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Geo-Demographic Factors Affecting Incidence of Measles

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I previously reported a correlation between the incidence of measles and population size among prefectures in Japan and among countries in the European Union (EU) that joined in 1995 or before. These two regions were chosen, because they have relatively advanced vaccination programs and relatively uniform social, economic, and geographic conditions (1). In the present report, I examine how this finding applies to a wider range of countries. Specifically, I assessed countries in the World Health Organization (WHO) Western Pacific Region (WPRO) and WHO Region of Americas (AMRO) and compared them with countries in the EU. The data used for the present analysis are shown in Table 1.

Table 1. Measles incidence, vaccine coverage, population size, and population density in countries of EU (member by 1995), WPRO, and AMRO

EU countries	Measles /million	Coverage (%) 2000–2006	Coverage (%) 2007–2010	Population /million	Density /km²
Austria	16.9	79	79.3	8.4	100
Belgium	5.4	83	92.7	10.92	355
Denmark	1.2	94	86	5.56	128
Finland	0.56	96	98	5.39	16
France	27.5	85	88.5	65.82	114
Germany	8.7	91	95.3	81.75	229
Greece	3.6		99	10.78	86
Ireland	42.4	73	89	4.58	65
Italy	10.8	83.8	90	60.6	194
Luxemburg	0.5	93	96	0.5	998
Netherland	2.2	96	96	16.68	404
Portugal	0.21	95	95.8	10.63	115
Spain	5.4	96	97	46.14	91
Sweden	0.9	94	96.5	9.44	21
UK	16.5	85	87.8	62.43	255

WPRO countries	Measles /million	Coverage (%) 2007–2010	Population /million	Density /km²
Australia	5.39	94	22.27	3
Brunei	4.25	97	0.4	69
Cambodia	156.9	88	14.14	82
China	25.06	97	1341.34	140
Japan	4.16	96	126.54	337
Lao	17.1	54	6.2	27
Malaysia	19.92	95	28.4	86
Mongolia	1.81	97	2.76	1.7
New Zealand	63.68	86	4.37	16
PPNG	0	57	6.86	15
Phillipines	51.53	91	93.26	307
Korea	1.2	94	48.18	487
Singapore	13.8	95	5.09	7148
VietNam	35.98	93	87.85	259

Table 1. (Continued)

AMRO countries	Measles /million	Coverage (%) 2007–2010	Population /million	Density /km²
Argentina	0.125	98	40	14
Bolivia	0	83.8	10	9
Brazil	0.089	99	192	23
Canada	2.09	93	33	3.5
Chili	0.015	94	17	23
Colombia	0	92.8	46	41
Costa Rica	0	87.8	4	90
Cuba	0	99	11	102
Dominican Republic	0	92.8	9	207
Ecuador	0.017	99	15	52
El Salvador	0	95.3	6	293
Guatemala	0	91.8	15	129
Haiti	0.6	53	10	362
Honduras	0	97.3	8	66
Jamaica	0.17	85.3	3	247
Mexico	0	96	112	57
Nicaragua	0	99	6	44
Panama	0	91.8	3	46
Paraguay	0	76.3	6	16
Peru	0.008	92.5	30	23
Trinidad and Tobago	0	92	1	261
USA	0.27	92	313	32
Uruguay	0	95	3	20
Venezuela	0.3	81	27	32

Measles incidence (cases/million) in 2000–2010 for European Union (EU) and the incidence in 2007–2010 for World Health Organization (WHO) Region of Americas (AMRO) were obtained from http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tsincidencemea.htm. Measles incidence in 2009–2011 for WHO Western Pacific Region (WPRO) was obtained from the same site for 2009–2010 and WPRO's Measles-Rubella Bulletin (7) for 2011. Data are averages from the source. The data set is not necessarily complete for every country for every year. Vaccine coverage (2006–2010) was obtained from http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tswucoveragemcv.htm. Data are averages from the data source. Population size for each country was obtained from http://en.wikipedia.org/wiki/List_of_countries_by_population, and population density was obtained from http://en.wikipedia.org/wiki/List_of_sovereign_states_and_dependent_territories_by_population_density.

