# Economic Burden of the Inadequate Management of Allergic Rhinitis and Urticaria in Asian Countries Based on the GA²LEN Model 

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Purpose: Across Hong Kong, Malaysia, the Philippines, Singapore, Thailand and Vietnam, (referred to as Asia) approximately 30-53 million individuals of the 151 million employed suffer from allergic rhinitis (AR) and urticaria. It is estimated that approximately $90 \%$ of patients with these allergic conditions are insufficiently treated, impacting the socioeconomic burden in terms of absence from work and decreased productivity. This study aims to estimate the socioeconomic burden of allergies in Asia and the cost savings that their adequate management can provide. Due to the limited availability of regional data, this study focused AR and urticaria in selected countries. Methods: Published literature, information from statistical bureaus, clinician surveys and extrapolation of selected data from the European Union were used to determine the socioeconomic costs of AR and urticaria. Results: Many patients in Asia suffer from perennial allergies and experience symptoms of AR and urticaria for up to 298 days per year. An estimate of the indirect costs of patients insufficiently treated for AR and urticaria amounts to USD 105.4 billion a year, which equates to USD 1,137-2,195 per patient due to absenteeism and presenteeism. Adherence to guideline-approved treatment can lead to estimated savings of up to USD 104 billion. Conclusions: The current study suggests that within Asia, the socioeconomic impact of AR and urticaria is similar to that seen in the European Union in spite of the lower wages in Asia. This is due to the mainly perennial allergens prevailing in Asia, whereas the sensitization patterns observed in the European Union are dominated by seasonal exposure to pollen. These results underline the need for governmental initiatives to increase public awareness on the prevention and treatment of these and other allergic diseases as well as greater research funding and large-scale studies to reduce their growing socioeconomic burden in coming years.
Key Words: Allergic rhinitis, urticaria, socioeconomic costs

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## INTRODUCTION

The economic burden of allergic diseases in the working population (between the ages of 15 and 65) of the European Union was previously investigated by the Global Allergy and Asthma European Network (GA ${ }^{2}$ LEN). ${ }^{1}$ The study found that the high socioeconomic cost of allergies was due to the high prevalence of allergies in the studied age group, and the associated presenteeism (working while feeling sick) and absenteeism, which were mainly caused by undertreatment and were thus avoidable. The study indicated that cost savings of over EUR 100 billion could be realistically expected through better treatment of allergic diseases. These findings have led to greater awareness about the management of allergic diseases among health politicians worldwide. However, there is dispute over whether results from the European study can be extrapolated to other regions such as Asia underscoring the need for an Asian-focused study.
Allergic diseases are comprised of a wide range of conditions including allergic rhinitis (AR) and urticaria and are commonly classified as intermittent, persistent, seasonal or perennial. Based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, AR is classified as either 'intermittent' (symptoms for <4 days a week), 'persistent' (symptoms present for $>4$ days a week and for $>4$ consecutive weeks), 'mild' or 'moderate.'.
There are important differences in the nature of allergies between European and Asian populations, which prevent direct application of data from European studies to Asia. Perennial allergies are common in Asia and are often associated with indoor allergens. Numerous studies have found that Asian patients experience a much longer duration of symptoms, due to the high sensitization rates to perennial allergens (e.g., mites and mold). For example, a study in Singapore found that $70 \%$ of the population is sensitized to house dust mite (HDM) allergens. ${ }^{3}$ Conversely, sensitization to seasonal allergens (e.g., pollen) prevails in European populations.
While the global prevalence of all allergic diseases is reported to be $20 \%-30 \%,{ }^{4}$ data for the general population and working adults are limited in Hong Kong, Malaysia, the Philippines, Singapore, Thailand, and Vietnam (collectively referred to as Asia). Furthermore, data available show large variations in the prevalence of allergic diseases across Asian countries. For instance, the World Allergy Association reported that AR, the most common allergic disease in Asia Pacific (APAC), has an overall prevalence rate of $10 \%-30 \%$, similar to the global rate. ${ }^{4}$ However, the Allergies in Asia-Pacific Survey, which assessed the impact of nasal allergy symptoms on the quality of life (QoL) in APAC respondents, found that the prevalence of AR ranged between $2.5 \%$ and $13.2 \%$. $^{5}$
Second-generation antihistamines and intranasal glucocorticoids have been recommended for the treatment of AR symptoms ${ }^{6,7}$ and have been found to improve patient QoL as shown
by studies utilizing the Rhinoconjunctivitis Quality of Life Questionnaire surveys. ${ }^{8-10}$ These medications are the preferred method of treatment for physicians and patients as they generally have minimal adverse effects on work performance and productivity. In this study, we assessed the economic burden of the inadequate management of AR and urticaria in selected Asian countries based on the GA ${ }^{2}$ LEN model ${ }^{1}$ and investigated the potential role of the main medications for AR and urticaria in reducing the socioeconomic burden of these allergic diseases. Given the limited availability of data within the region, the current study focused on AR and urticaria within the selected group of Asian countries.

