

Research priorities and strategies to improve asthma and allergy care in India

With a population of ~1.3 bn, India ranks as the second most populous country in the world. India shows a great diversity in culture, religion, languages and climate. Whilst India has the fifth largest economy in the world, ahead of high-income countries (HICs) such as the UK and France, paradoxically, nearly 180 m people are below the poverty line as per World Bank criteria (\$1.78/day). Twenty-one of the 30 most polluted world cities are in India. Air pollution is mainly from industrial combustion and vehicle exhausts in cities, and biomass fuel and agricultural waste burning in rural areas. Sources of indoor air pollution include using fossil fuels and cow dung for cooking, and burning mosquito coils and incense sticks. About 77% of the Indian population is exposed to PM_{2.5} levels exceeding 40 mcg/m³ (WHO limit, <10 mcg/m³).¹

India's literacy rate has improved, but nonetheless remains moderate at 71%. As one of the largest global information technology hubs and with globalization of trade and establishment of multinational companies, there has been a shift towards western lifestyle, particularly with respect to dietary habits in urban areas. India has a huge burden of infectious diseases including human immunodeficiency virus (HIV), tuberculosis (TB) and parasitic diseases. These are important considerations for noncommunicable diseases such as asthma and other allergic diseases in India, as they are underpinned by complex gene, lifestyle and environmental interplay.

Most of our knowledge regarding aetiopathogenesis, pharmacotherapy and immunomodulatory therapies of asthma and allergic diseases is generated from the research conducted in HICs involving predominantly Caucasian population. Hence, the fundamental question for low-middle income countries such as India is, "Is it acceptable and appropriate to directly extrapolate findings from research conducted in HICs to benchmark clinical practice in India?" This editorial focusses on gaps in evidence and highlights "high-priority" areas and strategies for research in asthma and allergy in India.

The burden of asthma and allergic rhinitis has gradually risen during the last 2 decades. There are an estimated 38 m people with asthma in India. The overall prevalence of asthma in children is 6%–8%. The prevalence of rhinoconjunctivitis in 6- to 7-year-old children in India is 4.5% in males and 3.8% in females, and among 13- to 14-year-old children is 11.7% in males and 9.7% in females as per ISAAC studies.² Importantly, 40%–50% of asthma amongst children is uncontrolled or severe.³ There is some evidence regarding poor compliance with therapy, taboo towards inhalers with preference for oral medications and a very high rate of oral corticosteroid use with one study reporting up to 10.5 courses per year.⁴ Hence, there

is an urgent need for qualitative studies to investigate reasons underpinning poor patient compliance with a view to putting in place supportive interventions to enhance the uptake of inhaled corticosteroid therapy. These tools should factor in cultural, social, religious elements, socio-economic status and literacy. Nearly 60%–70% of patients have co-existing allergic rhinitis and asthma, and it remains unclear at present how well the allergic rhinitis is controlled amongst asthmatics. There is also a need to explore views and perspectives of physicians managing asthma to investigate facilitators and barriers to therapy. Currently, there are no reliable data regarding asthma endotypes and phenotypes and multi-centre prospective studies characterizing clinical phenotypes alongside some basic biomarker analysis in induced sputum and peripheral blood will pave the way to describing disease clusters and shape national guidelines regarding targeted use of novel biologics. The determination of age-related reference ranges for eosinophils in peripheral blood and airway lining fluid and serum total IgE is particularly relevant in Indian patients given the high helminthic burden in children as well as exposure to other infections that drive eosinophilia and serum total IgE and exposure to high levels of air pollution.

At present, it also remains unclear what proportion of patients with uncontrolled asthma have severe disease. Health economic analysis is required to shape national policies to achieve an equitable distribution of resources and preferably providing free access to the most effective treatments, particularly for those belonging to lower socio-economic strata. There is some evidence that asthma with fungal sensitization amongst Indian patients is significantly associated with poor disease control and lung function, and future studies are required to assess the role for anti-fungal therapies in this patient cohort.⁵

There is considerable variation in climatic conditions between different parts of India with extreme weather conditions in certain geographical areas as in Northern and North-eastern states. This has an impact on pollen and fungal aero-biology and is further compounded by global warming. Lack of reliable and up-to-date pollen and fungal spore data is a major barrier to the optimization of allergen panels for skin tests and delineating allergen-specific immunotherapy extracts. The current allergen-specific immunotherapy practice is largely based on the research conducted in HICs, and there is a need for clinical trials in the native Indian population, preferably involving sublingual immunotherapy.

