International comparison of trends in patients commencing renal replacement therapy by primary renal disease

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Abstract

Aim: To examine international time trends in the incidence of renal replacement therapy (RRT) for end-stage renal disease (ESRD) by primary renal disease (PRD).

Methods: Renal registries reporting on patients starting RRT per million population for ESRD by PRD from 2005 to 2014, were identified by internet search and literature review. The average annual percentage change (AAPC) with a 95% confidence interval (CI) of the time trends was computed using Joinpoint regression.

Results: There was a significant decrease in the incidence of RRT for ESRD due to diabetes mellitus (DM) in Europe (AAPC=-0.9; 95%CI-1.3;-0.5) and to hypertension/renal vascular disease (HT/RVD) in Australia (AAPC=-1.8; 95%CI-3.3;-0.3), Canada (AAPC=-2.9; 95%CI-4.4;-1.5) and Europe (AAPC=-1.1; 95%CI-2.1;-

0.0). A decrease or stabilization was observed for glomerulonephritis in all regions and for autosomal dominant polycystic kidney disease (ADPKD) in all regions except for Malaysia and the Republic of Korea. An increase of 5.2% to 16.3% was observed for DM, HT/RVD and ADPKD in Malaysia and the Republic of Korea.

Conclusion: Large international differences exist in the trends in incidence of RRT by primary renal disease. Mapping of these international trends is the first step in defining the causes and successful preventative measures of CKD.

Introduction

The number of adult patients commencing renal replacement therapy (RRT) for end-stage renal disease (ESRD) varies considerably around the world, with the lowest 2014 incidence rates in Bangladesh (49 pmp), Iceland (58 pmp) and Russia (60 pmp) and the highest rates in Taiwan (455 pmp), the Jalisco region of Mexico (421 pmp) and the United States (US) (370 pmp).[1] In the majority of high-income countries the incidence of RRT for ESRD has remained relatively stable or even declined. [1,2] However, in other countries there has recently been a marked increase in the incidence rate, for example in Thailand, Bangladesh and Russia.[1]

Since 1998, the United States Renal Data System (USRDS) has consistently reported on the worldwide trends in the incidence of patients starting RRT with diabetes mellitus (DM) as their primary cause of ESRD.[3] Multiple renal registries around the world publish annual data not only on DM as primary renal disease (PRD) in patients receiving RRT but also on other PRDs, such as hypertension (HT), glomerulonephritis (GN) and autosomal dominant polycystic kidney disease (ADPKD).[1,2,4-13] With exception of DM, no recent international overview of the time trends of PRDs in patients initiating RRT is available. Such information might be useful for identifying successful preventive measures and treatment options for chronic kidney disease (CKD) with the ultimate goal of reducing the number of patients in need of RRT. The aim of this study was therefore to examine the international time trends in the incidence of RRT for ESRD according to different PRDs.

Methods

Identification of renal registries

In order to identify renal registries reporting trends in the number of patients (per million population) starting RRT by PRD we performed 1) an internet search for annual reports of patients commencing RRT

(performed in January 2017) and 2) a literature review via Embase, Medline and Pubmed (performed in January 2017). We included annual reports written in English, German, French and Spanish. The literature review included studies with at least five year time trends since 2005 on patients starting RRT for ESRD including at least three different PRDs. Appendix 1 shows the specific search queries.

The following renal registries were identified: the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry (representing the twenty-one European registries listed below), the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), the United States Renal Data System (USRDS), the Korean Renal Registry (Republic of Korea, i.e. South Korea), the Malaysian Dialysis and Transplant Registry (MDTR), the Canadian Organ Replacement Register (CORR), and the Uruguayan Dialysis Registry.

Primary renal disease

PRDs that were reported by the (majority of) registries were included and classified as DM (combined type 1 and 2 DM), hypertension and renal vascular disease (combined – hereafter referred to as HT/RVD), GN, ADPKD, and unknown or missing PRD (combined) (Table 1). The category "other PRDs" is defined as the total incidence of RRT minus the incidence of RRT for ESRD due to the PRDs that were reported by the renal registries (DM, HT/RVD, GN, ADPKD) and as unknown/missing.

