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Influenza H3N2 variant viruses with pandemic potential: Preventing catastrophe in remote and isolated Canadian communities

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ABSTRACT

Objective. To evaluate the impact of age-specific cross-reactive antibody protection levels on the outcomes of a pandemic outbreak of new variants of H3N2 influenza A viruses (H3N2v).

Methods. We calibrated a previously validated agent-based model of human-to-human transmission of influenza viruses to project the outcomes of various protection levels in a remote and isolated Canadian community, when demographics are drawn from the Statistics Canada census data. We then compared the outcomes with a scenario in which demographic variables were shifted to resemble an urban structure. This comparative evaluation was conducted using in-silico computer simulations, where the epidemiological data were drawn from relevant estimates in published literature.

Results. Simulations, using estimates of transmissibility for the 2009 H1N1 pandemic strain in the study population, show that the epidemic size is primarily affected by the cross-reactive protection levels of young children. A lower number of secondary infections at the early stages of an outbreak does not necessarily correspond to a lower epidemic size.

Conclusions. Demographic variables could play a significant role in determining the outcomes of an outbreak. The findings strongly suggest that, when an H3N2v-specific vaccine becomes available, children below the age of 17 should be prioritized for vaccination. This prioritization is essential in population settings with a low average age, including aboriginal communities in northern latitudes.

Introduction

In July 2011, a novel swine-origin triple reassortant influenza A/H3N2 variant (H3N2v) emerged in the US, containing seven genes from circulating North American swine H3N2 virus and one gene (matrix) from the 2009 H1N1 pandemic virus (Centers for Disease Control and Prevention, CDC, 2011; Lina et al., 2011). The acquisition of matrix gene from the 2009 H1N1 pandemic virus may enhance the transmission potential of H3N2v in humans, as observed in a guinea pig model (Chou et al., 2011). A recent CDC update (November 16, 2012) reported that H3N2v has caused a total of 319 (12 in 2011 and 307 in 2012) cases, predominantly children, since its emergence (Centers for Disease Control and Prevention, CDC, 2012a). The gradual increase in the number of human infections with H3N2v in the US is alarming, should human-to-human transmission of these variants be sustained. Pre-existing antibody-mediated immunity against seasonal H3N2 viruses appears to provide little or no protection against infection with the new antigenic H3N2v. Serological studies indicate a broad susceptibility to H3N2v among young individuals, particularly in children below 10 years of age (Centers for Disease Control and Prevention, CDC, 2012b; Skowronski et al., 2012; Waalen et al., 2012). As a result of limited pre-existing immunity in the very young, the elderly, and infirm individuals, and in the absence of a virus-specific vaccine, public health will face significant challenges in preventing severe outcomes, particularly in remote and isolated communities, if an H3N2v pandemic occurs. In Canada, many of these communities, especially aboriginal populations in northern latitudes, were affected disproportionately by the H1N1 pandemic of 2009, with severe outcomes often necessitating hospitalization and intensive care admission (Kumar et al., 2009; Zarychanski et al., 2010).

Reducing the impact of a potential pandemic of influenza H3N2v in these underserved communities requires interventions that focus on decreasing disease transmission, and on prevention. Using simulation, we sought to investigate possible scenarios for a pandemic outbreak in a remote and isolated Canadian community (referred to as RC), and project the effect of cross-reactive antibody protection levels of different age-groups in epidemic profiles. Using an established agent-based

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modeling framework (Laskowski et al., 2011), we compared the epidemic outcomes in silico (i.e., via computer simulations) for RC and a population setting of the same size with the distribution of demographic variables modified to resemble an urban center. The objectives of these scenario analyses were to evaluate the impact of age-specific protection levels on the outbreak size, and to identify age groups that should be prioritized for vaccination as a key preventive measure.

Methods

Modeling and population settings

We used a previously validated agent-based model (Laskowski et al., 2011), to simulate the spread of influenza H3N2v in a remote and isolated community in northern Manitoba, Canada, with a total population of 1895 individuals (see Supplementary Information). For comparison purposes, we implemented the model for a community of the same size with demographic variables shifted to represent the population profiles of Winnipeg, the largest urban structure in the province of Manitoba. Population variables were parameterized using Statistics Canada census data for age and gender, household compositions and private dwelling characteristics, employment rates, and time use of individuals (Fig. 1) (Statistics Canada, 2007a, 2007b). In order to investigate the effect of pre-existing immunity, we used age-specific estimates of cross-reactive antibody protection against H3N2v (Centers for Disease Control and Prevention, CDC, 2012a; Skowronski et al., 2012; Waalen et al., 2011), and analyzed age-specific model outcomes for groups of 0–36 months; 4–9 years; 10–17 years; 18–49 years; and 50 + years of age.

