

Review

Ethnic differences in susceptibilities to A(H1N1) flu: An epidemic parameter indicating a weak viral virulence

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The current A(H1N1) flu has showed sub-population dependent susceptibility and fatality as early as April and May of 2009 in its first wave of spreading. After the pandemic outbreak spreads globally for more than seven months, the subpopulation dependence of this flu, including ethnicity, age and gender selectivity, has been recognized by several research groups. This paper attempts to discuss how to identify ethnic selectivity from the released data by WHO relevant to this ongoing flu, review some recently published papers describing the presence of ethnic differences in susceptibilities to the H1N1 flu virus and further raised an argument that ethnic differences in susceptibilities to a virus might be a piece of evidence reflecting a weak virulence of that specific virus.

Key words: H1N1 flu, virulence, ethnic.

FULL TEXT

The morbidity and mortality of an infectious disease depend on the interaction between the pathogen and its host under specific environments. For viral infections in humans, the size of the susceptible subpopulation to a new type or subtype of virus largely determines the spreading width and the overall morbidity globally, whereas the viral virulence is associated with the mortality related to the specific virus. In other words, a pandemic outbreak may only cause a very low mortality when the virus is moderately or weakly virulent and a high death toll or high morbidity is generally reported as a result of a disease outbreak caused by a virulent virus.

It is well known that genetic heterogeneity or gene make-up plays a role in variable morbidity and mortality rates of both non-infectious and infectious diseases (Modiano et al., 1996; Neel, 1962; Schwartz, 2001; World Health Statistics, 2008). The ethnic difference in disease susceptibility is an advantageous gain during the evolution process. This advantage is made evident in two

ways. Firstly, the same ethnic group may have selected susceptibilities to different pathogens and secondly, various ethnic groups may have different susceptibilities to the same pathogen. Therefore, it is possible to express various morbidity and mortality rates among people depending on their ethnicities, regions, ages among others, during an epidemic particularly during a pandemic outbreak.

As early as April 29 and May 6 2009, an opinion was expressed that ethnic selectivity to the ongoing H1N1 might be a factor in minimizing the death toll of the new flu outbreak and Chinese population might not be highly susceptible to the H1N1 virus. This was presented to the public and biomedical communities (http://blog.sina.com.cn/s/blog_4e5eb50f0100deyl.html) (Zhou et al. 2009). At the epidemiological point of view, ethnic difference can be revealed by analyses of some specific epidemiologic parameters. For example, the following parameters can be used to evaluate whether there is an ethnic difference in susceptibility: i). the time interval between the first imported case and the first domestic case; ii). the case doubling time; iii). the ratio of symptomless infected individuals and clinically diagnosed cases; iv). the ratio of cases without contact history and those with clear contact

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history; v). The morbidity rate observed in different ethnic groups and vi). The case fatality ratios among ethnic groups.

It was first noticed that the possible ethnic dependent susceptibilities to A (H1N1) flu from the significant differences of case doubling time among countries in late April of 2009 and virtually all patients diagnosed in the first month since its transmission to China were input cases without single domestic second generation case until May 29 of 2009 (<http://www.gowod.cn/html/42/n-4642.html>). More solid evidence was from WHO update providing death toll by countries, which clearly documented significant differences among the case fatality ratio among countries (Figure 1b) (Pandemic (H1N1) 2009 - update 72). The North American region showed relatively high case fatality ratio, which is probably attributed to both ethnic and regional selectivity. Based on the latest update of WHO, the case fatality ratios were different among regions (Figure 1a) (Pandemic (H1N1) 2009 - update 71). Ethnicity dependent susceptibility to A (H1N1) flu has now been recognized by both biomedical community and the general public. Using the parameters mentioned above, one study from New Zealand reported ethnic related susceptibilities to H1N1 viral infection (Baker et al., 2009). Interestingly, National Geographic News published on October 9, 2009 reported that native peoples are suffering a swine flu infection rate four to five times higher than that of the general population (<http://news.nationalgeographic.com/news/2009/10/091009-swine-flu-deaths-children-pediatric-indigenous.html>). This newspaper also recalled similar ethnic selectivity in the Spanish influenza pandemic in 1918 in which indigenous peoples in Canada, Sweden, Norway and the United States had estimated mortality rates 3 to 70 times higher than non-indigenous populations. It seems that ethnic selectivity, rather than health care conditions is responsible for the major difference in modality and mortality rates observed among ethnic groups. As shown in Figure 1, a more reasonable explanation for the extremely low case fatality ratio as well as mortality rate in China so far during the A (H1N1) flu is ethnic dependent susceptibility, rather than the stringent strategies used in the prevention.