Incidence rate

The incidence rate was defined as the number of patients initiating the first RRT for ESRD in one year, and was expressed per million population (pmp) of that year. All respective renal registries reported the unadjusted incidence pmp for each year during in the study period, with the exception of ANZDATA and MDTR that only provided absolute numbers. For these two renal registries the unadjusted incidence rates were manually computed using general population data obtained from the website of Worldometers (http://www.worldometers.info/world-population). The Malaysian Dialysis and

Transplant Registry did not include data on paediatric patients. The USRDS and the Malaysian Dialysis and Transplant Registry collect data at day 91 after commencing RRT. Pre-emptive transplantation numbers were not included for the renal registries of Canada, Malaysia and Uruguay. We were unable to obtain information on whether the Korean Renal Registry includes data on paediatric patients and whether the data presented relate to patients at day 1 or day 91 of RRT.

Using the ERA-EDTA Registry database we combined the unadjusted incidence rates of the following twenty-one national or regional renal registries providing individual patient data to the ERA–EDTA Registry from January 1st 2005 to December 31st 2014: Austria, Denmark, Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, the Netherlands, the regional registries of Dutch- and French-speaking Belgium, and the Spanish regional registries of Andalusia, Aragon, Asturias, Basque, Cantabria, Castile-La Mancha, Castile and León, Catalonia, Extremadura, and Valencian region. The renal registries of Dutch- and French-speaking Belgium, Cantabria and Castile-La Mancha do not include paediatric RRT data.

All included renal registries had (almost) 100% coverage of the general population throughout the study period.

Statistical analysis

The average annual percentage change (AAPC) was computed with 95% confidence interval (CI) of the time trends on all patients initiating RRT for ESRD by country and by PRD using Poisson regression provided by the Joinpoint regression program [14]. Details of this method have been previously described.[15] All analyses were performed using SAS 9.4 or Joinpoint 4.0.4. A P-value of <0.05 was considered statistically significant.

Results

Figure 1 shows the incidence pmp of RRT for ESRD for the included countries and continents during the period 2005 to 2014, and Figure 2 shows the same data according to PRD (see appendix 2 and 3 for corresponding numbers pmp). Figure 3 (see appendix 4) shows the *percentage* of each PRD of patients starting RRT for ESRD in the same period for the included countries and continents (see appendix 5 for corresponding percentages).

Diabetes mellitus

Throughout the study period the US had the highest incidence rate of RRT for ESRD due to DM (155.6 pmp in 2005 and 163.6 pmp in 2014) (Figure 2a). The incidence of RRT for ESRD due to DM increased in most countries with Malaysia (AAPC 9.0%, 95% CI: 7.6, 10.5) and the Republic of Korea (AAPC 5.9%, 95% CI: 3.3, 8.6) showing the highest average annual percentage change in incidence among all countries throughout the study period. For the Republic of Korea, the increase was especially pronounced from 2010 onwards (AAPC 9.9%, 95% CI: 6.1, 13.9). Within this study period, the incidence rate was stable in New Zealand and in the US. Europe had the lowest number of patients starting RRT with DM as a PRD throughout the study period (32.9 pmp in 2005 and 31.4 pmp in 2014), with the incidence rate decreasing significantly throughout the study period (AAPC -0.9%, 95% CI: -1.3, -0.5). Of note, the incidence did not increase in any of the European countries (when analysed individually).

