学　位　論　文

Estimation of the diagnosed proportion of people living with HIV/AIDS among foreign residents in Japan

（日本における外国籍 HIV 感染者・AIDS 患者診断割合の推定）

2022 年 3 月

北海道大学

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Table of Contents

List of Publications and Presentations

List of Publications

Shimizu, K., Nishiura, H., Imamura, A. (2019). Investigation of the proportion of diagnosed people living with HIV/AIDS among foreign residents in Japan. J Clin Med. *8*, 804.

List of Presentations

Shimizu, K., Nishiura, H. Estimation of the diagnosed proportion of people living with HIV/AIDS (PLWHA) among foreign residents in Japan. Joint Congress on Global Health 2020. November 1-3, 2020, Osaka, Japan.

Abstract

Background and Objectives

While the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) undoubtedly remains a disease responsible for a substantial number of deaths, great progress has been made in constraining it. Japan has been no exception to the global epidemiological trends of HIV/AIDS. The incidence of HIV diagnoses and AIDS cases continued to steadily increase for the two decades from 1985, followed by declines starting in 2008 and 2010, respectively. Nevertheless, several estimates of the diagnosed proportion of people living with HIV/AIDS (PLWHA) through epidemiological and modeling approaches indicate that the diagnosed proportion of HIV infections in Japan has stayed below 90%, suggesting the necessity of substantial efforts to achieve the UNAIDS cascade. Besides, there has been notably little epidemiological research focused on the increasing proportion of foreign residents among newly diagnosed HIV infections and AIDS cases in Japan. Considering that the number of foreign nationals entering Japan has increased with time, estimating the number of PLWHA among foreign residents would play a key role in clarifying the full picture of the epidemiology of HIV/AIDS in Japan. Therefore, the present dissertation aimed to estimate the diagnosed proportion of PLWHA among foreign residents in Japan, covering 1990–2017, stratified by the geographic region of the country of origin.

Materials and Methods

The study was premised on an analysis of surveillance data based on physicians' notification of HIV diagnoses or AIDS cases following the Infectious Disease Control Law, Japan. Datasets on international travel, which included items such as visit duration and travel volume, were also explored. By combining the incidence and prevalence data with the travel data, the incidence and cumulative incidence of HIV infection were measured as person–time at risk. Five different datasets from 1990 to 2017 were explored: estimated incidence and prevalence of HIV infection in individual countries; population size in each country; the average length of stay in Japan, by country of origin; the number of foreign nationals entering Japan, by country; and yearly notification data of newly diagnosed HIV infections and AIDS cases in Japan. A balance equation model was employed to statistically estimate the diagnosed

proportion as a single parameter. Moreover, as the sensitivity analysis, challenges in the key assumption that the same risk of infection exists among foreign residents in Japan and their home countries, and differences of person-time at risk between countries were addressed.

Results

The reported number of HIV diagnoses among foreign residents in Japan peaked in 1992 and gradually declined by 1998, while an upward trend has been seen since 2014. South and South-East Asia dominated the group, followed by Latin America and Sub-Saharan Africa countries. The cumulative number of HIV diagnoses and AIDS cases among foreign residents in Japan was 4,526 in 1990–2017. The three most highly represented regions were South and South-East Asia (36.6%), Latin America (11.4%), and Sub-Saharan Africa (6.6%). The proportion varied widely by region: people from Western Europe, East Asia and Pacific, Australia and New Zealand, and North America were underdiagnosed, while those from Sub-Saharan Africa, South and South-East Asia, and Latin America were more frequently diagnosed. In the sensitivity analysis, these characteristics were mainly followed; however, different trends of the estimates were partly observed among people from Eastern Europe and Central Asia and East Asia and Pacific. Overall, the diagnosed proportion of PLWHA among foreign residents in Japan has shown a moderate but steady improvement over the years. The value amounted to 68.6% (95% CI: 66.6%, 70.8%) in 2014. However, the estimate in 2017 was as low as 55.3% (95% CI: 53.8%, 57.0%). The estimated number of PLWHA among foreign residents in 1990–2017 in Japan was 5,100 (95% CI: 4,951, 5,248), while 2,822 persons were observed, exclusive of “unknown” nationals. A similar difference appeared in Western Europe and East Asia and Pacific. In contrast, the observed data were higher than the upper 95% confidence intervals in Sub-Saharan Africa, South and South-East Asia, and Latin America.

Discussion

It is clear that the first component of the UNAIDS cascade was not satisfied among foreign residents in Japan, indicating a critical need to investigate the underlying mechanisms. In addition, the diagnosed proportion of PLWHA among foreign residents differed greatly by the geographic region of their country of origin. The

estimated number of PLWHA clearly showed that HIV infection among those from South and South-East Asia was likelier to be diagnosed than in other groups. HIV among residents from Sub-Saharan Africa and Latin America was also more effectively diagnosed than among those from other regions. HIV in residents from higher-income and low-HIV-prevalence countries, which are majorly constituted by industrialized countries (Western Europe, Australia and New Zealand, and North America), tended to be underdiagnosed. As leaving patients undiagnosed and untreated serves as a risk factor for the secondary transmission of HIV, and treatment as prevention (T as P) and Undetectable = Untransmittable (U = U) have been widely acknowledged, along with elimination of sexual transmission by early initiation of antiretroviral therapy and successful treatment of HIV, which yields both direct and indirect benefits, the issue of HIV among foreign residents should be proactively tackled, and their access to healthcare should be ensured.

Conclusion

This is the first study to provide statistical estimates of the diagnosed proportion of HIV infections and PLWHA among foreign residents in Japan. To contain HIV/AIDS, designing effective programs that maximize access to HIV testing, treatment, and care to reduce HIV transmission, as well as the early engagement of political leadership, is imperative. While many obstacles exist to more meticulous approaches, the present study provides essential perspectives on HIV diagnoses among foreign residents in Japan that were interpretable from existing empirical data. Given the findings indicate a critical need to deeply examine foreign residents, investigate the underlying mechanisms, and consider the heterogeneity of transmission, scrutinizing nationality data is vital, potentially constituting an important component for establishing an effective country-specific tailored approach to PLWHA. Moreover, to truly construct evidence-based, tailored testing, treatment, and care programs, more comprehensive details of risk profiles and critical pieces of information should be identified. Launching the national HIV registry system, recording these characteristics, incorporating migration data, and considering additional methods such as the use of CD4 count data, will assist in capturing the transmission dynamics of HIV among foreign residents in Japan, and both quantitatively and qualitatively exploring the details of HIV/AIDS in Japan. It is expected that in a globalized world with large-scale human mobility,

estimates presented in this study can serve as a beachhead for considering better access to HIV testing and care in the future in Japan.

List of Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
COHERE	Collaboration of Observational HIV Epidemiological Research Europe
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
HIV	Human Immunodeficiency Virus
IHME	Institute for Health Metrics and Evaluation
MSM	Men who have sex with men
PEP	Post-exposure prophylaxis
PLWHA	People Living with HIV/AIDS
PrEP	Pre-exposure prophylaxis
T as P	Treatment as Prevention
U = U	Undetectable = Untransmittable
UNAIDS	Joint United Nations Programme on HIV and AIDS

1. Introduction

1.1. Global trends of HIV/AIDS

While a substantial number of deaths due to the human immunodeficiency virus (HIV) /acquired immunodeficiency syndrome (AIDS) is recorded globally, there has been great progress (Jones et al., 2019), supported by medical advancements, largely through widespread testing and antiretroviral therapy (ART), referred to as treatment as prevention (T as P) (Cohen et al., 2011; Cohen et al., 2016; Bavinton et al., 2018). The global number of AIDS-related deaths, which was recorded at 1.9 million in 2005, decreased to below one million in 2016. The incidence of HIV infection also decreased from 2.8 million in 2000 to 1.8 million in 2017 (UNAIDS, 2018b). An annually estimated incidence of HIV infection by region is illustrated in Figure 1. In 1999, the incidence of global HIV peaked, followed by a marked decline by 2005. Between 2005 and 2015, the decreasing trend levelled off. In 2017, the number of newly acquired HIV infections was 1.9 million, of which 62.4% were reported from Sub-Saharan Africa, 11.0% from South and South-East Asia, and 9.3% from Eastern Europe and Central Asia.

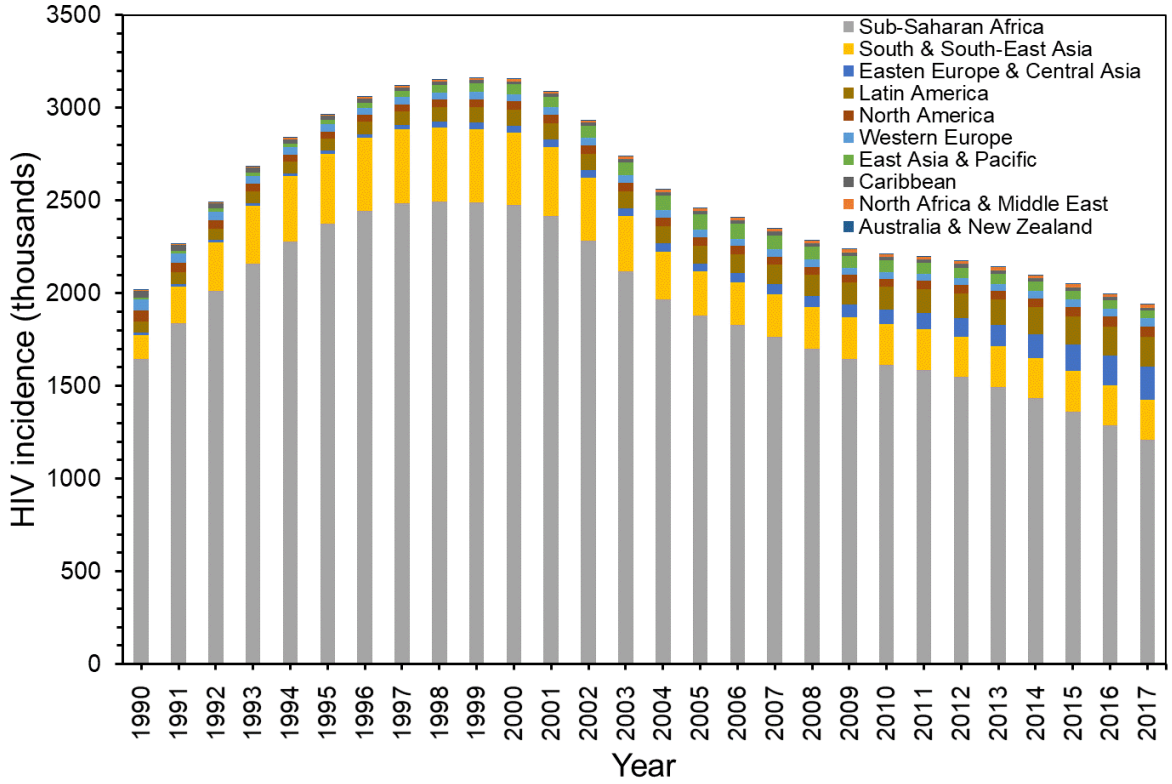

Figure 1. Estimated yearly incidence of HIV infections in the home country by region.

Data were extracted by the Institute for Health Metrics and Evaluation (IHME).

