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Relation between Measles Incidence and Population Size under the Advanced Vaccine Program

Hiroshi Yoshikura*

National Institute of Infectious Diseases, Tokyo 162–8640, Japan

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This study provides an evidence for a positive correlation between measles incidence (the number of cases per million population) and the population size of a community (either a prefecture in a single country or countries in a region) when the community has attained a certain level of vaccine coverage (>80–90%).

Japan experienced a resurgence of measles epidemics from late 2007 to 2008. As a result of this incident and to attain the World Health Organization (WHO) measles elimination goal (less than one case per million) before 2012 (1), Japan temporarily modified their measles immunization schedule to enhance national immunization rates (2) and changed the reporting system from sentinel-based reporting to the reporting of all cases (2).

Figure 1 shows the number of measles cases per million against coverage of measles-rubella (MR) combined vaccine (Panel A), the unvaccinated population among the 1-year-old vaccine target population (Panel B), and the total 1-year-old vaccine target population (Panel C). Here, each point corresponds to a prefecture, and the data used for the plot are the means of 3 years (2008 to 2010). The correlation coefficient (CC) between measles incidence and the vaccine coverage rate was −0.010, indicating that there was no correlation between measles incidence and vaccine coverage in Japan when nearly all the prefectures attained ≥90% vaccine coverage. The CC for measles incidence and both the unvaccinated population within the target population (Panel B) and the total target population (Panel C) was 0.64. As the target population size is generally proportional to the actual population size, the correlation between measles incidence and population size (Panel D) and between measles incidence and population density (Panel E) was examined. The correlation between measles incidence and population size was 0.65, and that between measles incidence and population density was 0.59. In contrast, the correlation between rubella incidence and population size (Panel F) was weaker (CC = 0.47). It was unexpected that there was a significant correlation between incidence and population size rather than density.

The observed correlation between measles incidence and population size was interesting in view of the long-known dependency of the measles epidemic on population size (3–6). Therefore, I examined the possible correlation between measles incidence and population size among different countries. For this study, European Union (EU) members that joined in 1995 or before (the fourth expansion of EU) were chosen. These countries, Austria, Belgium, Denmark, Germany, Greece, Finland, France, Luxemburg, Portugal, Spain, Sweden, Netherlands, and the UK, were chosen because they were considered to be on a similar economic level (recall that the EU started as the European Economic Community). Since vaccination coverage was particularly low (below 80%) for Ireland (2001–2006) and Austria (2001–2010) (Panel B in Fig. 2), these two countries were excluded from the analysis. Panel A in Fig. 2 shows a plot similar to that for prefectures in Japan. The mean number of cases/million in 2007–2010 was plotted on the vertical axis and the population in 2010 was plotted on the horizontal axis. The CC for these EU countries was 0.70, which was roughly equivalent to or slightly higher than that for the Japanese prefectures. Interestingly, the correlation between measles incidence and population size was observed even at the country level.

To confirm the observed correlations using an entirely different method, I used rank correlation. Although the original method (7) is entirely mathematical, here, I took a simplified approach. Prefectures were ranked from large to small according to population size and according to disease incidence. If a prefecture was the ath in terms of population size and bth in the incidence rate, the prefecture was given the coordinates (a, b), which defines its point on a plane defined by the ranking number of population on the horizontal axis and that of measles incidence on the vertical axis. Panel A in Fig. 3 shows such a plot for measles in the 47 prefectures. If there is 100% correlation between the coordinates, all the points will fall on a diagonal line connecting the origin of the coordinates (0, 0) and the opposite corner (47, 47); if there is no correlation, the points will be distributed at random. Next, two lines parallel to this diagonal line at the same distance from the diagonal line were drawn so that the area between the two lines ($IN_{20\%}$) is 20% of the total area. Since the total area is 47 × 47, the sum of area outside of the two lines (OUT) is 47 × 47 × 0.8 = 1,767, which is ~42^2. Therefore, one of the two lines bordering $IN_{20\%}$ and OUT connected (5, 0) and (47, 42), while the other connected (0, 5) and (42, 47). If the points are randomly distributed, the probability that any point will be within a given area is proportional to the size of the area, i.e., 9.4 (47 × 0.2) points in $IN_{20\%}$. Since 20 of the 47 points were counted within the area of $IN_{20\%}$, the number was 2.1-fold