Hypertension/renal vascular disease

Throughout the study period the US had by far the highest incidence rate of patients starting RRT for ESRD due to HT/RVD (ranging from 96.8 pmp in 2005 to 105.8 pmp in 2014) (Figure 2b). This incidence rate continued to increase during the study period (AAPC 0.9%, 95% CI: 0.5, 1.4). Malaysia and the Republic of Korea showed a much steeper increase in the incidence rate (AAPC 16.3%, 95% CI: 9.5, 23.5 and AAPC 6.5%, 95% CI: 3.9, 6.2, respectively), for Malaysia particularly in the last 5 years (AAPC 26.5%, 95% CI: 13.3, 41.3). By contrast Australia (AAPC -1.8%, 95% CI:-3.3; -0.3), Canada (AAPC -2.9%, 95% CI: -

4.4; -1.3) and Europe (AAPC -1.1%, 95% CI: -2.1, 0.0) showed a significant decrease in the incidence of RRT for ESRD due to HT/RVD.

Glomerulonephritis

The US also had the highest incidence rate of patients starting RRT for ESRD secondary to GN (33.7 pmp in 2005 and 27.9 pmp in 2014) but the difference with other countries was less pronounced (Figure 2c). For all countries included in this study, the incidence rate of RRT for ESRD secondary to GN was either stable (Canada, Malaysia, New Zealand, and Uruguay) or decreasing (Australia, Europe, Republic of Korea and the US) throughout the study period.

ADPKD

In 2005 the incidence of RRT for ESRD secondary to ADPKD was four times lower in Malaysia (1.2 pmp) and three times lower in the Republic of Korea (2.7 pmp) compared to the other countries (between 8 and 9 pmp) (Figure 2d). However, throughout the study period, in both Malaysia (AAPC 7.6%, 95% CI: 5.2, 10.0) and Republic of Korea (AAPC 5.2%, 95% CI: 2.5, 8.0) there was an increase in the incidence rate of patients starting RRT for ESRD due to ADPKD. For the Republic of Korea this increase was especially pronounced after 2010 (AAPC 10.0%, 95% CI: 4.3, 16.1). In all other countries the incidence rates were stable, with exception of the US, the only country to show a significant decrease in the incidence rate (AAPC -1.2%, 95% CI: -1.7, -0.6). It should be noted that Uruguay did not have data on ADPKD as a PRD.

Other primary renal diseases

The incidence rate of RRT for ESRD secondary to all other causes combined was highest in the Republic of Korea and increased significantly in Canada (AAPC 4.8%, 95% CI: 1.8, 8.0), Europe (AAPC 1.4%, 95% CI: 0.8, 2.0) and the Republic of Korea (AAPC 5.1%, 95%CI: 1.3, 9.1)(Figure 2e).

Unknown/missing primary renal diseases

There was a large variation in the incidence of PRD reported as unknown or missing ranging from almost none in Uruguay to more than 50 pmp in 2011 in Malaysia (Figure 2f). Europe was the only region where there was an increase in reports of unknown/missing over time (AAPC 1.1%, 95% CI: 0.4, 1.9).

Discussion

This study provides an overview of recent international trends for the most common PRDs in patients with ESRD starting RRT from countries having the required data in the study period. The results show large variability between the countries and continents, both in incidence rates and in trends. These international differences may have resulted from several causes including the prevalence of risk factors for the different underlying kidney diseases in the general population, the rate of progression to ESRD, and access to RRT.[16] A stabilization of the incidence of RRT might suggest improved success in the prevention or treatment of CKD, thereby avoiding ESRD. On the other hand, especially in low or middle income countries where access to RRT is limited, economic growth may lead to expansion of dialysis services resulting in an apparent increase in the incidence of RRT. We will discuss these three factors in more detail below.

The prevalence of risk factors for CKD

The prevalence of the most important risk factors for CKD in the general population, such as DM, HT, physical inactivity, obesity, salt intake and smoking, varies considerably around the world. Countries or regions with a greater burden of these CKD risk factors may have a higher prevalence of CKD, and a higher incidence of RRT.[17,18]

The rapid economic growth in both Malaysia and the Republic of Korea may have led to a change in lifestyle factors, such as an increase in physical inactivity, smoking and a greater salt intake which could have caused a higher prevalence of DM and HT in the general population.[19,20] It should be noted that compared to the Caucasian population, in general the Asian population are at a higher risk of developing DM and do so at a younger age.[19,21]