The HIV pandemic is far from over, and the pathway to end it is still strenuous (UNAIDS, 2018c). However, these declines are positively linked with “90–90–90” targets launched by the Joint United Nations Programme on HIV and AIDS (UNAIDS) in 2014, which aimed to ensure that 90% of people living with HIV know their status, 90% of infected individuals receive ART, and 90% of infections under ART benefit from viral load suppression (UNAIDS, 2017). Recent evidence also supports the idea that having an undetectable viral load by ART can eliminate the transmission of HIV, which is referred to as Undetectable = Untransmittable (U = U) (Rodger et al., 2016; Cohen, 2019; Rodger et al., 2019). Currently, UNAIDS is raising a global target to achieve “95–95–95” by 2030 (UNAIDS, 2014; Granich et al., 2017). While the global target itself is encouraging, a combined approach, such as coordination of globally scaled-up prevention programs, pre-exposure prophylaxis (PrEP), and detection and treatment programs, is deemed essential, due to the highly heterogeneous risk profile and the dynamics of HIV infection (Piot et al., 2008; Piot et al., 2015; UNAIDS, 2015).

1.2. HIV among foreign residents and migration

Due to globalization, migration between geographic regions has rapidly grown, which is of substantial importance in medicine and public health. While there has been furious debate regarding the impact of migration and its political and social challenges, fewer people argue about its impact on their health, challenging to grasp their true medical needs, whether their access to care is ensured in the destination and the impact of migration on long-term health outcomes (Gill and Krentz, 2015). In particular, due to the nature of its infection and the high fatality risk if untreated, the migration process, before, during, and after, can increase the risk of contracting HIV (Haour-Knipe, et al., 2014), and the vulnerability, namely social and structural factors, also links to it (Nöstlinger and Loos, 2018). Some migrants have no opportunity to be aware of their HIV status ahead of migration. Even HIV-positive individuals who are taking ART could be exposed to a higher risk of interrupting treatment during the migration process (Gill and Krentz, 2015). In addition to challenges to retain care during the migration process, it could be worrisome for migrants to settle down into the destination, even provided that they could safely be accepted in a new country. It can be difficult to successfully reach HIV care locally due to inadequate community

engagement for migrants and barriers that constitute multiple social determinants of health, both at the individual and population levels (O'Donnell et al., 2013; Royo-Bordonada et al., 2013).

While there is a variation between countries and regions, according to the European Centre for Disease Prevention and Control (ECDC), in 2018, over two-fifths of people newly diagnosed with HIV in the territory of the European Union/European Economic Area (EEA) were born outside the country where they were diagnosed (ECDC and WHO Regional Office for Europe, 2019), indicating its substantial impact on population health globally.

1.3. HIV/AIDS in Japan

The global epidemiological trends of HIV/AIDS have impacted Japan, and the incidence of HIV diagnoses and AIDS cases has shown a steady increase for nearly two decades from 1985, followed by declines in 2008 and 2010, respectively (Nemoto, 2004; UNAIDS, 2016).

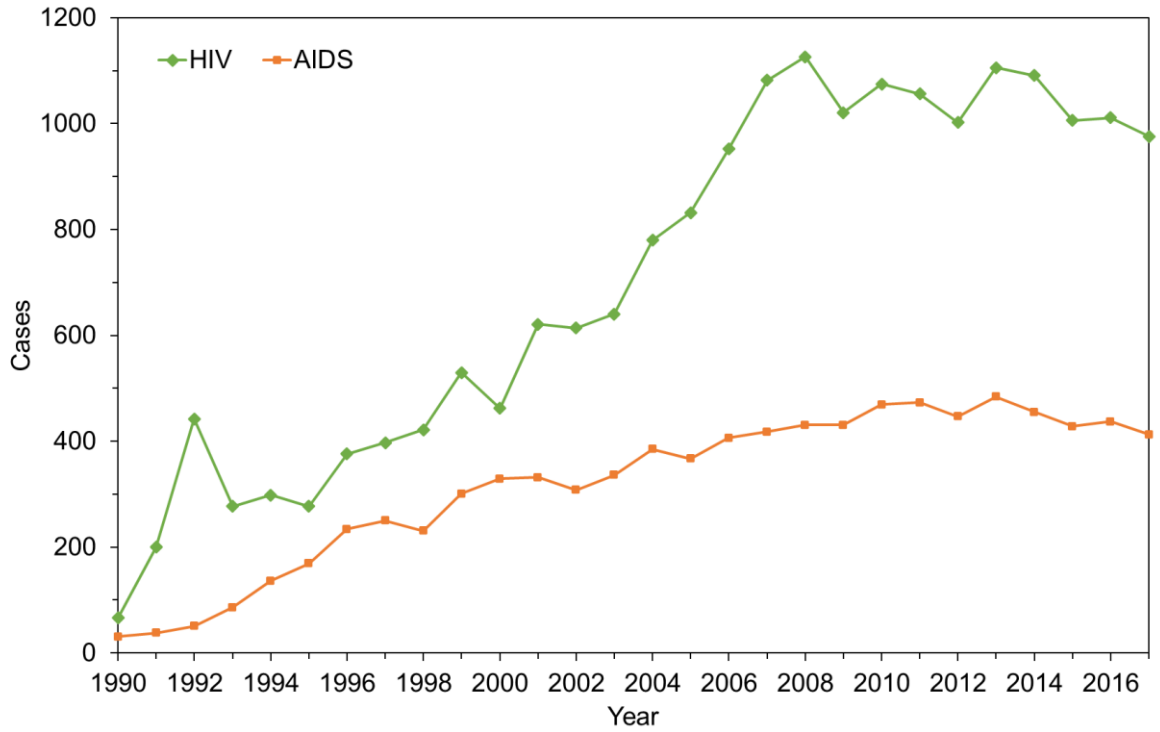

Figure 2. HIV/AIDS in Japan from 1990–2017.

There are two categories: HIV (cases that are laboratory confirmed with HIV infection without manifesting AIDS-indicator diseases) and AIDS (cases that are laboratory confirmed with HIV infection and manifest AIDS-indicator diseases at the initial diagnosis and reporting).

Nevertheless, several studies have reported that substantial efforts are needed to achieve the 90–90–90 target (Suguimoto et al., 2014; UNAIDS, 2016). While the disease burden of HIV/AIDS is relatively lower and good adherence and treatment retention are recognized (Iwamoto et al., 2017), the diagnosed proportion of HIV infections in Japan has been estimated to be remained lower than 90% (Iwamoto et al., 2017; Nishiura, 2019). The analysis that used first-time blood donors presented estimates that 85.6% of infected individuals were aware of the infection at the end of 2015 (Iwamoto et al., 2017). The modeling study, using an extended back-calculation method, estimated that the diagnosed proportion as of the end of 2017 had ranged between 77% and 84% among the Japanese (Nishiura, 2019). The relatively higher prevalence in men who have sex with men (MSM) demonstrates that there is a critical need to appropriately identify risk groups and reach them through testing and continued treatment (Ezoe et al., 2012; Gilmour et al., 2012; Iwamoto et al., 2017; Sherriff et al., 2017).

1.4. Foreign visitors to Japan

Human mobility has increased significantly due to globalization, and Japan has been no exception to this. The evolution of the yearly number of foreign nationals entering Japan is illustrated in Figure 3 and is classified by region. While two dips were recorded, in 2009 when the H1N1 influenza pandemic restricted human mobility, (which was also the year following the financial crisis in 2008), and 2011 when the Great East Japan Earthquake hit Japan, a general upward trend was evident (Ministry of Justice, Japan, 2018; Immigration Services Agency of Japan, 2019; Ministry of Justice, Japan, 2019). In 2017, 72.4% of people came from East Asia and Pacific countries, followed by people from South and South-East Asia, which ranked second (12.5%).

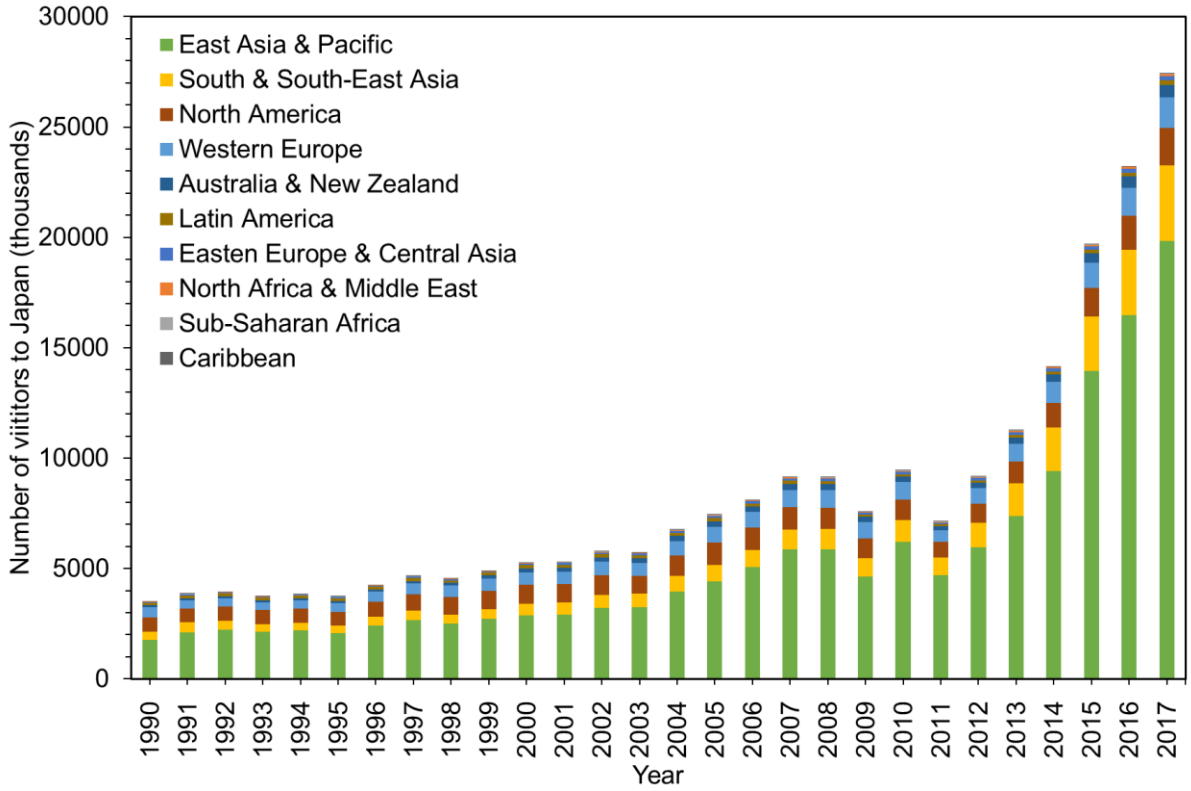

Figure 3. Temporal distribution of the yearly number of foreign visitors to Japan, by region of the country of origin.

1.5. HIV/AIDS among foreign residents in Japan and research objectives

In Japan, the number of newly reported cases of HIV diagnoses among foreign residents was recorded at 78 in 2010, but it increased to 152 in 2017, and AIDS cases also recorded an increase from 33 in 2010 to 44 in 2017. The cumulative total amounted to 4,526 (15.8%) out of all 28,614 diagnoses between 1990 and 2017 (Figure 4). While HIV prevalence remains low in Japan, it is plausible to consider that an increase in the number of visitors to Japan could have increased the risk of transmission of HIV/AIDS.