## MATERIALS AND METHODS

## Study design and population

Data for calculating the socioeconomic cost of AR and urticaria were obtained through the published literature, individual country statistics and statistical information from the relevant statistical bureaus. Surveys were also carried out on clinicians (allergists, ear, nose and throat specialists and dermatologists) practicing in Asia to obtain country-specific information and considerations. Patients included in this analysis were from Hong Kong, Malaysia, the Philippines, Singapore, Thailand, and Vietnam. These countries were selected as sufficient data (e.g., prevalence rates of AR) were publicly available and they reflect the diverse range of economic states, levels of development, patient access and physician/patient knowledge in Asia.

## Assessment

To calculate the socioeconomic cost incurred of AR and urticaria, absenteeism, presenteeism and the effects on cognitive functioning were considered. The cost of treatment was also calculated to enable an estimation of the savings if AR and urticaria were sufficiently treated. Direct and indirect costs were used for the purpose of the calculation (note, intangible costs were difficult to quantify).
The methodology for obtaining the cost for unmet needs in treating AR and urticaria was based on the following: 1) the number of persons in the working age group of 15-64 years, 2) the prevalence of AR and urticaria in Asia, 3) the duration of symptoms, 4) statistics for untreated or insufficiently treated patients, 5) absenteeism due to allergic disease in the working age group, 6) effects of AR and urticaria on cognitive, social and emotional functioning as well as on presenteeism, and 7) treatment cost of AR and urticaria. The calculation of employment costs was simplified as only direct employment costs were used without considering loss of profits or other overhead costs. Innovator and non-innovator drug costs of second-generation antihistamines and nasal corticosteroid sprays, annual cost per patient for doctor visits, as well as reimbursement schemes present in the participating Asian countries, were considered when calculating
the treatment cost of AR and urticaria.

## Data sources for assessment

Asian data were obtained through PubMed, local journal searches (refer to supplementary material for further details), and government and clinical databases. Any unavailable data were extrapolated using data from a neighboring country, which were obtained through clinical practice or by an informed and consensual decision to append the European GA ${ }^{2}$ LEN study data. ${ }^{1}$
Country-specific statistics were used to calculate the population within the 15 - to 64 -year age group and the numbers employed within this group. ${ }^{11-17}$ The total number of people in the employable age group was added and used in the subsequent calculations. ${ }^{13,15,17-20}$ To assess the cost and socioeconomic impact of treating AR and urticaria, the fees for doctor+ visits, prices of second-generation antihistamines and nasal corticosteroid sprays (innovator and non-innovator), and details of drug reimbursements (where applicable) were either collated from clinicians in the selected Asian countries or obtained from independent studies.
Details of the specific data sources are provided in supplementary materials (Supplementary Tables 1-6). The results section below also provides further information about how the cost for unmet needs in treating AR and urticaria were calculated.

## RESULTS

Employable population within the 15- to 64-year old age group Based on local statistics (from 2015-2016) for the countries included in the study (Supplementary Table 1), 151,288,775 of the $175,438,157$ people in the 15-64 age group were employed. This number comprises all residents, regardless of residency status or citizenship.

## Prevalence of AR and urticaria within the employable age group

Overall, data on the prevalence of AR and urticaria in adults in Asia are scarce. A previous study reported that $70 \%-80 \%$ of the Singapore population was sensitized to HDM. ${ }^{3}$ Meanwhile, the average prevalence of AR in APAC countries was $8.7 \%$, and the survey showed a range of $2.5 \%-13.2 \%$ in some of these countries ( $4.2 \%, 7.1 \%, 2.5 \%, 4.9 \%$, and $12.3 \%$ for Hong Kong, Malaysia, Philippines, Singapore, and Vietnam, respectively). ${ }^{5}$ A prevalence of $26.3 \%$ was reported in a separate study in Thailand, which is similar to those of other studies in the Philippines which were reported to be approximately $20 \% .^{21,22}$ In Vietnam, the prevalence of AR ranged between $12 \%$ and $15 \%$ (unpublished data from specialist hospitals).
In the Philippines, urticaria had a recorded prevalence of $2.29 \%$ (Supplementary Table 2). The prevalences of urticaria were $2.29 \%$ in Thailand (Supplementary Table 2) and $42 \%$ in Singapore. ${ }^{23}$
The data available also do not indicate the proportion of AR
and urticaria sufferers in either the employed age group or among those aged $<65$ years. The prevalences of these allergies were therefore assumed to be similar among the employed population and the rest of the population in the same age group.
The disparities in the reported prevalences of allergic diseases in Asia demonstrate wide variability across regions, which may be due partly to differences in socioeconomic development and levels of urbanization between countries and within individual countries. ${ }^{24}$ This was supported by the relationship between allergic diseases and socioeconomic status in studies of school children and adults, which found that a higher socioeconomic status was associated with higher prevalences of asthma, rhinitis and eczema. ${ }^{25,26}$ Considering the variation between countries in the reported prevalences of allergies, a consensus was reached among the clinicians surveyed to assume a prevalence of $20 \%-35 \%$ for AR and urticaria in Asia.

