Disproportionate drug allergy labelling among middle-aged patients and barriers to excipient allergy testing from the Hong Kong Comprehensive Excipient and Drug Allergy Registry (CEDAR)

Chiang Valerie[1], Andy Ka Chun Kan[2], Saha Chinmoy[2], Elaine Au Y L[1], and Philip Li[2]

[1]Queen Mary's Hospital Department of Pathology and Department of Microbiology
[2]The University of Hong Kong Li Ka Shing Faculty of Medicine

April 18, 2023

Abstract

Background: Longitudinal whole-population studies can explore new dimensions in drug allergy research. Excipient allergy testing remains a barrier to allergy evaluation in countries without legislations mandating ingredient disclosure in registered drugs. The Comprehensive Excipient and Drug Allergy Registry (CEDAR) was established to investigate Hong Kong's drug allergy landscape and potential role of excipient registries. Methods: Drug allergy data from over 7,337,778 individuals between 2016-2021 was analyzed. Excipient lists were gathered from all formulations of the top 50 reported drug allergies and checked for the presence of polyethylene glycol (PEG). Results: The absolute-prevalence and -incidence of reported drug allergy was 5.61% and 277/100,000 population in 2021, respectively. Annual incidence of newly reported drug allergy was stable between 2016-2019, until a significant drop in 2020 (-16.3%, p=0.037). The most common implicated drugs were anti-infectives (245,832 [44.5%]), NSAIDs (106,843 [19.3%]), and nervous system drugs (45,802 [8.3%]). There was significant higher incidence among individuals aged >40, contributing to the majority of newly reported allergies (377,004, 68.2%). Beta-lactams and nervous system drugs were the most common reported culprits of anaphylaxis and Stevens-Johnson syndrome. CEDAR was unable to confirm presence or absence of PEG in any of the top reported culprits due to insufficient excipient information. Conclusion: We report the detailed drug allergy landscape of the Hong Kong population. Excipient registries are ineffective in countries without mandatory excipient listings . Contrary to traditional doagma, we identified a disproportionately higher incident drug allergy among middle-aged and older patients. Findings need to be confirmed by region-specific big data studies.

Title:

Disproportionate drug allergy labelling among middle-aged patients and barriers to excipient allergy testing from the Hong Kong Comprehensive Excipient and Drug Allergy Registry (CEDAR)

Short running title:

Hong Kong Comprehensive Excipient and Drug Allergy Registry (CEDAR)

Authors:

Valerie Chiang[1], Andy K C Kan[2], Chinmoy Saha[2], Elaine Y L Au[1], Philip H Li[2]

[1] Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital, Hong Kong

[2] Division of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

Corresponding Author:

Dr Philip H Li, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong (liphilip@hku.hk, Tel: +852 2255-5995).

Acknowledgments:

Dr Joyce Ka Yin Chan, and her team from the Information Technology and Health Informatics Division, Hospital Authority Head Office, assisted with data extraction and analysis.

Funding:

This work was supported by the Health and Medical Research Fund (Food and Health Bureau) - COVID1903011.

Author contributions:

VC, AK, CS, EA, and PL researched the data. VC, AK, and PL analyzed and interpreted the data. VC and AK performed statistical analyses. VC drafted the manuscript. PL supervised the project, critically reviewed and edited the manuscript. All authors reviewed and contributed to the final version of the manuscript.

Word count: 250 (abstract), **2837** (main text)

Conflict of Interest:

The authors have no conflicts of interest in relation to this work.

Abstract

Background

Longitudinal whole-population studies can explore new dimensions in drug allergy research. Excipient allergy testing remains a barrier to allergy evaluation in countries without legislations mandating ingredient disclosure in registered drugs. The Comprehensive Excipient and Drug Allergy Registry (CEDAR) was established to investigate Hong Kong's drug allergy landscape and potential role of excipient registries.

Methods

Drug allergy data from over 7,337,778 individuals between 2016-2021 was analyzed. Excipient lists were gathered from all formulations of the top 50 reported drug allergies and checked for the presence of polyethylene glycol (PEG).

Results

The absolute-prevalence and -incidence of reported drug allergy was 5.61% and 277/100,000 population in 2021, respectively. Annual incidence of newly reported drug allergy was stable between 2016-2019, until a significant drop in 2020 (-16.3%, p=0.037). The most common implicated drugs were anti-infectives (245,832 [44.5%]), NSAIDs (106,843 [19.3%]), and nervous system drugs (45,802 [8.3%]). There was significant higher incidence among individuals aged >40, contributing to the majority of newly reported allergies (377,004, 68.2%). Beta-lactams and nervous system drugs were the most common reported culprits of anaphylaxis and Stevens-Johnson syndrome. CEDAR was unable to confirm presence or absence of PEG in any of the top reported culprits due to insufficient excipient information.

Conclusion

We report the detailed drug allergy landscape of the Hong Kong population. Excipient registries are ineffective in countries without mandatory excipient listings . Contrary to traditional doagma, we identified a disproportionately higher incident drug allergy among middle-aged and older patients. Findings need to be confirmed by region-specific big data studies.

