Estimates of H5N1 critical parameters from past transmission and current situation

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Overview

Aims

- Summarise key epidemiological parameters for H5N1 in humans
- Compare parameter estimates from Clade 2.3.4.4b outbreaks with previous outbreaks of H5N1

Approach

- Use systematic reviews and meta-analyses (where available)
- Undertake additional reviews & data analysis where necessary

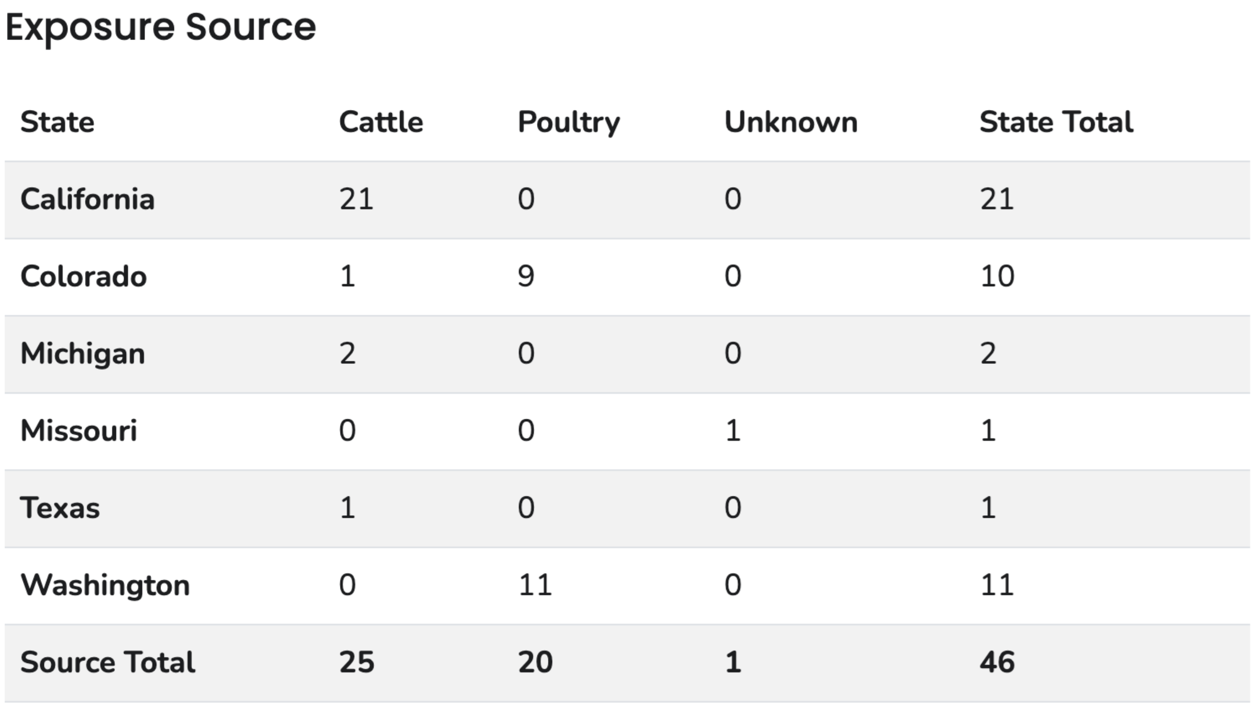
Current US cases (CDC 2024)

46 total cases

25 cases linked to exposure to cattle

20 cases linked to exposure to poultry

1 case of unknown exposure source



Exposure Source

State	Cattle	Poultry	Unknown	State Total
California	21	0	0	21
Colorado	1	9	0	10
Michigan	2	0	0	2
Missouri	0	0	1	1
Texas	1	0	0	1
Washington	0	11	0	11
Source Total	**25**	**20**	**1**	**46**

https://www.cdc.gov/bird-flu/situation-summary/index.html (11th of November 2024)

Case description

- As of 7th November all of the patients experienced mild conjunctivitis or mild respiratory symptoms and all have recovered (CDC 2024; Kekatos 2024)

Outbreak in context

- In H5N1 previous outbreaks; 37% and 12.5% of hospitalised cases in Egypt (2006–07) and Turkey(2006) presented with conjunctivitis(Belser et al. 2018).
- 2003 H7N7 outbreak in the Netherlands. 88% of cases developed conjunctivitis as their only symptom, with one fatality(Fouchier et al. 2004).

Outbreak in the USA, Reproduction number

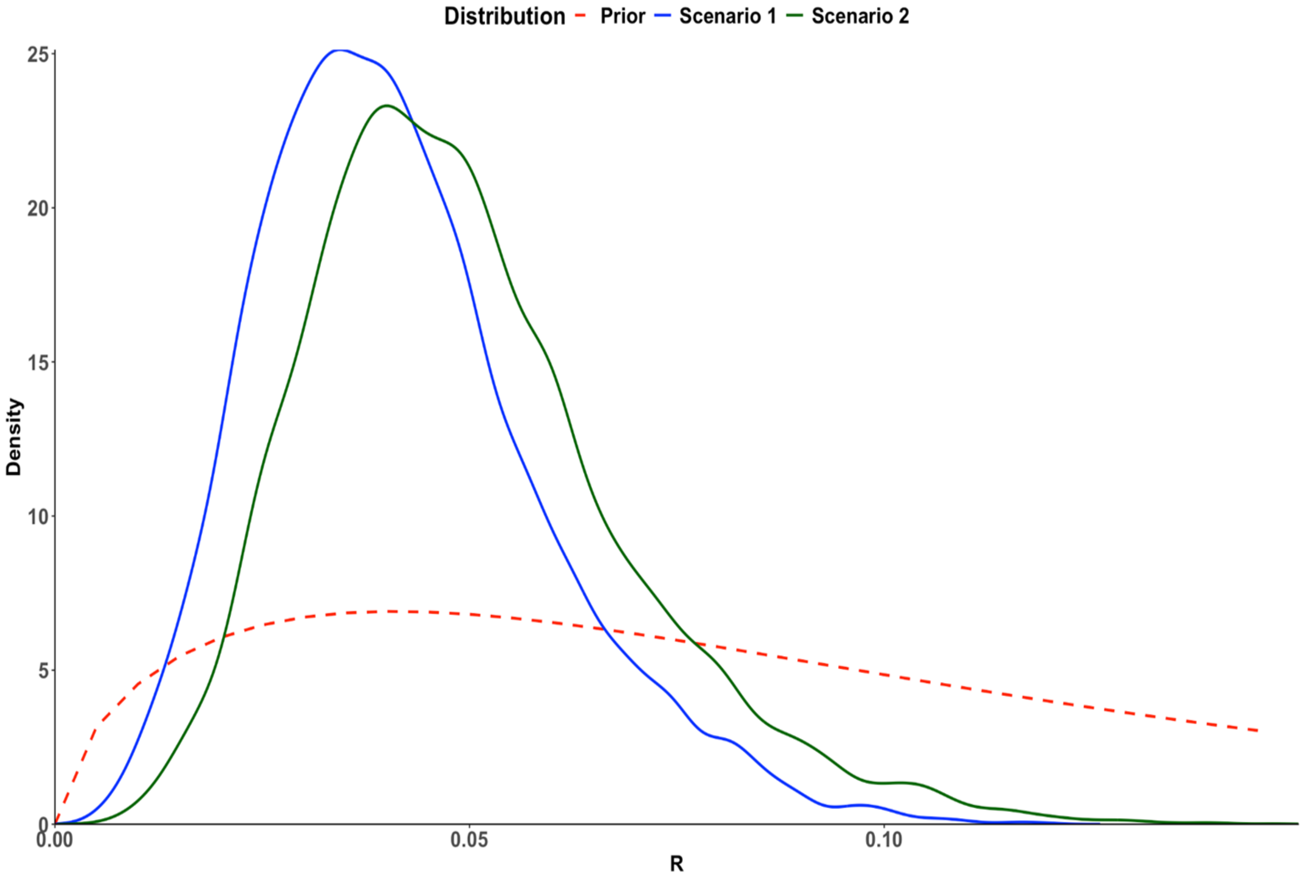
- Estimated using the epiverse-trace package epichains (Azam et al. 2024; Valle 2023)
- Prior based on Aditama et al. 2012

