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Message from the President

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I am most appreciative, as always, to the Chief Editor, Dr. Jane Chan, the Associate Editor, Dr. Jaime Sou Da Rosa Duque, and our group of dedicated subeditors for producing another exceptional issue of the newsletter which has become a "must read." It's sometimes difficult for the readers to understand fully the amount of time needed to prepare, write, check and edit an article, let alone an entire newsletter, for publication. It's a very time consuming and demanding exercise especially when it's on top of an already heavy clinical burden of patient care. We are indebted to them all.

This is the last time I will be writing the President's column for the newsletter because I step down in November at the AGM. I would like to take this opportunity to thank the officers, Council, advisors, members and the secretariat team at MIMS for their support during my tenure. It's been my privilege and honour to serve HKIA.

HKIA looks very different from 3 years ago. Most importantly we have revised our constitution to limit the time any Council members can serve. This will create opportunities for new colleagues to join Council and be involved with the governance of the Institute. The only exception is the honorary secretary who, while still needing to be re-elected at regular intervals, has no need to take a fallow period to ensure an element of continuity.

It's a delicate balance to achieve more involvement of members, retaining accountability and progressing to greater professionalism, while preserving HKIA's renowned friendships among the leadership team which has seen the Institute through 'thick and thin'. The fact that this has been successfully implemented says a lot for Council's visionary determination and the support from the membership-at-large.

As a result of much hard work from Council and the 10 new subcommittees, HKIA now offers travel and research grants. It honours deserving local and international colleagues of distinction, who have made significant contributions to the specialty, through HKIA awards and a President's medal.

HKIA publishes regular newsletters, guidelines, position papers, scholarly articles and authoritative commentaries. It has an active presence on Facebook, Twitter as well as on its own website. It organises frequent educational seminars for doctors, nurses, dietitians and other allied health professionals. HKIA has worked with the Environmental Protection Department of the Government of the HKSAR to develop educational video clips on pollution for the public. It continues to organise its very successful international congresses every two years and from this year, it will also host an annual scientific meeting every intervening year.

In collaboration with other related societies and AllergyHK, public engagement has never been more active. There is a social programme for members. Membership has almost doubled in 3 years with a massive increase in the category of allied health. The finances of the Institute are very healthy and industry has been very supportive in providing unconditional grants for our educational initiatives. The profile of allergy in HK has never been higher. HKIA with AllergyHK are often the first ports of call when there are media enquiries about hot items in the news about allergy.

The constant encouragement by HKIA and others has fostered environments which have facilitated the creation of two new drug allergy services in public hospitals in 2017; the creation of the first training post in adult allergy in 20 years; and maybe even the recent increase in numbers of paediatric allergy trainees. While the recent progress is encouraging, it is of course slower than we prefer. However, service development is akin to water dripping on stone - the stone will eventually crack but we must keep the water dripping.

There is much more to do. The current representation of allergists in HK is one allergist per 1.17 million head of population which is very low. There are about 5-fold more paediatric allergists than adult allergists per head of population which needs to be rebalanced. HKIA has estimated that HK needs about 16 full time equivalent (FTE) paediatric allergists and 54 FTE adult allergists to meet a target of 1 allergist per 100,000 head of population.[1] If this can be achieved, HK will be close to international standards and will match other major medical specialties locally.

What is the next step? My personal view is that the allergy community needs to develop a cogent business case. My past experience has shown that even when the logic, epidemiology and case histories are compelling, business managers and bodies such as the Hospital Authority (HA) also require a fully worked up business case to support allocation of resources. They have to weigh up competing priorities when there is a limited pot of funds.

We have made a good start to giving the profession and our patient community a voice. I now invite HKIA to consider how to arrive at a health economics analysis of allergy service provision. If it can be shown, as many of us believe, that establishment of allergy services in HK would actually save the HA money (as has already been shown for allergen-specific injection immunotherapy in the USA[2]) and that any saved resources could be potentially devolved to support other specialties, this would be very powerful support for an expansion of services in the discipline.

With these final remarks, let me say how delighted I am that Dr. Marco Ho is HKIA's next President. Marco is a past Chairman of AllergyHK and a Consultant at Queen Mary Hospital. He understands well the workings of the HA. I am confident that he will bring forth new ideas and craft a vision to continue the momentum, embrace the challenges and lead HKIA to greater heights. He deserves our strongest support.

Thank you for working with me to set the Institute on a steep upward trajectory. There are outstanding and enthusiastic colleagues in place now to drive HKIA's future agenda to honour our founders for the benefits of our community. God bless and may you sail with a following wind!

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It is our great pleasure to bring to your attention the 6th issue of the HKIA e-newsletter. By now, the HKIA editorial board is entering the 4th year of its existence, and thriving. In addition to the continued dedication from our "old" guards, the e-newsletter is further blessed with expert input from new additions to the Editorial Board. For this issue, the two new subeditors Dr. Jason Chan and Dr. Birgitta Wong have contributed, and our Associate Editor Dr. Jaime Sou Da Rosa Duque has been working hard in various capacities: as co-editor for the whole issue, and as author on the section on drug allergy. The quiet but highly significant support we have been receiving from our subeditors has been largely understated and deserves big round of applause from us.

The organization of this issue follows our earlier issues: topics are grouped into different corners for ease of reading. Our commitment to limiting the choice of publications for our subeditors' review to the publications within the past 6 months remains strong, and that is how we believe we can provide the most helpful educational information to you: to provide an update on the latest thinking on the various issues relevant to allergy.

In an effort to align the bedside practice among all practitioners of allergy, the HKIA has regularly chosen topics where updates and guidelines may come in handy. In this issue, we have published for consultation the draft guidelines jointly prepared by the HKIA and The Hong Kong Society for Paediatric Immunology Allergy and Infectious Diseases on the vaccination of egg-allergic patients. This is an important topic of considerable practical importance. Many countries have issued revised guidelines recently as summarised in the draft guidelines. It is therefore timely that HKIA and our partner society should issue our own recommendations for Hong Kong. The consultation period is one month so please send in any comments and suggestions for change to HKIA Secretariat Ms. Sigourney Liu, at sigourney.liu@mims.com by 1 Dec 2017.

The field of Allergy is rapidly evolving as more scientific evidence is gathered, at times challenging our old dictum and beliefs. In this issue, we have the perfect example of such, when for years bedside practitioners have thought that there is no scientific data to support the use of dust mite-impermeable bed covers for control of asthma in children, and yet we have the first-ever scientific study which strongly supports the clinical efficacy of dust mite-impermeable bed covers for asthma management. Another study discussed in this e-newsletter finally affirmed, after years of speculation but absence of evidence base, the therapeutic role of maintenance azithromycin in the persistent uncontrolled asthmatic in a group of adult patients at age ~ 60, inclusive of both eosinophilic asthma and non-eosinophilic asthma. Our “journal club” style writing in this e-newsletter becomes an important avenue for the Editorial Board to share new exciting, at times ground-breaking, scientific findings with HKIA members.

Last but not the least, we would like to give our special thanks and best wishes to Dr. Tak-hong Lee, who will soon step down from his post as the HKIA President. Dr. Lee has been highly entrepreneurial and instrumental with regard to this e-newsletter. Not only did he give birth to the idea that the HKIA should have a newsletter for its members, he has also been tirelessly facilitating the preparatory work for each and every one of the 6 issues we have had so far. Without him, this e-newsletter would not have commanded the kind dedication and commitment from each member of the Editorial Board. We do hope that Dr. Lee will remain the inspiration for this e-newsletter for years to come.

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The Lancet Commission on pollution and health: a summary

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As freshly off the press as 19 October 2017, Lancet e-published a landmark statement referred to as the "Lancet Commission on pollution and health".[1] This work "builds upon work undertaken in the past decade by international organizations and national funders to address the challenges of modern-day pollution." The aim of this Lancet Commission on pollution and health is "to end the neglect of pollution, especially of the modern forms of pollution, in low-income and middle-income countries, to focus the world's attention onto the silent threat of pollution-related disease, and to mobilise the national and international resources and the political will needed to effectively confront pollution."

