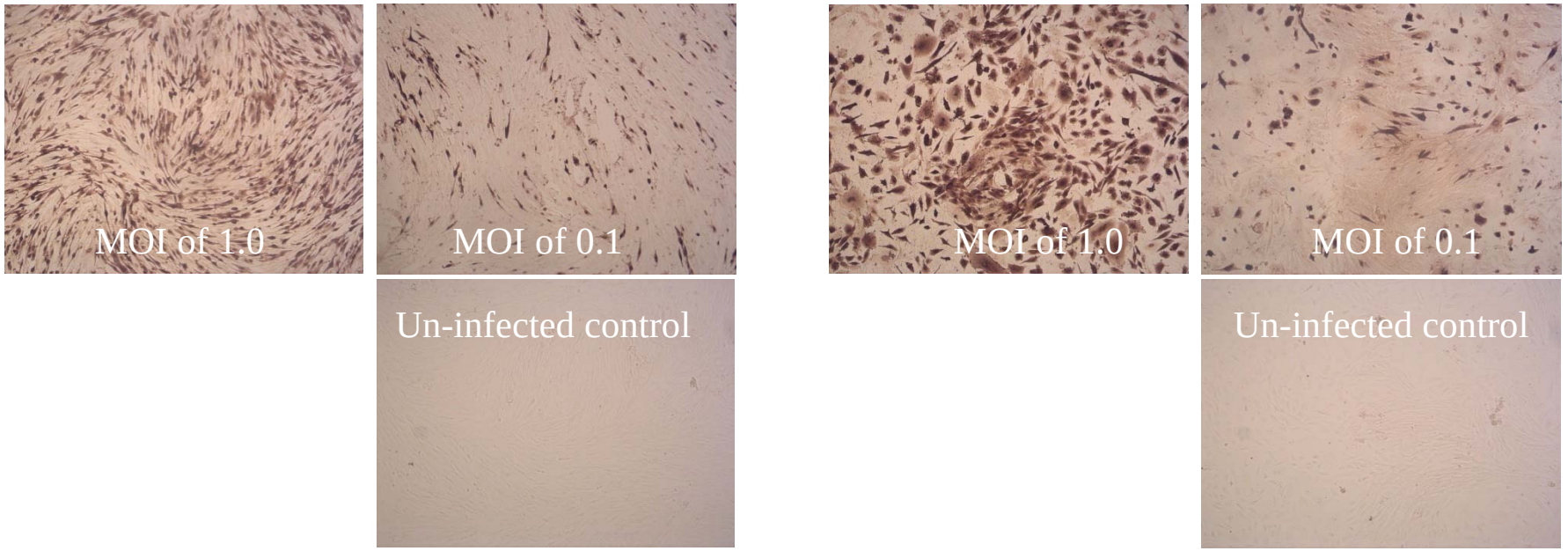
# Difference in cell death was not due to differences in level of infection

