

# Evidence for history-dependence of influenza pandemic emergence

**Edward Hill<sup>1</sup>**

**Joint work with: Michael Tildesley<sup>1</sup>, Thomas House<sup>2</sup>**

<sup>1</sup> Zeeman Institute: SBIDER (Systems Biology & Infectious Disease Epidemiology Research), University of Warwick, UK

<sup>2</sup> School of Mathematics, The University of Manchester, UK

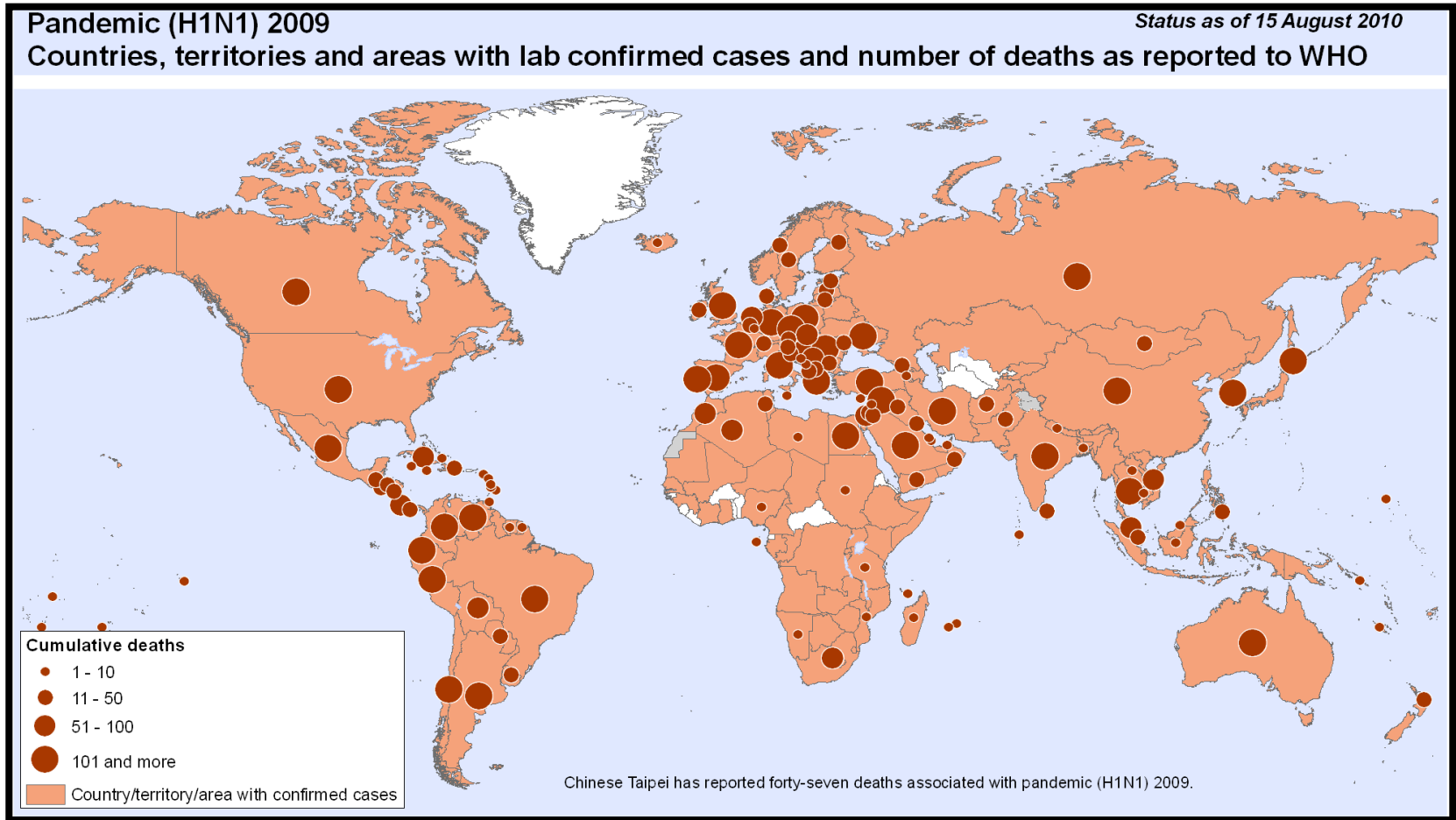
# Influenza pandemic definition

---

**“World-wide epidemic, caused by an emergent influenza A strain that transmits among humans, was not previously circulating among humans and to which most people do not have immunity”**

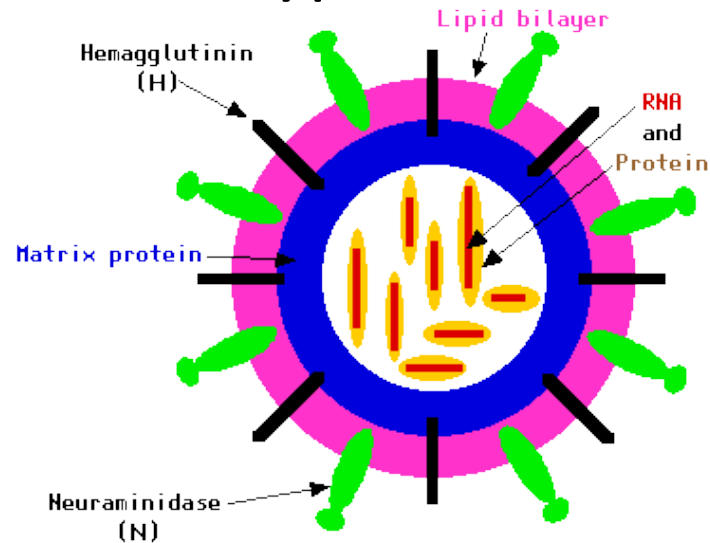
# Impact of influenza pandemics

1918 flu pandemic: Infected 500 million, killed 20-40 million.



