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Assessing the trend of HIV/AIDS mortality rate in Asia and North Africa: an application of latent growth models

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SUMMARY

Over the last 30 years, HIV/AIDS has emerged as a major global health challenge. This study evaluates the change of HIV/AIDS mortality rates in Asian and North African countries from 1990 to 2010 using the Global Burden of Disease (GBD) study. HIV/AIDS mortality rates were derived from the GBD database from 1990 to 2010, for 52 countries in Asia and North Africa. First, a Latent Growth Model was employed to assess the change in AIDS mortality rate over time in six different regions of Asia, and also the change in AIDS mortality rate over time for males and females in Asia and North Africa. Finally, Latent Growth Mixture Models (LGMMs) were applied to identify distinct groups in which countries within each group have similar trends over time. Our results showed that increase in mortality rate over time for males is about three times greater than for females. The highest and lowest trend of AIDS mortality rates were observed in South-East Asia and high-income Asia-Pacific regions, respectively. The LGMM allocated most countries in the South and South-East region into two classes with the highest trend of AIDS mortality rates. Although the HIV/AIDS mortality rates are decreasing in some countries and clusters, the general trend in the Asian continent is upwards. Therefore, it is necessary to provide programmes to achieve the goal of access to HIV prevention measures, treatment, care, and support for high-risk groups, especially in countries with a higher trend of AIDS mortality rates.

Key words: GBD study, growth mixture model, HIV/AIDS, latent growth model.

INTRODUCTION

Acquired immune-deficiency syndrome (AIDS) is a disease caused by the human immunodeficiency virus (HIV). AIDS is a syndrome which appears in advanced stages of HIV infection. Both the virus and the disease are often referred to together as HIV/AIDS. The illness alters the immune system, making people much more vulnerable to infections and diseases. Since the beginning of the epidemic, almost 75 million people have been infected with HIV and about 36 million people have died from HIV around the world. Globally, the number of people living with HIV rose from around 8 million in 1990 to 34 million by the end of 2011 [1]. According to the WHO, the annual number of people dying from AIDS-related causes worldwide has been steadily decreasing from a peak of 2·3 million in 2005 to an estimated 1·6 million in 2012 [2, 3].

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In the early- to mid-1980s, while other parts of the world were beginning to deal with serious HIV and AIDS epidemics, Asia remained relatively unaffected. By the early 1990s, however, AIDS epidemics had emerged in several Asian countries and by the end of the decade HIV was spreading rapidly in many areas of the continent. Almost 5 million people are living with HIV in South, East and South-East Asia [4]. Of these, 2–3 million are estimated to be in South Asia [5]. The WHO has claimed that AIDS-related mortality began to decline in 2004–2005 in South and South-East Asia [2]. In South-East Asia, the estimated number of new infections declined by 34% from 2001 to 2010 [1]. Conversely, the number of people living with HIV in Central Asia has more than tripled since 2000. In Central Asia, around 92 000 people died from AIDS-related illnesses; there was a 21% increase in AIDS-related mortality between 2005 and 2011 [6]. In the Middle East and North Asia there were about 39 000 AIDS-related deaths and this figure almost doubled between 2001 and 2012, while it declined by 16% worldwide [7, 8]. In the Asian continent as a whole, there is no single 'Asian epidemic'; each country in the region faces a different situation and there are great variations within different countries. Therefore, it is necessary to investigate every region separately and determine clusters of countries with similar trends. Longitudinal data are necessary to assess the trends. Various statistical methods have been developed for longitudinal data analysis, such as random effects, marginal and transition models. Compared to other models for assessing the trend in longitudinal data, Latent Growth Models (LGMs) are more complicated approaches that can readily include latent variables in the modelling process to handle multiple outcome growth trends. Our literature review showed that there are numerous published papers about the prevalence and mortality rates of AIDS in Asian and North African countries. However, we were unable to find any paper about assessing the trend of AIDS mortality rates in the previous decade in these countries. Thus, we decided to conduct this study in order to identify the trend of AIDS mortality rates in six regions of Asia and North Africa during 1990–2010, using data from the Global Burden of Disease study's (GBD) mortality database. In this study we also use growth mixture models (GMMs) to classify these countries according their AIDS mortality rate trend during the study period.

