Characterization of the 1918 influenza virus

Collaborative effort among different research groups and institutions

- Armed Forces Institute of Pathology, Washington DC — *Jeffery K. Taubenberger*
- Mount Sinai School of Medicine, New York — *Adolfo García-Sastre*, *Peter Palese*, *Christopher F. Basler*
- CDC — *Terrence M. Tumpey*
- USDA, Athens, Georgia — *David E. Swayne*
- University of Washington, Seattle — *Michael G. Katze*
- Scripps Research Institute, La Jolla — *Ian A. Wilson*

NIH/NIAID support: P01 AI0581113

Virulence of influenza virus in humans

- **Interpandemic years: 20,000-36,000 deaths/year in the U.S.**

  Thompson et al., JAMA, 2003, 289:179-186

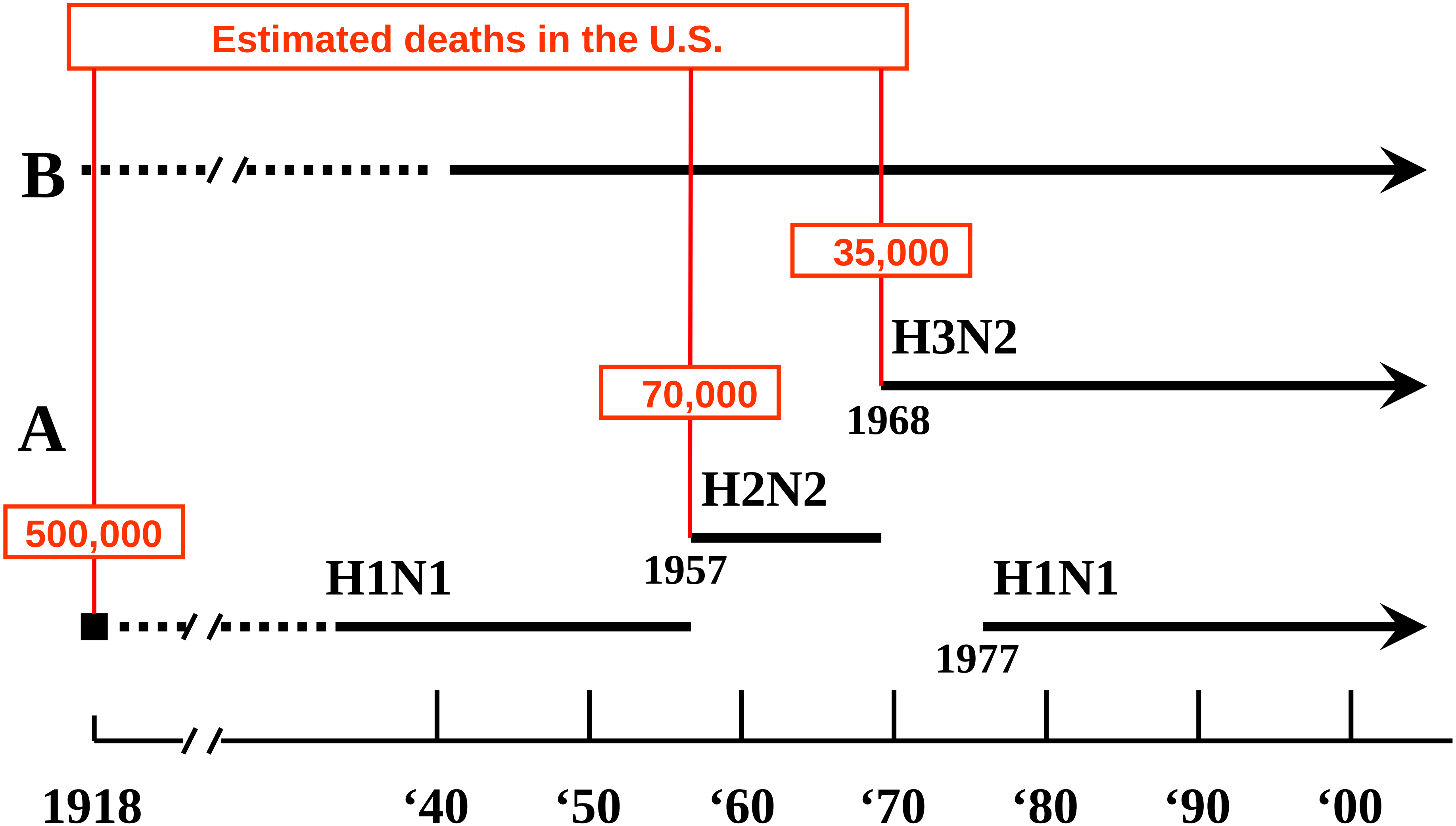
- **Pandemic years: Higher morbidity and mortality**

