

Childhood Asthma: Low and Middle-Income Countries Perspective

Manuel E. Soto-Martínez^{1,2}, Manuel E. Soto-Quiros³, Adnan Custovic⁴

¹Respiratory Department, Hospital Nacional de Niños “Dr. Carlos Sáenz Herrera”, Caja Costarricense Seguro Social, San José, Costa Rica, ²Section of Pediatrics, School of Medicine, Universidad de Costa Rica, San José, Costa Rica, ³Respiratory Medicine, Section of Pediatrics, Hospital CIMA San José, San José, Costa Rica, ⁴National Heart and Lung Institute, Imperial College London, London, UK

Correspondence: *mesotom@ccss.sa.cr*; Tel.: + 506 8843 2240; Fax.: + 506 2255 0363

Received: 9 March 2020; **Accepted:** 30 May 2020

Abstract

Our aim is to review current asthma epidemiology, achievements from the last 10 years, and persistent challenges of asthma management and control in low-middle income countries (LMICs). Despite global efforts, asthma continues to be an important public health problem worldwide, particularly in poorly resourced settings. Several epidemiological studies in the last decades have shown significant variability in the prevalence of asthma globally, but generally a marked increase in LMICs resulting in significant morbidity and mortality. Poverty, air pollution, climate change, exposure to indoor allergens, urbanization and diet are some of the factors that contribute to inadequate control and poor outcomes in developing countries. Although asthma guidelines have been developed to raise awareness and improve asthma diagnosis and treatment, problems with underdiagnosis and undertreatment are still common. In addition, important social, financial, cultural and healthcare barriers are common obstacles in LMICs in achieving control. Given the high burden of asthma in these countries, adaptation and implementation of national asthma guidelines tailored to local needs should be a public health priority. Governmental commitment, education, better health system infrastructure, access to care and effective asthma medications are the cornerstone of achieving success. **Conclusion.** Asthma poses significant challenges to LMICs. Whilst there are ongoing efforts in improving asthma diagnosis and decreasing asthma burden in LMICs; reasons for inadequate asthma control are also common and difficult to tackle. Improving asthma diagnosis, access to appropriate treatment and decreasing risk factors should be key goals to reduce asthma morbidity and mortality worldwide.

Key Words: Low-Middle Income Countries ■ Asthma ■ Asthma Guidelines ■ Children.

Introduction

Asthma is one of the most common chronic diseases in children and adults, leading to significant morbidity and mortality worldwide (1, 2). The World Health Organization (WHO) estimates that more than 300 million people currently suffer from asthma. The Global Burden of Disease estimated that asthma is the 15th highest ranked cause of Years Lived with Disability (3). Epidemiological studies in the last 30 years such as the International Study of Asthma and Allergies in Childhood (ISAAC), showed a marked increase in the prevalence of childhood asthma worldwide over the last few decades, particularly in low- and middle-income countries (LMICs) (4). Striking obser-

vation from these studies include large geographical variations, and the high prevalence reported from some centres in Africa, Latin America and Asia, which equalled that in high-income countries (HICs) such as UK or Australia. Like many other chronic diseases, asthma results from complex gene-environment interactions (5), and the diversity of genetic and environmental exposures between populations may explain the heterogeneity in the prevalence, phenotypes, and severity of asthma around the world.

It is increasingly recognized that asthma is not a single disease, but a complex heterogeneous condition in which clinical presentation may vary depending on different pathophysiological mechanisms that are associated with diverse ge-

netic backgrounds (6-8). It adversely affects quality of life of patients, may limit daytime activity, sleep, school and work attendance, and impacts upon children, their families, healthcare systems and the society. Preventable asthma deaths are still occurring due to a lack of (or inappropriate) asthma management, and in many cases the fatal outcome is associated with avoidable factors (9). Unfortunately, the burden of the disease is higher in low-middle income countries (LMICs) and in underserved populations in HICs (10). For example, a recent large study in the US has highlighted that mortality continues to be higher in African American women (11), and we need to better understand these disparities to develop accurate risk-prediction tools (12).

Asthma in LMICs is not only rising, but is becoming a major public health problem in countries where infectious disease and other health priorities often predominate. Extreme social inequalities, poor access to medical services, poor health education, lack of access to basic infrastructure, fast modernization and 'urbanization' of rural environment, increasing air pollution, smoking habits and change in the diet are some of the factors associated with the rise of asthma. Low accessibility to basic medications, weak healthcare services, poor adherence with prescribed therapy, lack of asthma education, and social and cultural factors have been proposed causes for the lack of control of the disease (13).

In this article which focusses on LMICs, we review asthma epidemiology, achievements from the last 10 years, and persistent challenges of asthma management, and discuss what is needed to improve asthma control, prevent avoidable deaths and decrease the burden of disease.