MATERIAL AND METHODS

Database used in the study

Data on HIV/AIDS mortality were compiled from the GBD database according to a list of countries in Asia and North Africa. The information includes mortality rate due to HIV/AIDS in 52 countries, from 1990 to 2010 (in 5-year intervals). We initially considered six areas which were classified by the GBD: East Asia, South Asia, Central Asia, high-income Asia Pacific, Middle East, and South-East Asia. The regions include all the countries designated by the GBD study. The mortality rates (per 100 000) due to AIDS for each country, as well as mortality rates for both genders were considered as the main outcome of the study. The GBD study compiles causes of mortality and disability and computes the number and proportion of disability-adjusted life-years (DALYs) lost to individual conditions, the proportion of total DALYs lost, the percentage of mortality attributable to the condition and the proportion of global mortality and disability due to the condition that occur in each country. More details about the GBD study and the data can be found elsewhere [4]. Mplus software, version 6.0 (www.statmodel.com), was used for fitting the models.

Statistical approaches

Assessing the trend by the LGM

The LGM assumes outcome growth trajectory over time is captured by continuous latent variables and can be described by the following equations:

$$y_{ti} = \eta_{oi} + \eta_{1i}\lambda_t + \varepsilon_{ti},$$
$$\eta_{0i} = \eta_0 + \varepsilon_{oi},$$
$$\eta_{1i} = \eta_1 + \varepsilon_{1i},$$

where η_0 represents the estimated overall mean level of the initial outcome, and η_1 is the average rate of outcome change over time [9]. The LGM assumes that all individuals in the sample have a similar trend over time.

To show the rate of AIDS mortality change over time in the six regions of Asia and North Africa, we employed a LGM for countries within each region. Moreover, this model was applied to determine the trend of AIDS mortality rates in all of the 52 countries, separately for males and females.

Clustering countries by GMMs

LGMs can be extended to GMMs taking into account heterogeneity in growth trajectories. GMMs are often

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Table 1. *AIDS mortality rates (per 100 000) and estimates from the Latent Growth Models (LGMs) by Global Burden of Disease study regions*

Region	Gender	Year					LGM estimate
		1990	1995	2000	2005	2010	
East Asia	Male	1·76	13·06	70·28	137·52	177·45	—
	Female	0·01	0·09	0·64	1·21	1·59	
South Asia	Male	0·86	3·29	9·92	16·75	16·17	Intercept: 0·36
	Female	0·22	1·02	3·44	6·33	6·50	Slope: 1·07
Central Asia	Male	0·39	1·20	2·70	5·40	7·50	Intercept: 0·53
	Female	0·16	0·43	1·14	2·67	4·32	Slope: 0·66
High-income Asia Pacific	Male	0·52	0·52	0·39	0·50	0·56	Intercept: 0·68
	Female	0·24	0·19	0·13	0·18	0·20	Slope: 0·03
Middle East and North Africa	Male	0·24	0·46	1·07	2·00	2·26	Intercept: 0·41
	Female	0·16	0·33	0·52	0·70	0·83	Slope: 0·30
South-East Asia	Male	1·19	8·72	17·36	19·00	17·59	Intercept: 1·06
	Female	0·78	5·13	9·15	8·56	7·22	Slope: 5·74
Total	Male	0·84	2·89	5·35	6·16	6·09	Intercept: 0·78 Slope:1·91
	Female	0·45	1·56	2·83	3·23	3·07	Intercept: 0·37 Slope: 0·60

used to determine if subgroups exist within the population that follow similar trends over time. Therefore, GMMs accommodate population heterogeneity in outcome growth by classifying individuals into different trajectory classes.