## Duration of symptoms of AR and urticaria

As allergic diseases in Asia tend to be perennial rather than seasonal, limited data are available on the duration of symptoms for AR and urticaria. A study of Singapore- and Malaysiaborn Chinese individuals indicated that patients show symptoms throughout the year, that $65 \%$ of the respondents suffered from persistent AR, and that two-thirds of asthmatics displayed symptoms of AR. ${ }^{3}$ In addition, a study in Singapore reported that $80 \%$ of the individuals suffered from symptoms for more than 1 year due to indoor perennial allergens. ${ }^{27}$ A study in Thailand described a prolonged symptom duration of 19 months in patients with chronic idiopathic urticaria who were positive in a skin prick test for sensitivity to mites; however, no studies were found about the duration of symptoms of AR in the Thai population. ${ }^{28}$ Similarly, no data were available from Hong Kong, Malaysia, or the Philippines. As HDM constitute the major sensitizing allergen in Asia, it is reasonable to consider that patient symptoms could persist throughout the year. ${ }^{29}$
A conservative estimate of 75 days was used in an equivalent study involving a European population, where more studies have been performed to evaluate the duration of allergy symptoms due to seasonal pollen and other indoor and outdoor allergens. ${ }^{1}$ Due to the limited data available in Asia, this study used 298 days as the duration of symptoms, which was estimated from the average percentage of persistent $(80 \%)^{27}$ and nonpersistent AR, and urticaria, assuming 30 days of seasonal allergies.

## Number of untreated or insufficiently treated persons in the group

A limited number of studies in Asia have demonstrated that there is an unmet need in the treatment of AR and urticaria in the region. For example, in a Singapore study assessing the use of intranasal steroids in patients with persistent AR, the objective compliance of each patient was calculated using the weight
of medication consumed, $87 \%$ of whom subjectively reported high levels of compliance to the therapy; however, the calculated objective compliance rate was only $65 \%{ }^{27}$ In another study of patients with chronic urticaria, $71.9 \%$ had low adherence to the medical therapy. ${ }^{30}$
Treatment adherence data from the European studies by Zu berbier and colleagues ${ }^{1}$ were extrapolated for the current analysis as these studies were more conclusive and it is unlikely that treatment adherence would be higher in Asia than in Europe. It was assumed that only $10 \%$ of patients were treated optimally and that the remaining $90 \%$ remained either untreated, insufficiently treated or incorrectly treated.

## Absenteeism due to AR and urticaria in the employable age group

There are no data available in Asia for the number of missed working days due to AR and urticaria. The Allergies in Asia-Pacific Survey, which assessed the impact of nasal allergies on QoL, found that AR interference led to absenteeism in 3\% (Hong Kong), $4 \%$ (Malaysia), $1 \%$ (Philippines), $6 \%$ (Singapore), and 2\% (Vietnam) of the respondents. ${ }^{5}$
A study in the USA showed that AR was the most prevalent of the allergic conditions investigated and that employees experienced symptoms of AR for up to 52.5 days and missed work for 3.6 days per year. ${ }^{31}$ As conservative estimate for the current analysis in Asia, the absenteeism rate of 3 days per year reported in Europe ${ }^{1}$ was divided by half ( 1.5 days), after general agreement among the authors that workers in Asia tend to turn up for work even when unwell.

## Effects of AR and urticaria on cognitive, social and emotional functioning, and related presenteeism

AR-induced tiredness and cognitive impairment are associated with presenteeism, which is an important factor for the socioeconomic cost of allergic conditions. ${ }^{1}$ Studies have also found that sleep is frequently affected in patients with AR. ${ }^{32}$
The Allergies in Asia-Pacific Survey reported that $50 \%$ of AR patients complained that their symptoms interfered with work. When the symptoms of nasal allergies were most severe, participants in the survey reported a reduction in work productivity of $20 \%$ (Hong Kong), $16 \%$ (Malaysia), $31 \%$ (Philippines), and $22 \%$ (Singapore). ${ }^{5}$ Similarly, Meltzer and colleagues ${ }^{33}$ reported a $24 \%$ reduction in productivity for patients in APAC when their nasal allergies were most severe. These results were comparable to the reduction in productivity observed in Latin America and the USA, which reported to be a $33 \%$ and $23 \%$ reduction, respectively. ${ }^{33}$ A study of Korean patients with respiratory diseases also found that presenteeism caused a significantly greater loss of workplace productivity than absenteeism. ${ }^{34}$ Of the diseases studied, AR was associated with the highest loss of productivity. ${ }^{34}$ Additionally, the Allergies in Asia-Pacific Survey found that more than one-third of adults and caregivers for children
reported that AR affected their QoL. ${ }^{5}$
Given the nature of perennial allergens in the region, it was important to create a range for presenteeism estimates that included a conservative as well as generous estimate for subsequent calculations. For example, mites and mold are indoor allergens with high exposure levels in the work place. Depending on the occupation and workspace, storage mites and fungal allergens can be found at even higher levels than at home. Due to the lack of studies in Asia directly comparing the effects of treatment of AR and urticaria, the figures were obtained from the parallel European study ${ }^{1}$ and an estimated presenteeism rate of $10 \%-20 \%$ was used for subsequent calculations.