This 51-paged Lancet Commission is authored by over 40 public health scientists/policy-makers from multiple universities/centres around the world, as well as from international/national entities, including the United Nations, The World Bank, the European Commission, Office of the Ministry of Public Health of Qatar, Office of the President of the Philippines, Ministry of Environment, Ecology and Forests of Madagascar, Parliament of India, etc. China is represented by Professor M. Zhong of the School of Environment and Natural Resources at Renmin University of China, Beijing, China. This lengthy paper carries 5 sections: (1) on the burden of disease attributable to pollution, (2) on economic costs of pollution, (3) on the links between pollution, disease and poverty, (4) on pathways and priorities and proven interventions that can be adopted to control pollution, prevent disease, and advance economic development, and (5) on Commission's plans for future initiatives.

The Commission defines pollution as "unwanted, often dangerous, material that is introduced into the Earth's environment as the result of human activity, that threatens human health, and that harms ecosystems." While on one hand, the types of pollution historically associated with profound poverty and traditional lifestyles, namely household air and water pollution, are on the decline, ambient air pollution, chemical pollution and soil pollution, mostly in the form of industrial emissions, vehicular exhausts, and toxic chemicals, are all on the rise in many parts of the world as a result of the following socio-economic drivers:

- Uncontrolled growth of cities
- Rising demands for energy
- Increasing mining, smelting and deforestation
- Global spread of toxic chemicals
- Progressively heavier applications of insecticides and herbicides, and
- Increasing use of petroleum-powered cars, trucks, and buses

In particular, fuel combustion, as a source of energy, including fossil fuel combustion in high-income and middle-income countries, and biomass burning in inefficient cookstoves, open fires, agricultural burns, forest burning, and obsolete brick kilns in low-income countries accounts for 85% of airborne particulate pollution and for almost all pollution by oxides of sulfur and nitrogen. Fuel combustion, by releasing greenhouse gases and short-lived climate pollutants, is also a major driving force for global climate change.

The Lancet Commission on health and pollution, taking example from pollution control strategies proven to be cost-effective in high-income and middle-income countries, further emphasizes the importance of establishing pollution control strategies based in law, policy, regulation, and technology, and are science-driven focusing on the protection of public health. Such strategies include:

- Targeted reductions in emissions of pollutants
- Transitions to non-polluting, renewable sources of energy
- Adoption of non-polluting technologies for production and transportation, and
- Development of efficient, accessible, and affordable public transportation systems

To achieve their aims of ending the neglect of pollution, zeroing in on the silent threat of pollution-related disease, and mobilsing the national and international resources and the political will needed to effectively confront pollution, the Lancet Commission on pollution and health makes the following key recommendations:

1. Make pollution prevention a high priority nationally and internationally and integrate it into country and city planning processes.
2. Mobilise, increase and focus funding and the international technical support dedicated to pollution control.
3. Establish systems to monitor pollution and its effects on health.
4. Build multi-sectoral partnerships for pollution control.
5. Integrate pollution mitigation into planning processes for non-communicable diseases.
6. Research pollution and pollution control.

One example of governmental initiative in combating ambient air pollution quoted in this Lancet Commission paper is the National Improved Stove Programme undertaken in China between 1982 and 1992 in conjunction with provincial programmes. During this period, 180 million improved cookstoves were distributed to people in rural areas of China, with the aim of increasing efficiency and thus reducing use of biomass fuel. As a result of this programme, the household air pollution levels were lowered, but not sufficient to meet China's indoor air quality standards, as the designed stoves primarily moved the smoke outside without reducing emissions. Nevertheless, the programme constitutes one of the world's largest and most successful national programmes for improved stoves, and a study of 21,232 Chinese farmers followed from 1976 to 1992 showed that stove improvement was associated with a greater than 30% reduction in incidence of lung cancer.

There is so much food for thought that this Lancet Commission paper should quickly become one of the "must-reads" for the high governmental officials in all the rapidly developing countries in the world, including China and India. As global citizens, the healthcare professionals in Hong Kong must participate in thought and in action this global initiative to end the neglect of pollution.

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Azithromycin in adults with persistent uncontrolled asthma

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Asthma is a chronic disease in which inflammation of the airway causes symptomatic coughing, wheezing, and difficult breathing. Despite effective treatment with inhaled corticosteroids (ICS) and long-acting beta-2 agonist (LABA) or other controller medications, approximately 5 to 10% asthma patients have persistent uncontrolled disease with substantial morbidity, disability and healthcare cost.[1] This group of patients has very limited treatment options. Frequent or maintenance use of systemic corticosteroids significantly increases morbidity rates of type II diabetes, osteoporosis, dyspeptic disorders and cataracts.[2] Targeted add-on treatment with monoclonal antibodies directed against immunoglobulin E (omalizumab) or interleukin-5 (mepolizumab and reslizumab) are effective for allergic or eosinophilic phenotype, but their high costs preclude widespread use in most parts of the world.

Macrolide antibiotics have antibacterial, antiviral, anti-inflammatory and immunomodulatory effects. Maintenance treatment with macrolides such as azithromycin has been proven to be effective in most chronic inflammatory airway diseases including cystic fibrosis[3], bronchiectasis[4], diffuse panbronchiolitis[5] and chronic obstructive pulmonary disease (COPD).[6] Previous studies of macrolides on asthma are inconclusive due to small sample sizes, short study periods, and highly variable inclusion criteria, interventions and outcomes.[7]

Recently, Peter Gibson and colleagues[8] reported the results of the AMAZES study in *The Lancet*. This is a large multicenter, randomized, double-blind, placebo-controlled trial of azithromycin in adult patients with persistent uncontrolled asthma despite treatment with maintenance ICS plus LABA. The study designs and patient characteristics were summarized in Table 1. Subjects included were phenotyped for prespecified subgroup analyses. Inflammatory phenotype was classified as eosinophilic or non-eosinophilic, depending on whether sputum eosinophils were ≥3% or blood eosinophil counts were ≥300 per μL. Exacerbation phenotype was defined as having a history of at least two severe exacerbations, requiring oral corticosteroid courses or hospitalization for asthma in the previous 12 months.

There was no commercial input into any aspect of the trial. The main treatment outcomes were summarized in Table 2.

Incidence of total asthma exacerbation was significantly reduced in the azithromycin group. The beneficial effect of azithromycin remained significant after adjustment for moderate or severe exacerbation, maintenance dose of inhaled corticosteroid, eosinophilic or non-eosinophilc phenotype, exacerbation phenotype, infective or non-infective phenotype (those with or without bacterial pathogen isolation from sputum using standard culture techniques).

Azithromycin significantly improved asthma quality of life, as measured by Asthma Quality of Life Questionnaire (AQLQ). There was also a reduction in asthma symptoms, as measured by Asthma Control Questionnaire (ACQ6), nasal symptoms, cough and sputum production. Lung function and sputum cell count did not differ significantly between azithromycin and placebo groups. Azithromycin-treated group had fewer patients reporting respiratory tract infection and lower rates of antibiotic courses for respiratory infection. At the end of treatment, there was a non-significant increase in azithromycin-resistant organisms in sputum of patients treated with azithromycin compared with placebo.

Azithromycin treatment was well tolerated. There was no significant difference in the overall rate and type of serious adverse events. Diarrhoea was more common in azithromycin-treated group. Two patients were withdrawn due to abnormal QTc prolongation observed during the study (one in each group), and three patients were withdrawn due to tinnitus or hearing loss, all from the placebo group.

