Population Size Dependency of Measles Epidemic That Was Scalable from Japanese Prefectures to European Countries

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SUMMARY: The relationship between the number of measles patients (y) and the population size (x) was expressed by the equation y = ax^s, where a is a constant and s the slope of the plot; s was 2.04–2.17 for prefectures in Japan, i.e., the number of patients was proportional to the square of the population size of the prefecture. For European countries that joined the European Union (EU) no later than 2009, the slope was 1.43–1.87. The population dependency of measles found among prefectures in Japan was thus scalable to European countries. This was surprising because, unlike Japan, the population densities of EU countries were not uniform and not proportional to the population size. The population size dependency was not observed among Western Pacific and South-East Asian countries probably due to confounding from interacting socioeconomic factors. The correlation between measles incidence and birth rate, infant mortality or gross domestic product per capita was almost insignificant. The size distribution of local infection clusters (LICs) of measles and rubella in Japan followed a power law. For measles, although the population dependency remained unchanged after “elimination,” there were changes in the Zipf-type plots of LIC sizes. After “elimination,” LICs linked to importation-related outbreaks in less populated prefectures emerged as the top-ranked LICs.

INTRODUCTION

The World Health Organization (WHO) Western Pacific Region (WPR) initiated measles elimination programs in 2003. Japan established the “Measles Prevention Guiding Principles” in 2007. This policy successfully reduced measles incidence from 11,012 in 2008 to 35 in 2015, when the WPR Regional Verification Committee (RVC) verified that Japan had “eliminated measles” (1). In 2016 and 2017, however, Japan experienced importation-related measles outbreaks.

We previously reported that the measles epidemic was population size dependent (2), and that the size distribution of the local infection clusters (3) followed a power law. We were interested in possible changes in these parameters after the “elimination,” because, in principle, outbreaks after elimination were all importation-related while epidemics before elimination were largely endemic.

In addition, we examined the incidences of measles in various WHO regions so as to evaluate the impact of the WHO’s measles initiatives on the geodemography of measles.

MATERIALS AND METHODS


RESULTS

Measles and rubella in Japan: The measles incidence from 2009 to 2017 (42 weeks) is shown as open circles in Fig. 1A. The number of patients per prefecture was plotted on the y-axis against population size of the prefecture on the x-axis in Fig. 1B. The slope of the
Fig. 1. Measles and Rubella in Japan. A: Annual number of patients for 2009–2017 (○ measles; ● rubella). B and C: Number of patients (y-axis) vs. population size of prefecture (x-axis) respectively for measles and rubella. D: Summary table of slopes and $R^2$ in panels B and C. E-1: Zipf type plots for measles in 2011–2013. E-2: Zipf type plots for measles in 2016–2017 with enlarged symbols for top LICs. F: Zipf type plots for rubella in 2011–2017. G: Plot of slope sizes vs. total number of the patients for measles (○) and rubella (●).
plots was 1.6 for 2009–2010, and 2.0–2.1 for 2011–2017 (Fig. 1B and 1D). The plot pattern remained essentially the same before and after the “elimination of measles” in 2015.

The local infection cluster (LIC), a surrogate metric of the infection spread size, was defined as a group of patients reported from the same prefecture in successive weeks sandwiched between at least 1 week of zero reporting before and after (3). The LICs were arranged in descending size order, ranked, and the LIC size was plotted on the y-axis against the rank number on the x-axis (Zipf-type plot) (4). The plots fell on straight lines (Fig. 1E-1): the LIC size distribution was thus scale-free. The values of the slopes were plotted on the y-axis against the total number of patients on the x-axis for respective years. As the total number of patients decreased, the slopes of the plots got less steep from −1.8 to −0.4 (Fig. 1G, open circles) and the y-axis intercepts got smaller (Fig. 1E-1).

Close examination of Fig. 1B revealed that more of the plots for middle-sized prefectures were scattered above the approximation line after 2011, indicating that measles outbreaks increased in more rural prefectures after 2011. In the Zipf plots, large LICs of similar size emerged above the approximation line after the “elimination” in 2015 (Fig. 1E-1). Such LLCs represented by larger symbols (Fig. 1E-2) included 2016 outbreaks in Osaka and Hyogo (▲) linked to the Kansai International Airport measles incident (caused by genotype H1 measles probably imported from China) (5), an independent outbreak in Chiba in the same year (▲), and 2017 outbreaks in the rural prefectures Yamagata (▲) and Mie (〇), which were caused by D8 genotype probably imported from Indonesia (https://www.niid.go.jp/niid/ja/iiasr-measles.html). As importation is a random event, measles outbreaks may occur randomly in prefectures irrespective of their population sizes. The LICs of other prefectures fell on descending straight lines; the highest among them was the LIC of Tokyo (Fig. 1E-2), which had always been ranked number 1 till 2015.