Like the LGM model, the GMM uses similar notation. The GMM utilizes the following equations for specifying each of the K latent classes:

$$y_{it}^{k} = \eta_{i0}^{k} + \eta_{i1}^{k}\lambda_{t}^{k} + \varepsilon_{it}^{k},$$
$$\eta_{i0}^{k} = \eta_{00}^{k} + \sum_{j}\beta_{01j}^{k}X_{j} + \varepsilon_{i0}^{k},$$
$$\eta_{i1}^{k} = \eta_{10}^{k} + \sum_{j}\beta_{11j}^{k}x_{j+}\varepsilon_{i1}^{k},$$

where η_{00}^{k} represents the estimated overall mean level of the initial outcome in the kth class, and η_{10}^{k} is the average rate of outcome change over time for the kth class. In the next section, we apply the GMM to identify subgroups with similar trends of AIDS mortality over the study period.

RESULTS

In general, 52 Asian and North Africa countries were studied. As mentioned earlier, AIDS mortality rates per 100 000 were considered for each country for 1990–2010 (in 5-year intervals).

Table 1 shows the descriptive statistics of AIDS mortality rate as well as estimates from the LGM by sex in different GBD regions. These rates reveal that the AIDS mortality rate had an increasing trend over this period of time. The raw mortality rates in Table 1 reveal that East Asia (for males) and South Asia (for females) had the highest, and the high-income and the Pacific countries had the lowest AIDS mortality rate during these years. The LGM estimate column in Table 1 shows the obtained result from fitting the LGM to these data. The estimates can be interpreted based on both the intercepts and slopes.

Both the estimated intercepts and slopes can help to reveal more about mortality trends in these regions. For instance, the estimates for high-income Asia Pacific (intercept = 0·68, slope = 0·03) state that the initial AIDS mortality rate in this region was 0·68% (in 1990) and the mortality rate has a stable trend with a slope of 0·03 during 1990–2010. In the other regions, there were increasing trends in AIDS mortality rate. The highest and the lowest increase in the AIDS mortality rate was observed in the South-East and the Middle East, respectively. The LGM could not be fitted for the East Asian countries, because of small sample size in this region (three countries).

The last row (total row) of Table 1 gives information on the intercept and trend of mortality rates, separately for all Asian males and females. Regarding this, it can be concluded that initial mortality rate in men was about twofold greater than in women

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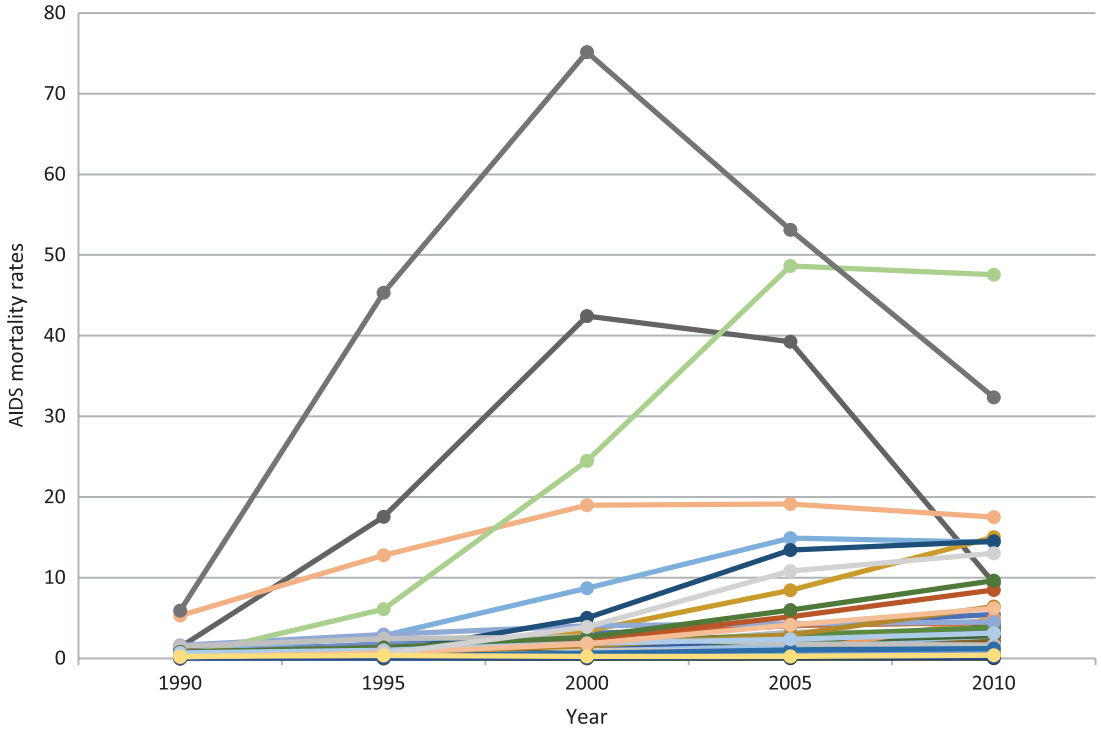