This landmark study had many strengths. First, the large number of patients provided sufficient power to unequivocally show that add-on therapy with azithromycin in adult patients with uncontrolled asthma reduced exacerbation rates and improved quality of life. Second, all study patients were well phenotyped. Consistently, azithromycin reduced exacerbations in all phenotypes, including both eosinophilic and non-eosinophilic asthma, both infective and non-infective phenotype, both patients with more frequent and less frequent exacerbations, both moderate and severe exacerbations. Third, the long duration of treatment of azithromycin was safe and well tolerated. The authors reminded us to have routine pre-screening of risk factors such as prolongation of the corrected QT interval to prevent cardiac arrhythmia, as well as regular monitoring of hearing problems and diarrhea.

There are also limitations to this study. First, the AMAZES population was an older age group with long-standing asthma. The results might not be applicable to children or younger adults with new-onset asthma and further evaluation is required in these age groups. Second, microbial resistance is a known effect of antibiotic use. In this study, azithromycin was associated with a non-significant increase in resistant organisms at the end of treatment, but the study was not adequately powered to fully assess this effect. Third, mechanism of azithromycin in reducing asthma exacerbation is still not fully understood. Macrolides have anti-inflammatory, antibacterial, antiviral, and immunomodulatory effects.[9] However, the authors did not observe a reduction in inflammatory cell counts in sputum to support a definite anti-inflammatory effect.

For patients with poor asthma control despite inhaled corticosteroid and long-acting bronchodilators, there are limited options of add-on treatments available. Maintenance oral corticosteroids have substantial toxic effects. Monoclonal antibody therapy is effective in patients with eosinophilic asthma, but access is limited by cost and requirement for injection. Comparing with monoclonal antibody therapy, azithromycin is less costly. Moreover, it has broader benefits in that it is effective in patients with both eosinophilic and non-eosinophilc asthma, and also reduces lower respiratory tract infections. However, the effects of long-term therapy with macrolides on community microbial resistance remain a public health concern. Add-on therapy with azithromycin in asthma may need to be restricted to those patients with the highest unmet medical needs (e.g. frequent exacerbations) and to time periods with the greatest risk of exacerbations (e.g. winter).[10]

Table 1. Summary of the study design and patient characteristics

		Placebo (n=207)	Azithromycin (n=213)
Design		Multicentre, randomized, double-blind, placebo controlled, parallel group trial	
Inclusion criteria		● Adults (≥ 18 years) ● Symptomatic asthma despite maintenance inhaled corticosteroid plus long-acting bronchodilators ● Clinically stable for at least 4 weeks before study entry ● Non-smokers – confirmed by exhaled carbon monoxide < 10 parts per million	
Exclusion criteria		● Ex-smoker with substantial parenchymal lung disease – confirmed by having diffusing capacity for carbon monoxide <70% predicted value ● Having hearing impairment ● Having abnormally prolonged QTc inverval	
Treatment		As add-on therapy with inhaled ICS plus long-acting bronchodilator	
		Placebo, three times weekly	Azithromycin 500mg, three times weekly
Duration		48 weeks	
Age (years)		60 (50-68)	61 (51-69)
Age asthma diagnosed (years)		20 (5-44)	21 (5-42)
Sex		Female 58%; male 42%	Female 63%; male 37%
Spirometry (FEV1 % predicted)		73.6 (18.8)	72.3 (20.7)
Sputum phenotype	**Eosinophilic**	77/46%)	67 (41%)
	Non-eosinophilic	89 (53%)	98 (59%)
Blood eosinophils (x10^9) per L		0.28 (0.16-0.41)	0.20 (0.11-0.40)
Medications			
Low dose ICS (<400μg/day)		4 (2%)	5 (2%)
Moderate dose ICS (400-800μg/day)		26 (13%)	23 (11%)
High dose ICS (≥800μg/day)		176 (85%)	185 (87%)
Long acting beta agonist		205 (99%)	208 (98%)
Leukotriene modifier		6 (3%)	8 (4%)
Long-acting anti-muscarinic		33 (16%)	40 (19%)
Theophylline		6 (3%)	7 (3%)
Oral corticosteroids		6 (3%)	8 (4%)

Data were median (interquartile range), mean (standard deviation), or number of patients (%). FEV1= forced expiratory volume in 1 second. ICS = inhaled corticosteroid daily dose, beclomethasone equivalent.

Table 2. Summary of treatment outcomes

	Placebo (n=207)	Azithromycin (n=213)	P value
Primary outcome			
Asthma exacerbations per person-year (95% CI)	1.86 (1.54-2.18)	1.07 (0.85 -1.29)	p<0.0001
	Incidence rate ratio =0.59 (95% CI 0.47-0.74)		
Quality of life (AQLQ) (mean, 95%CI)	5.55 (5.40-5.70)	5.73 (5.58-5.88)	p=0.001
	Difference vs placebo = 0.36 (0.21-0.57)		
Secondary endpoints			
Asthma symptoms (ACQ6) (mean, 95% CI)	1.31 (1.18-1.44)	1.21 (1.07-1.35)	P<0.05
Nasal symptoms	3.46 (3.07-3.85)	2.95 (2.58-3.32)	P<0.05
Sputum production	2.83 (2.45-3.21)	2.16 (1.81-2.51)	P<0.05
Cough	2.99 (2.60-3.38)	2.45 (2.11-2.79)	P< 0.05
Safety			
Serious adverse event (%)	26 (13%)	16 (8%)	P=0.27
Diarrhea	39 (19%)	72 (34%)	P=0.001
Infection	74 (36%)	42 (20%)	P<0.001
Antibiotic courses for respiratory infections	65 (31%)	42 (20%)	P<0.0001
Azithromycin-resistant organism at end of treatment	12 (29%) of 42	19 (49%) of 39	P=0.062

AQLQ= Asthma Quality of Life Questionnaire. ACQ6= Asthma Control Questionnaire. CI =confidence interval.

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Risk factors and predicting tool for severe asthma exacerbations in children

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Introduction

Severe asthma exacerbations are events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma.[1]

The joint statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) defined a severe asthma exacerbation for clinical trials should include at least one of the following[1]:

(a) The need to use systemic corticosteroids (tablets, suspension, or injection) or increase from a stable maintenance dose for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.

(b) A hospitalization or ER visit because of asthma, requiring systemic corticosteroids.

However, the assessment of asthma control in children is not easy, which is usually based on parent reports and may be influenced by poor symptom perception by parents or children. Spirometric assessment in children is also challenging especially for young children. Moreover, the ATS/ERS definition by means of systemic corticosteroids use cannot be applied easily in children, as there is no adequate evidence of beneficial effects of systemic corticosteroids on recurrent wheezing exacerbations in preschool children.[2]

Childhood asthma is a major concern worldwide which exerts a substantial burden on the family, healthcare services and society. It can also impair the child's academic achievement and social interaction due to a large number of lost school days. Severe asthma exacerbations are risk markers for both subsequent exacerbations and mortality from asthma.

Prevention of severe asthma exacerbation in children requires identifying patients at high risk. Puranik S et al.[3] reviewed the risk factors and predictive tools for severe asthma exacerbations in childhood:

Risk factors for severe asthma exacerbation

Race, ethnicity, and socioeconomic status

Non-Hispanics blacks and Hispanics have an increased risk of ED visits for asthma compared with non-Hispanics whites, with similar findings in Asians and members of other race.[4]

Genetics

A genome-wide association study identified cadherin-related family member 3 (CDHR3) as a susceptibility locus for recurrent severe asthma exacerbations in children ages 2-6 years.[5]

Tobacco smoke

Second-hand smoke is associated with worsening lung functions, decreased response to treatment, and ED visits for asthma.[6]

Viral infections

Viral infections can enhance production of proinflammatory cytokines and chemokines, which in turn induce the recruitment and activation of neutrophils and eosinophils, leading to airway inflammation and severe asthma exacerbations.[7]

Air pollution
Outdoor air pollution, including traffic-related pollution, can be a cause of severe asthma exacerbation in children.[8]

Vitamin D insufficiency
Observational study showed that vitamin D insufficiency was associated with severe asthma exacerbations in school-aged children, and this may be medicated by altered immune modulation of viral infections or reduced response to ICS.[9]

Allergens and indoor pollutants
Exposure to allergens, whether indoors or outdoors, can lead to poor asthma control and severe asthma exacerbations in sensitized children.