Scenario 1 - Assuming 45 single spillover cases and a cluster of 2 (Missouri case of unknown exposure source and a hypothetical source case)

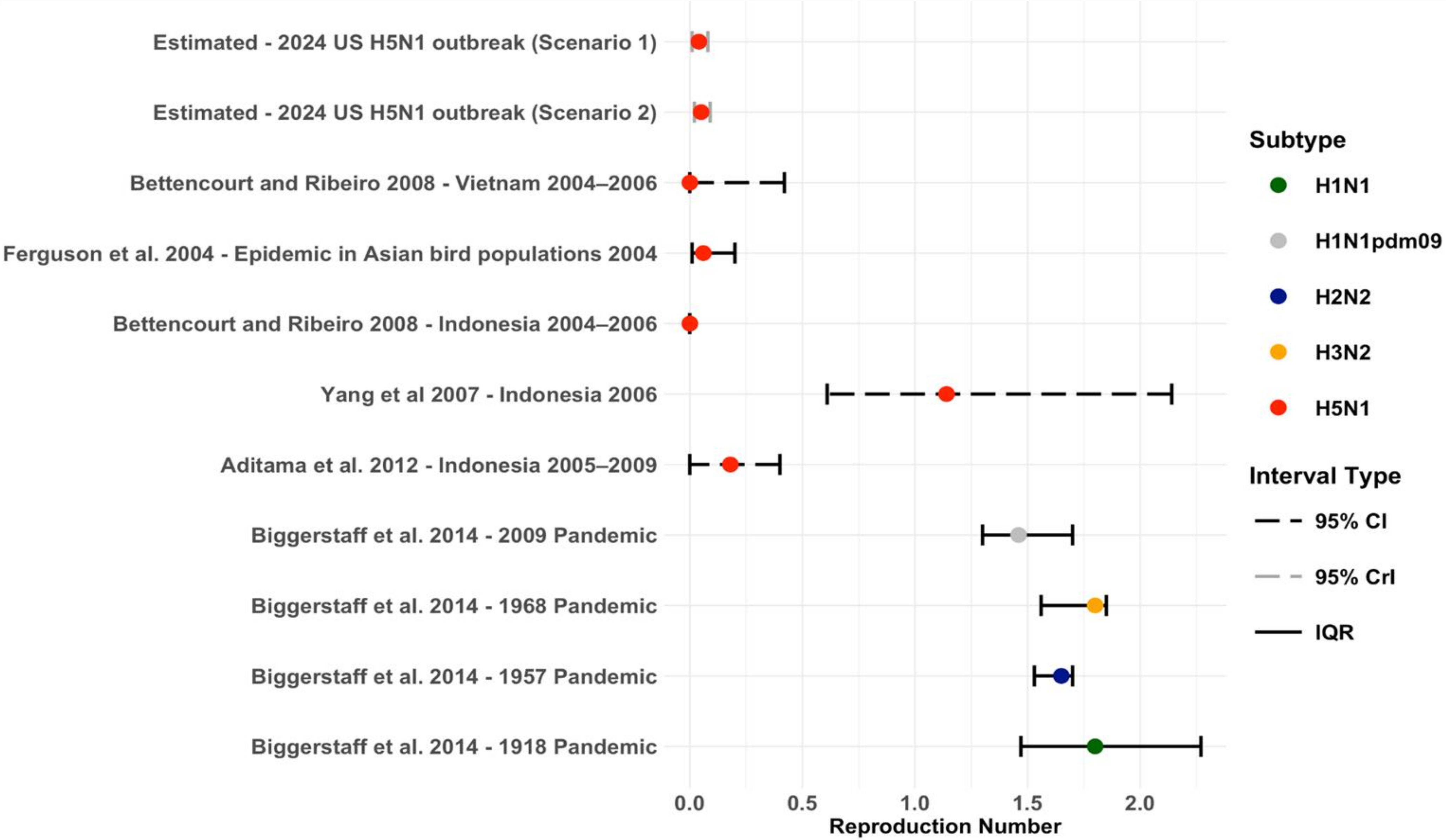
- Median = 0.04 (95% CrI: 0.01-0.08)

Scenario 2 - Assuming 45 single spillover cases and a cluster of 3 (Missouri case of unknown exposure source, their probable household contact and a hypothetical source case)

- Median = 0.05 (95% CrI: 0.02-0.09)



Reproduction number estimates for H5N1 & compared to previous influenza pandemics