Fig. 1. AIDS mortality rate trajectories of 52 Asian and North Africa countries.

(0·78 *vs.* 0·37). In addition, the trend of mortality rate in men was about three times that of women (1·9 *vs.* 0·6).

Figure 1 displays the growth trajectories for 52 countries (each line shows mortality rate trend over time for each country). Apparently, these trajectories show different trends for these countries; thus, we utilized the GMM to classify the countries according to their mortality trend over time.

The goodness-of-fit indices of models under comparison (classes 1–6) was summarized (not shown here) and solutions showed that the 5-class model was the best choice. Linear growth trajectories were specified for classes 1, 2 and 4 (time score 1, 2, 3, 4, 5), and nonlinear growth trajectories were specified for classes 3, and 5 (free time scores were specified). Table 2 shows the results of fitting this latent GMM. According to these results, countries were classified into five classes with different mortality intercepts and trends. The entropy statistics of 0·89 showed good quality for latent class membership classification. Figure 2 shows latent growth trajectories for five classes obtained from GMMs.

Classes 1 and 2 can be defined as having a slow and moderate increase in AIDS mortality over time, respectively. Countries in class 3 had a steeper trend of AIDS mortality over time until 2005, but they reached a fixed trend during 2005–2010. Additionally, there was a stable trend over time in countries in class 4. Countries in class 5 had a sharp increase from 1990 to 2000, so they experienced a marked decreasing trend from 2000 to 2010.

In classes 3 and 5, the obtained estimates in Table 2 can be interpreted regarding the specified free time scores. In class 3, for example, the difference in time scores between 1990 and 1995 is 4; as such the change in AIDS mortality rates would be slope*4 = 0·49*4 = 1·96, from 1990 to 1995. As another example in class 5, the difference in time scores between 2000 and 2005 is −10·3; so the change of AIDS mortality rate would be slope*(−10·3) = 0·98*(−10·3) = −10·09, which represents a decreasing trend over this period of time.

DISCUSSION

HIV/AIDS is an important health problem with an increasing trend of prevalence and mortality rates in many countries of Asia and North Africa. In the present study, the result obtained from LGM showed a positive slope of 1·69 for the total of Asian and North Africa countries. This result is worrying, because it means that the AIDS mortality rate increases (on average) about 1·7% every 5 years in this region. Since this increasing trend could not be generalized to all Asia and North Africa, and regions may have

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Table 2. *Results of growth mixture models for clustering of Asian and North African countries based on AIDS mortality rate*

