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Negative Impacts of Large Population Size and High Population Density on the Progress of Measles Elimination

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This paper will show that large population size and high population density negatively impact the progress of measles elimination.

In 2002, the World Health Organization (WHO) of the American Region (AMR) successfully interrupted the circulation of the endemic strain of measles virus; the WHO Regional Committee of the Western Pacific Region (WPR) aimed to eliminate measles by 2012 (1). However, the progress towards measles elimination in WPR and other WHO regions except AMR has not been so smooth (2). Japan has intensified measles elimination activity since 2008 by modifying the vaccination schedule and switching the reporting system from sentinel-based reporting to the reporting of all cases (1). However, measles elimination, defined as ''less than one confirmed measles case reported per million population per year (excluding imported cases)'' (3), has not yet been attained.

I previously reported that the measles incidence among different prefectures in Japan and different European Union (EU) member countries (that joined in or before 1995) correlated with population size, i.e., the larger the population size, the higher the measles incidence (4). More recently, I discovered that measles incidence strongly depends on population size and density (size/density) in the EU (2000–2010), WPR (2009–2011), and AMR (2007–2010) by using a population size-density matrix graph, on which countries stratified according to measles incidence are plotted (5). In the present article, using the same methodology, I examined the possible impact of population size/density on the progress of measles elimination in Japan since 2008, when the intensified measles vaccination program was implemented (1). Japan is suitable for study because the vaccination program was implemented uniformly, and relatively accurate data are available.

Data on the population size and density (2006) and measles incidence per year (2008–2011) in all prefectures in Japan are listed in Table 1. At the bottom of the table, the correlation coefficients (CC) between measles incidence and population size (population size CC) and between measles incidence and population density (population density CC) are shown. Both CCs increased from an almost insignificant level in 2009 to a nearly significant level in 2011, i.e., 0.48 in 2009 to 0.66 in 2011 for population size CC, and 0.42 in 2009 to 0.61 in 2011 for population density CC. This indicates that as the

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Table 1. Measles incidence (2008–2011) and population size/density