*Corresponding address: Mailing address: Department of Food Safety, Ministry of Health, Labour and Welfare, 1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8916, Japan. E-mail: yoshikura-hiroshi@mhlw.go.jp

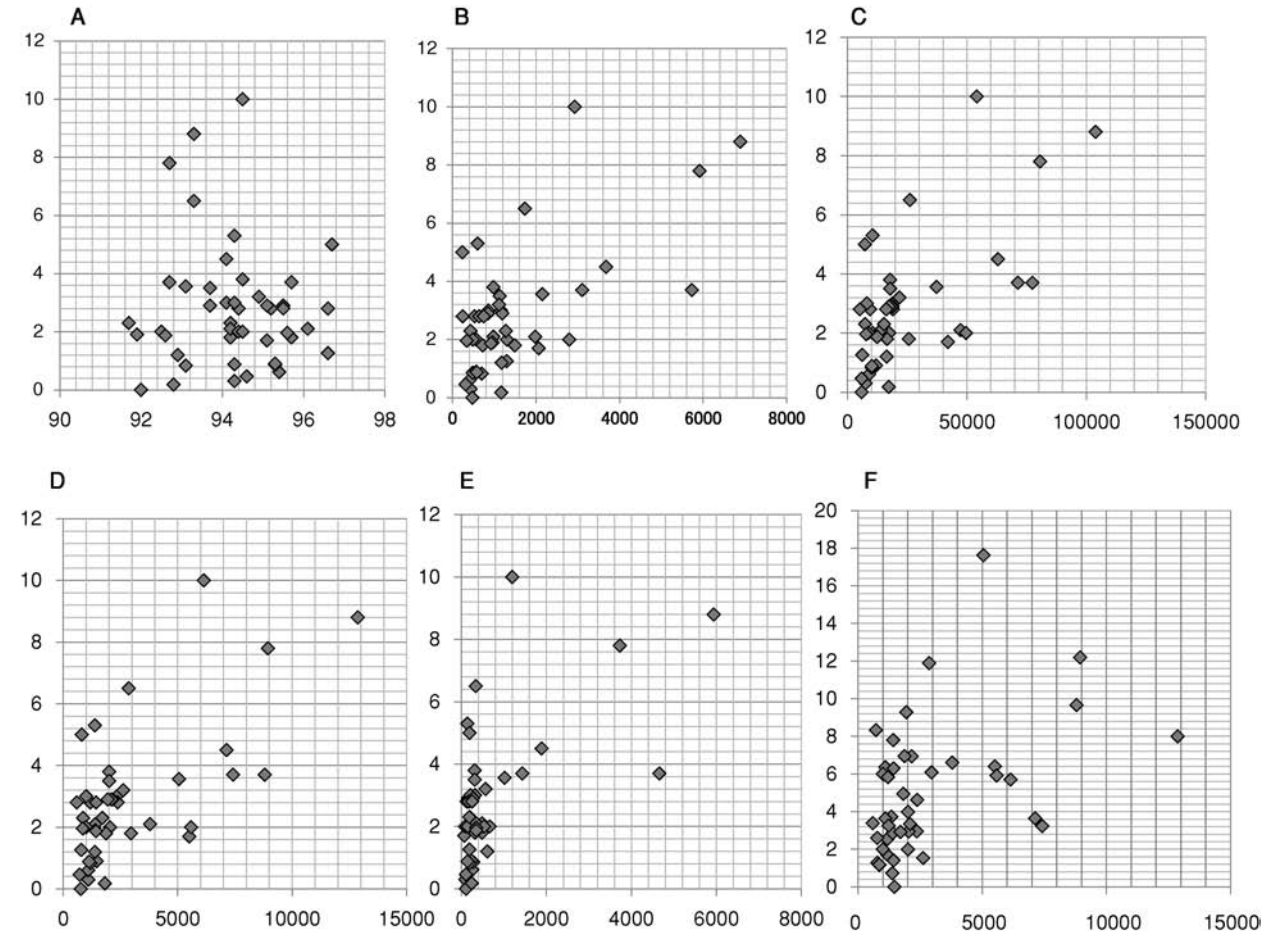

Fig. 1. Relation between the measles incidence (2008–2010) and vaccine coverage, community population and other parameters among prefectures in Japan. (A) Relation between the measles incidence (cases/million population) in the vertical axis versus MR vaccination coverage (%) in the horizontal axis. (B) Relation between the measles incidence (cases/million population) in the vertical axis versus number of unimmunized population among the target group in the horizontal axis. (C) Relation between the measles incidence (cases/million population) in the vertical axis versus number of immunization target population in the horizontal axis. (D) Relation between the measles incidence (cases/million population) in the vertical axis versus total population in a prefecture (×1,000) in the horizontal axis. (E) Relation between the measles incidence (cases/million population) in the vertical axis versus population density (population/km^2) (in year 2011) in the horizontal axis. (F) Relation between the rubella incidence (total number of cases in 2008–2010/million population) in the vertical axis versus population (×1,000) in a prefecture (in year 2010) in the horizontal axis. The measles incidence and MR coverage data are the mean values of 2008–2010 data. The data source for measles incidence was http://idsc.nih.go.jp/disease/measles/2010pdf/meas10-52.pdf; http://idsc.nih.go.jp/disease/measles/2009pdf/meas09-53.pdf; http://idsc.nih.go.jp/disease/measles/2008pdf/meas08-52-01.pdf, that for rubella incidence was http://idsc.nih.go.jp/disease/rubella/IDWR11week1718.html, that for coverage of MR combined vaccine (population receiving other forms of measles vaccine