Obesity
Compared with children of normal weight, obese children have been shown to have a decreased response to ICS, chronic systemic inflammation, variations in hormonal levels, and cormorbidities such as gastroesophageal reflux that may serve as the link between obesity and severe asthma exacerbations.[10]

Psychosocial stress
Chronic stress has been linked to decreased expression of the genes for the β2-adrenergic receptor (ADRB2) and the glucocorticoid receptor (NR3C1) in leukocytes of children and adults with asthma.[11]

Airway microbiome
A difference in the pattern of bacterial colonization of the upper airway may predispose children to severe asthma exacerbations. According to a prospective study of children monitored from birth to age 5 years, neonatal colonization of the hypopharyngeal region with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* was significantly associated with acute severe exacerbation and hospitalization for wheeze.[12]

Poor adherence to treatment
Poor adherence to controller medications was significantly associated with severe asthma exacerbations in children.

Predictive tools for severe asthma exacerbations in children

There are a number of validated questionnaires that can be used to clinically to approximate asthma severity or control, such as the Asthma Control Test and the Asthma Control Questionnaire. However, none of them can accurately predict asthma exacerbation in an individual child.

Bateman et al. investigated the predictors of failure to achieve good asthma control (Global Initiative for Asthma GINA-defined) and to develop a simple risk score for exacerbations for clinical use by using data from 7,446 subjects in three studies.[13] In the multivariable analysis, GINA step 4 versus 3 treatment, reliever use, postbronchodilator FEV1, and the five-item Asthma Control Questionnaire score were dominant predictors of both uncontrolled asthma and severe exacerbations; smoking status and body mass index also predicted severe asthma exacerbations.

With better understanding of the pathophysiology of asthma, there had been a number of novel biomarkers identified including fractional exhaled nitric oxide (a biomarker for eosinophilic airway inflammation), airway eosinophilia (inflammatory characteristic of Th2-driven/corticosteroid –responsive asthma), serum periostin (a biomarker of allergic eosinophilic asthma) and urinary LTE4 converted in circulation from the cysteinyl leukotrienes LTC4 and LTD4 (signaling molecules involved in airway inflammation). But none of them can predict severe asthma exacerbations and most of them are still limited to the confines of research.

Conclusion

Currently, there is no predictive model (clinical or biological markers) to predict severe asthma exacerbations in children. A history of one recent severe exacerbation remains the best predictor for future severe asthma exacerbations. Haselkorn T et al.[14] found that future severe exacerbations at 6 months were most strongly predicted by recent severe exacerbations in children aged 6 to 11 years in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens 3-year observational study.

Therefore, optimal asthma care for paediatric patients who have had a severe asthma exacerbation in the prior year should include adjustments of their controller medications according to their asthma control. Reinforcement on avoidance of exposure to second hand smoke and adherence to controllers should also be emphasized as a part of the treatment plan of children at high risk for future severe asthma exacerbations.

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Discrepancies in perceptions in asthma management between patients and healthcare providers should not be overlooked.

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In international asthma guidelines, establishing partnership between asthma patients and their healthcare providers has been emphasized to be an essential component for successful management of asthma.[1] Certain national quality improvement initiatives have also stressed the need for promoting patient engagement through effective communication, shared decision-making and self-care skills, rather than merely adopting the "main stream" clinician-led disease management.[2] However, because of the diverse socio-economic, cultural and educational background in patients, together with the lack of time available in busy clinics, alignment of doctor-patient perception may not be easily achievable.

Sapir et al.[3] carried out a multi-centred survey to both patients and physicians in 40 allergy and immunology practices in 20 states across the United States, before and after a 1.5-hour patient education session. It was found that physicians admitted to having the lowest knowledge levels in the more "personal" issues such as patient's financial status, adherence to asthma medications, lifestyle and workplace situation. In contrast, they are more knowledgeable on the "clinical" aspects of their patients such as exacerbations, hospitalizations, smoking status and co-morbidities. More providers than patients considered the following treatment goals to be important: reduction in time away from work or school, prevention of exacerbations, emergency room visits and hospitalizations. In contrast, more patients selected "improving spirometry results" and "ability to perform activities of daily living" as their treatment goals. It was also noted that physicians provided the least education on areas of pulmonary rehabilitation, exercise training and other non-pharmacologic therapies. Lastly, patients considered "having trouble remembering taking medications" and "feeling well with the medications" are barriers to compliance to treatment, in contrast to physicians' perception, namely side effects, insurance issues and costs.

Although this study has been limited by (1) its "pragmatic" context with the administration of a relatively short survey immediately before an educational program and (2) the selection biases arising from carrying out the survey amongst the program participants, its results did align with the findings of earlier studies on a similar theme. Cooper et al.[4] reported a significant disparity between physicians' estimate of the incidence of side effects (10%) with inhaled corticosteroids versus patient's own reports (46%). In another study of healthcare providers, Mowrer et al.[5] identified gaps in understanding of patient issues such as costs, insurance coverage and patient-centred communication. In that qualitative survey, Mowrer et al.[5] also revealed that proper use of inhalers, trigger avoidance and importance of controller medications were important areas that required strengthening during the provision of education to asthma patients.

In conclusion, it appears that "disconnects" in perception between patients and healthcare providers likely exist. Since the healthcare funding pattern and the degree of utilization of private healthcare sector in the United States and Hong Kong are rather different, issues such as costs and health insurance may not carry as much weight on medication adherence in Hong Kong as in the U.S. Nevertheless, clearer understanding of the patient's needs, goals and personal issues would better equip the healthcare providers in the provision of education and formulation of management strategies. Alignment of doctor-patient perception and management goals would facilitate patient engagement and would likely achieve better management outcomes in chronic diseases like asthma.

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Is chronic rhinosinusitis an infectious disease?

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Chronic rhinosinusitis (CRS) is a common disease with prevalence rates ranging from 4.5 – 12.5% of the western populations and significant socio-economic burden.[1] CRS is characterized by symptoms of nasal congestion, anterior or posterior nasal drainage, facial pressure and olfactory dysfunction. Despite extensive research endeavours, the exact aetiology of CRS remains unclear and is thought to be likely multifactorial. Recent developments revealing the important roles of fungus, superantigens, biofilms and bacterial intramucsoal residence have renewed the interest in the involvement of microbes in the pathogenesis of CRS.

The sinonasal microbiome

In the recent past, the paranasal sinuses were thought to be a sterile environment. It was not until a study in 2009 when normal maxillary sinus mucosae sampled from patients who underwent orthognathic surgery revealed that bacteria were present in the sinuses in the absence of infection or inflammation[2] that began a shift in this paradigm. With the application of next generation sequencing, there has been an explosion in the evaluation of what constitutes the "normal" microbiological makeup in the paranasal sinuses, also known as the "normal" microbiome. However, this "normal" microbiome has yet to be established and no universal consensus has been reached as to what constitutes a normal sinus mucosal microbiome owing to differences in study designs, sampling sites, sequencing methodology and bioinformatics analysis. The most comprehensive analysis is a systematic review of all published sinonasal microbiome studies that showed the phyla Actinobacteria, Bacteroides and Firmicutes were present in the healthy sinus mucosa of all these studies.[3]

In chronic rhinosinusitis (CRS), a variety of changes in the sinonasal microbiome affecting patients had been shown when compared to normal healthy controls. The overall bacterial load in both states are similar; however, the amount and diversity of the microbiome in CRS patients are significantly reduced when compared to controls, which is a common finding in many chronic inflammatory diseases as well.[4] This dysbiosis in CRS patients also manifests as an increase in pathogenic bacteria with a concomitant reduction in commensal bacteria. Notably, there is also some evidence of an increase in the abundance of *Staphylococcus aureus* and *Corynebacterium* in CRS.[5]

Effects of medical and surgical management of chronic rhinosinusitis and the microbiome

The initial treatment of CRS primarily involves a medical approach including nasal saline irrigation, topical application of nasal steroids, and systemic antimicrobials and steroids when necessary. Surgical management is reserved for those that fail medical therapies. Antibiotic usage reduces the biodiversity of the microbiome and may increase the abundance of *Staphylococcus aureus*.[6] Antibiotic therapy also results in a selection pressure on the microbiota, resulting in an increase in the relative abundance of bacteria that are less sensitive to the antibiotics being used. Nasal saline irrigations and topical nasal steroids have no significant effect on the microbiome on patients with CRS and nasal polyposis; however, intranasal budesonide was associated with a distinct sinonasal microbiome in controls. These findings mirror the perturbations in the gut microbiota that can occur in response to broad-spectrum antibiotics.