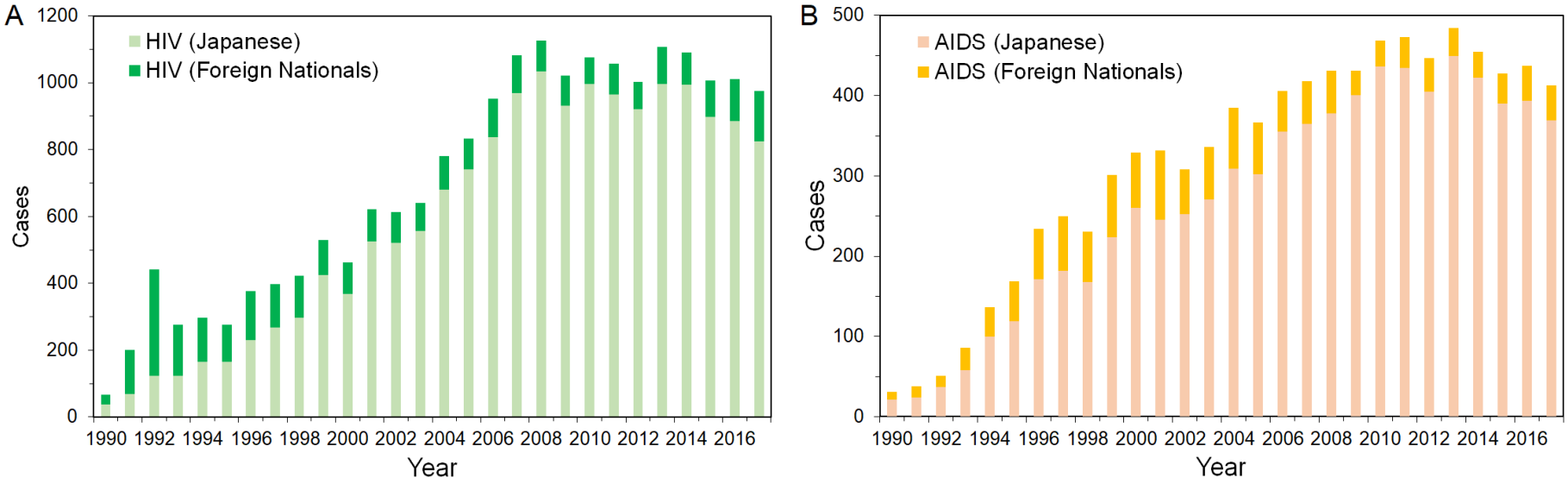

Figure 4. HIV/AIDS in Japan from 1990–2017, by nationality.

(A) The yearly incidence (i.e., the number of new infections) of HIV among Japanese and foreign nationals.

(B) The yearly reported AIDS cases among Japanese and foreign nationals.

However, scant epidemiological research has addressed the increasing proportion of foreign residents among newly diagnosed HIV infections and AIDS cases in Japan (Ministry of Health, Labour and Welfare, Japan, 2017; Kinoshita and Oka, 2018). This was different from an increasing focus on migration and its impact on infectious diseases, including HIV/AIDS in Europe and Central Asia (ECDC, 2017), and an attempt to estimate to what extent populations remained undiagnosed for HIV/AIDS, especially among those who were born in foreign countries (Andersson et al., 2019).

To truly achieve data-driven, tailored interventions that contain HIV/AIDS in Japan, clarification of the full picture of the epidemiology of HIV/AIDS in Japan will be pivotal and estimating the number of people living with HIV/AIDS (PLWHA) among foreign residents is an indispensable process. Therefore, this study aimed to estimate the diagnosed proportion of PLWHA among foreign residents in Japan and characterized them by regions of the country of origin.

2. Materials and Methods

2.1. Data descriptions

Although Japan has no individual registry of HIV-infected individuals, physicians must notify the government of all newly diagnosed HIV infections and AIDS cases, as HIV/AIDS are classified as one of the designated infectious diseases requiring such notice, as established by the Infectious Disease Control Law, Japan (Iwamoto et al., 2017). The reporting system went into effect in 1985, and the National AIDS Surveillance Committee publicly reported the annual dataset (Ministry of Health, Labour and Welfare, Japan, 2017). In addition, datasets on international travel that included items such as visit duration and travel volume were explored. The incidence and cumulative incidence of HIV infection were measured as person–time at risk, by combining the HIV incidence and prevalence with the travel data.

Five different datasets were explored from the period between 1990 and 2017: estimated incidence and prevalence of HIV infection by country; population size in each country; the average length of stay in Japan, by each country of origin; the number of foreign nationals entering Japan, by country; and yearly notification data of newly diagnosed HIV infections and AIDS cases in Japan.

2.1.1. Estimated incidence and prevalence of HIV infection in individual countries

Overall, two data sources are available on a global scale. AIDSinfo, assembled by UNAIDS in 1997, presents country-specific estimates (UNAIDS, 2018a). However, there are 42 countries with no available data, including the United States, Canada, and mainland China, reducing its comprehensiveness, and hindering a comparative analysis. Political controversies might have prevented estimates for countries or regions closely associated with Japan, such as Taiwan and Hong Kong.

Alternatively, the Institute for Health Metrics and Evaluation (IHME) seeks to ensure comprehensive data (GBD 2015 HIV Collaborators, 2016; IHME, 2018) and offers estimates in countries and regions that AIDSinfo does not cover. They are based on the availability and quality of data from antenatal care clinics or population-based

seroprevalence surveys, and address differences of diagnosed proportion of HIV at national and sub-national levels (GBD 2017 HIV Collaborators, 2019). While methodological differences and disagreements with UNAIDS estimates are argued (Kelly and Wilson, 2016), the dataset has strengths and is suitable for conducting comparative analysis.

2.1.2. Population size in each country

The size of the population in each country was extracted from the United Nations Population Division (United Nations, 2018). “Estimates” between 1990 and 2015 and the “medium variant” in 2016–2017 were referred to.

2.1.3. Average length of stay in Japan by each country of origin

Data were extracted from the Annual Report of Statistics on Legal Migrants (Ministry of Justice, Japan, 2018), published by the Ministry of Justice, Japan. The length of stay in Japan by country of origin was classified into 15 categories: less than 5 days, 6–10 days; 11–15 days; 16–20 days; 21 days to one month; 1–2 months; 2–3 months; 3–6 months; 6 months to one year; 1–2 years; 2–3 years; 3–5 years; 5–10 years; over 10 years; and unknown. The average length of stay in Japan by country was calculated as the weighted average length.

Nations that were united and separated over time were manually corrected to be consistent with present-day classifications. Concretely, the number of people from the Socialist Federal Republic of Yugoslavia and the Federal Republic of Yugoslavia were summed up to reduce complexity. The average length of stay by people from North Macedonia, Serbia, Bosnia and Herzegovina, Croatia, Slovenia, and Montenegro in 1990–1991 was based on this result. Data recorded as those from the Federal Republic of Yugoslavia were used to compensate for data on the State Union of Serbia and Montenegro from 1992 to 2006. From 2007, the Republics of Serbia and Montenegro were calculated separately, and the number of people holding the nationality of the State Union of Serbia and Montenegro was integrated into the

dataset recorded as the Republic of Serbia. Data in the Soviet Union from 1990–1992 were substituted for those of Russia. Results in Czechoslovakia were used to supplement the lack of data on the Czech Republic and the Slovak Republic from 1990–1992.

2.1.4. Number of foreign nationals entering Japan, by country

The entire number of entries to Japan in a given year is listed by country. Data were extracted from the Annual Report of Statistics on Legal Migrants (Ministry of Justice, Japan, 2018), published by the Ministry of Justice, Japan. Hereafter, foreign residents were defined as the total number of foreign nationals entering Japan legally, and they included temporary visitors who entered Japan for sightseeing, business, and visiting relatives.

Nations that were united and separated over time were manually corrected to be consistent with present-day classifications. For 1990–1991, estimated numbers of visitors from North Macedonia, Serbia, Bosnia and Herzegovina, Croatia, Slovenia, and Montenegro were calculated proportionally by distributing the entry numbers from the Socialist Federal Republic of Yugoslavia and the Federal Republic of Yugoslavia. The 1990 population size for each country was employed to perform this process. The same method was used to estimate the number of visitors from the Republic of Serbia and Montenegro by employing the dataset recorded in the State Union of Serbia and Montenegro from 1997 to 2006. To do this, the population size in 2000 was used. The numbers of visitors from the State Union of Serbia and Montenegro and the Republic of Serbia were combined for 2007–2017. Similarly, both the Soviet Union and Russian data were merged. The same procedure was performed to estimate the number of visitors from the Czech Republic and the Slovak Republic in 1990–1992.

2.1.5. Newly diagnosed HIV infections and AIDS cases in Japan

The yearly notification data of HIV diagnoses and AIDS cases from 1990–2017 were used to extract data on involving individuals classified as being of foreign nationality.

In the original surveillance data, detailed nationality was not disclosed, but instead, nationalities were grouped into ten regions: Western Europe, North Africa and Middle East, Sub-Saharan Africa, South and South-East Asia, Eastern Europe and Central Asia, East Asia and Pacific, Australia and New Zealand, North America, Caribbean, and Latin America, in accordance with the classifications in the UNAIDS 1998 report (UNAIDS and WHO, 1998). Table 1 summarized the classification of regions.

Table 1. Classification of regions

Region (Number of countries)	Countries
Western Europe (25)	Albania, Andorra, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, North Macedonia, United Kingdom, Serbia, Montenegro
North Africa and Middle East (20)	Algeria, Bahrain, Cyprus, Egypt, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Sudan, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, Yemen
Sub-Saharan Africa (48)	Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
South and South-East Asia (20)	Afghanistan, Bangladesh, Bhutan, Brunei Darussalam, Cambodia, India, Indonesia, Islamic Republic of Iran, Lao People's Democratic Republic, Malaysia, Maldives, Myanmar, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Thailand, Timor-Leste, Vietnam

Eastern Europe and Central Asia (23)	Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
East Asia and Pacific (15)	China, Democratic People's Republic of Korea, Fiji, Hong Kong, Mongolia, Papua New Guinea, Republic of Korea, Taiwan, Kiribati, Marshall Islands, Micronesia, Samoa, Solomon, Tonga, Vanuatu
Australia and New Zealand (2)	Australia, New Zealand
North America (2)	Canada, United States
Caribbean (12)	Bahamas, Barbados, Cuba, Dominica, Dominican Republic, Haiti, Jamaica, Trinidad and Tobago, Antigua and Barbuda, Grenada, Saint Lucia, Saint Vincent and Grenadines
Latin America (20)	Argentina, Belize, Plurinational State of Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, Bolivarian Republic of Venezuela

2.2. Model construction–balance equation model

To analyze the diagnosed proportion of PLWHA among foreign residents in Japan by regions of the country of origin from available data, the balance equation model is employed. The model has been basically leveraged for estimating the potential magnitude of several infectious diseases, and the results have been utilized for maintaining situational awareness and bringing rational public health responses. For example, the number of actual cases of novel influenza in Mexico was estimated to exceed that of confirmed cases by two to three orders of magnitude, as of April 2009 (Lipsitch et al., 2009). It was indicated in 2017 that yellow fever internationally spread from Brazil to some countries, such as the United States and Argentina (Dorigatti et al., 2017). The expected number of exported cases of pneumonic plague from Madagascar in 2017 was estimated to be below 1, suggesting the lower risk of international spread (Tsuzuki et al., 2017).

An adopted modeling method will be described. Throughout the analysis, the incidence of HIV infection (i.e., the number of newly acquired HIV infections) in country *i* and PLWHA in country *i* are defined as N_i and M_i, respectively. The approach is premised on a balance equation that follows that the same risk of infection is present among people from foreign countries as they have in their home country. Person–time risk is calculated as the product of D_i and V_i, where D_i represents the average length of stay in Japan and V_i is the total number (volume) of foreign travelers from *i*. Supposing that the incidence in *i* is k_1 times greater than that among those from *i* in Japan, the balance equation of the incidence is given:

$$k_1 \frac{U_i}{D_i V_i} = \frac{1}{365} \frac{N_i}{P_i}, \quad (1)$$

where U_i is the reported number of HIV diagnoses among people from *i* in Japan and P_i is the population size in *i*. Assuming that the same balance applies to PLWHA, the following formula is formulated:

$$k_2 \frac{W_i}{D_i V_i} = \frac{1}{365} \frac{M_i}{P_i}, \quad (2)$$

where W_i is the reported number of PLWHA, assumed to be equal to the cumulative number of PLWHA, among people from *i* in Japan, and k_2 is the relative risk of having HIV infection in the country of origin compared with that in Japan. Each year, people in the original country experience a total of 365 days at risk, and each traveler from *i* experiences D_i days at risk, which is equal to their length of stay. As introduced in the previous section, in equations (1) and (2), estimates of U_i and W_i were extracted from surveillance data (Ministry of Health, Labour, and Welfare, Japan, 2017), and D_i and V_i were retrieved from Statistics on Legal Migrants (Ministry of Justice, Japan, 2018). N_i and M_i were obtained from IHME estimates (IHME, 2018), and P_i was retrieved from United Nations population estimates (United Nations, 2018).