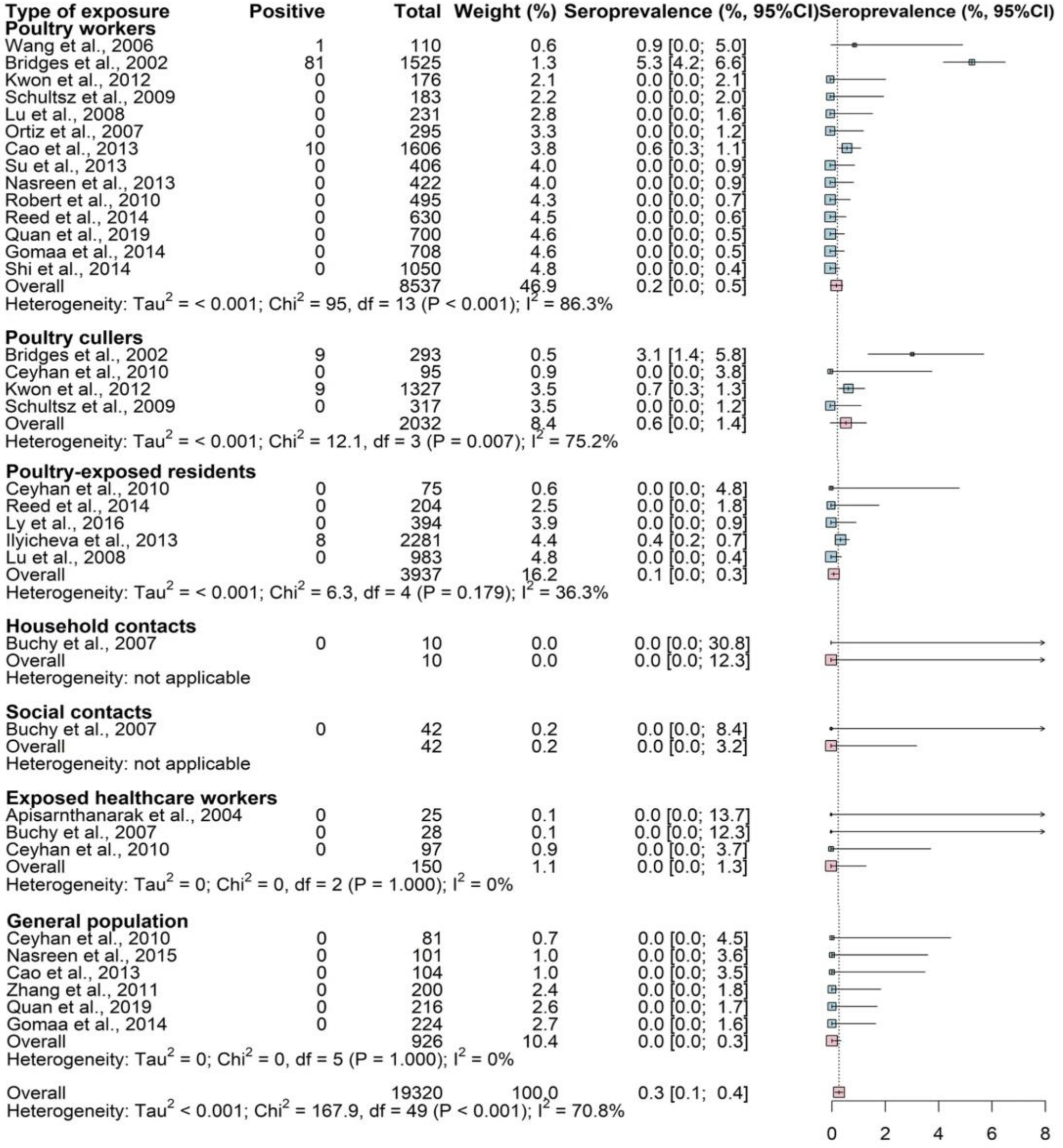
Serological evidence of H5N1 human infections

- **Systematic review by Chen et al. 2020 - 1997-2020**
- Seroprevalence of antibodies to avian influenza A (H5N1) virus (1997-2020) estimated through random effects models by type of exposure using WHO antibody titer threshold

- **Gomaa et al. 2023 - Egypt 2022/3**
- Between February 2022 and March 2023, 830 serum samples were taken from 394 Egyptian live bird market workers. Sera samples tested for antibodies against A/Duck/Egypt/BA20361C/2022 (H5N1) a clade 2.3.4.4b virus (Gomaa et al. 2023)
  - 38 (4.6%) of the samples had neutralising antibodies

- **Shittu et al. 2024 - Texas 2024**
- Microneutralization assays (MN) conducted on sera samples from farm workers' at two dairy farms in Texas 2024.
  - 2/14 (14.3%) farm workers showed evidence of being seropositive

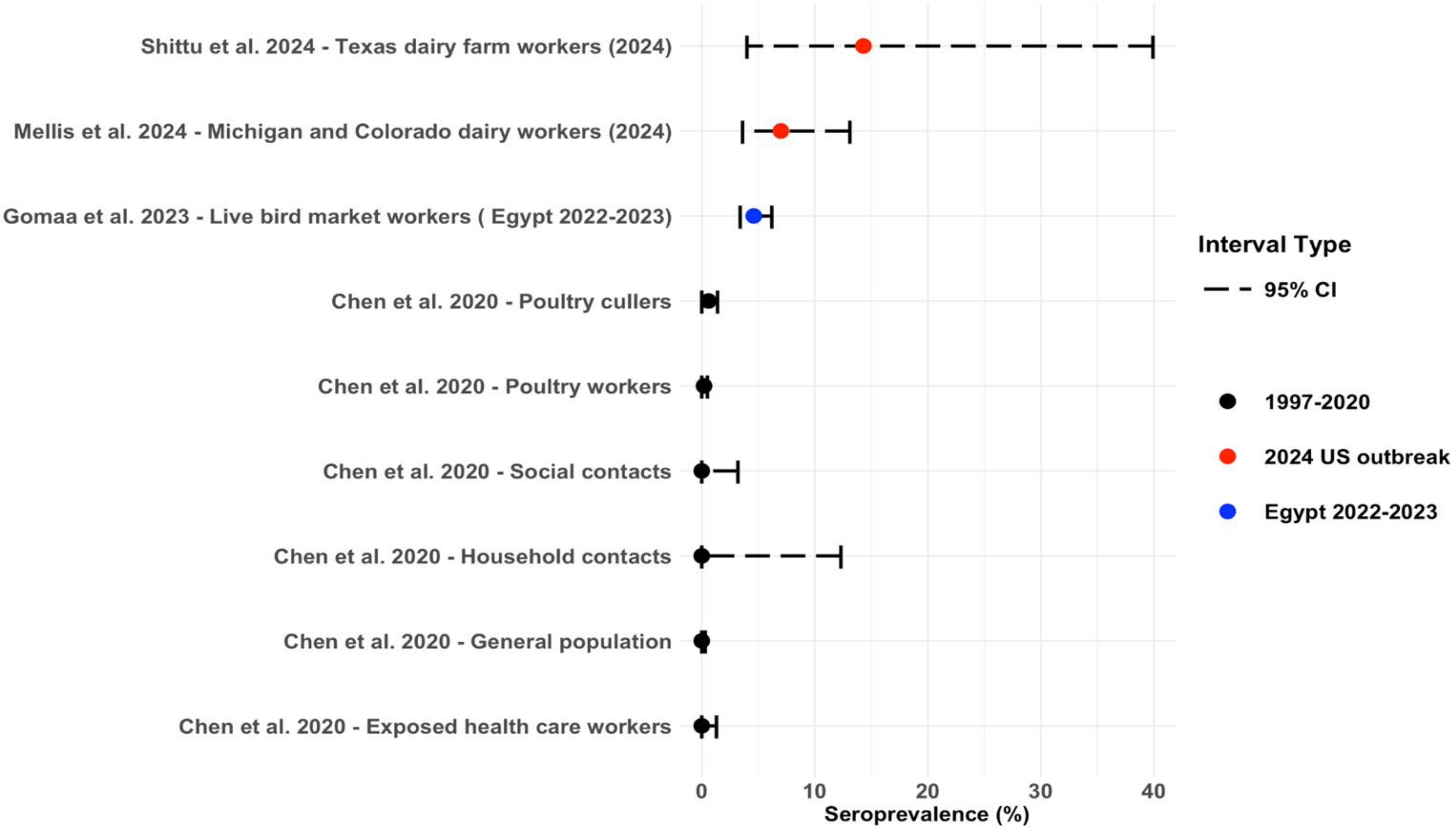
- **Mellis et al. 2024 - Michigan and Colorado 2024**
- MN assays conducted on sera samples from 115 dairy workers in Michigan and Colorado (June–August 2024)
  - 8/115 (7%; 95% CI = 3.6%–13.1%) had serologic evidence of infection
  - All positive cases reported milking cows or cleaning the milking parlour