Epidemiology of Asthma in LMICs

Asthma Prevalence

Most of the information about the prevalence of asthma worldwide originates from a series of repeated cross-sectional studies of the prevalence of asthma symptoms and other allergic diseases

(e.g. rhinitis and eczema) (1). One of the largest and most comprehensive studies in children was the ISAAC study, which demonstrated a striking variation in the prevalence of asthma symptoms between different countries, and between different centres within the same country (14, 15). The ISAAC Phase Three included more than 1.2 million children from 98 countries in all WHO regions, with reported prevalence of asthma in 6-7-year-old children ranging from 2.4% in Jodhpur, India to a staggering 37.6% in Costa Rica (14, 15). In some countries the prevalence increased, in others it plateaued, whilst in some the numbers of affected children decreased. For example, the prevalence had increased by 0.16% per year in Africa, 0.32% per year in Latin America, and 0.07% per year in the Asia/Pacific region, and had decreased by 0.07% per year in Western Europe (14, 15).

Another important finding from ISAAC surveys was the increased prevalence of severe asthma in LMICs, with substantial morbidity and economic costs (15). These findings were confirmed in other studies. For example, a recent study from Uganda, found that in a cohort of 449 children and adults with asthma who were followed for two years, 59.6% of patients with asthma experienced at least one exacerbation in a year, while almost a third experienced three or more exacerbations in a year (16). In Senegal, Hooper and colleagues (17) reported that 62% of children with asthma had severe symptoms. These studies demonstrated an unacceptable level of poor outcomes among patients with asthma in some LMICs and urged for a change.

One issue to take into account is that many factors influence the clinical diagnosis of asthma in different populations. For example, definition of asthma might not be the same everywhere, and the awareness of asthma symptoms, medical training, experience, cultural and social factors may differ as well. Further efforts are currently being made to continue monitoring asthma prevalence and severity globally for both children and adults. For example, the Global Asthma Network (GAN) (<http://www.globalasthmanetwork.org/>) was established in 2012 to regularly collect data on

asthma prevalence, severity and risk factors. GAN phase I is expected to report the current prevalence of asthma symptoms worldwide by 2020.

Asthma Mortality

The Global Burden of Disease estimated that 420,000 deaths occurred globally from asthma in 2016 (2). Although asthma prevalence is higher in HICs, most asthma-related mortality occurs in LMICs. Also, it should be noted that there are differences in mortality time trends between adults and children. For example, in the United States, the overall asthma-related mortality has declined from 1999 to 2015, but the mortality rate among children aged 1-14 years has not changed (11). Unfortunately, information is scarce on paediatric asthma mortality in LMICs.

In a recent analysis which included children and adults from 46 countries (mainly high- and middle-income), the estimated global asthma mortality rates did not change over the past decade (10). The important finding of this study was that asthma mortality significantly reduced from 1993 to 2006 (0.44 to 0.19 deaths per 100,000 people), but there were no further improvements since 2006, with the global asthma mortality remaining unchanged. As reported by others, it is likely that the reduction in asthma mortality in the 1990s through the 2000s was primarily due to the increase in use of the anti-inflammatory asthma treatments (particularly inhaled corticosteroids) (18). However, it is of concern that in the last 15 years, no further gains have been made.

Environmental Exposures and Other Risk Factors Associated with Poor Asthma Outcomes in Children in LMICs

Variability in the prevalence of asthma between countries and the increasing prevalence in the last few decades suggest that environmental exposures have an important role on asthma occurrence (19). Many risk factors which are amenable to intervention have been identified within LMICs, including

active smoking and environmental tobacco smoke (ETS) exposure, indoor and outdoor air pollution (such as biomass fuel), allergen exposure and overuse of antibiotics (20-23). Moreover, other factors related to poverty, including high-risk conduct exposures, early respiratory viral infections, dietary factors and urbanization may be determinants of the trends of increased asthma prevalence. For example, in an ecological study in Ecuador, Rodriguez et al. (23) showed that prevalence of asthma increased with increasing levels of urbanization. However, data from Ghana suggest that rather than urban living *per se*, it is affluence and westernized lifestyle that are associated with higher risk (24-26). In Brazil, better asthma outcomes (reduced hospital admission and mortality) were associated with living in an urban environment, possibly due to the better access to health care and free ICS supply (27). Although this rural-urban gradient in asthma remains poorly understood, it could be due to levels of outdoor and indoor pollution, microbial or parasitic infections, or changes in lifestyle (e.g. diet).

