Dynamical Differences Caused by Differences in Route of Infection

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Background

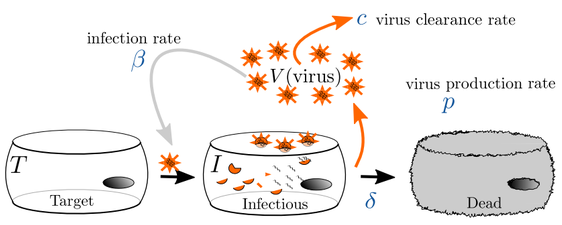
- Infections deriving from the highly pathogenic avian H5N1 influenza virus often result in severe respiratory diseases with a high mortality rate, with strains like H5N1 having a 60% mortality rate.[3]
- Although rarely transmissible to humans, recent events like the COVID-19 pandemic and avian flu outbreaks dating back to 1918[1] have shown that a proper understanding of deadly pathogens akin to H5N1 and variables that affect its lethality are vital.
- In this study, we test how the severity of H5N1 in Cynomolgus Macaques varies between different methods of entry: a combined direct oral/nasal inoculation or aerosol exposure.
- We use a mathematical model to estimate viral infection parameters and compare them in different cases.
- This is an example of how mathematical models are used to help understand how the method of entry of H5N1 impacts its progression and the life cycle of H5N1 in vivo.

Mathematical Model

- Both infectious virus and RNA measurements are available, so we will use a model of viral infection that includes both.

$$\begin{aligned}\frac{dT}{dt} &= -\beta T V_{inf}\\ \frac{dI}{dt} &= \beta T V_{inf} - \delta I\\ \frac{dV_{inf}}{dt} &= pI - c_{inf}V_{inf}\\ \frac{dV_{RNA}}{dt} &= \rho p I - c_{RNA}V_{RNA}\end{aligned}$$

- Uninfected target cells, T, become infected by infectious virions, V_{inf}, at a rate β.
- We will initially neglect internal replication of the virus and assume that cells immediately become productively infectious, I.
- Infectious cells produce infectious virus at rate p and produce viral RNA at rate ρp.
- Infectious cells die after a time $1/\delta$ while infectious virus decay at a rate c_{inf} and viral RNA degrades at a rate c_{RNA}.



Methods

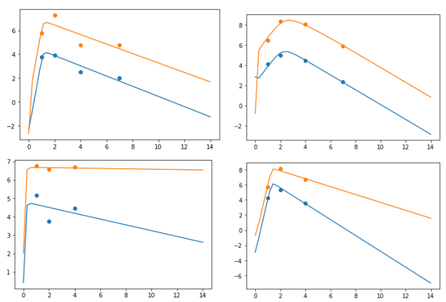
- All data for the viral loads resulting from each pathway were obtained from *Mooij et al.*
- We used the Python `odeint` function to solve the model system of differential equations.
- We used the `minimize` function in Python, which utilized both a Nelder-Mead algorithm to minimize the SSR, resulting in a line of best-fit and estimates of the best fit parameters.

Experimental Data

- Three groups of four cynomolgus macaques each were exposed to $6{\times}10^6$ $TCID_{50}$ of influenza A/Vietnam/1203/04 (H5N1) virus.
- The animals from the combined-route group were inoculated with a suspension containing virus by intra-bronchial (2 mL left lung, 2 mL right lung, with a bronchoscope), oral (1 mL), and intra-nasal (0.5 mL per nostril) administration.
- The aerosols were generated using an OMRON U22TM nebulizer and the animals were allowed to inhale the aerosols under general anesthesia via a mask until all the fluid was vaporized.
- One aerosol group had bronchoalveolar lavage collected via bronchoscope on days 2,4, and 7, while the other aerosol group did not have this invasive sample collection.

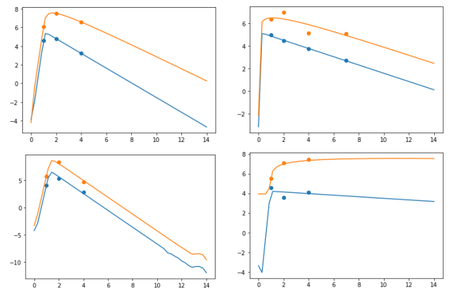
Direct Inoculation

Figures show the best fit model curves and the tables give the best fit parameter values.



