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Prospective Assessment of Penicillin Allergy (PAPA): Evaluating the performance of penicillin allergy testing and post-delabelling outcomes among Hong Kong Chinese

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Abstract

Background: Incorrect penicillin 'allergy' labels predispose patients to adverse outcomes but are under-recognised in many Asian countries. Studies on performance and post-delabelling outcomes of penicillin allergy evaluation among Chinese remain scarce.

Objective: To evaluate the diagnostic performance of allergy testing and post-delabelling outcomes among Chinese patients in a prospective penicillin allergy cohort – Prospective Assessment of Penicillin Allergy (PAPA).

Methods: All adult patients (age ≥ 18 years) who underwent penicillin allergy evaluation between January 2020 to December 2021 were recruited and prospectively reviewed by both medical records and individual interviews at least 6 months after delabelling or allergy confirmation.

Results: Out of 372 patients who completed penicillin allergy evaluation, 335 (90%) patients were delabelled. The overall negative predictive value of penicillin skin testing was 95%, but lower for patients with non-immediate type reactions (88%). History of non-immediate symptom onset (OR = 4.501 [95%CI = 2.085-9.716], $p < 0.001$) and duration since index reaction (OR = 0.942 [95%CI = 0.899-0.987], $p = 0.012$) were associated with positive skin testing. After at least 6 months, 60 (18%) of de-labelled patients had received penicillins again without any adverse reactions. Fluoroquinolone-use was significantly lower among delabelled patients compared to those with penicillin allergy (38[11%] vs 11[30%], $p = 0.004$).

Conclusion: After at least 6 months, one in six delabelled patients already received penicillins again safely, with significantly lower fluoroquinolone usage. None experienced adverse reactions. History of non-immediate onset and shorter duration since index reaction were associated with genuine allergy. In patients with severe non-immediate reactions, skin tests should be supplemented with thorough clinical history and adjunct diagnostic evaluations.

Key words: Allergy, Penicillin, Delabelling, Outcome, Prospective Study

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Introduction

Penicillins are the most prescribed class of antibiotics and one of the most implicated culprits of drug allergies worldwide.[1,2] In Hong Kong, the prevalence of reported beta-lactam and penicillin allergy among the general population and hospitalised patients was 2% and 5%, respectively; with more than 8000 new physician-reported allergy labels generated each year.[2,3] However, most penicillin 'allergy' labels are found to be inaccurate after evaluation and predisposes patients to a myriad of adverse clinical outcomes – including increased hospitalisation, morbidity, mortality as well as the emergence of multi-drug resistant organisms (MDRO).[4-8]

Evaluation of suspected penicillin allergy includes a comprehensive history, skin tests (ST), and, when indicated, drug provocation tests (DPT) to confirm current tolerance. The choice of ST modalities depends on classification of the index reaction(s) – with skin prick tests (SPT) and intradermal tests (IDT) for patients with history of immediate reactions or delayed IDT and patch tests (PT) performed for patients with history non-immediate reactions.[9] Although the overall negative predictive value (NPV) of penicillin ST has been proven and well reported (overall reported to be 90% in Chinese, except for piperacillin-tazobactam with a much lower NPV of only 70%), fewer studies have detailed its differential performance among patients with different types of reactions and even more scarce among Chinese populations.[2,10] There have been conflicting reports on the positive predictive values (PPV) of ST as most physicians would not advocate DPT after a positive ST results. Even if performed, most reported cases with mild or borderline positive ST have underwent DPT with an estimated PPV of around 80%.[11] Furthermore, to the best of our knowledge, the NPV of DPT (including possible 'resensitisation' among patients with an IgE-mediated hypersensitivity) and post-evaluation outcomes following penicillin allergy delabelling has also never been studied among Chinese.

Following the successful inauguration of Hong Kong's first dedicated penicillin clinic, a prospective penicillin allergy cohort was established since 2020 – Prospective Assessment of Penicillin Allergy (PAPA). After delabelling, patients are prospectively reviewed and interviewed at least 6 months thereafter to evaluate the performance of allergy testing and post-delabelling outcomes among Chinese patients with incorrect penicillin 'allergy'.