Indoor Air Pollution

WHO estimates that more than 3 billion people rely on solid fuels as a source of energy, contributing to indoor air pollution. Passive exposure to tobacco smoke and indoor biomass combustion are considered the most important sources of indoor pollution which may be relevant to the development of childhood asthma. Prevalence of ETS exposure in developing countries varies significantly from 10 to 60%. In most countries, active smoking is common and may be due to cultural factors, lack of regulation and poor law enforcement. In utero maternal smoking and postnatal exposures to cigarette smoking are associated with asthma development and asthma morbidity in childhood (28). Coal and wood combustion indoors have been reported to increase the risk of upper and lower respiratory infections in infants and preschool children, and may also be associated with increased asthma prevalence (2). Analysis of global ISAAC data reported an association between open-fire

cooking and asthma symptoms in both children aged 6-7 years and those aged 13-14 years (29). In Guatemala, indigenous children exposed to open fire for cooking had a higher prevalence and severity of asthma symptoms (30).

Outdoor Air Pollution

Outdoor pollution from motor vehicles, very common in urban areas, is associated with persistent respiratory symptoms and higher prevalence of asthma (31-34). A study in Puerto Rico showed joint detrimental effects of vitamin D deficiency and traffic-related air pollution on severe asthma exacerbations (35). In a recent meta-analysis, Orellano *et al* found that living in a polluted environment in Latin America and the Caribbean was associated with higher rates of asthma in children (31). In 2019, several large studies linked air pollution to poor lung function (36), increased risk of asthma deaths (37) and high risk of asthma development (38). A study in China on >7,000 asthma deaths between 2013 and 2018 found that short-term exposures to fine particulate matter <2.5 mm in diameter (PM_{2.5}), NO₂, and O₃ increased mortality (37). Among asthmatic children in Peru, air pollution adversely affected asthma control and quality of life (39, 40). Finally, perinatal exposure to ambient ultrafine particles (<0.1 mm diameter) has been linked to the onset of asthma in children (independent of PM_{2.5} and NO₂) (38). Air pollution may interact with other indoor environmental exposures. For example, ambient air pollutants and indoor endotoxin exposure act synergistically to increase increased emergency room visits for asthma in both children and adults (41). Importantly, the adverse health effects were apparent at concentrations below current standards in HICs, suggesting that air quality standards will need to be strengthened if we are to protect patients with chronic lung diseases (42), and emphasise the need for developing and implementing effective policy measures in LMICS, which are most affected by rising pollution (12, 43).

Allergen Exposure

Although sometimes considered a less important contributing factor for asthma prevalence in some regions of LMICs (44), atopy is high in most Latin American countries. Using data from phase two of the ISAAC study, Weinmayr *et al.* (44) found that the association between current wheeze and skin prick test positivity was statistically significant in both affluent (OR 4.0, 95%CI 3.5-4.6) and non-affluent (OR 2.2, 95%CI 1.5-3.3) countries. Exposure to common allergens is one of the triggers for developing asthma symptoms, but its relationship to asthma development is unclear (45). Allergens originate from a wide range of sources, including house dust and storage mites, animals, indoor moulds and cockroaches. Exposure to indoor allergens has been associated with asthma symptoms, airway hyperresponsiveness and severe asthma exacerbations in several cross-sectional studies in LMICs (46, 47). In a study performed in Costa Rica, we studied 403 asthmatics (ages between 6 and 14 years) who were carefully assessed using symptom questionnaires, spirometry, measurements of serum total and allergen-specific IgE, peripheral blood eosinophil count, and body mass index, and the assessment of airway responsiveness to methacholine. In a multivariate analysis, parental report of mould exposure in the house, low FEV₁/FVC ratio, and a positive IgE response to house dust mite were strongly associated with airway hyperresponsiveness to methacholine (46). In a cross-sectional study in Puerto Rico, Blatter *et al.* (48) found that among children with asthma, those with the highest exposure to glucan (a component of fungal cell wall) had much greater odds of one or more visits to emergency room for acute asthma symptoms (OR 8.7, 95%CI 2.7-28.4).

Diet and Obesity

Changes in diet and increasing obesity have been related with the increase of asthma prevalence worldwide. Vitamin D deficiency has been associated with asthma in several LMICs (49, 50). Among 616 school-aged Costa Ricans with asth-

ma, low vitamin D level (28% of children with levels of vitamin D <30 ng/ml), was associated with increased odds of asthma-related emergency department visits or hospitalizations in the previous year (50). This was also the first epidemiological study to demonstrate an association between low vitamin D levels and increased serum IgE and eosinophil counts (50). Other studies which focused on dietary patterns have shown that fast food or a “Western” dietary pattern is associated with higher risk of asthma presence, and also asthma severity. Overweight and obesity are common in LMICs, particularly in Latin America, where recent studies suggested a prevalence between 16-36% among children (51). Similar to HICs, overweight and obesity in LMICs have been associated with asthma presence and severity (52, 53).