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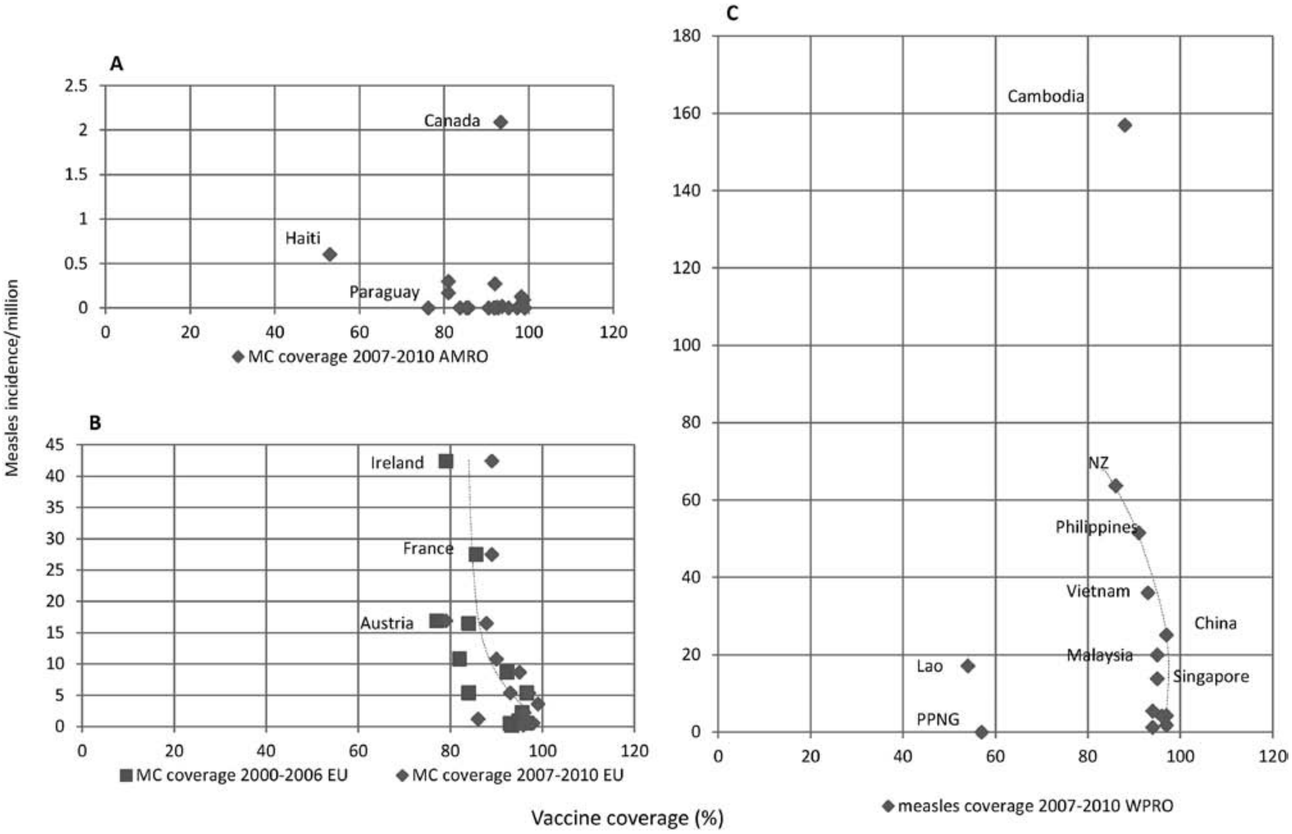

Fig. 1. Relationship between measles incidence (per million) and vaccine coverage. Vertical axis, measles incidence (cases/million); horizontal axis, vaccine coverage (%). (A) AMRO; (B) EU; (C) WPRO. The data are reported in Table 1.