## Treatment cost of AR and urticaria

The average consultation fee incurred per doctor visit due to allergies is approximately USD 2.50 in Thai government hospitals, USD 10-21 in the Philippines, USD 13.50 in Vietnam, USD 36.00 in Singapore and Malaysia, and USD 100 in Hong Kong, with the overall average for these Asian countries being USD 34.
The cost per daily dose of selected second-generation antihistamines ranged from USD 0.45 to 0.93 for bilastine, USD 0.19 to 0.79 for cetirizine, USD 0.62 to 0.75 for desloratadine, USD 0.22 to 0.58 for ebastine, USD 0.10 to 1.51 for fexofenadine, USD 0.06 to 1.29 for ketotifen, USD 0.42 to 0.57 for levocetirizine, USD 0.04 to 1.29 for loratadine and USD 0.31 to 1.16 for rupatadine (some data from Malaysia were obtained from private clinics, and data from Singapore and Thailand were obtained from clinical practice; see Supplementary Table 3 for further details). ${ }^{35,36}$ All prices refer to innovator and/or locally produced drugs. Most of the second-generation antihistamines listed in Supplementary Table 5 can be taken once-daily and the usual daily dosage is also shown. However, some clinicians prescribe the daily dosage for fexofenadine, ketotifen and levocetirizine as between 1 and 4 tablets daily (Supplementary Table 5). The cost per daily dose of nasal corticosteroid sprays ranges from USD 0.28 to 1.17 for mometasone furoate, USD 0.14 to 0.92 for fluticasone furoate, USD 0.14 to 0.49 for triamsinolone acetonide, USD 0.16 to 0.42 for fluticasone propionate, USD 0.37 to 0.49 for ciclesonide and USD 0.14 to 0.41 for budesonide (Supplementary Table 6). Reimbursement schemes varied among countries. In Singapore, reimbursement was available for most second-generation antihistamines, while only selected second-generation antihistamines were reimbursed in Thailand and Vietnam. Conversely, reimbursement is very limited or unavailable in the Philippines, Hong Kong, and Malaysia (Supplementary Table 5).

## Cost of socioeconomic burden

Using the above-mentioned estimated figures and data sources provided in the supplementary materials, a modelled calculation was made for the socioeconomic cost of undertreated AR and urticaria. The model considered cost due to absenteeism and presenteeism and was used to estimate the potential sav-

Table. Socioeconomic cost of absenteeism and presenteeism due to undertreatment of AR and urticaria, and the potential savings if these allergic diseases were sufficiently treated in Asia

| Variables | Assuming 20\% prevalence <br> with 10\% impairment | Assuming 20\% prevalence <br> with 20\% impairment | Assuming 35\% prevalence <br> with 20\% impairment |
| :--- | :---: | :---: | :---: |
| Cost of absenteeism/worker/year (USD) | 79 | 79 | 79 |
| Cost of presenteeism/worker/year (USD) | 1,058 | 2,116 | 2,116 |
| Total cost/worker/year (USD) | 1,137 | 2,195 | 2,195 |
| No. of workers with allergic diseases | $30,000,000$ | $30,000,000$ | $53,000,000$ |
| No. of workers with undertreated allergy | $27,000,000$ | $27,000,000$ | $48,000,000$ |
| Total allergy cost (USD) | $30,700,000,000$ | $59,300,000,000$ | $105,400,000,000$ |
| Total additional cost of guideline-approved treatment in the | $1,558,170,000$ | $1,558,170,000$ | $2,770,080,000$ |
| $\quad$ untreated population (USD) | $29,150,280,000$ | $57,716,280,000$ | $102,607,000,000$ |
| Total potential savings (USD) |  |  |  |

AR, allergic rhinitis.
ings if the untreated population was adequately treated (Table). Further details of the calculation used for the model are provided below.
The average number of working hours in the respective countries in Asia per week is 43.83 hours $^{37}$ with up to an average of 14 days of annual leave. ${ }^{38}$ It was assumed that each person who suffers from AR and urticaria experiences symptoms for 201.46 working days per year. This assumes that each person works for 5 days a week and experiences symptoms for 298 days per year (with 11.4 days taken off for vacation leave).
Data on labor cost per employee are not available for many countries in the region. Hence, the employer's daily cost per employee was determined with the assumptions that this is reflected by the employee's wages and that employees work for 5 days per week. The daily rate of pay was calculated by the following equation: ( $12 \times$ monthly salary)/( $52 \times 5$ days). Following the International Labor Organization (ILO) statistics, daily wages for the selected Asian countries were calculated as: Hong Kong, USD 77.40 (HKD 13,000); Malaysia, USD 26.20 (MYR 2,231); the Philippines, USD 20.90 (PHP 378); Singapore, USD 166.78 (SGD 4,892); Thailand, USD 17.60 (THB 13,386); and Vietnam, USD 8.52 (VND 4,120,470). ${ }^{37}$ The average employer's cost per worker was therefore USD 52.90, with the average number of working hours at 8.8 hours per day.
The rate of absenteeism due to AR and urticaria was estimated at 1.5 days per year. This equates to the employer's cost per worker per year, ranging from USD 12.78 to 250.17. The mean cost for these Asian countries was USD 79. The rate of presenteeism was extrapolated from the European GA² LEN study data described by Zuberbier and colleagues ${ }^{1}$ and was estimated as $10 \%-20 \%$. This is because presenteeism is subjective and the limited availability of data from Asia did not permit an independent calculation. To calculate the cost of presenteeism, the number of affected working days (calculated above) was approximated as 200. The cost of presenteeism was 20 or 40 days (based on the presenteeism rate of $10 \%$ or $20 \%$ ). Based on an average dai-
ly employer's cost of USD 52.90, this amounts to USD 1,058 or 2,116 per individual per year.
By assuming a prevalence rate of allergies of $20 \%, 30$ million workers would be affected by AR and urticaria. Using the higher estimate of a $35 \%$ prevalence rate, the number of workers affected by AR and urticaria amounts to 53 million. The percentage of patients optimally treated in Asia was estimated at $10 \%$, thus approximately $90 \%$ were untreated, incorrectly treated or insufficiently treated. By assuming a $20 \%$ prevalence rate of AR and urticaria in Asia, the total cost of absenteeism and presenteeism would apply to 27 million workers. A higher prevalence estimate of $35 \%$ would affect 48 million workers. After accounting for the total additional cost of guideline-approved treatment in the untreated population, the modelled calculation indicated the potential savings ranging from USD 29 to 105 billion (Table).

