MAJOR CURRENT PROBLEMS IN ASTHMA

* Unmet needs in asthma
* Asthma exacerbations
* Severe asthma
* Adherence to asthma treatment
* Social determinants of asthma
* Inequities and asthma
Unmet needs in asthma cover almost every aspect of the disease. They can be classified as unmet needs due to missing scientific knowledge, related to patient care and chronic nature of the disease, and related to socioeconomic factors.

Knowledge on pathomechanisms of asthma has several essential gaps (Table 1). One main historical reason was disregarding its complexity and consideration of asthma as a single disease entity. It is now becoming clear that the complex interplay between the environment and the immune system in combination with the response of the tissue cells ultimately determines the development and expression of asthma with different phenotypes and endotypes. Particularly, the intrauterine and lifelong exposure to every facet of the environment, the so called exposome and its role in activation and tolerance thresholds of the tissues and the immune system represent major targets for research.

Asthma prevention includes primary prevention to prevent the development of the disease and secondary prevention to prevent asthma development in subjects with atopy. There is no established way of primary prevention of asthma and a series of questions in the public remain unanswered such as, if parents have asthma, will the child also develop asthma? Is there any way to avoid this? If asthma develops, will it be possible to outgrow asthma?

A global unmet need is the international and regional burden of access to drugs and good patient care. Asthma prevalence is globally increasing in parallel to urbanization and economic development, however individuals with low socio-economic status, minorities and urban populations are deeply affected. Low socio-economic status individuals are highly exposed to triggers such as environmental pollutants, poor housing, indoor allergens, and psychosocial stressors. It is essential to develop global approaches to fight with inequities, educational deficits and delivery of high quality asthma care in the whole World to improve individual patient care.

The possibility of cure in asthma is a fundamental issue for research, because the currently used medications only temporarily relieve
Unmet needs in asthma

remain essential problems similar to many chronic diseases (Table 2). It is expected that patient-tailored therapies will improve and become a standard in patient care one day. Accordingly, problems in adherence to treatment, self management, prevention of exacerbations, development of severe asthma, side effects of medications are expected to diminish in time.

**Biomarkers** to diagnose, subgroup and follow patients represent an important need in most of the chronic diseases. We have no biological indicators that accurately predict the development of asthma, identify high risk children and the disease course of an asthmatic patient. In addition, there is very few indicators for the selection of a certain therapy responsive patients, such as allergen-immunotherapy or a treatment with a biological immune response modifier (Table 3). Apparently, novel biologicals should be developed together with their biomarker for the selection of responsive patients.

**Asthma exacerbations** are linked with high morbidity, significant mortality and represent an outstanding problem in the clinical management of asthma. They constitute the biggest immediate risk and anxiety to patients and their families, linked to continuous decline in lung function over time and generate a huge financial burden in health care systems. Targeting respiratory viruses with vaccines will be one of the most efficient ways to prevent exacerbations.

**Severe asthma** represents one of the most significant burdens of all diseases from all perspectives of affected patients and health care system. These individuals use a large proportion of public health resources devoted to the treat-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Major research gaps for asthma</th>
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<td>• Immunological basis of asthma epidemic</td>
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<td>• Innate immune response and tissue response to exposable such as molecules that are coexposed with allergens, microbes, pollutants</td>
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<td>• Role of novel subsets of T cells, B cells and innate lymphoid cells in asthma development</td>
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<td>• Epithelial barrier function and its role in asthma development and chronicity</td>
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<td>• Mechanisms of development of immune tolerance to allergens and novel ways to induce this</td>
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<td>• Understanding epigenetic regulation of the asthmatic inflammation</td>
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<td>• Development of novel biologicals for treatment</td>
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<td>• Identification of novel biomarkers for endotyping patients for the prediction of treatment response and prognosis</td>
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<td>• Development of immunological registries and disease-specific biobanks</td>
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**TABLE 2**

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<td>• Patient adherence</td>
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<td>• Inequities in asthma care in the whole World</td>
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<td>• Education of patients and careers</td>
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<td>• Self management of patients</td>
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<td>• Prevention of asthma exacerbations</td>
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<td>• Side effects of medications</td>
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<td>• Better drug delivery systems</td>
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<td>• Patient tailored therapies</td>
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**TABLE 3**