Figure 1 shows the relationship between the incidence of measles and vaccination coverage in AMRO (Fig. 1A), EU (Fig. 1B), and WPRO (Fig. 1C). With the exception of a few countries (Haiti and Paraguay in AMRO, Austria and Ireland in EU, and Lao and Papua New Guinea [PPNG] in WPRO), the countries had vaccination coverage rates above 80%. The incidence of measles increased as vaccination coverage decreased from 90% to 80% or less (see plots for New Zealand [NZ], Philippines, and Vietnam in WPRO and Ireland and Austria in EU). Notably, all AMRO countries reported lower incidences of measles than countries of WPRO or EU despite similar or lower vaccination coverage.

Figure 2 examines the correlation between measles incidence and population size (Fig. 2A) or population density (Fig. 2B). Because there was a wide distribution of population size and density, the log-log plot was used in order to reduce the size of the graph. Accordingly, countries reporting zero measles incidence do not appear in this figure. These countries include Bolivia, Colombia, Costa Rica, Cuba, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, and Uruguay in AMRO and PPNG in WPRO.

Figure 2A shows the relationship between measles incidence and population size. EU countries with a significant correlation between measles incidence and population size (correlation coefficient, 0.70) (1) were bordered by upper concave and lower convex lines. Ireland and Austria were excluded from correlation coefficient analysis, because they had low vaccine coverage (< 80% in 2000–2006 and/or 2007–2010). These countries were found above the upper border (encircled by a dotted line).

The correlation between measles incidence and population size among countries in the EU and among Japanese prefectures (1) was not observed among countries in the two WHO regions. The measles incidence was uniformly low among AMRO countries irrespective of population size or density. However, population size and population density are independent of each other: countries with large population sizes can have low population densities, and those with small population sizes can have high population densities. The potential for a measles epidemic in a given country could depend not on their population size or density, but rather on the combination of these factors.

In order to address this issue, the countries were plotted on a population size-density matrix, where population density is plotted on the vertical axis, and population size is plotted on the horizontal axis (Fig. 3A). In this graph, the countries can be categorized into those with a high population and high density (HP/HD), high population and low density (HP/LD), low population and high density (LP/HD), and low population and low density (LP/LD).

The countries were grouped according to their measles incidence: low (< 1 case per million), intermediate (1–10 cases per million), and high (> 10 cases per million). For each measles incidence group, a population size-density graph was produced (Fig. 3B). For the