was negligibly small) was http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/dl/080331a.pdf, that for target population was http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/dl/080331a.pdf, that for population size was http://rnk.uub.jp/rnk/prnk.cgi?T=p (the data was for the year 2006 but there has been no significant population change in recent years), and that for population density was http://ja.wikipedia.org/wiki/%E9%83%BD%E9%81%93%E5%BA%9C%E7%9C%8C%E3%81%AE%E4%BA%BA%E5%8F%A3%E4%B8%80%E8%A6%A7.

(20/9.4) more than expected with a random distribution. For rubella (Panel B in Fig. 3), 16 of 47 points were within $IN_{20\%}$, which was 1.7-fold (16/9.4) more than expected with a random distribution. For the EU countries, 8 of 13 points were located in $IN_{20\%}$, about 3.1-fold (8/(13 × 0.2)) more points than expected in $IN_{20\%}$ (Panel C in Fig. 3). Therefore, the rank correlation and the correlation coefficient both indicated a positive correlation between measles incidence and population size. The correlation between rubella incidence and population size was weaker. It can thus be hypothesized that under nearly complete immunization coverage, the attainable level of measles reduction depends on the population size. (Note that in the above rank correlation analysis, percentages other than 20% can be chosen for IN; however, percentages that are too small or too large will not yield meaningful results.)

The population size dependence of the measles epidemic has long been known (3–6). Bartlett observed that the periodicity of measles epidemics in large cities gradually disappeared as the population size of these cities decreased (4), and Black observed an inverse relation between epidemic frequency and population size among island communities (5). This phenomenon was attributed to the requirement for a minimum sensitive population for endemic measles circulation. These observa-