Early identification of highly susceptible subgroup is very important in order to provide medical services to those who are at high risk. In addition to ethnic subgroups, the current A (H1N1) flu also showed age and gender dependent modality and mortality rates different from other subpopulations. Young people and women with pregnancy have been confirmed to be high risk subpopulations, probably in any ethnic groups (Jain et al., 2009; Jamieson et al., 2009; CDC, 2009). Further report showed that the estimated rate of admission for pandemic H1N1 influenza virus infection in pregnant women during the first month of the outbreak was higher than it was in the general population (0.32 per 100 000 pregnant women vs 0.076 per 100 000 population at risk)

(Jamieson et al., 2009). In a report including 272 hospitalized patients, forty-five percent of the patients were children under the age of 18 (Jain et al., 2009). In particular situations, a case fatality ratio in hospitalized young flu patients had been reported in as high as 50% (Caprotta et al., 2009). Mechanisms responsible for age- and ethnic-dependent susceptibility to A (H1N1) flu are probably different. The former is more related to prior natural or artificial immunization and the latter is highly possibly attributed to the genetic heterogeneity of human beings.

In fact, it is already well recognized by the scientific community that the new H1N1 virus is far less virulent than what was predicted by official authorities even without the present prospective evaluation of its virulence. Compared to the predicted daily death rate of about 1000 patients from seasonal flu (250,000 to 500,000 fatal cases per year), the H1N1 flu caused an average less than 30 deaths daily in the past six months (Goodman et al., 2006; Pandemic (H1N1) 2009 - update 72). The lack of a commonly accepted criteria for the prospective evaluation of viral virulence caused a certain confusion in the public community between the WHO's alert stages and the viral virulence degrees (WHO), and led to some misinterpretations on its viral virulence.

The prospective evaluation of virulence of a new pathogen has enormous social and biomedical impacts. In order to be more effectively and cost-efficiently prepared in dealing with a new disease outbreak, assessing how virulent the new pathogen is will be the most important factor in determining the mobilization scale and intensity of the infection nationally or internationally. For this ongoing pandemic flu outbreak, intensive strategies such as national vacation with the shutting down of schools and businesses seemed like the proper response at the beginning when the prospective virulence was thought to be highly virulent. However, when ethnic and age differences in the propagation of the flu were observed, these intensive strategies might not be necessary anymore.

The traditional reporting system which presents data on the number of infected cases and death toll does not provide enough information for prospective virulence evaluation and has only limited value in guiding the prevention. The suggested classification requires more epidemiology-related parameters for the prospective evaluation of viral virulence. Whenever possible, ethnicity, age, gender and all other parameters included in this classification system should be released for adequate epidemiological study. In the present ongoing pandemic outbreak of the H1N1 flu, the identification of the higher susceptibility of young people and pregnant women is a reminder that more medical surveillance of these two subpopulations is required. If the ethnicity-related information would have been included and the ethnic difference officially reported during the early stages of this pandemic swine flu, an overreaction would probably have been avoided and