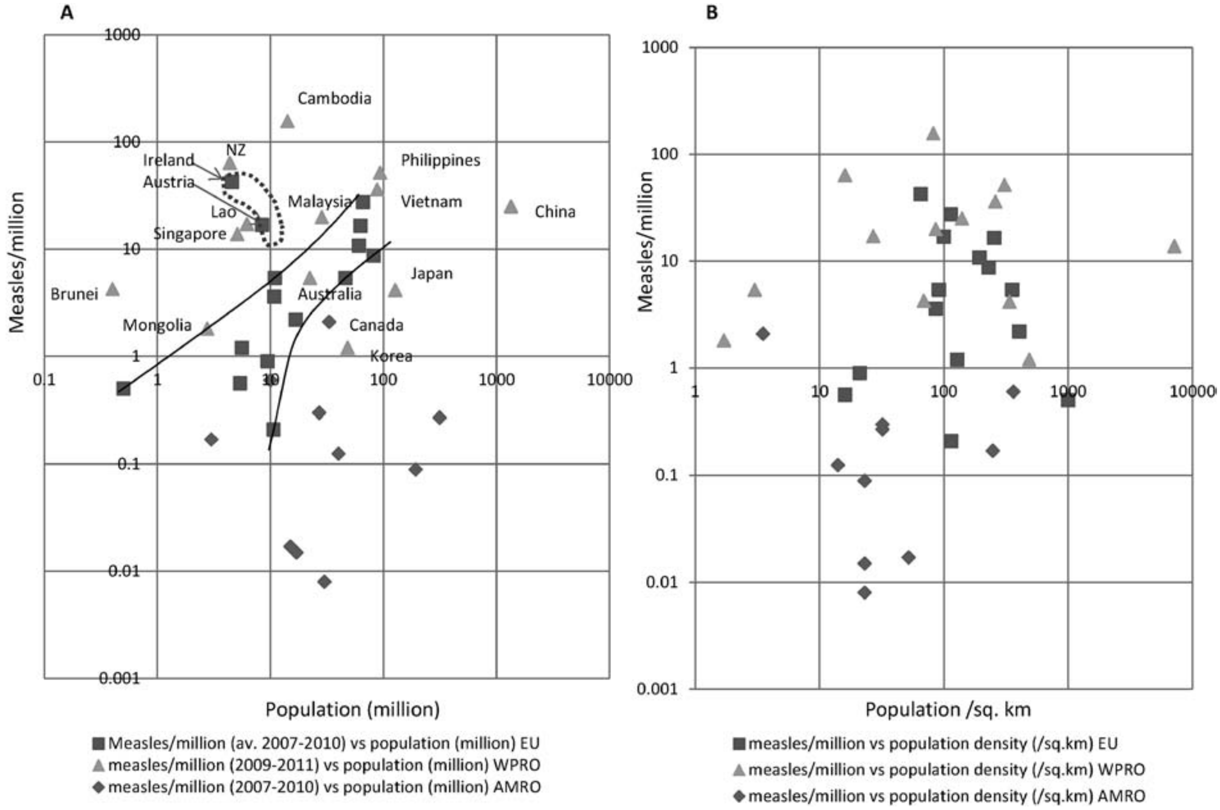

Fig. 2. Relationship between measles incidence and population size and relationship between measles incidence and population density. (A) Relationship between measles incidence and population size. All WPRO countries are identified near the corresponding data point. EU countries showing a significant correlation between measles incidence and population size (correlation coefficient, 0.70) (1) are bordered by convex and concave lines. Ireland and Austria were excluded from the calculation of correlation coefficients due to low vaccine coverage (<80% in 2000–2006 and/or 2007–2010). They are encircled by a dotted line. Vertical axis, measles incidence per million; horizontal axis, population size in millions. (B) Relationship between measles incidence and population density. Vertical axis, measles incidence per million; horizontal axis, population density per km^2.

low measles incidence group (bottom graph), most countries were distributed in the lower half of the graph (LP/LD and HP/LD), and some were in the LP/HD quadrant. For the intermediate incidence group (middle graph), there were more countries in the HP/HD quadrant. In this measles incidence group, four countries were found in the HP/LD quadrant (Australia, Brunei, and Canada) or in the LP/LD quadrant (Mongolia), but their incidences of measles were at the lower end of the range (5.39, 4.25, 2.09, and 1.81/million, respectively). For the high measles incidence group (top graph), most points were in or near the HP/HD quadrant. Four countries in this incidence group were found in the LP/LD quadrant, including Lao, NZ, Ireland, and Austria. The vaccination coverage was low in these countries (Fig. 1). These results indicate that

- in countries with high population densities (HD), as the measles incidence increased, the country distribution shifted from LP to HP (upper halves of the three graphs in Fig. 3B).
- in countries with large population sizes (HP), as the measles incidence increased, the country distribution shifted from LD to HD (right halves of the three graphs in Fig. 3B).
- for countries with LP (left halves of the three graphs in Fig. 3B), the population density did not affect the measles incidence except in Singapore. Singapore is the third most densely populated territory in the world, and its population size is one or two times higher than the top two densely populated territories, Macau and Monaco.

In conclusion, measles incidence increases as population size and density increase. Further, the incidence of measles in countries with low vaccination coverage (<90%) was higher than expected on the basis of their population sizes and densities.