## DISCUSSION

This study provides an overview of the socioeconomic burden of AR and urticaria in Asia including the potential savings with better treatment options. In the calculation of the cost of AR and urticaria, the number of persons employed, employer's cost and the prevalence of allergy symptoms were based on coun-try-specific statistics or studies carried out in each country or in the Asian region. Overall, this study shows that the health care cost involved in the management of AR and urticaria in Asia are substantial. Based on prevalence rates of $20 \%-35 \%$ and impairment rates of $10 \%-20 \%$, the socioeconomic burden of these diseases in Asian countries ranges from USD 30.7 to 105.4 billion. With better management of the untreated population (estimated at approximately $90 \%$ ) and an investment of approximately USD 1.6-2.7 billion, Asian countries could anticipate achieving the potential savings of USD 29.1-102.6 billion and increasing the productivity of the workforce.
In general, these findings are in line with those of other stud-
ies in the region, which have shown that allergic diseases carry a significant socioeconomic burden. In Singapore alone, the total (direct and indirect) cost associated with asthma is estimated at USD 33.93 million per year. ${ }^{39}$ This cost includes compromised QoL and decreased performance at work and school. Although allergic diseases affect QoL measures, studies on their socioeconomic burden are lacking in Asia, which highlights the need for a better understanding of the full impact of these conditions. For example, a QoL survey assessing the impact of chronic urticaria in Singapore found that patients were most affected by sleep interference and the occurrence of pruritus, followed by tiredness due to poor sleep quality and interference with free time. ${ }^{30}$ In Korea, a study evaluating the association between AR and mental health found that adults with AR were at higher risk of psychiatric disorders than the general population and that chronic or severe AR was associated with poorer mental health outcomes. ${ }^{40}$ In addition, the Allergies in Asia-Pacific Survey noted that $50 \%$ of patients with AR experienced work interference and that the impairment of productivity ranged between $10 \%$ and $31 \% .{ }^{5}$ Furthermore, asthma is a common comorbidity of AR , and a survey of parents found that $73 \%$ of children with asthma had pre-existing AR symptoms that substantially affected their QoL and worsened their asthma symptoms. ${ }^{41}$
It is important to note that, at present, accurate prevalence rates are limited for many diseases in the Asian population. As such, the burden of allergies in Asia is grossly underestimated because few large-scale epidemiological studies have been conducted due to financial constraints and underdiagnosis, especially in rural areas. However, as allergies are more prevalent in urban areas, the prevalence of allergic disorders in Asia is expected to rise over the next 2 decades, due to rapid economic development and urbanization. ${ }^{24}$ This has been documented in industrialized countries, where lifestyle changes associated with urbanization and high emissions from vehicles have been linked to the increasing prevalence of respiratory allergic diseases. ${ }^{42}$ In Asia, the growing population levels and adoption of Westernized lifestyle has contributed to the increasing prevalence of allergies. ${ }^{43}$ For instance, a recent population-based study of Korean children found that chronic continuous urticaria was significantly associated with higher parental incomes and living in a new house. ${ }^{44}$ The increase in sensitization to allergens of house dust (HD), HDM and cockroaches from $9.1 \%$ in 2004 to $14.1 \%$ in 2009 is in alignment with these observations. ${ }^{45}$ In Thailand, a study of children demonstrated that the prevalence of sensitization to HD and HDM allergens increased from $1.2 \%$ in 2004 to $34.3 \%$ in 2009. ${ }^{44}$
The approach used in this study to assess the economic burden of selected allergic diseases provides useful insights, but it is pertinent to evaluate the limitations of the analysis. Subjective parameters such as the reduction in cognitive function or the drop in QoL are difficult to quantify and depend on the personal experiences of those affected by the allergy. Other limita-
tions of this study include assumptions for parameters where Asian data are unavailable. Based on extrapolated data from the $\mathrm{GA}^{2}$ LEN study, this study assumed 1.5 days of absenteeism, leading to a cost of USD 79 per person per year for AR and urticaria. However, it should be noted that the real cost may differ due to the high levels of sensitization and exposure to perennial allergens in Asia. Similarly, a $10 \%-20 \%$ rate of presenteeism was used in the current model; however, the actual rate may vary depending on individual job types, including manual jobs and those requiring high levels of concentration, may be associated with higher rates of presenteeism. Additionally, the calculation of the burden of AR and urticaria included estimates of the cost incurred for the treatment of allergic diseases using second-generation antihistamines and nasal corticosteroid sprays, some of which are not available as generics. The price differences of innovator drugs between Asia and Europe could also create constraints on the computation of the economic burden. The differences are due to limited subsidies in healthcare and medication in some countries in Asia and differences in the economic status of countries as well as barriers to accessing medications in developing countries.