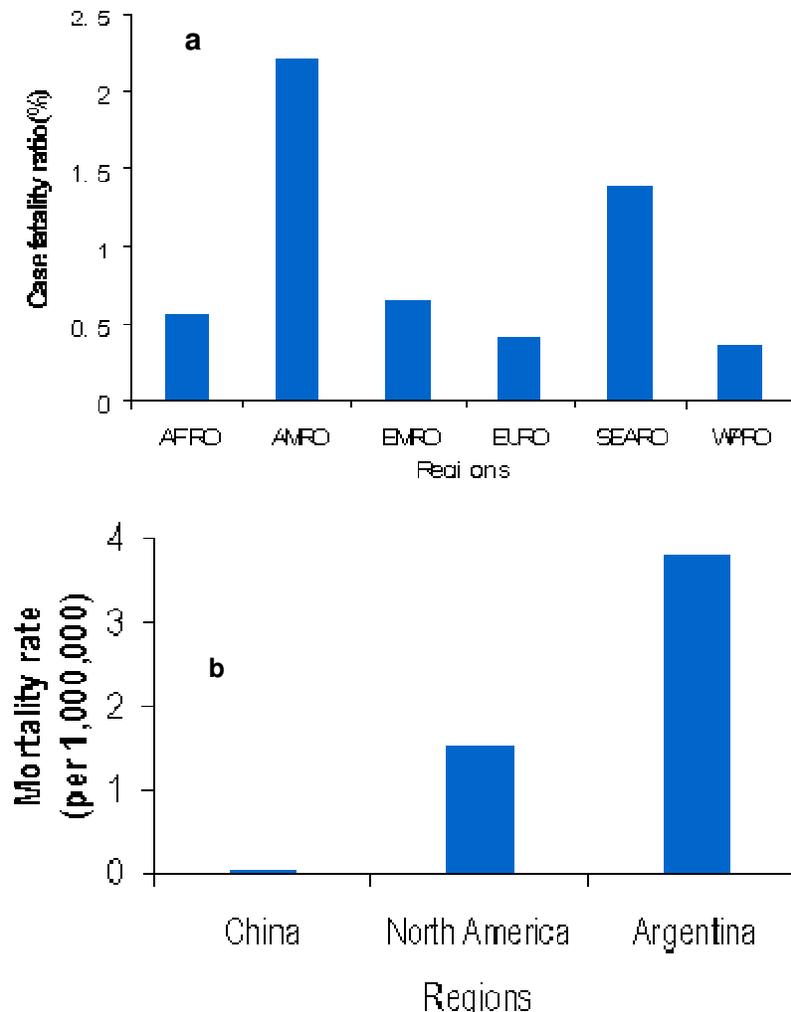


Figure 1. Different susceptibility to A (H1N1) flu among regions and countries. The regions in 1a represent the WHO Regional Offices for: Africa (AFRO), Americas (AMRO), Eastern Mediterranean (EMRO), Europe (EURO), South-East Asia (SEARO) and Western Pacific (WPRO). This data was the Cumulative total as of 18 October 2009. 1b: Mortality rates of selected countries including Mexico, the country of the A (H1N1) outbreak origin. The death toll was the latest update between August 4th and October 26 of 2009 from CDC of relevant countries.

precious resources used more effectively for specific subgroups such as young persons and pregnant women of specific ethnic groups.

The prospective evaluation of a new pathogen's virulence is not only able to provide an abstract classification number, but it also helps to estimate the worst mortality rate of the specific pathogen and to estimate the possible gap between the retrospective mortality and the worst prospective mortality. The worst mortality is simply extrapolated globally using the local mortality of a region or a nation where the outbreak of the new infectious disease begins. For example, the worst fatality of this A (H1N1) can be estimated using the regional mortality in the first wave in Mexico by simply assuming the same

level of global mortality it would be. That is, roughly a maximum of 14,000 to 70,000 fatal cases would be eventually accumulated in this new flu outbreak depending on how the regional mortality is calculated with the population of the country of Mexico or the city of Mexico. If there is no second wave of A (H1N1) flu outbreak in Mexico, the maximal number of death toll would be 14,000 or less. Otherwise, if a second wave occurs in Mexico, the worst death toll would then be 70,000 or less globally. This estimation is solely based on ethnic selectivity without taking seasonal factor into account. Therefore, the real worst situation of the death toll may reach or even a little bit more than 70,000. The death toll from this theoretical worst situation is still better than the average

number caused by seasonal flu. Thus, the prospectively evaluation of the ongoing spreading virus is not only theoretically useful but also with practical high impact to the national or international mobilization in battling with the spread of the new disease.

This prospective evaluation of viral virulence can be used for quick adjustments in handling outbreaks of viral diseases particularly the pandemic outbreaks. The virulence classification helps to predict the worst global mortality and estimate the gap between the prospective mortality and the retrospective mortality, which can be used to decide the scale of national or international mobilization in battling with the spread of the new disease, such as the decision of preparing a given amount of specific antiviral medicine and specific vaccine. Additionally, the assessment of susceptibilities among selected groups can help to focus on the prevention and treatment efforts or the international collaborations in targeting ethnic groups with high susceptibility, and to minimize overreactions in ethnic groups with low susceptibility. The ethnic differences are not just a concept. These differences can be identified quantitatively in a number of epidemiologic parameters. There is no doubt that the identification of different susceptibilities among various ethnic groups to a specific virus means that the viral virulence is relatively low and thus not a high risk to human beings. It is urgently needed in order to have a virulence classification adding to WHO's disease reporting system. The suggested inclusion of ethnic dependent susceptibility to viral infection discussed in the present paper cannot fulfill this important issue but it opens a new avenue to approach the goal.

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