**Chicken Lung cells** | **Duck Lung cells**

Avian H2N3- 6hours Post-infection



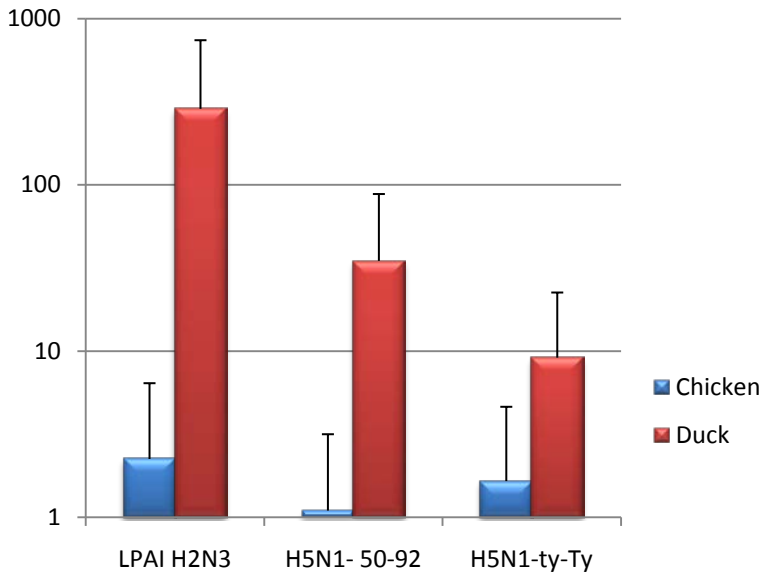

Classical Swine H1N1 - 6hours Post-infection



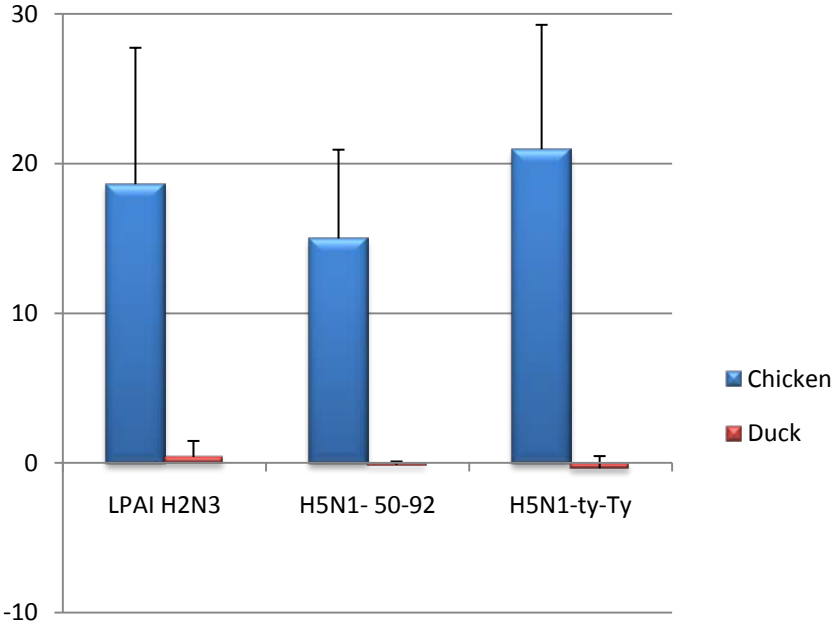
# Analysis of cytokine expression profiles

- Real time PCR analysis of the host mRNA post-virus infection
- Results normalized to 18S ribosomal RNA gene