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<th>Next steps in diagnosis of asthma endotypes</th>
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<td>• Improvement of molecular diagnostics methods</td>
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<td>• Discovery of surrogate biomarkers</td>
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<td>• Easy and standardized tests for cellular diagnosis from peripheral blood</td>
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<td>• Easy and standardized analysis of exhaled breath condensate and sputum</td>
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<td>• Development of point of care assays and devices</td>
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<tr>
<td>• Development of tests for prediction of exacerbations and treatment response</td>
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<tr>
<td>• Development of tests for the analysis of immune response to respiratory viruses</td>
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TABLE 4

Problems in drug development for asthma

- There is a huge amount of missing knowledge in the complexity of the whole disease spectrum with highly complex molecular mechanisms and multiple subgroups
- Almost no biomarkers exist for patients’ selection, therapy response, and for prediction of disease development
- There is limited space to improve the patients response over existing therapies, because currently used inhaled steroid and β-adrenergic agonist combination therapy is effective and relatively inexpensive
- Most drugs that are effective in mouse models have failed in clinical trials, because currently available animal models do not represent human asthma
- Individual outcomes are different due to molecular complexity and cannot be distinguished using a bulk approach
- Most novel biologicals are unlikely to be effective, when used alone and it is not possible to study the combination of two new biologicals that may potentiate each other until one of them is approved

Guidelines developed for asthma have grouped all asthma phenotypes and endotypes together as if they are a single uniform disease. The heterogeneity of asthma, defining of asthma subgroups and their particular needs have not been taken into account. Regional needs and differences have not been deeply considered and input of patients themselves have been neglected. An advance for currently existing guidelines was the implementation of evidence-based medicine as a movement toward a more structured assessment of clinical knowledge and was providing a method of evaluating health effects and economic impact. Next generation global guidelines will have to appreciate the needs of individuals, consider regional differences, different disease subgroups with a scientific approach.

KEY REFERENCES

The Global Initiative for Asthma (GINA), defines acute exacerbations of asthma as “episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms, accompanied by decreases in expiratory airflow that can be quantified by measurement of lung function.” They are a marker of severe loss of control and require urgent treatment to prevent a serious outcome. Exacerbations constitute the greatest immediate risk to patients, are associated with accelerated decline in lung function over time, significant anxiety to patients and family members alike, and generate the greatest financial burden for health care systems.

Airflow obstruction during exacerbations stems from a combination of concentric smooth muscle contraction, airway wall oedema, airway inflammatory cell infiltration and luminal obstruction with mucus and cellular debris (Figure 1). Exacerbations vary greatly in speed of onset, intensity and in time to resolution both between patients and for individual patients.

EPIDEMIOLOGY OF ASTHMA EXACERBATIONS

The frequency with which asthma exacerbations are reported in the clinical trial literature ranges from 0.3 - 0.9 /patient /year and varies according to the definition of exacerbation used and the severity and/or level of disease control of the asthmatic population being studied. However surveys of ‘real life’ asthma patients indicate that the incidence of exacerbations is much higher, particularly in poorly controlled asthmatics.

Additional factors reported to be associated with frequent exacerbations include female sex, obesity, psychopathology, chronic sinusitis, gastro-oesophageal reflux and obstructive sleep apnoea.

AETIOLOGY OF ASTHMA EXACERBATIONS

Since the early 1960s, viral respiratory tract infections have been reported as triggers for asthma exacerbations. Following the intro-
The introduction of polymerase chain reaction (PCR) technology in the 1990s a clear demonstration of this important link has been repeatedly observed with rhinoviruses consistently highlighted as the most frequently detected pathogens (Figure 2). Influenza viruses and respiratory syncitial virus (RSV) as well as other respiratory viruses are less common, but well recognised precipitants.

