Effect of tertiary infection

In the analyses in this paper, I have assumed that tertiary infection is negligible. However, this assumption is unlikely to be true in some cases. The goal of this document is too show that, although this assumption will not always be true, its impact on the results of the paper is minor.

Modeling tertiary infection

Population mortality rate m. Consider a family with *n* children and two parents and no resistant individuals. I will consider an individual child in this family and calculate his disease mortality rate. The number of *r* primary infections in the family (not including the target) has a binomial distribution with *n*+1 trials and probability π_0 of success. The probability of a non-infected family member being infected by one of these primary-infected individuals is

$$\Psi_0 = 1 - \left(1 - f_0\right)^r \tag{1}$$

The distribution for the number *v* of secondary-infected individuals (again not including the target individual) is binomial (n+1-*r*, Ψ_0). The total number of infections is *v*+*r*. The probability of infection for the target individual is

$$P\left(infection | r, v\right) = \pi_0 + \left(1 - \pi_0\right)\left(1 - \left(1 - f_0\right)^{r+v}\right) \tag{2}$$

Thus, the population mortality rate (ignoring resistant individuals) is

$$m = \sum_r \sum_v P\left(infected \mid r, v\right) P\left(r, v\right)$$

or

$$m = \sum_r \sum_v \left[\pi_0 + \left(1 - \pi_0\right)\left(1 - \left(1 - f_0\right)^{r+v}\right)\right] \binom{n+1-r}{v} \Psi_0^v \left(1 - \Psi_0\right)^{n+1-r-v} \binom{n+1}{r} \pi_0^v \left(1 - \pi_0\right)^{n+1-r} \tag{3}$$

Adding genetic variability. Now, we consider a family with one heterozygous *Aa* parent and one homozygous *aa* parent, where *A* is the resistance allele and *a* is the normal one. The distribution for the number n_1 of *Aa* children is binomial (*n*,½) and the number of normal children is $n_0 = n - n_1$. Take r_0 as the number of primary infections in normal family members and r_1 as the number of primary infections in resistant family members. Likewise, take v_0 as the number of secondary infections in normal family members and v_1 as the number of secondary infections in resistant family members. Then

$$r_i \sim binomial\left(n_i + 1, \pi_i\right)$$

$$v_i \sim binomial\left(n_i + 1 - r_i, \psi_i\right)$$

The probability of a target *Aa* individual being infected is

$$P\left(infected \mid r_0, r_1, v_0, v_1\right) = \pi_1 + \left(1-\pi_1\right)\left(1-\left(1-f_1\right)^{r_0+r_1+v_0+v_1}\right) \tag{4}$$

The probability of infection given n_0 and n_1 is

$$P\left(infection \mid n_0, n_1\right) = \sum_r \sum_v \left[\pi_0 + \left(1-\pi_0\right)\left(1-\left(1-f_0\right)^{r+v}\right)\right] P\left(r_0 \mid n_0\right) P\left(r_1 \mid n_1\right) P\left(v_0 \mid n_0, r_0\right) P\left(v_1 \mid n_1, r_1\right) \tag{5}$$

The distributions $P(r_0|n_0)$, $P(r_1|n_1)$, $P(v_0|n_0,r_0)$, $P(v_1|n_1,r_1)$ are as given above.

The iteration equation for the frequency of the *A* allele (assuming *A* is rare as in the main text) is

$$X_{t+1} = 2X_t \frac{\sum_{j=0}^{n} \binom{n}{j} j \left(\frac{1}{2}\right)^n \left(1-P\left(infection \mid n_1 = j-1, n_0 = n-j\right)\right)}{n\left(1-m\right)}, \tag{6}$$

with $P(infection|n_1,n_0)$ and m calculated as defined above.

The ratio of selection coefficients can be calculated using this iteration equation. An approximation for low infection rates similar to equation (11) in the text shows that the effect of tertiary infection on the ratio of selection coefficients is of approximate magnitude $f_0n/2$ relative to the impact of secondary infection. This will not be negligible except when f_0 is small. The effect of tertiary infection is to increase within-family infection and therefore to increase the importance of family structure. However, I will now show that if the amount of within-family infection is fixed, then the distribution of that mortality between secondary and tertiary mortality has minor impact on the selection coefficient.

In the tables below, I calculate the ratio of the selection coefficients with and without family structure using equation (6) for various combinations of parameter values both with and without tertiary infection. The secondary infection rate f_0 for the case with no tertiary infection is shown on the left side of the table and the corresponding value for the ratio of selection coefficients is shown in the body of the table. I then calculated the ratio of selection coefficients with tertiary infection for a range of values of f_0 in order to find the value of f_0 at which the proportion of infection coming from inside the family was the same as without tertiary infection for the same parameter values. The corresponding ratio of selection coefficients with tertiary infection is shown.

We see that overall the difference between the two cases is minor. The difference is negligible for all parameter values for the weak dose-increasing case. For the strong dose-increasing case, the difference is small except when f_0 reaches 0.5 and higher. For the dose-independent case, the differences become fairly substantial for f_0=0.3 and higher. However, in no case do the differences substantially change the qualitative results of this paper.

Dose-independent case:

	Ratio of selection coefficients					
	u_b=u_w=0.2		u_b=u_w=0.5		u_b=u_w=0.8	
f_0 for no tertiary case	no tert.	tertiary	no tert	tertiary	no tert	tertiary
0.1	1.034	1.039	1.075	1.08-1.09	1.123	1.145
0.2	1.052	1.085	1.122	1.15-1.16	1.192	1.247
0.3	1.064	1.089	1.151	1.21	1.235	1.327
0.5	1.077	1.12	1.19	1.29	1.284	1.448

Weak dose-increasing case

	Ratio of selection coefficients					
	u_b=0.2, u_w=1		u_b=0.5, u_w=1		u_b=0.8, u_w=1	
f_0 for no tertiary case	no tert.	tertiary	no tert	tertiary	no tert	tertiary
0.1	1.25	1.24	1.21	1.20-1.23	1.22	1.22
0.2	1.51	1.49	1.46	1.43-1.47	1.47	1.45
0.3	1.77	1.76	1.71	1.71	1.72	1.70
0.5	2.30	2.30	2.23	2.21	2.21	2.16

Strong dose-increasing case

	Ratio of selection coefficients					
	u_b=0, u_w=0.2		u_b=0, u_w=0.5		u_b=0, u_w=0.8	
f_0 for no tertiary case	no tert.	tertiary	no tert	tertiary	no tert	tertiary
0.1	1.04	1.04	1.10	1.10-1.11	1.18	1.19
0.2	1.06	1.07	1.17	1.18-1.20	1.35	1.36
0.3	1.07	1.09	1.22	1.26	1.49	1.52
0.5	1.09	1.13	1.29	1.39	1.71	1.80