Alternatively, it is possible that the observed correlation was not a result of population size or density per se, but rather that AMRO countries with successful measles control had populations of either low density or smaller size. However, even among WPRO countries, there was a correlation between measles incidence and population size/density. Specifically, sparsely populated PPNG had a very low vaccine coverage rate and reported no cases of measles, and Brunei, Mongolia, and Australia had lower population densities and reported lower measles incidences than more populated WPRO countries.

These results are schematically depicted in Fig. 3C. For the sake of simplicity, the population size of each country was the same between graphs (i.e., population size was proportional to the number of dot points). As the population size remains constant and the land area becomes smaller, the inter-community connectivity

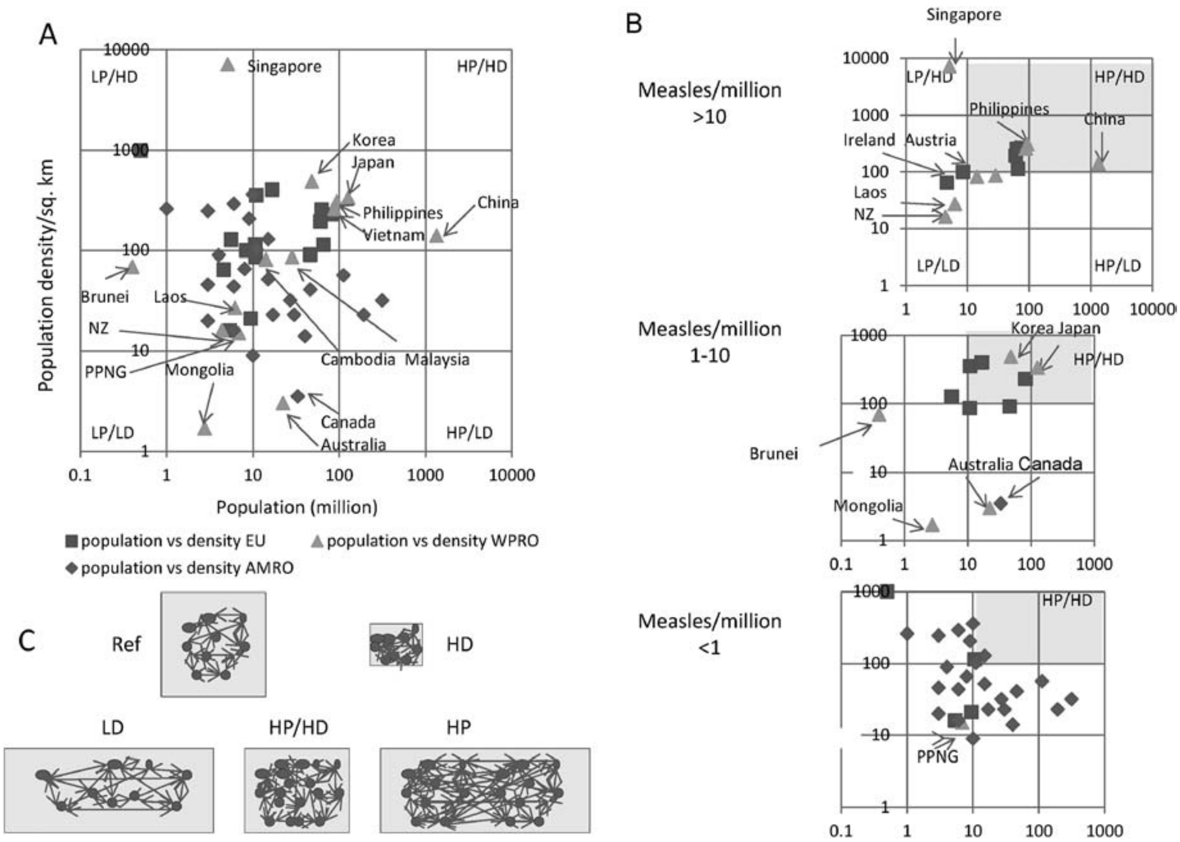

Fig. 3. Population size-density matrix. For all graphs, the vertical axis indicates population density per km^2, and horizontal axis indicates population size in millions. (A) Plot of EU, AMRO, and WPRO countries on the population size-density matrix. WPRO countries are named. (B) Population size-density matrix of countries by measles incidence. Top, >10/million; middle, 1–10/million; and bottom, <1/million. The high population/high density (HP/HD) quadrant is shaded. (C) Schematic representation of countries with different population sizes and population densities. Each square indicates a country, and dots in the square represent communities in a country. The arrows connecting the dots indicate connectivity (coupling) between communities.

(coupling) becomes stronger, and there is a higher likely hood of epidemic spread. This phenomenon is exemplified by the comparison of HD with Ref. As the land area increases in proportion to the population size, the inter-community connectivity does not change, but the number of connections increases, which increases the chance of virus propagation. This phenomenon is exemplified by comparing HP with Ref. As the land area increases and the population size remains the same, the population density and, thus connectivity between communities decreases. Therefore, there is a lower chance of epidemic spread. This phenomenon is exemplified by comparing LD with Ref. As the population size increases without an increase in land area, both the number of connections and inter-community connectivity increase. This is exemplified by comparing HP/HD with Ref. This schematic may fit the "cross-coupled metapopulation model" (2). In this model, a country with n communities is expressed by the following matrix:

$$\|a_{rs}\| = \begin{pmatrix} a_{11}a_{12} \cdots\cdots\cdots\cdots\cdots a_{1n} \\ a_{21}a_{22} \cdots\cdots\cdots\cdots\cdots a_{1n} \\ \cdots\cdots\cdots\cdots\cdots\cdots \\ a_{r1} \cdots\cdots a_{rr} \cdots a_{rs} \cdots a_{rn} \\ \cdots\cdots\cdots\cdots\cdots\cdots \\ a_{n}a_{n2} \cdots\cdots\cdots\cdots\cdots a_{nn} \end{pmatrix}$$

Here, a_{rs} is the function of population size/density (p_r) of a community, a_r and the degree of connectivity between communities a_r and a_s (c_{rs}) that influences epidemic spread from community a_s to community a_r. A country can be expressed simply as $\|a_{rs}\|$, where $a_{rs} = f(p_r, c_{rs})$, and $1 < r < n$ and $1 < s < n$. Mathematical handling of the matrix may be possible with appropriately defined operation rules (3).

Since Panum's analysis of the measles epidemic in Faroe Islands in 1846, several reports have demonstrated the impact of geo-demographic factors on measles epidemics (4,5). Cliff et al. (cited in 2) analyzed the spread of measles in Iceland and found that the lag time between the introduction of a disease to the capital and its spread to different communities in the country was a function of population size and distance from the capital. The present analysis is consistent with previous reports, suggesting that geo-demographic factors influence the elimination of measles even at the WHO regional level.

The WHO's goal is elimination of measles and is defined as <1 case confirmed by laboratory or epidemiological linkage (excluding clinically compatible and imported cases) per million in a population (6). To achieve this target, vaccination programs must be strengthened. However, the criteria for elimination may depend on the region's geo-demographic factors.

Importantly, vaccination is never 100% effective. For example, in 2011, among 434 measles cases reported in Japan, 38% (167 cases) had received at least 1 vaccine (http://www.nih.go.jp/niid/en/measles-e/measles-iasrtpc/1680-tpc384-e.html). Such cases of vaccine failure will accumulate over time, even with 100% vaccine coverage. Further, number of cases of vaccine failure will increase in proportion to the population size, particularly in countries with high birth rates.

Because the WHO's goal for measles control is elimination and not eradication, regional vaccination plans should be realistic and sustainable for the region's financial and human resource.

Conflict of interest None to declare.

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