In patients undergoing sinus surgery for CRS, a longitudinal analysis showed that patients who had improved symptom scores and quality of life outcomes based on the SNOT-22 questionnaire had an increase in the mean relative abundance of *Acinetobacter Johnsonii* to levels comparable with normal controls.[7] There was also a post-surgical increase in the bacterial microbiome richness overall.

These results do need to be interpreted with a grain of salt since most studies included antibiotic washout periods and it is known that certain classes of antibiotics have lasting effects on the microbiota despite their discontinuation, particularly macrolides. Therefore, any previous antibiotic use may influence results obtained in these studies that investigate the effects of medical and surgical treatments despite a 4- to 8-week washout period prior to enrollment.

A role for probiotics in chronic rhinosinusitis?

Probiotics are live mircoorganisms that may confer health benefits to the host when taken in appropriate amounts. Probiotics achieve their effects through augmentation of the epithelial barrier, active and passive inhibition of pathogenic organisms, elaboration of anti-microbial compounds and local immunomodulation.[1] Animal studies have provided valuable insight in the possible application of probiotics in CRS. In mice, it has been shown that pre-treatment with *Lactobacillius sakei* can mitigate the inflammatory response within the sinonasal mucosa after stimulation with *Corynebacterium tuberculostearicum*. Similarly, pre-treatment with *Staphylococcus epidermidis* lessens the pro-inflammatory effect of *Staphylococcus aureus* on the sinonasal mucosa. However, oral probiotics have been met with limited clinical success, possibly related to the individual microbiota variation that exists between individuals. There is also a lack of understanding of how gastrointestinal microbiota dysbiosis that has been linked to non-gastrointestinal chronic diseases may be related to sinonasal microbiota dysbiosis. Besides oral probiotics, the application of topical probiotics to manipulate the sinonasal microbiota in CRS is currently being evaluated. Finally, given the success of faecal transplants in the treatment of *Clostridium difficile* colitis and inflammatory bowel disease, there may be a potential future role for the transplantation of sinonasal secretions from healthy donors in the treatment of CRS.

Conclusions

Currently, our understanding of the sinonasal microbiome and its complex interaction with the host is at its infancy that is summarized in figure 1. Whether a change in the microbiome in CRS is a cause as opposed to an association with the disease process remains unclear. To improve our understanding of the role of sinonasal microbiome dysbiosis in CRS and how this can contribute to the treatment of CRS, further investigations are necessary in this exciting area of development that may offer further treatment options for CRS.

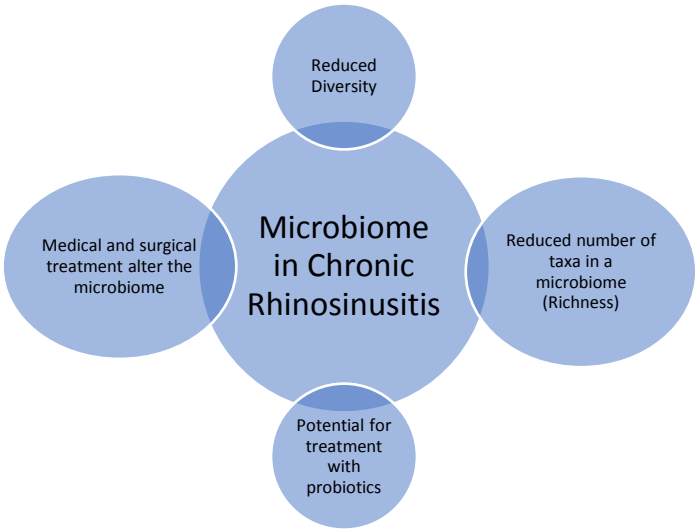

Figure 1. Summary of the changes of microbiome in chronic rhinosinusitis, following treatment and potential developments.

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Efficacy and safety of sublingual immunotherapy tablet in adult and adolescents with house dust mite-induced allergic rhinitis

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House dust mite (HDM) is the most common cause of perennial allergic rhinitis with or without conjunctivitis worldwide and in Hong Kong.[1] Symptoms can be treated with allergy pharmacotherapy or allergen immunotherapy (AIT).[2] In contrast to pharmacotherapy, AIT can alter the immune response to modify the underlying pathologic mechanisms. However, AIT has some limitations; in terms of subcutaneous immunotherapy, there is a need for frequent clinic visits, pain caused by injections and the risk of anaphylaxis.[3] Sublingual immunotherapy (SLIT) drops have been available but there is still inconvenience of use by patients with liquid form.[4] In 2016, the HDM SLIT tablet was proven to be effective for HDM-induced allergic rhinitis in European patients.[5]

Following the European study, results from the largest randomized HDM SLIT tablet trial for allergic rhinitis was published in late 2016.[6] It was a double-blind, placebo-controlled trial conducted at 182 sites in United States and Canada. The intervention medication, the SQ-HDM SLIT tablet (TO-203 ALK-Abello, or Merck & Co) was a fast-dissolving, freeze-dried tablet with 1:1 mixture of allergen extracts from the HDM species *D pteronyssinus* and *D farina*e that was manufactured and provided by ALK-Abello. This tablet formulation contains the broadest possible spectrum of *D pteronyssinus* and *D farinae* major and minor allergens. In the trial, a total of 1,482 subjects (aged > 12 years) with HDM-induced allergic rhinitis with or without asthma were randomized to a daily SQ HDM SLIT-tablet (12 SQ-HDM dose) or placebo for up to 52 weeks. The primary end point was the average total combined rhinitis sore (TCRS), which was defined as the rhinitis daily symptom score (DSS) plus rhinitis daily medication score (DMS), during the last 8 treatment weeks. Results showed a significant lower TCRS in favor of 12 SQ-HDM versus placebo ($P< 0.001$), with a treatment difference based on medians corresponding to an improvement of 17%. Furthermore, 12 SQ-HDM significantly improved respiratory symptoms for the 31% of the subjects who also had asthma compared to placebo. The trial was adequately powered and the results met the US Food and Drug Administration's criteria for clinically meaningful efficacy.

Treatment-related adverse effects (AE) reported by 10% or more of the subjects were documented. Local AEs were frequent but were considered tolerable with 12 SQ-HDM because of the mild intensity and short duration of these events.

Another study, the most recent on this topic, was a randomized, parallel-group, double-blind, placebo-controlled trial conducted at 90 sites in Japan and published in 2017.[7] Nine hundred and forty-six patients with ages ranging from 12-64 years who had moderate-to-severe HDM-induced allergic rhinitis were recruited. They were randomly assigned to receive either 6 SQ-HDM (10,000 JAU), 12 SQ-HDM (20,000 JAU) or placebo for 12 months. Results demonstrated statistical significant reductions in the total combined rhinitis score (TCRS) of 1.15 (22%, $P< 0.001$) in the 6 SQ-HDM group and 0.99 (19%, $P< 0.001$) in the 12 SQ-HDM group compared to the placebo group. The statistically significant treatment effect was evident from 12 weeks of treatment onward). Adolescents experienced similar improvements as adults ($P<0.05$). The treatment was well tolerated by both groups. Common AEs were mouth edema, pruritus and throat irritation.

