Inoculum Dose Dependency of Infection Outcome in Influenza Challenge Studies

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Introduction

Influenza challenge studies have been conducted for various purposes since 1946. These studies involve inoculation of a group of volunteers with a known amount of virus and recording subsequent outcomes. This study is a meta-analysis of these challenge studies using inoculum dose as a predictor and proportion infected as an outcome. Inoculum dose is typically measured in tissue culture infectious dose 50 (TCID50), which is the amount of inoculum required to infect 50% of a given tissue culture.
The variation in inoculum dose in these different studies allows exploration between the dose and the outcome of infection, particularly the proportion of people who became infected. Knowing this relationships might suggest some public health measures that could hinder the spread of influenza by lowering the inoculum a person exposed to, through measures such as the wearing of a mask when infected.

Models

The two most appropriate dose-response models for this outcome are the Exponential Model and the Approximate Beta-Poisson Model[1].

Exponential Model:

$$y = 1 - e^{-a*x}$$

Approximate Beta-Poisson Model:

$$y = 1 - (1 - \frac{x}{\beta})^{-\pi\beta}$$

Where y is the proportion infected, x is the inoculum dose, and a and β are constants. Both models are single-hit, low-dose linear, scalable, and concave.
The Allee effect, in which increase in population density correlates with increased establishment of the organism, also suggests the Two-Parameter Weibull Model[2]:

$$y = 1 - e^{(\frac{x}{\lambda})^k}$$

Previous Work

Teunis[3] et. al (2010) performed an analysis using 17 challenge studies utilizing nasal inoculation and 15 studies utilizing aerosol inhalation in order to discuss dynamics of host heterogeneity in influenza transmission. They assumed that one TCID 50 was not different from one viral particle due to the high infectivity of the virus.

Carrat[4] et. al. (2008) performed a similar literature review involving 1,280 volunteers, without the outcome of proportion shedding virus. They found new information regarding viral dynamics.

Both Teunis and Carrat only considered studies involving wild-type viruses.

Methods

A systematic literature review was performed and data was extracted twice, independently. The data was imported into R, which was used for the analysis. Since this analysis focused on inoculum dose as the predictor and proportion infected as the outcome, studies that did not include these variables were excluded from the rest of the study. Only studies which inoculated volunteers with live influenza were analyzed, including those utilizing live attenuated viruses.

Data were plotted using ggplot2, and the nls package was used to optimize variables for the different models. The studies were stratified by virus preparation to examine variation between wild-type viruses, cold- adapted viruses, egg-passaged viruses, etc. Some of the models were weighted by study group size in order to account for increased accuracy with increased sample size. Bootstrapping was used to create 95% confidence intervals.

Summary of Included Studies

The analysis was comprised of 333 studies involving 5,116 volunteers. 264 of these studies reported the inoculum dose used and the proportion of volunteers infected by this dose, and these studies involved 4,601 volunteers. Papers reporting these variables were published between 1965 and 2016.

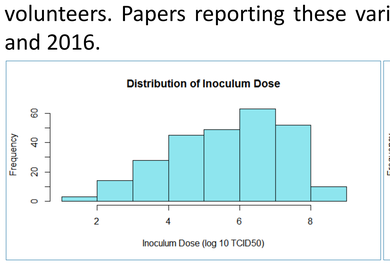

Figure 1a

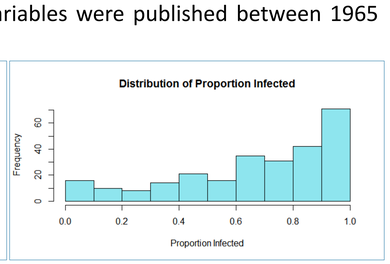

Figure 1b

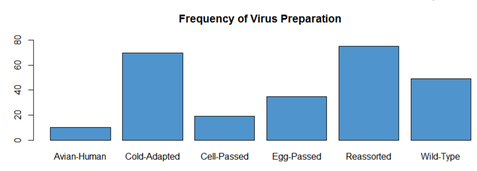

Figure 2

Results

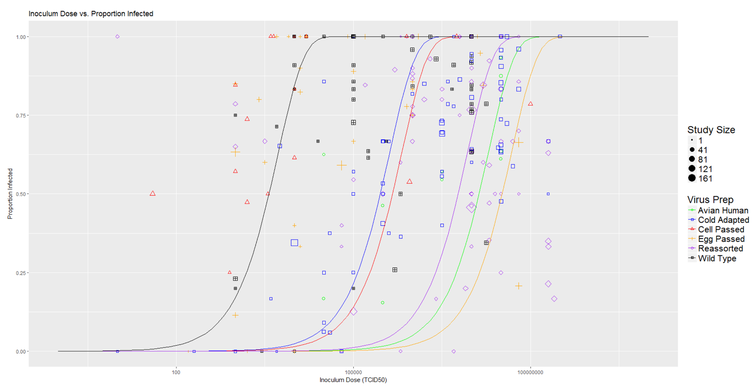

Figure 3: Exponential model by subgroup, weighted by study group size

Results (cont.)

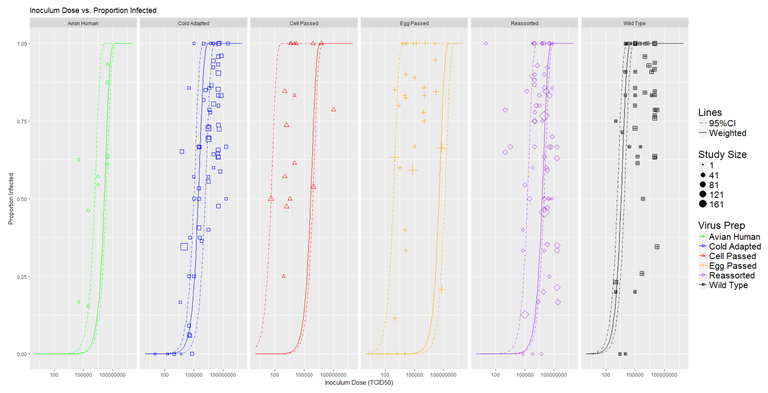

Figure 4: Exponential model weighted by study group size along with the 95% confidence intervals.

Conclusions

As expected, Figure 3 shows that wild-type infections occur more readily at lower doses than the attenuated virus types, implicating some type of fitness loss when passaged through human or nonhuman cells. However, when the 95% confidence intervals are evaluated as in Figure 4, it is apparent that they overlapped. Visualization comparison showed that the exponential function weighted by study size fit the data the best.

We were unable to converge the models for the Approximate Beta-Poisson models. Future work could involve using the nls or nloptr packages to fit the data to these models.

Works Cited

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[3]Teunis, Peter F.M. et.al. 2010. High infectivity and pathogenicity of influenza A virus via aerosol and droplet transmission. Epidemics 2 215-222.

[4]Carrat et. al. 2008. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. American Journal of Epidemiology 167 (7): 775-785.

Acknowledgements

This material is based on work supported by the National Science Foundation, Grant Number 1659683.