Due to challenges in HIV surveillance data, the incidence was only reported by regions rather than as country-specific data. In addition, only the total new HIV diagnoses and AIDS cases among foreign residents were reported between 2011 and 2015, and nationalities and even the regions of origin of newly infected HIV diagnoses were not monitored during the corresponding time period. To accommodate the country-grouped data, equations (1) and (2) are written as follows:

$$k_1^* \frac{U^*}{\sum_i D_i V_i} = \frac{1}{365s} \sum_{i=1}^{s} \frac{N_i}{P_i} \tag{3}$$

where U^* is the reported number of HIV diagnoses across those from different countries, in Japan, and *s* is the total number of countries in a specified group. The same approach applies to PLWHA, i.e.,

$$k_2^* \frac{W^*}{\sum_i D_i V_i} = \frac{1}{365s} \sum_{i=1}^{s} \frac{M_i}{P_i} \tag{4}$$

Datasets of *U* and *W* for Japan were scarce in empirical observations, and they were frequently zero-valued. Thus, an assumption that *U* and *W* follow zero-inflated Poisson distributions is employed, and the resulting likelihood function that allows an estimate of k_1 is decomposed as

$$L(k_1, q_1; X = j)$$
$$= \begin{cases} q_1 + (1-q_1)exp\left(-\dfrac{\sum_i D_i V_i}{365sk_1}\sum_{i=1}^{s}\dfrac{N_i}{P_i}\right) & if\ j = 0 \\ (1-q_1)\dfrac{exp\left(-\dfrac{\sum_i D_i V_i}{365sk_1}\sum_{i=1}^{s}\dfrac{N_i}{P_i}\right)\left(\dfrac{\sum_i D_i V_i}{365sk_1}\sum_{i=1}^{s}\dfrac{N_i}{P_i}\right)^j}{j!} & if\ j > 0 \end{cases} \quad (5)$$

where q is the probability of extra zeros.

Similarly, the likelihood function that allows k_2 to be estimated is given as

$$L(k_2, q_2; X = j)$$
$$= \begin{cases} q_2 + (1-q_2)exp\left(-\dfrac{\sum_i D_i V_i}{365sk_2}\sum_{i=1}^{s}\dfrac{M_i}{P_i}\right) & if\ j = 0 \\ (1-q_2)\dfrac{exp\left(-\dfrac{\sum_i D_i V_i}{365sk_2}\sum_{i=1}^{s}\dfrac{M_i}{P_i}\right)\left(\dfrac{\sum_i D_i V_i}{365sk_2}\sum_{i=1}^{s}\dfrac{M_i}{P_i}\right)^j}{j!} & if\ j > 0 \end{cases} \quad (6)$$

The mean incidence from equations (5) and (6) is respectively calculated as

$$(1-q_1)\frac{\sum_i D_i V_i}{365sk_1}\sum_{i=1}^{s}\frac{N_i}{P_i}$$

and

$$(1-q_2)\frac{\sum_i D_i V_i}{365sk_2}\sum_{i=1}^{s}\frac{M_i}{P_i}$$

Likelihood functions (5) and (6) are minimized to obtain maximum likelihood estimates.

2.3. Sensitivity analysis

To deal with challenges in the key assumption of this approach that the risk of infection among foreign residents in Japan and in their home country is same, an additional parameter is introduced into the balance equation as part of the sensitivity analysis. The following formula is obtained:

$$\alpha k_2^* \frac{W^*}{\sum_i D_i V_i} = \frac{1}{365s} \sum_{i=1}^{s} \frac{M_i}{P_i} \quad (7)$$

where the parameter α represents the ascertainment ratio. It is indicated that foreign residents in Japan were more frequently diagnosed in Japan than in their home country if $\alpha > 1$. Alternatively, it could be also interpreted that foreign residents in Japan might be at greater risk of infection than the average in their home country when $\alpha > 1$.

Furthermore, to address differences of person-time at risk between countries and by years and bring better consideration on the global risk of HIV/AIDS, equations (3) and (4) are reformulated and weighted as follows:

$$k_1^{**} \frac{U^*}{\sum_i D_i V_i} = \frac{1}{365} \sum_{i=1}^{s} \frac{N_i}{P_i} \times \frac{D_i V_i}{\sum_i D_i V_i} \quad (8)$$

$$k_2^{**} \frac{W^*}{\sum_i D_i V_i} = \frac{1}{365} \sum_{i=1}^{s} \frac{M_i}{P_i} \times \frac{D_i V_i}{\sum_i D_i V_i} \quad (9)$$

As part of the sensitivity analysis, the resulting likelihood functions are minimized to obtain maximum likelihood estimates in line with the methodology described in Section 2.2.

2.4. Ethical considerations

As this study analyzed secondary datasets that were anonymized in advance and were publicly available, ethical approval by an institutional review board was not required.

3. Results

3.1. HIV and PLWHA by region of origin

The reported number of HIV diagnoses among foreign residents in Japan is presented in Figure 5A. Newly reported HIV infections peaked in 1992, followed by a gradual decline by 1998. Then, an upward trend was observed from 2014. People from the South and South-East Asia region dominated the group, and Latin America and Sub-Saharan Africa countries ranked second and third, respectively. The cumulative number of HIV diagnoses and AIDS cases among foreign residents in Japan is shown in Figure 5B. Between 1990 and 2017, the total was calculated as 4,526. The highest represented region was South and South-East Asia (36.6%), followed by Latin America (11.4%) and Sub-Saharan Africa (6.6%).

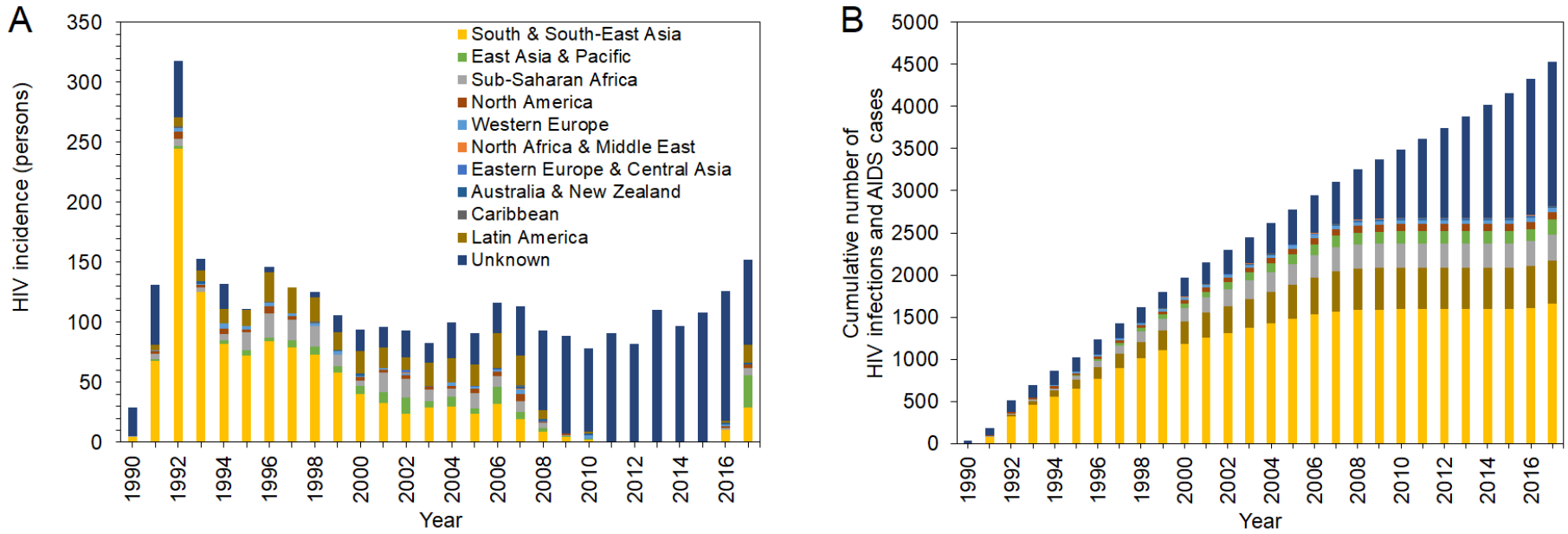

Figure 5. HIV among foreign residents in Japan in 1990–2017, by region of origin.

(A) The annual number of new HIV infections among foreign residents in Japan.

(B) The cumulative number of HIV infections and AIDS cases among foreign residents in Japan.

3.2. Estimated diagnosed proportion of new HIV infections among foreign residents in Japan by region

An estimated parameter $1/k_1^*$, namely, the reporting coverage of new HIV infections among foreign residents in Japan over time, is shown in Figure 6. Two separate panels are presented, due to varied estimates of the proportion. Foreign residents from Western Europe, North Africa and Middle East, East Asia and Pacific, and North America appear to have mostly recorded below 100%. East Asia and Pacific became the most underdiagnosed group, with 27.9% in 2017.

South and South-East Asia are classified into an over-reported group (Figure 6B), with an overestimation of 1,251% in 1992, followed by a decrease to around 100–200% between 2000 and 2007, and below 100% after 2008.

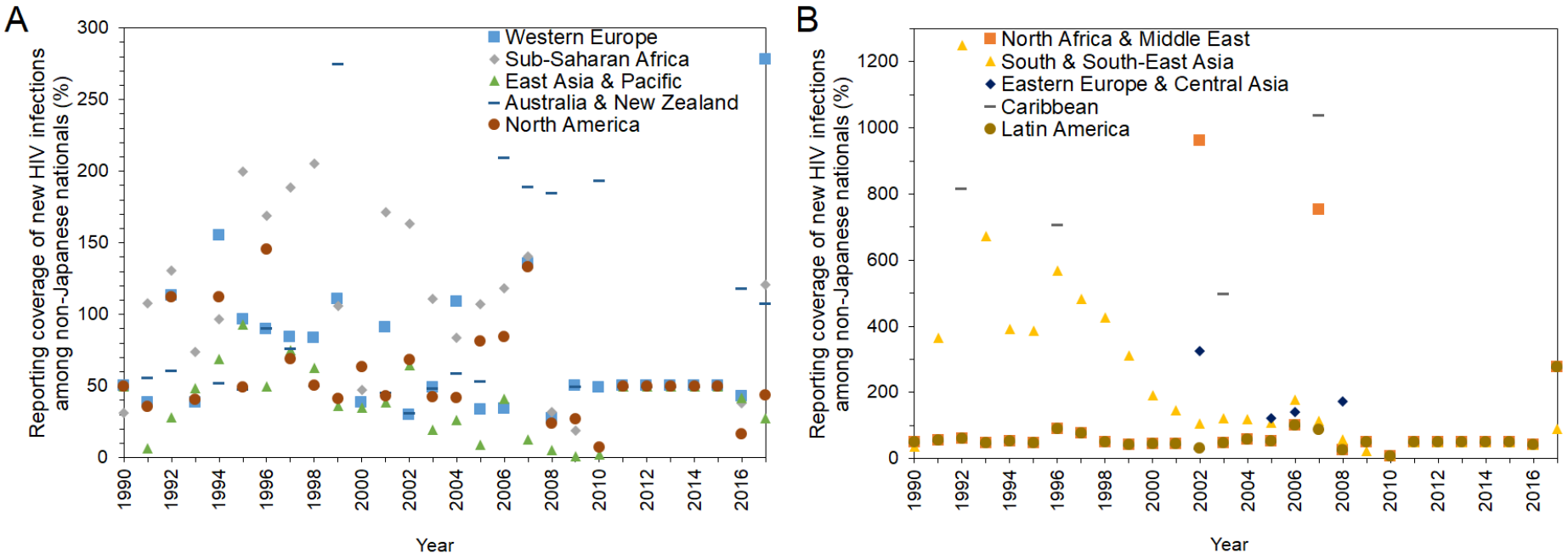

Figure 6. Estimated reporting coverage of new HIV infections among foreign residents in Japan by region.

