Population size dependency of measles epidemic that was scalable from Japanese prefectures to European countries

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Population size dependency of measles epidemic that was scalable from Japanese prefectures to European countries
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Key words: measles elimination, population size, Zipf plot, GDP and infant mortality, EU countries
Running head: Measles elimination

Summary
Relation between number of measles patients (y) and population size (x) was expressed by an 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 square of the prefecture population size. For European countries that joined European Union no later than 2009, the slope was 1.43-1.87. The measles’ population dependency found among prefectures in Japan was thus scalable up to European countries. It was surprising because, unlike Japan, population density in EU countries was 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 on account of confounding interacting socioeconomic factors. Correlation between measles incidence and birth rate, infant mortality or GDP per capita was almost insignificant.

Size distribution of local infection clusters (LICs) of measles and rubella in Japan followed power law. For measles, though the population dependency remained unchanged after “elimination”, there was change in the Zipf-type plot of LIC sizes. After the “elimination”, LICs linked to importation-related outbreaks in less populated prefectures emerged as the top-ranked LICs.

Introduction
WHO Western Pacific Region (WPR) started measles elimination
programs in 2003. Japan established “Measles Prevention Guiding Principles” in 2007. It successfully reduced measles incidence from 11,012 in 2008 to 35 in 2015, when the WPR Regional Verification Committee (RVC) verified that Japan “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 the size distribution of the local infection clusters (3) followed the 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 measles incidences in various WHO regions so as to see impact of the WHO’s measles initiatives on geo-demography of measles.

Materials and Methods

Results

Measles and rubella in Japan: Measles incidence from 2009 to 2017 (42 week) is shown in open circles in Fig. 1A. The number of patients per prefecture was plotted in the y-axis against population size of the prefecture in the x-axis in Fig. 1B. The slope of the plots was 1.6 for 2009-2010, and 2.0~2.1 for 2011-2017 (Figs. 1B and 1D). The plot pattern remained essentially the same before and after the “elimination of measles” in 2015.

The local infection cluster (LIC) is a surrogate metric of the infection spread size, which was defined as a group of patients reported from the same prefecture in successive weeks sandwiched between at least one week of zero reporting before and after (3). The LICs were aligned in descending size order, ranked, and the LIC size was plotted in the y-axis against the rank number in 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 in the y-axis against the total number of the patients in the x-axis for respective years: as the total number of the patients decreased, the slopes of the plots got milder (Fig. 1G, open circles); in addition, 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 similar sized LICs 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 rural prefectures Yamagata (〇) and Mie (〇), which were caused by D8 genotype imported probably from Indonesia (https://www.niid.go.jp/niid/ia/iasr-measles.html). As importation is a random event, measles outbreak may occur randomly in prefectures irrespective of their population sizes. The LICs of other prefectures fell on descending straight lines: the top of them was the LIC of Tokyo (Fig. 1E-2), which had always been ranked number 1 till 2015.

Rubella was monitored in parallel with measles under the Infectious
Disease Control Law (6). Japan experienced large rubella epidemic in 2012-2013 largely among unvaccinated male adults (7) (closed circles in Fig. 1A). Fig. 1C shows plots of number of rubella patients per prefecture against population size of prefectures. The slope of the approximation line was 1.63-1.88 (Figs. 1C and 1D). The Zipf type plots of LICs gave descending straight lines (Fig. 1F). The plot of the values of slopes in the y-axis against the total number of the patients in the x-axis gave descending straight line (Fig. 1G, closed symbols) similarly as that for measles. The above plot patterns remained essentially the same during the resurgence.

Measles in the region level: We examined measles in four WHO regions, European (EUR), American (AMR), Western Pacific (WPR) and South-East Asia (SEAR). Rubella data were not examined as the available data were patchy.

Fig. 2A shows epidemic curve of measles in countries that joined European Union no later than 2000 (“2000 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 in the y-axis against the population size in the x-axis fell on straight lines with slope 1.29 ~ 1.81 (Figs. 2B and 2C), which was close to 1.63 ~ 2.17 observed for measles epidemic in Japan. It was surprising because among 2000 EU countries the population density was not uniform and the population size and density were not correlated (correlation co-efficient was CC: 0.14 in contrast to 0.89 for Japanese prefectures). It suggested that population size was dominant over population density in determining measles epidemics. Exceptions were years 2005 and 2006 with slopes 1.07 ~ 1.17 and R² 0.288 ~0.373 (Figs. 2B and 2C), when less populated countries experienced large measles outbreaks (Fig. 3A).