Rubella is monitored in parallel with measles under the Infectious Disease Control Law (6). Japan experienced a large rubella epidemic in 2012–2013 largely among unvaccinated male adults (7) (closed circles in Fig. 1A). Fig. 1C shows a plot of the number of rubella patients per prefecture against the population size of the prefectures. The slope of the approximation line was 1.63–1.88 (Fig. 1C and 1D). The Zipf plots of LICs yielded descending straight lines (Fig. 1F). The plot of the values of slopes on the y-axis against the total number of patients on the x-axis yielded straight lines with slope 1.63–2.17 observed for the measles epidemic in Japan.

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**Measles at the regional level:** We examined the incidence of measles in 4 WHO regions, the European (EUR), American (AMR), WPR and South-East Asia (SEAR). Data regarding rubella were not examined as the available data were patchy.

Fig. 2A shows the epidemic curve of measles in countries that joined the European Union (EU) no later than 2,000 (“2,000 EU members”) (country names appear in bold letters in the panel for EU in Fig. 4B). They experienced a large resurgence in 2011. The plots of the number of measles patients on the y-axis against the population size on the x-axis yielded straight lines with slope 1.29–1.82 (Fig. 2B and 2C), which was close to the 1.63–2.17 observed for the measles epidemic in Japan. This was surprising because among the 2,000 EU countries, the population densities were not uniform and the population sizes and densities were not correlated (correlation coefficient [CC] = 0.14 in contrast to 0.89 for the Japanese prefectures). This suggested that population size was dominant over population density in determining measles epidemics. The exceptions were the years 2005 and 2006 with slopes 1.07–1.17 and R² 0.288–0.374 (Fig. 2B and 2C), when less populated countries experienced large measles outbreaks (Fig. 3A).

The number of measles patients was plotted on the y-axis against the population size on the x-axis for EUR, WPR, and SEAR countries (Fig. 2D) from 2008 to 2014 (country names are listed in descending order of population size in Fig. 4B). AMR countries were not examined as the region “eliminated measles” in 2016 and the patients were so few (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Aregion-americas-declared-free-measles). The plots were scattered diagonally ascending from the lower left to the upper right; the slope was −2 for EUR and −1 for WPR and SEAR. The slope −2 indicates population size dependency while the slope −1 indicates population size indifference.

**Measles incidence vs. population size/density:** As the measles incidence depended not only on population size but also on population density (8), symbols representing countries’ measles incidences were plotted onto the Cartesian coordinates with population size (× 1,000) on the x-axis and population density (population/km²) on the y-axis (Fig. 3) (see figure legend for allocation of symbol sizes according to the incidences).

Fig. 3A shows the plots for European countries (country list in Fig. 4B). The largest circles representing measles incidence > 10/million/year were given ISO country codes if they were 2,000 EU members and shaded if they were not. The largest unshaded circles representing populations of the United Kingdom, Italy, Germany, France, and Spain were generally on the right end. The largest unshaded circles represented moderately populated countries, i.e., Ireland (2003–2013) and Austria (2003, 2008, 2014); their vaccination coverage in 2000–2010 was low, however (9). There were many largest shaded circles representing countries with middle-sized populations, i.e., Romania (2005–2007, 2012–2013), Bulgaria (2009–2011), Cyprus (2010, 2013), Slovenia (2011, 2014), Estonia (2006), Lithuania (2013, Latvia (2014), Malta (2005), and Switzerland (2003, 2007–2009, 2011, 2013). Switzerland experienced repeated large outbreaks (2003, 2007–2009, 2011, and 2013) despite the high vaccination coverage (measles-containing-vaccine first-dose 92% and measles-containing-vaccine second-dose 84% in 2007–2015) (WHO/UNICEF Estimates of National Immunization Coverage [http://www.who.int/immunization/monitoring_surveillance/data/en/]). When the EUR experienced a resurgence of measles in 2011, the moderately populated countries Belgium, Denmark and Switzerland, and least populated Luxembourg were also affected. After the resurgence, the measles incidence returned to the pre-resurgence state, and in
2014, except for Austria, Slovenia, Czech, and Latvia in Eastern Europe, the outbreak size came down to < 10/ million/year in all the countries (data are, however, missing for countries like Italy [for 2013 and 2014]). As of 2016, the EUR RVC verified that 33 countries had “eliminated measles”; they were less populated countries. Six among 7 most populated countries in this region have not yet been verified for the elimination (countries with interruption for 12 or 24 months were excluded from countries verified for the elimination (http://www.euro.who.int/__data/assets/pdf_file/0019/348013/6th-RVC-final-for-web-posting.pdf?ua=1)).