# Why are influenza A viruses capable of causing global pandemics?

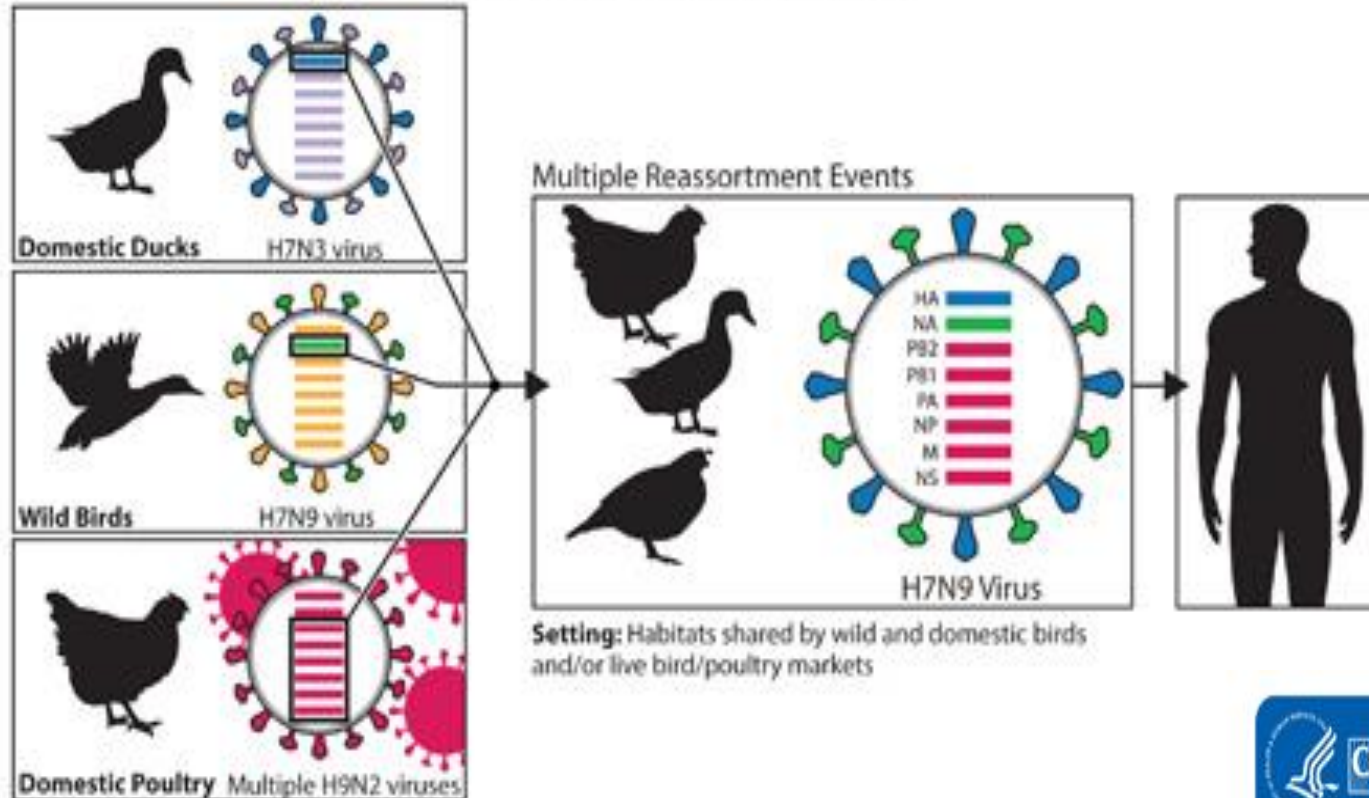
- There are several Influenza A virus strains, categorised into subtypes.



- Virus is notable for following dynamics:
  - **antigenic drift**
  - **antigenic shift**

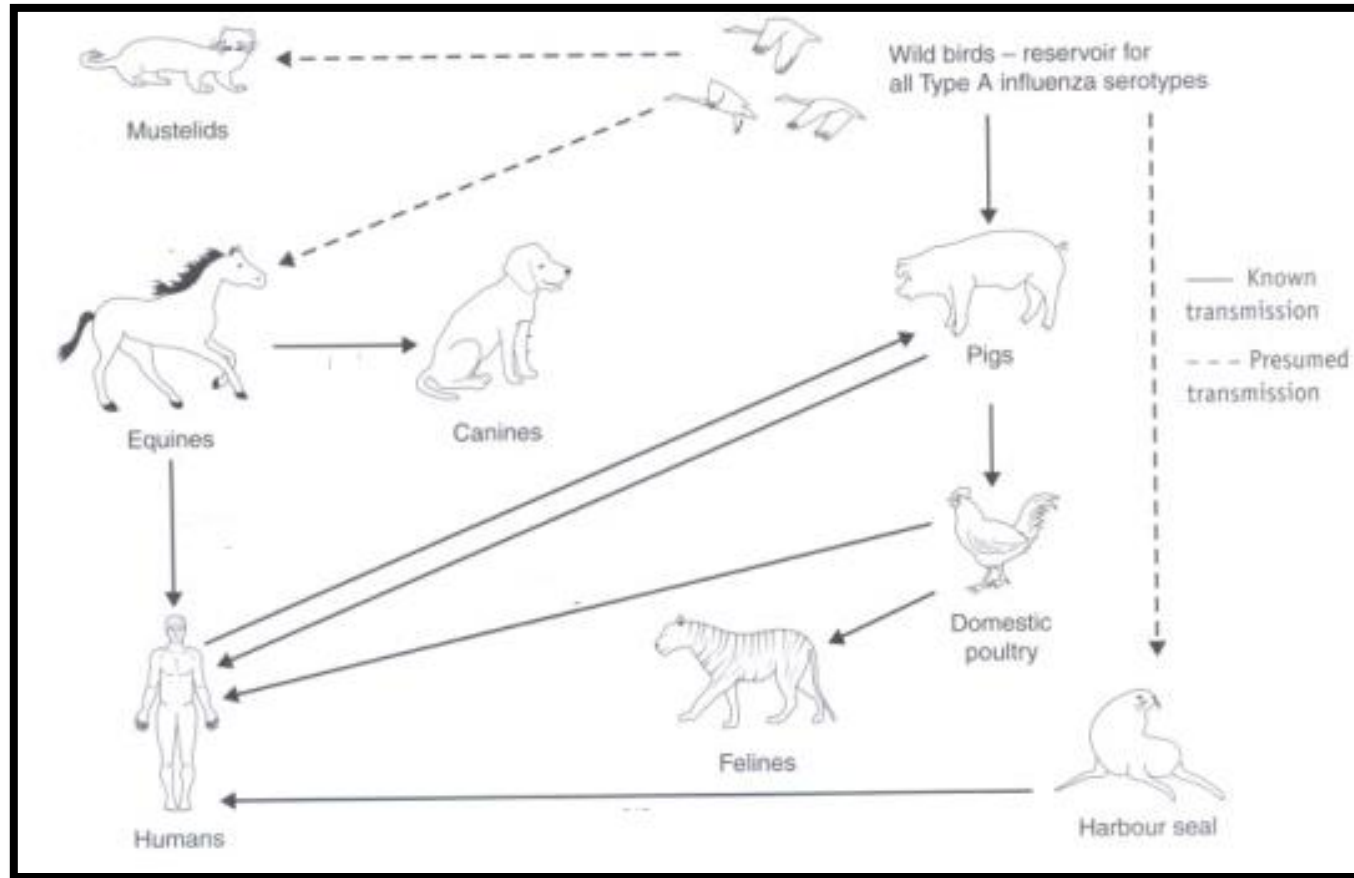
# Antigenic shift

Genetic Evolution of H7N9 Virus in China, 2013



Centers for Disease Control and Prevention  
National Center for Immunization and Respiratory Diseases

# Influenza A inhabits many hosts



**Source:** R. Jennings & R.C. Read, *Influenza: Human and Avian*. Royal Society of Medicine Press (2006).

# Objectives

## (1) Historic pandemic influenza data

- Produce timelines listing possible pandemics from 1700 to the present

## (2) Model Selection

- Are influenza pandemic waiting times plausibly generated by a memoryless or history-dependent process?