Type of exposure	Positive	Total	Weight (%)	Seroprevalence (%, 95%CI)
Poultry workers				
Wang et al., 2006	1	110	0.6	0.9 [0.0; 5.0]
Bridges et al., 2002	81	1525	1.3	5.3 [4.2; 6.6]
Kwon et al., 2012	0	176	2.1	0.0 [0.0; 2.1]
Schultsz et al., 2009	0	183	2.2	0.0 [0.0; 2.0]
Lu et al., 2008	0	231	2.8	0.0 [0.0; 1.6]
Ortiz et al., 2007	0	295	3.3	0.0 [0.0; 1.2]
Cao et al., 2013	10	1606	3.8	0.6 [0.3; 1.1]
Su et al., 2013	0	406	4.0	0.0 [0.0; 0.9]
Nasreen et al., 2013	0	422	4.0	0.0 [0.0; 0.9]
Robert et al., 2010	0	495	4.3	0.0 [0.0; 0.7]
Reed et al., 2014	0	630	4.5	0.0 [0.0; 0.6]
Quan et al., 2019	0	700	4.6	0.0 [0.0; 0.5]
Gomaa et al., 2014	0	708	4.6	0.0 [0.0; 0.5]
Shi et al., 2014	0	1050	4.8	0.0 [0.0; 0.4]
Overall		8537	46.9	0.2 [0.0; 0.5]
Heterogeneity: Tau^2 = < 0.001; Chi^2 = 95, df = 13 (P < 0.001); I^2 = 86.3%				
Poultry cullers				
Bridges et al., 2002	9	293	0.5	3.1 [1.4; 5.8]
Ceyhan et al., 2010	0	95	0.9	0.0 [0.0; 3.8]
Kwon et al., 2012	9	1327	3.5	0.7 [0.3; 1.3]
Schultsz et al., 2009	0	317	3.5	0.0 [0.0; 1.2]
Overall		2032	8.4	0.6 [0.0; 1.4]
Heterogeneity: Tau^2 = < 0.001; Chi^2 = 12.1, df = 3 (P = 0.007); I^2 = 75.2%				
Poultry-exposed residents				
Ceyhan et al., 2010	0	75	0.6	0.0 [0.0; 4.8]
Reed et al., 2014	0	204	2.5	0.0 [0.0; 1.8]
Ly et al., 2016	0	394	3.9	0.0 [0.0; 0.9]
Ilyicheva et al., 2013	8	2281	4.4	0.4 [0.2; 0.7]
Lu et al., 2008	0	983	4.8	0.0 [0.0; 0.4]
Overall		3937	16.2	0.1 [0.0; 0.3]
Heterogeneity: Tau^2 = < 0.001; Chi^2 = 6.3, df = 4 (P = 0.179); I^2 = 36.3%				
Household contacts				
Buchy et al., 2007	0	10	0.0	0.0 [0.0; 30.8]
Overall		10	0.0	0.0 [0.0; 12.3]
Heterogeneity: not applicable				
Social contacts				
Buchy et al., 2007	0	42	0.2	0.0 [0.0; 8.4]
Overall		42	0.2	0.0 [0.0; 3.2]
Heterogeneity: not applicable				
Exposed healthcare workers				
Apisarnthanarak et al., 2004	0	25	0.1	0.0 [0.0; 13.7]
Buchy et al., 2007	0	28	0.1	0.0 [0.0; 12.3]
Ceyhan et al., 2010	0	97	0.9	0.0 [0.0; 3.7]
Overall		150	1.1	0.0 [0.0; 1.3]
Heterogeneity: Tau^2 = 0; Chi^2 = 0, df = 2 (P = 1.000); I^2 = 0%				
General population				
Ceyhan et al., 2010	0	81	0.7	0.0 [0.0; 4.5]
Nasreen et al., 2015	0	101	1.0	0.0 [0.0; 3.6]
Cao et al., 2013	0	104	1.0	0.0 [0.0; 3.5]
Zhang et al., 2011	0	200	2.4	0.0 [0.0; 1.8]
Quan et al., 2019	0	216	2.6	0.0 [0.0; 1.7]
Gomaa et al., 2014	0	224	2.7	0.0 [0.0; 1.6]
Overall		926	10.4	0.0 [0.0; 0.3]
Heterogeneity: Tau^2 = 0; Chi^2 = 0, df = 5 (P = 1.000); I^2 = 0%				
Overall		19320	100.0	0.3 [0.1; 0.4]
Heterogeneity: Tau^2 < 0.001; Chi^2 = 167.9, df = 49 (P < 0.001); I^2 = 70.8%				