A growing body of evidence supports the view that viral infection and allergy interact to increase the risk of an exacerbation with the virus acting as a cofactor along with environmental allergens to initiate an exacerbation to an extent that neither alone can achieve. The apparent synergy between respiratory viruses and exposure to sensitising allergens has been reported in both children and adults and suggests atopic asthma is associated with more severe illness following virus infection than asthma in the absence of allergic sensitisation (Figure 3).

Bacteria (in particular the atypical organisms *Mycoplasma pneumoniae* and *Chlamyphila pneumoniae*) have also been reported as contributors to exacerbations however differences in sampling/diagnostic methodologies have led to inconsistent results. Standard bacterial infection has recently been reported as important as viral in children under 3 years of age. Further studies are required to confirm this and to investigate other ages. Other important but less common triggers include pollutants, smoking, and psychological factors.

**PREVENTION OF EXACERBATIONS**

Non-pharmacologic approaches emphasised in recent years include the role of patient education and self-management plans, which have been convincingly shown to reduce exacerbations requiring hospitalisation. A large number of clinical trials have also shown the benefit of drug therapies in reducing exacerbations including inhaled corticosteroid (ICS) treatment (with a combination of ICS and long-acting bronchodilators being more effective than ICS alone) as well as leukotriene receptor antagonists. In addition, monoclonal antibodies directed against IgE and the Th2 cytokines IL-5 & IL-13 have shown promise in selected asthmatics.

Finally, vaccination against respira-
Figure 3 Kaplan-Meier estimates of cumulative risk of hospital admission with wheeze or asthma during the first 8 years of life stratified on 5-class model. A - Age at first hospital admission for children who had a hospital admission with wheeze or asthma at any age. B - Age at first hospital admission among children who had a hospital admission after age 3 years. A significant increase in the risk of hospital admission with acute asthma is seen only among children in the multiple early class, but not among those in any of the other atopy classes. (Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Simpson A, Tan VY, Winn J, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. Am J Respir Crit Care Med 2010;181:1200-1206. Official journal of the American Thoracic Society.)

Asthma exacerbations

Vaccination

...tory viruses remains an attractive and potentially effective strategy. However, whilst influenza vaccination in asthmatic patients is recommended, an effective vaccine for rhinovirus infection remains a long way off at present.

KEY REFERENCES
**Global Atlas of Asthma**

**Section C - Major current problems in asthma**

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**Severe Asthma**

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**Epidemiology and Scope of the Problem**

Asthma is a global health problem resulting in approximately 250,000 deaths/year, many of which result from severe asthma. Severe asthmatics (5 to 10% of all patients) impose a significant burden on healthcare utilization through unscheduled primary care visits, emergency room visits, hospitalizations, days off work/school and a requirement for multiple asthma medications. In comparison with mild or moderate asthma, severe asthmatics are 15 times more likely to use emergency services and 20 times more likely to be admitted to hospital. Severe asthma is generally associated with poor asthma control (defined by daily symptoms, poor quality of life and deteriorated lung functions) and increased risk of frequent severe exacerbations (or death) and/or chronic morbidity (including impaired lung function or reduced lung growth in children) despite intensive treatment and/or adverse reactions to medications.

**Severe Asthma Defined**

There are many definitions of severe asthma, but perhaps one of the best came about as a result of a World Health Organization (WHO) meeting convened in 2009. The WHO panel stated that severe asthma includes 3 groups, each carrying different public health messages and challenges:  
1. Untreated severe asthma: untreated either because of failure to make the diagnosis or because basic access to care or to medications are not available or affordable.  
2. Difficult-to-treat severe asthma: asthma not adequately responding to prescribed treatment due to adherence issues, inappropriate or incorrect use of medications or other reasons.  
3. Treatment-resistant severe asthma (also known as severe, therapy-resistant asthma, or treatment refractory asthma). The last group includes asthma for which control is not achieved despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment which may result in untoward adverse effects from the therapeutic regimen.

Asthma severity is determined by the intensity and phenotype of the underlying disease, both of which may be characterized by pathological and physiological markers.
However, it is important to recognize there are no current biomarkers or even distinct physiological parameters that define severe asthma or its phenotypes. It is postulated that the effectiveness of a given pharmacotherapy may be dependent on asthma phenotype and genetics with this heterogeneity likely impacting the variable responses to medications observed in severe asthma.