## (3) Predictions

- What is the probability of a given number of influenza pandemics in the next 100 years?

# Objectives

---

## (1) Historic pandemic influenza data

- Produce timelines listing possible pandemics from 1700 to the present

## (2) Model Selection

- Are influenza pandemic waiting times plausibly generated by a memoryless or history-dependent process?

## (3) Predictions

- What is the probability of a given number of influenza pandemics in the next 100 years?





# Influenza pandemic definition

---

**“World-wide epidemic, caused by an emergent influenza A strain that transmits among humans, was not previously circulating among humans and to which most people do not have immunity “**

- Only during the virological era can we recognise a pandemic with certainty.
- Which pre-1900 epidemics were actually pandemics?

# The data

---

- Three distinct data sets (referred to as timelines) were constructed based on:
  - The century the pandemic occurred
  - The number of supporting sources for the epidemic being a pandemic.

## References:

1. KD Patterson (1986) Pandemic Influenza 1700-1900. Rowman and Littlefield, New Jersey.
2. W Beveridge (1991) The chronicle of influenza epidemics. *History and philosophy of the life sciences* **13**: 223-234.
3. CW Potter (2001) A history of influenza. *Journal of applied microbiology* **91**: 572-579.

# The data: Historic pandemic timelines

Date	Popular Name	Timeline A	Timeline B	Timeline C
1729				
1732		—		
1761		—		
1781		<b>52 yrs</b>		
1788		—		
1800		—		
1830		<b>49 yrs</b>		
1847		—		
1857		—		
1889	Russian Flu	<b>59 yrs</b>		
1918	Spanish Flu	<b>29 yrs</b>		
1957	Asian Flu	<b>39 yrs</b>		
1968	Hong Kong Flu	<b>11 yrs</b>		
1977	Russian Flu	—		
2009	Swine Flu	<b>41 yrs</b>		

# The data: Historic pandemic timelines

Date	Popular Name	Timeline A	Timeline B	Timeline C
1729				
1732		—	—	
1761		—	32 yrs	
1781		52 yrs	20 yrs	
1788		—	7 yrs	
1800		—	12 yrs	
1830		49 yrs	30 yrs	
1847		—	17 yrs	
1857		—	10 yrs	
1889	Russian Flu	59 yrs	59 yrs	
1918	Spanish Flu	29 yrs	29 yrs	
1957	Asian Flu	39 yrs	39 yrs	
1968	Hong Kong Flu	11 yrs	11 yrs	
1977	Russian Flu	—	—	
2009	Swine Flu	41 yrs	41 yrs	

# The data: Historic pandemic timelines

Date	Popular Name	Timeline A	Timeline B	Timeline C
1729				
1732		—	—	3 yrs
1761		—	32 yrs	29 yrs
1781		52 yrs	20 yrs	20 yrs
1788		—	7 yrs	7 yrs
1800		—	12 yrs	12 yrs
1830		49 yrs	30 yrs	30 yrs
1847		—	17 yrs	17 yrs
1857		—	10 yrs	10 yrs
1889	Russian Flu	59 yrs	59 yrs	59 yrs
1918	Spanish Flu	29 yrs	29 yrs	29 yrs
1957	Asian Flu	39 yrs	39 yrs	39 yrs
1968	Hong Kong Flu	11 yrs	11 yrs	11 yrs
1977	Russian Flu	—	—	9 yrs <sup>  </sup>
2009	Swine Flu	41 yrs	41 yrs	32 yrs

<sup>||</sup>Widely believed to have occurred due to human factors

# The data: Historic pandemic timelines

Date	Popular Name	Timeline A	Timeline B	Timeline C
1729				
1732		—	—	3 yrs
1761		—	32 yrs	29 yrs
1781		52 yrs	20 yrs	20 yrs
1788		—	7 yrs	7 yrs
1800		—	12 yrs	12 yrs
1830		49 yrs	30 yrs	30 yrs
1847		—	17 yrs	17 yrs
1857		—	10 yrs	10 yrs
1889	Russian Flu	59 yrs	59 yrs	59 yrs
1918	Spanish Flu	29 yrs	29 yrs	29 yrs
1957	Asian Flu	39 yrs	39 yrs	39 yrs
1968	Hong Kong Flu	11 yrs	11 yrs	11 yrs
1977	Russian Flu	—	—	9 yrs <sup>II</sup>
2009	Swine Flu	41 yrs	41 yrs	32 yrs

➤ Model 1 – Exponential; Model 2 – Gamma.

# Objectives

---

## (1) Historic pandemic influenza data

- Produce timelines listing possible pandemics from 1700 to the present

## (2) Model Selection

- Are influenza pandemic waiting times plausibly generated by a memoryless or history-dependent process?

## (3) Predictions

- What is the probability of a given number of influenza pandemics in the next 100 years?



# Model comparison method: Reversible-jump MCMC

---

- Allows simulation of posterior distribution on spaces of varying dimensions.