Keywords: Age Distribution; Big Data; Drug Allergy; Epidemiology; Excipients

Background

Population-based studies have demonstrated the potential of use of 'big data' in clinical and drug allergy research.[1-4] The availability of longitudinal datasets can explore new dimensions of drug allergy research which would not have been possible with only traditional single-centre or cross-sectional studies. For example, we previously reported one of the largest drug allergy epidemiological studies by taking advantage of Hong Kong's unified electronic healthcare record system with data from more than 95% (7.1 million) of the population.[1] Based on population-wide data, we were able to accurately report the near-absolute prevalence and annual incidence of reported drug and beta-lactam allergies. However, at the time, we were only able to provide a condensed one-year snapshot on the landscape of drug/beta-lactam allergy and did not further analyse the granularity of individual patient data; such as specific-drug allergy culprits, individual patients' age of reported drug allergy or duration of reported drug allergy. More detailed analyses are also important to identify country- or population-specific characteristics, which may vastly differ from Western cohorts, to further inform future drug allergy interventions and research.[5,6]

Another important limitation to drug allergy evaluation and research is the ability to accurately identify specific culprit allergens. For example, it is well established that up to 90% of all reported penicillin 'allergy' are incorrect after allergy evaluation, likely due to initial misdiagnoses or loss of sensitisation over time.[7-10]Alternatively, mislabelled drug allergy can also be due to the possibility of missing hidden allergens found within drugs or vaccines such as in the case of excipient allergies.[11,12]Although an uncommon cause of drug allergy, excipient allergy can almost never be excluded in countries lacking in pharmaceutical legislations to mandate complete ingredient disclosure in registered medications. This can and has led to cases of missed- and mis-diagnoses with potentially lethal consequences.[13-15] The devastating impact of such failures in pharmaceutical legislations have been exemplified during global COVID-19 vaccination campaigns. Despite genuine vaccine or excipient allergy being exceedingly rare, the indirect consequences from the fear of potential excipient allergy and inability to identify potential excipients among culprit drug formulations greatly impeded vaccine uptake and fuelled vaccine hesistancy.[16-18]

To overcome these issues, the Comprehensive Excipient and Drug Allergy Registry (CEDAR) was established in Hong Kong – allowing the use of big data to investigate reported drug allergies in detail, and to help establish an excipient registry to facilitate comprehensive drug allergy evaluations. Utilising CEDAR, we investigated the 5-year trend of detailed drug allergy epidemiology and the potential role of an excipient registry to aid drug allergy evaluation. In particular, we selected polyethylene glycol (PEG), one of the most widely implicated excipients since the launch of mRNA COVID-19 vaccines, as an example for the potential use of excipient registries.

Methods

Collection of anonymised patient data

Anonymised patient data from the Hospital Authority was collected by the Information Technology and Health Informatics Division, Hospital Authority Head Office. Informed consent was waived (because all data were anonymous and collected retrospectively) and data extraction was approved by the institutional review board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster. Hong Kong is a unique entity where the Hospital Authority is the sole publicly funded healthcare system for the entire territory. It possesses facilities in seven regions (Hong Kong East, Hong Kong West, Kowloon Central, Kowloon East, Kowloon West, New Territories East, and New Territories West), comprising 43 hospitals, 49 specialist outpatient clinics, and 73 general outpatient clinics; it provides approximately 90% of all in-patient services.[19] All clinical services utilise a unified 'Electronic Patient Records' system, providing medical records for over 7.3 million individuals. This system allows complete and uniform drug allergy data to be gathered and analysed. A snapshot of cross-sectional data from all available patient records was retrieved as of 23rd July, 2021. Physician-reported drug allergy, age at the time of reported drug allergy and names of reported culprits were collected. Incidence of newly reported drug allergy, as well as all cases of anaphylaxis and Stevens-Johnson syndrome from 1st January, 2016 to 31st December, 2020 were reviewed. Drugs were categorised according to the British National Formulary Drug Classes, except for non-steroidal anti-inflammatory drugs (NSAIDs), which were separated into its own category.[20] Drugs which

were entered as 'free text' into the electronic system were checked and converted back to structured drug items when possible. Those 'free text' reported drug allergy which could not converted or were incomplete were excluded from analysis. Drugs which did not fit into any drug classes were categorised as 'Others' and listed in Supplementary Text 1.

Construction of excipient allergy registry – using PEG as an example

An excipient registry was constructed based on the top 50 reported drug allergy culprits as retrieved from CEDAR. In view of the recent relevance for mRNA vaccines, PEG was selected as the pilot registry. An excipient registry was created by compiling the excipient lists pertaining to all available formulations of each of the drugs of the top 50 most implicated drug allergies. All excipient lists from drug product inserts, and if unavailable, through contacting individual pharmaceutical companies - as there is no pharmaceutical legislation to mandate listing of excipients of registered drugs in Hong Kong. Depending on the status of PEG, formulations were then categorised as either 'contains PEG', 'does not contain PEG', or 'unknown'.

Statistical Analysis

All statistics were analysed using IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA). Prevalence of drug allergy was calculated. Values were presented as numbers (percentages) as appropriate. Age distributions of drug allergy patients and individuals without drug allergy were compared using the binomial test. Trends of incidence of reported drug allergy were analysed using Spearman's correlation. Two-sided p-values <0.05 were considered statistically significant.