In contrast to many studies of Western cohorts, this prospective study is the first to report on the predictors of penicillin allergy and longitudinal outcomes of patients after undergoing penicillin allergy review among Chinese. We also elucidate the respective differences in diagnostic performances of ST between immediate and non-immediate type reactions, as well as the NPV of DPT by longitudinal analysis of delabelled patients with penicillin re-exposure. The findings of our study will provide insights on the efficacy of our allergy testing and delabelling programme, and help identify focal points in our delabelling triage that best enhance patient care.

Methods

Patient recruitment

All adult patients with penicillin allergy label (i.e., suspected penicillin allergy) who underwent penicillin allergy evaluation between January 2020 to December 2021 were included in the study. Inclusion criteria included adult patients (age ≥ 18 years) referred for suspected penicillin allergy. Exclusion criteria included: Patients with history of type A adverse drug reaction, pregnancy, inability to stop antihistamines within 5 half-lives (of specific antihistamine) of allergy testing, concurrent use of immunosuppressive medications/immunocompromised state or any other illness that would substantially increase the risk to the patient (as judged by the consulting Allergist), refusal for allergy testing or inability to give informed consent. Patients with incomplete workup (i.e., none of the tests had been performed, or skin test and/or *in vitro* test negative but drug provocation test not performed) were excluded. Penicillin ST and DPT protocols were performed according to the British Society for Allergy and Clinical Immunology and European Academy of Allergy and Clinical Immunology recommendations.[9,12] After completion of penicillin allergy evaluation, all patients were prospectively reviewed by both medical record review (via the Hospital Authority's integrated Clinical Management System) and individual interviews after at least 6 months following evaluation and thereafter. Interviews were either conducted in person or over the telephone in the form of a structured questionnaire. All patients gave informed consent, and this study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Penicillin allergy evaluation and testing procedures

Based on departmental protocol, a comprehensive history is first taken by medical record review and patient interview. Based on their history, with a focus on the timing of symptom onset of their index reaction, patients are stratified as either immediate (compatible symptoms [such as urticaria, angioedema, bronchospasm, vomiting, diarrhoea or anaphylaxis] with onset ≤ 1 hour), non-immediate-type (compatible symptoms [such as maculopapular rash, fixed drug eruptions, erythema multiforme, symmetrical drug-related intertriginous and flexural exanthema or severe cutaneous adverse reactions] with onset > 1 hour), or unknown (uninformative history) as deemed by an Allergist. Patients with suspected immediate reactions or uninformative histories are offered ST with SPT and IDT, and patients with suspected non-immediate reactions are offered delayed IDT. Choice of supplementary *in vitro* tests, such as basophil activation tests (BAT) and lymphocyte transformation tests (LTT) may be added at the Allergist's discretion.[13] Patients would only proceed to DPT only if the ST (and *in vitro* tests if performed) results were negative. Only patients with negative drug provocation test results were delabelled.

ST were performed with benzylpenicilloyl polylysine (0.04 mg/mL), sodium benzylpenilloate (0.5 mg/mL), benzylpenicillin (6 mg/mL), and amoxicillin (25 mg/mL). If clinically indicated or if it was the index penicillin, selected patients would also undergo additional SPT and IDT as per European Network and European Academy of Allergy and Clinical Immunology (EAACI) recommendations.[14] For suspected immediate-type reactions, both SPT and IDT were read at 15 minutes. For suspected delayed-type or unknown reactions, IDT results were also reassessed after two days. A positive SPT was defined as a wheal ≥ 3 mm diameter. A positive IDT was defined as an expansion of ≥ 3 mm from the original bleb.[15]

DPTs remain the 'gold-standard' to confirm the diagnosis of a genuine drug allergy. Negative DPTs can confidently allow physicians to exclude drug allergies and delabel incorrect allergy records. DPT protocols were carried out according to the latest EAAACI position paper: for immediate-type reactions, graded doses of the index penicillin (or amoxicillin, if index unknown) in intervals of 30-minutes would be administered under supervision until 100% of the cumulative dose equivalent to the maximum single unit dose (MSUD) was reached; for non-immediate type reactions, escalating doses of the index penicillin (or amoxicillin, if index unknown) would be given until an end dose equivalent to the MSUD was reached (the time between each dose would depend on the time interval of the index reaction).[9]