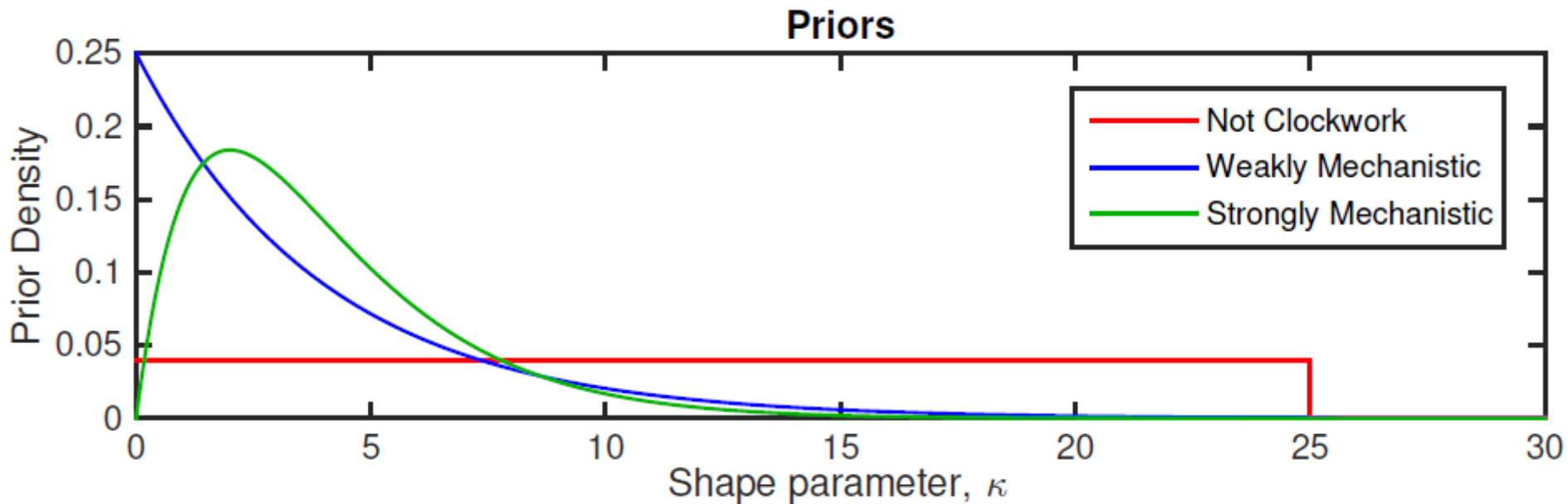
$$\pi(m, \theta_m | D) \propto L(D | m, \theta_m) p(\theta_m | m) p(m)$$

- Gives posterior model probabilities, as well as parameter posterior distributions.



# Reversible-jump MCMC priors

- Rate parameters: Uniform
- Gamma distribution shape parameter:



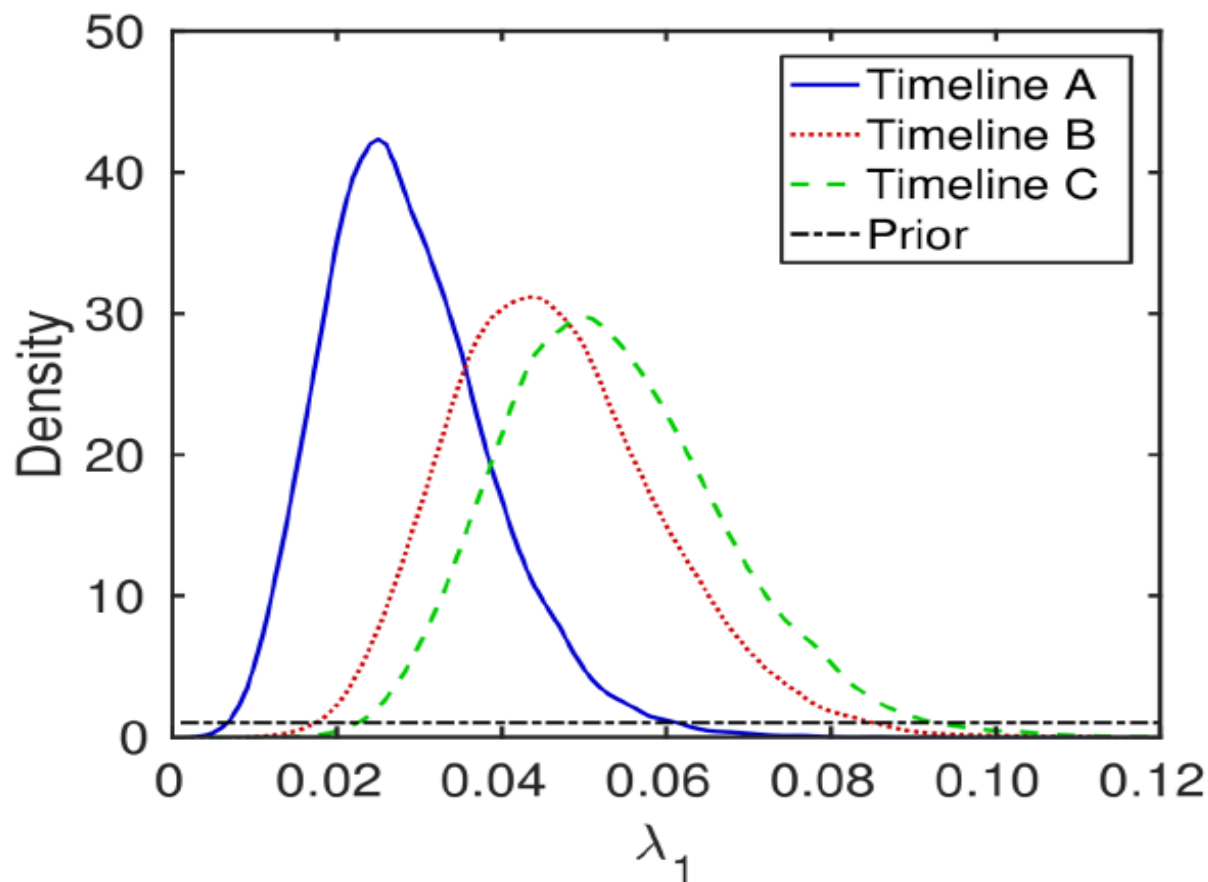
# The data: Historic pandemic timelines

Date	Popular Name	Timeline A	Timeline B	Timeline C
1729				
1732		—	—	3 yrs
1761		—	32 yrs	29 yrs
1781		52 yrs	20 yrs	20 yrs
1788		—	7 yrs	7 yrs
1800		—	12 yrs	12 yrs
1830		49 yrs	30 yrs	30 yrs
1847		—	17 yrs	17 yrs
1857		—	10 yrs	10 yrs
1889	Russian Flu	59 yrs	59 yrs	59 yrs
1918	Spanish Flu	29 yrs	29 yrs	29 yrs
1957	Asian Flu	39 yrs	39 yrs	39 yrs
1968	Hong Kong Flu	11 yrs	11 yrs	11 yrs
1977	Russian Flu	—	—	9 yrs <sup>II</sup>
2009	Swine Flu	41 yrs	41 yrs	32 yrs

➤ Model 1 – Exponential; Model 2 – Gamma.