Results

From over 7.3 million individuals, the absolute-prevalence of reported drug allergy in Hong Kong was 5.61%

Anonymised data was collected from the electronic health records of 7,337,778 unique individuals. Among them, 411,885 had at least one physician-reported drug allergy in 2021. The near-absolute prevalence of physician-reported drug allergy in Hong Kong was therefore 5.61%. A total of 552,897 drug allergy labels were shared amongst the 441,885 unique individuals; 346,969 (62.8%) of the reported drug allergy were found among female individuals. Among individuals with reported drug allergy, 28,467 (6.91%) had more than 2 concomitant reported drug allergies.

Stable incidence of newly reported drug allergy between 2016-2019 with a significant drop in 2020

In 2016, 25,810 new physician-reported drug allergy labels were created with an incidence of 352 per 100,000 population. The annual incidence remained relatively stable from 2016 to 2017 (352 per 100,000), 2018 (337 per 100,000) and 2019 (331 per 100,000) (p=0.200). There was no significant change in incidence rate until a significant decrease in 2020 to 277 per 100,000 (p=0.037). The annual incidence and relative differences of physician-reported drug allergy are shown in Figure 1.

Most common reported drug allergies were to beta-lactams, making up 26.0% of all labels

Out of the 552,897 reported drug allergy labels, the most common implicated drugs were anti-infectives (245,832 [44.5%]) and NSAIDs (106,843 [19.3%]), followed by nervous system drugs (45,802 [8.3%]) and cardiovascular system drugs (27,977 [5.1%]) (Figure 2). Among the 245,832 reported anti-infective allergy labels, 143,925 (58.5%) were towards beta-lactams (Table 1). Among beta-lactams, penicillins accounted for the vast majority (119,274 [82.9%]) of reported culprits. Amoxicillin-clavulanate was the most commonly reported (30,396 [21.1%]), followed by phenoxymethylpenicillin (penicillin V) (25,678 [17.8%]), amoxicillin (21,806 [15.2%]), ampicillin (16,335 [11.3%]), and cloxacillin (9,689 [6.7%]).

Most reported drug allergy among individuals aged 50-59 years, with disproportionately higher incidence of newly reported drug allergy above 40

The age distribution of reported drug allergy in comparison to non-allergic individuals (i.e. those without any reported drug allergy), is shown in Figure 3. Most drug allergies were reported among individuals in the 50-59 year age group (106,249, 19.2%); and more than half of all drug allergies (377,004, 68.2%) were reported

among individuals at or above the age of 40. There were disproportionately fewer individuals with reported drug allergy below 40, compared to the age distribution of non-allergic individuals (4.3% vs 14.7%, p<0.001 for 0-9 years; 4.1% vs 9.3%, p<0.001 for 10-19 years; 9.2% vs 13.5%, p<0.001 for 20-29 years; 14.2% vs 15.3%, p<0.001 for 30-39 years). On the contrary, there were disproportionately more reported drug allergies among individuals ages above 40 compared to non-allergic individuals (16.7% vs 15.5%, p<0.001 for 40-49 years; 19.2% vs 13.9%, p<0.001 for 50-59 years; 15.0% vs 8.6%, p<0.001 for 60-69 years; 10.9% vs 6.0%, p<0.001 for 70-79 years; 5.4% vs 2.7%, p<0.001 for 80-89 years; 1.0% vs 0.5%, p<0.001 for 90 years or above).

Beta-lactams and nervous system drugs were the most common reported culprits of drug-induced anaphylaxis and Stevens-Johnson syndrome

Between 2016 and 2020, there were a total of 1,325 reported cases of drug-induced anaphylaxis (0.32% of drug allergy) and 1,706 cases (0.41% of drug allergy) of Stevens-Johnson syndrome in Hong Kong. Breakdown of reported drug culprits are shown in Table 2 and Table 3, respectively. Anti-infectives (544 [41.1%]) were the most common culprits of drug-induced anaphylaxis (in particular, beta-lactams: 402 [30.3%]), followed by musculoskeletal system drugs (158 [11.9%]) and nervous system drugs (157 [11.8%]). Anti-infectives (735 [43.1%]) were also the most common culprits of Stevens-Johnson syndrome (in particular, beta-lactams 348 [20.4%]), followed by nervous system drugs (390 [22.9%]) and musculoskeletal system drugs (348 [20.4%]).

Unable to confirm presence or absence of PEG in any of the top 50 reported culprits of drug allergy

The top 50 reported drug allergy culprits are listed in Supplementary Text 2, which accounted for 72.5% (400,700/552,897) of all reported drug allergy (Figure 4). In total, there were 2,070 unique drug formulations of these 50 drugs available in Hong Kong. All 2,070 formulations were examined (either by extracting from product inserts or contacting individual pharmaceutical companies) for presence or absence of PEG. Complete excipient information was only available for 36.1% (748/2,070) formulations. Out of these, 124 (16.6%) were confirmed to contain PEG while the remaining 83.4% were confirmed to not contain PEG. Of the remaining 1,322 (63.9%) formulations, excipient information was not available and we were unable to confirm presence or absence of PEG despite attempts at contacting pharmaceutical companies. After re-mapping all 748 formulations with available excipient information back into the original 50 drugs, we were unable to confirm the presence or absence of PEG in any single one of these drugs registered in Hong Kong (i.e. there were formulations with unknown excipient information for each of the top 50 allergy culprits).