Estimated reporting coverage of HIV infections among foreign residents in Japan, 1990–2017. Two panels are shown because of varying estimates.

(A) People from Western Europe, Sub-Saharan Africa, East Asia and Pacific, Australia and New Zealand, and North America.

(B) People from North Africa and Middle East, South and South-East Asia, Eastern Europe and Central Asia, Caribbean, and Latin America.

3.3. Estimated diagnosed proportion of PLWHA among foreign residents in Japan by region

An estimated parameter $1/k_2^*$, namely, the diagnosed proportion of PLWHA among foreign residents in Japan over time, is shown in Figure 7. Two separate panels are presented, due to varied estimates of this proportion. Foreign residents from Western Europe, East Asia and Pacific, Australia and New Zealand, and North America appear to have mostly recorded below 100%. East Asia and Pacific became the most underdiagnosed group, with a high of 91.4% in 1999 and 23.1% in 2017. North Africa and Middle East, South and South-East Asia, and Sub-Saharan Africa are classified into an over-reported group (Figure 7B). An overestimation of 991% was calculated in the South and South-East Asia region in 1996. A rising trend of the proportion for those from Latin America began in 2011, reaching 829% in 2016 (Figure 7B).

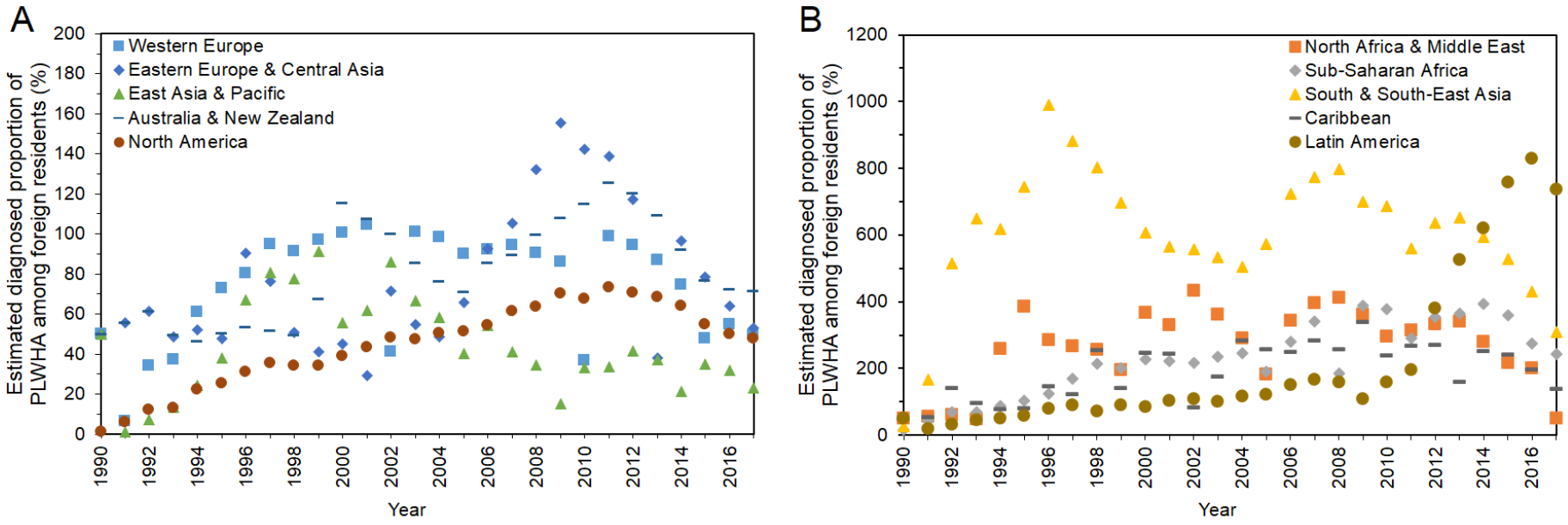

Figure 7. Estimated diagnosed proportion of PLWHA among foreign residents in Japan, 1990–2017.

Estimates of the proportion of diagnosed infections out of the cumulative number of HIV infections and AIDS cases. Two panels are shown because of varying estimates.

(A) People from Western Europe, Eastern Europe and Central Asia, East Asia and Pacific, Australia and New Zealand, and North America.

(B) People from North Africa and Middle East, Sub-Saharan Africa, South and South-East Asia, Caribbean, and Latin America.

3.4. Time-dependent estimate of diagnosed proportions of HIV infections and PLWHA among all foreign residents in Japan

The time-dependent estimates of the diagnosed proportions of HIV infections and PLWHA among all foreign residents in Japan are displayed in Figure 8. The diagnosed proportion of new HIV infections over the years is presented in Figure 8A. It reached the highest level with an estimation of 77.7% (95% confidence interval (CI): 70.0%, 87.3%) in 1992, when the Japanese Ministry of Health and Welfare revised the principles of comprehensive AIDS control strategy and launched the “Headquarters for Stopping AIDS” to accelerate the Stop AIDS campaigns. On the contrary, the lowest value was recorded in 2008, at 9.8% (95% CI: 8.2%, 12.3%). In 2017, the diagnosed proportion of new HIV infections was estimated at 39.5% (95% CI: 34.1%, 47.0%).

Estimates of the diagnosed proportion of PLWHA among all foreign residents are shown in Figure 8B. Over the years, there has been a moderate but steady improvement in detection. The value amounted to 68.6% (95% CI: 66.6%, 70.8%) in 2014. However, despite the improvements, the proportion plunged to 55.3% (95% CI: 53.8%, 57.0%) in 2017.

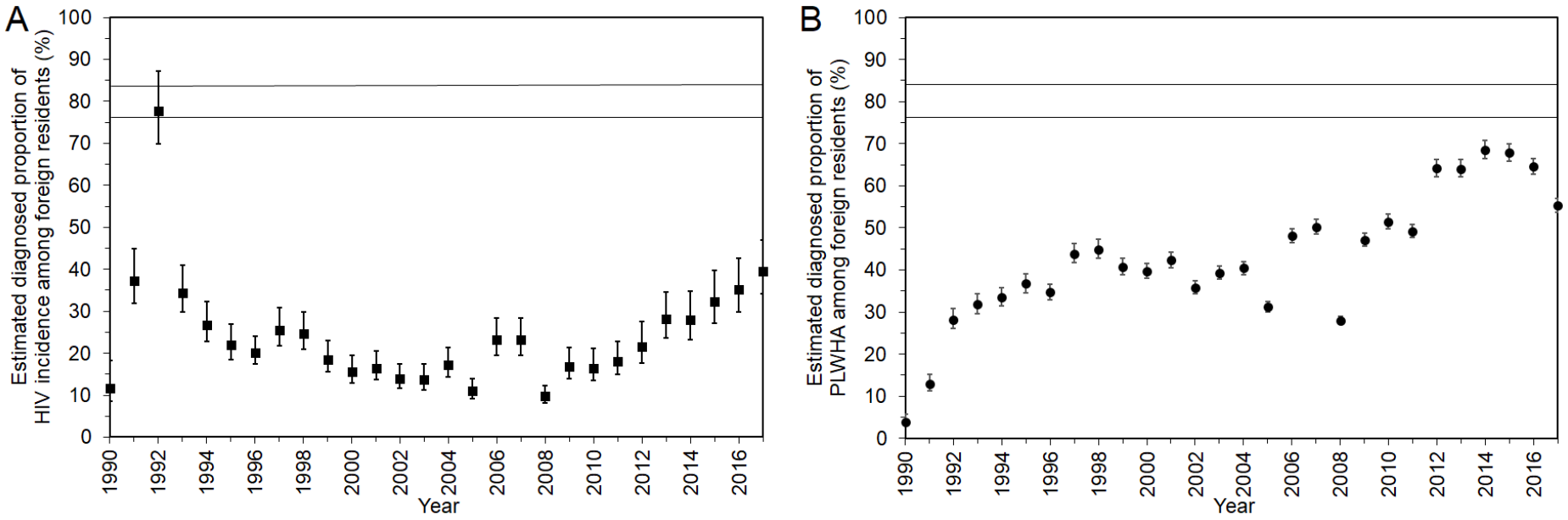

Figure 8. Overall estimate of diagnosed proportion of HIV infections among foreign residents in Japan, 1990–2017.

(A) Estimates of the diagnosed proportion of the yearly incidence of HIV infections.

(B) Estimates of the diagnosed proportion of the cumulative number of HIV infections and AIDS cases in 1990–2017.

In both figures, whiskers extend to the upper and lower 95% confidence intervals. Two horizontal lines show the estimated diagnosed proportions among Japanese nationals: 77–84% (Nishiura, 2019).

3.5. Comparison of observed and estimated HIV incidence and PLWHA among foreign residents in Japan

Figure 9A presents the estimated numbers of new HIV infections by region. As there were no newly reported HIV cases among foreign nationals from Western Europe, North Africa and Middle East, Eastern Europe and Central Asia, and Caribbean regions in 2017, the calculation was restricted to six regions. There was a remarkable difference between the observed and estimated numbers for the East Asia and Pacific region, where the reported number of cases was 27 (green bar), while the estimated number amounted to 97 (95% CI: 60, 133). Similar trends were observed among those from South and South-East Asia, Sub-Saharan Africa, and North America: while estimated HIV infections were 32 (95% CI: 20, 44), 5 (95% CI: 1, 9), and 7 (95% CI: 0, 15), respectively, 29, 6, and 3 infections were reported for these regions.

The estimated PLWHA is compared to the observed cumulative incidence in Figure 9B. Within the period between 1990 and 2017, an overall estimated PLWHA among foreign residents reached 5,100 (95% CI: 4,951, 5,248), while 2,822 persons were observed, exclusive of “unknown” nationals. Similar differences appeared in the regions of Western Europe, East Asia and Pacific; whereas the estimated numbers were 99 (95% CI: 71, 127) and 783 (95% CI: 669, 897), PLWHA were 49 and 181, respectively. The observed data recorded higher numbers than the upper 95% confidence intervals in Sub-Saharan Africa, South and South-East Asia, and Latin America. This indicated that people from these regions were more effectively diagnosed with HIV compared with other regions.

