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Review article

Implementation gaps for asthma prevention and control

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ABSTRACT

Asthma and allergic diseases can start in childhood and persist throughout life, but could also be manifested later, at any time for still misunderstood reasons. They are major chronic multifactorial respiratory diseases, for which prevention, early diagnosis and treatment is recognized as a priority for the Europe's public health policy and the United Nations. Given that allergy triggers (including infections, rapid urbanization leading to loss in biodiversity, pollution and climate changes) are not expected to change in a foreseeable future, it is imperative that steps are taken to develop, strengthen and optimize preventive and treatment strategies. Currently there are good treatments for asthma, several risk factors are known (e.g., allergies, rhinitis, tobacco smoke) and tools to control the disease have been developed. However, we are still uncertain how to prevent patients from developing asthma and allergic diseases. In this paper, we list the positive and negative experiences in this field as well as analyze the missing links in the process. This critical analysis will be the basis of setting-up an effective program for prevention and making, a process labeled as "implementation gaps".

Contents

1. What do we still have to learn regarding asthma control and prevention?

Asthma, associated with respiratory allergies, is recognized by the World Health Organization (WHO) [1] and the United Nations

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[2] as the most common chronic inflammatory disease characterized by paroxystic symptomatic periods [3,4]. It affects 5–7% of adults and 10–12% of children. In contrast to some countries in which frequency of asthma has been stabilized, morbidity statistics are still raising in others. In France, for example, asthma prevalence increased from 8.2% in 1998 to 10.2% in 2006 [5]. Though asthma mortality rates are higher in lower and lower-middle income countries, it has been accepted as a major public health problem in all countries.

Several facts related to the evolution of our environment, would be responsible for the increase or the non-decrease of asthma including increased potentiating factors such as (*i*) indoor pollution and chemicals (cleaning, wood combustion, fume, fine particles), and biological (mites, mold, animals); (*ii*) climate changes and external pollution, in particular, the fine particles emitted by diesel engines and ozone; the smoking habit leads to respiratory and non respiratory diseases (cancers, atherosclerosis, chronic obstructive pulmonary disease, for example), but is also related with the development of asthma and allergies in newborns from smoking pregnant women; (*iii*) rapid urbanization and its negative consequence leading to changes in biodiversity [6] and loss of protective factors, which is the basis of the popular "hygiene hypothesis". This hypothesis is based on the population observation over the past 30 years in which there was an inverse relationship between the prevalence of infectious diseases and the frequency of allergic and autoimmune diseases. The immunological explanation comes from farmer-based studies. Thus, exposure in the youngest age to endotoxins through the inhaled air (from the wall of bacteria living in the digestive tract of farm animals) could protect against the development of allergenic sensitization and respiratory allergies.

Many international initiatives have been launched to prevent and decrease morbidity and mortality of these conditions, which are considered a global public health problem [3,7]. However, the WHO's international classification and coding systems such as the International Classification of Diseases (ICD) have grouped them under topographic distribution, regardless of the underlying mechanisms and triggers. This has led to the framework of ICD to be deficient in capturing the concepts currently in use for allergic and hypersensitivity conditions, in particular for allergic and hypersensitivity conditions of the respiratory tract. As a result, the lack of accurate morbidity and mortality epidemiological data impacts directly on the healthcare prevention planning and resource allocation, quality patient management and public health policies.

The public health's core mission is prevention of injury or disease and there are several potential strategic interventions. Most population interventions have historically focused on primary and secondary prevention measures, but all health professionals worldwide are most familiar with asthma tertiary prevention actions since they are addressed to existing disorders and focused on their accurate diagnosis and control in order to avoid new exacerbations [1].

Though the epidemiological and genetic studies have been looking for many different risk factors for asthma [8], they have failing to reach objective makers to substantiate preventive measures. These studies have supported some broad hypotheses and proposed some effective tips. In families where there is a history of asthma and allergies, we should indeed try to prevent asthma in young children by simple measures, such as avoiding smoke during pregnancy or in the presence of infants and young children, preferring breastfeeding for the first 3 months and provide early diversification from the age of four months.