  Lack of pre-existing immunity

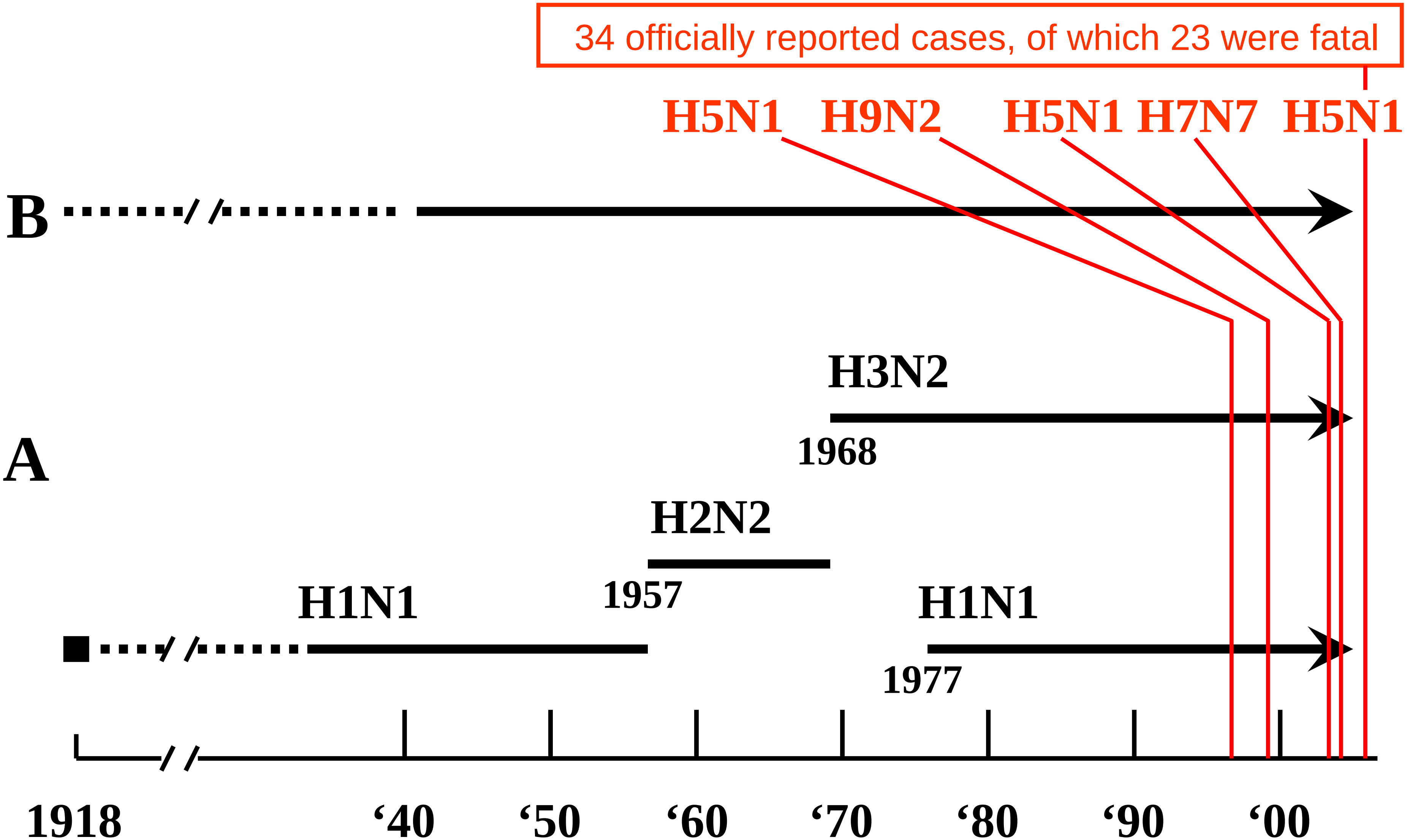
- **Some strains are more virulent than others**

- **Host factors, e.g. age, also play a role**

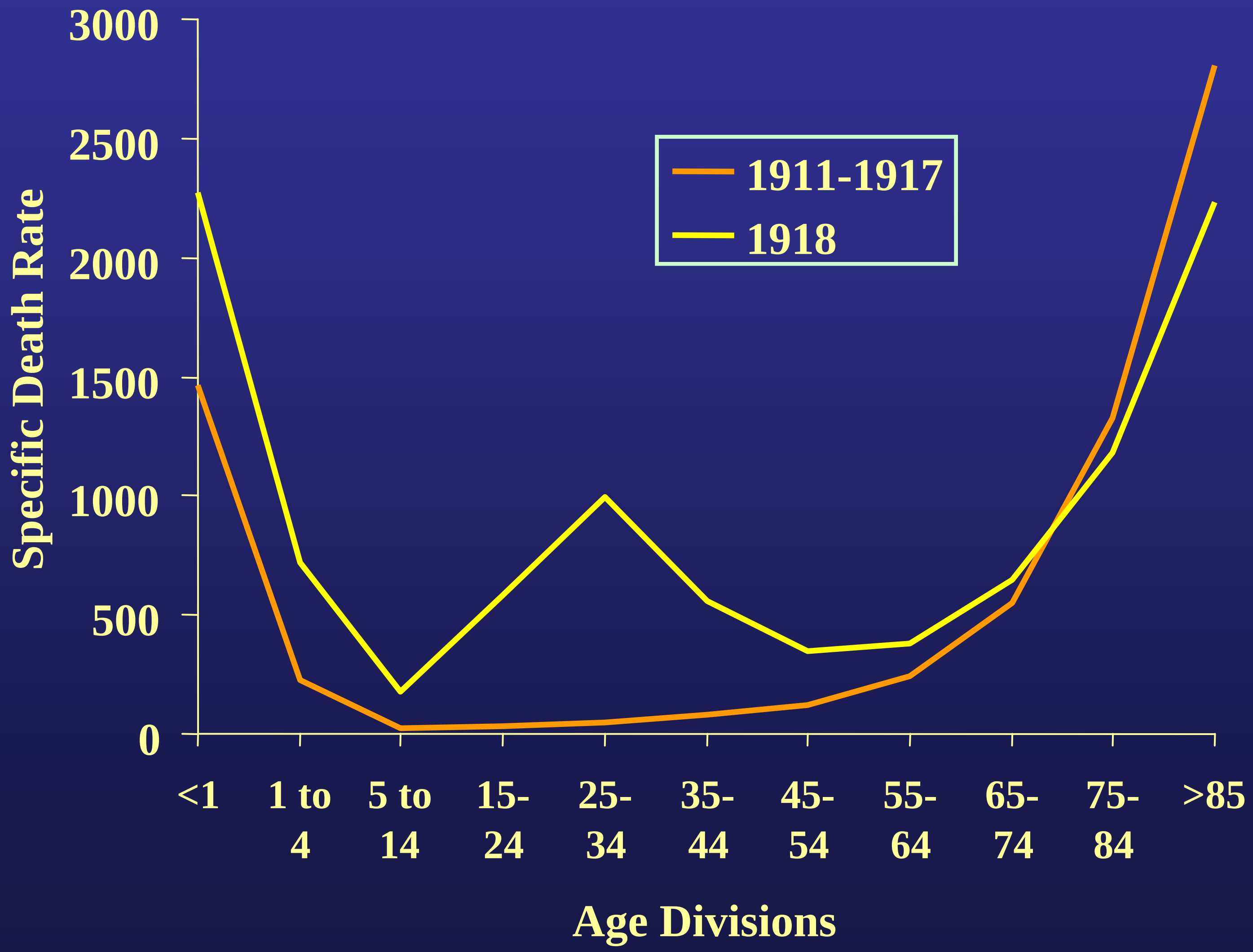
EPIDEMIOLOGY OF HUMAN INFLUENZA VIRUSES



EPIDEMIOLOGY OF HUMAN INFLUENZA VIRUSES



Influenza and Pneumonia Deaths by Age



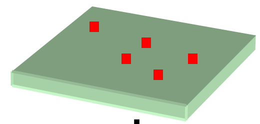
Why to study the 1918 virus?

