On the relative role of different age groups in influenza epidemics

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ABSTRACT

The identification of key "driver" groups in influenza epidemics is of much interest for the implementation of effective public health response strategies, including vaccination programs. However, the relative importance of different age groups in propagating epidemics is uncertain.

During a communicable disease outbreak, some groups may be disproportionately represented during the outbreak's ascent due to increased susceptibility and/or contact rates. Such groups or subpopulations can be identified by considering the proportion of cases within the subpopulation occurring before (Bp) and after the epidemic peak (Ap) to calculate the subpopulation's relative risk, RR =Bp/Ap. We estimated RR for several subpopulations (age groups) using data on laboratory-confirmed US influenza hospitalizations during epidemics between 2009 and 2014. Additionally, we simulated various influenza outbreaks in an age-stratified population, relating the RR to the impact of vaccination in each subpopulation on the epidemic's initial effective reproductive number $R_e(0)$.

We found that children aged 5–17 had the highest estimates of RR during the five largest influenza A outbreaks, though the relative magnitude of RR in this age group compared to other age groups varied, being highest for the 2009 A/H1N1 pandemic. For the 2010–2011 and 2012–2013 influenza B epidemics, adults aged 18–49, and 0–4 year-olds had the highest estimates of RR, respectively.

For 83% of simulated epidemics, the group with the highest RR was also the group for which initial distribution of a given quantity of vaccine would result in the largest reduction of $R_e(0)$. In the largest 40% of simulated outbreaks, the group with the highest RR and the largest vaccination impact was children 5–17.

While the relative importance of different age groups in propagating influenza outbreaks varies, children aged 5–17 play the leading role during the largest influenza A epidemics. Extra vaccination efforts for this group may contribute to reducing the epidemic's impact in the whole community.

1. Introduction

The relative importance of different age cohorts in driving influenza epidemics is not fully understood. One reason for this is the lack of consensus on what makes an age group "important" in transmission, and how this should be quantified. School age children (aged 5–17) were found to have experienced the highest influenza attack rate during the 2009 A/H1N1 pandemic (Reed et al., 2012), as well as during certain influenza seasons prior to the pandemic (Monto et al., 1985), though for other seasons, age-specific attack rates for influenza A infection were relatively similar for different age groups (Monto and Kioumehr, 1975). Studies have shown that influenza transmission decreases during school closure periods (Cauchemez et al., 2008) and increases when schools are opened (Huang et al., 2014), suggesting the importance of schoolchildren in propagating influenza. However, estimates of the magnitude of change in transmission dynamics of influenza during time periods when schools are open vs. periods when they are closed are variable (Jackson et al., 2013a; Flasche et al., 2011). Studies based on transmission modeling have also suggested the key role of school age children in driving influenza epidemics (Basta et al., 2009; Wallinga et al., 2006). However, conclusions of those studies hinge on certain assumptions behind transmission models that are rarely calibrated against data from specific influenza

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seasons, particularly in the non-pandemic context. For example, in age-stratified transmission models, distribution of individual susceptibility to infection within each age stratum is one aspect that received very little attention in the literature. Earlier peaks of influenza epidemics in younger age groups have been documented, but their interpretation has been controversial. In one study (Olson et al., 2007), they were cited as evidence of the importance of these groups in transmission, yet it has been argued on the contrary (Schanzer et al., 2011) that small magnitude of the differences in peak times in different age groups "casts doubt on the hypothesis that younger school-age children actually lead influenza epidemic waves". One could further counter that assertion, suggesting that transmission in different age groups is strongly interconnected, leading to so-called "slaved" dynamics in which incidence grows at a similar rate in all age groups (Keeling and Rohani, 2008). In this scenario, the peak incidence in the driver groups – that is, groups for which depletion of susceptibles has the largest relative impact on the epidemic's reproductive number (Wallinga et al., 2010; Goldstein et al., 2010) – corresponds with peak incidence in the community.