This estimation does not take into consideration factors that cannot be quantified, including the loss of school days as well as detrimental effects on children's education and opportunity cost to industry. The socioeconomic cost of allergies, such as AR and urticaria, is not limited to the impact on absenteeism and presenteeism. Additional expenses also arise through cost of consultation and medication (see Supplementary Tables 2 and 3). However, with proper management of allergic diseases, these aspects also present an opportunity for potential savings, a finding which had previously been demonstrated in rhinitis and AR. ${ }^{46,47}$
In summary, the calculations to derive the cost of AR and urticaria were performed using the most objective approach possible; nevertheless, educated estimates had to be made that limited some values of the input parameters. Due to these limitations, it is important to note that the economic cost estimated in this study is preliminary. However, the current study provides a useful insight into the possible extent of the socioeconomic burden of AR and urticaria, and provides a good platform to promote further studies to be conducted in the region in order to obtain more representative data on the socioeconomic cost of these and other allergic diseases.
Zuberbier and colleagues ${ }^{1}$ previously highlighted that allergies deserve better public attention in Europe, and the same could be said for Asia. The current analysis suggests that there may be insufficient emphasis on the management of the burden of AR and urticaria in Asia. This may be because such allergic diseases are usually not fatal and are thus not perceived as urgent. As such, most health care funding has been placed into the research and management of more severe diseases such as cardiovascular disease and cancer. However, severe and persis-
tent AR has been associated with other life-threatening comorbidities, such as asthma, stressing the need for better treatment options. This is reflected by the notable lack of large scale epidemiological studies on the prevalence and burden of AR and urticaria in Asia. These results highlight the impact of allergic diseases, such as AR and urticaria, on the economy in Asia, underlining the need for governments to consider initiatives for their prevention and treatment.
A survey assessing the perceptions and paradigms of patients with AR reported that approximately two-thirds of respondents took prescription medication to alleviate their symptoms and that this figure was 1.5 times greater than that of respondents that relied only on the use of over-the-counter drugs. ${ }^{5}$ Additionally, a study on the treatment decision of clinicians and patients with AR found that while $77 \%$ of patients reported adherence to treatment, most preferred oral antihistamines (41\%) over intranasal treatment ( $22 \%$ ). ${ }^{48}$ Commonly cited reasons for this preference include dislike of nasal sprays, perception of insufficient symptom severity, concerns regarding side effects and dependence, and a perceived lack of effectiveness. ${ }^{5}$
Many patients still purchase first-generation antihistamines to manage the symptoms of AR and urticaria; however, their sedative effects can lead to a loss of concentration and are detrimental to manual jobs. Previous studies have found that untreated AR and the use of first-generation sedating antihistamines correlated with a higher number of accidents. ${ }^{49}$ A call to action should therefore ask for guideline-recommended and safe treatment including nasal corticosteroids and modern antihistamines (e.g., bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine). Of these, bilastine is the most recent antihistamine to market. Due to its optimal ben-efit-to-risk ratio, it is non-sedating and meets the safety requirements for driving. ${ }^{50}$ The sedative properties of antihistamines were examined by positron emission tomography measurements of H1-receptor occupancy ${ }^{51}$; bilastine has been found to have the lowest cerebral histamine H1-receptor occupancy relative to hydroxyzine. ${ }^{52}$ Finally, to manage allergic disease, guidelines also recommend allergen avoidance. In Asia, a special focus should be put on the correct maintenance of air conditioners as these may be a source of allergen (e.g., mold) exposure at the work place.
Public awareness about the management of AR and urticaria could be increased by government education programs and campaigns. Examples of current initiatives include the annual World Allergy Week, and educational activities organized by the World Federation of Allergy, Asthma and Clinical Immunology and the World Allergy Organization Societies. Such programs provide a model for consideration by other societies and governments in Asia for better prevention and treatment of allergic diseases.
To conclude, this study provides a preliminary estimation of the economic burden of AR and urticaria in Asia. Surprisingly,
the socioeconomic impact of undertreated AR and urticaria in Asia is similar to that in the European Union despite the lower wages in Asia. This is because perennial allergens (e.g., mites and mold) prevailing in Asia impact on presenteeism in the labor force, whereas sensitization patterns observed in the European Union are dominated by seasonal exposure to pollen. An important message of this study is that the cost of AR and urticaria can be mitigated by adequate disease management. These findings also emphasize the need for greater funding and largescale studies on the prevalence and burden of allergic diseases in Asian countries as well as awareness campaigns for better treatment for allergic conditions. The calculations in this study also show that government investments in the management of allergies can lead to significant potential savings that far outweigh the cost. These findings are a clear call to action for governments to raise public awareness, for employers to minimize exposure to allergens in the workplace, and for health care professionals and patients to follow current treatment guidelines in choosing and adhering to effective treatment options such as modern antihistamines.