The steep increase in the number of patients with RRT for ESRD due to DM in both Malaysia and the Republic of Korea is in line with the substantial rise in the prevalence of DM in the general population in these countries, which in 2014 was estimated to be 9-10%, a percentage similar to that in the US.[20] On the contrary, the significant increase in the number of patients initiating RRT for ESRD due to HT/RVD in Malaysia and the Republic of Korea cannot be explained by a trend in the prevalence of HT in the general population. Both in Malaysia and the Republic of Korea the percentage of HT in the general population remained similar or increased only slightly throughout the study period and was approximately 20% in 2015.[22] It is noteworthy that the prevalence of HT in the general population was previously highest in affluent Western countries like Australia, Canada, Europe, and New Zealand as well as in Uruguay (approximately 40% in 1980), but decreased almost linearly in most of these countries to about 20% in 2015, with differences across countries.[17,22]

Interestingly, within Europe the incidence rate of patients initiating RRT for ESRD due to DM has decreased[2,12,13,23], despite an increasing prevalence of DM in the European general population.[24] It is possible that this decrease is may partly be a consequence of early detection of DM, and, probably even more likely, due to more effective control of glycaemia, proteinuria and blood pressure in patients with DM (see also discussion further below).[25-27]

In many countries, the healthcare authorities have initiated national programmes for the prevention and control of non-communicable diseases like DM and HT.[17,19] By implementing lifestyle measures in the general population, the prevalence of risk factors for ESRD, such as physical inactivity, smoking and high salt intake, can be reduced.[28-31] Moreover, lowering the prevalence of one risk factor for CKD may also

have decreased the prevalence of other CKD risk factors. For example, a decrease in physical inactivity is associated with a decreased prevalence of both HT and cardiovascular disease. So far, none of the existing studies examined the effect of lowering risk factors of ESRD on hard renal outcomes such as the onset of RRT.

In addition, among important causes of CKD are specific kidney diseases, such as various types of GN and ADPKD. The incidence rates of primary GN in the general population differ around the world, but part of these geographical variations can be explained by the rate of differences in diagnosis rather than by genuine differences in disease frequency.[32] ADPKD is a hereditary disease, and therefore the prevalence of ADPKD in the general population is likely to remain more or less similar through the years. Furthermore given that it is likely to affect all ethnic groups equally the prevalence should be similar across countries.[33]

Progression to ESRD

Regardless of the underlying cause, the progression of CKD is almost always a result of either the kidney disease itself, or metabolic factors which may arise from the PRD or risk factors associated with the PRD. According to international guidelines, screening for CKD is strongly recommended in high-risk patients, such as those with DM and/or HT. Nevertheless, the identification of CKD is rather poor in many countries.[34,35] In an Italian study among hypertensive patients, 23% had CKD, but was diagnosed correctly by general practitioners in only 3.9% of cases.[34] Better systems are needed to support timely and accurate CKD identification.[36] A correct CKD diagnosis is a prerequisite for treatment aimed at slowing CKD disease progression, cardiovascular protection, and timely preparation for RRT.[37]

Improved screening, better metabolic control and a reduction in proteinuria due to the introduction of improved antihypertensive therapies, particularly increased use of renin-angiotensin system blockers,

may be responsible for a delay in the progression of CKD to ESRD. This may be a potential reason for the decrease in the number of patients initiating RRT due to HT/RVD observed in Australia, Canada, and Europe and the decreasing trend of patients commencing RRT for ESRD due to GN in Australia, Europe, Republic of Korea and the US.

Progression of CKD to ESRD, as mentioned, could also be a result of the underlying kidney disease itself. The incidence of RRT secondary to a PRD of GN did not increase in any of the renal registries included in this study throughout the time period. Most types of GN are immune-mediated disorders and, therefore, tend to require immunosuppressive treatment along with the standard management to slow the progression of CKD. The reasons for the decreasing trend of patients commencing RRT for ESRD due to GN in Australia, Europe, the Republic of Korea and the US are not clear, but may be, at least in part, a result of improved treatment outcomes of immunosuppressive agents, antihypertensive and antiproteinuric treatments.