Although not fully demonstrated, some measures have been recommended to prevent allergy. Removing allergens from the indoor environment (dust mites, pets, mold) showed to be ineffective as primary prevention, but it is effective in secondary prevention, when the eviction is completed and prolonged.

Delayed diagnosis of allergies and asthma, primarily linked to the lack of knowledge of asthma-like symptoms or misinterpretation of laboratory tests related to allergies, precludes the development of early prevention. Rhinitis, which includes hay fever (allergic rhinitis to grass pollen) and allergic rhinitis due to mites are risk factors for the development of asthma later in life and of uncontrolled established asthma [7]. Based on it, some national screening and prevention campaigns have been set up. The best example is from Finland [9]. After 10 years of intensive work of training health professionals, providing information for the population, implementing of treatment guidelines, the cost of asthma for the Finnish health has fallen considerably and the amounts originally invested appear to have been fully repaid. However, the incidence of asthma has not decreased during that period, which means that the causes of the disease have not been affected and/or the methodology applied to reach precise asthma epidemiological data was not optimal. The same country, while others have since copied, bounced and implemented a national program of allergy prevention, thinking to tackle one of the causes of asthma [10]. The question that therefore arises is indeed the subject of this article: can we really prevent asthma? What are the obstacles? Can we overcome them? Should other countries engage in such a process?

2. Can we really control asthma?

The goal of treatment of asthma is to control the disease with minimal drug and to reach an appropriate quality of life for patients. In France, it has been observed that uncontrolled asthma affects nearly one child in two (44.2%) [11] and three in five adults (62%) [5].

Asthma control has two main goals: (I) clinical control and (II) limitation or reduction of future risk of adverse outcomes. Actions to reach both objectives have to be taken concurrently for a successful control. In the case of children, the disease control should lead to the absence of symptoms in the performance of a normal life without limitation (at school, in recreation, sport), standardization of lung function, allowing a good development height and weight, and of course to prevent mortality caused by the disease, which unfortunately still exists (with 10 deaths from asthma in 0–14 of a total of just under 1000 asthma deaths in France in 2010) [12]. Similarly, older people with asthma are under-diagnosed and under-treated, increasing mortality statistics [13].

Preventive measures should be able to change the natural history of the disorder, preventing asthma development and/or evolution providing its control. Asthma attacks start in early ages and are only the visible part of the iceberg. Childhood asthma is a chronic disease that comes in many forms (known clinical phenotypes) some strongly linked to allergies and others not [14–16]. Recently several studies have explored the treatment of intermittent and persistent forms of the disease. Generally, inhaled short-acting beta2-agonists acting in minutes are pointed as the treatment of choice in crises by numerous recommendations [17–20]. In addition, the daily use of inhaled corticosteroids (ICS), which constitutes the reference indication in overall control of the long-term asthma, has shown effective in reducing asthma exacerbations and rescue medications use [21]. The occasional use of several treatments in intermittent forms especially during infectious episodes was investigated in seven recent studies. In the case of ICS, there was no [22–24] or low [25,26] positive effects in terms of reducing the number of exacerbations; the beneficial effect was modest for leukotriene receptor antagonists (LTRA) [27,28]. The lack of written asthma action plan and education of parents and teenagers is also a paramount difficulty of achieving asthma control, notably due to the "no symptom, no asthma" belief and the lack of knowledge

regarding the finality of controller therapy.

From all the existing recommendations [17–20], taking daily ICS is effective in controlling persistent forms of asthma. The benefits of ICS are to be balanced with decreased of children growth with short terms (1.1 cm on average in the first year, potentially reversible the years after), dependable on the dose and on the ICS formulation [29].