The number of the measles patients was plotted in the y-axis against the population size in the x-axis for EUR, WPR and SEAR countries (Fig. 2D) from 2008 to 2014 (country names are listed in descending order of the 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 slope $\sim 1$ population size indifference.

**Measles incidence vs. population size/density:** As 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 (x1,000) on the x-axis and population density (population/km$^2$) on the y-axis (Fig. 3) (see figure legend for allocation of symbol sizes according to the incidence sizes).

Fig. 3A shows the plots for European countries (country list in Fig. 4B). To the largest circles representing measles incidence $>10$/million/year given was ISO country code if they were 2000EU members and shaded if they were not. The largest unshaded circles representing populated United Kingdom, Italy, Germany, France and Spain were generally on the right end. There were unshaded largest circles representing moderately populated countries, too: they were Ireland (2003-2013) and Austria (2003, 2008, 2014); their vaccination coverage in 2000-2010 was low, however (9). There were many shaded largest circles representing countries of middle-sized population; they were Romania (2005-2007, 2012-2013), Bulgaria (2009-2011), Cyprus (2010, 2013), Slovenia (2011, 2014), Estonia (2006), Lithuania (2013), Latvia (2014), Malta (2003, 2008, 2014) and Switzerland (2003, 2007-2009, 2011, 2013). Switzerland experienced repeated large outbreaks (2003, 2007-2009, 2011 and 2013) despite of high vaccination coverage (MCV1 92% and MCV2 84% in 2007-2015) (WHO/UNICEF Estimates of National Immunization Coverage
(http://www.who.int/immunization/monitoring_surveillance/data/en/).

When European region experienced resurgence of measles in 2011, moderately populated Belgium, Denmark and Switzerland and least populated Luxemburg 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, EUR RVC verified that 33 countries “eliminated measles”; they were less populated countries. Six among seven most populated countries in this region have not been yet 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-f
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. The both coincided with measles outbreaks in Europe (compare Fig. 3A and Fig. 3B), which may suggest transcontinental measles spread.

In WPR, countries with population <1,000,000, which are mostly islandic, rarely experienced large epidemics; the incidence was <1/million/year except for several epidemics occurring only after long intervals. Populated countries, China, Philippines and Viet Nam, almost continuously reported measles at an incidence >10/million/year. Japan and Republic of Korea, despite of large population size, 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), Rep. Korea and Japan (http://iris.wpro.who.int/bitstream/handle/10665.1/13936/RS-2017-GE-49-CHN-eng.pdf?ua=1); except for Rep. Korea and Japan, these countries were small in population size and/or low in the population density.

In SEAR (Fig. 3D), the incidence was always 10 ~ 100/million/year for heavily populated Thailand, Indonesia, Bangladesh and India, and <1/million/year for 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 the population size in the x-axis and the population density in the y-axis. The area of population size >20,000,000 and density >100/ km² is shaded. No AMR countries (closed circles) are found in this area, which probably prompted this region to “eliminate” measles ahead of other regions. All the European countries (shaded circles) except two were in an area with population size 1,000,000~100,000,000 and population density 10~1,000/sq. km (with a few exceptions), i.e., geo-demographically relatively uniform. WPR and SEAR countries (open squares and open triangle, respectively) were distributed widely in size and density; 5 in 30
countries in WPR and 7 in 11 countries in SEAR were in the shaded area.

