

ABSTRACT

Purpose

Determine the relationship between influenza inoculum dose and disease outcomes.

Methods

A systematic review to identify and abstract data from all influenza challenge studies. Exponential and linear models were used to assess the impact of inoculum dose on disease outcomes.

Results

Inoculum dose has a positive relationship on the proportion infected. However, there was a negative trend between inoculum dose and proportion of fever or systemic symptoms and between inoculum dose and the mean peak viral titers. There was also a rise of inoculum dose given to individuals and a decrease in the proportion of individuals with disease outcome over time.

Conclusion

Inoculum dose has a definite impact on disease outcomes.

METHODS

Data Collection

Data for this analysis was obtained from influenza challenge studies where individuals are inoculated with influenza virus (Figure 1). A systematic review and data abstraction were performed. In the data abstraction phase, we collected information on study design, study participants, and study outcomes. Each study can have multiple sub-studies where individuals are challenged by different influenza virus and varying inoculum dose.

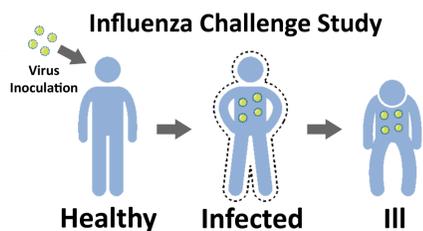


Figure 1: In a challenge study a healthy volunteer is inoculated with influenza virus and monitored for specific outcomes.

Data Model

An exponential model was used to fit the proportion infected as function of dose (D):

$$P_{infected}(D) = 1 - e^{-D}$$

METHODS CONTIN.

A linear model was used to analyze remaining relationships:

$$P_{infected}(D) = b_1D + b_0$$

RESULTS

Statistic:	Infected:	Systemic or Fever:	Mean Peak
Published Articles (N)	106	46	33
Challenge groups (N)	323	137	129
Participants (N)	5,652	2,345	2,332
Inoculum Dose Range (\log_{10} TCID ₅₀)	1.0-8.5	2.9-8.5	3.4-8.5

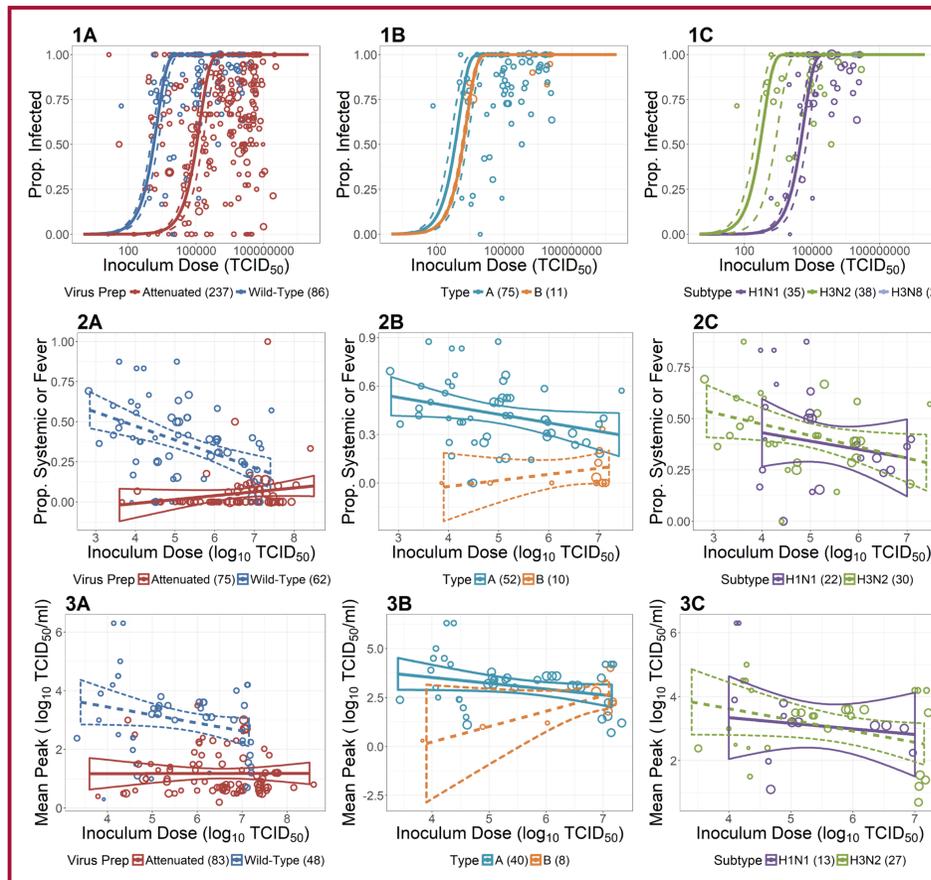


Figure 2: Inoculum dose impact weighted by study group size on (1) Proportion infected. (2) Proportion with systemic illness or fever. (3) Mean peak viral titer. (a) Stratified by virus prep. (b) Wild-type stratified by virus type. (c) Influenza A wild-type stratified by subtype.