Prefecture	Population		Measles incidence per million				
	Size (× million)	Density (/km²)	2008	2009	2010	2011	Mean (2009–2011)
Hokkaido	5.5	70.36	265.48	3.09	0.91	1.45	1.81
Aomori	1.4	143.36	45.69	7.98	5.80	0.00	4.59
Iwate	1.3	87.76	8.21	1.49	3.73	1.49	2.23
Miyagi	2.3	321.18	9.42	3.85	1.28	0.00	1.71
Akita	1.1	94.33	144.16	0.00	0.00	0.91	0.30
Yamagata	1.2	126.56	14.42	6.79	1.70	0.00	2.83
Fukushima	2.0	148.22	10.78	4.41	1.47	0.00	1.96
Ibaraki	3.0	486.80	34.12	3.72	1.69	0.00	1.80
Tochigi	2.0	313.77	22.93	5.48	2.49	5.48	4.48
Gunma	2.0	315.39	42.85	5.98	2.49	2.49	3.65
Saitama	7.1	1888.30	54.56	6.17	4.07	4.21	4.81
Chiba	6.1	1199.19	174.46	19.06	7.00	4.24	10.10
Tokyo	12.9	5937.33	91.23	8.63	5.91	13.68	9.40
Kanagawa	8.9	3727.54	397.85	10.85	8.61	4.47	7.97
Niigata	2.3	189.42	18.08	7.57	0.84	1.26	3.22
Toyama	1.1	257.84	7.31	1.83	0.00	0.00	0.61
Ishikawa	1.2	278.73	6.01	0.86	0.00	0.00	0.28
Fukui	0.8	193.00	21.04	4.95	9.90	1.24	5.39
Yamanashi	0.9	194.64	31.14	1.15	3.46	3.46	2.69
Nagano	2.2	159.31	28.25	6.02	2.32	0.46	2.93
Gifu	2.1	196.46	10.52	4.30	3.35	1.43	3.02
Shizuoka	3.8	486.86	64.61	2.37	3.16	2.11	2.54
Aichi	7.4	1435.57	26.56	3.91	4.31	4.18	4.13
Mie	1.9	322.40	22.99	1.07	4.28	1.07	2.14
Shiga	1.4	349.02	27.76	4.98	0.71	0.71	2.10
Kyoto	2.6	570.42	73.61	4.42	4.20	1.14	3.34
Osaka	8.8	4657.71	44.54	6.48	3.52	1.36	3.78
Hyogo	5.6	666.92	25.79	1.43	2.33	2.51	2.09
Nara	1.4	379.55	8.58	2.14	2.14	1.43	1.90
Wakayama	1.0	212.79	39.84	6.97	1.99	0.00	2.98
Tottori	0.6	168.55	11.84	3.38	5.08	1.69	3.38
Shimane	0.7	107.35	5.57	1.39	0.00	0.00	0.46
Okayama	1.9	273.25	67.97	5.15	1.54	2.06	2.91
Hiroshima	2.9	338.07	52.04	8.03	2.79	8.73	6.51
Yamaguchi	1.5	238.28	13.75	2.06	0.69	0.00	0.91
Tokushima	0.8	190.34	3.80	2.53	0.00	1.27	1.26
Kagawa	1.0	532.99	10.01	5.01	0.00	1.00	2.00
Ehime	1.4	253.18	29.94	4.18	2.09	2.79	3.02
Kochi	0.8	108.02	6.53	0.00	0.00	0.00	0.00
Fukuoka	5.1	1018.01	133.78	4.95	4.95	1.19	3.69
Saga	0.9	349.57	9.39	3.52	2.35	0.00	1.95
Nagasaki	1.4	348.90	23.08	2.10	1.40	2.80	2.10
Kumamoto	1.8	245.21	49.61	0.00	0.55	0.00	0.18
Oita	1.2	188.85	75.31	2.51	0.00	0.84	1.11
Miyazaki	1.1	146.45	9.72	0.88	0.88	0.88	0.88
Kagoshima	1.7	186.29	14.05	4.10	2.34	1.76	2.73
Okinawa	1.3	608.85	28.94	3.62	0.00	0.00	1.20
CC between measles incidence and population size			0.54	0.48	0.48	0.66	0.66
CC between measles incidence and population density			0.40	0.42	0.44	0.61	0.61

Data sources are http://idsc.nih.go.jp/iasr/33/384/graph/f3842.gif and http://idsc.nih.go.jp/idwr/CDROM/Main.html for measles incidence for 2008–2011, 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#2006.E5.B9.B4 (in Japanese) for population size (2006), and http://rnk.uub.jp/prnk.cgi?T=p (in Japanese) for population density (2006). Correlation coefficient (CC) was calculated by using Microsoft Office Excel 2007.

vaccination program progressed, the measles incidence became increasingly correlated with population size/density. The initial lower correlation may reflect the frequently observed asynchrony in the early implementation phase of many programs, and the later higher correlation may reflect more uniform implementation, making the demographic impact more visible. The measles incidence was correlated more with population