Socioeconomic Factors

Socioeconomic factors and poverty play important role in asthma control. Among children of different Latino ethnicities, girls from low-income families had lower adherence to inhaled corticosteroids (ICS) over a 12-month period, and Puerto Rican children had poorer outcomes than Mexican (54, 55). Worryingly, less than a quarter of children were adherent with treatment. Low income and other social determinants result in poor access to care, low accessibility to essential basic therapy, and wide disparities in health care (56). However, additional issues besides access to healthcare and availability of asthma medications may contribute to high asthma burden in underserved populations, including psychosocial stressors, behavioural risk factors, poor medication adherence, underuse of primary care providers, but overuse of emergency health services, increased school and work absenteeism and increase in general morbidity and mortality (57, 58). For example in a cohort of 98 children from low income families in Brazilian rural area, Jentzsch et al. (59) showed that compliance to recommendations to reduce or minimize allergen and/or trigger factor exposure was achieved in less than 9.2% of patients. Moreover, in HIC, socially disadvantage paediatric pa-

tients have elevated asthma morbidity as a result of socio-economic status, minority affiliation, psychosocial stress and high adverse environmental exposures (60).

Managing asthma in poor or disadvantaged population can be challenging and is often associated with worse outcomes. However, interventions to address some modifiable factors in these population are possible and have had good results. Examples of these interventions include asthma education and self-management, environmental control in the home, culture-specific asthma programs, school-based programs, home visits by health workers (e.g. nurses, doctors, social workers), tobacco smoke cessation or a combination of the above (18, 61).

Difficulties in Asthma Care in LMICs

It has been recognized that management of asthma is a difficult task in HICs, and even more so in LMICs. As most other common non-communicable diseases, asthma represents a challenge to public health because of its high prevalence, increasing severity, projected trends, and economic burden. The financial impact for persons with asthma and their families, as well as for healthcare systems and governments, is very high. At the same time, most LMICs face communicable diseases such as pneumonia, tuberculosis, dengue, HIV and other infectious diseases.

Amongst many obstacles to good disease control, we wish to highlight the lack of education about asthma, issues related to medication availability and delivery, cultural barriers, and low priority by health authorities. Global asthma guidelines have played an important role in raising the awareness of childhood asthma and improving diagnosis and management in LMICs. However, most asthma guidelines are long and complex, making them difficult to implement in the healthcare systems already overstretched by the pressure of communicable diseases. To be effective in reducing the burden of asthma, guidelines must be relevant to the specific population, must be culturally acceptable, and must be adapted to each health

system formalized with political engagement and commitment. Various national and/or regional asthma strategies in LMICs have emphasised aspects which are of relevance to specific areas or countries, including the medication access and affordability, specific environmental exposures, lack of asthma education, co-morbidities, and psychological problems (62).

Similar to other chronic diseases such as hypertension and diabetes; asthma control is not achieved in most patients, despite available management guidelines. A survey performed in 11 countries in Latin America showed that only 2.4% of patients met all of the GINA criteria for total asthma control, suggesting under-recognition of uncontrolled asthma, underuse of appropriate controller treatment, inadequate patient education, and patient denial as possible explanations (63). Since the development of worldwide guidelines on the diagnosis and management of asthma, special attention on achieving and maintaining asthma control as the key goal in asthma treatment has been a priority. In clinical studies of children with asthma in LMICs, the most cost-effective intervention for improving asthma control and preventing acute exacerbations is emphasis on the use and availability of controller medications, such as ICS for mild asthma, with the addition of long-acting β -2 agonist for moderate asthma (18).

Comprehensive approaches such as developing models for highly cost-effective, affordable and feasible interventions are critical for asthma control. Unfortunately, there is limited information on the impact of population-based interventions for asthma control, but some studies from LMICs indicate it may be cost-effective. Public health efforts have improved management in some countries. In Brazil, an ecologic study showed that municipalities which were offering free medication for asthma had lower hospital admission rates and lower mortality from asthma (64). In a study in Costa Rica, a marked decrement in hospitalizations (53%) and mortality (80%) was seen following implementation of the National Asthma Plan (NAP) and the use of beclomethasone as an affordable preventive medication (18). This NAP consisted of education

meetings at all major public (both urban and rural) healthcare centres, which facilitated early diagnosis, implementation of non-pharmacological measures (smoking ban, adherence, reduction of indoor allergens), early treatment using ICS as first-line therapy for asthma control, the use of spacers, early use of reliever medication to treat exacerbations, appropriate referral to specialists for asthma care, and avoidance of common allergen sources (e.g. dust-mite and cockroaches) or tobacco smoke.

Despite undeniable fact that effective national asthma strategy results in a reduction of the burden of asthma on society as a whole, many countries lack such program. This problem has been highlighted by the recent email survey of investigators from 112 countries which participate in the Global Asthma Network. Of the 112 countries, only 26 (23.3%) had a national plan for children, 24 (21.4%) had a national asthma plan for adults, and 22 (19.6%) countries had a strategy for both children and adults. Unfortunately, the proportion of LMICs with a strategy was lower than that in high-income countries (62).