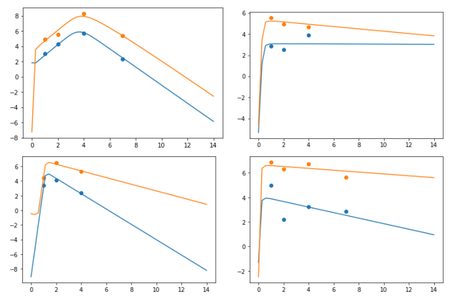
Parameters	J15001	J15007	J15011	J15033	Median
β (mL/($TCID_{50}\cdot d$))	1.24×10^{-3}	1.07×10^{-5}	8.87×10^{-3}	1.46×10^{-5}	6.27×10^{-4}
δ (d^{-1})	2.48×10^{1}	1.88	8.33	2.68×10^{1}	1.66×10^{1}
c_{inf} (d^{-1})	9.84×10^{-1}	1.23×10^{1}	3.63×10^{-1}	2.42	1.70
c_{RNA} (d^{-1})	9.13×10^{-1}	2.32	2.47×10^{-2}	1.20	1.06
p ($TCID_{50}$/(mL$\cdot$d))	4.65×10^{5}	8.36×10^{6}	4.99×10^{5}	5.58×10^{7}	4.43×10^{6}
ρp (copies/(mL$\cdot$d))	1.57×10^{8}	2.34×10^{9}	4.02×10^{7}	4.32×10^{9}	1.25×10^{9}
V_{inf} ($TCID_{50}$/mL)	5.06×10^{-3}	6.87×10^{2}	2.63	1.22×10^{-3}	1.32
V_{RNA} (copies/mL)	2.31×10^{-3}	1.69×10^{-1}	1.06×10^{2}	2.01×10^{-1}	1.85×10^{-1}

Aerosol Infection



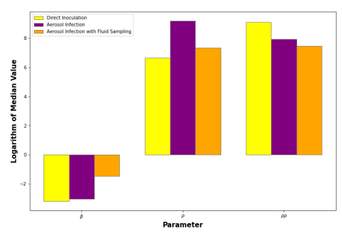
Parameters	J14013	J14017	J15025	J15028	Median
β (mL/($TCID_{50}\cdot d$))	9.51×10^{-5}	3.69×10^{-2}	4.83×10^{-6}	1.65×10^{-3}	8.73×10^{-4}
δ (d^{-1})	1.82	8.45×10^{-1}	3.56	1.85×10^{-1}	1.33
c_{inf} (d^{-1})	5.68×10^{1}	1.32×10^{1}	5.81×10^{2}	8.20×10^{5}	3.19×10^{2}
c_{RNA} (d^{-1})	1.50	1.05	9.35	$4.34\times106{-}2$	1.28
p ($TCID_{50}$/(mL$\cdot$d))	1.89×10^{7}	2.04×10^{6}	3.24×10^{9}	1.43×10^{10}	1.60×10^{9}
ρp (copies/(mL$\cdot$d))	1.67×10^{8}	8.03×10^{6}	8.22×10^{9}	1.08×10^{7}	8.89×10^{7}
V_{inf} ($TCID_{50}$/mL)	1.27×10^{-4}	6.48×10^{-4}	6.04×10^{-5}	4.72×10^{-4}	3.00×10^{-4}
V_{RNA} (copies/mL)	6.04×10^{-5}	6.30×10^{-3}	5.10×10^{-4}	9.34×10^{3}	3.41×10^{-3}

Aerosol Infection with Fluid Sampling



Parameters	J14020	J14024	J14037	J15010	Median
β (mL/($TCID_{50}\cdot$ d))	1.43×10^{-6}	6.18×10^{-1}	2.00×10^{-4}	6.64×10^{-2}	3.33×10^{-2}
δ (d^{-1})	6.14	4.31	2.54×10^{2}	6.14	6.14
c_{inf} (d^{-1})	1.22×10^{1}	1.18×10^{-2}	2.41	5.20×10^{-1}	1.47
c_{RNA} (d^{-1})	2.82	2.54×10^{-1}	1.05	1.75×10^{-1}	1.30
p ($TCID_{50}$/(mL$\cdot$d))	1.01×10^{8}	5.40×10^{3}	4.36×10^{7}	6.66×10^{4}	2.18×10^{7}
ρp (copies/(mL$\cdot$d))	3.07×10^{7}	9.11×10^{5}	1.17×10^{9}	2.69×10^{7}	2.88×10^{7}
V_{inf} ($TCID_{50}$/mL)	6.61×10^{1}	4.66×10^{-6}	8.17×10^{-10}	4.80×10^{-2}	2.40×10^{-2}
V_{RNA} (copies/mL)	5.69×10^{-8}	2.19×10^{-5}	3.42×10^{-1}	3.36×10^{-3}	1.69×10^{-3}

Comparison of β, p, and ρp



Conclusions

- For the direct inoculation, aerosol infection, and aerosol infection with fluid sampling initial fit graphs, the line of best fit for each Cynomolgus Macaque is relatively precise.
- The direct inoculation treatment has the greatest rate of infection β as well as the greatest rate of production of Viral RNA ρp.
- In addition, the aerosol infection treatment group produces infectious virus the fastest at a rate p.
- The aerosol with fluid sampling has a markedly lower infection rate than the other two cases, perhaps because fluid containing virus is periodically removed from the respiratory tract.

Future Work

- In the near future, our first objective is to construct a confidence interval to depict the range of parameter values that are possible for each Cynomolgus Macaque using either bootstrapping or the Markov Chain Monte Carlo method.
- This analysis used only the throat swabs, but nasal swabs are also available and will be assessed.

Works Cited

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3. Poovorawan Y, Pyungporn S, Prachayangprecha S, Makkoch J. Global alert to avian influenza virus infection: from H5N1 to H7N9. Pathog Glob Health. 2013;107(5):217-223. doi:10.1179/2047773213Y.0000000103

Acknowledgements

We would like to sincerely thank Dr.Gerrit Koopman for providing us the data for this project.