# Exponential model posterior distributions

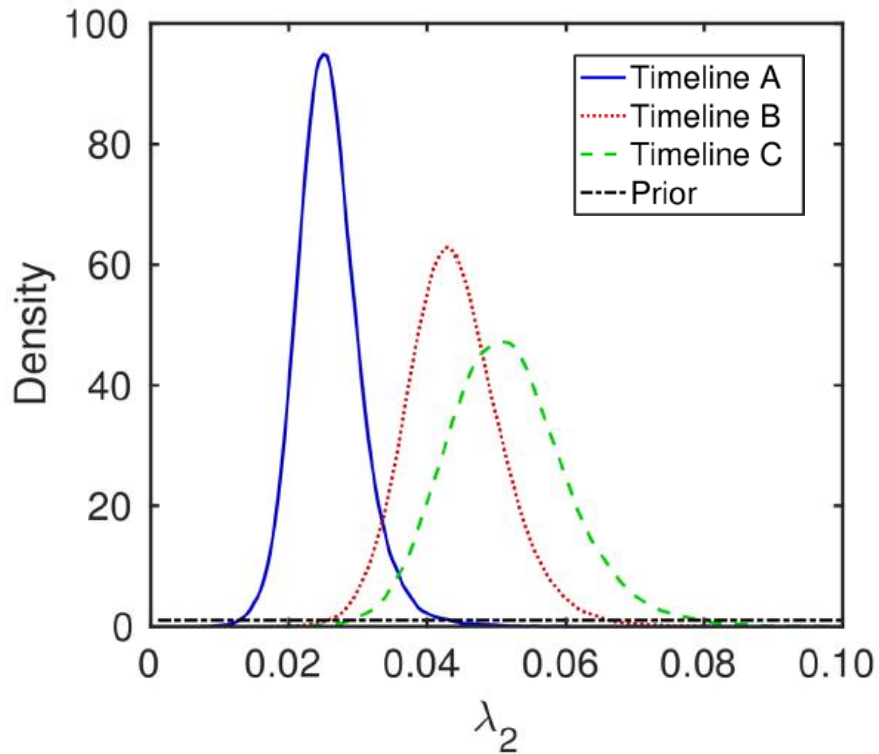
Rate parameter:



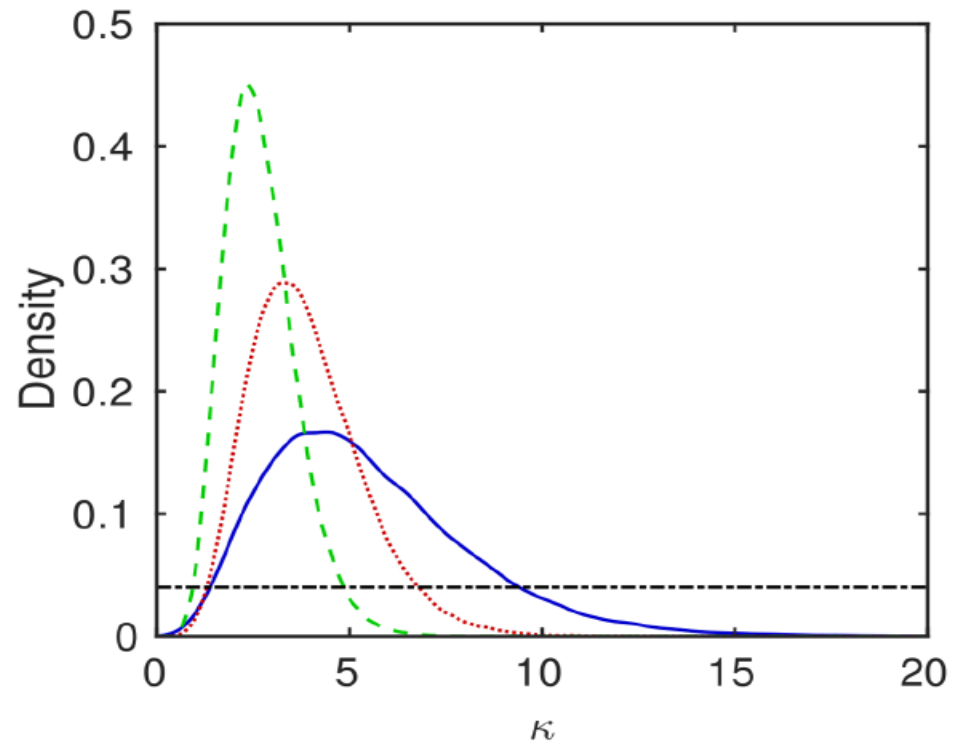
# Gamma model posterior distributions

## – *Not clockwork* assumption

Rate parameter:



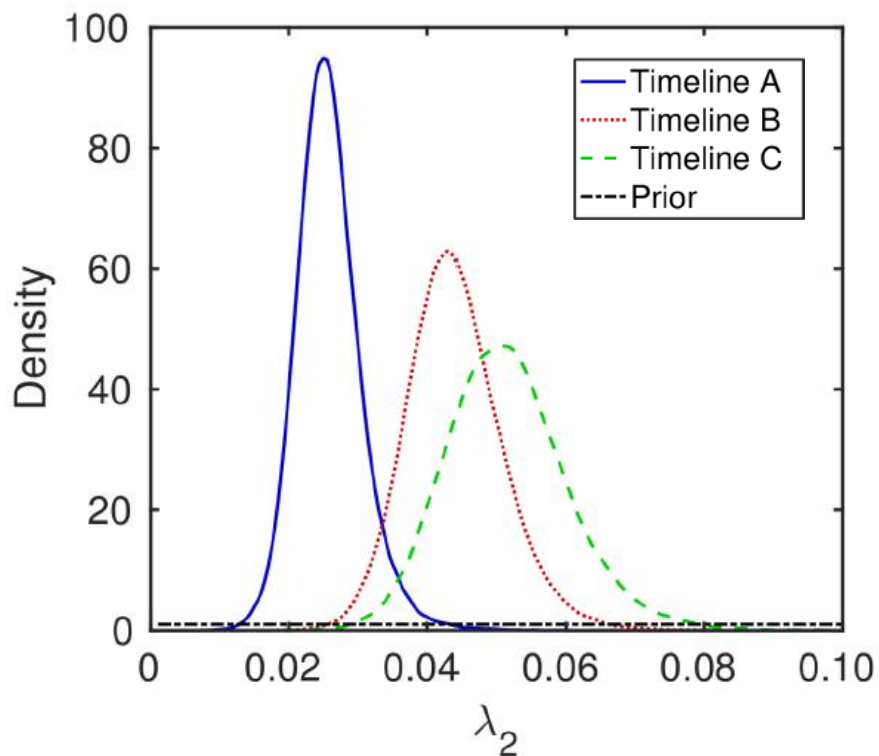
Shape parameter:



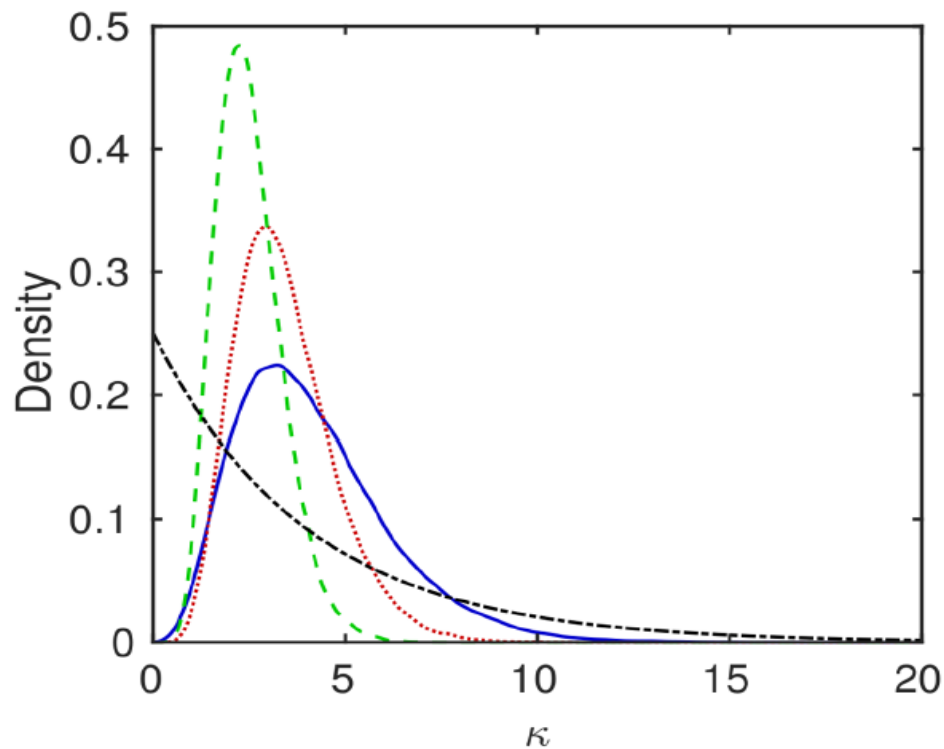
# Gamma model posterior distributions

## – *Weakly mechanistic* assumption

Rate parameter:



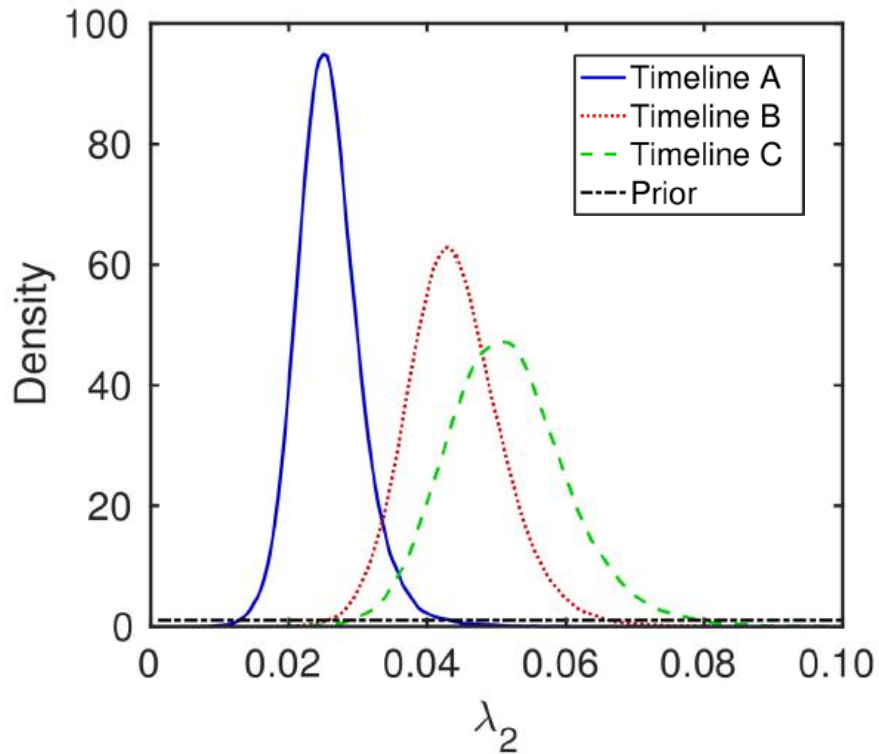
Shape parameter:



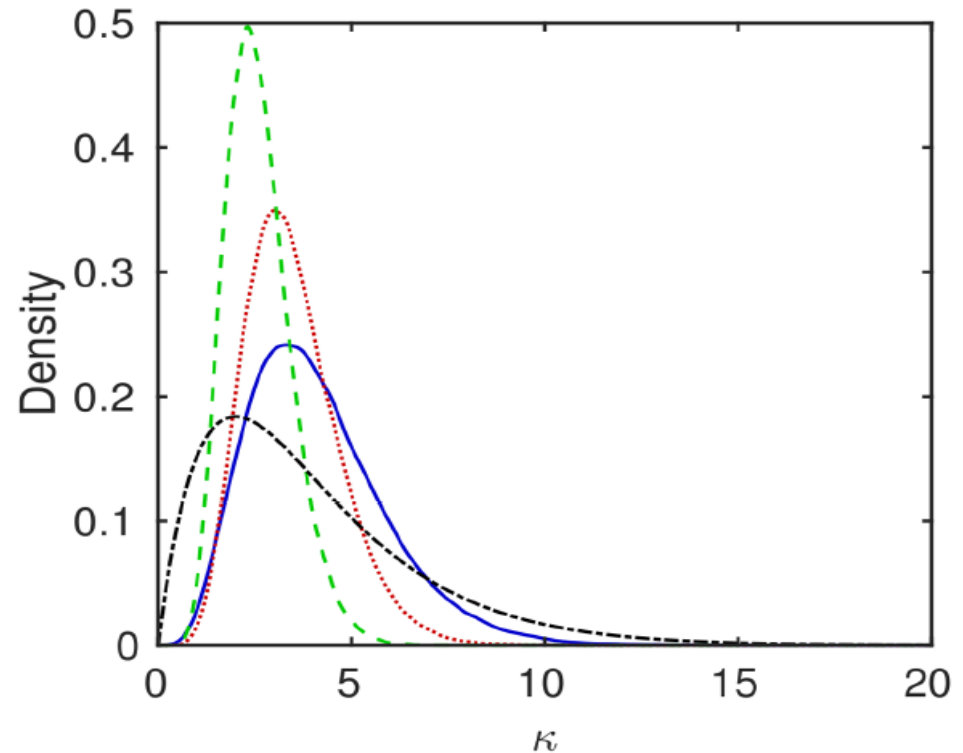
# Gamma model posterior distributions

## – *Strongly mechanistic* assumption

Rate parameter:



Shape parameter:



# Model selection results

Table: Posterior probabilities given to the history-dependent hypothesis.