Limited data sets regarding food allergy from the EuroPrevall-INCO study⁶ conducted in two South Indian cities showed a very

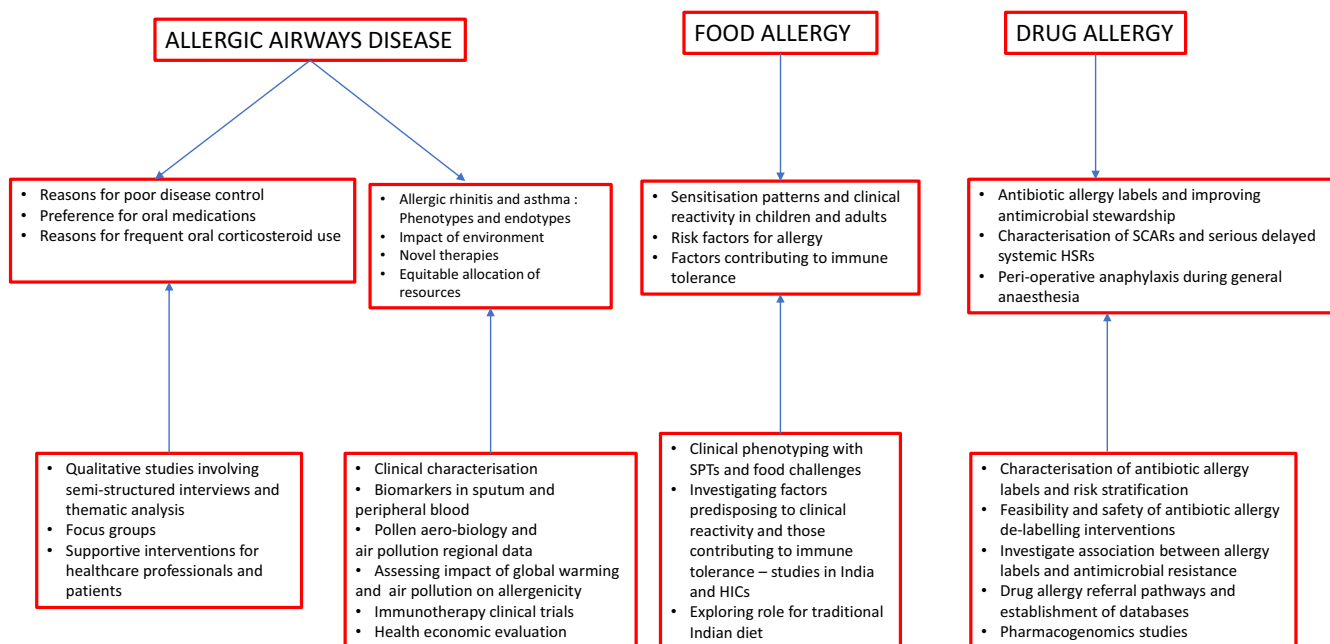


FIGURE 1 Priorities and strategies for asthma and allergy research in India

high rate (26.5%) of sensitization to foods (frequent allergens—legumes, prawn, eggplant, milk) in the adult population but with a very small proportion (1.2%) of patients reporting clinical reactivity. Similarly, high rate of sensitization (19%) was also reported with very low clinical reactivity in children. The most frequent foods involved in sensitization were sesame, jackfruit and milk. It is unclear whether these findings are generalizable to other parts of the country, given cultural and dietary differences. This raises some key research questions relating to risk factors and breakdown of immunotolerance, since the risk of allergic airways disease and food allergy is significantly enhanced amongst immigrant Indian population in HICs.⁷ Studies involving sensitization patterns, risk factors in childhood (weaning, diet, breastfeeding, mode of delivery, childhood infections, antibiotic use, gut microbiome, etc.) alongside immunotolerance might pave the way for appropriate primary and secondary prevention strategies both in India and amongst immigrant Indian population in HICs. There are currently no data sets regarding the rates of anaphylaxis in patients with food allergy (and for other triggers including insect stings, drugs and latex). Generating reliable prospective data for anaphylaxis is challenging, given the relatively weak health service framework in the public sector with some sections of the population accessing private care for emergency treatment.