**RISK FACTORS FOR SEVERE ASTHMA**

Although largely unknown, there are many factors known to influence severe asthma development and persistence (Figure 1). Low pre-bronchodilator FEV1% of predicted increases the risk of being classified as severe asthma. Thus, abnormalities in genes related to poorer lung functions, racial background, male sex, sputum eosinophilia and personal smoking are likely to play a role. Other identified risk factors include a history of pneumonia and secondhand tobacco smoke exposure.

**THERAPY OF SEVERE ASTHMA**

Improved care of severe asthma is a major unmet medical need. Optimal therapy includes appropriate environmental modifications, management of comorbidities and pharmacotherapy, assuring adherence (Figure 2). According to the Innovative Medicine Initiative, all patients with severe asthma should be on high intensity asthma treatment defined as:

- 1000 mcg/day fluticasone equivalent combined with long acting beta-2- agonists or other controllers (adults)
- 500 mcg/day fluticasone equivalent (school-aged children)
- 400 mcg/day budesonide equivalent and oral leukotriene receptor antagonists (pre-school children).

In patients unresponsive to this regimen and having a significant allergic component, the anti-IgE monoclonal antibody, omalizumab, may be added.

There are many therapies in development for severe asthma. However several unanswered questions surround these novel treatments including:

- Will therapies be phenotype/endotype/biomarker driven?
- Which treatments will decrease symptoms and exacerbations and improve quality of life with a favorable risk/benefit ratio?
- Will any of the novel therapies truly be immunomodulators capable of preventing the onset or reversing asthma pathophysiological changes?

**KEY REFERENCES**


Figure 2 Severe asthma management paradigm.

Adherence to medical recommendations is defined by the extent to which the patient’s behavior matches agreed recommendations from the prescriber. The patient is free to decide whether to adhere to the doctor’s recommendations or not and failure to do so should not be a reason to blame the patient. Concordance describes the patient/prescriber relationship and the degree to which the prescription represents a shared decision, in which the beliefs and preferences of the patient have been taken into consideration.

Two types of non-adherence are described: intentional, usually due to lack of motivation, and non-intentional, which occurs when patients/caregivers do not properly understand the prescription or the use of the medication, as well as when they forget or are unable to administer the inhaled medication. Usually, the attending physician measures the adherence to treatment, while lifestyle changes receive less attention.

Several methods were used to measure adherence to treatment in asthma: patient or family reports, clinical judgment, weighing/dispensing of medication, electronic medication monitoring and biochemical analysis.

Adherence to asthma treatment has been found to be globally poor. True adherence rates are lower than those reported by patients, and this should be considered first in cases of poor control of asthma. The outcome of non-adherence is loss of opportunities for patients to improve their health, loss of medication by health-care systems, loss of working and school days. The financial perspective of non-adherence in asthma is impressive: approximately £230 million of medicines are returned to pharmacies in the UK each year, with a great deal more disposed of by patients themselves, while in the US non-adherence to medical regimens has been estimated to cost the US healthcare system $100 billion per year.

An epidemiological study called Asthma Insights and Reality in Japan in 2011 (AIRJ 2011) collected data representative for real life Japanese asthmatics using a computer assisted telephone interview. The study included 400 adult asthmatics (27% males, mean age 46.4 years old), with mild intermittent asthma (65 %), mild persistent asthma (17%), moderate persistent asthma (8%) and severe persistent asthma (11%). In the last month thirty-four percent of adult asthmatics received inhaled corticosteroids (ICS) or ICS and long acting β2-agonists (LABA) combination (ICS/LABA). Only 41% of 304 asthmatics used regularly the drugs for 10 months or longer and 14% did not use any drug in the last year (Figure 1). The reasons for stopping the medication were:
disappearance of asthma symptoms (61%), relief from the asthma attack (39%) and unexpectedly, doctor’s suggestion (17%). As a result of poor adherence, 62% of the patients were symptomatic in the last month. Eighty-five percent of the asthmatics did not receive any information on the existence of guidelines for the management of asthma.