Parameters and model calibration

The reproduction number of disease transmission is defined as the average number of secondary infections generated by a single infectious case introduced into an entirely susceptible population (Diekmann and Heesterbeek, 2000). To calibrate the model for the probability of transmission (see Supplementary Information), we used recent estimates of the reproduction number of the H1N1 pandemic (Mostaço-Guidolin et al., 2012), with a mean value of 2.26 (95% CI: 1.57 to 3.75) for RC and 1.57 (95% CI: 1.35 to 1.87) for Winnipeg. In the absence of parameter estimates for H3N2v transmission, we used H1N1 estimates of reproduction number as plausible values. The infectious period for each infected individual was sampled from a log-normal distribution with the mean of 3.38 days (Tuite et al., 2010). We assumed an average period of 1.5 days for an exposed case to become infectious and shed the virus (Lessler et al., 2009). To investigate the effect of pre-existing immunity, we used estimates of age-based cross-reactive antibody against H3N2v (Centers for Disease Control and Prevention, CDC, 2011), with the mean values given for the baseline scenarios in Table 1. We estimated the reproduction number and the epidemic final size (total number of infections throughout an outbreak) with varying levels of protection for different age groups.

Results

Outcomes of varying protection levels

For model calibration, the average of 1000 sample realizations with random seeding of the initial infection in the model simulations was calculated. In the absence of any pre-existing immunity, we estimated reproduction numbers of 2.38 and 1.50 for original demographics (OD) and shifted demographics (SD) scenarios, respectively, with the corresponding epidemic final sizes of 44% and 19% of the population. Using the probability of disease transmission obtained from this calibration (see Supplementary Information), we simulated the model for various levels of age-specific pre-existing immunity. The baseline level of immunity for each age-group was chosen as the mean of the corresponding range estimated for cross-reactive antibody protection against H3N2v (Centers for Disease Control and Prevention, CDC, 2011). Fig. 2a and b illustrate age-specific epidemic curves (as the average of 1000 sample realizations) using baseline protection levels for the original and shifted demographics of RC, respectively. We estimated reproduction numbers of 1.98 and 1.16, with the epidemic final sizes of 33% and 9% for scenarios in Fig. 2a and b, respectively.

Using the calibrated model, we ran the simulations to determine the level of protection required for reducing the epidemic final size of RC with original demographics to that obtained with the baseline protection levels for RC with shifted demographics. As reported in Table 1, several scenarios were considered by increasing the age-based protection levels. Estimates of cross-reactive antibody protection indicate broad susceptibility to H3N2v among children and the elderly. We focused primarily on increasing the protective levels of young groups below 18 years of age. As indicated by the outcome of simulations, protecting these age groups contributes significantly towards reducing disease incidence. This is particularly evident by comparing the outcomes of two scenarios OD(3) and OD(4) in Table 1. A 7% reduction in the protection level of individuals below 18 years of age (from 70% to 63%), would require an increase of 25% and 40% to the baseline protection levels of individuals in groups of 18–49 and 50 + years of age, respectively, in order to achieve the same epidemic final size. This result is notwithstanding the fact that a larger proportion of the population (54%) belongs to the groups of 18 + years of age. However, the reproduction number in OD(3) scenario