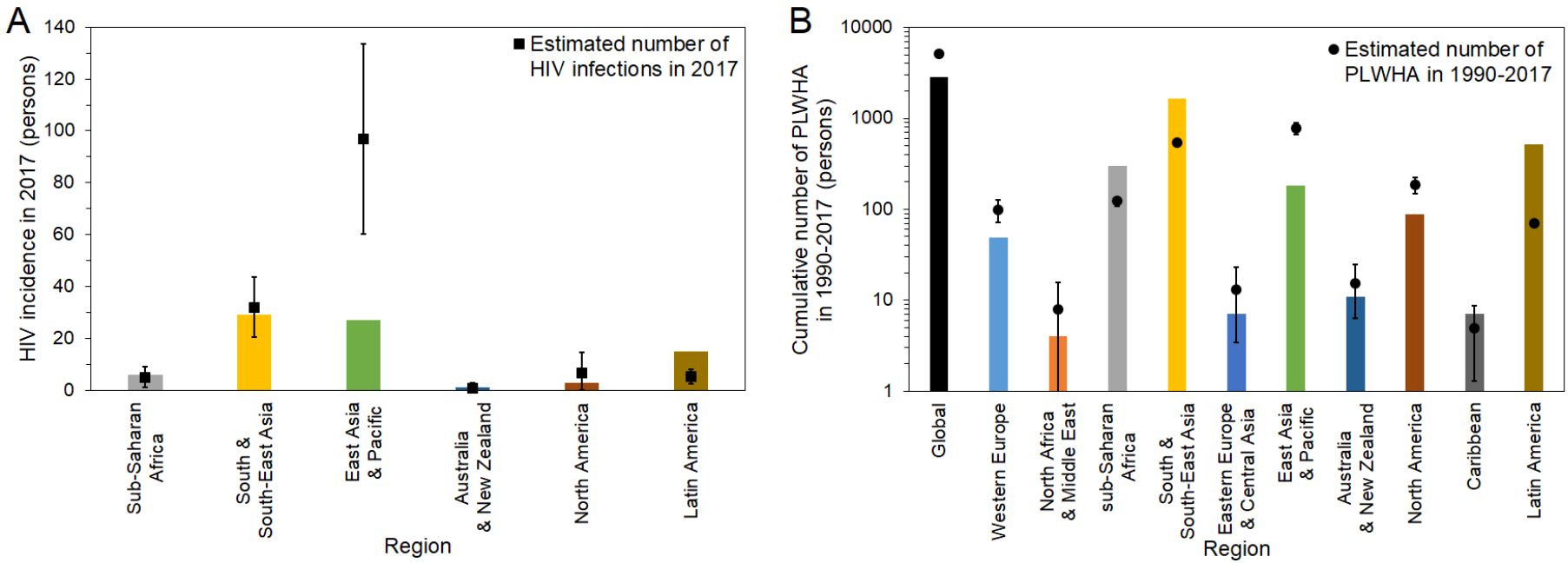

Figure 9. Comparison of observed and estimated HIV incidence and PLWHA among foreign residents in Japan.

(A) Bars represent the observed incidence of HIV diagnoses in Japan in 2017 by region of the country of origin. Solid squares represent the estimated number of HIV diagnoses when using the model.

(B) Bars represent the observed cumulative number of HIV infections and AIDS cases in Japan from 1990 to 2017, by region or the country of origin. Solid circles show the estimated cumulative number of HIV infections and AIDS cases by region in Japan when using the model. Whiskers extend to the upper and lower 95% confidence intervals. A common logarithmic scale is used on the vertical axis.

3.6. Variations of estimates

As estimated diagnosed proportions of PLWHA by region sometimes exceeded 100%, their sensitivity under ascertainment was examined. How the estimate of the diagnosed proportion of PLWHA in 2017, 55.3% (95% CI: 53.8%, 57.0%), was sensitive to the variation in α (ascertainment ratio) is graphically shown in Figure 10. The estimate of 553% (95% CI: 538%, 570%) was calculated when α is 10, suggesting that foreign residents in Japan were more frequently diagnosed in Japan than in their home country, warranting detailed epidemiological investigation of their possible timing of infection. On the contrary, when α is 0.1, the estimate of 5.5% (95% CI: 5.4%, 5.7%) was drawn, indicating that possible factors that impede their access to testing and treatment in Japan should be explored.

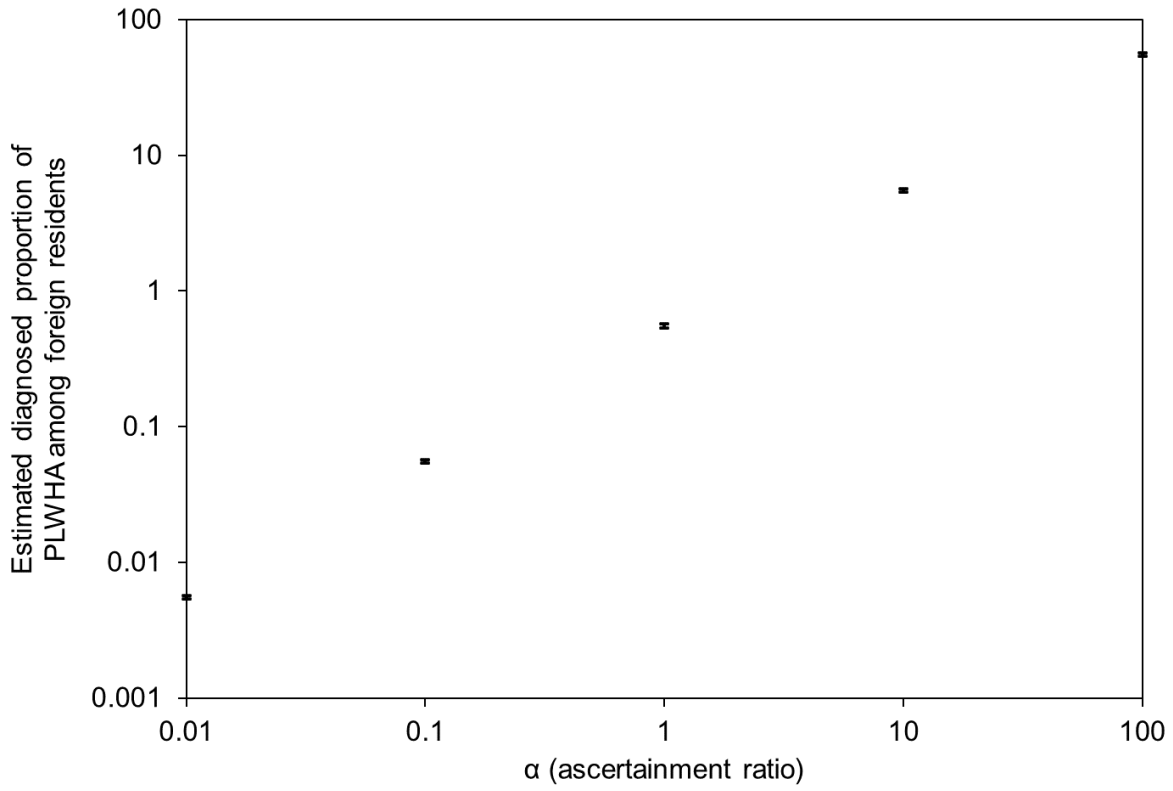

Figure 10. Variations of estimated diagnosed proportion of PLWHA in 2017 by ascertainment ratio.

Whiskers extend to the upper and lower 95% confidence intervals. A common logarithmic scale is used on the vertical axis. Further, the vertical axis is the fraction (i.e., the value 1 is equivalent to 100%).

The reporting coverage of new HIV infections among foreign residents in Japan over time (parameter $1/k_1^{**}$), estimated as part of the sensitivity analysis, is shown in Figure 11. Foreign residents from Eastern Europe and Central Asia, North America, and Latin America appear to have mostly recorded below 100%, and North America became the most underdiagnosed group, with 37.8% in 2017. South and South-East Asia are classified into an over-reported group (Figure 11B), with an overestimation of 1,401% in 1992, followed by a decrease to around 100–200% between 2001 and 2007, and below 100% after 2008.

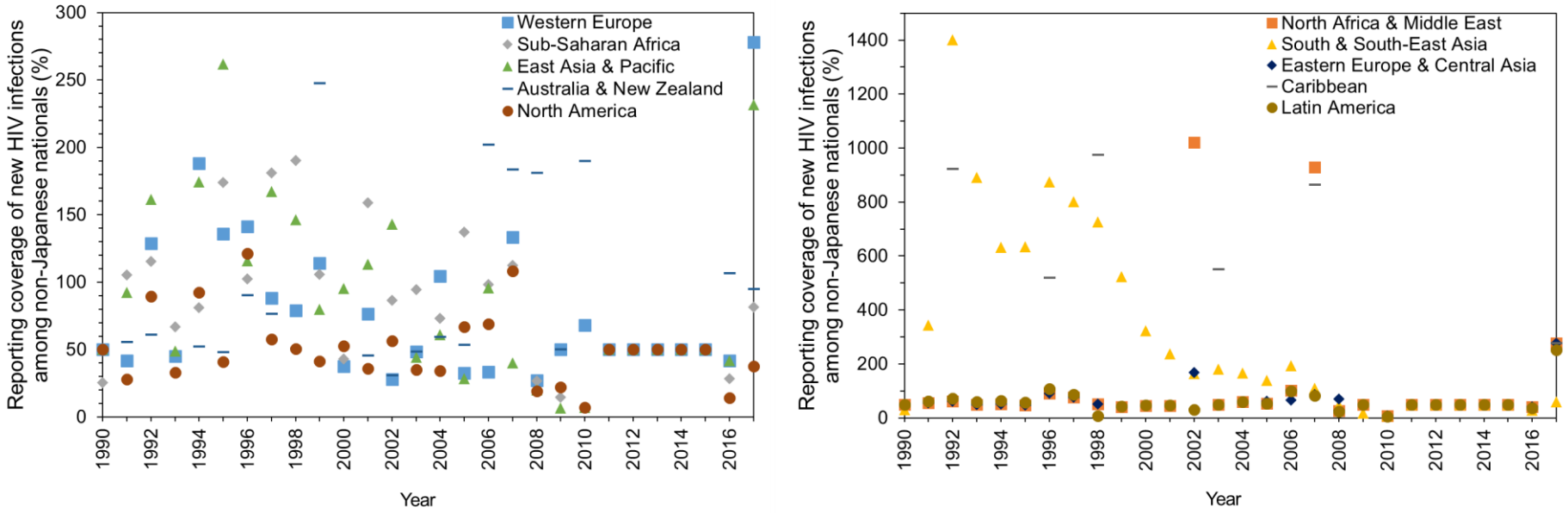

Figure 11. Reporting coverage of new HIV infections among foreign residents in Japan by region (parameter $1/k_1^{**}$).

Reporting coverage of HIV infections among foreign residents in Japan, 1990–2017, estimated from the sensitivity analysis. Two panels are shown because of varying estimates.

(A) People from Western Europe, Sub-Saharan Africa, East Asia and Pacific, Australia and New Zealand, and North America.

(B) People from North Africa and Middle East, South and South-East Asia, Eastern Europe and Central Asia, Caribbean, and Latin America.

The diagnosed proportion of PLWHA among foreign residents in Japan over time, is shown (parameter $1/k_2^{**}$), estimated as part of the sensitivity analysis, is shown in Figure 12. Foreign residents from Western Europe, Eastern Europe and Central Asia, and North America appear to have mostly recorded below 100%. Australia and New Zealand transitioned below 100% in 1990–1999 and 2002–2007, followed by a small increase to above 100% in 2008. Although the estimates were above 100% in East Asia and Pacific between 1995 and 2008, the proportions have decreased to below 100% afterwards. North Africa and Middle East, Sub-Saharan Africa, and South and South-East Asia, are classified into an over-reported group (Figure 12B). An overestimation of over 1,000% was calculated in the South and South-East Asia region in 1996-1998. A rising trend of the proportion for those from Latin America began in 2011, reaching 830% in 2016 (Figure 12B).