A cohort study evaluating 5563 new users of ICS and 297 new users of ICS/LABA (age <35 years) in The Netherlands also showed poor adherence to maintenance treatment with ICS regular use by less than 10% of patients and ICS/LABA use by less than 15%. Similar rates were observed when stratified for age (Figure 2). This study concluded that adherence to regular treatment in asthma is influenced by patient factors, such as asthma severity, and treatment-related factors, such as once-daily dosing frequency.

In the 2012 the updated Global Strategy for Asthma Management and Prevention (GINA) classified factors involved in poor adherence to treatment as drug factors (Table 1) and non-drug factors (Table 2). Most of the non-drug factors can be overcome by an improved doctor-patient communication. GINA 2012 recommends for the usual care level short questionnaires to identify poor adherence instead of prescription monitoring and pill counting. The approach is dependent on the level of trust subsidized in the doctor-patient relationship. An example question offered by GINA is “So that we may plan therapy, do you mind telling me how often you actually take medicine?” Improving the reliability of clinical
Adherence to asthma treatment

Table 1: Drug factors involved in poor adherence *

- Difficulties with inhaler devices
- Awkward regimens (e.g. four times daily or multiple drugs
- Side effects
- Cost of medication
- Distant pharmacies

* Reproduced from the Global Strategy for Asthma Management and Prevention 2012 with permission of Global Initiative for Asthma (GINA).

Table 2: Non-drug factors involved in poor adherence *

- Misunderstanding or lack of instruction
- Fears about side-effects
- Dissatisfaction with health care professionals
- Unexpressed/undiscussed fears or concerns
- Inappropriate expectations
- Poor supervision, training, or follow-up
- Anger about condition or its treatment
- Underestimation of severity
- Cultural issues
- Stigmatization
- Forgetfulness or complacency
- Attitudes toward ill health
- Religious issues

* Reproduced from the Global Strategy for Asthma Management and Prevention 2012 with permission of Global Initiative for Asthma (GINA).

Adherence patterns in asthmatic children.

Figure 3

judgment implies a correct evaluation of the patient’s expectations from the drug and for the course of the disease (the necessity-concern construct) and of the potential impediments (financial, psycho-social and cultural, such as steroid phobia). Clear instructions provided by health professionals, social support and discussion groups for a better understanding of the disease and active measures of maintaining contact with patients are recommended.

Key References

Asthma is a complex developmental condition, the impact of which is highly socially patterned. Though asthma prevalence and morbidity are on the rise globally, this increase is not uniformly distributed, with a disproportionate asthma burden falling on low socio-economic status (SES) and/or minority populations residing in urban areas. Moreover, in the United States this burden has been found to be highly clustered within urban communities particularly marked by social adversity and deprivation, most notably those containing a high percentage of African-American or Puerto Rican residents. This community-level inequality is mirrored by worldwide trends in asthma prevalence and severity published in the most recent Global Asthma Report of the International Study of Asthma and Allergies in Childhood (ISAAC). Time trends analyses contained within this 2011 report found that rising global prevalence estimates are being driven primarily by rapid increases in low and middle-income countries with large populations, while prevalence in many high-income countries reached a plateau or even began to decrease. Similarly, phase three of ISAAC found that asthma is more severe in low and middle-income countries.

A social determinants of health approach acknowledges that social stratification can significantly influence health outcomes through mediation of exposure to risk and protective factors at both the household and community levels. For instance, individuals living in poverty are more likely to be exposed to environmental pollutants (e.g. particles related to the combustion of diesel and cooking fuels), indoor allergens (e.g. mold and dust containing mouse or cockroach excrement), and other respiratory irritants (e.g. tobacco smoke). However, these differences in environmental exposures alone do not fully explain the significantly increased asthma risk found in certain socially disadvantaged populations. Though the etiology of this excess asthma burden remains unclear, exposure to violent crime was recently implicated as an environmental factor impacting pediatric asthma prevalence in a large urban cohort, with exposure to community violence conceptualized as a source of psychosocial stress. Indeed, community, family and individual-level...
exposure to psychosocial stressors (Figure 1) increasingly characterized as “social pollutants”, has been shown to predict some of this additional variation in asthma risk. Beyond exposure to community and domestic violence, these stressors can include food, housing, and financial insecurity as well as social marginalization. Conversely, there is evidence that community vitality/collective efficacy, increased maternal-child interaction, and effective utilization of psychological coping strategies (e.g. “shift-and-persist”) may positively impact asthma outcomes at the community, family, and individual levels.