Data collection

Patient demographics and baseline characteristics such as age-adjusted Charlson Comorbidity Index, history of asthma or chronic obstructive pulmonary disease, atopic dermatitis and spontaneous urticaria were collected during the first patient encounter. During penicillin allergy evaluation, additional clinical parameters including duration since index reaction, Allergist's classification of index reaction (immediate type [compatible symptoms with onset ≤ 1 hour], non-immediate type [compatible symptoms with symptom onset > 1 hour], or unknown [uninformative history]), results of allergy tests (including SPT, IDT, delayed IDT, DPT as well as *in vitro* tests such as BAT, LTT and ELISpot) and outcomes of testing ('confirmed allergy' by positive ST, DPT or *in vitro* tests; or 'delabelled' by negative DPT), were collected. During follow-up review (at least 6 months following completion of workup or after), prospective data including drug history; use of antibiotics; as well as number, duration and frequency of infections, Emergency Department attendances, hospitalisation and absenteeism were collected.

Statistical analysis

SPSS Statistics 27.0 (IBM, Armonk, NY) was used for all analyses. Categorical variables were reported as percentages, and continuous variables were reported as mean ± standard deviation or median (25th percentile to 75th percentile) where appropriate. Assumption of normality of continuous variables was tested using Shapiro–Wilk test. Variables between the confirmed allergy and delabelled cohorts were compared using logistic regression analysis. Variables reaching statistical significance in the univariate analysis were included in the multivariable analysis to identify predictors of penicillin allergy. Student's t-test, Mann-Whitney U test, chi-squared test, and Fisher's exact test were used to compare outcomes upon follow-up between the confirmed allergy and delabelled cohorts. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 440 patients were referred for evaluation of suspected penicillin allergy during the study period. Among these, 68 patients were excluded from analysis (58 with incomplete workup, and 10 patients passed away prior to allergy testing) (**Figure 1**). Among the 10 deceased patients, 8 (80%) patients died of sepsis. The remaining 372 patients participated in and completed penicillin allergy workup and were included in the study.

90% of penicillin allergy were delabelled after negative drug provocation tests

Out of 372 remaining patients who completed penicillin allergy evaluation, 335 (90%) patients were successfully de-labelled. The remaining 19 (5%), 17 (5%) and 1 (0.3%) patients were diagnosed by positive skin tests, drug provocation tests and lymphocyte transformation test, respectively. Comparisons of demographics and clinical features between patient with their penicillin allergy confirmed and delabelled are shown in **Table 1**.

Overall negative predictive value of penicillin skin testing 95%, but was lower for patients with history of non-immediate type reactions (88%)

Breakdown of penicillin allergy evaluation according to clinical and chronological classification (i.e., symptom onset during index reaction) is shown in **Figure 2**. Out of 372 ST performed, 19 (5%) were positive. All (100%) of patients with unknown reaction type were had negative ST. One patient with negative ST had LTT performed due to history suggestive of severe non-immediate reaction which was positive. The remaining 352 patients with negative ST underwent DPT, of which 17 were positive. The overall negative predictive value of skin testing was therefore 95%. Subgroup analysis by symptom onset (immediate, non-immediate and unknown) showed that the negative predictive value for skin testing were 97%, 88%, and 97%; respectively.

All patients with confirmed penicillin allergies by positive *in-vivo* tests (ST or DPT) only showed minor reactions during workup. All reactions were self-limiting and did not require any additional treatment other than oral antihistamines. No patients developed anaphylaxis or systemic reactions during evaluation.