In previous work (Wallinga et al., 2010) we defined a measure of the importance of a particular age (or other demographic) group as follows: importance in transmission is proportional to the (negative) change in the epidemic's effective reproductive number that would result from successfully immunizing a small, fixed number of persons randomly chosen from within this group. While this definition is clearly relevant to vaccination policies (vaccinating the most "important" groups yields the highest impact on the epidemic's dynamics in the whole community), estimating the potential impact of vaccination for a particular epidemic is quite difficult due to a variety of data limitations. Here, we hypothesized that a simple, heuristic but precisely defined measure that is readily estimated for each age group from age-stratified epidemiologic data would be highly predictive of importance defined above, and that it should in general be possible to estimate relative importance of different groups in driving transmission of an infection even when probabilities of case-reporting vary systematically across groups, a common feature in surveillance data. This measure, which for influenza can be estimated separately for each of the circulating (sub) types, A/H1, A/H3 and B, is a simple relative risk (RR) of cases in a particular age group before the peak of the epidemic compared to after the peak of the epidemic. The rationale for this choice is the idea that the key age groups in transmission will experience a disproportionate depletion of susceptible individuals (attack rates) relative to the whole population during the ascent stages of influenza epidemics. This would translate into a lower proportion of such age groups in overall influenza incidence (or other influenza-associated outcomes that can be measured from data) during the descent stages of epidemics.

Estimating incidence of influenza infections in different age groups before and after the epidemic peak is challenging with the available data. At the same time, our proposed summary statistic RR requires only the relative change in such incidence before vs. after the epidemic peak. This relative change can be assessed by considering the corresponding relative change for a surrogate measure (proxy) of influenza incidence. Such a proxy would need to represent a fixed (but not necessarily high) proportion of the true incidence during those periods (Supporting information). This requires high *specificity*, which, for example, precludes the ILI data stream from serving as such proxy because the frequency of other conditions causing a nonspecific diagnosis like ILI will change through the season. It does not require high *sensitivity*, only time-invariant (or more precisely, equally time-varying) sensitivity for each age group. In our analysis, such a proxy is provided by laboratory-confirmed, (sub)typed influenza hospitalizations in the Influenza Surveillance Hospitalization

Network (FluSurv-NET). Importantly, interpreting this statistic does not require prior knowledge of either the overall or the group-dependent reporting rate (in this instance, case-hospitalization rate). This means that when laboratory-confirmed hospitalizations, representing only a small, age-specific fraction of all incident cases, are used as a surrogate measure of infections for the estimation of RR, it will estimate the importance of particular age groups in transmitting infection.

Here we report the estimation of the RR from data on laboratory-confirmed US influenza hospitalizations during epidemics associated with influenza A/H1N1, A/H3N2 and B between 2009 and 2014. This recent period is particularly interesting as influenza vaccination coverage rates have increased following the 2009 pandemic, at least in the US, potentially resulting in different distributions of susceptibility compared to what has taken place in the pre-pandemic period, and the impact of that on the relative roles of the different age groups has not been assessed in detail in the literature. We then go on to test the hypothesis that the group identified as most important by the RR statistic is predictably the one with the highest importance by our definition—the group for which immunization of a fixed number of persons would cause the greatest reduction in the reproduction number of the epidemic in the population as a whole. In order to investigate this correspondence, we simulated influenza epidemics in an age-stratified population with contact rates between the age groups borrowed from the POLYMOD study (Mossong et al., 2008) and explored a variety of scenarios for the relative susceptibility to infection for the different age groups to reflect the diversity of influenza epidemics.

2. Materials and methods

2.1. Data

We used the Influenza Surveillance Hospitalization Network (FluSurv-NET) data for the 2009 pandemic and the 2010–2011 through 2012–2013 influenza seasons collected between October and April (with no data on sub-typing of influenza A hospitalizations available prior to 2009). This network conducted population-based influenza-associated hospitalization surveillance in over 80 selected counties located in California, Colorado, Connecticut, Georgia, Idaho, Maryland, Michigan, Minnesota, New York, Oklahoma, Ohio, Oregon, Rhode Island, Tennessee and Utah. The surveillance area encompassed a total of 276 reporting hospitals serving over 29 million children and adults and representing about 9% of the US population. Laboratory testing for influenza was ordered at the discretion of clinicians providing clinical care. Laboratory confirmation was defined as a positive result from viral culture, direct or indirect fluorescent antibody staining, rapid antigen test, or reverse transcription polymerase chain reaction (rt-PCR). Aggregate hospitalization counts were used in the study.

This activity was determined to be routine public health surveillance by the US Centers for Disease Control and Prevention and by state and local institutional review boards and no informed consent from the participants was sought. This study, based on the analysis of aggregated existing data, was determined to be not "Human Subjects Research".

2.2. Hospitalization data analysis

For each season and influenza (sub)type, we determine the periods before and after the peak of that (sub)type's epidemic as follows: For each age group g $g = (1, \ldots, 5)$ and week t, let $X1_t^g$, $X3_t^g$, XB_t^g be the counts for the number of confirmed hospitalizations in that group on that week with the (sub)types A/H1N1, A/H3N2, and B, respectively, and XA_t^g be the number of un-subtyped