Figure 4 from Chen et al. 2020

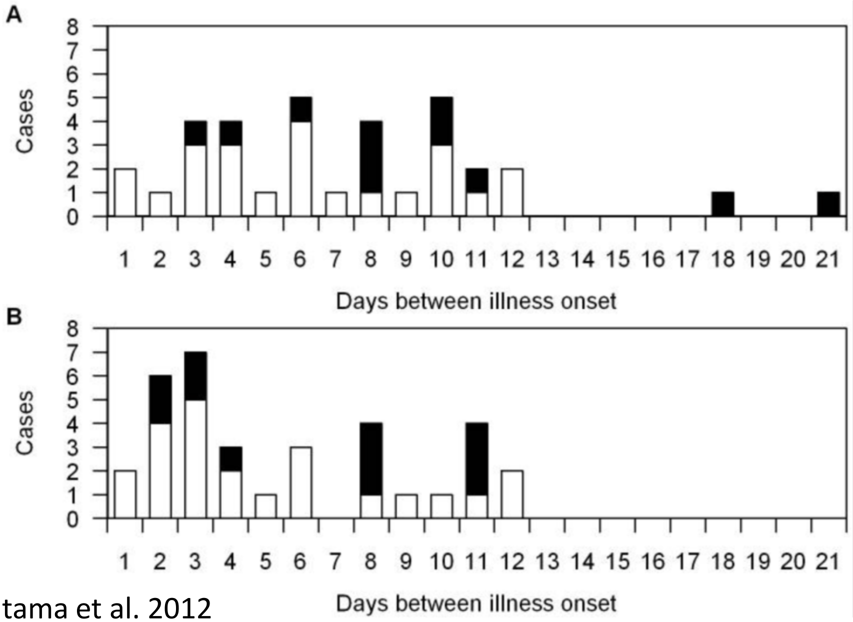
Serological evidence of H5N1 human infections



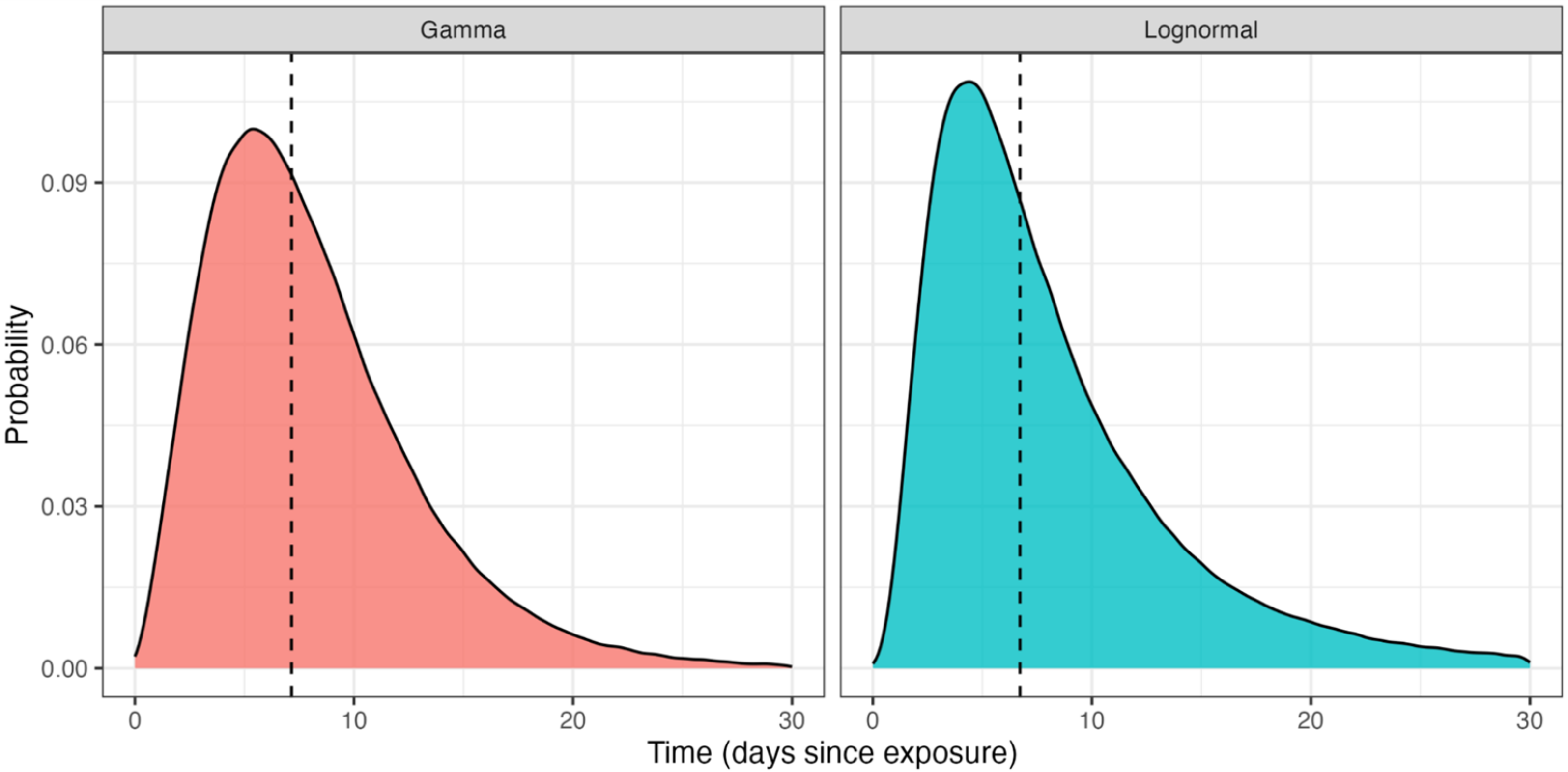
Serial interval estimation

- Data from Aditama et al. 2012 (below)
- Interval between onsets of illness between cases in Indonesia 2005–2009
- **A** - interval between onsets of illness of index and secondary cases
- **B** - interval between onsets of illness of serial cases
- **Black** denotes cases **not exposed to zoonotic sources** of virus
- **White** denotes cases **exposed to zoonotic sources** of virus