Development and Implementation of Asthma Guidelines in LMICs

The development and implementation of asthma treatment guidelines can be expensive and challenging. Figure 1 illustrate most components that should be included in an asthma strategy to achieve better outcomes. Guidelines should include realistic recommendations on how to improve early detection of asthma symptoms, control of environmental risk factors, and provide mechanisms of access to effective anti-inflammatory treatment.

Many obstacles are faced by LMICs in implementing asthma guidelines. Table 1 lists most barriers that have to be overcome by these countries in order to achieve better outcomes and decrease the economic and social burden of asthma. Although some problems may be unique to particular countries, most LMICs share similar barriers to asthma management. Thus, collaborative public health and research efforts could have a major impact at

a regional level. Such efforts should include vigorous campaigns to control and eliminate tobacco use, asthma education and non-pharmacological interventions (e.g. replacing biomass fuels, reducing allergen exposure, psychological support and weight loss).

One of the most important issues is the availability and affordability of essential asthma medications. Optimal asthma care requires universal access to medications, and yet many asthmatics in LMICs or in the underserved population in HICs have difficulty accessing necessary medications. In a cross-sectional study conducted in 52 countries,

huge variability was found in affordability across countries. In this study, the availability of ICS was particularly low, with some countries subsidizing the asthma medicines thereby making them free or less expensive to patients, but other increasing their price. Many patients have only access to a bronchodilators, and those who may benefit from affordable ICS such as beclomethasone, can spend between half a day's wages to even 14-days wage for one inhaler device (65). We would argue that cheap inhaled anti-inflammatory agents (e.g. beclomethasone) should be available free of charge for children with asthma in LMICs.

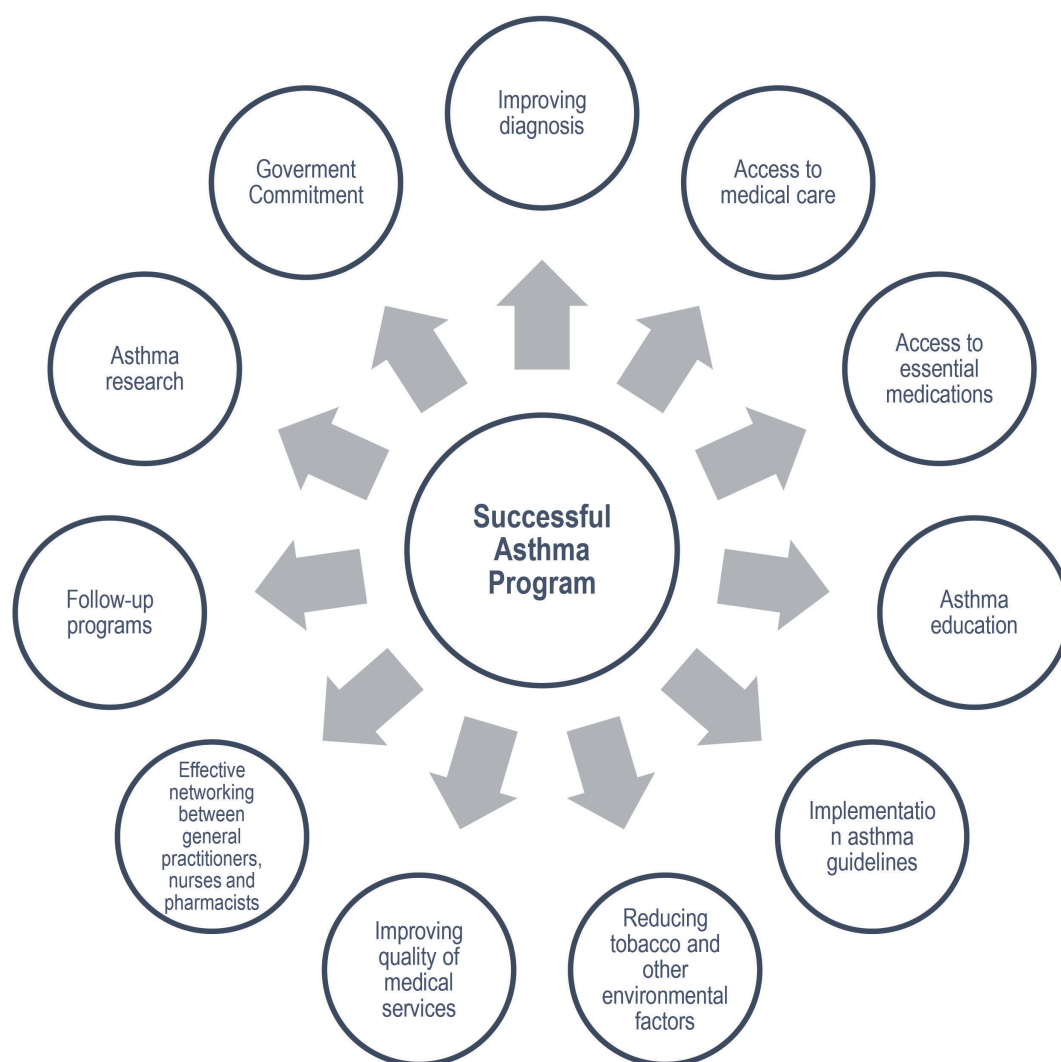


Figure 1. Components of a Successful Asthma Program; Adapted from (66, 67).