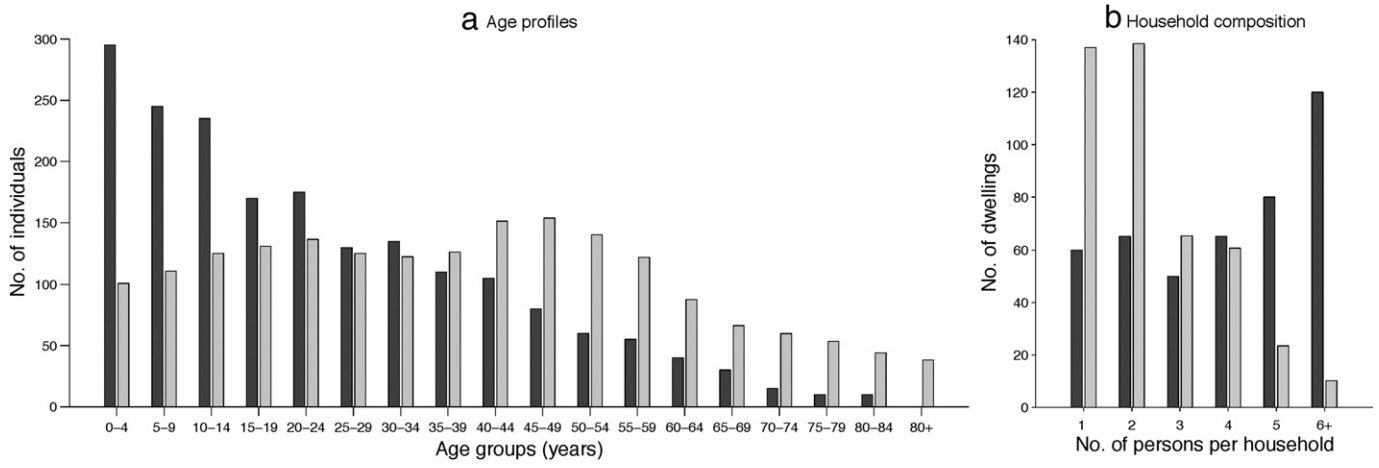

Fig. 1. Population age distributions and number of persons per household for RC with original (blue) and shifted (red) demographics. Bar plots in red corresponds to a scaled down demographics of Winnipeg.

Table 1
Scenario outcomes for various age-specific protection levels.

	Age-specific protection levels (%)						
	0–36 months	4–9 years	10–17 years	18–49 years	50+ years	Reproduction number	Epidemic final size (% of the population infected)
Baseline OD	0	6.5	27.5	38	23.5	1.98	33
Baseline SD	0	6.5	27.5	38	23.5	1.16	9
OD(1)	38	38	38	38	38	1.66	26
OD(2)	50	50	50	50	50	1.40	18
OD(3)	63	63	63	63	63	1.04	9
OD(4)	70	70	70	38	23.5	1.18	9

OD (original demographics) and SD (shifted demographics) of the remote community (RC).

with 63% protection level in all age-groups is lower than the reproduction number in OD(4) scenario.

Discussion

While the sustainability of human-to-human transmission of H3N2v remains undetermined, the pandemic risk and potential impact of these viruses (e.g., through genetic reassortment) cannot be disregarded (European Centre for Disease Prevention and Control, 2012). Despite the susceptibility of these viruses to antiviral drugs (oseltamivir and zanamivir) (Centers for Diseases Control and Prevention, CDC, 2012), the danger of the development of resistance exists, and therefore preparedness plans should include preventive measures, such as vaccination. The current vaccine composition of seasonal influenza A (H3N2) is not expected to provide any protection against H3N2v (Centers for Disease Control and Prevention, CDC, 2011; European Centre for Disease Prevention and Control, 2012). To overcome this shortfall, a new H3N2v reassortant vaccine strain has been developed and will undergo clinical trials in the United States for evaluating its immunological response and safety (European Centre for Disease Prevention and Control, 2012). Should the H3N2v-specific vaccine become available, prioritization and roll-out strategies are among key policy questions that public health will need to address.

Given the experience of the 2009 H1N1 pandemic, protecting vulnerable populations, in particular remote and isolated communities, will be an important priority for public health in Canada. Our comparative analysis of age distribution of infection and hospitalization in the province of Manitoba for pandemic H1N1 in 2009 demonstrates that First Nations (FN) populations, many of which are remote and isolated, were at higher risks compared with non-FN populations (Mostaco-Guidolin, 2012). The highest age-specific infection and hospitalization rates among FN populations were observed in young children, 0–4 years of age, with as much as 12 times higher rates of infection and 22 times higher rates of hospitalization when compared with the same age group in non-FN populations during the first wave of H1N1 pandemic (Mostaco-Guidolin, 2013). These higher rates are of particular concern as recent serological studies indicate no pre-existing immunity against H3N2v in children under 4 years of age (Centers for Disease Control and Prevention, CDC, 2011; Skowronski et al., 2012; Waalen et al., 2012).