A systematic review of the literature [30] of the last 16 years has shown the advantages of using the combination of ICS + long-action β2-agonists (LABA) compared to ICS alone in children and adolescents with uncontrolled persistent asthma, from prospective randomized clinical studies (9 studies), 1641 children with asthma, allowing to compare ICS + LABA vs. double dose of ICS (7 studies) and ICS vs. higher doses (2 studies). The ICS + LABA association significantly improved morning and evening peak expiratory flow (PEF) and was associated with reduced use of rescue medication. Compared with high doses of ICS, the ICS + LABA combination also reduced the risk of asthma exacerbations, and the ICS + LABA combination was not affecting the growth of the children.

Results are contradictory regarding the LTRA in asthma. Two previous studies showed the decrease of bronchial hyperreactivity and exhaled nitric oxide fraction (bronchial eosinophilic inflammation marker) [31], asthma symptoms and doctor visits [32], but no difference was observed when LTRAs were associated with the usual treatment in another study [33].

The choice of the optimal system for the administration of inhaled drugs is also crucial in the management of asthma in pediatric patients. The inhaled drugs currently remain the most effective forms of treatment administration for respiratory disorders. The optimal devices should allow bringing a significant amount of drugs directly to the bronchi. Two inhalation systems can be used in children: inhalation chambers and nebulization. The spacer accessory intended to be fixed on the mouthpiece of the metered dose inhalers to facilitate taking the drug by eliminating the hand-mouth coordination function. The use of a spacer is part of the international recommendations for mild to moderate exacerbations [17,18]. However, the use of chambers brings up some questions in children. To date, there is no strong evidence suggesting major differences in efficacy between the inhalation systems, each system having its advantages and limitations [34]. If unsuccessful by using inhalation chamber, nebulization, especially with a pneumatic nebulizer should be discussed [35,36].

The non-observance of the drugs used for asthma in children and adolescents is alarming [37,38]. The adherence to the treatment of children depends on the family, the health care system and the child health status. Young children are completely dependent of their parents while teenagers take in, but at a period of life often associated with experimentation with risky behaviors [37].

Finally, due to lack of appropriate data, one wonders about the possibility of treating differently the various asthma phenotypes, particularly the non-allergic asthma in children, the efficacy of long-term treatments, the dose-response relationship and the aerosol deposition in small children. Further investigation is needed to fill these knowledge gaps and optimal control of asthma.

3. Which lessons to learn from the prevention studies?

From the public health perspective, efforts taken in collaboration with WHO ICD leadership and six allergy international academies to have an improved classification of allergic and hypersensitivity conditions in current ICD-11 revision [39,40], resulted in the construction of a pioneer section entitled “Allergic and hypersensitivity conditions”, in which asthma is one of the main sub-headings of the “Allergic or hypersensitivity disorders involving the respiratory tract” section [39,41–48] (Fig. 1). The construction of the new section detailing asthma means that the latter both allergic and non-allergic asthma will now be recognized as clinical conditions requiring specific documentation and management, such as the indication of allergen immunotherapy or biologicals (*e.g.*, Omalizumab) for allergic asthma.

Preventive measures must be effective for individuals and reliable and financially acceptable to the community. ***Primary prevention*** aims to reduce the incidence of the disease by identifying *individuals or populations at risk* and reducing exposure to potential risk factors. In other words, primary prevention is applied to change the natural history of the disorder. While ***secondary prevention*** intends to avoid the development of allergic diseases in sensitized subjects and ***tertiary prevention*** is for sick patients and the consequences of the disease so as to reduce the burden for the individuals and for the society [49]. In general, optimal public health strategies are focused on primary and secondary prevention. However, in practice, most of the actions to prevent asthma are tertiary prevention efforts.

Interventional epidemiology evaluates preventive actions undertaken with a set of methodological specifications [50]. The evaluation of the success of a prevention program is measured by feasibility criteria, outcomes and costs. The comparison of groups established by sorting out (randomized intervention trials) represents the best methodological solution for measuring the effectiveness of such actions, but is not always ethically possible. We can then make use of observational studies including registries and cohorts of patients. When the effectiveness of the proposed measures has been demonstrated, it is necessary to assess the actual feasibility of these actions at the level of a greater population. The results obtained from the research program shall be tested and adapted to the existing, far less controllable in routine than in research.