Discussion

Using our population-wide data, CEDAR was able to generate a registry of comprising of more than 7,337,778 individuals. To our knowledge, this is the largest population-wide drug epidemiology study to date; allowing detailed characterisation of the absolute-prevalence and -incidence, individual drug culprits, as well as the age of incident drug allergies of our entire population.

Our study is also the first to investigate the longitudinal incidence of drug allergy labelling on a population-wide basis. CEDAR revealed that the annual incidence of reported drug allergy Hong Kong remained relatively stable over the 5-year study period (331-352 per 100,000 population), until a significant 16.3% drop in 2020. This was likely due to the COVID-19 pandemic resulting in a population-wide reduction in medical visits, drug prescriptions, or allergy reporting.[21] It would be interesting to see if the incidence of drug allergy will rebound back to pre-COVID figures following relaxation of social distancing restrictions. Our study also confirmed that about 1 in 18 (5.61%) of Hong Kong's population have physician-reported drug allergies, which differs quite substantially with other regions (especially in Western cohorts), as well as our own previous hospital-based studies.[8,22-26] Although drug allergy prevalence varies across time and region (likely due to combination of differing prescribing practices and biological differences) we postulate discrepancies may also arise due to previous type I errors from inadequate sampling, which would be minimised from this population-wide study. This needs to be confirmed by collaborative inter-regional and -ethnic big data studies in the future.

Interestingly, our unified physician-reported drug allergy system revealed that most drug allergies were

reported among middle-aged individuals, with disproportionately higher incidence among those above 40. This is contrary to the traditional dogma reflected from the previous experience from Western cohorts, suggesting the majority of individuals acquire drug allergy labels during childhood and carry them into adulthood.[27] We postulate this stark difference may be due to either genuine inter-population differences, or a paradigm shift that has remained unnoticed due to the paucity of prior systematic or large population-based drug allergy studies. This emphasises the importance of region-specific big data studies, which can discover unique features and trends of drug allergy labelling among different populations. Furthermore, identifying target subpopulations would inform the best strategy for allergy education and proactive delabelling at a population level. For example, there are significantly fewer adult allergists than paediatric allergists in Hong Kong (1:2,800,000 vs 1:540,000 per population), which is disproportionate to the incidence and burden of drug allergy in our locality.[28] Hence, we advocate for more active drug allergy delabelling initiatives among adults, further resources and positions for training of adult allergists, as well as strengthening the ability of frontline healthcare professionals to discern symptoms of genuine allergy – especially among adult patients.

This study also confirms the severity of a penicillin-dominated drug allergy landscape in Hong Kong. Within anti-infectives, beta-lactams constituted the majority of all reported drug allergy, with penicillins contributing to almost 82.9% of all beta-lactam labels. Penicillins were among the most commonly reported culprits of drug-induced anaphylaxis and Steven-Johnson syndrome. However, our previous studies revealed that only 10-13.8% of reported penicillin allergy are found to be correct after evaluation.[1,10] Incorrect labels lead to unnecessary penicillin avoidance, posing immense challenges in antimicrobial stewardship. This is especially relevant in Hong Kong, where there has been an upsurge of various multi-drug resistant organisms.[29,30] Penicilin allergy labels have also shown to affect geriatric and immunocompromised patients, associated with a multitude of adverse clinical outcomes, including increased healthcare costs, more frequent and longer hospital stays, and even death.[22,31-33] Despite the severe lack of allergists in the Asia-Pacific region, previous multi-disciplinary initiatives have shown much promise in tackling drug allergies.[10,34,35]For example, a nurse-led penicillin allergy delabelling initiative demonstrated superior outcomes compared to traditional allergist evaluation in Hong Kong and similar strategies employing trained pharmacists are underway.[10] Further research on wider applications of similar multidisciplinary drug allergy initiatives is warranted.

Given the direct and indirect consequences of genuine or perceived excipient allergy – from rare cases of excipient-associated anaphylaxis to inappropriate fear of excipient allergy leading to vaccine hesitancy – the ability to accurately disprove excipient allergy is of paramount importance.[13-17] However, diagnosis of excipient allergy is near impossible when excipient information is not available. This is a common problem for many regions where no pharmaceutical legislations exist to mandate excipient disclosure in registered medications. Despite our best efforts to construct a excipient registry, we were unable to obtain excipient information from the vast majority of drug formulations. Using PEG as an example, we were able to confirm its presence or absence among only 724 of 2,070 formulations investigated, only representing a mere 36% included in the registry. This made it impossible to exclude or confirm presence of PEG in all formulations of any of the top 50 reported drug allergy culprits in Hong Kong. Lack of transparent drug information impedes in comprehensive evaluations in drug allergy, and undermines the safety and public confidence of population-wide vaccination programmes. Despite past efforts to advocate for regulartory improvements, ingredient disclosure remains to be a persistent issue in our locality and legislative changes have yet to materialise.[16,17]

Given its observational nature, this study has several limitations. First, only limited patient data was available, and more detailed clinical data such as comorbidities, medication use or hospitalisation records were not available for further subgroup analysis. Second, we did not include reported drug allergies which were entered as 'free text' into the patient's electronic health record that could not be manually converted into structured item (often due to incomplete information). Third, drug allergy labels in Hong Kong were physician-reported, and albeit more preferred than patient-reported adverse reactions, may still be inaccurate and do not reflect only genuine and confirmed drug allergy. This highlights the importance of dedicated and interventional studies in the future.