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## REFERENCES

1. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the european union: a GA(2) LEN review. Allergy 2014;69:1275-9.
2. Björkstén B, Clayton T, Ellwood P, Stewart A, Strachan D; ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. Pediatr Allergy Immunol 2008;19: 110-24.
3. Andiappan AK, Puan KJ, Lee B, Nardin A, Poidinger M, Connolly J, et al. Allergic airway diseases in a tropical urban environment are driven by dominant mono-specific sensitization against house dust mites. Allergy 2014;69:501-9.
4. Pawankar R, Canonica GW, Holgate ST, Lockey RF. World Allergy Association (WAO) white book on allergy. Milwaukee (WI): World Allergy Association; 2011.
5. Katelaris CH, Lai CK, Rhee CS, Lee SH, Yun WD, Lim-Varona L, et al. Nasal allergies in the Asian-Pacific population: results from the Allergies in Asia-Pacific Survey. Am J Rhinol Allergy 2011;25 Suppl 1:S3-15.
6. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA)
guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.
7. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122:S1-84.
8. Saverno KR, Seal B, Goodman MJ, Meyer K. Economic evaluation of quality-of-life improvement with second-generation antihistamines and montelukast in patients with allergic rhinitis. Am Health Drug Benefits 2009;2:309-16.
9. Lee CF, Sun HL, Lu KH, Ku MS, Lue KH. The comparison of cetirizine, levocetirizine and placebo for the treatment of childhood perennial allergic rhinitis. Pediatr Allergy Immunol 2009;20:493-9.
10. Ridolo E, Montagni M, Bonzano L, Incorvaia C, Canonica GW. Bilastine: new insight into antihistamine treatment. Clin Mol Allergy 2015;13:1.
11. Official Statistics Registration Systems (TH). Demographic and home - population age [Internet]. Pathum Thani: Registrar Administration Department; 2016 [cited 2016 Feb 26]. Available from: http:// stat.dopa.go.th/stat/statnew/upstat_age.php.
12. Philippine Statistics Authority. Current labour statistics [Internet]. Quezon City: Philippine Statistics Authority; 2016 [cited 2016 Feb 26]. Available from: http://www.census.gov.ph/.
13. Census and Statistics Department (HK). Hong Kong in figures (latest figures) [Internet]. Hong Kong: The Government of Hong Kong Special Administrative Region; 2016 [cited 2016 Apr 18]. Available from: http://www.censtatd.gov.hk/hkstat/hkif/index.jsp.
14. Countrymeters. Malaysia population 2016/current population of Malaysia [Internet]. New York (NY): United Nations; 2016 [cited 2016 Feb 26]. Available from: http://countrymeters.info/en/Malaysia.
15. Department of Statistics Singapore. Statistics Singapore - latest data [Internet]. Singapore: Department of Statistics Singapore; 2016 [cited 2016 Feb 26]. Available from: http://www.singstat.gov.sg/statis-tics/latest-data\#14.
16. United Nations. World population prospects: the 2015 revision [Internet]. New York (NY): United Nations; 2015 [cited 2016 Apr 18]. Available from: https://esa.un.org/unpd/wpp/Download/Standard/ Population/.
17. Philippine Statistics Authority. Statistical tables on labor force survey (LFS): October 2015 [Internet]. Quezon City: Philippine Statistics Authority; 2016 [cited 2016 Jul 21]. Available from: https://psa. gov.ph/content/statistical-tables-labor-force-survey-lfs-october2015.
18. Department of Statistics Malaysia Official Portal. Labour force and social statistics [Internet]. Putrajaya: Department of Statistics, Malaysia; 2016 [cited 2016 Feb 26]. Available from: https://www.statistics.gov.my/.
19. General Statistics Office of Vietnam. Annual employed population at 15 years of age and above by age group 2014 [Internet]. Hanoi: General Statistics Office of Vietnam; 2016 [cited 2016 Jul 1]. Available from: http://www.gso.gov.vn/default_en.aspx?tabid=774.
20. National Statistical Office (TH). Population 15 years and over by labor force status and sex, whole kingdom: 2007-2016 [Internet]. Bangkok: Ministry of Information and Communication Technology; 2016 [cited 2016 Apr 18]. Available from: http://service.nso.go.th/nso/ web/statseries/tables/00000_Whole_Kingdom/2.1.xls.
21. Vichyanond P, Sunthornchart S, Singhirannusorn V, Ruangrat S, Kaewsomboon S, Visitsunthorn N. Prevalence of asthma, allergic rhinitis and eczema among university students in Bangkok. Respir Med 2002;96:34-8.
22. Abong JM, Kwong SL, Alava HD, Castor MA, De Leon JC. Prevalence of allergic rhinitis in Filipino adults based on the National Nutrition and Health Survey 2008. Asia Pac Allergy 2012;2:129-35.
23. Goh CL, Tan KT. Chronic autoimmune urticaria: where we stand? Indian J Dermatol 2009;54:269-74.
24. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-pacific region. Allergy Asthma Immunol Res 2013; 5:251-7.
25. Goh DY, Chew FT, Quek SC, Lee BW. Prevalence and severity of asthma, rhinitis, and eczema in Singapore schoolchildren. Arch Dis Child 1996;74:131-5.
26. Ng TP, Tan WC. Epidemiology of chronic (perennial) rhinitis in Singapore: prevalence estimates, demographic variation and clinical allergic presentation. Ann Acad Med Singapore 1994;23:83-8.
27. Loh CY, Chao SS, Chan YH, Wang DY. A clinical survey on compliance in the treatment of rhinitis using nasal steroids. Allergy 2004; 59:1168-72.
28. Kulthanan K, Wachirakaphan C. Prevalence and clinical characteristics of chronic urticaria and positive skin prick testing to mites. Acta Derm Venereol 2008;88:584-8.
29. Tham EH, Lee AJ, Bever HV. Aeroallergen sensitization and allergic disease phenotypes in asia. Asian Pac J Allergy Immunol 2016;34: 181-9.
30. Heng JK, Koh LJ, Toh MP, Aw DC. A study of treatment adherence and quality of life among adults with chronic urticaria in Singapore. Asia Pac Allergy 2015;5:197-202.
31. Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. Curr Med Res Opin 2006; 22:1203-10.
32. Bender BG, Leung DY. Sleep disorders in patients with asthma, atopic dermatitis, and allergic rhinitis. J Allergy Clin Immunol 2005;116: 1200-1.
33. Meltzer EO, Blaiss MS, Naclerio RM, Stoloff SW, Derebery MJ, Nelson HS, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. Allergy Asthma Proc 2012; 33 Suppl 1:S113-41.
34. Yoo KH, Ahn HR, Park JK, Kim JW, Nam GH, Hong SK, et al. Burden of respiratory disease in Korea: an observational study on allergic rhinitis, asthma, COPD and rhinosinusitis. Allergy Asthma Immunol Res 2016;8:527-34.
35. Ministry of Health Malaysia. Consumer price guide [Internet]. Putrajaya: Ministry of Health Malaysia; 2016 [cited 2016 Apr 18]. Available from: http://www.pharmacy.gov.my/v2/en/apps/drug-price.
36. SRP Price Mercury Drug November 2015 survey [personal communication, data on file]. Philippines: Mercury Drug; [cited 2016 Apr 18]. https://www.mercurydrug.com/. Data on Mercury Drug Price from August 2015-June 2017 retrieved by Dr Marysia Tiongco Recto of the University of the Philippines-Philippine General Hospital, Manila, Philippines.
37. International Labour Organization. ILOSTAT Database - country profiles [Internet]. Geneva: International Labour Organization; 2016 [cited 2016 Apr 18]. Available from: http://www.ilo.org/ilostat/fac-es/home/statisticaldata/ContryProfileId?_adf.ctrl-state=3xdwsgafi _158\&_afrLoop=603017453833265.
38. International Labour Organization. Working conditions laws report 2012: a global review [Internet]. Geneva: International Labour Organization; 2013 [cited 2016 Apr 18]. Available from: http://www.
ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---travail/ documents/publication/wcms_235155.pdf.
39. Chew FT, Goh DY, Lee BW. The economic cost of asthma in Singapore. Aust N Z J Med 1999;29:228-33.
40. Kim DH, Han K, Kim SW. Relationship between allergic rhinitis and mental health in the general Korean adult population. Allergy Asthma Immunol Res 2016;8:49-54.
41. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. BMC Pulm Med 2006;6 Suppl 1:S3.
42. D'Amato G, Pawankar R, Vitale C, Lanza M, Molina A, Stanziola A, et al. Climate change and air pollution: effects on respiratory allergy. Allergy Asthma Immunol Res 2016;8:391-5.
43. Pawankar R, Baena-Cagnani CE, Bousquet J, Canonica GW, Cruz AA, Kaliner MA, et al. State of world allergy report 2008: allergy and chronic respiratory diseases. World Allergy Organ J 2008;1:S4-17.
44. Lee SJ, Ha EK, Jee HM, Lee KS, Lee SW, Kim MA, et al. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. Allergy Asthma Immunol Res 2017;9:212-9.
45. Yuenyongviwat A, Koonrangsesomboon D, Sangsupawanich P. Recent 5-year trends of asthma severity and allergen sensitization among children in southern Thailand. Asian Pac J Allergy Immunol 2013;31:242-6.
46. Bousquet J, Bewick M, Arnavielhe S, Mathieu-Dupas E, Murray R,