In asthma, very few prevention programs have been a breakthrough success [8]. Eviction of respiratory allergens, pharmacological treatment, allergen immunotherapy, diets, pre/pro/symbiotic education campaign among others are discussed. It has been shown that not only the eviction measures proposed to patients allergic to mites cause a significant decrease in allergic exposure, but there is a correlation between the reduction in allergen load and clinical improvement [51]. However, to be efficacious these measures must be early, complete (that is to say, not limited to a single allergen or a single irritant) and prolonged and should not be extended for primary prevention of sensitization to inhalant allergens [51]. Indeed, no study has been shown that primary prevention of allergens prevents the onset of new sensitizations (except as regards occupational latex allergy) [52], as opposed to recent prevention trials in peanut allergy [53]. Studies with pre/pro/symbiotic show no prevention of asthma, at most they are able to delay eczema [54]. The therapeutic management mainly includes three components (drugs, allergen immunotherapy, education), which are implemented in combination or in steps, depending on the control of symptoms. A century after the first allergen immunotherapy trial, it remains the only treatment that can modify the course of the allergic disease [55]. However, prevention studies (of asthma in rhinitis patients) are of poor quality methodology [56] and better studies need to be in place, particularly with the new allergen immunotherapy products.

The Finnish plan for asthma (FAS-P: 1994–2004), extended to seven countries (Brazil, Chile, China, Hong Kong, Ireland, Japan, Poland, Singapore), incorporating several strategies was more effective, has shown a cost-effectiveness reduction of asthma but without reducing its incidence [9]. This program, uncontrolled, had clearly stated objectives of promoting early diagnosis and treatment (by ICS) of asthma (by general practitioners and pediatricians), self-management of asthma and action plans, actions