- **The reasons for increased virulence of this virus are not evident from the sequence data**

- **Influenza viruses having 1918-like virulent properties might evolve again**

- **Identification of signatures of virulence in influenza viruses will allow for:**
  - ***Early recognition of potentially high virulent strains***
  - ***Identification of new antiviral targets***
  - ***Improved vaccine strategies against high virulent viruses***

Signatures of virulence of the 1918 influenza virus



Pathological specimen (circa 1918)

↓

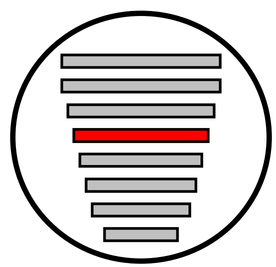
Gene sequencing

↓

Gene reconstruction

↓

Reverse genetics



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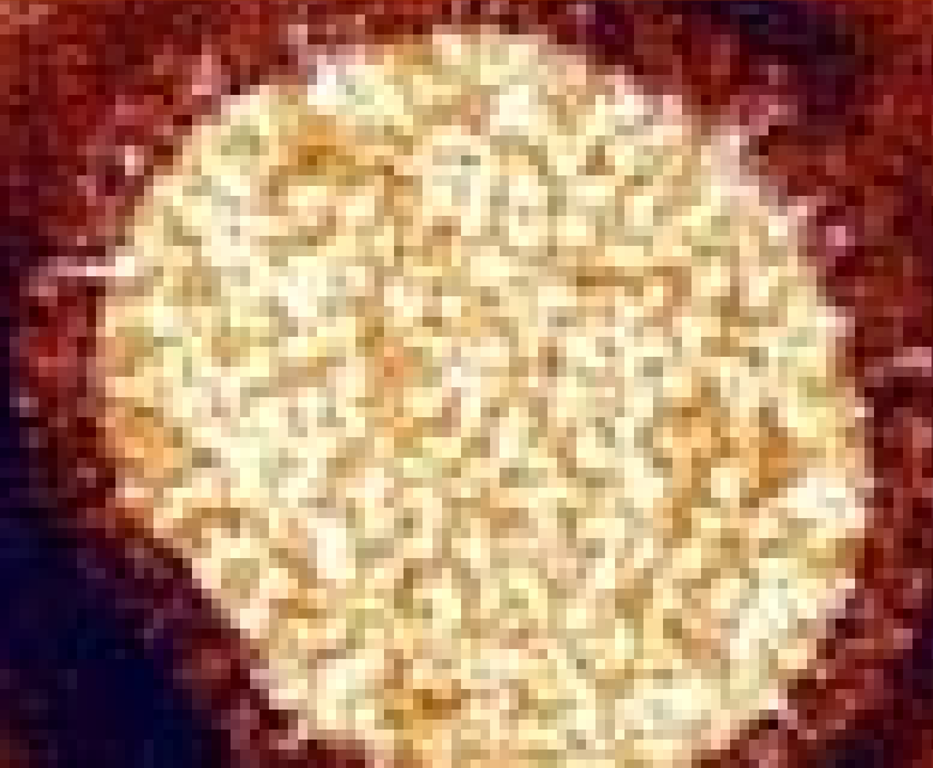
Phenotypic characterization in: Tissue culture
Animal models

Risk Assessment



For Work With Recombinant Influenza Virus

Containing Genes from

A/Brevig Mission/1/18

Risk assessment
Pathogenicity

- **Of backbone H1N1 virus:**
  - ***Mild infections in humans***
  - ***Used under BSL2 containment***
- **Associated with 1918 genes inserted:**
  - ***Lower than backbone?*** **Maybe**
  - ***Intermediate between backbone and 1918?*** **Probably**
  - ***Higher than 1918?*** **Probably not**
  - ***Proportional to number of inserted genes?*** **Probably**
- **Other factors:**
  - ***Immunity to H1N1 viruses is higher than back in 1918***

Risk assessment

- **ROUTE OF TRANSMISSION**
  - *Respiratory via aerosols*
- **AGENT STABILITY**
  - *Survives for a long time on wet surfaces*
  - *Susceptible to a number of disinfectants and to heat and radiation*
- **INFECTIOUS DOSE**
  - *2-1000 viral particles through the respiratory route*
- **CONCENTRATIONS USED**
  - *Maximum titers are in the order of 10^8 pfu/ml*

Risk assessment

- **Risk is decreased:**

- To personnel by the use of primary barriers such as

Protective clothing

PAPRs

Biological safety cabinets

- To environment by using enhanced BSL3-plus facilites:

Negative air pressure

HEPA filtration

Rigorous decontamination and exit procedures

- To both by minimizing aerosol generating techniques

Risk assessment

Lab personnel

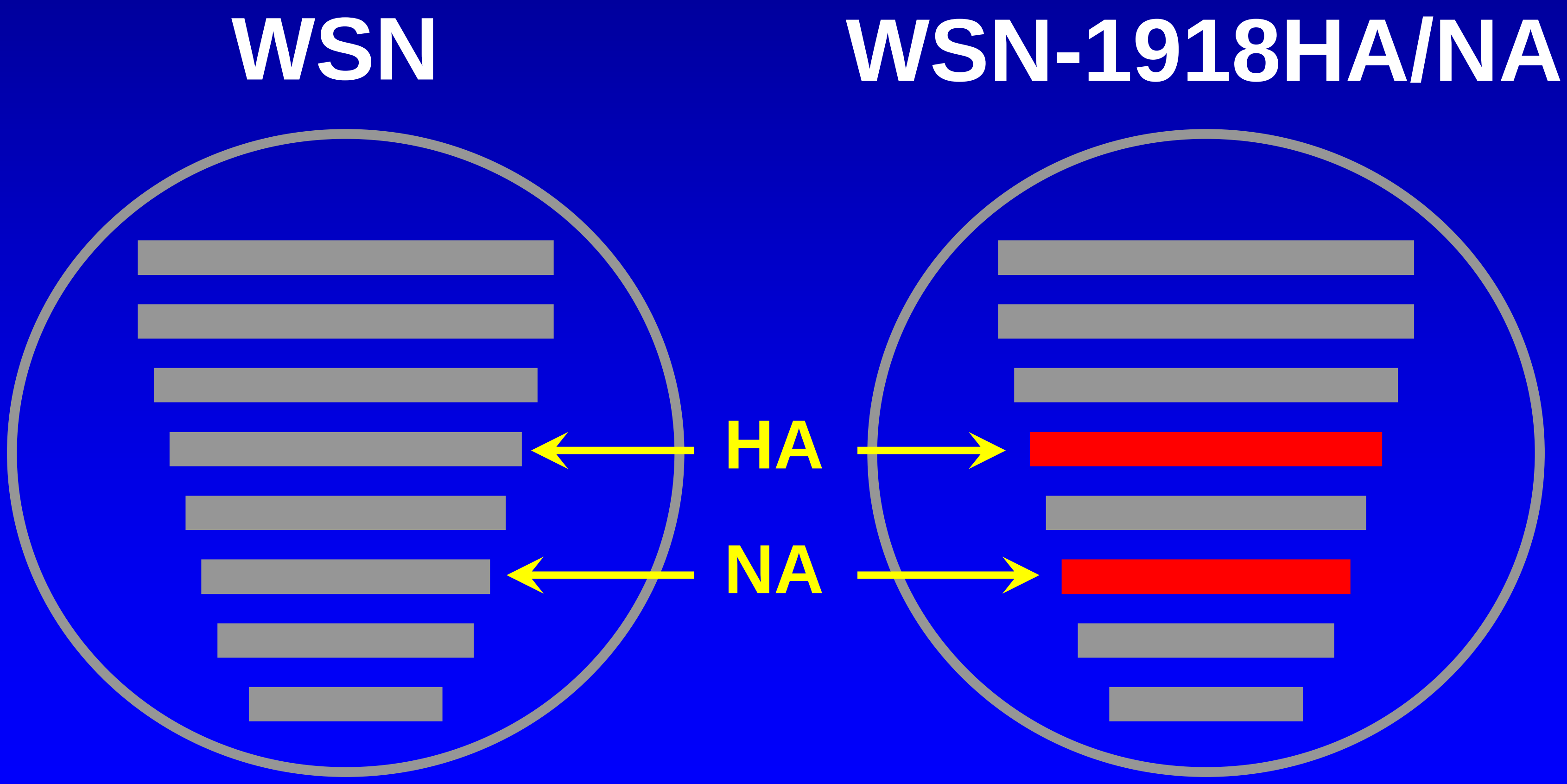
- Demonstrate proficiency
- Receive appropriate training
- Use of appropriate S.O.Ps
- Report incidents
- Participate in medical surveillance


EVOLUTION ONE

Risk assessment

Data from animal studies (virulence)

Do the HA and NA genes of the 1918 virus contribute to enhanced virulence?



Viruses containing 1918 NA and/or HA genes

HA	NA	Titer in MDCK cells (pfu/ml)	LD50 in mice (logPFU)	Mouse lung titers (day 4, pfu/ml)
WSN	WSN	8.6×10^7	2.75	7.1×10^6
New Cal 1999	New Cal 1999	2.5×10^7	> 6	2.5×10^4
1918	1918	2.1×10^7	2.75	2.0×10^7
WSN	1918	5.0×10^7	4.5	7.9×10^6
1918	WSN	2.0×10^7	4.5	2.0×10^4