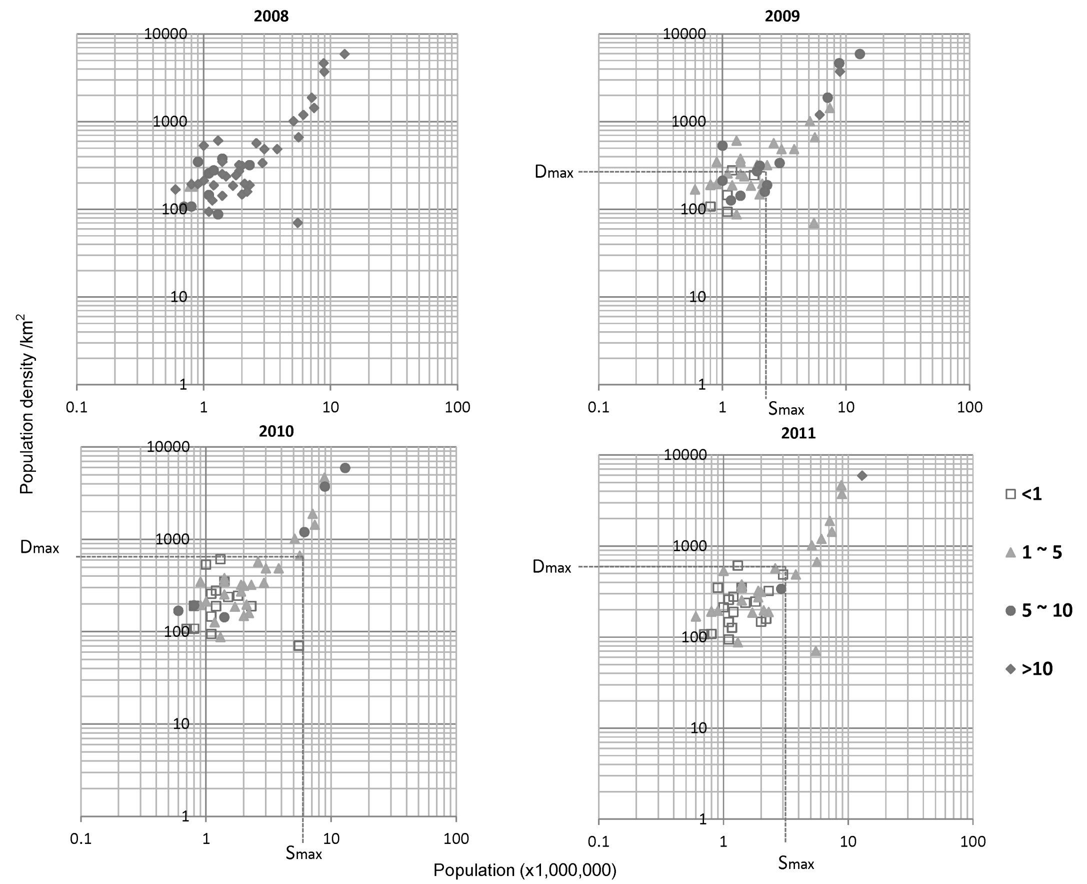

Fig. 1. Plot of prefectures on the population size-density matrix graph (population size on the horizontal axis and population density on the vertical axis). Prefectures are stratified according to measles incidence (I); open squares, I < 1/million/year; triangles, 1/million/year ≤ I < 5/million/year; closed circles, 5/million/year ≤ I < 10/million/year; diamonds, I ≥ 10/million/year. Smax and Dmax indicate the highest population size and the highest population density, respectively, among prefectures that attained an incidence < 1/million/year. Note: the plot for Tochigi whose measles incidence was 5.48 in 2011 is hidden behind other prefectures with the similar population size/density.

Table 2. Summary table of the observation made with Fig. 1

Measles incidence/million (I)	(a) All Prefectures				(b) Prefectures: size >2.9 million				(c) Prefectures: size <2.9 million and density <615/km²			
	2008	2009	2010	2011	2008	2009	2010	2011	2008	2009	2010	2011
I < 1	0*	5	15	19	0*	0	1	0	0*	5	14	19
1 ≤ I < 5	1	26	26	25	0	4	6	9	1	22	20	16
5 ≤ I < 10	9	14	6	2	0	4	3	0	9	10	3	2
10 ≤ I	37	2	0	1	10	2	0	1	27	0	0	0
Dmax (popilation/km²)		278	533	615	*Number of prefectures							
Smax (million)		1.8	5.5	2.9								

The data are for all prefectures (a), for prefectures with population size >2.9 million and population density >615/km² (b), and for prefectures with population size <2.9 million and/or population density <615/km² (c).

size than with population density.