In conclusion, population-specific drug allergy research is needed to inform the directions of appropriate public health initiatives in an evidence-based manner. The use of big data can unlock new dimensions of drug allergy research - such as drug allergy incidence and comparative age distribution of reported drug allergies. Using our population-based data, we were able to report the longitudinal incidence of reported drug allergy, specific allergy culprits as well as identifying disproportionate drug allergy labelling among middle-aged patients. Future inter-regional and -ethnic big data studies will be required to confirm external validity of our findings to other populations. Lastly, excipient registries remain ineffective and proper allergy evaluation cannot be conducted in countries where excipient information are unavailable. International and collaborative efforts should be united to advocate for universal recommendations toward ingredient disclosure for all registered medications.

References

1. Li PH, Yeung HHF, Lau CS, Au EYL. Prevalence, Incidence, and Sensitization Profile of β-lactam Antibiotic Allergy in Hong Kong.*JAMA Netw Open.* 2020;3(5):e204199.

2. Zhou L, Dhopeshwarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system.*Allergy.* 2016;71(9):1305-1313.

3. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet.* 2019;393(10167):183-198.

4. Mayer-Schönberger V, Ingelsson E. Big Data and medicine: a big deal?*J Intern Med.* 2018;283(5):418-429.

5. Thong BY, Lucas M, Kang HR, et al. Drug hypersensitivity reactions in Asia: regional issues and challenges. *Asia Pac Allergy.*2020;10(1):e8.

6. Mak HWF, Yeung MHY, Wong JCY, Chiang V, Li PH. Differences in beta-lactam and penicillin allergy: Beyond the West and focusing on Asia-Pacific. *Front Allergy.* 2022;3:1059321.

7. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. *JAMA.* 2019;321(2):188-199.

8. Li PH, Siew LQC, Thomas I, et al. Beta-lactam allergy in Chinese patients and factors predicting genuine allergy. *World Allergy Organ J.* 2019;12(8):100048.

9. Siew LQC, Li PH, Watts TJ, et al. Identifying Low-Risk Beta-Lactam Allergy Patients in a UK Tertiary Centre. *J Allergy Clin Immunol Pract.* 2019;7(7):2173-2181.e2171.

10. Kan AKC, Hui HKS, Li TS, et al. Comparative Effectiveness, Safety, and Real-World Outcomes of a Nurse-Led, Protocol-Driven Penicillin Allergy Evaluation From the Hong Kong Drug Allergy Delabelling Initiative (HK-DADI). *J Allergy Clin Immunol Pract.*2023;11(2):474-480 e472.

11. Venturini Díaz M, Vidal Oribe I, D'Elia Torrence D, Hernández Alfonso P, Alarcón Gallardo E. New Challenges in Drug Allergy: the Resurgence of Excipients. *Curr Treat Options Allergy.*2022;9(3):273-291.

12. Li PH, Wagner A, Thomas I, Watts TJ, Rutkowski R, Rutkowski K. Steroid Allergy: Clinical Features and the Importance of Excipient Testing in a Diagnostic Algorithm. *J Allergy Clin Immunol Pract.*2018;6(5):1655-1661.

13. Li PH, Yeung HHF, Lau CS, Au EYL. Excipient allergy and importance of complete allergy histories. *J Allergy Clin Immunol Pract.*2020;8(6):2122-2123.

14. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone CA, Jr. Hidden Dangers: Recognizing Excipients as Potential Causes of Drug and Vaccine Hypersensitivity Reactions. *J Allergy Clin Immunol Pract.*2021;9(8):2968-2982.

15. Caballero ML, Quirce S. Immediate Hypersensitivity Reactions Caused by Drug Excipients: A Literature Review. *J Investig Allergol Clin Immunol.* 2020;30(2):86-100.

16. Chiang V, Leung ASY, Au EYL, et al. Consensus Statements on the Approach to COVID-19 Vaccine Allergy Safety in Hong Kong. *Front Allergy.* 2021;2.

17. Chiang V, Leung ASY, Au EYL, et al. Updated consensus statements on COVID-19 Vaccine Allergy Safety in Hong Kong. *Asia Pac Allergy.*2022;12(1):e8.

18. Kan AKC, Wong TTH, Chiang V, Lau CS, Li PH. Chronic Spontaneous Urticaria in Hong Kong: Clinical Characteristics, Real-World Practice and Implications for COVID-19 Vaccination. *Allergy Asthma Immunol Res.* 2023;15(1):32-42.

19. Hospital Authority. Hospital Authority Annual Report. [Internet]. 2018; about 215 p. Available at: https://www.ha.org.hk/haho/ho/cc/HA_Annual_Report_2020-21_en.pdf. Accessed Jun 13, 2022.

20. British Medical Association, Royal Pharmaceutical Society. *BNF 83.* London, United Kindgom: BMJ Group and the Royal Pharmaceutical Society of Great Britain; 2022.