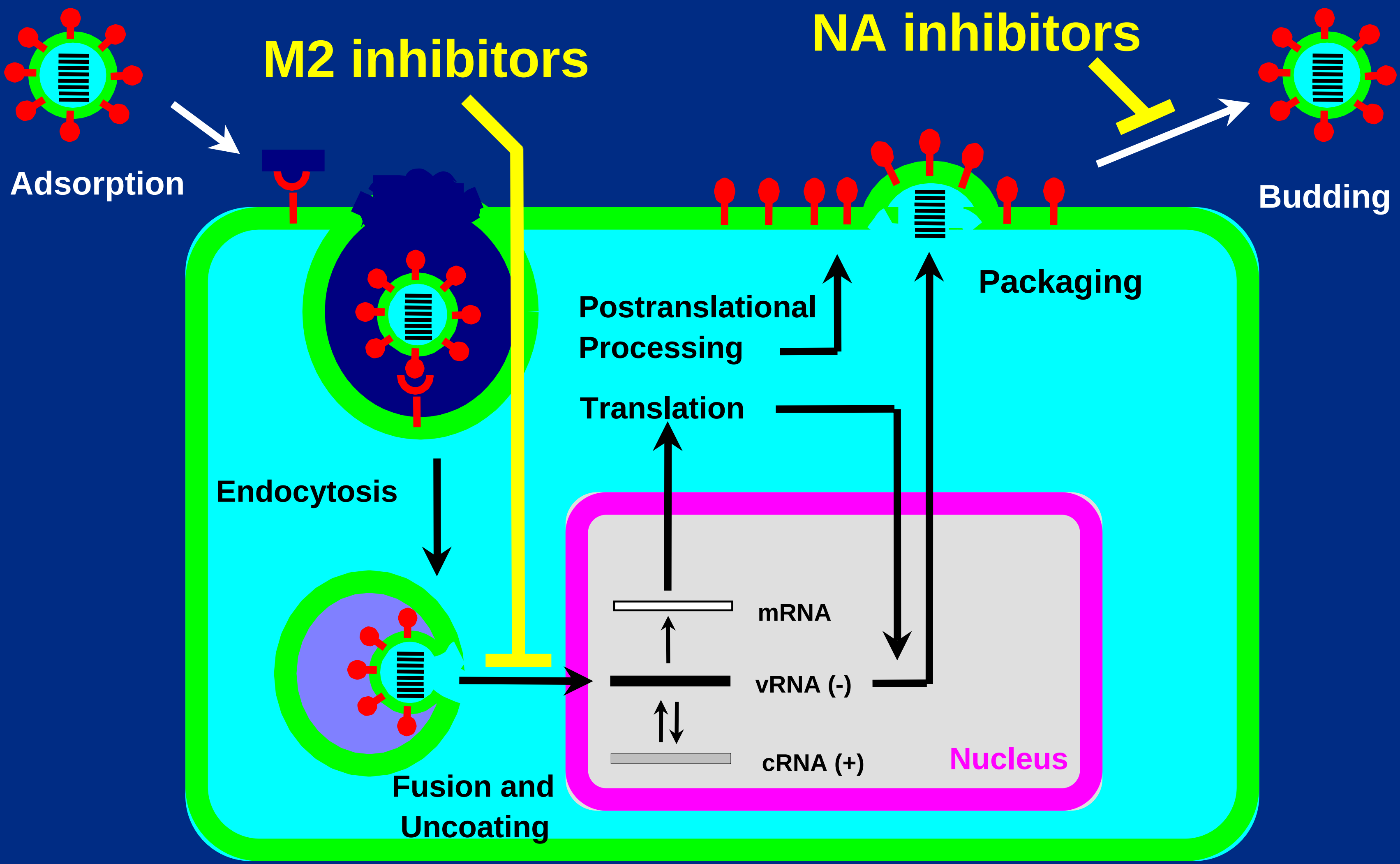
Both 1918 HA and NA genes are likely to contribute to enhanced virulence in mice

Risk assessment

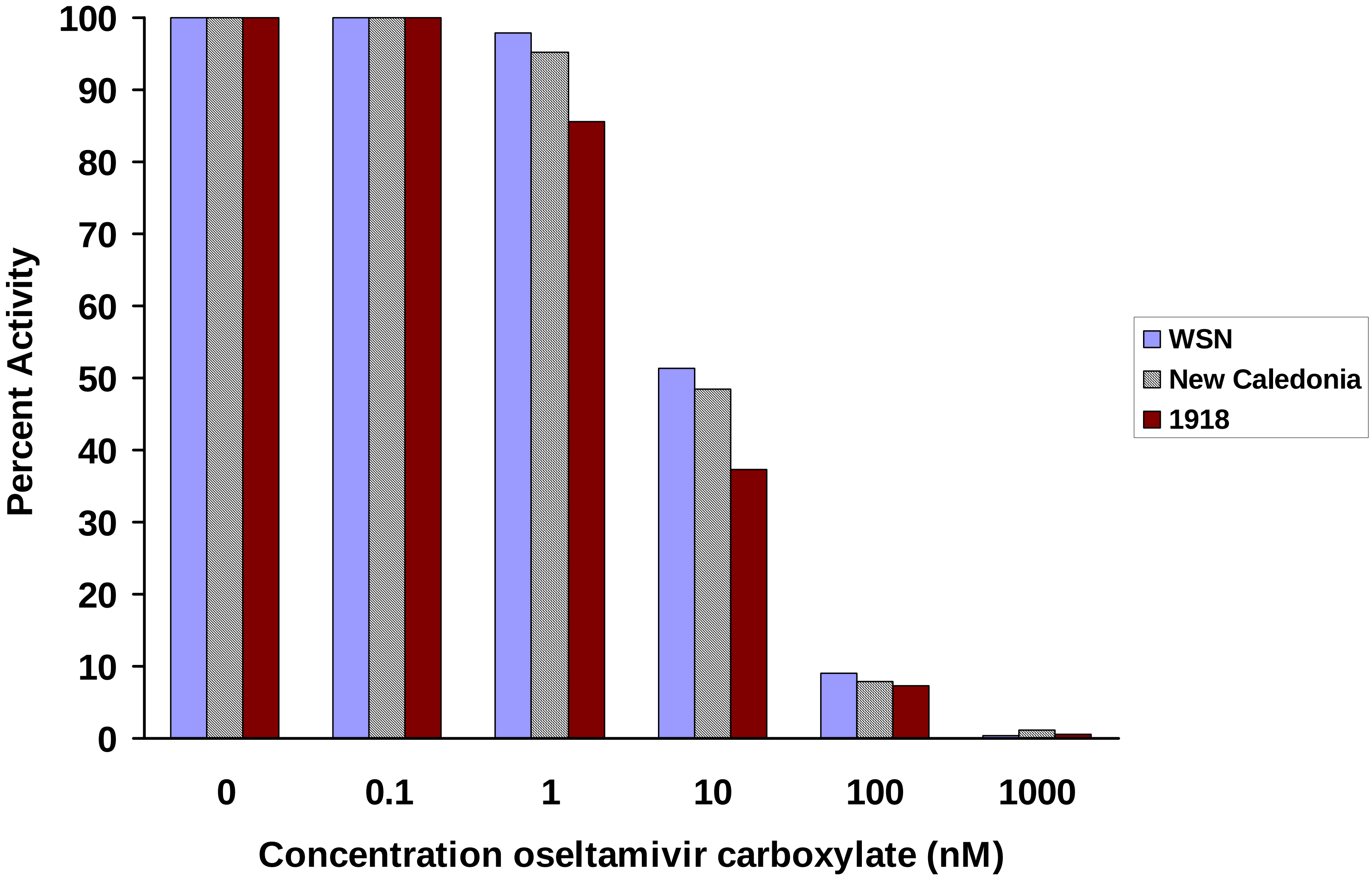
Availability of effective prophylaxis or therapeutic intervention