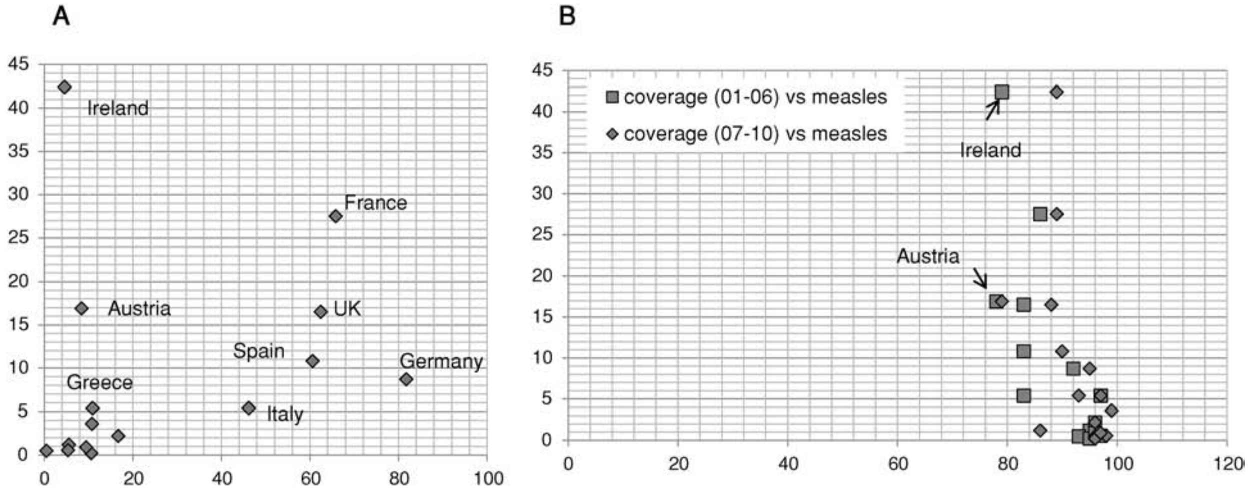

Fig. 2. Relation between measles incidence and population size for EU countries. (A) Relation between the measles incidence (mean number of cases in 2007–2010/million population) in the vertical axis versus country's total population ($\times$ 1,000,000) in the horizontal axis. (B) Relation between the measles incidence (mean number of cases in 2007–2010/million population) in the vertical axis versus mean measles vaccination coverage (%) for 2001–2006 (squares) and for 2007–2010 (diamonds) in the horizontal axis. The data source for measles incidence (2007–2010) was http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tsincidencemea.htm, that for measles vaccine coverage (2001–2010) was http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tscoveragemcv.htm and that for national population size (2010) was http://ja.wikipedia.org/wiki/%E5%9B%BD%E3%81%AE%E4%BA%BA%E5%8F%A3%E9%A0%86%E3%83%AA%E3%82%B9%E3%83%88.