21. Xin H, Wu P, Wong JY, et al. Hospitalizations and mortality during the first year of the COVID-19 pandemic in Hong Kong, China: An observational study. *Lancet Reg Health West Pac.* 2023;30:100645.

22. Li PH, Chung HY, Lau CS. Epidemiology and outcomes of geriatric and non-geriatric patients with drug allergy labels in Hong Kong. *Hong Kong Med J.* 2021;27(3):192-197.

23. Yuson C, Shakib S, Smith W. Prevalence of drug allergy in South Australia. *Intern Med J.* 2022;52(11):1957-1961.

24. Kvedariene V, Sitkauskiene B, Tamasauskiene L, et al. Prevalence of self-reported drug hypersensitivity reactions among Lithuanian children and adults. *Allergol Immunopathol (Madr).* 2019;47(1):32-37.

25. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy.*Br J Clin Pharmacol.* 2011;71(5):684-700.

26. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med.* 2009;122(8):778 e771-777.

27. Stone CA, Jr., Trubiano J, Coleman DT, Rukasin CRF, Phillips EJ. The challenge of de-labeling penicillin allergy. *Allergy.*2020;75(2):273-288.

28. Lee TH, Leung TF, Wong G, et al. The unmet provision of allergy services in Hong Kong impairs capability for allergy prevention-implications for the Asia Pacific region. *Asian Pac J Allergy Immunol.* 2019;37(1):1-8.

29. Cheng VC, Wong SC, Ho PL, Yuen KY. Strategic measures for the control of surging antimicrobial resistance in Hong Kong and mainland of China. *Emerg Microbes Infect.* 2015;4(2):e8.

30. Li PH, Cheng VC, Yip T, Yap DY, Lui SL, Lo WK. Epidemiology and Clinical Characteristics of Acinetobacter Peritoneal Dialysis-Related Peritonitis in Hong Kong-With a Perspective on Multi-Drug and Carbapenem Resistance. *Perit Dial Int.* 2017;37(2):177-182.

31. Chan SCW, Yeung WWY, Wong JCY, et al. Prevalence and Impact of Reported Drug Allergies among Rheumatology Patients. *Diagnostics (Basel).* 2020;10(11).

32. West RM, Smith CJ, Pavitt SH, et al. 'Warning: allergic to penicillin': association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antibiotic prescribing and health outcomes. *J Antimicrob Chemother.*2019;74(7):2075-2082.

33. Mattingly TJ, 2nd, Fulton A, Lumish RA, et al. The Cost of Self-Reported Penicillin Allergy: A Systematic Review. *J Allergy Clin Immunol Pract.* 2018;6(5):1649-1654.e1644.

34. Chiang V, Saha C, Yim J, et al. The Role of the Allergist in Coronavirus Disease 2019 Vaccine Allergy Safety: A Pilot Study on a "Hub-and-Spoke" Model for Population-Wide Allergy Service. *Ann Allergy Asthma*

Immunol. 2022;129(3):308-312.e301.

35. Chiang V, To KKW, Hung IFN, et al. COVID-19 Vaccine Allergy Safety Track (VAS-Track) pathway: real-world outcomes on vaccination rates and antibody protection. *Asian Pac J Allergy Immunol.* 2023.

