INTRODUCTION

The global prevalence of asthma has increased over the past few decades and it has been estimated that asthma currently affects 300 million people worldwide. Asthma mortality and hospitalization trends in selected countries as well as their relationship with asthma drug utilization patterns were examined. Japan showed a decreasing trend in pediatric asthma mortality whereas an increase was observed in Thailand. Hospitalizations decreased in Australia and Singapore but increased in Taiwan, Republic of China. C:R ratios increased significantly across the countries. Mixed trends in pediatric asthma mortality and hospitalization rates were observed, which coincided with a uniform increase in C:R ratios. This may reflect importance of other aspects of asthma management besides pharmacotherapy.

Key Words: Asia Pacific, pediatric asthma, asthma mortality trends, asthma hospitalization trends, asthma drug utilization pattern, controllers, relievers, inhaled corticosteroids, short-acting β-agonists

Material and Methods

Data were sourced from members of the Asia Pacific Association of Pediatric Allergy, Respirology and Immunology (APAPARI) [Australia, China, Hong Kong SAR].
Indonesia, Japan, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan [Republic of China, ROC] and Thailand], which although not comprehensive does represent the diversity of this region in terms of culture and economic development. To examine temporal trends from a common time period, the earliest year for which respective data were available for most countries was used as the starting point of data collection and analysis.

Yearly mortality and population data of the selected countries (including special territories and regions) from 1990 to latest data available (range, 1996–2006) were sourced from the World Health Organization’s (WHO) mortality database. Annual data on hospitalization from 1994 to latest data available (range, 2002–2006) were obtained by direct inquiry and from government and scientific publications. Data on asthma drug use from 1997 to 2007 were provided by IMS Health Incorporated, a pharmaceutical market intelligence company.

Cause-specific mortality data from the WHO mortality database were reported according to the International Classification of Diseases (ICD). When member countries used ICD-9 (the ninth revision), deaths due to asthma were extracted using Basic Tabulation List code B323, which included deaths due to bronchitis and emphysema. Extracting absolute asthma deaths was possible only in less than 5 countries studied that adopted the ICD-10 coding system, in which deaths due to asthma were separately classified. Because Anderson et al found that in 5- to 14-year-olds asthma constitutes 89.8% of deaths under the B323 category and a temporal trend in deaths coded B323 reflected mainly that of asthma, asthma mortality rates of the same age group in each country were calculated using the total number of asthma deaths, by proxy of deaths coded ICD-9 B323 or its equivalent in ICD-10 (J40-43, J45-46), divided by the total population to maintain consistency. For countries where population data were missing from some years, a cubic regression line was fitted to interpolate the missing data.

Annual hospitalization rates of 0- to 14-year-olds in each selected country were examined. The 0- to 4-year olds were included to improve consistency of data between countries as data were stratified from 0 to 18 years in Taiwan, ROC. Drug utilization patterns in terms of the ratio of corticosteroids to bronchodilators (C:B) have been demonstrated to be a reliable indicator of quality of asthma prescribing in primary care, and it is also associated with asthma outcomes. In this study, drug utilization patterns were examined through a modified C:B, where we defined controller-to-reliever ratio (C:R) as the ratio of the total number of units of controllers (ICS and its combinations) to the total number of units of relievers (SABA) sold in each selected country. C:R was chosen in consideration of the Global Initiative for Asthma program guidelines in asthma prescribing, which recommend as needed SABA with the option of adding a controller to achieve asthma control. In addition, expressing drug utilization patterns as C:R circumvents the problem of missing population data from the WHO mortality database for some countries.

Statistical Analyses

Statistical software SPSS 16.0 for Windows was used for data analyses. Poisson regression analysis was used to analyze temporal trends in yearly death counts of individual countries. An offset of log-transformed population variables was used to account for population growth. In addition, to account for the step change associated with the change in ICD coding in some countries during the study period, a dummy variable was introduced in the analyses of WHO mortality data from countries that adapted from ICD-9 to ICD-10.

Linear regression analysis was used to analyze trends in hospitalization rates and C:R (both with log-transformation). Three countries—Australia, Hong Kong SAR, and Singapore—that had the most comprehensive annual data were chosen for further analysis of association between drug utilization patterns and mortality or hospitalization rates.