Our study has important implications for response planning in the event of human H3N2v outbreaks, particularly in remote and isolated communities. The first and foremost conclusion of our modeling results is the fact that epidemic outcomes depend not only on the protection levels of different age groups, but also on the distribution of demographic variables (e.g., age profile and household composition) in a population. As shown by our simulations (i.e., baseline scenarios in Table 1), the epidemic outcomes in RC with original demographics and RC with shifted demographics (to resemble an urban center) are vastly different in terms of the final size, even when the age-based protection levels are the same. We should point out that simulations for RC with shifted demographics are not meant to project the epidemic outcomes in an urban population, but rather to highlight the fact that variability in demographic characteristics of a remote community could play an important role in determining disease dynamics. Our findings show that the reproduction number is a key parameter to consider when developing effective responses; but our results also highlight that the reproduction number is not the sole factor determining epidemic outcomes. As illustrated in scenarios baseline SD, OD(3) and OD(4) in Table 1, the same final size of epidemic can be achieved for different age-based protection levels, even when reproduction numbers are measurably different. This finding should be considered when making policies for optimal distribution of potentially limited vaccine quantities in order to maximize population-wide benefits of vaccination. Finally, our results highlight the importance of protecting young individuals in populations with a low average age, such as found in aboriginal communities. Due to population-specific factors (e.g., demographics and network of interactions between individuals) in remote and isolated communities, small variations in protection levels of young age groups could result in a large impact on

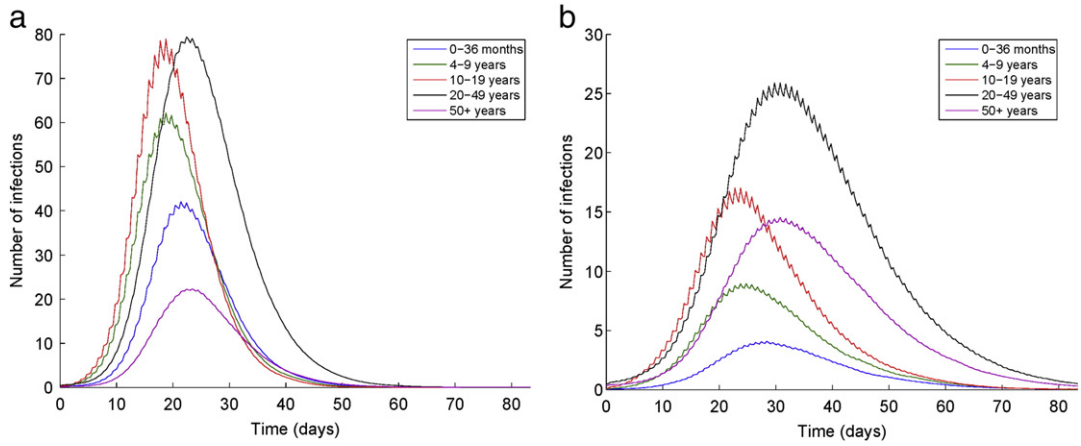

Fig. 2. Age-specific epidemic curves with baseline protection levels given in Table 1 for: (a) original demographics (OD); (b) shifted demographics (SD) of RC.

epidemic outcomes, not only in terms of the epidemic size, but also in regard to healthcare resource utilization (e.g., hospitalization) for the management of severe disease outcomes.

Conclusions

The broad susceptibility of young age groups, particularly in individuals below 10 years of age, is a cause for concern, especially in light of severe outcomes observed in this age group during the 2009 H1N1 pandemic. Based on the results reported here, we strongly recommend that, when an H3N2v-specific vaccine becomes available, the very young and school-aged children should be prioritized for vaccination. This prioritization is particularly important for population settings with a low average age, including many aboriginal populations residing in geographically remote and isolated areas.

Authors' contributions

SM conceived and designed the study. SM and ML conceptualized the simulation model based on a previously validated model. ML performed simulations and analyzed the outputs. SM, ML, DB wrote the first draft of the manuscript. VD, GW, JW contributed reagents/materials/analysis tools. All the authors have contributed to the final version, and approved its content.

Conflict of interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2013.04.011.

References

Centers for Disease Control and Prevention (CDC), 2011. Limited human-to-human transmission of novel influenza A (H3N2) virus — Iowa, November 2011. MMWR Morb Mortal Wkly Rep 60, 1615–1617.