Parameter	Class 1*	Class 2†	Class 3‡	Class 4§	Class 5‖
Intercept	0·247	0·509	0·468	0·689	4·264
Slope	0·188	0·631	0·492	0·022	0·98
Time scores	(0, 1, 2, 3, 4)	(0, 1, 2, 3, 4)	0, 4, 15·4, 30·2, 29·7)	(0, 1, 2, 3, 4)	(0, 22, 42, 31·7, 14·5)

* Afghanistan, Algeria, Azerbaijan, Bangladesh, Egypt, Indonesia, Iraq, Jordan, Kuwait, Laos, Lebanon, Libya, Maldives, Mongolia, Oman, Pakistan, Palestine, Philippines, Qatar, Saudi Arabia, Singapore, Sri Lanka, Syria, Tunisia, Turkey, United Arab Emirates, Yemen.
† Armenia, Bahrain, China, Georgia, Iran, Israel, Kyrgyzstan, Morocco, North Korea, Taiwan, Uzbekistan.
‡ India, Kazakhstan, Myanmar, Nepal, Vietnam.
§ Bhutan, Brunei, Japan, Oman, South Korea, Tajikistan, Turkmenistan.
‖ Cambodia, Malaysia, Thailand.

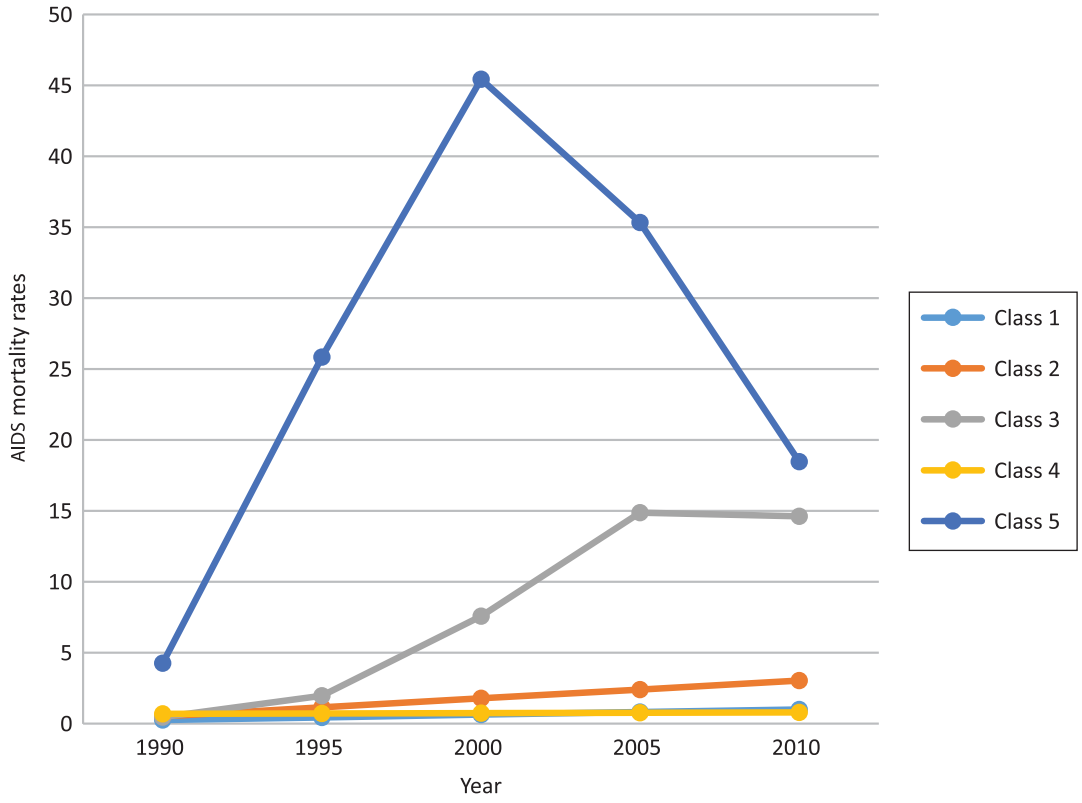

Fig. 2. Estimated trends from the latent growth mixture model.