The equations for the respective models of Poisson and linear regressions are shown together with Tables 1–4 (footnotes). The regression coefficients, β1 and β2, each refer to the slope when the dependent variable—death counts, hospitalization rates, or C:R—is reexpressed on the independent variable, time in years or log(C:R). These regression coefficients (β1 and β2) would be interpreted as the average annual percentage change of the dependent variable in relation to the independent variable.

Data on prevalence of asthma in children were gathered from published ISAAC studies to look at trends in prevalence and to compare those with trends in asthma mortality and hospitalization rates. Further analysis between trends in prevalence of current wheeze (any wheeze in the past 12 months) and trends in mortality and hospitalization was done using Spearman’s rank correlation, comparing the average change per year in prevalence and the average change per year in mortality or hospitalization rates over the same period.

There were some limitations in the availability of data. Few countries in this study had reported both ISAAC Phase I and Phase III prevalence data. Data on mortality and prevalence of current wheeze were available from 7 countries (Australia, Hong Kong SAR, Japan, Korea, New Zealand, Singapore, and Thailand) for 6- to 7-year-olds, and from 6 countries (Hong Kong SAR, Japan, Korea, New Zealand, Singapore, and Thailand) for 13- to 14-year-olds. There were only 4 countries (Australia, Hong Kong SAR, Singapore, and Taiwan, ROC) with relevant hospitalization and prevalence data for 6- to 7-year-olds, and only 3 countries (Hong Kong SAR, Singapore, and Taiwan, ROC) had comparable data for 13- to 14-year-olds.

RESULTS

Time-series plots of trends in crude asthma mortality, hospitalization rates, and pattern of drug utilization for each selected country are shown in Figures 1–3. For Figure 1, 3-year moving averages were plotted to smooth out fluctuations in mortality rates, and log-scale was also chosen to show the trends more clearly. Where no deaths were recorded in any year, 0.5 deaths was replaced to obtain valid estimates with log-transformation. A summary of data availability is presented in Table 1. Results from regression analyses of
trends and correlation analyses are presented in Tables 2–4. Mixed trends in asthma mortality and hospitalizations were observed across Asia Pacific (Figs. 1, 2). However, 6 of 9 selected countries with data available showed a decrease in mortality, albeit not statistically significant except for Japan ($\beta_1 = -0.163, P < 0.001$). A small but significant increase was noted for Thailand ($\beta_1 = 0.093, P = 0.006$) (Table 2).

Similar results were found for hospitalizations, with 4 of 5 countries registering a decrease, with significant decreases in both Singapore ($\beta_1 = -0.090, P < 0.001$) and Australia ($\beta_1 = -0.067, P < 0.001$), whereas a significant increase was observed in Taiwan, ROC ($\beta_1 = 0.065, P < 0.001$) (Table 2).

The general decline in asthma mortality and hospitalizations across Asia Pacific (Figs. 1, 2) coincided with significant increases in C:R ratios across the region (Fig. 3).

Despite China having the highest increase in C:R ($\beta_1 = 0.190, P < 0.001$), an increase in mortality was observed, although not significant. In contrast, Japan, which had a comparable increase in C:R ($\beta_1 = 0.188, P < 0.001$), showed the highest significant decrease in mortality rates (Table 2). Negative associations were also observed for both asthma mortality and hospitalizations with C:R in Australia, Hong Kong SAR, and Singapore, but these were not statistically significant (Table 3).

No significant correlations existed between trends in prevalence of current wheeze and trends in asthma mortality or hospitalizations. Interestingly, a negative correlation ($P = 0.072$) was found between prevalence in 13- to 14-year-olds and mortality (Table 4).

**DISCUSSION**

This was an exploratory study to provide an overview of childhood asthma mortality and hospitalization, and the pattern of asthma drug use across the Asia Pacific. It is acknowledged that the data obtained may not be uniformly accurate. Mortality data from WHO are subject to inherent errors as they are dependent upon individual country’s report of statistics. Completeness of death and population registration coverage and accuracy of asthma death certification would likely differ between countries. Further, variations in management practices, including severity threshold for hospital admission, and patient behavior would affect the
TABLE 1. Summary of Data Availability

