June 17, last updated March 25, 2020

Goals

1. Challenge the CDC's unrejected implicit null hypothesis that testing does not influence behavior for asymptomatic individuals who are diagnosed positive.

   - Show that the observed prevalence (# positive and negative diagnoses) for reasonable parameters is simultaneously consistent with both of the following hypotheses:

     H_0) Testing does not influence behavior for asymptomatic individuals.

     H_1) Asymptomatic individuals with positive diagnoses are responsible for fewer new infections per person than their undiagnosed peers.

     In both cases, we partition the population into a group whose members behaves as though they are susceptible and a group whose members behave as though they are infected. In the null hypothesis, only infected people who are diagnosed positive and have experienced symptoms behave as though they are infected. In the alternate hypothesis, infected people with false positive diagnoses and people with true positive diagnoses who have never experienced symptoms also behave as though they are infected.
   - Argue that a higher rate of infection due to false positive diagnoses may counteract a lower rate of infection caused by asymptomatic people following true positive diagnoses.

2. Simulate the effect of various combinations of interventions:

   (a) Increase testing. This may increase prevalence because false positives are more likely to become infected, assuming they serosort with positives.

   (b) Provide better information for people with borderline diagnoses, encouraging protection and retesting. This should decrease prevalence.

   (c) Increase testing and provide better information. This should further decrease prevalence.

   (d) Recalibrate the common test by decreasing specificity. This may decrease prevalence without changing behavior.

   (e) Replace the common test with a more accurate one. This should decrease prevalence.

Population Groups

S^- Negative people who believe to be negative (due to lack of diagnosis or true negative).

S^+ Negative people who believe to be positive (due to false positive diagnosis).

I^- Positive people who believe to be negative (due to lack of diagnosis or false negative diagnosis).

I_a^+ Diagnosed positive people who have never experienced symptoms.

I_s^+ Diagnosed positive people who have experienced symptoms at least once.

Population N is partitioned into N^+ and N^-, who behave as infected/not infected, resp.

$N^+ = I_s^+$ under the null hypothesis; $N^+ = S^+ + I_a^+ + I_s^+$ under the alternate hypothesis.

Starting values should reflect true population: 1/6 infected, 4/5 of infected are undiagnosed.

Parameters

Λ Birth rate. Rate of entry into the sexually active population (as S^-).

Use $\Lambda = .0125$; http://www.cdc.gov/nchs/nvss/births.htm

μ Death rate. Rate of exit from the sexually active population.

Use $\mu = .008215$; http://www.cdc.gov/nchs/fastats/deaths.htm

τ Testing rate. Rate at which people without a positive diagnosis get tested.

Use $\tau = \Lambda/4 = .003125$; maintains that 80% of infections are undiagnosed

p_p Sensitivity. Probability of a positive diagnosis given that the patient is positive.

p_n Specificity. Probability of a negative diagnosis given that the patient is negative.

Use $p_p = .98, p_n = .935$; http://www.medscape.com/viewarticle/451062

λ Force of infection. Rate at which susceptible individuals become infected.

β denotes per contact transmission rate; c denotes contact rate; σ denotes serosorting, proportion of sexual contacts that are intentionally of same apparent serostatus.

Use $\beta c = .1$ or $.07$; http://www.uptodate.com/contents/genital-herpes-beyond-the-basics or https://herpesopportunity.com/downloads/herpes-opportunity-disclosure-handout.pdf (averaging M-F and F-M rates). Experiment with values of $\sigma \in [0, 1]$.

γ Rate at which infected individuals experience symptoms for the first time.

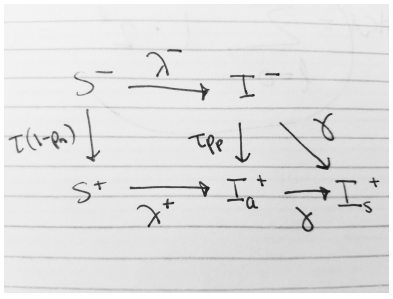
$\gamma = \lambda/4 = .000625$ maintains that 80% of infected individuals are asymptomatic;[1]

http://projectaccept.org/straight-dope-herpes-statistics/

Note $\lambda = \Lambda/5$ maintains that 1/6 of the population is infected.

Differential Equations

$$\frac{dS^-}{dt}(t) = \Lambda \cdot N(t) - (\lambda^-(t) + \tau(1 - p_n) + \mu) \cdot S^-(t)$$
$$\frac{dS^+}{dt}(t) = \tau(1 - p_n) \cdot S^-(t) - (\lambda^+(t) + \mu) \cdot S^+(t)$$
$$\frac{dI^-}{dt}(t) = \lambda^-(t) \cdot S^-(t) - (\tau p_p + \gamma + \mu) \cdot I^-(t)$$
$$\frac{dI_a^+}{dt}(t) = \lambda^+(t) \cdot S^+(t) + \tau p_p \cdot I^-(t) - (\gamma + \mu) \cdot I_a^+(t)$$
$$\frac{dI_s^+}{dt}(t) = \gamma \cdot I^-(t) + \gamma \cdot I_a^+(t) - \mu \cdot I_s^+(t)$$



[1] This is inconsistent with the assumption that only 20% of infected individuals are diagnosed and all others are asymptomatic; we should correct this somehow, possibly by assuming an even lower rate of displaying symptoms for the first time.

