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Note on 'Age, influenza pandemics and disease dynamics' by Greer *et al.* (2010)

To the Editor

In an interesting recent 'for debate' paper, Greer *et al.* [1] tackled the important issue of explaining the epidemiology of the 2009 novel H1N1 pandemic. It is indeed a crucial task for epidemiologists of infectious diseases to explore the data generated during this pandemic, using modelling tools, with the aim of understanding the mechanisms underlying observed patterns. Greer *et al.* propose the hypothesis that the percentage of susceptible individuals varies by age group, presumably due to prior exposure to related strains of influenza, and use this hypothesis to explain (i) varying attack rates among different age groups in a given population, and (ii) varying attack rates in different populations due to different age structures. In order to demonstrate their claims, the authors make some calculations using classical epidemic theory, applying it to estimate the potential impact of the difference in the age structures of the general Canadian population and the Indigenous population of Canada on the epidemic curves in the respective populations. The purpose of this Letter is to point out an error in their application of the theory, and correct it. This does not invalidate the conclusions of Greer *et al.* and indeed the result of the corrected calculation strengthens the authors' conclusion about the potential impact of differences in age structure among populations on attack rates. I do believe, however, that it is important to correct the error made, so that future studies apply the models and formulae of epidemic theory in an appropriate way.

The calculation in Greer *et al.* [1] begins from the hypothesis that the proportions of susceptibles in three age groups are as follows: 1·0 in individuals aged <34 years, 0·42 in individuals aged 33–52 years, and 0·15 in people aged $\geqslant 53$ years. This hypothesis is based on data from the initial phase of the pandemic in Ontario, Canada [2] and will now be accepted as given. The authors then calculated the consequences of this assumption for the epidemic dynamics in two different populations: the general Canadian population and Indigenous populations of Canada (First Nations), populations which differ in their age structure. Taking the respective age structures and the above hypothesis on the percentage of susceptibles in each age group into account, it is calculated that the fraction of susceptibles in the general Canadian population is $S_0^{\mathrm{Can}}=0{\cdot}59$, while in the Indigenous population it is $S_0^{\mathrm{FN}}=0{\cdot}73$. The aim is now to calculate the effect of this difference in the fraction of susceptibles among the two populations on the resulting epidemics.

In an epidemic with a basic reproductive number $R_0>1$, occurring in an *entirely* susceptible population (i.e. when $S_0=1$), the attack rate (or size of the epidemic), that is the fraction of the population infected during the epidemic, is given as the positive solution of the 'final-size equation' $Z=1-\mathrm{e}^{-R_0 Z}$. In a population of which only a fraction S_0 is susceptible at the beginning of an epidemic, one defines the effective reproductive number $R_{\mathrm{e}}=S_0R_0$, and writes the modified final-size equation $Z=1-\mathrm{e}^{-R_{\mathrm{e}}Z}$. However the solution Z of this equation is *not* the attack rate of the epidemic, but rather the fraction of the *initially susceptible* population which is infected during the epidemic. The attack rate is thus given by $A=S_0Z$, so that $A=Z$ only in the case that the entire population is susceptible ($S_0=1$) ([3], ch. 2.3, [4], [5], ch. 10.2).

Under the assumption that the basic reproductive number for the novel H1N1 influenza is $R_0=2{\cdot}7$ (as estimated in a study of an outbreak in a school setting [6]), it follows that the respective effective reproductive numbers in the two populations under consideration are $R_{\mathrm{e}}^{\mathrm{Can}}=R_0\times S_0^{\mathrm{Can}}=2{\cdot}7\times 0{\cdot}59=1{\cdot}6$, $R_{\mathrm{e}}^{\mathrm{FN}}=R_0\times S_0^{\mathrm{FN}}=2{\cdot}7\times 0{\cdot}73=2{\cdot}0$. Greer *et al.* correctly use the modified final-size equation, with R_{e}

replacing R_0, that is $Z = 1 - e^{-R_e Z}$. However, they take the solutions $Z^{Can} = 0{\cdot}64$, $Z^{FN} = 0{\cdot}79$ of this equation for the two population to be the sizes of the corresponding epidemics, and this is an error. The actual attack rates are, as explained above, $A^{Can} = S_0^{Can} \times Z^{Can} = 0{\cdot}59 \times 0{\cdot}64 = 0{\cdot}38$, $A^{FN} = S_0^{FN} \times Z^{FN} = 0{\cdot}73 \times 0{\cdot}79 = 0{\cdot}58$. The ratio of attack rates, or the relative risk for the entire epidemic is then $A^{FN}/A^{Can} = 1{\cdot}53$. Note that this number differs substantially from the relative risk at the initial phase of the epidemic, which is given simply by the ratio of the initial fractions of susceptibles, $S^{FN}/S^{Can} = 1{\cdot}24$. Thus the final attack rate in the Indigenous Canadian population, is predicted, under the assumptions of [1], to be 53% larger than the attack rate in the general Canadian populations, and not 23% larger as claimed there. This in fact strengthens the authors' claim about the potential effect of age structure on the size of an epidemic.

A similar remark should be made with respect to figures 3, 4 in [1] which are based on simulations of the epidemics in two populations that are entirely susceptible, that is with initial condition $S(0) = 1$ with the corresponding reproductive numbers 1·9 and 1·5. The appropriate way to simulate epidemics in two population with the same basic reproductive number R_0 but with different fractions of the populations susceptible, would be to use the same R_0 for the two curves but different initial conditions $S(0) = S_0$ for the two populations, where for each population S_0 is the initial fraction of susceptibles in that population. This is *not* equivalent to taking $S(0) = 1$ and reducing the reproductive numbers for the two curves in proportion to the fraction of sucsceptibles. It turns out, however, that when the simulations are performed in this corrected way, and the ratio of attack rates (i.e. the relative risk) up to time t, is plotted as a function of time, in the manner of figure 4 of [1], the results are *qualitatively* similar to those obtained in [1]: the relative risk in the population with a higher fraction of susceptibles is much higher at the stage when the epidemic in this population has begun, while the incidence in the population with a lower fraction of susceptibles is still low. Therefore the authors' general point that the relative risk in the two populations varies considerably with time remains valid.

As more data about the 2009 novel H1N1 pandemic, both from surveillance and from serological studies, becomes available, it will be of great interest to test the extent to which observed patterns can be accounted for by the hypothesis put forth by Greer *et al.*, according to which differences in attack rates among age groups and populations can be accounted for as results of different percentages of susceptibles among different age groups.

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Declaration of Interest

None.

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The authors reply

We thank Dr Katriel for providing such a clear and appropriate discussion of what was clearly an oversight on our part.

We did not multiply our calculated final size values by the proportion of the population susceptible which does change the calculated values obtained. However, as Dr Katriel's letter clearly highlights, the effect of this oversight is that the estimated risk in populations with large proportions of the population susceptible is even greater than we had previously described and in fact, the true effect is more significant than we described in the original version of our paper.

We are looking forward to further testing the hypothesis we proposed in our paper empirically by using Canadian surveillance data to further examine the effect of age on pandemic influenza epidemics in different populations and commend Dr Katriel for correcting the formula that we included in the original paper.

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