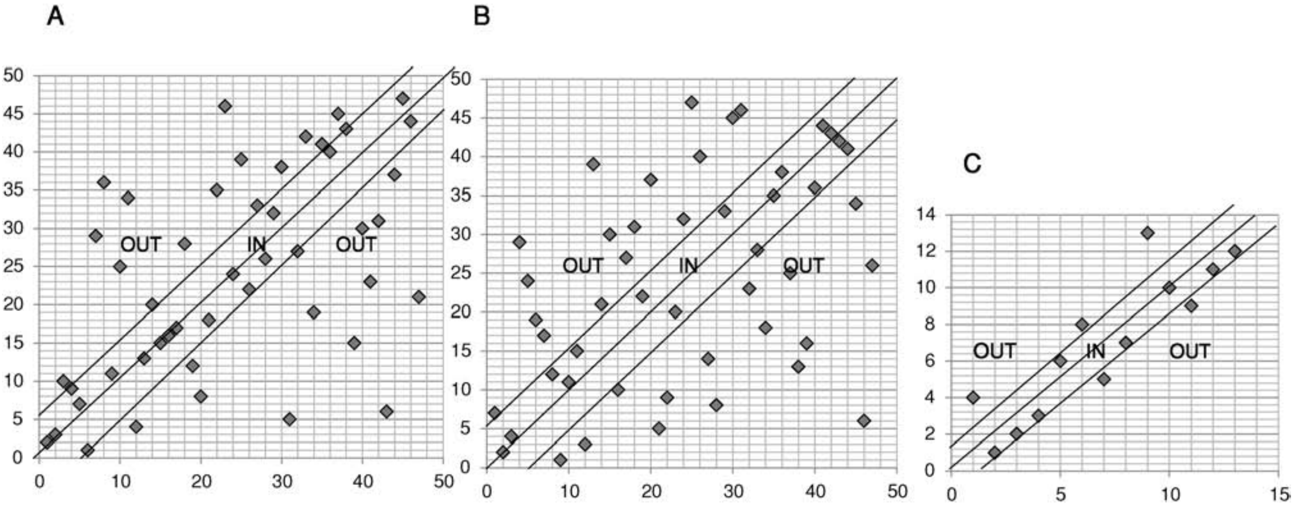

Fig. 3. Ranking relation between measles incidence and population size evaluated by a simplified ranking correlation analysis. (A) Ranking relation between measles incidence (cases/million) and the population size of a prefecture ($\times$ 1,000) in Japan. (B) Ranking relation between rubella incidence (cases in 3 years from 2008 to 2010/million) and the population size of a prefecture ($\times$ 1,000) in Japan. (C) Ranking relation between measles incidence (mean number of cases in 2007–2010/million) and the population size ($\times$ 1,000,000) in EU countries. Note that difference between ranking of measles incidence and that of the population size, i.e., difference of co-ordinates, is maximum 5 rankings for (A) and (B) and less than 2 rankings for (C).

tions were made more than half a century ago, when the measles vaccine was not widely available and immunity was obtained only through natural infection. Now in the 21st century, the population size dependence of the measles epidemic was again observed. However, in the latter case, countries have already achieved significant measles reduction through intensive vaccination. Therefore, the current situation surrounding the measles epidemic is entirely different from that a half century ago. The question is whether there is a common mechanism.

It is interesting to note that the correlation between the incidence rate and population size was higher than that between the incidence rate and population density (the CC was 0.65 for the former and 0.59 for the latter). Naturally, the latter had higher correlation. Suzuki (8) noted, referring to figure 7 showing population density (1925) and percentage of measles deaths in October to December of 1921–1930, Nihon Teikoku Siin Tokei: Eiseikyoku Nenpo, that in the pre-war period, the higher was the population density, the higher was the measles mortality. The population density counts, however, only when people are more evenly dispersed within a community and human activities are more localized, similar to in the pre-World War II period. However, advanced urbanization in Japan after the War brought economic, cultural, administrative, and other activities into large cities and has made human movements more fluid. In such a situation, the probability that a measles patient will encounter susceptible persons is more proportional to the population size rather than the population density. At the same time, it should be recalled that a larger population attracts more people. Although there are no statistics to support this statement at the prefecture level, evidence exists on the international level. According to international immigration statistics in 2009 (website of the Japan Tourism Agency; http://www.mlit.go.jp/kankocho/siryou/toukei/ranking.html [in Japanese]), France, Spain, Italy, the UK, and Germany were ranked first, third, fifth, sixth, and eighth, respectively, in the number of immigrants per year (the second, fourth, and seventh were the United States, China, and Turkey, respectively), and these five countries were the top five EU countries both in measles incidence and population size (Panel A in Fig. 2). Therefore, the higher measles incidence in these countries may be due to the large number of immigrants who often carry human pathogens, including the measles virus. Actually, in Europe, despite the reduction of endemic measles virus, importation of measles virus from other continents has caused prolonged and large outbreaks (9). The situation is the same for Japan (2). However, it may not be appropriate to attribute the population size dependence of the measles epidemic to a single event. The dependency may be brought about by complex interactions among the large population size, the large number of immigrants, as well as ethnic, religious, and economic heterogeneities.

In any event, if measles incidence really does depend on population size, it is natural that the Pan American Health Organization (PAHO) attained measles elimination rather quickly because the American continent is rather sparsely populated (http://en.wikipedia.org/wiki/List_of_sovereign_states_and_dependent_territo ries_by_population_density) and its total population is relatively smaller than on other continents. Recall that the total population of PAHO (around 7.5 billion) is just slightly more than half of China's population (~13.5 billion). Measles elimination will be particularly difficult for populated countries, such as China and India. WHO's operational definition of measles elimination, ''less than one confirmed measles case reported per million population per year (excluding imported cases),'' may have to be applied flexibly taking the population size and other relevant factors into account.

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Conflict of interest None to declare.

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