The force of infection λ for both susceptible population groups are given below. All group sizes depend on t (and therefore so does λ), but this dependence is omitted below for readability only.

Under the null hypothesis with $N^+ = I_s^+$, both S^- and S^+ behave as though they are uninfected, and so they have the same force of infection, given by:

$$\lambda^- = \lambda^+ = \beta c \left[\sigma \cdot \frac{I^- + I_a^+}{N^-} + (1 - \sigma) \cdot \frac{I^- + I_a^+ + I_s^+}{N^- + N^+} \right].$$

Under the alternate hypothesis with $N^+ = S^+ + I_a^+ + I_s^+$, we assume S^+ engages in different serosorting than S^-, so there is a separate force of infection for the two susceptible groups:

$$\lambda^- = \beta c \left[\sigma \cdot \frac{I^-}{N^-} + (1 - \sigma) \cdot \frac{I^- + I_a^+ + I_s^+}{N^- + N^+} \right]$$
$$\lambda^+ = \beta c \left[\sigma \cdot \frac{I_a^+ + I_s^+}{N^+} + (1 - \sigma) \cdot \frac{I^- + I_a^+ + I_s^+}{N^- + N^+} \right]$$

Future Goals

The following may be incorporated as needed when simulating interventions:

- Retesting and different tests.
- Vary β across groups, incorporating condom/antiviral use and reduced transmission for asymptomatic people.

Fitting β

We will set all parameters as above except for β_c, which we will fit using nonlinear least squares with levenburg marquardt in R.

We are fitting to the following values

- S - percentage of all people that are not infected with HSV2 - 85, the newest values say 11.9 percent in the US but this includes 14-19 year olds...
- I - perecentage of all people that are infected - 15, rough estimate
- Ia - percentage of people who are infected by not symptomatic
- Is - percentage of people who are infected and symptomatic

We could start with a simple fitting of the transmission rate assuming that we only have S and I to fit the transmission rate, assume a constant population size so that the entrance in is the same as the exit.

$$\frac{dS}{dt} = \mu(I + S) - \beta SI - \mu S \tag{1}$$
$$\frac{dI}{dt} = \beta SI - \mu I \tag{2}$$

But if $N = S + I$ is constant, then $S = (N - I)$, and we can calculate S once we know I. I can be solved from

$$\frac{dI}{dt} = \beta(N - I)I - \mu I \tag{3}$$

$$= \beta((N - \frac{\mu}{\beta}) - I)I \tag{4}$$

which is a logistic equation with a known solution. It also has the equilibria, $I = 0$ and $I = N - \frac{\mu}{\beta}$.

The latter equilibrium is asymptotically stable, and is known as the carrying capacity. $I = 0$ is unstable.

To have $I = k\%$ be the equilibrium of the population, we let $N = 1$ and then have $\mu = 0.008215$ (NEED TO CHECK THIS VALUE) then the transmission rate is $\beta = \frac{\mu}{(N-k)}$. So for a value of $k = 0.15$, $\beta = 0.009664706$.

0.0.1 Adding asymptomatic effects

$$\frac{dS}{dt} = \mu(S + I_a + I_s) - \beta S(I_a + I_s) - \mu S \tag{5}$$

$$\frac{dI_a}{dt} = \beta S(I_a + I_s) - (\gamma + \mu)I_a \tag{6}$$

$$\frac{dI_s}{dt} = \gamma I_a - \mu I_s \tag{7}$$

Again, if $N = S + I_a + I_s$ is constant, then $S = (N - (I_a + I_s))$, and we can calculate S once we know I_a and I_s. I_a and I_s can be solved from

$$\frac{dI_a}{dt} = \beta(N - (I_a + I_s))(I_a + I_s) - (\gamma + \mu)I_a \tag{8}$$

$$\frac{dI_s}{dt} = \gamma I_a - \mu I_s \tag{9}$$

This is a typical SEIR model with known equilibria and stability.

Again, we get two equilibria, $(S, I_a, I_s) = (1, 0, 0)$, where noone is infected and $(S, I_a, I_s) = (1 - Ia - Is, (-\mu^2 + \beta\mu)/(\beta\gamma + \beta\mu), (-\gamma\mu + \beta\gamma)/(\beta\gamma + \beta\mu))$, where the disease remains in the population. This is the case now in the US, where we see the disease is endemic.

Once we know these values, we can solve for γ to get the proper proportions of I_a and I_s.

