Modelling self spreading vaccines in a reasonable worst case influenza pandemic in the UK

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Why Influenza?

Motivation

Why is influenza a priority?

- In 1918 Spanish flu killed 50-100 million people. [6]
- It's the number 1 risk on the national risk register. [9]

Why was Spanish flu very bad?

- Miss-copied viral RNA over stimulates the cytokine generation pathway. [10] People literally drowned in their own white blood cells.
- Unlike normal flu can grow in lung, throat and nose facilitating secondary lung infection. [11]


RIG1

J. Clark
2018 ©
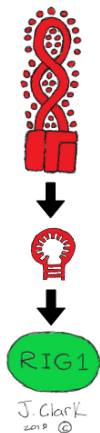
Why self spreading vaccines?

- Vaccine delay. Several months till first doses of pandemic specific vaccine delivered.
- Limitation of prepandemic vaccines.
    - Less effective than specific vaccine.
    - Almost completely ineffective if H type of virus different from vaccine.
    - Need to be replaced periodically.
- Recombinant vaccines difficult to manufacture at scale. One or 2 million doses of a recombinant vaccine is a drop in the ocean.

What is a self spreading vaccine?

- Spreads like a disease
- Does very little harm (compared to the pandemic)
- Acquired immunity to vaccine also confers immunity to the pandemic.
- Get cow pox now to avoid small pox later

Constructing a pandemic flu self spreading vaccine

- Immune system primarily recognize a virus by the proteins on its surface, antibodies can block these neutralizing the virus.

- genes expressed in infected cells can vary with out effecting immune system recognition

- Genetically modify pandemic to replace high lethality genes with low lethality counterparts.

- Release into general population.
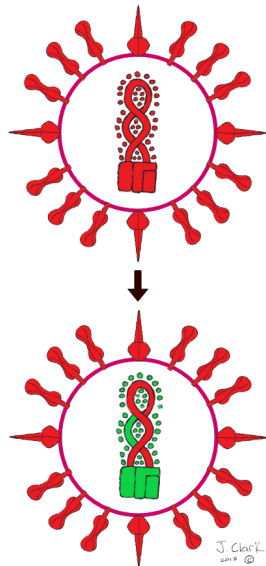
Genes of interest

- swapping polymerase complex genes (PA, PB1, PB2 & NP) between ordinary flu and 1918 flu swaps the lung infecting capability. [11]
- Replacing polymerase gene PB1 in H5N1 with a high-fidelity mutant gene prevented the triggering of cytokine storm and reduced lethality roughly 10 fold.[10]

SEIR Equations

$$\frac{dS}{dt} = -\frac{\beta \left(I_A + I_B\right) S}{N} \tag{1}$$

$$\frac{dE_A}{dt} = \frac{\beta I_A S}{N} - \gamma_1 E_A \qquad \frac{dE_B}{dt} = \frac{\beta I_B S}{N} - \gamma_1 E_B \tag{2}$$

$$\frac{dI_A}{dt} = \gamma_1 E_A - \gamma_2 I_A \qquad \frac{dI_B}{dt} = \gamma_1 E_B - \gamma_2 I_B \tag{3}$$

$$\frac{dR_A}{dt} = \gamma_2 I_A \qquad \frac{dR_B}{dt} = \gamma_2 I_B \tag{4}$$

Parameters

- $\frac{\beta}{\gamma} = R_0 = 2.011797$ [1]
- $\frac{1}{\gamma_1} = 0.64$ average incubation period. [4] (2 in sensitivity analysis) [2]
- $\frac{1}{\gamma_2} = 1.27$ average infectious period. [4] (4 in sensitivity analysis) [2]
- proportion of infections that are symptomatic cases 62.5% [1]
- case fatality rate 2.5% for pandemic (based on reasonable worst case). 0.4% for self spreading vaccine (based on 1968 pandemic next most severe of 20th century) [1]

Starting Conditions

Vaccine Production by Cell Culture

"A single use bioreactor with a working volume of 30 L would provide sufficient LAIV for the preparation of approximately 2.4 million doses of monovalent vaccine in a single run." [8]

- We assume 1.8m to 2.8m doses
- Assumed initially 1 infection and no vaccine infections.
- First official day of pandemic calculated as average day first fatality enters infectious phase.
- Vaccine introduced in one day measured relative to official start.
- Doses administered to infected individuals assumed to have no effect.
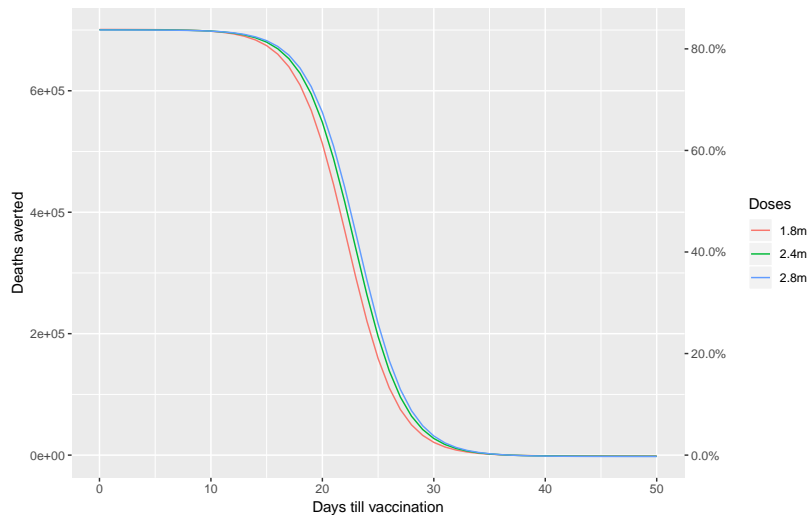
Impact in Lives [3]