The Japanese study confirmed the previously reported European and North America data and supported the efficacy and safety profiles of the SQ-HDM SLIT tablets. Owing to a mere modest difference apparent between the 2 doses, the 6 SQ-HDM was chosen as the marketed dose in Japan. Taken collectively, the comparable clinical responses suggest that both 6 SQ-HDM and 12 SQ-HDM may be effective and tolerated allergic rhinitis treatments in Caucasians and Asians, although further studies will be needed in other ethnic groups, younger children, and pregnant women.

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Allergies to herbal medicines: do they exist?

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Allergies to medications are relatively common and they can be life-threatening.[1] Mislabeling of patients with drug allergies may lead to use of more expensive alternative medications and less efficacious treatment options for these patients.[1,2,3] Therefore, recent international guidelines recommend a thorough investigation which includes obtaining a comprehensive history, reviewing past and present medications, and performing skin testing when indicated for patients who report or have documented drug allergies.[1,2,3]

What about allergic reactions to herbal (e.g., traditional, oriental, complementary) medicines? Do they occur? If so, what are the frequencies and severity? This is an important topic given the high prevalence and growing popularity of herbal medicine use in Hong Kong and globally.[4,5,6]

Meincke and her colleagues recently retrieved data from VigiBase® ranging from 1968 to 2014 to describe the statistics of paediatric cases of hypersensitivities to herbal products that have been reported to the Uppsala Monitoring Center (UMC) of the World Health Organization's (WHO) global individual case safety report (ICSR) system.[7] Despite the high overall population in China and Hong Kong that take herbal medicines, neither was listed as a major country that contributed to the reporting of adverse reactions (ADRs); the investigators found that Germany (29.1 %), Thailand (21.5 %), and Australia (11.4 %) had the highest numbers of ADRs, most of which were entered into the database by health care providers.[4,5,7] The majority of cases occurred in the age range of 7-12 years old (30.4%) who presented with cutaneous eruptions such as urticaria (22.4 %), rash (22.4%), and rash erythematous (15.0%), although there were also a few cases which were more severe which involved airway involvement (1.8%) and anaphylaxis (6.5%). The most frequently reported herbal preparations leading to allergic symptoms were mixed herbals (51.4%), Hedera helix (15.0 %), Echinacea purpurea (5.6%), and Andrographis paniculata (4.7%). Although eucalyptus oil was the most frequently reported herbal drug causing severe ADRs in adults, due to the limitation of use in children under 12 years old, there was only one boy's reaction to this agent listed in the dataset.[8]

The most striking is the low reporting from China and Hong Kong of ADRs due to herbal products. Today, China ranks first with the highest population in the world (Table I), and a lack of reporting by China and other countries with high populations and prevalence of herbal medicine use are a major bias in this study. Therefore, I encourage countries with the most people and patients to consider contributing to this international database by the WHO in the future and conduct additional research in this area so that more information will be available on this important topic (Table I). For reference, online reporting and retrieving of VigiBase® data for research can be accessed at the following website: https://www.who-umc.org/vigibase/vigibase/

Table I. Countries ranked by population, top ten.

Rank	Country	Population	Date of Reporting	% of World Population	References
1	China	1,386,440,000	19 Sep 2017	18.30%	National Bureau of Statistics of China
2	India	1,321,450,000	19 Sep 2017	17.50%	http://worldpopulationclock.info
3	United States	325,788,000	19 Sep 2017	4.30%	http://worldpopulationclock.info
4	Indonesia	261,890,900	1 Jul 2017	3.46%	Badan Pusat Statistik, Indonesia
5	Pakistan	208,958,000	19 Sep 2017	2.76%	Pakistan Bureau of Statistics
6	Brazil	208,016,000	19 Sep 2017	2.75%	http://worldpopulationclock.info
7	Nigeria	193,500,543	1 Jul 2016	2.56%	National Bureau of Statistics, Nigeria
8	Bangladesh	163,162,000	19 Sep 2017	2.16%	http://worldpopulationclock.info
9	Russia	146,787,329	1 Jul 2017	1.94%	Official estimate by census in Russia
10	Japan	126,750,000	1 Jul 2017	1.67%	Statistics Bureau, Japan

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Mite-proof bedcovers: are they helpful?

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Do dust mite-proof bedcovers really work? House dust mite is the commonest indoor allergen found in Hong Kong and Southeast Asia.[1] It has been the main risk factor for wheezing in children from Guangzhou, and is closely related to asthma, the commonest chronic disease in childhood.[2] Respiratory infections and house dust mite allergy act synergistically to markedly increase the risk of asthmatic exacerbation and hospital admission.[3]

Measures to minimize dust mite exposure have been widely adopted by many patients in our locality, although evidence of their efficacy is not convincing. Major meta-analysis has failed to show any definitive clinical benefit from measures to reduce dust mite exposure.[4,5] However, a recently published randomized double-blind placebo-controlled trial which studied the effect of mite-proof bedcovers on the risk of severe asthmatic exacerbations and emergency department (ED) attendance may change our current understanding of the role of dust mite-impermeable bedcovers in asthma control. The results significantly add to the body of evidence on the efficacy of measures to minimize dust mite exposure.[6]

A cohort of 284 children in the U.K. aged 3-17 years with physician-diagnosed asthma were recruited after an episode of asthmatic exacerbation requiring emergency attendance. They were skin prick-tested to confirm their sensitization to house dust mite, and were then randomized into two groups using, over the following 12-month period, either dust mite-proof bedcovers or conventional bedcovers with matched design and texture, the latter serving as placebo. The dust mite concentrations in the cohort's mattress (ng/m^2) at recruitment and after the study period were also measured.

The primary outcome was that significantly fewer children in the active group (using dust mite-proof bedcovers) attended the hospital ED because of asthmatic exacerbations (29.3% vs 41.5%, OR 0.58, CI 0.34-0.99, P=0.047) using intention-to-treat analysis. The risk of emergency hospital admission was 45% lower in the active group (Hazard Ratio 0.55, CI 0.36-0.85, P=0.006). The secondary outcome was the significantly improved quality of life during the study period in the active group using PACOLO (quality of life questionnaire), and up to 90% of the children in the active group expressed their wish to continue to use those bedcovers to relieve their asthmatic symptoms even after the study period. The dust mite level from the children's mattresses was reduced by 84% in the active group with no significant change in the placebo group.

This is the first prospectively conducted randomized double-blind placebo-controlled trial studying the impact of the avoidance of dust mite exposure using mite-proof bed encasings on clinical exacerbation, ED attendance and hospital admission related to asthmatic attacks. In general, asthmatic exacerbation-related ED visits and hospital admissions are mainly contributed by those patients at higher risk of life-threatening asthmatic attacks and unstable disease control, and are associated with higher health care cost. This clinical trial affirmed the role of mite proof-bedcovers in reducing asthmatic exacerbations, ED attendance and hospital admissions, and in improving their quality of life. The avoidance of dust mite allergen may serve as a simple and potentially most cost-effective intervention for all asthma patients of any severity, while sparing them of the side effects associated with pharmacological treatments.

Although the study results were encouraging in this cohort of U.K. children and adolescents, there is still not enough information to extrapolate such clinical efficacy to the adult patients, nor to the use of mite-proof bedcovers from other non-studied brands, nor to other allergic diseases such as allergic rhinitis, allergic conjunctivitis and atopic dermatitis. Earlier randomized studies of using various environmental measures to reduce dust mite exposure in adults have failed to show any significant difference in control or reduction of allergic symptoms nor in airways inflammatory markers. It is important to note that in some of these negative studies, the ineffective measures have failed to reduce the actual mite density in the environment.