Figure legends

Figure 1: Annual incidence of new drug allergy labels from 2016 to 2020

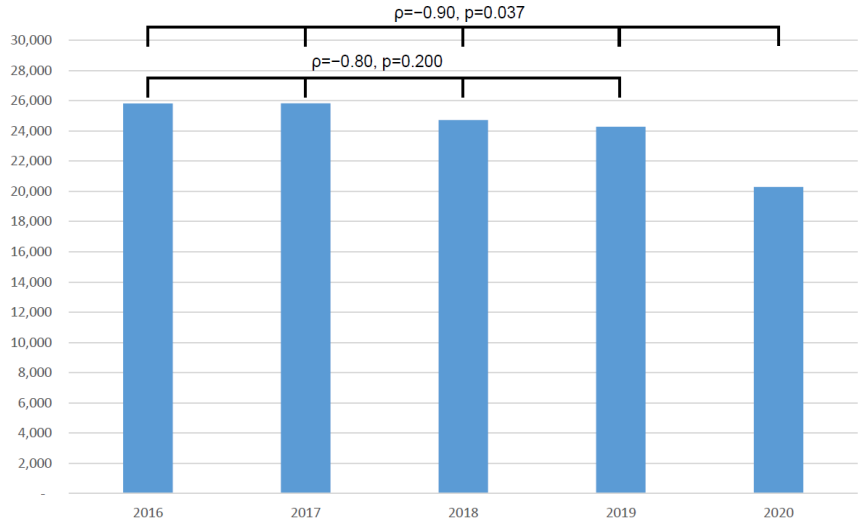
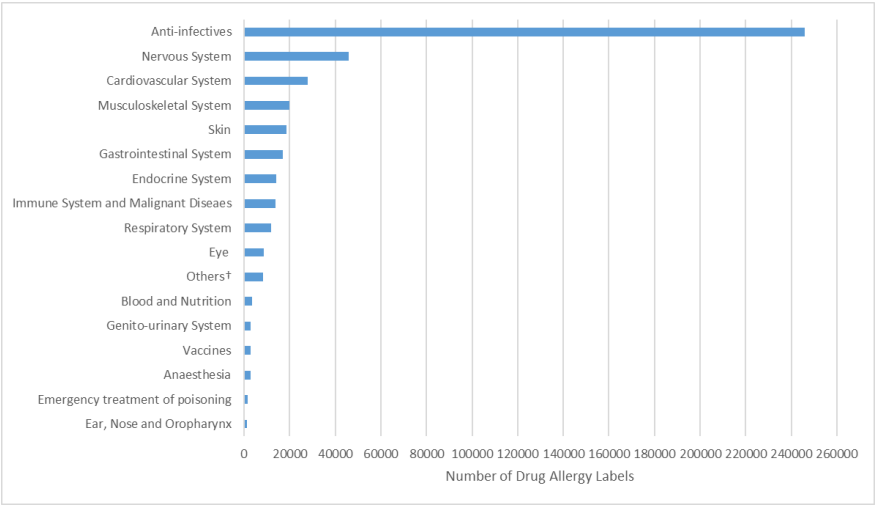
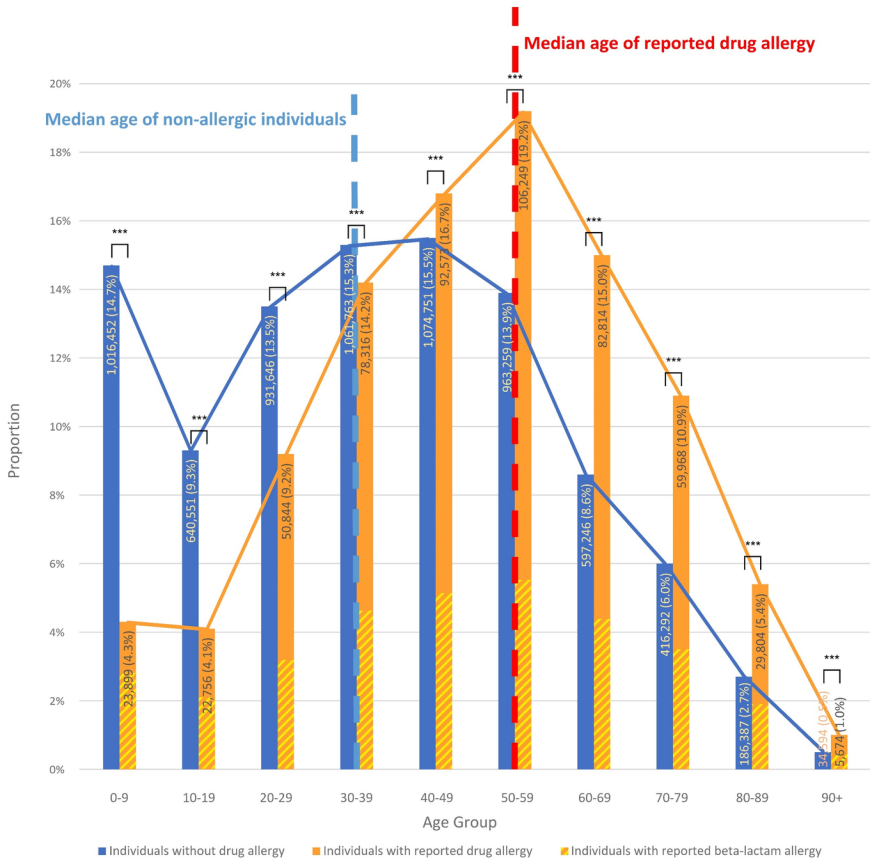


Figure 2: Distribution of all 552,897 drug allergy labels according to drug category



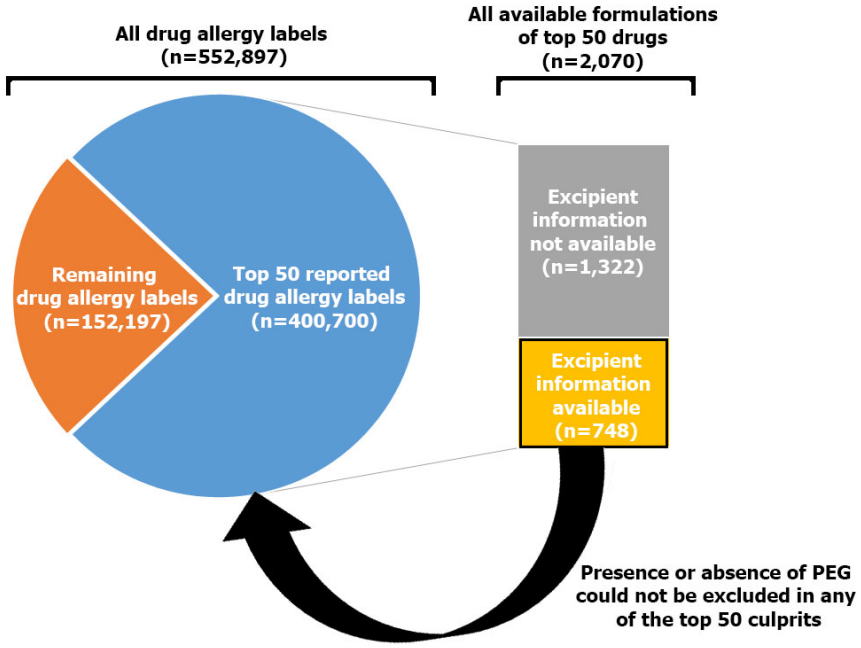
+Others: Please refer to Supplementary Text 1

Figure 3: Age distribution of individuals with reported drug allergy in comparison to non-allergic individuals



*p<0.05, **p<0.01, ***p<0.001.