AMR countries started measles elimination since 1994, interrupted measles transmission in 2002, and declared measles elimination as a region in 2016 (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Aregion-americas-declared-free-measles). The region, however, occasionally experienced large outbreaks in populated countries, like Ecuador and Canada in 2011, and USA, Brazil, and Canada in 2013–2014. They both coincided with measles outbreaks in Europe (compare Fig. 3A and 3B), which may suggest transcontinental measles spread.

In the WPR, countries with population < 1,000,000, which were mostly islandic, rarely experienced large epidemics; the incidence was < 1/million/year except for several epidemics occurring only after long intervals. The populated countries, China, Philippines, and Vietnam, almost continuously reported measles at an incidence rate of > 10/million/year. Japan and Republic of Korea, despite their large population sizes, controlled measles to the level of 1–10/million/year; their geographical isolation may have contributed to this success. Measles “elimination” was verified for, as of 2017, Australia, Brunei Darussalam, Cambodia, Hong Kong SAR (China), Macao SAR (China), Republic of Korea, and Japan (http://iris.wpro.who.int/bitstream/handle/10665.1/13936/RS-2017-GE-49-CHN-eng.pdf?ua=1); except for Republic of Korea and Japan, these countries were small in population size and/or low in population density. In the SEAR (Fig. 3D), the incidence was always 10–100/million/year for the heavily populated Thailand, Indonesia, Bangladesh, and India, and < 1/million/year for

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**Fig. 2.** Relation between number of measles patients and population size in 2000 EU countries. A: annual incidence of measles in 2000 EU countries. B: Plot of number of measles patients (y-axis) against population size (× 1,000) in the x-axis for EUR, WPR, and SEAR countries in 2008–2014. C: Summary table of slopes and $R^2$ in panel B. D: Plot of number of patients in the y-axis against population size (× 1,000) in the x-axis for EUR, WPR, and SEAR countries in 2008–2014.
Fig. 3. Measles incidence (per million population) plotted on Cartesian co-ordinates with population size (∗ 1,000) in the x-axis and population density (/km²) in the y-axis. The sizes of the circles reflect number of patients per million: for EUR (A) and AMR (B), the incidences, < 1/million, 1–10/million, and > 10/million, are represented by sizes 4, 8, and 16 in the Excel graphics; for WPR (C) and SEAR (D), incidences, < 1/million, 1–10/million, 10–100/million, and > 100/million, are represented respectively by 2, 6, 18, and 64 in the Excel graphics.
the lowly populated Maldives and Bhutan, which were verified for the “elimination” in 2017.

In Fig. 4A, all the countries examined above were plotted on the Cartesian coordinates with population size on the x-axis and population density in the y-axis. Countries in the same WHO regions are represented by the same symbols (see the bottom of the figure). Shaded area: population size > 20,000,000 and density > 100/km². B: Names of countries in EUR (2000 EU members in bold letters), WPR, and SEAR regions, which are listed in the descending order of population size.

Non-demogeographical factors: We evaluated birth rate, infant mortality rate and GDP per capita, because high birth rate enlarges susceptible population size and poor economy results in poor public health infrastructure and also in high infant mortality rate. Fig. 5A-1, 5B-1, and 5C-1 respectively show plots of birth rate per 1,000 population, infant deaths under 1 year old per 1,000 live births, and GDP per capita in 2017 (x-axis in logarithm) against their cumulative frequencies (y-axis in ordinary scale). They respectively fell on straight lines with equations $y = 86.6 \ln(x) - 0.80$, $y = 61.7 \ln(x) - 51.45$, and $y = 38.2 \ln(x) - 236.7$. The ranges of x were 7.7–33.4 for birth rate (101 countries), 1.8–112.8 for infant mortality (223 countries) and 319–120,799 for GDP (191 countries). (Using these equations, the frequency of a parameter size range can be estimated, because for the range $[x_i, x_{i+r}]$, frequency is $y_{i+r} - y_i = k \ln \left[ \frac{x_{i+r}}{x_i} \right]$, where k is 86.6, 61.7 and 38.2, respectively for birth rate, infant mortality, and GDP per capita).