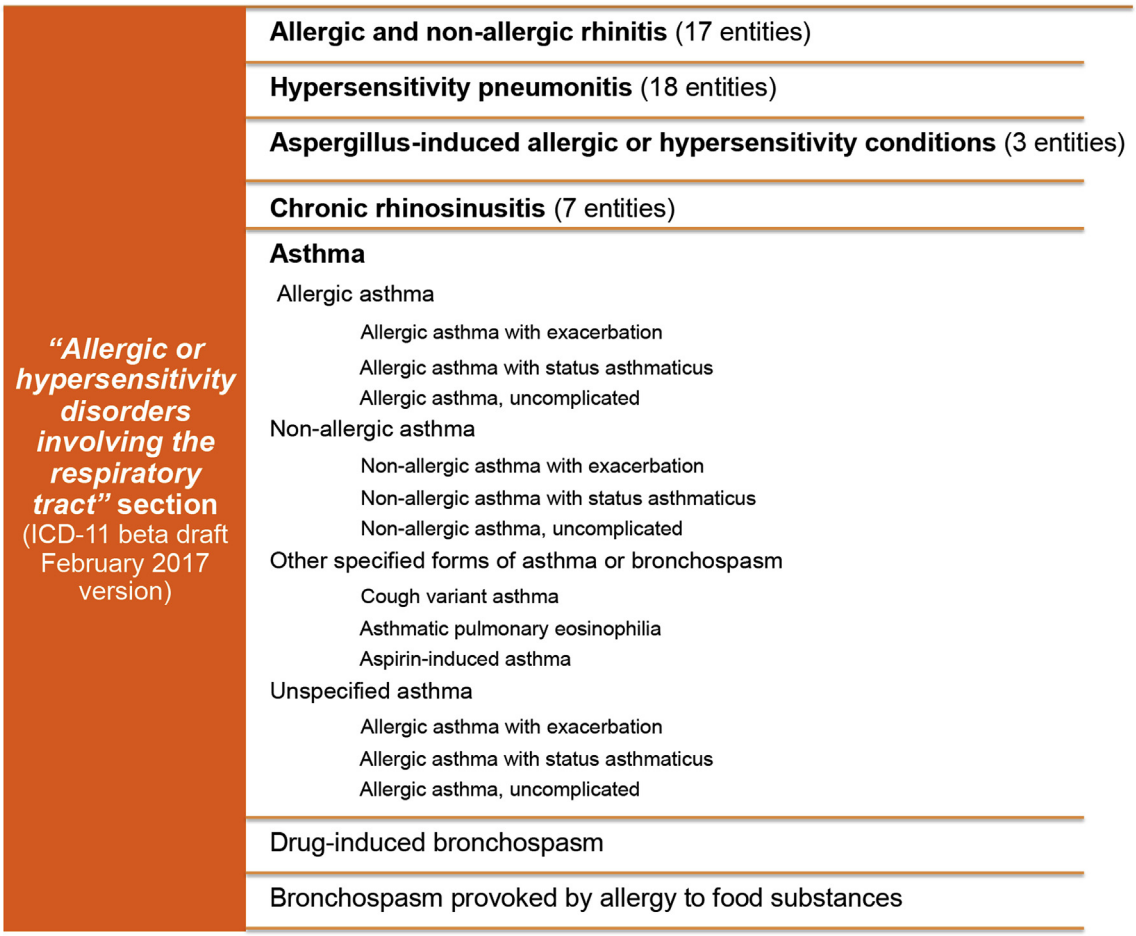

Fig. 1. The "Allergic or hypersensitivity disorders involving the respiratory tract" subsection scattered into the pioneer ICD-11 "Allergic and hypersensitivity conditions" section.

against active and passive smoking and the promotion of educational measures. The plan was implemented with the help of doctors, pharmacists and nurses relay during 700 meetings involving more than 35,000 health professionals. The patient association was involved. The success of this program is probably related to the relay set up by the 21 district hospitals, 271 regional health centers, 200 doctors, 580 nurses and 695 pharmacists asthma referents which, once educated, assured themselves other training sessions. This was facilitated by the Finnish health system, totally centered around five university hospitals and 21 peripheral hospitals nationwide and by centralized decisions to completely cover asthma (which is part of the "Special Refund Categories" covering 10 (groups of) diseases).

The cost of this first program was 0.65M € and regular evaluations were performed. In 10 years, the number of hospitalizations for asthma per year dropped by half and the number of asthma deaths has also decreased (123 in 1993 against 85 in 2003). The number of patients on treatment has almost doubled during this period. No impact on smoking was observed. The overall cost of asthma decreased from € 218M (€ 1611/year/patient) to € 213.5M (€ 1031/year/patient), thus largely repaying the initial investment, despite the increased number of asthmatics and of drug consumption (from 44 to € 79M). In the absence of such a program, the estimated cost would have been € 341.5M, giving an economy of € 128M [57]. But despite this, the prevalence of asthma has continued to increase during this period showing that the causes of asthma are not affected by this program.

Finland has launched in 2008 an allergy plan with a stated objective to reduce the incidence and burden to the society of allergic diseases (FAL-P, 2008–2018) [10]. This program is based on the success/limits of the previous program [9] and the hygienist and loss of biodiversity assumptions. Echoing the farmers' environment studies [64,65], Finnish authors showed a net decline of biodiversity in 118 adolescents living in Karelia 100–150 km apart, some in Eastern Finland and the other in Russia [58]. The plant biodiversity (3 km around each adolescent) and microbial (on their skin) were analyzed [6]. Atopic adolescents, more in Finland, were at the center of a poor background in plant and microbial species (especially gamma-proteo bacteria).