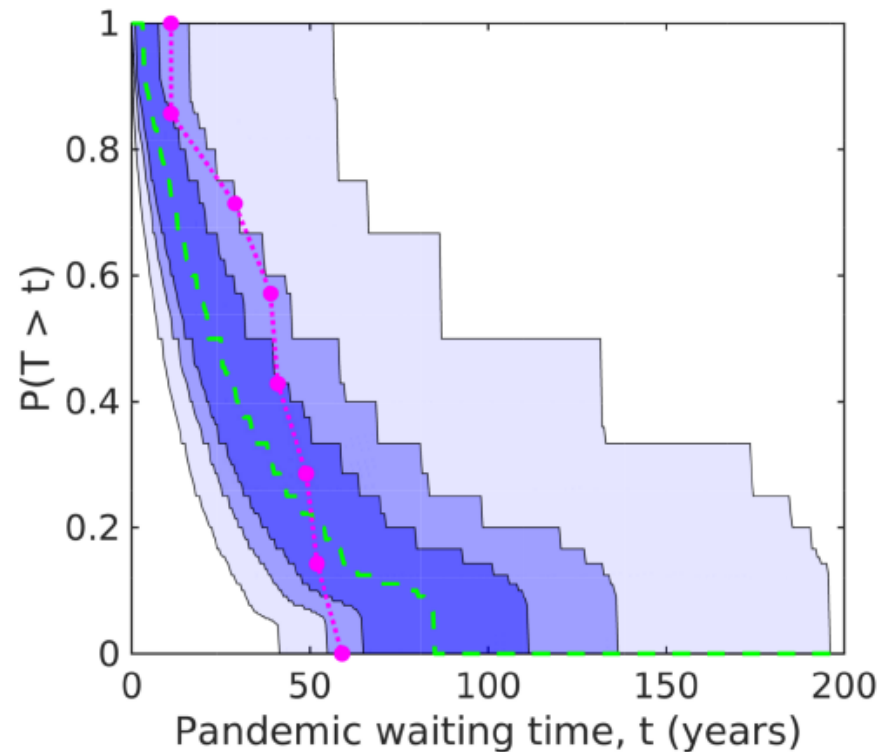
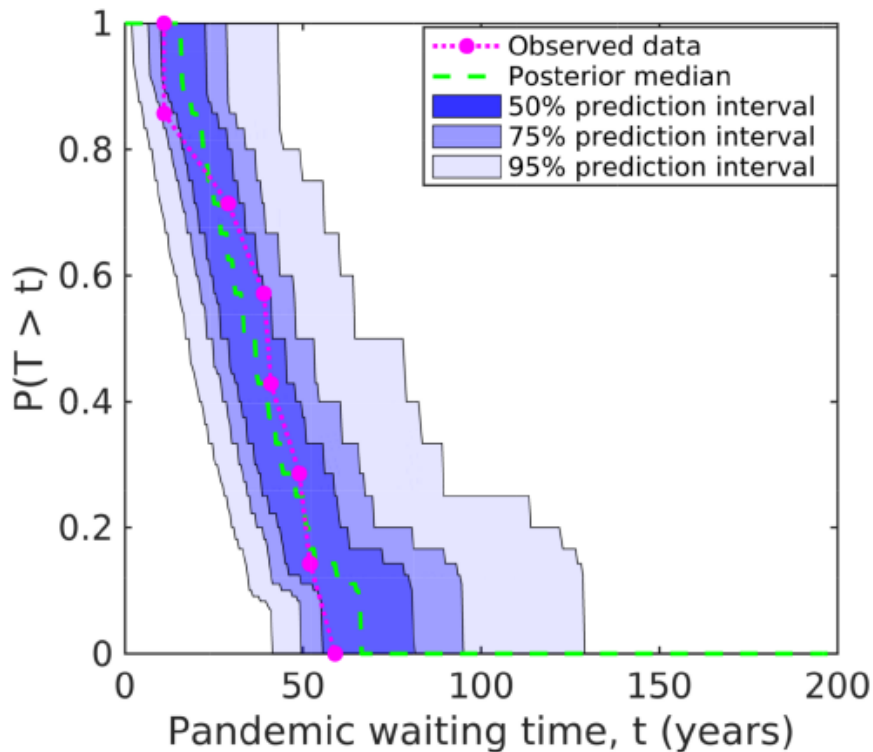
	Kappa prior		
	Not Clockwork	Weakly mechanistic	Strongly mechanistic
Timeline A	0.70	0.82	0.86
Timeline B	0.77	0.89	0.92
Timeline C	0.45	0.73	0.77

- **Gamma distributed model preferred for eight out of nine sets of modelling assumptions.**

# Goodness-of-fit verification

Figure: Predicted posterior influenza pandemic inter-event time survival functions versus the empirical survival function.

(left) history-dependent model; (right) memoryless model





# Objectives

---

## (1) Historic pandemic influenza data

- Produce timelines listing possible pandemics from 1700 to the present

## (2) Model Selection

- Are influenza pandemic waiting times plausibly generated by a memoryless or history-dependent process?

## (3) Predictions

- What is the probability of a given number of influenza pandemics in the next 100 years?