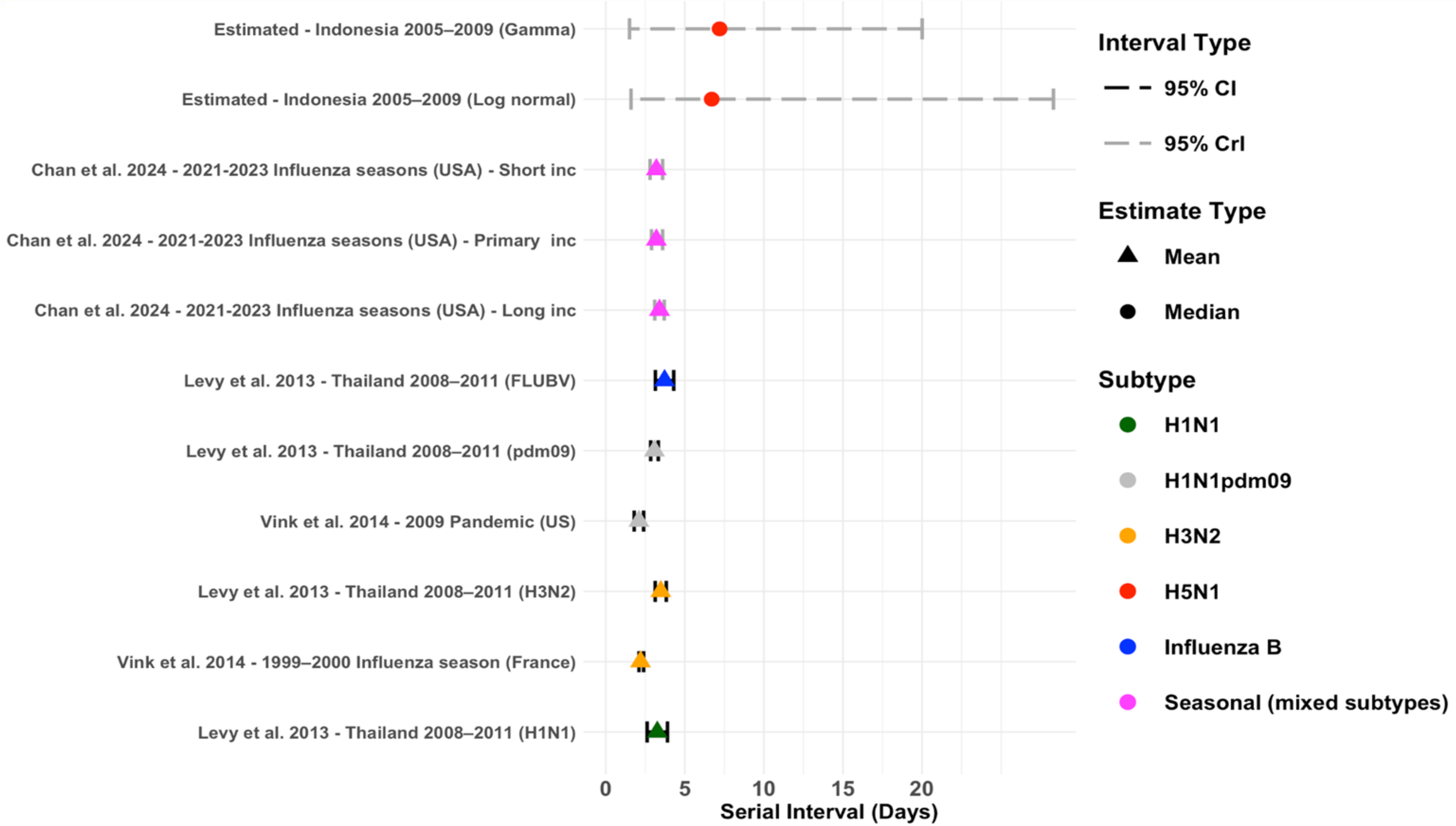
- Estimated serial interval
  - Mean of gamma fit: 8.1 days, Median: 7.2 (95% CrI: 1.5-20.0)
  - Mean of lognormal fit: 8.8 days. Median: 6.7 (95% CrI: 1.6-28.3)