In conclusion, further similarly well-designed studies are called for to answer these questions before a general recommendation on mite-proof bedcovers could be made. Meanwhile, our asthma patients should be well informed of the potential clinical benefit of mite-proof bedcovers, and their consideration for the use of such bedcovers should involve balancing the potential clinical benefit and the additional cost of these bedcovers.

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Vaccination in egg-allergic individuals – A local guideline 2017 (in draft)

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Background

Vaccination is an important and effective method to develop active immunity against certain pathogens. It helps to prevent or reduce the risks of developing certain infectious diseases as well as their severities. However, the administration of certain vaccines, including influenza; measles-mumps-rubella (MMR) vaccine; and measles-mumps-rubella-varicella (MMR-V) vaccines, has historically been relatively, if not absolutely, contraindicated among egg-allergic individuals. This is because these vaccines are developed in chicken egg embryos or chicken cell fibroblasts, therefore raising the concern that egg proteins (notably ovalbumin) in these vaccines could trigger immediate allergic reactions in egg-allergic individuals. As a result, previous vaccination guidelines and vaccine product information recommended avoidance of influenza and MMR or MMR-V vaccines among individuals with history of anaphylaxis to egg exposure.

Local epidemiological studies showed that 0.4-0.7% -of Hong Kong children were reported by their parents to have adverse reactions after intake of hen's eggs.[1, 2] There is concern that administration of vaccines that could contain egg proteins, notably ovalbumin, might potentially cause allergic reactions in egg-allergic subjects. The Centre for Health Protection (CHP) recommends that mildly egg-allergic individuals can be safely administered with inactivated influenza vaccine (IIV) in primary care. But those with confirmed or suspected egg allergy who have experienced severe reactions should be seen by an allergist/immunologist for evaluation of egg allergy before administration of IIV.[3]

Recently published international guidelines have updated their recommendations regarding the administration of vaccines to egg-allergic individuals. This article summarizes the updates and aims to provide a local recommendation for general practitioners and paediatricians. For practical reasons, this guideline will only cover influenza and MMR/MMR-V vaccines.

Yellow fever vaccine is less commonly administered and has higher egg protein content (≤ 5μg/dose*). Specialist evaluation is recommended prior to vaccination. Q fever vaccine is not available in Hong Kong and therefore is not covered in this guideline.

**Information obtained through direct communication with manufacturer*

Influenza vaccine

Influenza vaccination is well known to be effective in preventing infections caused by influenza viruses and in reducing the risks of developing complications. Table 1 summarizes three influenza vaccines that are available in Hong Kong, which includes their product information recommendations in egg-allergic patients and the respective concentration of ovalbumin in the respective vaccine.

Moneret-Vautrin et al reported that only 1% of patients with egg allergy would develop allergic reactions at a threshold as low as 1mg.[4] As the quantity of ovalbumin in influenza vaccines is ≤1ug/dose, such a level of egg protein in influenza vaccines is very unlikely to trigger allergic response in this group of patients. Therefore, despite the product information recommendations and the trace amounts of ovalbumin present in these influenza vaccines, they should be safe to be administered to egg allergic individuals, including those with a history of anaphylaxis to egg proteins.

Brands	Product Information Recommendations	Quantity of ovalbumin
Vaxigrip	Contraindicated in patients with egg or chicken protein hypersensitivity	<0.1ug/ml*
Fluarix Tetra	Contraindicated in patients with egg (ovalbumin) or chicken protein hypersensitivity	<0.1ug/ml*
FluQuadri	Contraindicated in history of severe allergy reaction (e.g. anaphylaxis) to egg protein	<0.1ug/ml

Table 1 – Summary of influenza vaccines available in Hong Kong

**Information obtained through direct communication with manufacturer*

Our view is supported by numerous international guidelines on administering influenza vaccines to egg-allergic individuals summarised in Table 2.

Authorities (Country)	Recommendations
ASCIA (Australia)[5]	- Presence of egg allergy does not increase the risk of allergic reactions to the influenza vaccines. - Entire vaccine can be administered in community vaccination clinics as a single dose followed by 15 – 20minutes waiting period. Longer waiting period (30 minutes) may be warranted if there is significant parental or health professional anxiety. - The immediate availability of medical practitioner care is recommended and staff should be familiar with the recognition and treatment of anaphylaxis. - Should there be anaphylaxis to influenza vaccine itself, further vaccination should be avoided without specialist allergy assessment. - The followings are NOT RECOMMENDED: o Split dosing o Allergy testing with the vaccine or to egg prior to administration o Ingestion of egg as a pre-condition to administering the vaccine; o Vaccination in specific hospital-based vaccination clinics o Allergy specialist review before influenza vaccination unless anaphylaxis to the influenza vaccine itself has occurred previously
CDC (USA)[6]	- Any licensed and recommended flu vaccines are recommended to egg-allergic individuals who have experienced only urticaria. - Egg-allergic individuals who had other symptoms, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, may receive any licensed and recommended flu vaccine. Flu vaccines should be administered in an in-patient or out-patient medical setting. - Vaccine administration should be supervised by a healthcare provider who is able to recognize and manage severe allergic conditions. - A previous severe allergic reaction to flu vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

AAAAI (USA)[7]	- Influenza vaccines should be administered to individuals with egg allergy of any severity, just as they would be to individuals without egg allergy (Evidence level A/B) - No special precautions beyond those recommended for the administration of any vaccine to any patient are necessary for administration of influenza vaccine to egg-allergic individuals (Evidence level A/B) - Use of non-egg-based influenza vaccines (ccIIV3 or RIV3) in egg-allergic individuals in the age groups for which they are approved is acceptable but not medically necessary or preferred (Evidence level C/D) - Live attenuated influenza vaccine (LAIV) may be administered to patients with egg allergy of any severity in the age group for which it is approved (ages 2-49 years), in particular countries and seasons when LAIV is recommended as an agent (based on effectiveness in prior seasons).
AAP (USA)[8]	- IIV administered in a single, age-appropriate dose is well tolerated by recipients with an egg allergy of any severity. Special precautions for egg-allergic recipients of IIV are not warranted, because the rate of anaphylaxis after IIV administration is no greater than in egg-allergic than in non-egg allergic recipients from other universally recommended vaccines. - All children with an egg allergy of any severity can receive an influenza vaccine without any additional precautions beyond those recommended for any vaccine - Patients who refuse to receive an egg-based vaccine may be vaccinated with an age-appropriate recombinant or cell-culture product - Quadrivalent live attenuated influenza vaccine (LAIV4) is not recommended for use in any setting in the United States during the 2017–2018 influenza seasons.
AAP (USA)[9]	- Approximately 1% of children have immunoglobulin E (IgE)-mediated sensitivity to egg, and of those, a rare minority has a severe allergy - Recent data have shown that IIV administered in a single, age-appropriate dose is well tolerated by most recipients with a history of egg allergy - More conservative approaches in children with a history of egg allergy, such as skin testing or a 2-step graded challenge, no longer are recommended. - No data have been published on the safety of administering LAIV to egg allergy recipients - Clinicians should determine whether the presumed egg allergy is mild or severe reaction. Paediatricians should consult with a allergist for children with a history of severe reaction - Standard immunization practice should include the ability to respond to acute hypersensitivity reaction. Influenza vaccine should be given to children with mild egg allergy with the following preconditions: i) appropriate resuscitate equipment must be available; ii) the vaccine recipient should be observed in the office for 30 minutes after immunization - Providers may consider the use of ccIIV3 or RIV3 vaccines produced via non-egg based technologies for adult with egg allergy in settings in which these vaccines are available and otherwise age appropriate. Because there is no known safe threshold for ovalbumin content in vaccines, ccIIV3, which does contain trace amount of ovalbumin, should be administered according to the guidelines for other IIVs. In contrast, RIV3, which contains no ovalbumin, may be administered to people with egg allergy of any severity who are 18 years or older and do not have any contraindications. - However, vaccination of individuals with mild egg allergy should not be delayed if RIV3 or ccIIV3 are not available. Instead, any licensed, age-appropriate IIV should be used
BSACI (UK)[10]	- Children with egg allergy can safely be vaccinated with Fluenz Tetra in any settings - Children who have previously required admission to an intensive care unit for severe anaphylaxis to egg should be referred to a specialist for immunization in hospital. - Fluenz Tetra should not be administered to a child with current or recent acute wheezing in the 72 hours preceding vaccination, or who have required oral steroids in the previous 2 weeks - Facilities and staff trained to recognize and treat anaphylaxis should be available.