## IFN- alpha



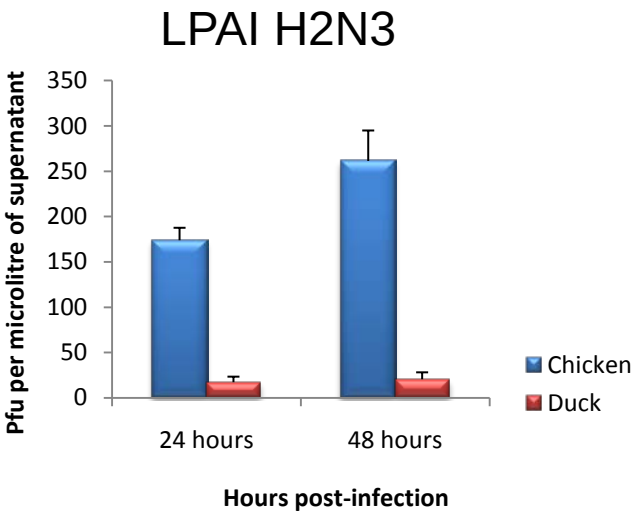

## TNF- alpha

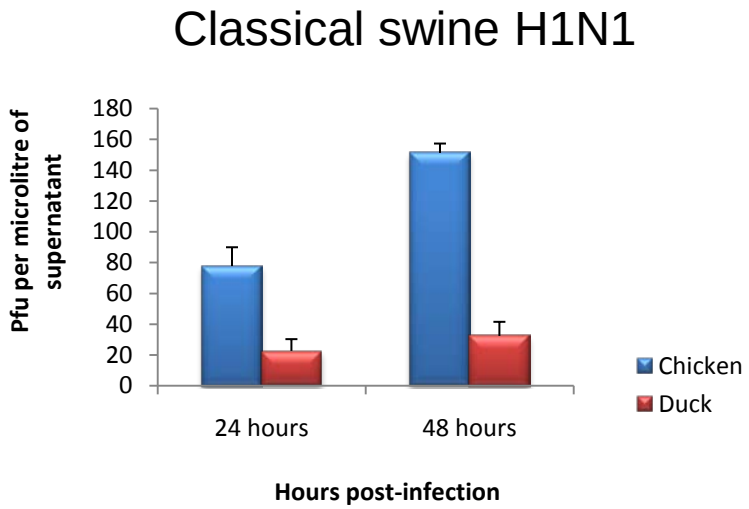


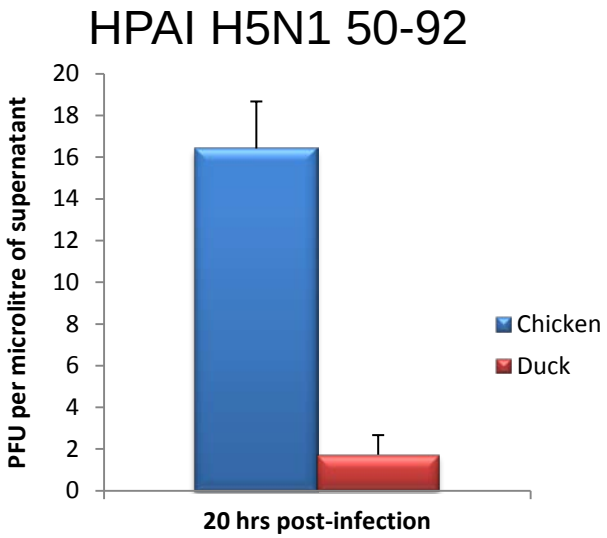

## Contrasting cytokine expression

- **A/turkey/England/50-92/91 (H5N1)** **A/turkey/Turkey/1/05 (H5N1)**

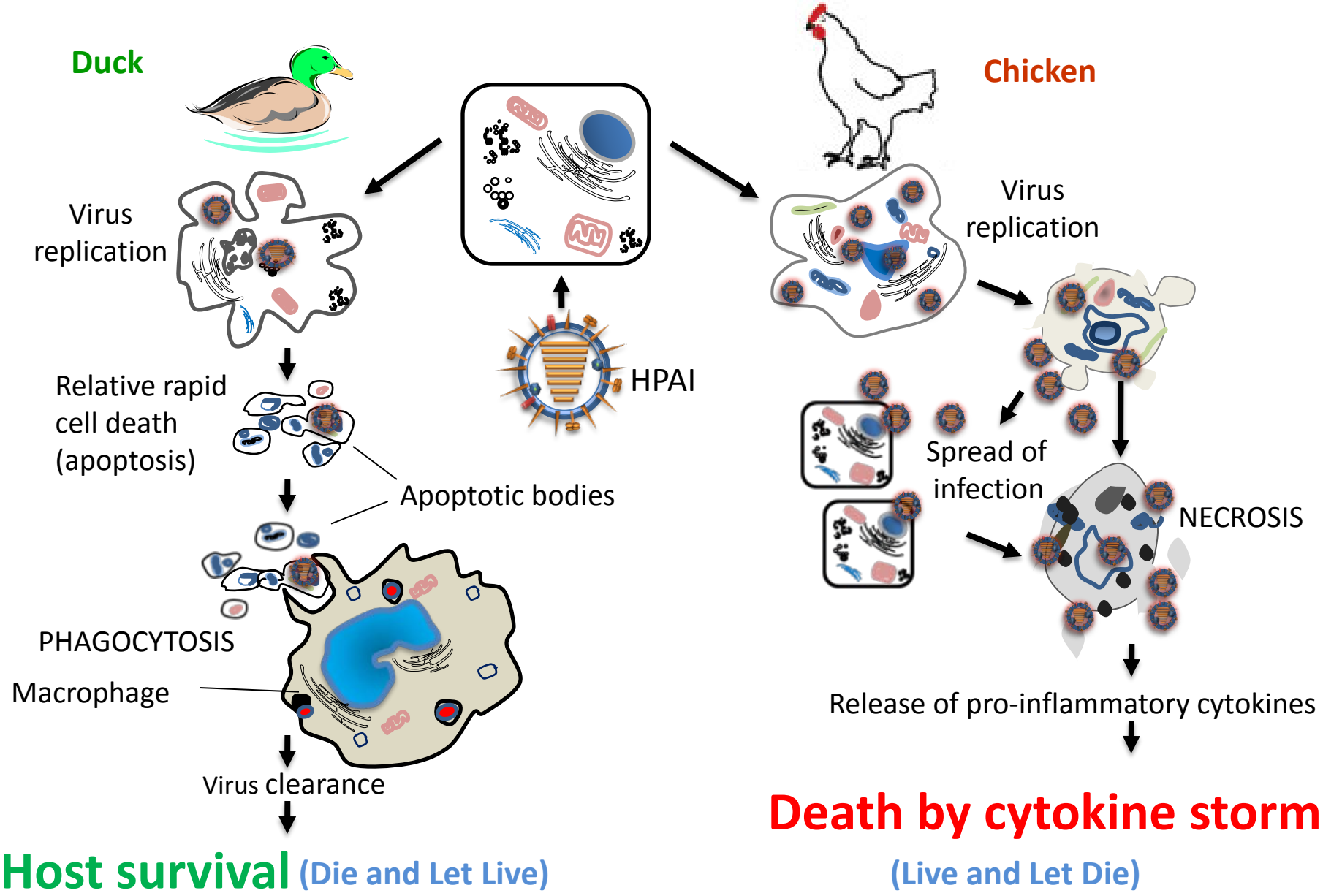
# Measurement of infective virus production by immuno-cytochemistry