Much as environmental pollutants like diesel exhaust enter the body and disrupt biological systems via pro-inflammatory processes, the “social pollutant” model of psychosocial stress hypothesizes that it also “gets under the skin” leading to the dysregulation of inflammatory processes. In general, low-SES individuals are more likely to encounter both psychosocial stressors and physical environmental toxins that may each independently contribute to the increased asthma burden levied upon these populations (Figure 2). Moreover, given that these psychosocial and physical stressors often co-occur in disadvantaged environments and may influence common physiological pathways, it is possible that the aforementioned psychosocial stressors may potentiate an individual’s susceptibility to environmental exposures, thus giving rise to further asthma disparities.

Given the considerable evidence linking social inequality to population-level asthma disparities, it is clear that health equity cannot be achieved without taking concrete steps to address societal inequality more broadly. Efforts to eliminate asthma disparities must include direct acknowledgement of social determinants of health such as poverty, racism, lack of economic opportunity and community deprivation. Furthermore, structural and policy interventions must address these root causes of asthma disparities at the community and broader societal level, and accompany efforts to ensure effective disease self-management at the family and individual levels.

**KEY REFERENCES**

The International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 study has demonstrated that the prevalence of asthma in African and Latin American children, assessed by a self-reported questionnaire, is higher than the global average. In addition, children with asthma in low and middle-income countries, have more severe symptoms than those in high-income settings, possibly due to lack of diagnosis, poor access to care, lack of affordability of therapy, environmental irritants, genetic susceptibility to more severe disease or a combination of these.

Despite access to appropriate healthcare resources, several studies have demonstrated that asthma is often underdiagnosed and undertreated in many parts of the world.

The multinational Asthma Insights and Reality (AIR) surveys show the rate of exacerbation, including hospitalizations, emergency room visits and unscheduled visits to physician office, are higher in Asia Pacific and Latin America compared to Europe and USA. The same observation was made for the indirect cost of asthma evaluated by the level of school and work absenticism.

Close to 50% of medical expenditures for asthma are a consequence of exacerbations. There are only a few pharmacoeconomic studies in developing countries. In Latin America, unscheduled health care resource use was particularly high among patients with uncontrolled asthma. For both adults and children, scheduled health care costs were approximately 3-fold higher in those with severe persistent symptoms than in those with mild intermittent symptoms. Regardless of symptom severity, almost three-quarters of expenditure was due to unscheduled health care.

One successful program (ProAR) was developed in 2003 in Salvador, Brazil, prioritising the control of severe asthma. By facilitating referrals from the public health system and providing proper multidisciplinary, but simple, management including education and medication for free, ProAR enrolled >4,000 patients with severe asthma. The patients were offered regular follow-up and were referred back to primary healthcare only when asthma control could be maintained without requirement of a combination therapy. This intervention was associated with a steep decline in health resource utilisation and remarkably reduced the rate of hospital admissions due to asthma by 74% in 3 yrs in the entire 2.8 million city habitants. Cost analysis demonstrated that this intervention was very cost-effective and provided a financial relief to the families and the government.
In many areas of the World, persons with asthma do not have access to basic asthma medications or medical care (Figure 1).

The solution to the problem in developing countries will not be achieved only by improving access to medication; National Health Ministries must consider asthma as a public health priority, and national programmes need to be implemented in order to improve diagnosis, management, and reduce direct and indirect related costs.

Evidence from the studies conducted in countries with well-established or developing national asthma management programmes suggests that establishment of an overall successful programme requires a logical progression through specific stages, starting with epidemiological evaluation and leading up to optimisation and maintenance therapy for individual patients (Figure 2). Each development stage is likely to present a multitude of local and national challenges and specific implementation strategies, which will determine the overall success level of the asthma management programme.

KEY REFERENCES