Aditama et al. 2012



Serial interval comparison



Incubation period comparison across subtypes

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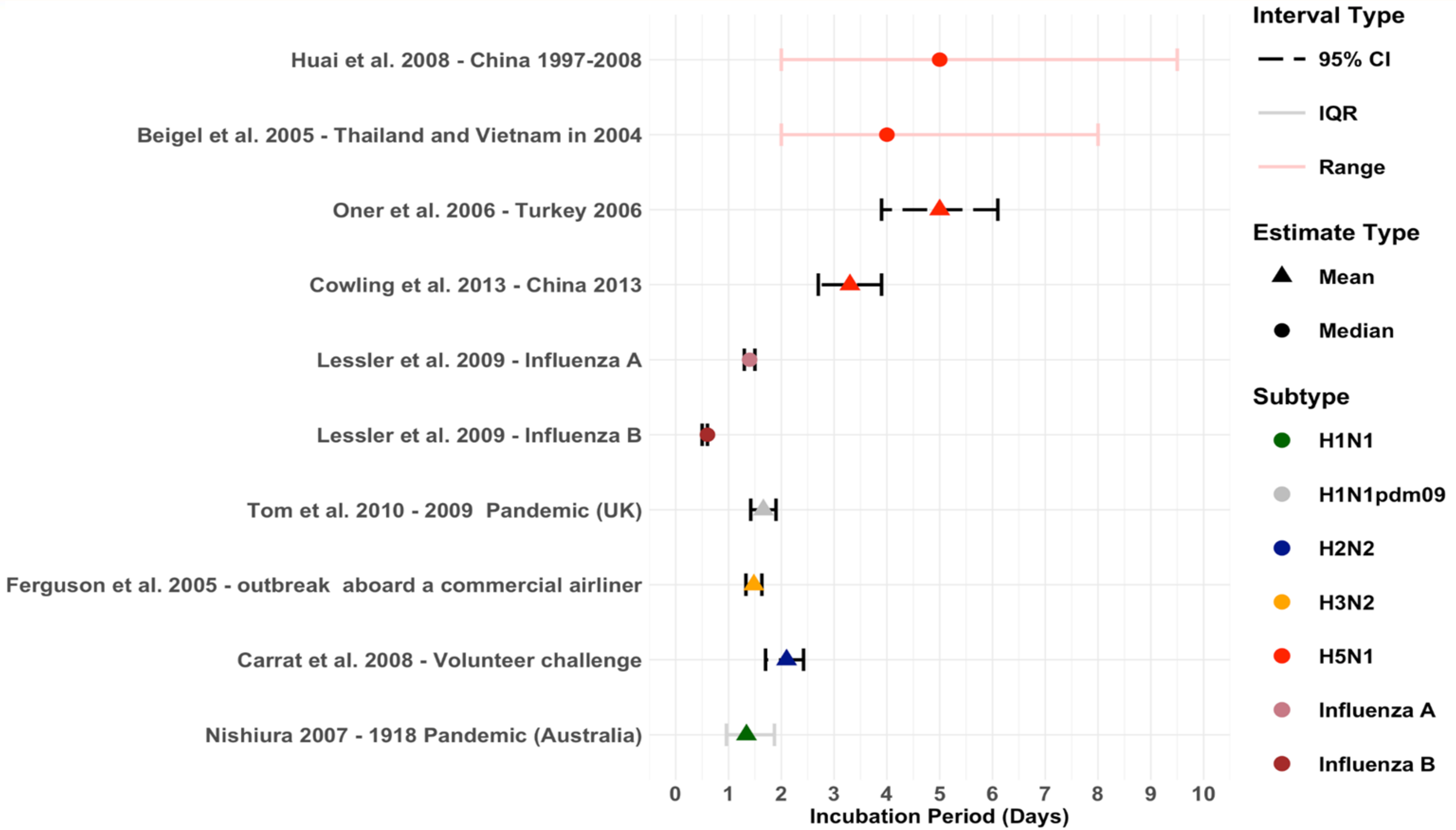
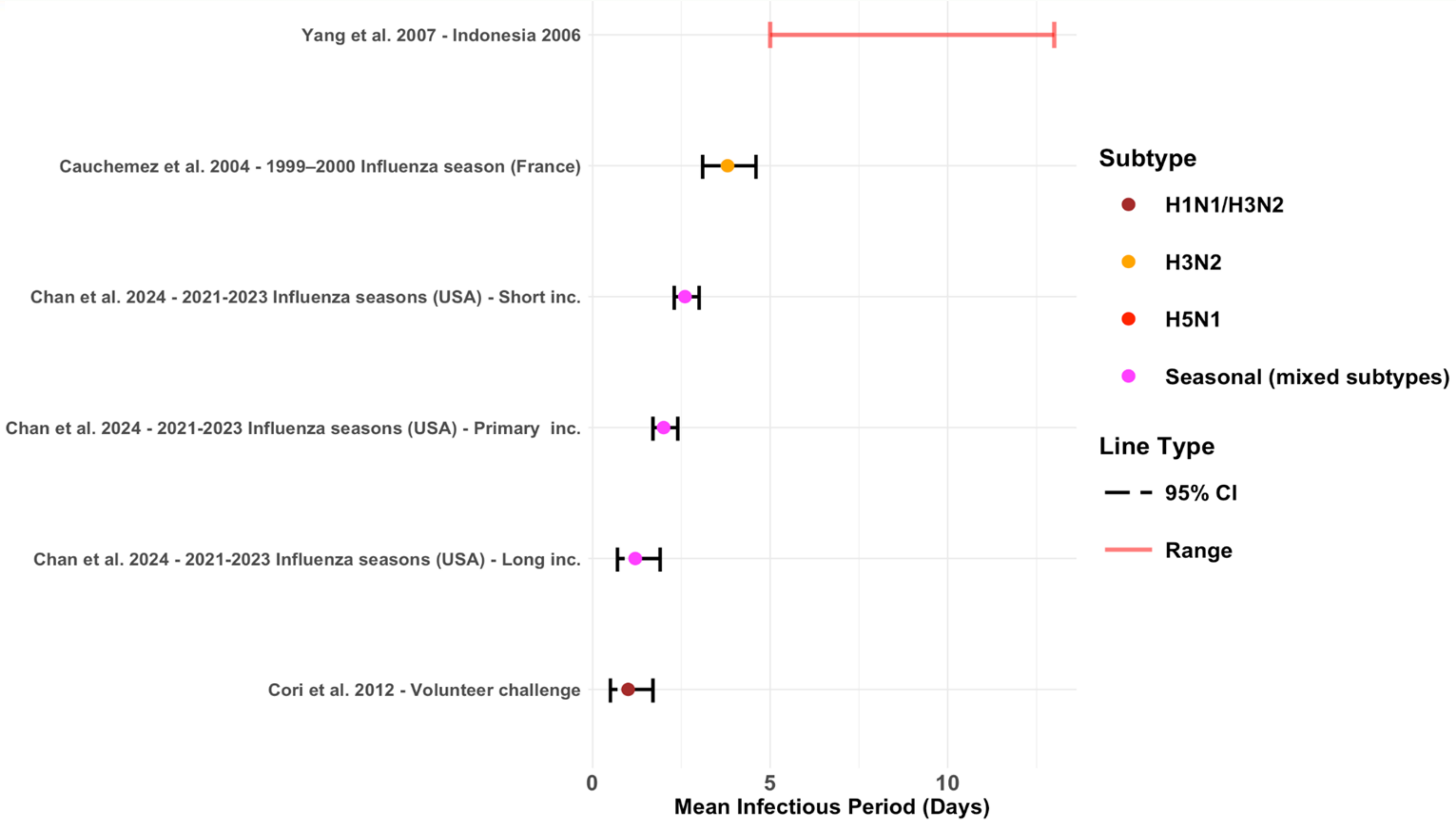