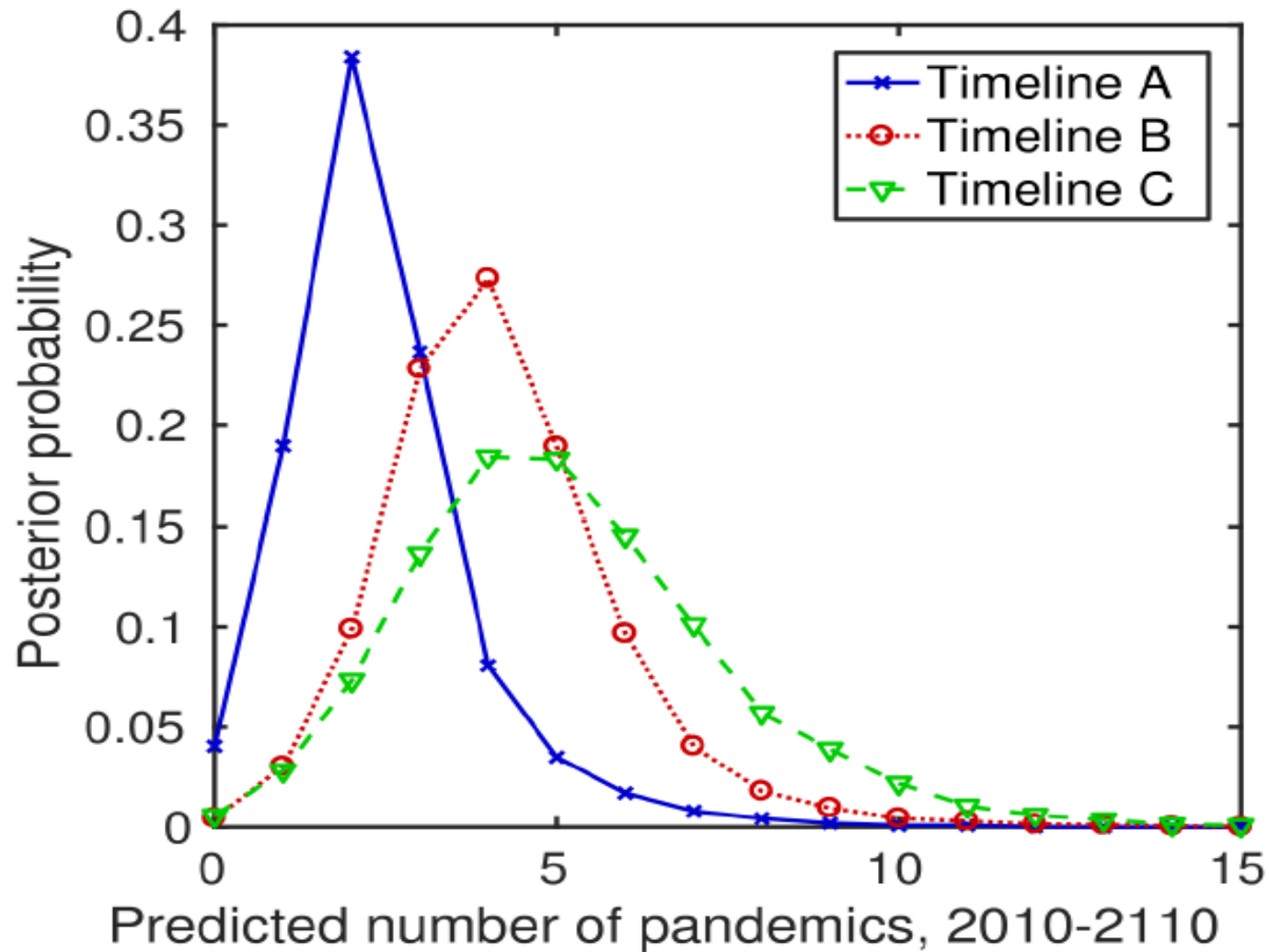
# Predicted pandemic event number distributions

---

➤ Carried out forward simulations using Gillespie algorithm:

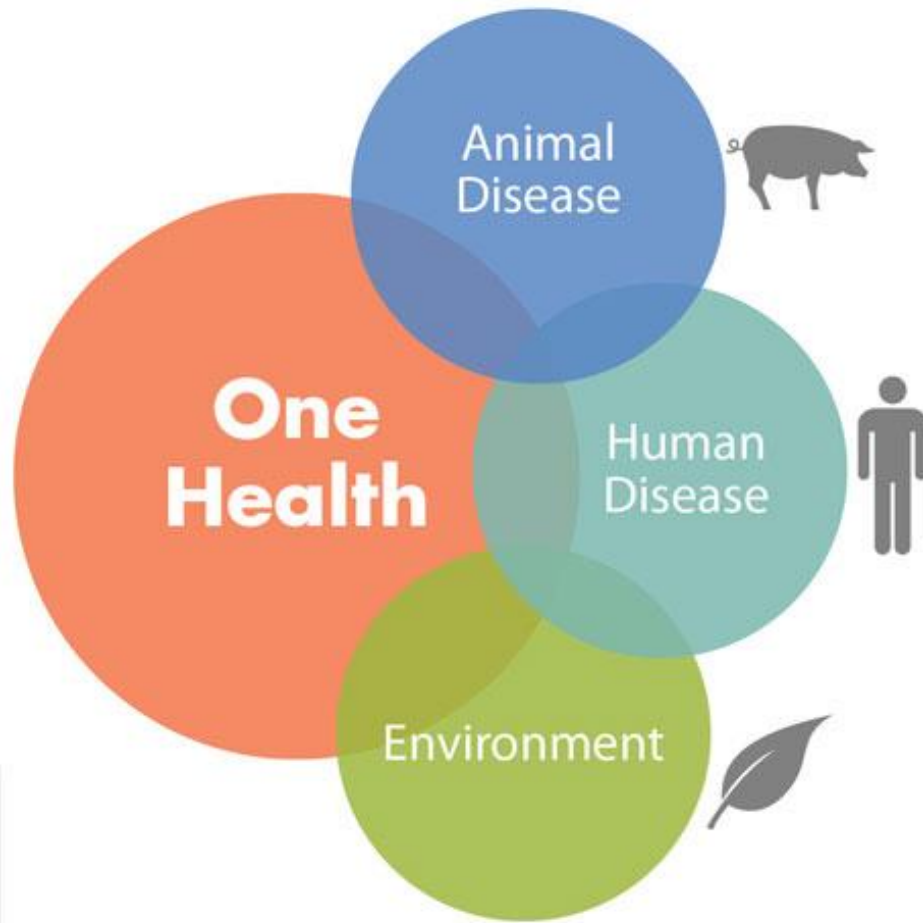
- 1) Posterior model probabilities used to choose the model used for each forward simulation.
- 2) For the selected model, pick sample parameters generated from RJMCMC.

**Figure: Proportion of simulations predicting the specified number of pandemics between 2010-2110.**



# One Health approach?

ONE HEALTH



The One Health concept recognizes the interrelationship between animal, human and environmental health.

# Limitations & future work

---

- Data uncertainty and small nature of the dataset
  - Including pre-1700 outbreaks avenue for further study
- Alternative distributions for history-dependent model
  - Weibull distribution
- Alternative priors for shape parameter

# Summary of findings

## (1) Historic pandemic influenza data

- Constructed three alternative timelines of presumptive influenza pandemics since 1700.

## (2) Model Selection

- Spillover of strains with pandemic potential is a **history-dependent process**.

## (3) Predictions

- Shown a **high level of variability** in the predicted number of pandemics.

# Acknowledgements

---

- Thomas House (University of Manchester)
- Michael Tildesley (University of Warwick)

**EPSRC**

Engineering and Physical Sciences  
Research Council



For further details:

EM Hill et al. (2017) Evidence for history-dependence of influenza pandemic emergence. *Scientific Reports*, **7**: 43623. doi: 10.1038/srep43623

**Email:** Edward.Hill@warwick.ac.uk

**Webpage:** www.edmhill.com