Figure 4: Breakdown of the formulations and excipient information available of the top 50 reported drug allergies in Hong Kong



PEG, polyethylene glycol.

Table 1: Distribution of reported allergy toward anti-infectives

Total number of drug allergy labels	245,832
Drug class/name	
Beta-lactams, n (%)	143,925 (58.5)
Tetracyclines, n (%)	22,711 (9.24)
Anti-fungals, n (%)	17,797 (7.2)
Macrolides, n (%)	17,301 (7.0)
Quinolones, n (%)	16,844 (6.9)
Nitroimidazole, n (%)	5,975 (2.4)
Amphenicols, n (%)	4,670 (1.9)
Aminoglycosides, n (%)	3,803 (1.5)
Glycopeptides, n (%)	2,591 (1.1)
Other anti-infectives, n (%)	2,529 (1.0)
Anti-virals, n (%)	2,107 (0.9)
Anti-mycobacterial, n (%)	1,928 (0.8)
Lincosamides, n (%)	1,751 (0.7)
Anti-protozoals, n (%)	1,287 (0.5)
Sulphonamides, n (%)	531 (0.3)
Anti-helminths, n (%)	82 (0.0)

Table 2: Reported culprits of drug-induced anaphylaxis according to drug category

Total number of patients with reported drug-induced anaphylaxis	1325
Drug class/name	

Total number of patients with reported drug-induced anaphylaxis	1325
Anti-infectives, n (%)	544 (41.1)
Beta-lactams, n (%)	402 (30.3)
Quinolones, n (%)	30 (2.3)
Macrolides, n (%)	25 (1.9)
Aminoglycosides, n (%)	24 (1.8)
Glycopeptides, n (%)	19 (1.4)
Anti-protozoals, n (%)	13 (1.0)
Sulphonamides, n (%)	9 (0.7)
Tetracyclines, n (%)	9 (0.7)
Anti-fungals, n (%)	4 (0.3)
Lincosamides, n (%)	3 (0.2)
Anti-virals, n (%)	2 (0.2)
Anti-mycobacterials, n (%)	1 (0.1)
Other anti-infectives, n (%)	3 (0.2)
Musculoskeletal System, n (%)	158 (11.9)
Nervous System, n (%)	157 (11.8)
Anaesthesia, n (%)	155 (11.7)
Immune System and Malignant Diseases, n (%)	99 (7.5)
Gastrointestinal System, n (%)	46 (3.5)
Respiratory System, n (%)	28 (2.1)
Blood and Nutrition, n (%)	25 (1.9)
Skin, n (%)	19 (1.4)
Cardiovascular system, n (%)	19 (1.4)
Eye, n (%)	12 (0.9)
Endocrine System, n (%)	10 (0.8)
Ear, Nose and Throat, n (%)	6 (0.5)
Vaccines, n (%)	4 (0.3)
Genito-urinary system, n (%)	1 (0.1)
Emergency treatment of poisoning, n (%)	1 (0.1)
Unknown drug culprit, n (%)	40 (3.0)

Table 3: Reported culprits of Stevens-Johnson syndrome according to drug category

Total number of patients with reported Stevens-Johnson syndrome	**1706**
Drug class/name	
Anti-infectives, n (%)	735 (43.1)
Beta-lactams, n (%)	348 (20.4)
Sulphonamides, n (%)	81 (4.7)
Tetracyclines, n (%)	70 (4.1)
Quinolones, n (%)	64 (3.8)
Macrolides, n (%)	50 (2.9)
Anti-mycobacterials, n (%)	31 (1.8)
Anti-protozoals, n (%)	22 (1.3)
Aminoglycosides, n (%)	21 (1.2)
Anti-virals, n (%)	14 (0.8)
Glycopeptides, n (%)	12 (0.7)
Anti-fungals, n (%)	8 (0.5)

Total number of patients with reported Stevens-Johnson syndrome	**1706**
Lincosamides, n (%)	7 (0.4)
Other anti-infectives, n (%)	7 (0.4)
Nervous System, n (%)	390 (22.9)
Musculoskeletal System, n (%)	348 (20.4)
Cardiovascular system, n (%)	55 (3.2)
Gastrointestinal System, n (%)	39 (2.3)
Respiratory System, n (%)	33 (1.9)
Anaesthesia, n (%)	24 (1.4)
Immune System and Malignant Diseases, n (%)	16 (0.9)
Ear, Nose and Throat, n (%)	8 (0.5)
Eye, n (%)	7 (0.4)
Skin, n (%)	5 (0.3)
Blood and Nutrition, n (%)	5 (0.3)
Genito-urinary system, n (%)	4 (0.2)
Vaccines, n (%)	2 (0.1)
Endocrine System, n (%)	2 (0.1)
Unknown Aetiology, n (%)	33 (1.9)