The FAL-P is based on the rich network of asthma professionals established for 10 years. It is much more child and allergies-centered than asthma-centered. It is structured around six main axes with quantified secondary objectives: prevent asthma symptoms, prevent allergic rhinitis and atopic dermatitis (promotion of the concept of good health of the allergic patient, fight against indoor pollution), increase tolerance to allergens (including food, evictions to targeted cases only) improve the diagnosis of allergies (by allergists), reduce occupational allergies, finance severe allergies treatment (based on the FAS-P, insisting on control of asthma, rhinitis and atopic dermatitis and the management of anaphylaxis), and reduce the overall cost of allergies.

Aligned to the Finnish example, the Canadian Towards Excellence in Asthma Management/Vers l'Excellence dans les Soins aux Personnes Asthmatiques (TEAM/VESPA) program used a

population-based approach to reduce the asthma-related morbidity, improve patients' quality of life, and optimize the use of health system resources to improve asthma treatment and to encourage patient self-management. For it, the TEAM/VESPA program included the development, implementation and evaluation of innovative care improvement strategies that would affect clinical management, dissemination and adoption of best practices through clinical expertise and continuing education, as well as through reinforcement of patient self-management via education [59].

4. Which are the barriers to asthma prevention?

Knowing that triggers of allergic diseases will persist for the coming few years, it is essential to develop and strengthen measures of prevention and treatment of allergies. The fact that we still do not know precisely why a child becomes allergic and asthmatic is an obstacle, but the analysis of prevention programs that work and those that do not work sheds light on the needs, barriers and missing links to succeed prevention.

From the ***primary prevention*** perspective, the better understanding of the mechanisms of allergies and asthma is fundamental. For this, we have for the past 10 years associated geneticists to our fundamental research; however the found polymorphisms have posed more questions than solved the issues, and these polymorphisms, when they are confirmed, explained at most a third of asthma [60,61].

Epigeneticists are now associated and in a recent paper three loci accounted for 13% of IgE variation [62] and we hope that less than 10 years will be needed to further advance in this complex area. The increased risk of asthma or atopy associated with the presence of a particular variant is very low (<1.5) and any new drug, no useful prediction, no substantial progress in understanding the pathophysiology have emerged so far. We may have to rethink the research strategy in this area; this so-called missing heritability is observed in the genetic study of several other complex traits and diseases and could be explained by [63] (i) the existence of many other variants to discover; (ii) the interaction between multiple genetic variants; (iii) the presence of structural variants or strong effects of rare variants (present at less than 0.5% of the population, so too infrequent to be captured by current screening studies); and (iv) gene - environment interactions, particularly *in utero* and in the first 3–5 years of life. The first examples of genes - environment interactions [64,65] related to exposure to microbial endotoxins; the presence of a variant of the CD14 (endotoxin receptor) −159T variant CD14 is indeed associated with an increased risk of asthma and allergies in people heavily exposed (endotoxin in house dust, animal work, a pet at home since birth, contact with farm animals) and the variant CD14 -159C in subjects not exposed. The mechanisms by which the environment influences genes belong to the field of epigenetics. They include all the phenomena of modifying the gene expression pattern without modifying the nucleotide sequence (methylation of cytosine to 5-methylcytosine in the DNA CG dimer, histone methylation at lysine residues, the auto-activation of the transcription of certain genes, microRNA) and are transmitted from one generation to another.

Secondary prevention actions in the context of asthma aim to identify sensitized individuals in order to prevent the development of allergic disorders. Although validated scientific data are lacking to support the screening the whole population for sensitization, it might be appropriate to do so in individuals with known risk factors. An example of secondary prevention to avoid development of asthma is the hygiene hypothesis. The competitive duality of atopy and certain infections goes beyond the scope of the hygiene hypothesis according to which being born in a large family, being in kindergarten before the age of six months, being raised on a farm increase the risk of exposure to respiratory infections in early childhood for the former and decrease the risk of allergen sensitizations and asthma. The frequent contacts with animal lipopolysaccharides present in their excrements prevent atopy, allergic rhinitis and (sometimes) asthma. So our Western lifestyle highly urbanized, would result in the decline of biodiversity in turn promoting the emergence of chronic diseases such as asthma, allergies, but also diabetes, obesity, cardiovascular diseases and cancers. The recent examples of the changes of the microbiota (skin, digestive or respiratory) on and around allergic teenagers [6,54] open new horizons. Thus, associating other scientists (microbiologists here) to our thinking is very important. Further studies are required to identify risk factors for asthma exacerbations (role of viruses, allergens, behavioral disorders, stress) [66, 67] and to identify the best window (age) is fundamental to intervene.