Data regarding drug allergy are also sparse. Inaccurate penicillin allergy labels are a major public health problem in HICs and have been linked to an enhanced risk of antimicrobial resistance (AMR) and hospital-acquired infections such as *Clostridioides difficile*.⁸ Alarming rates of AMR (50%–80%) have been reported in India (AMR-India-SCOPING-REPORT.pdf.org). As per the AWaRe WHO classification (2019 WHO AWaRe Classification Database of Antibiotics for evaluation and monitoring of use), there is a high rate of prescription of

“Watch” group of antibiotics (e.g. quinolones and later generation cephalosporins) in India, and this coupled with unauthorized self-medication of antibiotics and high rates of inappropriate antibiotic prescriptions might potentially contribute to inaccurate antibiotic allergy labels. Whilst there are no published data regarding prevalence of antibiotic allergy labels at present, anecdotal experience suggests that around 3%–5% of inpatients in secondary and tertiary care declare antibiotic allergies. Further research is needed to quantify and characterize antibiotic allergy labels to put in place novel strategies for safe antibiotic allergy de-labelling including pathways for “direct de-labelling” and “direct oral antibiotic challenges” (i.e. without skin tests) for “low-risk” patients, as these interventions have been reported to be successful in HICs including USA and Australia. Supportive strategies to facilitate such an approach in India should include raising awareness and provision of validated relatively simple educational tools for healthcare professionals to enhance uptake and safe delivery of novel interventions.

The Asia-Pacific network reported drug hypersensitivity to beta lactams, NSAIDs, anti-convulsants, anti-retrovirals and anti-TB drugs of particular relevance to South-East Asian countries.⁹ HLA associations for severe cutaneous adverse drug reactions and serious systemic delayed hypersensitivity have been described for abacavir, carbamazepine, phenytoin, dapsone, phenobarbital, etc.,⁹ The establishment of robust pharmacovigilance data sets for serious systemic delayed hypersensitivity reactions is needed in the Indian healthcare system. Prospective studies to determine incidence rates of hypersensitivity reactions to anti-TB drugs and pathways for prompt investigation and management including desensitization protocols are needed to reduce the risk of multi-drug-resistant TB. Furthermore, there are no data regarding incidence rate of peri-operative anaphylaxis during general anaesthesia in India.

The establishment of research should take into account current barriers to the provision of basic asthma and allergy care. First, allergy and clinical immunology has not yet received independent specialty recognition by Medical Council of India. Allergy care is therefore mainly delivered by organ-based specialists and general practitioners without formal training. Second, there are no standardized skin prick test extracts and access to in vitro platforms for serum-specific IgE testing is limited to few laboratories without quality assurance and these are unaffordable for vast majority of patients. Third, standardized extracts for injection immunotherapy and sublingual immunotherapy are not easily accessible and are unaffordable for patients from lower socioeconomic strata. Fourth, funds for research are limited and infectious diseases, respiratory diseases, oncology and cardiovascular medicine take precedence over asthma and allergy. Figure 1 summarizes high-priority areas and strategies for research into asthma and allergy in India.

Working in partnership with global health funding agencies in HICs and pharmaceutical companies for the establishment of research hubs and improving capacity might be a way forward for asthma and allergy research in India. There is an urgent need to train and upskill healthcare professionals in primary and secondary care, and collaborative projects with international societies such as WAO, BSACI, EAACI and AAAAI might help in sharing knowledge and expertise.

CONFLICT OF INTEREST

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