Figure 1 shows the plot of prefectures stratified according to measles incidence per million per year in the population size-density matrix graph. The population density is plotted on the vertical axis and population size on the horizontal axis. In 2008, the measles incidence in almost all prefectures was >10/million/year (diamonds) or 5–10/million/year (closed circles); there were no prefectures with measles incidence <1/million/year. One year after the implementation, prefectures with measles incidence <1/million/year (open squares) appeared, and their number increased from 5 in 2009 to 15 in 2010, and then to 19 in 2011 (Table 2, all prefectures). The area occupied by prefectures with measles incidence <1/million/year gradually expanded; in 2009, the maximum population size (Smax) and the maximum population density (Dmax) for prefectures with measles incidence <1/million/year were 1.8 million and 278/km², respectively. In 2011, Smax was increased to 2.9 million and Dmax to 615/km² (Fig. 1).

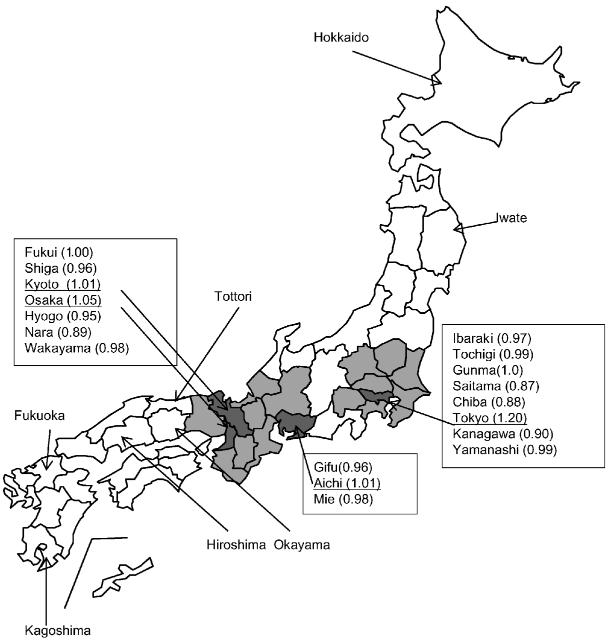

Fig. 2. Administrative map of Japan. Tokyo, Aichi, and Osaka/Kyoto are shaded dark and their neighbor prefectures are lightly shaded. The daytime-nighttime population ratio is given after the prefecture name.

Prefectures were classified according to population size and density, i.e., more-populated prefectures were those with a population size $\geq$2.9 million and population density $\geq$615/km^2, and less-populated prefectures were those with a population size $<$2.9 million and/or population density $<$615/km^2. Although 19 of the 37 less-populated prefectures successfully eliminated measles, all the 10 more-populated prefectures failed to do so (Table 2).

In other words, the measles elimination goal (incidence $<$1/million/year) was achieved first by prefectures with lower population size/density, and then by prefectures with higher population size/density. Therefore, the progress in measles elimination is strongly influenced by population size/density, and the progress is slower in regions with high population size/density.

There were some prefectures with smaller population size ($<$2.9 million)/density ($<$615/km^2), which had never attained a measles incidence of $<$1/million/year by 2011 (2011 included): they are Iwate, Tochigi, Gunma, Fukui, Yamanashi, Gifu, Mie, Nara, Tottori, Okayama, Hiroshima, Ehime, Nagasaki, and Kagoshima (Nagano and Tokushima do not belong to this category because measles incidence went below 1/million once in 2010) (Table 1).