Non-demo-geographical factors: We examined 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. Figs. 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, \( y = 86.6 \ln(x) - 0.80 \), \( y = 61.7 \ln(x) - 51.45 \), and \( y = 38.2 \ln(x) - 236.7 \). The range of \( x \) was 7.7 - 33.4 for birth rate (101 countries), 1.8 - 112.8 for infant mortality (223 countries) and 319 - 120,799 GDP (191 countries). [Using these equations, frequency of a parameter size range can be estimated, because for range \([x_i, x_{i+r}]\), frequency is \( y_{i+r} - y_{i-1} = k \ln(x_{i+r}/x_{i-1}) \), 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 (Figs. 5A-2, 5B-2 and 5C-2). EU countries were of low birth, low infant mortality and of high GDP per capita. SEAR was on the opposite end; it was of high birth, high infant mortality and of low GDP per capita. AMR and WPR were in between; AMR closer to EU and WPR closer to SEAR. The pattern for birth rate and that for infant mortality rate were almost superimposable in WPR and SEAR (Figs. 5A-2 and 5B-2) indicating that high birth rate and high infant mortality rate were correlated in these regions.

Possible quantitative relation between these parameters was examined. Infant mortality and GDP per capita were inversely interrelated with correlation coefficient (CC) -0.592 and -0.499 in WPR and in AMR, respectively (Fig. 5D). Measles incidence and GDP per capita in WPR were inversely interrelated in WPR with CC: -0.386 (Fig. 5E) and measles incidence and infant mortality in WPR positively but very weakly with CC: 0.233 (Fig. 5F). Interpretation of the above data needs caution as CC between the parameters was low and multiple factors must be interacting. For example, vaccination infrastructure needs money (high GDP per capita), money attracts people, and people transmit measles. In Japan, number of measles patients per population and tax income per capita were positively
correlated with CC: 0.691 (10).

DISCUSSION

WPR started polio eradication programs in 1988 and was certified as polio free in 2000 (http://www.wpro.who.int/topics/poliomyelitis/en/). Based on similar successes in the world, WHO Assembly (WHA) launched measles elimination 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/; WHA endorsed elimination of measles in four WHO regions by 2015. Though AMR achieved the goal in 2016 (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Areregion-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 low in population density.

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

Both polio and measles replicate only in humans. Interrupting transmission chain through vaccination should work for the both. Big problem for measles elimination is that measles is transmitted by humans, while polio by fecal-oral routes. Hygienic improvement helps eradication of polio but not that of measles.

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 1960s (14). This paper showed that the population size dependency of measles epidemic was scalable (15) from Japanese prefectures to 2009EU 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 total population in the American continent 982,093,000 or that in 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. 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

Legend for Figures
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 R² in panels B and C. E-1: Zipf type plots for measles in 2011-2017. 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 (●).

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 (x-axis).
C: Summary table of slopes and $R^2$ in panel B. D: Plot of number of patients in the y-axis against population size (x1,000) 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 (x 1,000) in the x-axis and population density (/km$^2$) 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.

Fig. 4: Population size/density profile of countries. A: countries are 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 the figure). Shaded area: population size >20,000,000 and density >100/ km$^2$. B: Names of countries in EUR (2000EU members in bold letters), WPR and SEAR regions, which are listed in the descending order of population size.

Fig. 5: Birth rate, infant mortality rate and GDP per capita. A-1, B-1 and C-1: Cumulative frequency distributions of births/1000 population, infant deaths under 1 year/ 1000 live births and GDP per capita in US$, respectively. A-2, B-2 and C-3: 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).
D: Summary table of slopes and $R^2$ values for panels B (measles) and C (rubella)

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E: Measles LcIC rank plots 2011-2017

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F: Rubella LcIC rank plots 2011-2017

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G: Slope (y) vs. number of patients (x)

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Fig. 1
A: Number of measles patients per year in 2000 EU members

B: Plot of number of patients vs. population size for 2000 EU members

C: Summary of slopes and $R^2$ in panel B

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<th>Year</th>
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<td>2009</td>
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<tr>
<td>2014</td>
<td>1.47</td>
<td>0.601</td>
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D: Plot of number of patients (y) vs. population size from 2008 to 2014

Fig. 2
Measles in EUR WPR AMR and SEAR countries plotted on Cartesian coordinates with population size on the y-axis and population density on the x-axis.

Fig. 3
\[ y = 8.66 \ln(x) - 0.80 \]
\[ y = 6.17 \ln(x) - 51.45 \]
\[ y = 3.82 \ln(x) - 236.7 \]

Fig. 5