Table 1. Barriers for Asthma Control and National Asthma Strategies Implementation Adapted from The Global Asthma Network Report 2018 (2)

Disease inherent barriers
Underdiagnosis
Undertreatment or inadequate treatment
Lack of adherence
Environmental
Air pollution (both indoor and outdoor pollution)
Tobacco smoke
Occupational triggers
Healthcare system
Low public health priority
Low rates of strategies dissemination
Lack or weak health system infrastructure
Poor access and distribution of asthma medications
Inadequate governmental resources for asthma care
Lack of continuing medical education and training systems
Patient barriers
Lack of information
Over-reliance on acute medication (e.g. SABA)
Use of unproven or alternative therapies
Cultural and social problems and beliefs
Medication beliefs

Conclusions

Asthma burden in LMICs is high and continues to increase. Whilst there are ongoing efforts to develop novel (often expensive) therapies targeting patients in high-income countries, a great impact can be achieved by improving asthma control, preventing asthma attacks, and decreasing asthma burden in LMICs. Reasons for inadequate asthma control in underserved populations include low accessibility of effective controller medications, weak infrastructure of health services for the management of chronic diseases, poor adherence to therapy, lack of educational approaches, persistent exposure to risk factors and social, cultural and language barriers. Improving access to appropriate treatment including ICS, salbutamol and spacers should be a key goal to reduce asthma morbidity and mortality worldwide.

Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. *Front Pediatr*. 2019;7:246.
2. The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network; 2018.
3. DALYs GBD, Collaborators H, Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet*. 2015;386(10009):2145-91.
4. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, 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):758-66.
5. Custovic A, Marinho S, Simpson A. Gene-environment interactions in the development of asthma and atopy. *Expert Rev Respir Med*. 2012;6(3):301-8.
6. Saglani S, Custovic A. Childhood Asthma: Advances Using Machine Learning and Mechanistic Studies. *Am J Respir Crit Care Med*. 2019;199(4):414-22.
7. Custovic A, Henderson J, Simpson A. Does understanding endotypes translate to better asthma management options for all? *J Allergy Clin Immunol*. 2019;144(1):25-33.
8. Oksel C, Haider S, Fontanella S, Frainay C, Custovic A. Classification of Pediatric Asthma: From Phenotype Discovery to Clinical Practice. *Front Pediatr*. 2018;6:258.
9. Levy ML. The national review of asthma deaths: what did we learn and what needs to change? *Breathe (Sheff)*. 2015;11(1):14-24.
10. Ebmeier S, Thayabaran D, Braithwaite I, Benamara C, Weatherall M, Beasley R. Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet*. 2017;390(10098):935-45.
11. Pennington E, Yaqoob ZJ, Al-Kindi SG, Zein J. Trends in Asthma Mortality in the United States: 1999 to 2015. *Am J Respir Crit Care Med*. 2019;199(12):1575-7.
12. Saglani S, Wisnivesky JP, Charokopos A, Pascoe CD, Halayko AJ, Custovic A. Update in Asthma 2019. *Am J Respir Crit Care Med*. 2020 Apr 27. Epub ahead of print.
13. Bousquet J, Bousquet PJ, Godard P, Daures J-PP. The public health implications of asthma. *Bulletin of the World Health Organization*. 2005;83(7):548-54.
14. Asher IM, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, 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):733-43.
15. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-83.
16. Kirenga BJ, de Jong C, Mugenyi L, Katagira W, Muhofa A, Kanya MR, et al. Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study. *Thorax*. 2018;73(10):983-5.
17. Hooper LG, Dieye Y, Ndiaye A, Diallo A, Fan VS, Neuzil KM, et al. Estimating pediatric asthma prevalence in rural senegal: A cross-sectional survey. *Pediatr Pulmonol*. 2017;52(3):303-9.
18. Soto-Martínez M, Avila L, Soto N, Chaves A, Celedon JC, Soto-Quirós ME. Trends in hospitalizations and mortality from asthma in Costa Rica over a 12- to 15-year period. *J Allergy Clin Immunol Pract*. 2014;2(1):85-90.
19. Custovic A, Simpson A. Environmental allergen exposure, sensitisation and asthma: from whole populations to individuals at risk. *Thorax*. 2004;59(10):825-7.
20. Masoli M, Fabian D, Holt S, Beasley R, Global Initiative for Asthma P. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004;59(5):469-78.
21. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clin Exp Allergy*. 2015;45(1):137-45.
22. Soto-Martínez ME, Yock-Corrales A, Camacho-Badilla K, Abdallah S, Duggan N, Avila-Benedictis L, et al. The current prevalence of asthma, allergic rhinitis, and eczema related symptoms in school-aged children in Costa Rica. *J Asthma*. 2019;56(4):360-8.
23. Rodríguez A, Vaca M, Oviedo G, Erazo S, Chico ME, Teles C, et al. Urbanisation is associated with prevalence of childhood asthma in diverse, small rural communities in Ecuador. *Thorax*. 2011;66(12):1043-50.
24. Addo-Yobo EO, Custovic A, Taggart SC, Asafo-Agyei AP, Woodcock A. Exercise induced bronchospasm in Ghana: differences in prevalence between urban and rural school-children. *Thorax*. 1997;52(2):161-5.
25. Addo-Yobo EO, Custovic A, Taggart SC, Craven M, Bonnie B, Woodcock A. Risk factors for asthma in urban Ghana. *J Allergy Clin Immunol*. 2001;108(3):363-8.
26. Addo-Yobo EO, Woodcock A, Allotey A, Baffoe-Bonnie B, Strachan D, Custovic A. Exercise-induced bronchospasm and atopy in Ghana: two surveys ten years apart. *PLoS Med*. 2007;4(2):e70.
27. Ponte EV, Cruz AA, Athanazio R, Carvalho-Pinto R, Fernandes FLA, Barreto ML, et al. Urbanization is associated with increased asthma morbidity and mortality in Brazil. *Clin Respir J*. 2018;12(2):410-7.
28. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics*. 2012;129(4):735-44.
29. Wong GW, Brunekreef B, Ellwood P, Anderson HR, Asher MI, Crane J, et al. Cooking fuels and prevalence of asthma: a global analysis of phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Lancet Respir Med*. 2013;1(5):386-94.
30. Schei MA, Hessen JO, Smith KR, Bruce N, McCracken J, Lopez V. Childhood asthma and indoor woodsmoke from cooking in Guatemala. *J Expo Anal Environ Epidemiol*. 2004;14 Suppl 1:S110-7.
31. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Association of outdoor air pollution with the prevalence of asthma in children of Latin America and the Caribbean: A systematic review and meta-analysis. *J Asthma*. 2018;55(11):1174-86.
32. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. *PLoS One*. 2017;12(3):e0174050.
33. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet*. 2014;383(9928):1581-92.
34. Escamilla-Núñez MC, Barraza-Villarreal A, Hernández-Cadena L, Moreno-Macias H, Ramírez-Aguilar M, Siemra-Monge JJ, et al. Traffic-related air pollution and respiratory symptoms among asthmatic children, resident in Mexico City: the EVA cohort study. *Respir Res*. 2008;9:74.
35. Rosser F, Brehm JM, Forno E, Acosta-Pérez E, Kurland K, Canino G, et al. Proximity to a major road, vitamin D insufficiency, and severe asthma exacerbations in Puerto Rican children. *Am J Respir Crit Care Med*. 2014;190(10):1190-3.
36. Wooding DJ, Ryu MH, Huls A, Lee AD, Lin DTS, Rider CF, et al. Particle Depletion Does Not Remediate Acute Effects of Traffic-related Air Pollution and Allergen. A Randomized, Double-Blind Crossover Study. *Am J Respir Crit Care Med*. 2019;200(5):565-74.
37. Liu Y, Pan J, Zhang H, Shi C, Li G, Peng Z, et al. Short-Term Exposure to Ambient Air Pollution and Asthma Mortality. *Am J Respir Crit Care Med*. 2019;200(1):24-32.
38. Lavigne E, Donelle J, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, et al. Spatiotemporal Variations in Ambient Ultrafine Particles and the Incidence of Childhood Asthma. *Am J Respir Crit Care Med*. 2019;199(12):1487-95.
39. Hansel NN, Romero KM, Pollard SL, Bose S, Psoter KJ, Underhill LJ, et al. Ambient Air Pollution and Variation in Multiple Domains of Asthma Morbidity among Peruvian Children. *Ann Am Thorac Soc*. 2019;16(3):348-55.
40. Mutlu GM, Peker Y. Air Pollution, Asthma, and Sleep Apnea: New Epidemiological Links? *Ann Am Thorac Soc*. 2019;16(3):307-8.