| Countries | Asthma Prevalence | Years for Which Data Are Available | Asthma Mortality* | Asthma Hospitalization† | C:R‡ |
|-----------|-------------------|-----------------------------------|-------------------|-------------------------|------|
|           | Phase I | 6- to 7-Year-Olds | 13- to 14-Year-Olds | Phase III | 6- to 7-Year-Olds | 13- to 14-Year-Olds | Phase III | 1990–2003 | 1994–2003 | 1990–2003 | 1994–2005 | 1990–2005 | 1994–2005 |
| Australia | 1993 | NA | 2002 | NA | 1990–2003 | 1994–2003 |
| China | NA | 1994 | NA | 2001 | 1990–1999 | NA |
| Hong Kong SAR | 1995 | 2001 | 2002 | 1990–2005 | 1994–2005 |
| Indonesia | 1996 | 2002 | NA | NA |
| Japan | 1994 | 2002 | 1990–2006 | 1993–2002† | 1997–2007‡ |
| Korea | 1995 | 2000 | 1990–2006 | NA |
| Malaysia | 1995 | 2001 | NA | NA |
| New Zealand | 1993 | 2001 | 1990–2004 | NA |
| Philippines | NA | 1994 | NA | 2001 | 1992–1998 | NA |
| Singapore | 1994 | 2001 | 1990–2006 | 1994–2006 |
| Taiwan, ROC | 1995 | 2001 | NA | 1990–2002‡ | NA |
| Thailand | 1995 | 2001 | 1990–2002 | 1996–2002‡ |

*Data on asthma mortality in 5- to 14-year-olds.
†Data on asthma hospitalization in 0- to 14-year-olds (except Taiwan).
‡Data on drug sales for total population.
§ Cross-sectional data in 1 day; data reported every 3 years.
¶ Data from 0- to 18-year-olds.
NA = data missing from 1993 and 2001.

TABLE 2. Trends in Pediatric Asthma Mortality, Hospitalization, and C:R

| Countries | Asthma Mortality* | Asthma Hospitalization† | C:R‡ |
|-----------|-------------------|-------------------------|------|
|           | $\beta_I$ | $P$ | $\beta_I$ | $P$ | $\beta_I$ | $P$ |
| Australia | −0.076 | 0.054 | −0.067 | <0.001 | 0.074 | <0.001 |
| China | 0.028 | 0.312 | NA | NA | 0.190 | <0.001 |
| Hong Kong SAR | −0.120 | 0.072 | −0.015 | 0.227 | 0.051 | 0.433 |
| Indonesia | NA | NA | NA | NA | 0.129 | <0.001 |
| Japan | −0.163 | <0.001 | −0.003 | 0.840 | 0.188 | <0.001 |
| Korea | −0.007 | 0.859 | NA | NA | 0.127 | <0.001 |
| Malaysia | NA | NA | NA | NA | 0.087 | <0.001 |
| New Zealand | −0.092 | 0.397 | NA | NA | 0.015 | 0.011 |
| Philippines | 0.005 | 0.475 | NA | NA | 0.079 | <0.001 |
| Singapore | −0.069 | 0.098 | −0.090 | <0.001 | 0.054 | <0.001 |
| Taiwan, ROC | NA | NA | 0.065 | <0.001 | 0.125 | <0.001 |
| Thailand | 0.093 | 0.006 | NA | NA | 0.106 | <0.001 |

*Poisson regression analysis: log(expected no. of age-specific deaths due to asthma) = $\beta_0 + \log(\text{age-specific population size}) + \beta_I \times \text{year}$.
†Linear regression analysis: log(hospitalization rates) = $\beta_0 + \beta_I \times \text{year}$.
‡Linear regression analysis: log(C:R ratio) = $\beta_0 + \beta_I \times \text{year}$.
plausible that the quality of and access to health care is better. Further, the higher prevalence of asthma could have encouraged local health authorities or health care institutions to place a greater emphasis on management of asthma. In Australia, where asthma prevalence is one of the highest in the world,24,25 organizations like the National Asthma Council Australia26 and Asthma Foundations Australia27 have been set up to improve the quality of life of asthma sufferers. Similarly, the Singapore National Asthma Program (SNAP) was implemented in 2001, with the goal to ease asthma burden by encouraging the use of controllers and reducing the reliance on relievers, among other initiatives.28