World Allergy Organization[11]	- Egg allergy does not appear to impart an increased risk of an anaphylactic reaction to immunization with either inactivated or live attenuated influenza vaccines - Immediate hypersensitivity reactions such as urticaria are no more common in egg-allergic than non-egg allergic vaccine recipients - Any age approved influenza vaccine can be used in any patient irrespective of egg allergy status and that special precautions are not required

Table 2 – Summary of overseas authorities' recommendations on administrating influenza vaccines to egg-allergic individuals.

Strength of recommendation

Strength	Implications
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB	Laboratory Based
NR	Not Rated

MMR/MMR-V Vaccines

MMR-V vaccines are safe and effective at preventing mumps, measles, rubella and varicella. The local vaccination schedule recommends the first dose to be administered at 1 year old and second dose is administered at Primary 1.[12] Table 3 summarizes two MMR-V vaccines available in Hong Kong, including their product information recommendations to egg-allergic patients and the respective quantity of ovalbumin in the vaccines. Table 4 summarizes overseas authorities' recommendations on administering MMR/MMRV vaccines to egg-allergic individuals.

Brands	Product Information Recommendations	Quantity of ovalbumin
Priorix-Tetra (GSK)	Individuals who have experienced anaphylaxis after egg ingestion should be vaccinated with extreme caution, with adequate treatment for anaphylaxis on hand should such a reaction occur.	May contain traces of egg proteins. Amount not measured in final product.*
ProQuad	Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions subsequent to egg ingestion may be at an enhanced risk of immediate - type hypersensitivity reactions. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination in such cases.	Internal analysis done for ProQuad for its egg protein content but manufacturer refused to disclose the information as it is considered proprietary.*

Table 3 – Summary of MMR-V vaccines available in Hong Kong.

**Information obtained through direct communication with manufacturer*

Authorities (Country)	Recommendations
ASCIA (Australia)[5]	- MMR vaccine is cultured on chicken fibroblast cell cultures, which contains no residual egg allergen and has been safely administered to large numbers of egg-allergic individuals. - Rare allergic reactions have been attributed to non-egg ingredients such as gelatin. - MMR-V vaccine is considered not to contain food-derived protein allergens and can be given to any patient with food allergy, even those with food-induced anaphylaxis

CDC (USA)[13]	- The vaccine ingredients extremely rarely cause anaphylactic reactions. Children should not get MMRV vaccine if they have ever had a life-threatening allergic reaction to any component of the vaccine, including gelatin or the antibiotic neomycin. - No specific recommendations mentioned for egg-allergic individuals
AAP (USA)[14]	- Measles vaccine is produced in chicken embryo cell culture and does not contain significant amounts of egg white (ovalbumin) cross-reacting proteins. - Children with egg allergy are a low risk of anaphylactic reactions to measles-containing vaccines (including MMR and MMRV) - Skin testing of children for egg allergy is not predictive of reaction to MMR vaccine and is not recommended before administering MMR or other measles-containing vaccines
BSACI (UK)[15]	- Administration of the MMR vaccine to egg-allergic children has an excellent safety record and may be administered to all egg-allergic children as a routine procedure in primary care. - The MMR vaccine is grown on cultured-embryo-chick fibroblasts and is therefore generally free of hen's egg protein. - When traces of hen's egg protein are found, the protein is highly processed and the concentrations are too low to represent a risk
World Allergy Organization[11]	- The manufacture of vaccines containing live virus produced in chick embryo cultures (measles and mumps) and human diploid cell culture (rubella) has resulted in a vaccine that contains no, or at most picogram quantities of egg protein, insufficient to cause an allergic reaction

Table 4 – Summary of overseas authorities' recommendations on administrating MMR/MMR-V vaccines to egg-allergic individuals.

Our recommendations

1. Influenza and MMR/MMR-V vaccines can be safely administered, and are recommended, to egg-allergic individuals for disease prevention. They are recommended to be administered in out-patient/ambulatory settings.
2. Should there be any significant concerns from patients, parents or healthcare professionals, healthcare professionals who are capable of recognizing signs and symptoms of allergic reactions can provide 15 – 30 minutes of monitoring after vaccination
3. Children who have previously required admission to an intensive care unit for severe anaphylaxis to egg should be referred to a specialist for immunization in hospital.
4. Individuals who developed or are suspected to have developed allergic reactions to the vaccine or other vaccine components (such as gelatin or neomycin), should not undergo further vaccination to these products. Referral to an allergy specialist for further evaluation can be considered.

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Summary on dinner symposium: early nutrition as a major determinant of gut microbes, immune health and allergy prevention

Date: **16 June 2017**
Venue: **Zhejiang Heen, Hong Kong**

On 16 June 2017, a dinner symposium titled “Early Nutrition as a Major Determinant of Gut Microbes, Immune Health and Allergy Prevention” lectured by Professor Susan Prescott (Australia) and Dr. Alson Chan (Hong Kong) took place at Zhejiang Heen in Wanchai. It was well attended by over 100 healthcare professionals.

The symposium discussed the role of the gut microbiome in immune health, and how maternal and early-life nutrition (particularly in the first 1,000 days of early life) can positively influence long-term health outcomes. The contents of the new HKIA allergy prevention guidelines were highlighted.

Hong Kong Institute of Allergy - Annual Scientific Meeting 2017

Date: 26 November 2017 (Sunday)
Venue: Hong Kong Convention and Exhibition Centre, Hong Kong

Registration and Program:
www.icc-hk.com/HKIAASM2017/index.asp

The Joint Congress of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology & the Asia Pacific Association of Pediatric Allergy, Respirology and Immunology (APAAACI & APAPARI) 2018

Date: 11 – 14 October 2018
Venue: Centara Grand Hotel & Convention Center, Bangkok, Thailand

Registration and Program:
www.apaaaci2018.com/

Overseas Meetings

Asia Pacific Association of Pediatric Allergy, Respirology and Immunology (APAPARI) 2017 Congress

3 – 5 November 2017 / Beijing, China (www.apapari2017.org/)

Congress of Asian Pacific Society of Respirology (APSR) 2017

23 – 26 November 2017 / Sydney, Australia (www.apsr2017.com/)

American Thoracic Society (ATS) International Conference 2018

18 – 23 May 2018 / San Diego, USA (http://conference.thoracic.org/about/index.php)

European Academy of Allergy and Clinical Immunology (EAACI) Congress 2018

26 – 30 May 2018 / Munich, Germany (www.eaaci.org/eaaci-congresses/eaaci-2018)

European Respiratory Society (ERS) International Congress 2018

15 – 19 September 2018 / Paris, France (https://erscongress.org/)

CHEST 2018 (The American College of Chest Physicians Annual Meeting 2018)

6 – 10 October 2018 / San Antonio, USA (www.chestnet.org/Education/CHEST-Meetings/CHEST-Meetings/)

American College of Allergy Asthma and Immunology (ACAAI) Annual Scientific Meeting 2018

15 – 19 November 2018 / Seattle, USA (http://annualmeeting.acaai.org/2018/proposal_intro.cfm)

Local Meeting

Autumn Respiratory Seminar of Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau

19 November 2017 (www.hkresp.com)

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