Bedbrook A, et al. Work productivity in rhinitis using cell phones: the MASK pilot study. Allergy 2017;72:1475-84.
47. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. J Allergy Clin Immunol 2004;114:838-44.
48. Navarro A, Valero A, Rosales MJ, Mullol J. Clinical use of oral antihistamines and intranasal corticosteroids in patients with allergic rhinitis. J Investig Allergol Clin Immunol 2011;21:363-9.
49. Church MK, Maurer M, Simons FE, Bindslev-Jensen C, Van CP, Bousquet J, et al. Risk of first-generation $\mathrm{H}(1)$-antihistamines: a GA(2) LEN position paper. Allergy 2010;65:459-66.
50. Jáuregui I, Ramaekers JG, Yanai K, Farré M, Redondo E, Valiente R, et al. Bilastine: a new antihistamine with an optimal benefit-to-risk ratio for safety during driving. Expert Opin Drug Saf 2016;15:89-98.
51. Yanai K, Zhang D, Tashiro M, Yoshikawa T, Naganuma F, Harada R, et al. Positron emission tomography evaluation of sedative properties of antihistamines. Expert Opin Drug Saf 2011;10:613-22.
52. Farré M, Pérez-Mañá C, Papaseit E, Menoyo E, Pérez M, Martin S, et al. Bilastine vs. hydroxyzine: occupation of brain histamine H 1 -receptors evaluated by positron emission tomography in healthy volunteers. Br J Clin Pharmacol 2014;78:970-80.


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