In contrast, the 2 countries—Thailand and Taiwan, ROC—that experienced increases in asthma mortality and hospitalization rates have relatively lower asthma prevalence rates.24 However, the recent upward trend in asthma prevalence in these countries2,3 may at least in part explain the observed rising trends in asthma mortality and hospitalizations, as suggested by the positive correlation coefficients ($P \geq 0.05$) (Table 4). These results are also consistent with those reported by Anderson et al,19 who analyzed international data from various ISAAC centers. Another plausible factor is a lack of good management practices by general practitioners, as asthma is mostly managed in the primary care setting.18

Negative correlations, though not attaining statistical significance, between trends in asthma mortality or hospitalization rates and C:R were found in 3 countries—Australia, Hong Kong SAR, and Singapore. It should however be noted that C:R obtained represented those of the entire population and not just the pediatric age group. Stafford et al,29 who looked at the US national data, reported similar results; an increase in controller use coupled with a decrease in reliever use corresponded with stabilization of asthma visits.

Although a uniform increase in C:R was observed in the Asia Pacific countries studied, the characteristics of a ratio should be considered. As long as the increase in controllers surpasses that of relievers, or the decrease in relievers outstrips that of controllers, both will result in an increase in C:R. However, our data showed that sales of controllers have been increasing in all countries studied, despite a mixed trend in sales of relievers.

Of interest is a downward kink in both the hospitalization rates and C:R from Hong Kong SAR, which coincided with the outbreak of severe acute respiratory syndrome (SARS) in 2003. There was a sharp decline in asthma hospitalization rates following the SARS outbreak. This observation further suggests that hospital admissions for asthma in developed countries may be affected by extraneous factors. One of the reasons for the drop in asthma hospitalizations could be due to changes in hospital policies that resulted in the prohibition of nebulizer use. In its replacement, metered-dose inhalers with spacers, which were also more readily available in households, were used. This practice could also explain the sharp decline in C:R. The total number of units of relievers sold in 2004 (924,700 units) more than doubled that in 2003 (409,400 units). Similar changes were not observed in other countries affected by SARS. The low asthma hospitalization rates and C:R were sustained in the years after SARS in Hong Kong SAR. Although difficult to verify, the practice of health-seeking behaviors like frequent hand washing, adherence to doctors’ advice, regular exercise, and frequent use of masks when having symptoms of influenza post-SARS as described by Lau et al30 may have reduced respiratory viral infections and, therefore, viral-triggered wheezing. Hospitals in Hong Kong SAR also continued to abide by the policy introduced during SARS, prohibiting use of nebulizers, which possibly explains the sustained high reliever sales.

On one hand, although the data suggest that the burden of asthma in children in terms of hospitalization and mortality appears to be declining, there is also concern that these indicators seem to be increasing in some countries across Asia Pacific. On the other hand, these observations coincided with a uniform increase in C:R ratios across this region. Thus, it is prudent to note that medication is only 1 aspect of asthma management, reflected by the opposing mortality and hospitalization trends observed in different countries. A multi-pronged approach, including proper counseling, social support, and access to quality medical care, is probably necessary to reduce the mortality and hospitalizations in asthmatic children.

**ACKNOWLEDGMENTS**

We thank IMS Health Inc for contributing data on asthma drug sales, Professor Andrew Kemp from the Children's
REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59(5):469–478.

2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733–743.

3. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758–766.

4. Lim DL, Ma S, Wang XS, Cutter J, Chew SK, et al. Trends in sales of inhaled corticosteroids and asthma outcomes in Singapore. Thorax. 2006;61(4):362–363.

5. Sussa S, Ernst P. Use of anti-inflammatory therapy and asthma mortality in Japan. Eur Respir J. 2003;21(1):101–104.

6. Gupta R, Anderson HR, Strachan DP, Maier W, Watson L. International trends in admissions and drug sales for asthma. Int J Tuberc Lung Dis. 2006;10(2):138–145.

7. Kumana CR, Kou M, Lauder IJ, Ip MS, Lam WK. Increasing use of inhaled steroids associated with declining asthma mortality. J Asthma. 2001;38(2):161–167.

8. Sly RM. Decreases in asthma mortality in the United States. Ann Allergy Asthma Immunol. 2000;85(2):121–127.

9. Bollag U, Capkun G, Caesar J, Low N. Trends in primary care consultations for asthma in Switzerland, 1989–2002. Int J Epidemiol. 2005;34(5):1012–1018.