different trends of AIDS mortality rates, the use of appropriate statistical methods is necessary to cluster these countries according their trends over time. Growth models were used to characterize the trend of AIDS mortality rate during 1900–2010 for two genders and for different regions. Our results showed a gender-based growth in the mortality rate of AIDS. This result is not surprising. The higher level of AIDS mortality rate in men compared to women is because HIV predominates among men. About 64% of people living with HIV are men [10]. The higher prevalence of AIDS in men may be justified by reasons such as: men have a higher risk of being a client of sex workers, injecting drugs and having sex with other men. It is noteworthy that the incidence of HIV in men who have sex with men has increased in some Asian countries and this mode of transmission is a major contributor to the HIV epidemics, due to the criminalization of male-to-male sex, there are no legal safeguards for men who have sex with men and

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transgender people [10, 11]. In the different regions of Asia and North Africa, the highest increase in AIDS mortality rate was revealed respectively in East, South East and South Asia, according to our analysis. Some reasons can be viewed as the main causes for this high level of mortality rates in this region; first, South East countries are the destination of many travellers for sex tourism. The prevalence of sexually transmitted infections in this region is unacceptably high, particularly in men who have sex with men and transgender people [1]. As mentioned before, injecting drug use is one of the most important causes of AIDS throughout the world. High prevalence of injecting drug use in this region may be the second reason for greater increase in AIDS mortality rates [1]. In addition to the factors mentioned above, labour migrants and truckers represent high-risk groups in this region, because they are clients of sex workers in their own country and abroad [12–14]. Here, it should be noted that despite high mortality rates of AIDS in South and South-East Asia, there are some countries such as Cambodia, Malaysia and Thailand with a substantial decline in AIDS mortality rates in the new century. To decrease the prevalence of sexually transmitted HIV/AIDS, which is the most important mode of HIV transmission, it is necessary to present better services to train prevention practices, voluntary counselling and testing, receiving care, support and treatment including antiretroviral therapy (ART), especially for men who have sex with men [15]. In the Middle East and North Africa (which includes Muslim countries), although the prevalence of HIV is lower than in many parts of Asia and North Africa, an increasing trend of 0·3% was observed in AIDS mortality rates during 1990–2010. One of the reasons for this increasing rate may be that these regions have the lowest treatment coverage and management of HIV in the world [16]. On average, across the Middle East and North Africa, only one in five people in need of therapy receive the medicines they need – the lowest coverage rate in world regions [16]. Between 2001 and 2012, the annual number of AIDS-related mortality in the region more than doubled, while the worldwide number dropped by 16% [7].

Our results also show that Asia Pacific and high-income countries had stable mortality rates during this time. Recent researches have shown that there are associations between country-income level and the AIDS mortality rate. Improved immunological programmes have reduced mortality in patients with HIV infection and a reduction of 70% in the risk of dying from AIDS was reported in the Asia-Pacific region between 1999 and 2007 [17].