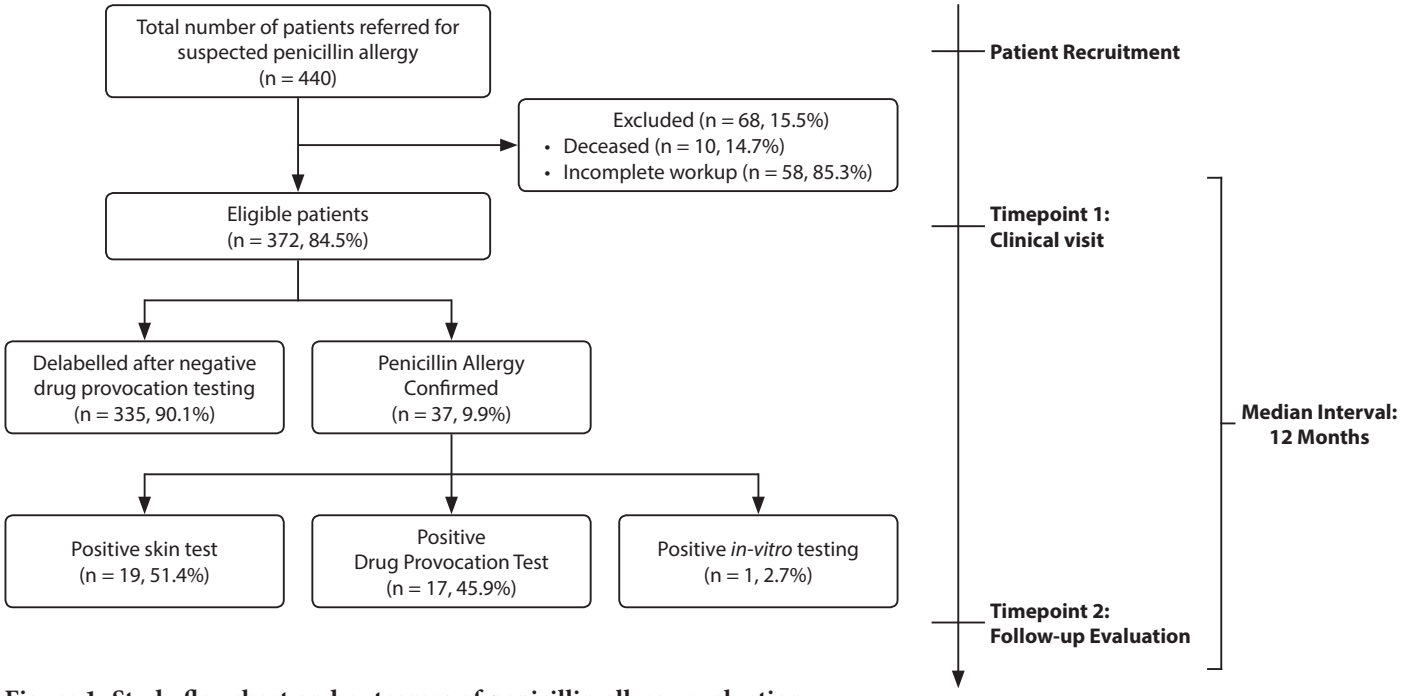

Figure 1. Study flowchart and outcomes of penicillin allergy evaluation.

Table 1. Comparisons of demographics and clinical features between patients with confirmed and delabelled penicillin allergy

	All (n = 372)	Confirmed penicillin allergy (n = 37)	Delabelled penicillin allergy (n = 335)	*p*-value
Male sex, n (%)	131 (35.2)	10 (27.0)	121 (36.1)	0.275
Age, years	59.4 (45.3-70.5)	60.8 (45.6-68.9)	59.4 (45.3-70.6)	0.995
Age-adjusted Charlson Comorbidity Index	2.0 (1.0-4.0)	3.0 (1.0-5.0)	2.0 (0.0-4.0)	0.161
History of asthma or chronic obstructive pulmonary disease, n (%)	45 (12.1)	3 (8.1)	42 (12.5)	0.437
History of atopic dermatitis, n (%)	66 (17.7)	5 (13.5)	61 (18.2)	0.480
History of spontaneous urticaria, n (%)	115 (30.9)	6 (16.2)	109 (32.5)	**0.048**
Duration since index reaction, years	10 (3.0-20.0)	3.0 (1.0-10.0)	10.0 (4.0-20.0)	**< 0.001**
Classification of index reaction				
Immediate (≤ 1 hour), n (%)	135 (36.3)	8 (21.6)	127 (37.9)	0.056
Non-immediate (> 1 hour), n (%)	105 (28.2)	25 (67.6)	80 (23.9)	**< 0.001**
Unknown, n (%)	132 (35.5)	4 (10.8)	128 (38.2)	**0.003**