Antivirals

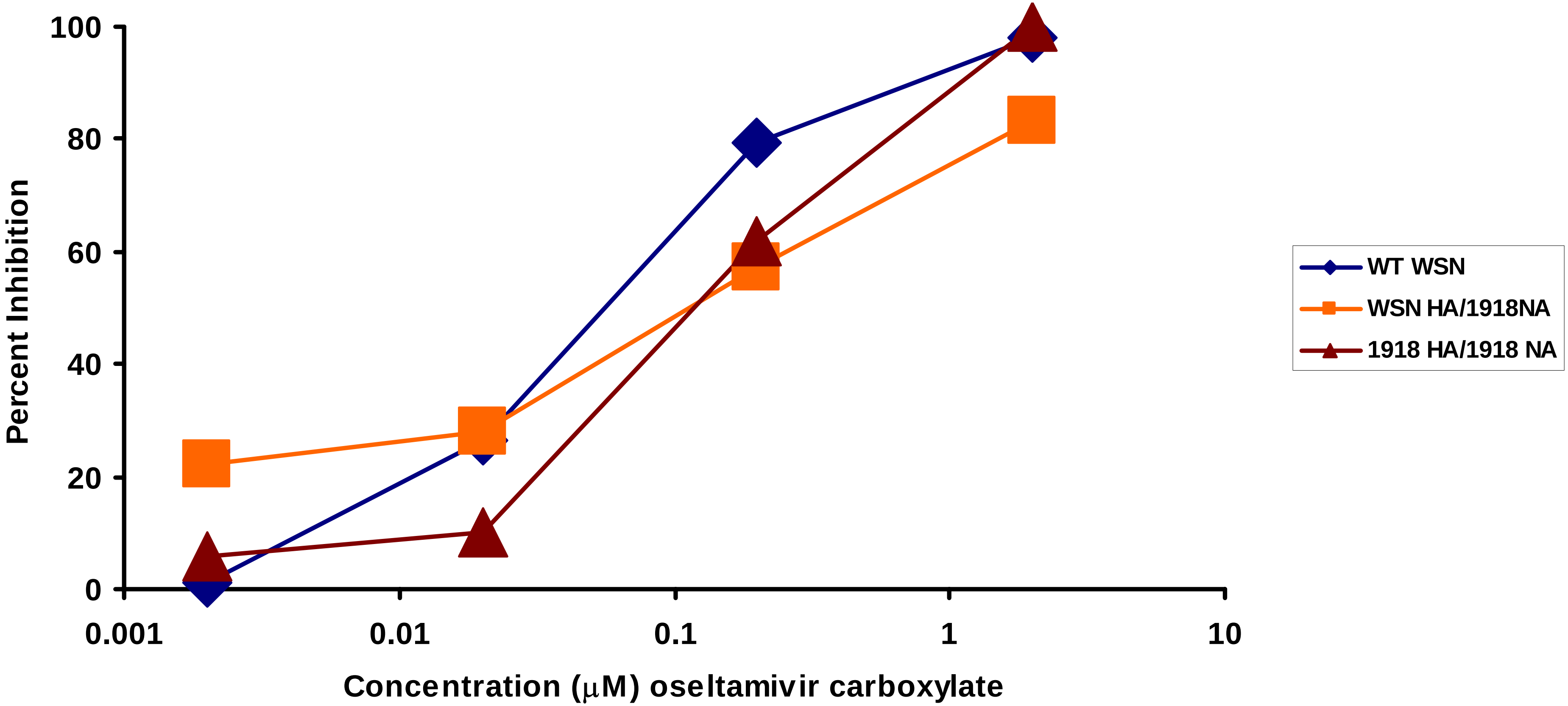
Approved antiviral agents against influenza A virus