RESULTS CONTIN.

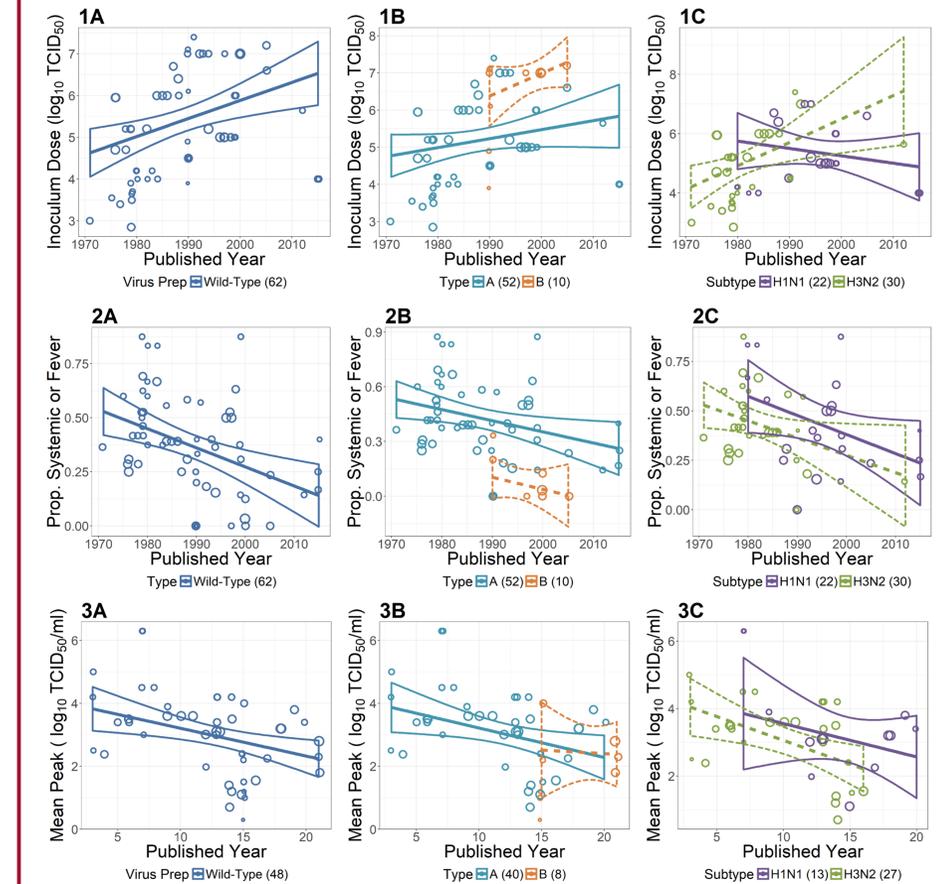


Figure 3: Published year impact weighted by study group size on (1) Inoculum dose. (2) Proportion with systemic illness or fever. (a) Wild-type. (b) Wild-type stratified by virus type. (c) Influenza A wild-type stratified by subtype.

A positive link between inoculum dose and proportion infected (Figure 2.1) and a negative trend between proportion with fever and inoculum dose was observed (Figure 2.2). These findings are supported by previous research [1,2]. However, an unanticipated negative trend between mean peak viral titer and inoculum dose was observed (Figure 2.3).

An attempt to explain the unexpected negative trends, we explored possible systematic differences between studies. Overall, inoculum dose has increased (Figure 3.1) and mean peak and proportion with fever or systemic symptoms has decreased over time (Figure 3.2 & 3.3).

CONCLUSION

- The trends over time indicates a weakening of wild-type influenza virus used in challenge studies.
- The negative trends observed may not be the result of systematic differences in challenge studies but are instead explained by an unknown immunologic mechanism.

1. Carrat, F., Vergu, E., Ferguson, N.M., Lemaître, M., Cauchemez, S., Leach, S. and Valleron, A.J., 2008. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. American journal of epidemiology, 167(7), pp.775-785.
2. Teunis, P.F., Brienen, N. and Kretzschmar, M.E., 2010. High infectivity and pathogenicity of influenza A virus via aerosol and droplet transmission. Epidemics, 2(4), pp.215-222.