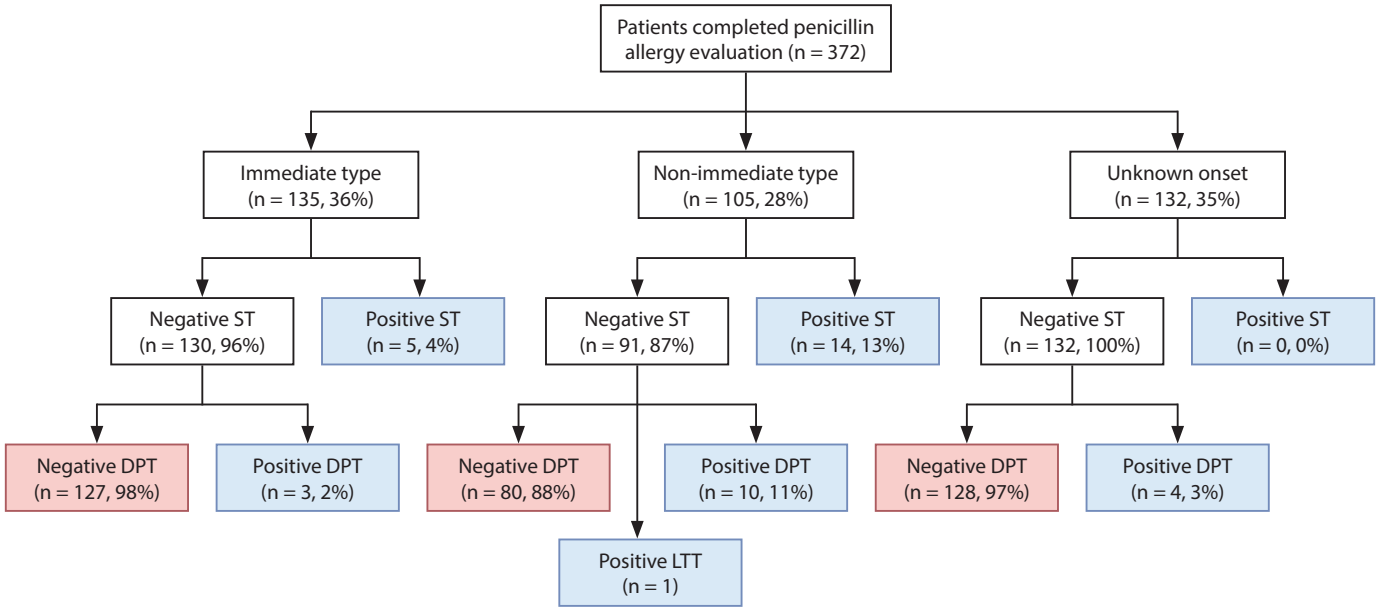

Figure 2. Breakdown of penicillin allergy evaluation according to symptom onset during index reaction.

Table 2. Multivariable logistic regression of factors associated with confirmed penicillin allergy.

	Adjusted odds ratio (95%CI)	*p*-value
History of spontaneous urticaria	0.438 (0.172-1.116)	0.084
Duration since index reaction, years	0.942 (0.899-0.987)	**0.012**
Non-immediate (> 1 hour) onset during index reaction	4.501 (2.085-9.716)	< **0.001**

History of non-immediate onset and shorter duration since index reaction and were associated with confirmed penicillin allergy

History of spontaneous urticaria, classification (immediate vs non-immediate type) and duration since index reaction were significantly associated with confirmed penicillin allergy and included in multivariate analysis. Multivariate logistic regression revealed that non-immediate type (OR = 4.501 [95%CI = 2.085-9.716], $p < 0.001$) and duration since index reaction (OR = 0.942 [95%CI = 0.899-0.987], $p = 0.012$) were independently associated with confirmed penicillin allergy after adjusting for history of spontaneous urticaria (**Table 2**).

After at least 6 months, 18% of delabelled patients were re-exposed to penicillin and did not experience any adverse events

All patients who completed penicillin allergy evaluation were reviewed after at least 6 months following delabelling or confirmation of allergy. The overall median duration after penicillin evaluation for all patients was 12 months (IQR: 7.4-19.6). The median duration for delabelled and confirmed penicillin allergic patients was 12 months (IQR: 7.4-19.7) and 11 months (IQR: 6.8-18.8), respectively. There was no significant difference between duration of follow-up between the two groups ($p = 0.544$). No patients with confirmed penicillin allergy received penicillins again during follow-up, while 60 (18%) of de-labelled patients had received penicillins again ($p = 0.005$). All (100%) of delabelled patients who received penicillins again did not report any adverse reactions. Subsequent antibiotic use after penicillin allergy evaluation for both groups is shown in **Figure 3**. There was significantly less fluoroquinolone use among delabelled patients compared to those with confirmed penicillin allergy (38 [11%], vs 11 [30%], $p = 0.004$). Other parameters (including number, duration and frequency of infections, Emergency Department attendances, hospitalisation and absenteeism) did not reach statistical significance.