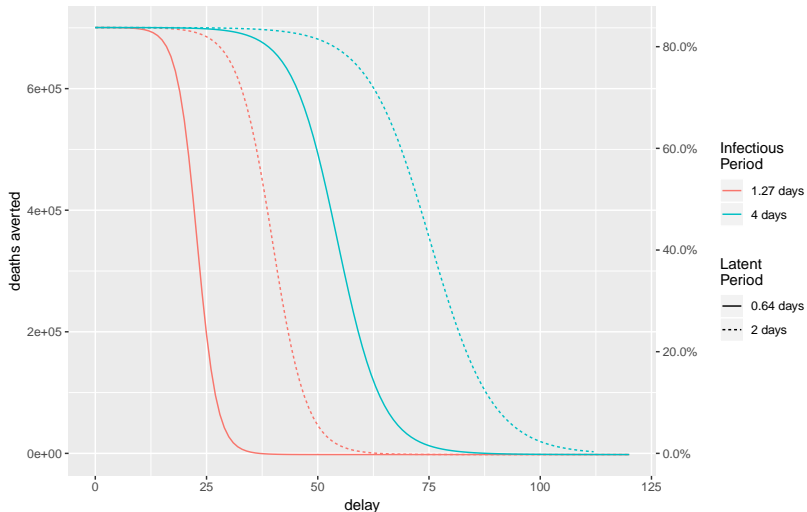Figure 1: $\gamma_1^{-1} = 0.64$ & $\gamma_2^{-1} = 1.27$

Impact in Lives [3]

Figure 2: 2.4m doses

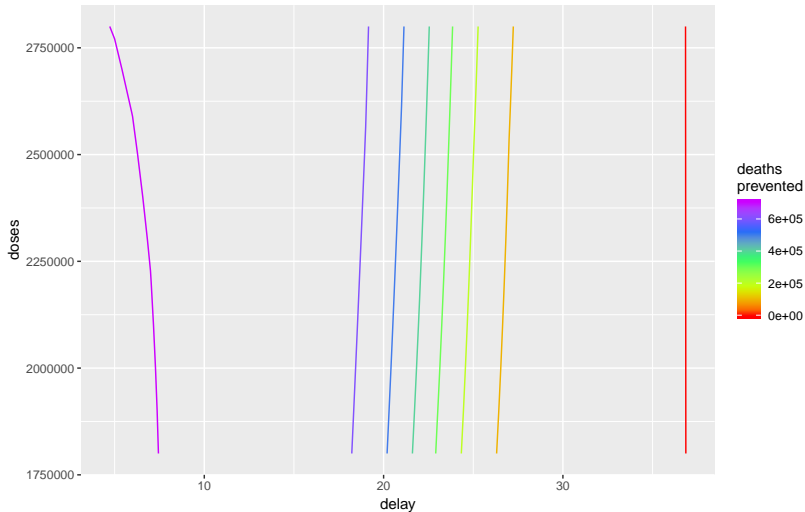# Speed is more important than Doses [3]

Figure 3: $\gamma_1^{-1} = 0.64$ & $\gamma_2^{-1} = 1.27$

Implementation (How I'm getting my mad science badge!)

- Next generation sequencing of Influenza virus. (days) [7]
- Gibson assembly of insilico designed vaccine. (within a day) [5]
- Production in Bioreactor.

- Administration. Approximately 2.3m higher education students in uk.
- Concentrated in geographically small areas.
- Mostly in age group where vaccine most beneficial.
- Do not work so absence will not cause economic disruption.
- Mostly have 2nd homes to go to spreading the vaccine.
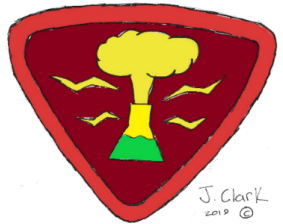
Ethics and Implications

- Self spreading vaccine is less lethal not non lethal. It can still kill.
- For most people infection reduces risk of death.
- No consent possible from majority of patients.
- Some people will die who would other wise have lived even though fewer people die over all. (trolley problem)

Potential for further work

- Age structured models.
- Models addressing geographical spread.
- Models that take into account the application of antivirals and antibiotics.

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