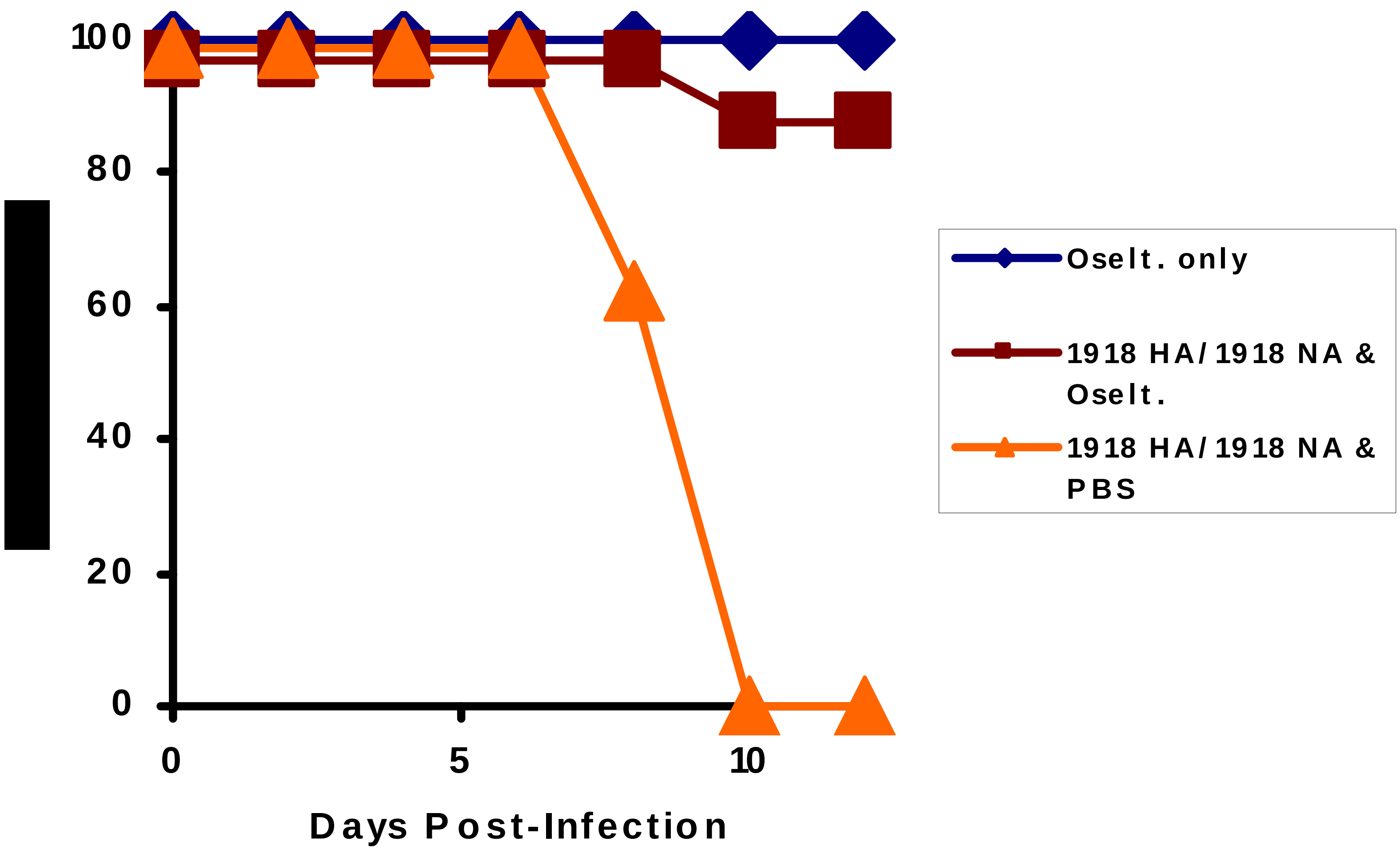
Inhibition in vitro by Oseltamivir carboxylate (GS4071) of WSN, New Caledonia and 1918 Neuraminidases



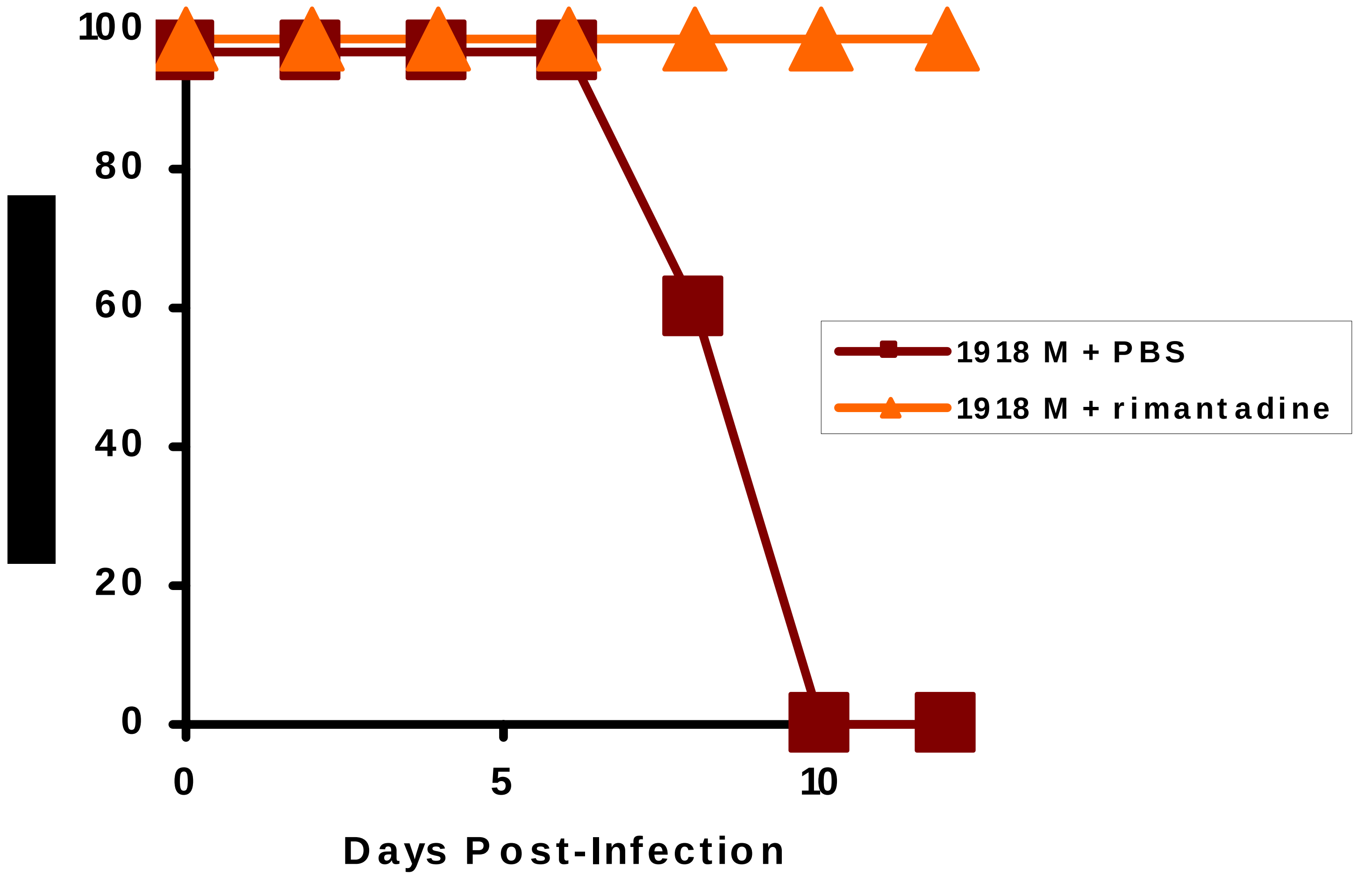
Inhibition of plaque formation by Oseltamivir carboxylate (GS4071)