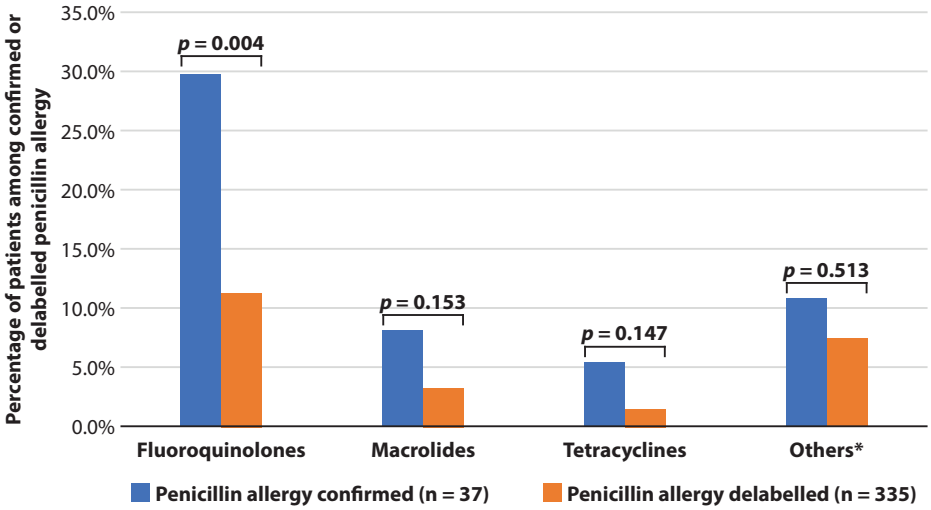

Figure 3. Comparison of subsequent antibiotic use between patients with confirmed and delabelled penicillin allergy. *Others: Aminoglycosides (n = 7), Carbapenems (n = 4), Cephalosporins (n = 7), Fusidic acid (n = 13), Isoniazid (n = 1), Nitrofurantoin (n = 1), Rifabutin (n = 2).

Discussion

To the best of our knowledge, this is the first prospective study to report on predictors of successful penicillin allergy delabelling and the longitudinal outcomes of delabelled patients among Chinese. Our study is also the first to elucidate the respective differences in diagnostic performances of ST between patients with history of immediate and non-immediate type reactions, as well as the investigating the NPV of penicillin DPT after subsequent re-exposure.

We identified 2 factors associated with confirmed penicillin allergy in the PAPA cohort, namely (1) history of non-immediate reaction and (2) shorter duration since index reaction. Our findings are consistent with previous reports, with only a quarter to one-third of patients continue to test positive 5 years following their index reaction, and down to 5-22% after 10 years.[16-20] This is likely due to a combination of initial mislabelling as well as natural loss of penicillin sensitisation through time – especially for IgE-mediated, i.e., immediate-type, reactions.[21] In contrast, non-immediate type reactions may be more easily recognisable due to more distinct clinical presentations and have sustained sensitisation in comparison to immediate-type reactions.[17] These two factors serve as cardinal pillars for identifying and predicting high-risk patients during penicillin allergy evaluation.

We also analysed the differences in NPV of ST between patients indexed with non-immediate and immediate-type reactions. The NPV for ST was lower among patients with history of non-immediate reactions. Although we did not routinely perform PT in addition to delayed IDT for non-immediate reactions, PT are known to be less sensitive than delayed IDT and would unlikely improve the overall NPV.[22,23] To minimise the risk of positive DPT, we advocate that a more cautious approach towards counselling and investigation in patients with history of severe non-immediate reactions. In such cases, supplementary diagnostic tests such as complementary *in vitro* tests (such as LTT or ELISpot) or graded DPT should be considered. This was demonstrated in one case of the PAPA cohort, with a patient with history suggestive of a severe non-immediate reaction, which was diagnosed by positive LTT following a negative ST. However, *in vitro* tests are rarely routinely employed outside research settings owing to their costs and time-consuming nature.[24] As such, the scalability of such approaches in a clinical setting is potentially limited.