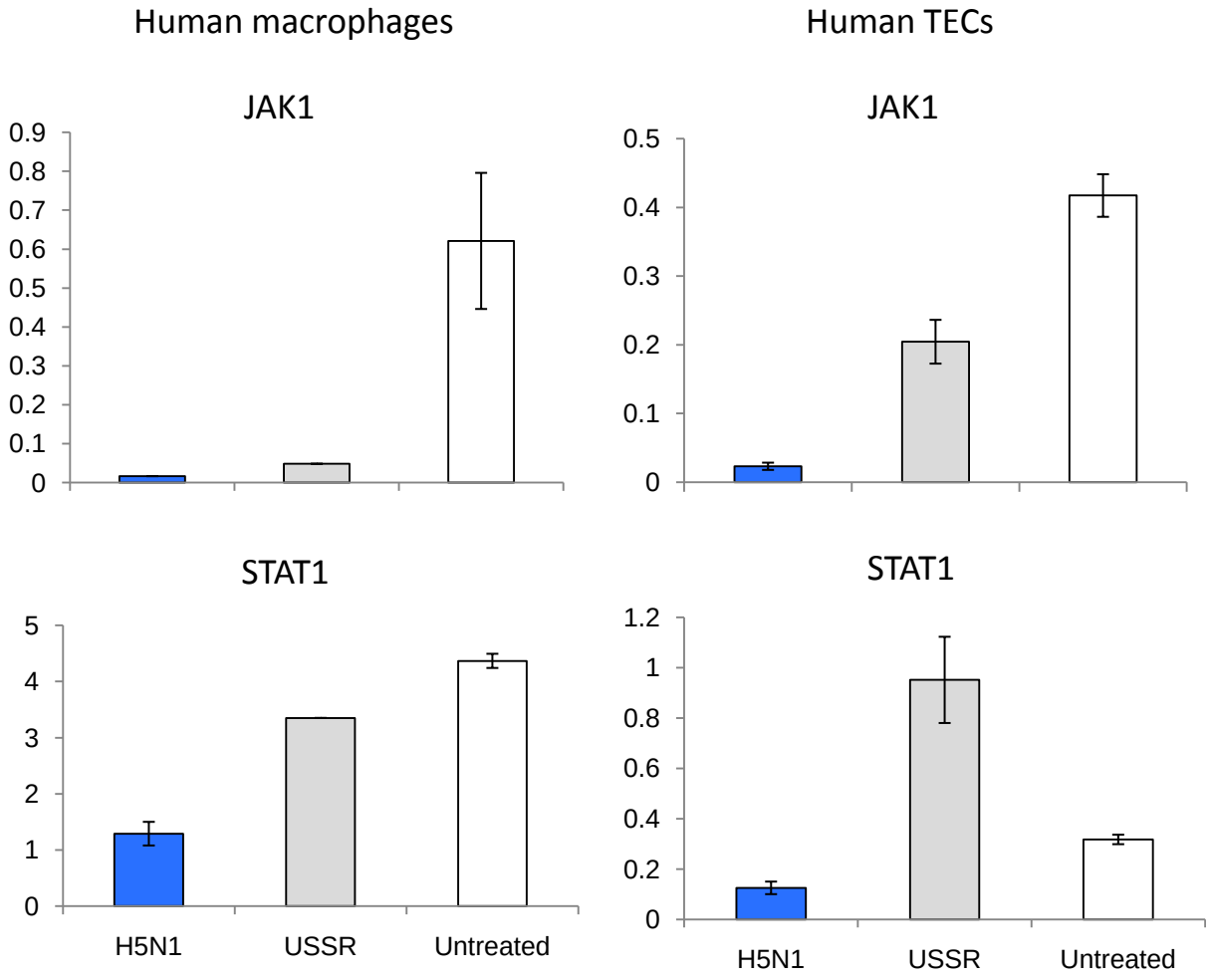



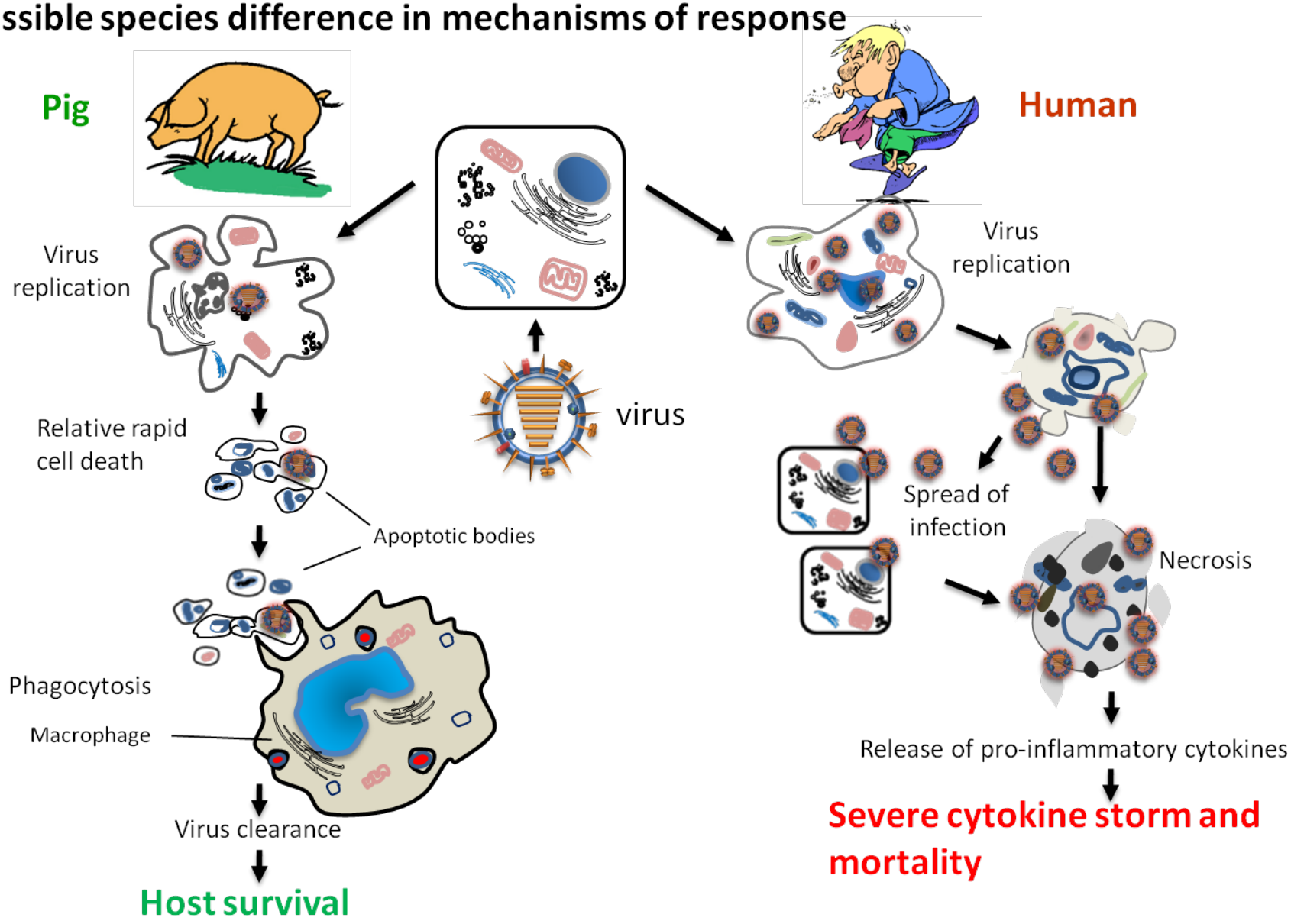
# Contrasting host response to avian influenza virus infection



# Down-regulation of JAK1 and STAT1 by avian H5N1 and USSR/77 virus in human macrophages and tracheal epithelial cells



# Contrasting host outcomes to highly pathogenic avian influenza virus infection: possible species difference in mechanisms of response



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**Dr. Marek Slomka**
**Dr. Sharon Brookes**
**Vivien Coward**