41. Mendy A, Wilkerson J, Salo PM, Weir CH, Feinstein L, Zeldin DC, et al. Synergistic Association of House Endotoxin Exposure and Ambient Air Pollution with Asthma Outcomes. *Am J Respir Crit Care Med*. 2019;200(6):712-20.
42. Abramson MJ, Guo Y. Indoor Endotoxin Exposure and Ambient Air Pollutants Interact on Asthma Outcomes. *Am J Respir Crit Care Med*. 2019;200(6):652-4.
43. Beamer PI. Air Pollution Contributes to Asthma Deaths. *Am J Respir Crit Care Med*. 2019;200(1):1-2.
44. Weinmayr G, Weiland SK, Bjorksten B, Brunekreef B, Buchele G, Cookson WO, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med*. 2007;176(6):565-74.
45. Custovic A. To what extent is allergen exposure a risk factor for the development of allergic disease? *Clin Exp Allergy*. 2015;45(1):54-62.
46. Ly NP, Soto-Quiros ME, Avila L, Hunninghake GM, Raby BA, Laskey D, et al. Paternal asthma, mold exposure, and increased airway responsiveness among children with asthma in Costa Rica. *Chest*. 2008;133(1):107-14.
47. Herrera AB, Rodriguez LA, Niederbacher J. Biological pollution and its relationship with respiratory symptoms indicative of asthma, Bucaramanga, Colombia [in Spanish]. *Biomedica*. 2011;31(3):357-71.
48. Blatter J, Forno E, Brehm J, Acosta-Perez E, Alvarez M, Colon-Semidey A, et al. Fungal exposure, atopy, and asthma exacerbations in Puerto Rican children. *Ann Am Thorac Soc*. 2014;11(6):925-32.
49. Brehm JM, Acosta-Perez E, Klei L, Roeder K, Barmada M, Boutaoui N, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. *Am J Respir Crit Care Med*. 2012;186(2):140-6.
50. Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179(9):765-71.
51. Rivera JA, de Cossio TG, Pedraza LS, Aburto TC, Sanchez TG, Martorell R. Childhood and adolescent overweight and obesity in Latin America: a systematic review. *Lancet Diabetes Endocrinol*. 2014;2(4):321-32.
52. Noal RB, Menezes AM, Macedo SE, Dumith SC, Perez-Padilla R, Araujo CL, et al. Is obesity a risk factor for wheezing among adolescents? A prospective study in southern Brazil. *J Adolesc Health*. 2012;51(6 Suppl):S38-45.
53. Forno E, Acosta-Perez E, Brehm JM, Han YY, Alvarez M, Colon-Semidey A, et al. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. *J Allergy Clin Immunol*. 2014;133(5):1308-14, 1314.e1-5.
54. Arcoleo KJ, McGovern C, Kaur K, Halterman JS, Mammen J, Crean H, et al. Longitudinal Patterns of Mexican and Puerto Rican Children's Asthma Controller Medication Adherence and Acute Healthcare Use. *Ann Am Thorac Soc*. 2019;16(6):715-23.
55. Wisnivesky JP, Federman AD. The "Nonadherent" Patient with Asthma: Time to Revise the Paradigm. *Ann Am Thorac Soc*. 2019;16(6):676-7.
56. Sanchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. Asthma care in resource-poor settings. *World Allergy Organ J*. 2011;4(4):68-72.
57. Cardet JC, Louisias M, King TS, Castro M, Codispoti CD, Dunn R, et al. Income is an independent risk factor for worse asthma outcomes. *J Allergy Clin Immunol*. 2018;141(2):754-60.e3.
58. Rona RJ. Asthma and poverty. *Thorax*. 2000;55(3):239-44.
59. Jentzsch NS, Camargos PA, de Melo EM. Compliance with environmental control measures in the homes of children and adolescents with asthma. *J Bras Pneumol*. 2006;32(3):189-94.
60. Coleman AT, Teach SJ, Sheehan WJ. Inner-City Asthma in Childhood. *Immunol Allergy Clin North Am*. 2019;39(2):259-70.
61. Li P, Guttmann A. Recent innovations to improve asthma outcomes in vulnerable children. *Curr Opin Pediatr*. 2009;21(6):783-8.
62. Asher I, Haahtela T, Selroos O, Ellwood P, Ellwood E, Global Asthma Network Study G. Global Asthma Network survey suggests more national asthma strategies could reduce burden of asthma. *Allergol Immunopathol (Madr)*. 2017;45(2):105-14.
63. Neffen H, Fritscher C. Asthma control in Latin America: the asthma insights and reality in Latin America (AIRLA) survey. Asthma control in Latin America: the asthma insights and reality in Latin America (AIRLA) survey. *Rev Panam Salud Publica*. 2005;17(3):191-7.
64. Cruz AA, Souza-Machado A, Franco R, Souza-Machado C, Ponte EV, Moura Santos P, et al. The impact of a program for control of asthma in a low-income setting. *World Allergy Organ J*. 2010;3(4):167-74.
65. Babar ZU, Lessing C, Mace C, Bissell K. The availability, pricing and affordability of three essential asthma medicines in 52 low- and middle-income countries. *Pharmacoeconomics*. 2013;31(11):1063-82.
66. Ait-Khaled N, Enarson D, Bousquet J. Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management. *Bull World Health Organ*. 2001;79(10):971-9.
67. Tan WC. Asthma management in the developing world: achievements and challenges. *Expert Rev of Respir Med*. 2014;2(3):323-8.