Assuming $k = 0.15$, $Ia = 0.8 * k$ and $Is = 0.2 * k$, so that 80% of those that are infected are asymptomatic, we get $\gamma = .00205375$. There is a mathematica file that can solve for these things.

0.1 Adding testing

Now that we have some of the basic parameters (and of course these change if we decide we need to change k or μ), we can start developing our model to ask questions about testing.

Interesting motivating article:

https://www.modernhealthcare.com/providers/lack-knowledge-unreliable-testing-feed-stigma-herpes

Another interesting article that makes claims about diagnosis that goes against the no change in behavior argument: https://www.cnn.com/2018/02/07/health/herpes-rates-declining-report/index.html

Also, they are using the same bad test to determine an estimate for who has herpes.

Claims about safer sex:

importance: https://www.ncbi.nlm.nih.gov/books/NBK47447/

Discuss importance of more awareness as a way to de-stigmatize the disease as well as to reduce transmission from people making more informed decisions.

Let's first model this as a mass action transmitted disease, so that we won't be dividing by N anywhere. This changes the units of β. We can let the population stay constant by letting $\Lambda = \mu$. We might be able to calculate R_0 in terms of parameters and talk about how to remove the disease.

$$\begin{aligned}
\frac{dS^-}{dt}(t) &= \Lambda \cdot N(t) - (\lambda^-(t) + \tau(1-p_n) + \mu) \cdot S^-(t) \\
\frac{dS^+}{dt}(t) &= \tau(1-p_n) \cdot S^-(t) - (\lambda^+(t) + \mu) \cdot S^+(t) \\
\frac{dI^-}{dt}(t) &= \lambda^-(t) \cdot S^-(t) - (\tau p_p + \gamma + \mu) \cdot I^-(t) \\
\frac{dI_a^+}{dt}(t) &= \lambda^+(t) \cdot S^+(t) + \tau p_p \cdot I^-(t) - (\gamma + \mu) \cdot I_a^+(t) \\
\frac{dI_s^+}{dt}(t) &= \gamma \cdot I^-(t) + \gamma \cdot I_a^+(t) - \mu \cdot I_s^+(t)
\end{aligned}$$

The force of infection λ for both susceptible population groups are given below. All group sizes depend on t (and therefore so does λ), but this dependence is omitted below for readability only.

Here, we are going to use mass action transmission two susceptible groups:

$$\begin{aligned}
\lambda^- &= \beta c \left[\sigma \cdot I^- + (1-\sigma) \cdot (I^- + I_a^+ + I_s^+)\right] \\
\lambda^+ &= \beta c \left[\sigma \cdot (I_a^+ + I_s^+) + (1-\sigma) \cdot (I^- + I_a^+ + I_s^+)\right]
\end{aligned}$$

We first need to determine parameters for this model that puts the percentages of people in the compartments that we think are reasonable.

We can also discuss how different parameters lead to the same equilibria, showing that different choices of partnering strategies lead to the same final outcomes when false positive rates are high enough. No one has an exact number of false positive and false negative rates, we should look into this more.

1 Testing Model

When people test but they don't change their behavior if they are not symptomatic:

$$\frac{dS}{dt} = \mu N - \sigma\beta S I_s - \beta S(I_{a-} + I_{a+}) - \mu S \tag{10}$$

$$\frac{dI_{a-}}{dt} = p(\sigma\beta S I_s + \beta S(I_{a-} + I_{a+})) - \tau I_{a-} - \mu I_{a-} \tag{11}$$

$$\frac{dI_{a+}}{dt} = \tau I_{a-} - \mu I_{a+} \tag{12}$$

$$\frac{dI_s}{dt} = (1-p)(\sigma\beta S I_s + \beta S(I_{a-} + I_{a+})) - \mu I_s \tag{13}$$

- I_{a-} are people who are infected, asymptomatic, and haven't been tested
- I_{a+} are people who are infected, asymptomatic, and have been tested (assuming 100% accuracy on test although we could change this)
- τ is the testing rate
- σ is the proportion that people partner between susceptible and symptomatic people.

When people test but they do change their behavior even if they are not symptomatic:

$$\frac{dS}{dt} = \mu N - \sigma\beta S I_s - \beta S(I_{a-} + \sigma_\tau I_{a+}) - \mu S \tag{14}$$

$$\frac{dI_{a-}}{dt} = p(\sigma\beta S I_s + \beta S(I_{a-} + \sigma_\tau I_{a+})) - \tau I_{a-} - \mu I_{a-} \tag{15}$$

$$\frac{dI_{a+}}{dt} = \tau I_{a-} - \mu I_{a+} \tag{16}$$

$$\frac{dI_s}{dt} = (1-p)(\sigma\beta S I_s + \beta S(I_{a-} + \sigma_\tau I_{a+})) - \mu I_s \tag{17}$$

- σ_τ is the proportion of people who partner between susceptible and asymptomatic tested positive people.

Can really just use this second model and set $\sigma_\tau = 1$.