ADPKD progression is difficult to predict and there is a clear need to identify prognostic indicators that could be used to predict ADPKD progression, therefore aiding in the clinical management of these patients. It has recently been shown that overweight and, particularly, obesity is strongly and independently associated with rate of progression in early-stage ADPKD .[38] Another possible cause is that the improved prognosis of these patients may extend their life long enough to allow the progression to ESRD. The latter may also be true for patients with DM, HT and GN.

Access to RRT

In countries like Malaysia and the Republic of Korea, the sharp increase in the number of patients starting RRT pmp might be the consequence of rapid economic growth and an expansion of dialysis services. It should be noted that the enhanced public support for dialysis programmes in these countries is likely to be the largest contributor in the rise in incidence counts of patients with ESRD who gained access to RRT in recent years, with smaller contributions from increased population size, growth in

ageing populations, and growing prevalence of risk factors like DM.[16,39] Regardless the sharp increase in the number of patients starting RRT pmp as a main consequence of increased access to RTT, the results of our study showed only a slight increase in the *percentage* of DM as PRD in patients starting RRT in the study period in Malaysia (0.8% per year) and Republic of Korea (2.3%) (see appendix 4 and 5). The largest increase was found for HT as PRD in Malaysia (7.9%). Please note that a decrease in the percentage of a certain PRD automatically increases the percentage of another PRD and vice versa. In contrast, the incidence pmp of one primary renal disease does not depend on the incidence pmp of the other primary renal diseases, and therefore the trends in the incidence rates provide insight in the real increase or decrease.

Interestingly, a recently published paper by Anand et al. (2015)[40] demonstrated the widest gap between the expected incidence of ESRD and the actual initiation of RRT in East Asia and the Pacific region. Fewer than five percent of patients projected to develop ESRD related to DM and HT have access to RRT in East Asia and the Pacific region, although this may not be true for each individual country in this region.

Previous studies from the East Asia and Pacific region have shown that older people with ESRD in particular are not treated with RRT.[41] With the exception of Japan, Taiwan, the Republic of Korea, Australia, and New Zealand, where RRT is widely available, access to this life-saving but expensive therapy is limited in other countries in the East Asia and Pacific region. The limited access to RRT is particularly in poor countries, to a large extent caused by the high costs and low availability.[16,42]

The decrease in the numbers of patients initiating RRT in high-income countries could possibly be due to an increase in conservative management of ESRD without RRT.[43] Finally, this decrease may also be due to a later start of RRT over time (e.g. at lower glomerular filtration rate).

Strengths and limitations

The principal strength of this study is that it provides a robust international comparison of recent time trends in incidence rates not only of DM but also of HT/RVD, GN and ADPKD as a cause of ESRD in

patients initiating RRT, using data from renal registries with a (close to) 100% data coverage. Several limitations are inherent to the study design. Many countries and regions were not included in this study as they did not have a renal registry (please note that RRT is in many countries practically non-existent) or their renal registry did not have the required data, for instance Taiwan, Argentina and Japan. Moreover, the data from Europe did not include all European countries. In addition, the use of publicly available data (with the exception of Europe) precludes analysis of adjusted incidence rates. The age distributions differ across countries, with Malaysia, Uruguay, Australia and US having younger populations than many European countries and the Republic of Korea. Standardization for age distributions is likely to have caused higher incidence RRT rates, for instance DM and HT/RVD as a PRD in countries with younger populations. Furthermore, the determination of the primary cause of ESRD may differ across countries and may have altered in some countries over the study period, probably due to a temporal change in the number of kidney biopsies performed, and thus have potentially contributed to observed changes in the incident rates of RRT for ESRD by PRD. Finally, a degree of caution is needed for the interpretation of the results due to low numbers (for ADPKD) and the number of missing and unknown PRDs in several renal registries, which may even change during the study period like in Malaysia. Patients with DM are likely to have their renal function monitored, and therefore, it may be unlikely that these patients with ESRD have their PRD classified as unknown. Non biopsied glomerulonephritis, for instance may be more frequently misclassified as 'unknown'.