Among the 60 patients that were re-exposed to penicillins after undergoing our penicillin allergy evaluation, no patients reported any adverse reactions reported during the follow-up after at least 6 months from delabelling. We did not identify any false-negative DPT nor cases of resensitisation, even among patients with history of severe immediate-type reactions.[25-27] This finding of a 100% NPV for DPT corroborates other studies that deem direct oral challenge a safe and effective 'gold-standard' to delabel patients evaluated as low risk for genuine allergies.[28] A limitation may be due to the relatively shorter follow-up period and the majority of patients who were delabelled have not been re-exposed to penicillins yet, or a genuine biological difference between Chinese and Western populations. Interestingly, it is well established that certain high-risk human leucocyte antigens (HLA) alleles have been identified to be associated with certain drug allergies, for example with carbamazepine and allopurinol-induced drug allergy among Asian patients.[29,30] More recently, studies from the West also postulated certain HLA alleles may also be associated with specific penicillin allergies such as HLA-B62 with non-immediate piperacillin-tazobactam reactions.[31] However, these differences in outcomes are yet to be elucidated and highlights the importance of larger multi-centre and -ethnic studies in the future. Nonetheless, the fact that more than one sixth of the patients managed to safely re-use penicillins even within such a short duration of follow-up robustly demonstrates the safety and efficacy of our penicillin allergy evaluation.

The use of second-line, broad spectrum antibiotics as a result of inaccurate allergy labels has previously been demonstrated.[6,32,33] Our study demonstrates a lower utilisation of second-line antibiotics, in particular to fluoroquinolones, among delabelled patients in comparison to confirmed penicillin allergics. Reduced use of 'big-gun' antibiotics have also been found to lower inpatient and outpatient prescription costs by up to $609USD and $193USD per patient-episode respectively, as well as improve clinical outcomes and mortality by re-introducing antibiotics with a safer and more tolerable side-effect profile.[5,34] Notably, 8 out of the 10 patients died of sepsis prior to completion of penicillin allergy. The long-term benefits of mitigating the proliferation of MRDO from penicillin allergy delabelling are likely substantial and wide-reaching.[35] The issue of MRDO is particularly pertinent to Hong Kong, with rates of antimicrobial resistance to 'big gun' antibiotics such as fluoroquinolones and third generation cephalosporins surpassing those of many developed countries.[35] The long-term effect of reduced second-line antibiotic use is likely underestimated in our study due to a short follow-up time and the benefits from allergy delabelling will likely exceed extrapolations from our findings. While there is no 'silver bullet' approach to alleviating the burden of antimicrobial resistance, penicillin allergy delabelling is a low-cost and high-reward strategy that should be strongly considered as a key player in the battle against MRDO in upcoming policies.

This study has several limitations. Firstly, the relatively short follow-up period and restricted data availability on patient outcomes post-delabelling limited our ability to comprehensively evaluate long-term patient outcomes after delabelling. We did not observe significant differences in clinical outcomes such as hospital admissions, length of stay and duration and frequency of infective episodes between the delabelled and confirmed-allergy cohorts after matching for comorbidities and infection risk. This is likely be due to the short duration of follow-up, as well as the concurrent COVID-19 pandemic waves that may have affected infection risks, health-seeking and medication practices during the period. Further prospective studies over more extensive periods of follow-up would be valuable to gain more accurate insights on the long-term clinical outcomes and quality of life in patients after penicillin allergy delabelling. Secondly, external validity may be limited as it was a single-centred study with Chinese patients only. Future large-scale studies with longer periods of follow-up and a more comprehensive evaluation of delabelling programme efficacy, such as quality of life indices and programme cost-effectiveness, would help enhance existing delabelling programmes.

Conclusion

This study is the first, to our knowledge, to report on longitudinal outcomes following penicillin allergy delabelling and inferior NPV of ST for non-immediate reactions among Chinese. We also identified that history of non-immediate onset and shorter duration since index reaction were associated with genuine penicillin allergy. Our penicillin allergy evaluation programme has proven to be very safe and has effectively mitigated the use of second-line antibiotics. Lastly, physicians should be aware of the comparably lower NPV of ST in non-immediate reactions and we advocate that ST should be supplemented with thorough clinical history and adjunct diagnostic evaluations in patients with history of severe non-immediate reactions.

Acknowledgments

Nil.

Conflicts of interest

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

Authors' contributions

- T.S.L., H.K.S.H. and A.K.C.K. researched the data, performed statistical analyses and wrote the manuscript.
- M.H.Y.Y., J.C.Y.W. and V.C. researched the data.
- P.H.L. supervised the project and critically reviewed and edited the manuscript.
- All authors contributed to the final version of the manuscript.

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