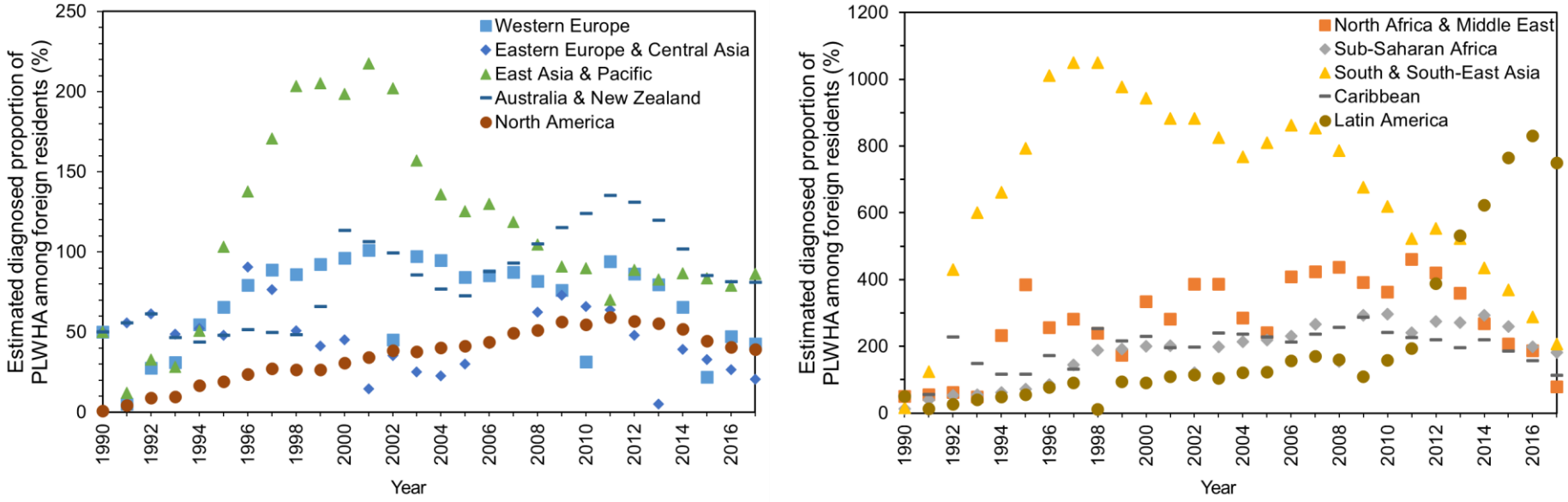

Figure 12. Diagnosed proportion of PLWHA among foreign residents in Japan by region (parameter $1/k_2^{**}$).

Estimates of the proportion of diagnosed infections out of the cumulative number of HIV infections and AIDS cases among foreign residents in Japan, 1990–2017, estimated from the sensitivity analysis. Two panels are shown because of varying estimates.

(A) People from Western Europe, Eastern Europe and Central Asia, East Asia and Pacific, Australia and New Zealand, and North America.

(B) People from North Africa and Middle East, Sub-Saharan Africa, South and South-East Asia, Caribbean, and Latin America.

4. Discussion

4.1. Findings from the modeling study

This study could provide estimates of the diagnosed proportion of HIV incidence and PLWHA among foreign residents in Japan between 1990 and 2017 by employing a balance equation modeling approach and assuming that the risk of HIV infection among foreign residents was identical to the population average of the risk calculated based on their country of origin. Key estimates of the diagnosed proportion were denoted as a parameter through maximum likelihood estimation. It was revealed that the diagnosed proportion varied widely by geographic region of the country of origin, and people from Western Europe, East Asia and Pacific, Australia and New Zealand, and North America tended to be underdiagnosed. Although there has been an improving trend of an overall diagnosed proportion of PLWHA among foreign residents in Japan, the estimate in 2017 was as low as 55.3%, which was far from satisfying the 90% target declared by UNAIDS (UNAIDS, 2017).

In the context of Japan, this is the first study to estimate statistically the diagnosed proportion of HIV infections and PLWHA among foreign residents. Three important findings must be extracted. First, the first 90 of the UNAIDS 90–90–90 target seemed to be far from satisfied among foreign residents in Japan, which recorded much lower compared to the assumed proportion of around 80% among the Japanese (Iwamoto et al., 2017; Nishiura, 2019), indicating a need to investigate their underlying mechanisms. Second, although the lower diagnosed proportion is concerning, it has gradually improved and exceeded 50% since 2012. Third, the estimated diagnosed proportion of PLWHA among foreign residents varied greatly by the geographic regions of their country of origin. The estimated number of PLWHA demonstrated that people from South and South-East Asia were more likely to be diagnosed with HIV infection compared to other groups, and residents from Sub-Saharan Africa and Latin America tended to be more effectively diagnosed with HIV rather than those from other regions. On the contrary, residents from higher-income countries where the HIV prevalence is low, such as Western Europe, Australia and New Zealand, and North America, tended to be relatively underdiagnosed. As a matter of course, varying estimates may not only reflect different rates of diagnosis but also indicate

heterogeneous characteristics of residents that hold several groups that are recognized as at risk.

Besides, these characteristics were mainly followed in the sensitivity analysis that aimed at addressing differences of person-time at risk between countries and by years. Yet, different trends of the estimates were partly observed among people from Eastern Europe and Central Asia, and East Asia and Pacific. The former was mainly due to weighting of several countries in the region, especially Russia, Ukraine and Romania. For the latter, although the estimated diagnosed proportion of PLWHA remained less than 100% after 2009, the relatively higher estimates were presented in the sensitivity analysis. Despite the weighting of countries in East Asia, such as China and Republic of Korea, where the travel volume with Japan was higher compared to other countries and territories in the region, the overestimation of the involvement in Pacific Island countries might result in the lower value of right side of the equation and bring higher estimates of the diagnosed proportion of PLWHA, implying the necessity of a more robust method on how to handle data in small countries and regions.

4.2. Challenges in HIV/AIDS among foreign residents

Numerous challenges around HIV/AIDS among foreign residents are widely acknowledged in Western Europe and the United States. The major characteristics of foreign residents who live in high-income countries with a low HIV prevalence include the relatively higher incidence of HIV diagnoses and late presentation (Hernando et al., 2015; Deen et al., 2018). A higher rate of HIV diagnoses was reported among foreign residents from countries with a high prevalence of HIV, as represented by the Sub-Saharan Africa region (Pottie et al., 2007; Redditt et al., 2015; The Lancet Global Health, 2016), and it was recognized that the transmission of HIV can be driven by the movement of high-risk individuals across geographic areas with completely different HIV prevalence (Cheong et al., 2014). However, recently, there has been an increasing proportion of new HIV diagnoses among foreign residents from low-prevalence countries in Europe (Hernando et al., 2015; ECDC, 2017). Moreover, acquiring HIV infection after migration has recently been captured as one of the public health agendas, both in the setting of high-income countries including EU/EEA (Rice

et al., 2012; Desgrées-du-Loû et al., 2015; Fakoya et al., 2015; Alvarez-del Arco et al., 2017; Pannetier et al., 2018) and low-income countries (Olawore et al., 2018), indicating the necessity for targeted interventions in this group. Also, it was reported in Australia that HIV infections with advanced clinical symptoms were mostly observed among migrants from South-East Asia, putting an additional strain on controlling HIV/AIDS (Peach et al., 2018; Gunaratnam et al., 2019).

Although the magnitude estimated from the analysis may seem less substantial, and several uncertainties that were implied from the sensitivity analysis need to be addressed, people from the East Asia region have been considered as an imminent majority of residents for the next decades due to a fairly large population in the region. The decrease in HIV incidence was estimated in East Asian countries; however, an absolute number of new HIV infections in China exceeded 30,000 in 2017 (IHME, 2018), and the geographical proximity to Japan should be noted. Furthermore, it was reported that a substantial risk of infection was posed by several risk groups, such as mobile men with money (Uretsky, 2008; Aggleton et al., 2014) and/or sex tourism, which led to risky sexual behaviors, such as unprotected anal intercourse, forgoing condom use, and other behaviors that increase HIV risk (Richens, 2006; Lau et al., 2012; Berghe et al., 2013), and amplified HIV epidemics at the regional level (Mao et al., 2018). Indeed, through modernization in Asian cities such as Hanoi, Shanghai, and Taipei, considerable changes in sexual behaviors were monitored (Zabin et al., 2009).

It is important to enhance global collaboration in investigating the transmission dynamics of HIV in overreported regions and countries. Simultaneously, it is worth arguing that diagnosed proportions will be heavily affected by available healthcare resources and citizens' access to testing. It is acknowledged that many migrants face barriers to accessing essential health services due to multi-layered determinants of health, which could impair achieving an HIV diagnosis in a timely manner and accessing life-saving treatments (Migrants Working Group on behalf of COHERE in EuroCoord, 2015), and possible factors that impeded the access to testing and treatment must be examined by reflecting on the global debate that ensuring the right to health of foreign nationals and migrant populations, regardless of where they are and live, must be underpinned for the commitment to universal health coverage and

sustainable development goals (Legido-Quigley et al., 2019). In addition to biomedical viewpoints, the root causes of discrimination and stigmatization, which PLWHA face and work as major obstacles for prevention, detection and care, need to be well understood and addressed (Negro Calduch et al., 2008). Simultaneously, while migrants share several challenges, migrants are highly a heterogenous group—conceptualizing all migrants into a single group could potentially hinder the understanding of risks affecting specific groups. The geographic factors, namely, region of origin or country of origin, as well as gender, are recognized as crucial factors for considering social determinants of health and HIV/AIDS among migrants, and there also needs to be consideration for the diversity of risks depending on the groups of transmission. Moreover, clarifying the high-risk populations and analyzing underlying inequalities will be necessary to develop tailored interventions to respond to the needs of each group of migrants (Migrants Working Group on behalf of COHERE in EuroCoord, 2015), which could help ensure that nobody is left behind for an approach of combination prevention (Nöstlinger and Loos, 2018).

4.3. Implications for addressing HIV/AIDS among foreign residents in Japan

Due to globalization, Japan has continuously received an increasing number of foreign residents (Immigration Services Agency of Japan, 2019). However, adapting them to the context of Japan has been a political challenge, because the background of their medical characteristics and risk factors for diseases are widely different from those of the Japanese. Also, foreign migrants tend to experience barriers to accessing essential health services (Norredam et al., 2010). Achieving inclusive healthcare for foreign residents is a strenuous process, as this requires engagement both at the individual and community levels, participatory practices, increased diversity of the health workforce, and ensured competency in planning health policy and implementing its practice (Spitzer et al., 2019). This also needs a deeper understanding of history, sociopolitics, economics and legal contexts and racism depending on responses to diverse groups of foreign residents (Spitzer et al., 2019). There is no magic bullet but a combination of essential measures to combat HIV/AIDS. Even provided that medicalization has been heavily centralized for the response strategy, employing a

range of tailored interventions depending on residents' risk profiles is vital for successful outcomes, which include task shifting to specific foreign sub-populations based on their social, cultural, and traditional norms (Beyrer et al., 2010a; Foster et al., 2010; McMahon and Ward, 2012; Peach et al., 2018), and findings of this study suggest that more tailored approaches depending on the needs of sub-population will be needed for PLWHA among foreign residents in Japan.