Conclusion

This current international comparison shows decreasing incidence rates of RRT for ESRD due to DM in Europe and to HT/RVD in Australia, Canada and Europe. In addition, a decrease or stabilization of the incidence was observed for GN as primary cause of ESRD in all regions and for ADPKD in all regions except Malaysia and the Republic of Korea. However, an increasing trend in patients commencing RRT

for ESRD due to DM, HT/RVD and ADPKD was obvious in Malaysia and the Republic of Korea. The results of this study may prove useful for identifying the reasons for differences in the trends of PRDs among patients initiating RRT which hopefully will facilitate the development of successful preventive measures.

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Table 1. Overview of primary renal diseases in patients starting renal replacement therapy for end-stage renal disease used by the included renal registries

	Primary renal disease						
Renal registry	**DM I**	**DM II**	**HT**	**RVD**	**GN**	**ADPKD**	**Unknown/ Missing**
Australia New Zealand (ANZDATA)	**Combined**		**Combined**		✓	✓	✓
USA (USRDS)	**Combined**		**Combined**		✓	✓	✓
Canada (CORR)	**Combined**		**Combined**		✓	✓	✓
Europe (ERA-EDTA)	✓	✓	✓	✓	✓	✓	✓
Republic of Korea	**Combined**		**Combined**		✓	✓	✓
Malaysia (MDTR)	**Combined**		**Combined**		✓	✓	✓
Uruguay	**Combined**		**Combined**		✓	X	✓

ANZDATA, USRDS and the Republic of Korea may include other rare diseases classified as ADPKD.

DM, diabetes mellitus; HT, hypertension; RVD, renal vascular disease; GN, glomerulonephritis; ADPKD, autosomal polycystic kidney disease; ✓, yes; X, no.

Legends

Figure 1. International time trends in patients commencing renal replacement therapy for end-stage renal disease between 2005 and 2014, per million population.

The Malaysian Dialysis and Transplant Registry does not include data on paediatric patients. The USRDS and the Malaysian Dialysis and Transplant Registry collected data at day 91 after commencing RRT. Pre-emptive kidney transplantation numbers were not included for the renal registries of Canada, Malaysia and Uruguay. We were unable to obtain information on whether the Korean Renal Registry includes also data on paediatric patients and whether data presented relate to patients at day 1 or day 91 of RRT.
For Europe we included the countries Austria, Denmark, Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, the Netherlands, and the regional registries of Dutch- and French-speaking Belgium, and the Spanish regional registries of Andalusia, Aragon, Asturias, Basque, Cantabria, Castile-La Mancha, Castile and León, Catalonia, Extremadura, and Valencian region. Please note that y-axis scale is not the same in each Figure a - f.

AAPC, Average annual percentage change; ADPKD, Autosomal polycystic kidney disease; CI, Confidence interval; Pmp, per million population; ↑, increasing; ↓, decreasing; --, stable.

Figure 2. International time trends of patients commencing renal replacement therapy for end-stage renal disease by primary renal diseases between 2005 and 2014, per million population.

The Malaysian Dialysis and Transplant Registry does not include data on paediatric patients. The USRDS and the Malaysian Dialysis and Transplant Registry collected data at day 91 after commencing RRT. Pre-emptive transplantation numbers were not included for the renal registries of Canada, Malaysia and

Uruguay. We were unable to obtain information on whether the Korean Renal Registry includes also data on paeditaric patients and whether data presented relate to patients at day 1 or day 91 of RRT.
For Europe we included the countries Austria, Denmark, Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, the Netherlands, and the regional registries of Dutch- and French-speaking Belgium, and the Spanish regional registries of Andalusia, Aragon, Asturias, Basque, Cantabria, Castile-La Mancha, Castile and León, Catalonia, Extremadura, and Valencian region. Please note that y-axis scale is not the same in each Figure a - f.