Centers for Disease Control and Prevention (CDC), 2012a. Case Count: Detected U.S. Human Infections with H3N2v by State since August 2011. http://www.cdc.gov/flu/swineflu/h3n2v-case-count.htm (accessed November Centers for Disease Control and Prevention, CDC, CDC, CDC, CDC, 2011, 2009., 2011, CDC, CDC, CDC, 2011, 2009.).

Centers for Disease Control and Prevention (CDC), 2012b. Antibodies cross-reactive to influenza A (H3N2) variant virus and impact of 2010–11 seasonal influenza vaccine on cross-reactive antibodies — United States. MMWR Morb. Mortal. Wkly Rep. 61, 237–241.

Centre for Disease Control and Prevention (CDC), 2012. CDC Reports More Cases, Hospitalizations and Nation's First H3N2v-Associated Death. http://www.cdc.gov/flu/spotlights/h3n2v-more-cases.htm (accessed September 2012c.).

Chou, Y.Y., Albrecht, R.A., Pica, N., Lowen, A.C., Richt, J.A., García-Sastre, A., et al., 2011. The M segment of the 2009 new pandemic H1N1 influenza virus is critical for its high transmission efficiency in the guinea pig model. J. Virol. 85, 11235–11241.

Diekmann, O., Heesterbeek, J.A.P., 2000. Mathematical Epidemiology of Infectious Diseases. John Wiley and Sons Ltd.

European Centre for Disease Prevention, Control, 2012. Update — swine-origin triple reassortant influenza A(H3N2) variant viruses in North America. http://ecdc.europa.eu/en/publications/Publications/1208-TER-Rapid-risk-assessment-influenza-AH3N2-US.pdf (accessed September 2012.).

Kumar, A., Zarychanski, R., Pinto, R., et al., 2009. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. J. Am. Med. Assoc. 302, 1872–1879.

Laskowski, M., Mostaço-Guidolin, L.C., Greer, A.L., et al., 2011. The impact of demographic variables on disease spread: influenza in remote communities. Sci. Rep. 1, 105.

Lessler, J., Reich, N.G., Brookmeyer, R., Perl, T.M., Nelson, K.E., Cummings, D.A., 2009. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect. Dis. 9 (5), 291–300.

Lina, B., Bouscambert, M., Enouf, V., Rousset, D., Valette, M., van der Werf, S., 2011. S-OtrH3N2 viruses: use of sequence data for description of the molecular characteristics of the viruses and their relatedness to previously circulating H3N2 human viruses. Euro. Surveill 16 (pii:20039).

Mostaco-Guidolin, L.C., Towers, S.M.J., Buckeridge, D.L., Moghadas, S.M., 2013. Age distribution of infection and hospitalization among Canadian First Nations during the 2009 H1N1 pandemic. Am. J. Public Health 103, e39–e44.

Mostaço-Guidolin, L.C., Bowman, C.S., Greer, A.L., et al., 2012. Transmissibility of the 2009 H1N1 pandemic in remote and isolated Canadian communities: a modelling study. BMJ Open 2, e001614.

Skowronski, D.M., Janjua, N.A., De Serres, G., Purych, D., Gilca, V., Scheifele, D.W., Dionne, M., Sabaiduc, S., Gardy, J.L., Li, G., Bastien, N., Petric, M., Boivin, G., Li, Y., 2012. Cross-reactive and vaccine-induced antibody to an emerging swine-origin variant of influenza A virus subtype H3N2 (H3N2v). J. Infect. Dis.. http://dx.doi.org/10.1093/infdis/jis500.

Statistics Canada, 2007a. Manitoba (Code4622048) (table). 2006 Community Profiles. 2006 Census. Statistics Canada Catalogue no. 92-591-XWE. Ottawa (Released March 13, 2007).

Statistics Canada, 2007b. Winnipeg, Manitoba (Code4611040) (table). 2006 Community Profiles. 2006 Census. Statistics Canada Catalogue no. 92-591-XWE. Ottawa (Released March 13, 2007).

Tuite, A.R., Greer, A.L., Whelan, M., et al., 2010. Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. CMAJ 182, 131–136.

Waalen, K., Kilander, A., Dudman, S.G., Ramos-Ocao, R., Hungnes, O., 2012. Age-dependent prevalence of antibodies cross-reactive to the influenza A(H3N2) variant virus in sera collected in Norway in 2011. Euro Surveill 17 (19), 20170.

Zarychanski, R., Stuart, T.L., Kumar, A., et al., 2010. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. CMAJ 182, 257–264.