With regard to testing and surveillance, it is encouraging that early detection and treatment to improve the prognosis of PLWHA have been recognized and an expansion of getting oral consent from patients has been argued in the latest guidelines (Shimizu, 2021); however, access to HIV testing has still been limited (Hill et al., 2019), and this has been exacerbated by social discrimination against PLWHA (Eguchi et al., 2014). Although various barriers exist, voluntary counselling and HIV testing need to be available to foreign residents for early diagnosis, overcoming HIV-related stigma, and preferable clinical outcomes (Alvarez-del Arco et al., 2013; Esteban-Vasallo et al., 2014; Baggaley et al., 2017; Pottie et al., 2018). Recently, it has been reported that postal HIV testing could be useful for marginalized groups in Japan (Takano et al., 2018), and its applicability to PLWHA among foreign residents could be argued from both biomedical and human rights perspectives while controlling the quality of service with external evaluation. At the same time, the cost-effectiveness of opt-out screening, which was originally considered to eliminate mother-to-child transmission of HIV in high-prevalence settings (Creek et al., 2007), has been reported in settings with low HIV prevalence (Sanders et al., 2005). An opt-out approach was proactively adopted in 2006 in the United States (Branson et al., 2006), and its benefits have already been argued in the United Kingdom (Hamill et al., 2007). The introduction of provider-initiated opt-out HIV screening could be openly discussed, even in Japan, along with a pilot trial. Finally, despite several previous efforts, very little information is available on the key drivers of HIV infection among foreign residents in Japan, such as risk behaviors, testing and treatment rates and its retention, to say nothing of the use of PrEP and/or post-exposure prophylaxis (PEP), along with the latest information. To properly mobilize people for prevention and detection, introducing sentinel surveillance, which is linked with the current reactive surveillance, could be an option.

Now that T as P and U = U have been widely acknowledged, it has been confirmed that early initiation of ART and successful treatment of HIV could reduce and even eliminate the sexual transmission of HIV, yielding both direct and indirect benefits (Cohen et al., 2011; INSIGHT START Study Group, 2015; Cohen et al., 2016; Rodger et al., 2016; Bavinton et al., 2018; Cohen, 2019; Rodger et al., 2019), leaving patients undiagnosed and untreated will pose a risk of secondary transmission of HIV (Kinoshita and Oka, 2018). While there has been progress in recognizing the significance of the early initiation of therapeutic interventions for HIV/AIDS patients in Japan, regardless of their CD4 counts, it takes at least a few months for confirmed cases to start ARTs in Japan due to some regulations (Gilmour et al., 2020). It should be advised that effective curative interventions would not only be useful for preventing new infections and overcoming challenges in ARTs but be beneficial for combatting the stigma and discrimination that PLWHA face, thus lessening the financial burden for long-term care of HIV (Dybul et al., 2021).

To clarify susceptible pockets of health services, grasping the overall scope of PLWHA among foreign residents in Japan will be of utmost importance. However, scant discussion has considered the disaggregated prevalence of PLWHA among foreign residents by nationalities and/or regions of origin (Shimizu, 2021). Considering that there has been no central registry of PLWHA in Japan, and free HIV testing at healthcare facilities is not ensured in outpatient settings, which could bring biased data, assessing the prevalence of PLWHA by free testing in designated settings, and/or establishing clinical cohorts by region could be helpful to kick off the process of continuous monitoring and evaluation of links to HIV care. This will be a beachhead to evaluate whether the diagnosed proportion of PLWHA among foreign residents has reached the UNAIDS cascade and to promote targeted interventions based on risk profiles. Along with these efforts, campaigns in health promotion should also be aimed at eliminating social prejudice and discrimination against PLWHA among foreign residents. In particular, enhancing the capacity of healthcare workers regarding the recognition of HIV/AIDS and mitigating their anxiety and fear for conducting medical examination for foreign residents could help accelerate community engagement (Shimizu, 2021). The historical global response to HIV/AIDS clearly indicates that political leadership, mobilization of civil society and PLWHA themselves, and multisectoral collaboration and sector-wide partnerships, are pivotal not just for

containing the HIV epidemic but for upholding human rights and combatting against discrimination and social stigma (Piot et al., 2015; Dehne et al., 2016). Addressing structural inequalities and exploring the detailed social determinants of health among PLWHA in Japan is important, and PLWHA who are foreign nationals is no exception. As highlighted in the latest guidelines, healthcare services, including HIV testing, should be ensured for foreign residents with HIV/AIDS by mapping existing resources in public health, including public health centers, and mobilizing and building partnerships with non-governmental organizations (Shimizu, 2021).

4.4. Limitations

The present study has some limitations. First, the modeling approach was premised on a balance equation, which ignored the detailed information of human mobility and instead used the average values by nationality. However, the risk profile of HIV is acknowledged as heterogeneous, and it is expected that there is geographic heterogeneity in the risk of infection in Japan. Besides, the cumulative incidence data of infectious diseases have been typically used for the balance equation model (Lipsitch et al., 2009; Dorigatti et al., 2017; Tsuzuki et al., 2017; Akhmetzhanov et al., 2021), and in line with these previous studies, the principle of its modeling method was followed. While applying the cumulative data of HIV diagnoses and AIDS cases to the model would be unequivocal, the applicability and challenges of the method for data in newly reported HIV infections could be considered further, with additional epidemiological parameters. Second, the estimated number of PLWHA may considerably differ from the actual number. The natural mortality was ignored, and the calculation of PLWHA was almost equivalent to the cumulative incidence of HIV infection. Also, foreigners were sometimes triggered to leave the country after the identification of HIV infection and/or the onset of AIDS-related illnesses; however, due to a lack of sufficient empirical datasets that could explicitly quantify the processes of migration of foreign residents with their purposes, it was challenging to consider these components, which might bring an overestimation of the actual number of PLWHA over the years. Incorporating their involvement will be helpful to consider transmission dynamics, which needs to be prudently conducted (Nishiura, 2019). Third, epidemiological surveillance data of HIV/AIDS spanning 1990–2017, on which the

study relied, did not present data that are specific to countries. Instead, the data classified the countries of origin into ten regions. Moreover, the present surveillance did not consistently pursue nationality data, especially for 2011–2015. A substantial number of “unknown” nationalities were included in the empirical data. Although data collection seemed to be restarted in 2016, 82.8% (140/169) in 2016 and 42.9% (84/196) in 2017 of HIV diagnoses among foreign residents were still reported as of “unknown” nationality. While additional sensitivity analyses tried to overcome this challenge moderately, it could not be fully excluded that the trends presented in this study were, to some extent, driven by a small number of countries in specific years. Further discussions on the challenges in handling data and weighting of countries and regions will be helpful, especially in the context of East Asia and pacific. Disclosure of the nationality information will definitely bring better analysis. Fourth, the balance equation absolutely assumed that the risk of infection was determined by the risk in the country of origin among residents, which ignored possible new infections in Japan. This might contradict the documented evidence (Rice et al., 2012; Alvarez-del Arco et al., 2013; Fakoya et al., 2015; Valverde et al., 2017). Fifth, as described in the methods, temporary visitors were included in the analysis. While this conceptualization would be defended by the reported heterogeneity of HIV transmission, additional discussion and clarification on their roles in transmission dynamics will be warranted to elaborate further. As HIV/AIDS has been recognized as a chronic disease that is treatable and manageable, primarily focusing on the migration data of the long-term residents (i.e., holders of residence card) could be useful. Nevertheless, pitfalls in this approach need to be fairly argued beforehand. Indeed, the upward trend of the estimated diagnosed proportions of PLWHA were observed in Latin America from 2009 to 2016, which was contrary to trends in other regions. It has been clarified that this change was mainly brought by the consistent decline of person-time at risk in Latin America region during the period, which was majorly caused by the significant decline in their average length of stay in Japan. To eliminate these challenges, selecting targeted countries and reconstructing the dynamics of foreign residents in detail would be considered (Nishiura and Inaba, 2011; Ejima et al., 2014; Anzai et al., 2020). Nonetheless, to precisely employ this approach, improved HIV surveillance data that include nationality will be warranted. Sixth, which is partly related to the previous point, more detailed information in age, sex, history of education, socioeconomic status, language, country of origin, and purpose of migration will be necessary to consider the heterogeneity,

namely the diversity of foreign residents (Gill and Krentz, 2015). However, various critical pieces of information, including patients' age at diagnosis, sex, mode of exposure (e.g., heterosexual, homosexual, intravenous drug user, mother-to-child), year of arrival, visa status, and duration of residence were omitted for the analysis due to a lack of linkage in surveillance data.

How to incorporate the data on migration has been a critical research agenda for grasping an overall picture of HIV/AIDS. For example, in Sweden, where, as of the year 2016, migrants from Sub-Saharan Africa accounted for around 40% of newly reported HIV infections, but which has been reported to originate in their countries of origin, an assumption that a similar rate of migration occurs between HIV-infected and uninfected individuals was employed (Andersson et al., 2019). However, estimation of the proportion of undiagnosed PLWHA who were born in foreign countries has been one of the main challenges (Andersson et al., 2019). To address several uncertainties, additional methods for estimation, such as the use of CD4 count data, could be potentially useful (Likatavicius and van de Laar, 2011). For example, in Italy in 2012–2014, the number of undiagnosed PLWHA, who face an immediate necessity for diagnosis, linkage to care and ARTs, has been estimated to be around 15,000 by using the data in the national HIV surveillance system, which includes information on CD4 count in diagnosis (Regine et al., 2018). Moreover, it has been suggested that using the data of CD4 count in diagnosis, combined with data on the known year of arrival, could help in estimating the timing of HIV infection, indicating the need to expand public health response only by ensuring their access to HIV testing to involving them for primary prevention soon after their arrival (Yin et al., 2021). As missing data in migration status and/or CD4 cell count data in diagnosis, as well as reporting delay of data, could bring uncertainties to the analysis (Tavoschi et al., 2017), minimizing them will be crucial. High-quality case-based surveillance data remain the key components for monitoring the disease burden of HIV and evaluating the effectiveness of countermeasures (Likatavicius and van de Laar, 2011; Rosinska et al., 2018), finally bringing a better strategy for containing HIV/AIDS, assisting in validating this study, and enhancing international commitments.

5. Conclusion and Future Prospects

In the present study, the diagnosed proportion of HIV incidence and PLWHA among foreign residents in Japan in 1990–2017 was estimated by using a balance equation modeling approach. The major findings are as follows:

- The diagnosed proportion varied widely by geographic region of the country of origin. People from Western Europe, East Asia and Pacific, Australia and New Zealand, and North America were underdiagnosed.
- The overall diagnosed proportion of PLWHA among foreign residents in Japan has improved over time, but in 2017, it was still as low as 55.3%, which was well below the UNAIDS target of 90%.

While several limitations exist and various uncertainties should be addressed, to the best of the author's knowledge, the present study firstly provided essential perspectives on HIV diagnoses among foreign residents in Japan by using publicly available empirical data. In a globalized world with large-scale human mobility, estimating the diagnosed proportion of HIV infections and PLWHA among foreign residents, as presented in this study, can contribute to support monitoring the HIV prevention strategies at the national level, revising the overall strategy and relevant health policies, mapping available resources for prevention and control efforts (Op de Coul et al., 2015), thus serving as an impetus to ensure better access to testing and care in the future in Japan. Given the findings advocating a critical need to deeply investigate foreign residents, and considering the heterogeneity of HIV transmission as discussed elsewhere (Beyrer et al., 2010b; Baral et al., 2012; Beyrer et al., 2012), scrutinizing nationality data is vital (Foster et al., 2010; McMahon and Ward, 2012; Peach et al., 2018), potentially constituting an important component for establishing an effective tailored approach to PLWHA among foreign residents in Japan in a country-specific manner.

To contain HIV/AIDS, designing effective programs that maximize access to HIV testing, treatment, and care to reduce HIV transmission, as well as the rigorous engagement of political leadership from an early stage, are imperative (Piot et al., 2007). Moreover, to truly construct evidence-based, tailored testing, treatment, and care programs, identifying comprehensive details of risk profiles and critical pieces of

information is pivotal. In line with today's advancements of HIV/AIDS policy in Japan, launching the national HIV registry system and recording various critical pieces of information and characteristics will assist in capturing the transmission dynamics of HIV among foreign residents in Japan, giving opportunities to explore details of HIV/AIDS in Japan quantitatively and qualitatively, and implement a more effective policy that is guided by science.

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Conflict of Interest

The author declares no conflict of interest.

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