Countries represented by different size symbols reflecting the parameter sizes were plotted on Cartesian coordinates representing population sizes and densities in the x- and y-axes, respectively (Fig. 5A-2, 5B-2, and 5C-2).
Fig. 5. Birth rate, infant mortality rate, and GDP per capita. A-1, B-1, and C-1: Cumulative frequency distributions of births/1,000 population, infant deaths under 1 year/1,000 live births, and GDP per capita in US$, respectively. A-2, B-2, and C-2: Birth rate, infant mortality rate, and GDP per capita represented by the sizes of circles (see the bottom of the figures for correspondence between the symbol size and parameter size) are plotted on the Cartesian coordinates with population size on the horizontal axis and population density on the vertical axis. D: Plot of GDP per capita (x-axis) vs. infant mortality rate (y-axis); E: plot of GDP per capita (x-axis) vs. measles/million (y-axis); F: plot of infant mortality rate (x-axis) vs. measles/million (y-axis).
We evaluated the possibility of a quantitative relation in these regions. Birth rate and high infant mortality rate were correlated and SEAR (Fig. 5A-2 and 5B-2), indicating that high birth rate and high infant mortality rate were correlated in these regions.

We evaluated the possibility of a quantitative relationship between these parameters. Infant mortality rate and GDP per capita were inversely correlated (CC = −0.592 and −0.499 in WPR and AMR, respectively) (Fig. 5D). Measles incidence and GDP per capita in WPR were inversely correlated in WPR with CC = −0.386 (Fig. 5E), and measles incidence and infant mortality rate in WPR were positively but very weakly correlated (CC = 0.233) (Fig. 5F). The above data should be interpreted with caution as CC between the parameters was low and multiple factors must be interacting. For example, vaccination infrastructure requires money (high GDP per capita), money attracts people, and people transmit measles. In Japan, the number of measles patients per population and tax income per capita were positively correlated (CC = 0.691) (10).

**DISCUSSION**

The WPR started polio eradication programs in 1988 and was declared polio free in 2000 (http://www.wpro.who.int/topics/poliomyelitis/en/). Based on similar successes in the world, the WHO Assembly (WHA) launched a measles elimination campaign in 2010. One milestone criterion was to “reduce and maintain annual measles incidence to less than 5 cases per million” (http://www.who.int/mediacentre/factsheets/fs286/en/). The WHA endorsed elimination of measles in 4 WHO regions by 2015. Although AMR achieved the goal in 2016 (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Aregion-americas-declared-free-measles), progress in other regions lags behind. With the newly introduced elimination criterion “absence of endemic measles virus transmission in a defined geographical region (e.g. region or country) for >12 months” (http://www.wpro.who.int/immunization/documents/measles_elimination_verification_guidelines_2013/en/), several countries, including Japan, were verified for the elimination, but many of them were small in population size and/or have low population densities.

China eradicated polio in 1995, 6 years after the big polio outbreak in Shandong (11). However, China and other populated countries in the WPR are still unable to eliminate measles 14 years after the WPR established the elimination goal.

Both polio and measles viruses replicate only in humans. Interruption of the transmission chain through vaccination should work for both viruses. The problem with measles elimination is that the measles virus is transmitted by humans, while polio is transmitted through the fecal-oral route. Hygienic improvement promotes the eradication of polio but not that of measles.

The population size dependency of measles was discovered by Panum through observation of the Faroe island measles epidemics in the 19th century (12). The phenomenon was confirmed by Bartlett (13) and Black in the 1960s (14). This paper showed that the population size dependency of the measles epidemic was scalable (15) from Japanese prefectures to 2009 EU countries. There is no reason why the population dependency rule does not apply to WPR or to SEAR: the population size/density dependency will emerge, when socio-economic and other confounding factors are removed.

China’s population in 2017 was 1,415,870,000, and India’s 1,282,390,000; each alone far exceeds the total population of the American continent 982,093,000 or that of the Western European countries listed in Fig. 4B, 509,394,000. As the number of measles patients was very probably proportional to the square of the population size (2), reducing measles incidence to < 5/million will be extremely difficult for China and India to achieve. Even with the help of the criterion “interruption of endemic measles transmission,” their large territory and large population sizes will prevent them from being verified for the “elimination.”

**Conflict of interest** None to declare.

**REFERENCES**