AAPC, Average annual percentage change; ADPKD, Autosomal polycystic kidney disease; CI, Confidence interval; Pmp, per million population; ↑, increasing; ↓, decreasing; --, stable.

Appendix 4

Figure 3. International time trends of patients commencing renal replacement therapy for end-stage renal disease by primary renal diseases between 2005 and 2014, percentage.

The Malaysian Dialysis and Transplant Registry does not include data on paediatric patients. The USRDS and the Malaysian Dialysis and Transplant Registry collected data at day 91 after commencing RRT. Pre-emptive transplantation numbers were not included for the renal registries of Canada, Malaysia and Uruguay. We were unable to obtain information on whether the Korean Renal Registry includes also data on paeditaric patients and whether data presented relate to patients at day 1 or day 91 of RRT.
For Europe we included the countries Austria, Denmark, Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, the Netherlands, and the regional registries of Dutch- and French-speaking Belgium, and the Spanish regional registries of Andalusia, Aragon, Asturias, Basque, Cantabria, Castile-La Mancha, Castile and León, Catalonia, Extremadura, and Valencian region.

AAPC, Average annual percentage change; ADPKD, Autosomal polycystic kidney disease; CI, Confidence interval; Pmp, per million population; ↑, increasing; ↓, decreasing; --, stable.

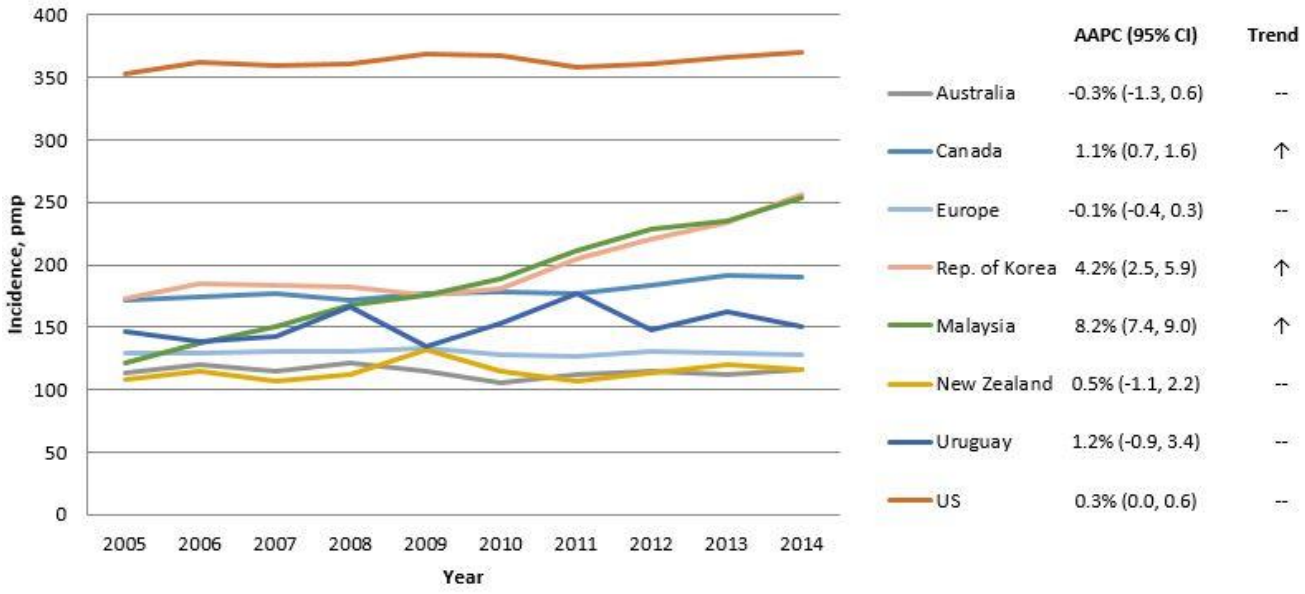

Figure 1

Figure 2