Oseltamivir Protects Mice from a Lethal Challenge with 1918 HA/1918 NA Virus



Rimantadine Protects Mice from a Lethal Challenge with 1918 M Virus



Risk assessment

Availability of effective prophylaxis or therapeutic intervention

Vaccines

Antigenicity of the 1918 HA

Hemagglutinin inhibition of H1N1 virus variants with ferret antisera

	HI titer with ferret antisera							
Virus	**1918**	**Sw/Ia/30**	**WS/33**	**PR/8/34**	**USSR/77**	**Chili/83**	**Tx/91**	**N.Cal/99**
1918 HA	**2560**	1280	320	40	<10	10	80	20
Sw/Ia/30	1280	**2560**	20	320	80	10	80	20
WS/33	<10	<10	**640**	40	<10	<10	<10	40
PR/8/34	20	<10	160	**2560**	10	<10	10	10
USSR/77	<10	<10	10	<10	**1280**	20	<10	<10
Chili/83	<10	<10	10	<10	40	**320**	20	10
Tx/91	<10	<10	20	<10	<10	<10	**2560**	40
N.Cal/99	10	<10	10	20	<10	<10	40	**1280**

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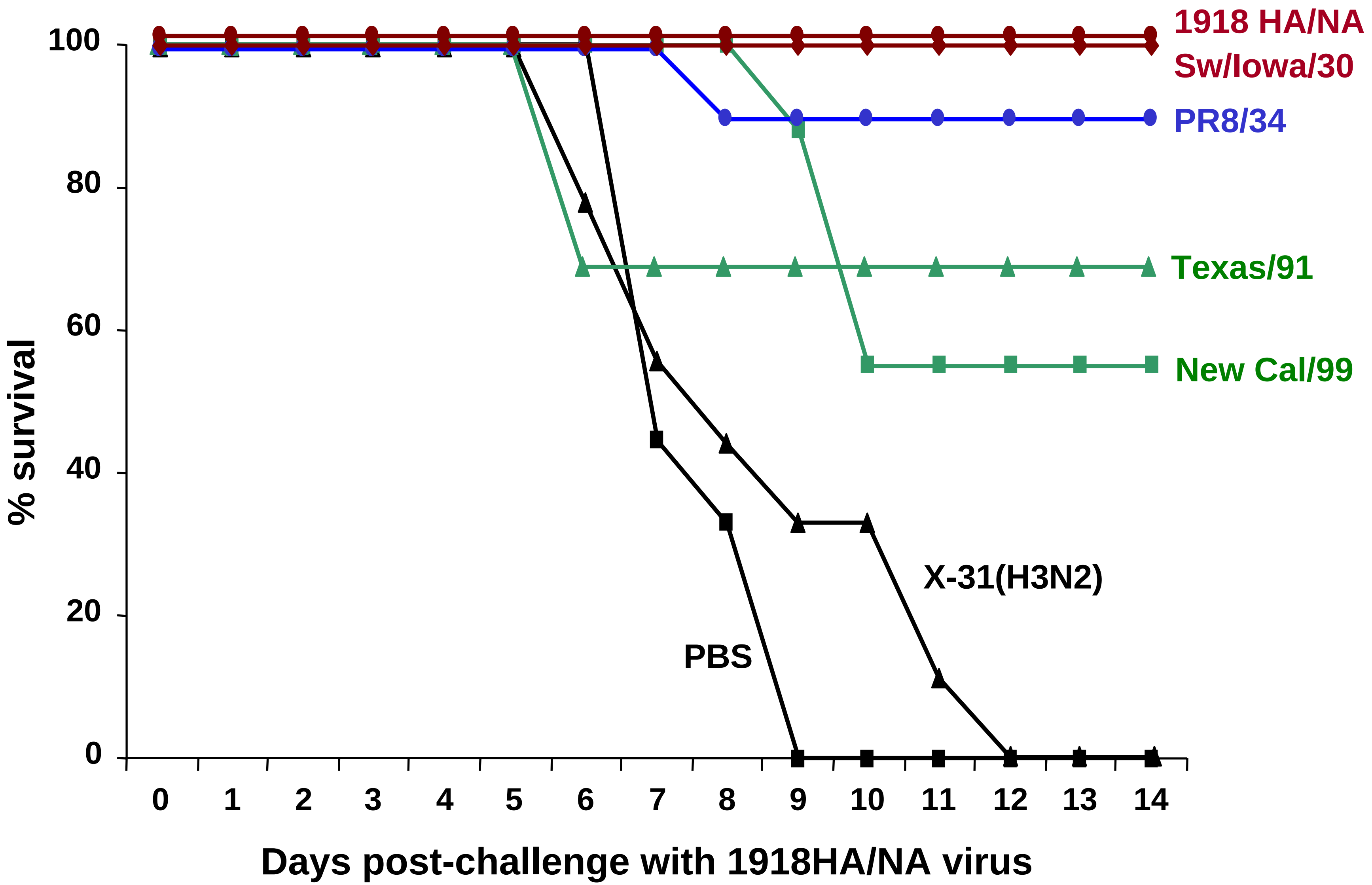
1918 HA Neutralizing Antibodies in Human Sera

Serum sample	DOB	1918 HA/NA Neutralization titer	1918 HA/NA HI titer
A	1910	160	80
B	1911	320	160
C	1928	160	160
D	1932	10	10
E	1933	160	80
F	1944	<10	<10
G	1962	10	10
H	1966	20	20
I	1977	10	10

Protective Killed Inactivated Vaccines against the 1918 HA/1918 NA Virus



1918 VIRUS
What do we know now?

1. The glycoprotein genes of the virus might have contributed to enhanced virulence.
    - Other animal models?
    - Domains responsible?
    - Molecular and immunological mechanisms?

2. Viruses containing 1918 genes are sensitive to existing antivirals

3. H1N1 based vaccines are likely to be protective

Would a 1918-like HIN1 virus be today as lethal as in 1918?

1918 Influenza and Pneumonia Deaths by Age