Class 1 which mostly includes West Asian and North African (Middle East) Muslim countries had a mildly upward trend by 0·188% during the study period. Religion may be the cause of slow growth in this class. Some cultural practices including child marriage, polygamy, prohibitions against condom use, gender inequalities stemming from the low status of girls and women in the family and society, and hindrance of political, economic, and social development may exacerbate the spread of HIV in some Muslim countries [7]. Countries allocated to class 2 had a rather sharply increasing trend of 0·63% in AIDS mortality rates. These countries could not be assigned to a specific geographical area, so it is difficult to have a general discussion about this increment in this class. For instance, in our country (Islamic republic of Iran) because of religious and cultural beliefs, people do not have good attitude about AIDS, so patients are generally forced to hide their disease. In addition, there are no adequate training programmes in Iranian schools about AIDS and the preventive methods of this disease. Class 3 consists of the South and South-East Asian countries (except Kazakhstan) which had an upward trend until 2005 and then remained steady during 2005–2010. This steady trend from 2005 may be due to the significant increase in people receiving ART and promoting the level of knowledge about this disease in this region. Class 5 consists of three South-East countries (Cambodia, Malaysia, Thailand) which had a very sharp increase from 1990 to 2003 and then had a significant decrease in mortality rate. Preventive programmes may be the most important reason for this recent downward trend in the AIDS mortality rate in this class. The reports for these countries show a 25% decline in HIV prevalence between 2001 and 2011. Cambodia has 94% coverage and Thailand has reached coverage levels >50% and has achieved universal access under the 2010 WHO treatment guidelines criteria [18]. However, preventive programmes received nearly 8% of the national HIV/AIDS budget in 2000 and this has increased to only 13% in 2011.

Class 4 which mostly includes high-income Asia Pacific and central countries of Asia had no significant trend with a small slope over time. The upward trend in AIDS cases is rare for a high-income country, given modern medical breakthroughs in halting the disease's progression from HIV to AIDS. Regarding this,

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AIDS case reports and AIDS mortality have been markedly reduced in industrialized countries with the introduction of ART. Although, South Korea has maintained a low prevalence of HIV/AIDS, the government strategy was to define high-risk groups and provide HIV testing among them, i.e. sex workers, homosexuals, workers who had contact with soldiers from the US army. Then, HIV-positive individuals were placed under the government's special monitoring and surveillance programme [19, 20]. Until 1994, there were few cases of HIV infection in the countries of Central Asia. Their traditional and rural society may be the cause of the slow growth in this region. However, the disease is now spreading in this region more rapidly than in many other parts of the world [21]. In all of these countries (except for Kyrgyzstan), the national law on HIV was adopted ('On Prevention of AIDS' in 1990); it contains very broad provisions on compulsory HIV testing. This law also contained general provisions on the rights of people living with HIV in relation to care, treatment and support [21]. This may exacerbate the controlled trend of the AIDS mortality rate in this region. HIV/AIDS in Bhutan remains a relatively rare disease among the Buddhist population. In addition, in 1988, 5 years before the first HIV infection was detected in the country, the Royal Government established a National HIV/AIDS and STD Control Programme (NACP).

In a longitudinal data analysis, where subjects are followed up over time with repeated measures of each variable of interest, heterogeneity may exist in growth trajectories. Therefore, it is necessary to use approaches that handle multiple outcome growth processes and take into account heterogeneity in trend over time. Latent growth modelling approaches have been increasingly recognized for their usefulness in identifying homogeneous subgroups within the larger heterogeneous population and determining meaningful groups or classes of individuals [22]. Here, we highlight this key point, i.e. that defined classes based on these models may be better than classification based on other features such as geographical classification, which is implemented in the GBD study. Reporting of AIDS mortality rates vary substantially from country to country and low reporting rates in developing countries may be due to weaknesses in the healthcare and epidemiological systems. In the present study, we found that economic patterns had a strong effect on reducing AIDS mortality rate, and industrialized and high-income countries had a low rate of AIDS mortality. In addition, due to the growing trend of AIDS mortality in countries such as Middle Eastern countries, these countries need to develop more efficient training programmes and change their attitude towards HIV/AIDS. Moreover, basic programmes are necessary for HIV prevention, control, treatment, care, and support in high-risk groups. Finally, HIV prevention strategies depend on the twin efforts of care and support for those living with HIV or AIDS, and targeted prevention for all people at risk or vulnerable to the infection.

This study encountered important limitations such as low sample size in some regions and small number of repetitions during years. Lack of accurate and reliable data for AIDS mortality rate in some countries may be considered as another limitation of the present study. This limitation makes it necessary for GBD to report an estimated mortality rate for some diseases like AIDS.

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DECLARATION OF INTEREST

None.

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