In the administrative map of Japan (Fig. 2), Tokyo, Aichi, and Osaka/Kyoto, the three most populated prefectures/regions in Japan, are darkly shaded, and their neighboring prefectures are lightly shaded. The neighboring prefectures were within commutable range of the populated prefectures, and their nighttime population is higher than their daytime population (http://www.stat.go.jp/data/kokusei/2005/jutsu1/00/03 [in Japanese]). Tochigi, Gunma, Fukui, Yamanashi, Gifu, Mie, and Nara in the above list were among them. They are considered to be within ''economic'' as well as ''epidemic'' zones of the populated prefectures. As the current measles epidemics in Japan are caused by imported viruses (1), the numbers of registered foreigners were compared in the prefectures (http://www.e-stat.go.jp/SG1/estat/GL08020103.do?_toGL08020103_&tclassID = 000001037709&cycleCode = 0&requestSender = search [in Japanese]). Gifu, Gunma, Hiroshima (population size was relatively high, 2.9 million, though the density was $<$615/km^2), Okayama, and Yamanashi in the above list were among the top 22 prefectures that housed more than 12,000 foreigners. Some prefectures in the above list had relatively low vaccine coverage. Nagasaki and Kagoshima have not attained coverage rates above 95% since 2008 (93.9% and 93.8%, respectively, in April 2010–March 2011). Ehime's coverage was below 95% in 2008–2009, though it attained 96.5% in April 2010–March 2011. Iwate's coverage was below 95% (94.8%) in April 2010–March 2011, though the coverage in preceding years was above 95% (http://www.nih.go.jp/niid/images/idsc/disease/measles/pdf02/20110819.pdf [in Japanese]; http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/dl/110331a.pdf [in Japanese]). Thus, prefectures with low population size/density that failed to achieve measles elimination were, at least, either neighboring more-populated prefectures, housing immigrants, or had relatively poor vaccination coverage. Only Tottori Prefecture did not fit any of these categories.

Though we have to continue to monitor the situation in coming years, the following prediction can be made. Prefectures which have not attained measles elimination ($<$1/million/year) because of poor vaccination coverage will be able to eliminate measles by increasing the vaccination coverage. However, measles elimination will be particularly difficult for prefectures of high population size/density, their neighboring prefectures, and prefectures receiving high numbers of immigrants. It should be noted that, in contrast to the good progress made from 2008 to 2010, the progress has slowed since 2010, particularly in populated prefectures (Table 2).

The above prediction is entirely in line with observations made in Panum's report from the 19th century, which suggested that measles epidemics are dependent on population size (6–9). An important question here is ''what is the maximum population size and density that will allow attainment of measles elimination (which is defined as measles incidence $<$1/million/year)?'' or ''what is the achievable level of measles elimination for a country with a given population size/density?'' Data from large and heavily populated countries like China will be invaluable for answering such questions.

The current globalization trend will facilitate the easy and rapid movement of measles virus across borders; this will make measles elimination all the more difficult. The WHO's current ''target'' (not ''definition'') of measles elimination is ''the absence of endemic measles transmission in a defined geographical area for $\geq$12 months in the presence of a well performing system'' (3). This criterion is useful so long as there are endemic strains in a country because imported cases can be easily distinguished from endemic ones by genotyping. However, as importation/exportation becomes the rule rather than the exception (1,10), this criterion becomes difficult to use. For example, when a virus strain has a genotype identical to that of the previous year's isolate, it will be difficult to judge whether the virus is newly imported or a persistent strain from the preceding year. Tracing the epidemic back to the first patient may be the only way to confirm the virus's origin, but that is not always possible.

Once multiple strains of measles virus start to circulate regionally or globally, whether a strain is imported or not will be of little relevance in practice. In such a situation, we may have to revise the measles elimination criteria based on measles incidence. If the measles incidence is related to population size/density, some WHO member countries with high population size/density may not be able to achieve measles elimination as defined (< 1/million/year). We may have to consider a demographically/geographically adjusted elimination level, which is achievable, sustainable, and appropriate for controlling measles epidemics among children. Nevertheless, it is worthwhile considering how to use the above observation to improve the implementation of a vaccination program. The greater dependency of measles incidence on population size means that it is the number, rather than the density, of susceptible people that matters. Therefore, to reduce measles incidence in more-populated prefectures to the level of less-populated prefectures, attainment of the same vaccination coverage (i.e., the same level of susceptible population) is not sufficient; the number of susceptible people has to be reduced to that in the less-populated prefectures. This is possible only through a more intensified vaccination program in the populated prefectures possibly by expanding vaccination target population to higher age groups. The same argument may hold regionally and globally.

Note added in proof I conducted the same type of analysis for AMR countries in their measles elimination phase (1989–2002). However, the study did not show any influence of population size/density on the progress of measles elimination, which may probably be due to their unique geo-demographic characters, i.e., though there were countries with high population density or countries with large population size, there were no countries with both high population density and large population size (5).

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Conflict of interest None to declare.

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