Tertiary prevention programs have to have both short-term

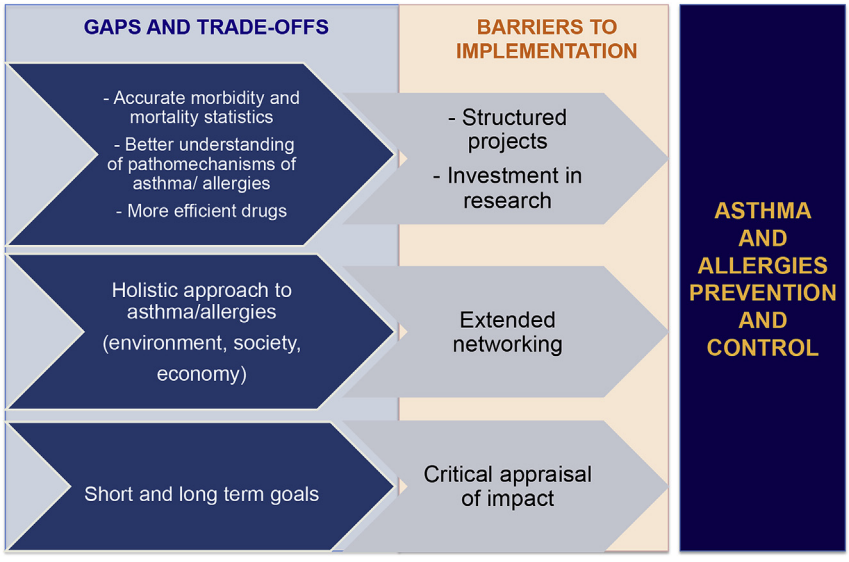

Fig. 2. The implementation gaps for asthma prevention and control.

objectives on morbidity (emergency and unscheduled visits, hospitalizations, mortality, other morbidity) and longer terms objectives of reducing the incidence of the disease. They have to involve a plan (Fig. 2) addressing both allergies and asthma. New anti-inflammatory therapies, immunomodulators (with promotion of allergen immunotherapy), new combination therapies, combined with an extensive educational program may allow to act on the control of the diseases and the prevention of severe forms. Although clinical research has been developing substantially over the last years to ensure efficacy and safety of drugs, challenging is reaching the best therapies for each patient or group of patients. Considering asthma as a heterogeneous disease with different phenotypes and endotypes, it is expected for the forthcoming years developments in the personalized medicine and the worldwide availability of these pharmacological formulations in affordable prices.

The Finnish FAS-P/FAL-P and the Canadian models fulfill many of these gaps and should certainly be followed. The implementation of a specific section dealing with allergic and hypersensitivity disorders of the respiratory tract will allow reaching refined and comparable morbidity and mortality data in the forthcoming years. It is a relevant academic, political and economic move, which will support new perspectives for a better diagnosis and management of asthmatic patients.

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Author contributions'

Luciana Kase Tanno and Pascal Demoly contributed to the construction of the document. Co-authors contributed in tuning the document and with the revision of the manuscript.

Conflict of interests

The authors declare that they do not have any conflict of interests related to the contents of this article.

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Abbreviations

ICD	International Classification of Diseases
ICS	inhaled corticosteroids
LABA	long-action β2-agonists
LTRA	leukotriene receptor antagonists
PEF	peak expiratory flow
WHO	World Health Organization

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