10. Adams RJ, Fuhlbrigge A, Finkelstein JA, Lozano P, Livingston JM, Weiss BK, Weiss ST. Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. Pediatrics. 2001;107(4):706–711.

11. Sussa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. J Allergy Clin Immunol. 2001;107(6):937–944.

12. Nelson HS. Is there a problem with inhaled long-acting beta-adrenergic agonists? J Allergy Clin Immunol. 2006;117(1):3–16.

13. Sears MR. Adverse effects of beta-agonists. J Allergy Clin Immunol. 2002;110(suppl):S322–S328.

14. Sussa S, Ernst P, Bovin JF, Horwitz RI, Habick B, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med. 1994;149(3):604–610.

15. Lai CK, De Guia TS, Kim YY, Kuo SH, Mukhopadhyay A et al. Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study. J Allergy Clin Immunol. 2003;111(2):263–268.

16. WHO Statistical Information Service [Mortality database]. Available at: http://www.who.int/whosis/mort/download/en/index.html. Accessed July 10 2008.

17. Australian Centre for Asthma Monitoring. Asthma in Australia 2005. Canberra: Australian Institute of Health and Welfare; 2005. Asthma Series 2.

18. Yeh KW, Fang W, Huang JL. Increasing the hospitalization of asthma in children not in adults - from a national survey in Taiwan 1996–2002. Pediatr Allergy Immunol. 2008;19(1):13–19.

19. Anderson HR, Gupta R, Kapetanakis V, Asher MI, Clayton T, et al. International correlations between indicators of prevalence, hospital admissions and mortality for asthma in children. Int J Epidemiol. 2008;37(3):573–582.

20. Frischer M, Heafie H, Chapman S, Norwood J, Bashford J, Millson D. Should the corticosteroid to bronchodilator ratio be promoted as a quality prescribing marker? Public Health. 1999;113(5):247–250.

21. Shelley M, Croft P, Chapman S, Pantin C. Is the quality of asthma prescribing, as measured by the general practice ratio of corticosteroid to bronchodilator, associated with asthma morbidity? J Clin Epidemiol. 2000;53(12):1217–1221.

22. GINA. Global Strategy for Asthma Management and Prevention [report]. December 2008. Available at: http://www.ginasthma.org. Accessed February 3, 2009.

23. SPSS for Windows [computer program]. Version 16.0.1. Chicago: SPSS Inc.; 2008.

24. ISAAC Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J. 1998;12(2):315–335.

25. Beasley R, Crane J, Lai CKW, Pearce N. Prevalence and etiology of asthma. J Allergy Clin Immunol. 2000;105(2):S466–S472.

26. National Asthma Council Australia [Web site]. Available at: http://www.nationalasthma.org.au/html/home/index.asp. Accessed October 10, 2008.

27. Asthma Foundations Australia [Web site]. Available at: http://www.asthmaaustralia.org.au. Accessed October 10, 2008.

28. Chong PN, Tan NC, Lim TK. Impact of the Singapore National Asthma Program (SNAP) on preventer-reliever prescription ratio in polyclinics. Ann Acad Med Singapore. 2008;37(2):114–117.

29. Stafford RS, Ma J, Finkelstein SN, Haver K, Cockburn I. National trends in asthma visits and asthma pharmacotherapy, 1978–2002. J Allergy Clin Immunol. 2003;111(4):729–735.

30. Lau JT, Yang X, Tsui HY, Kim JH. Impacts of SARS on health-seeking behaviors in general population in Hong Kong. Prev Med. 2005;41(2):454–462.

APPENDIX

APAPARI members:
Prof S Prescott (Australia)
Prof YZ Chen (China)
Dr S Siregar (Indonesia)
Dr A Tam, Prof GK Wong, Dr D Ng, and Dr MHK Ho (Hong Kong SAR)
Prof A Morikawa (Japan)
Prof JA deBruyne (Malaysia)
Dr A Liang (New Zealand)
A/Prof M Bautista and Prof MW Sumpaico (Philippines)
Prof BW Lee, Prof HPS Van Bever, and A/Prof LP Shek (Singapore)
Prof SI Lee, Prof HR Lee, and Prof YH Rha (South Korea)
Prof JL Huang and Dr KW Yeh (Taiwan, ROC)
Prof P Vichyanond and Prof S Benjaponpitak (Thailand)