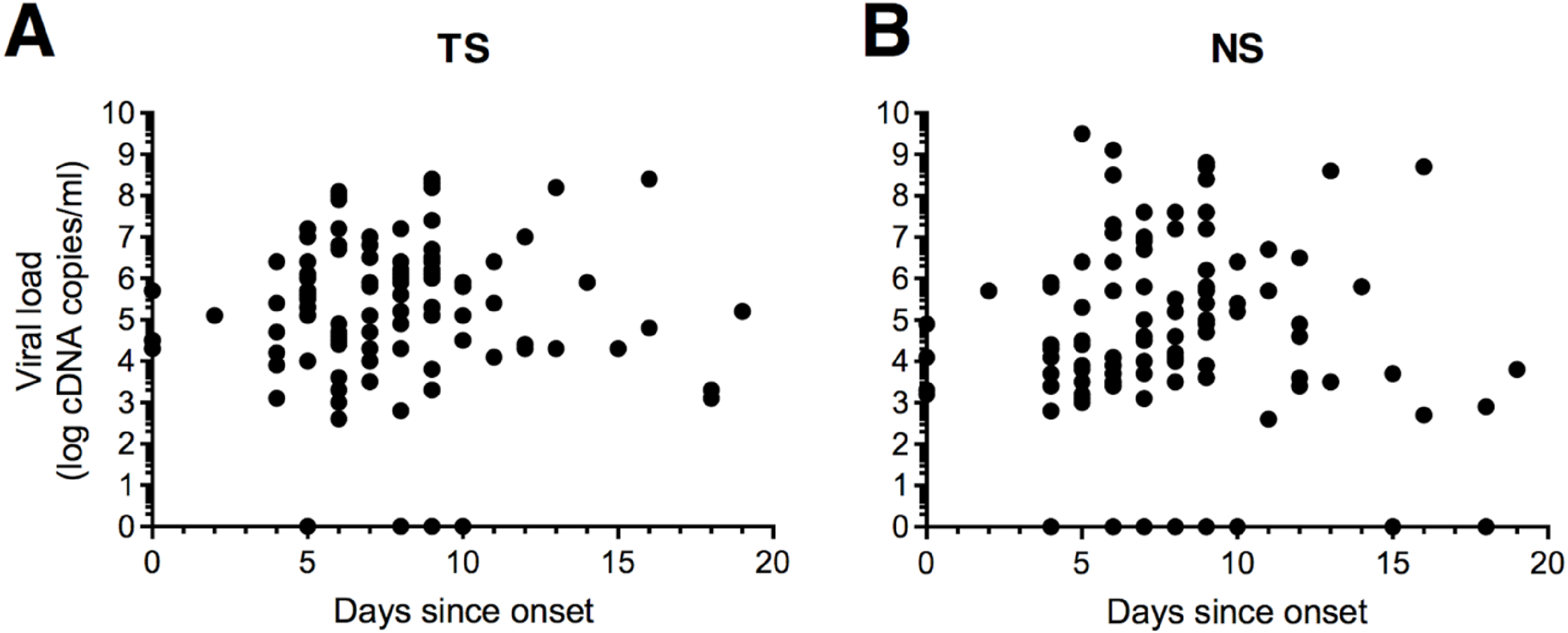
Infectious period across influenza subtypes



H5N1 viral load

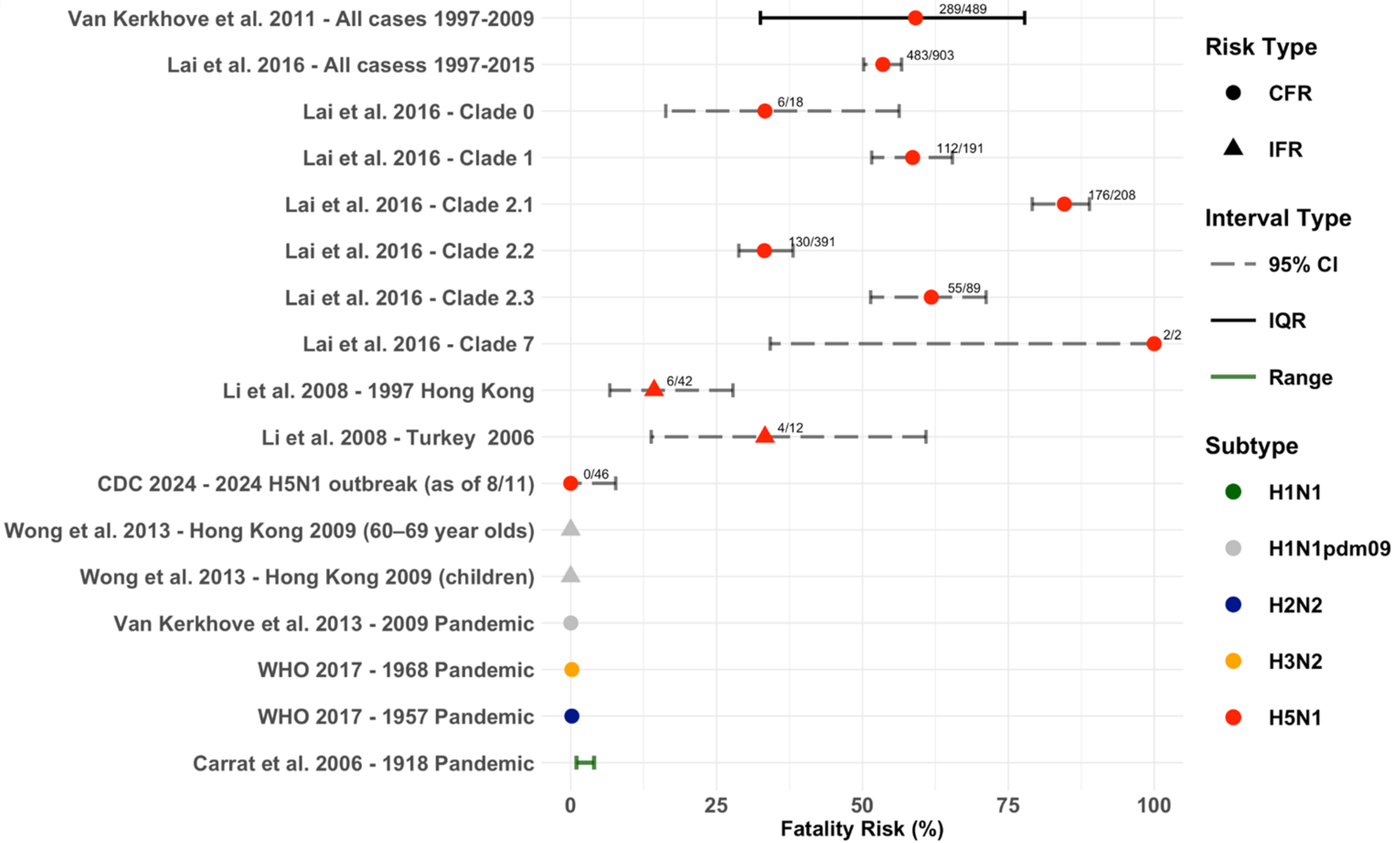
Figure S2 - Pawestri et al. 2020. TS = Throat swap, NS = Nasal swab

- H5N1 RNA quantified from 180 patients with confirmed infection between 2005 and 2017
- High viral RNA loads in nasal and pharyngeal specimens associated with fatal outcome.
- Mortality increased over time correlating with increasing viral RNA loads on admission



Fatality risk across influenza subtypes

WHO crude CFR from 1 January 2003 to 27th September 2024 = 51% (464/904)(WHO 2024)



Summary & conclusions

- Low R_0
  - Small clusters have been observed, but no sustained transmission
- Little evidence of asymptomatic infection (low seroprevalence)
  - Possibility of increased asymptomatic infection with Clade 2.3.4.4b
- Potentially longer incubation and infectious periods (no data on latent period)
- Evidence for longer serial interval than pandemic and seasonal strains
- US outbreak (Clade 2.3.4.4b) has much lower CFR than previously observed H5N1 outbreaks

- Data need to be carefully monitored to detect any changes
  - Updated regularly and rapidly

Acknowledgments

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