

Return to Sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand

Authors: Trubiano JA^{1,2,3}, Worth LJ^{2,3}, Urbancic K^{1,4}, Brown TM⁵, Paterson DL⁵ on behalf Australasian Society for Infectious Diseases Clinical Research Network, Lucas M⁶ on behalf of Australasian Society of Clinical Immunology & Allergy, Phillips E^{7,8}.

Affiliations

1. Department of Infectious Diseases, Austin Health, VIC, AUS.
2. Department of Infectious Diseases, Peter MacCallum Cancer Centre, VIC, AUS.
3. Department of Medicine, University of Melbourne, VIC, AUS.
4. Department of Pharmacy, Austin Health, VIC, AUS.
5. Centre for Clinical Research, University of Queensland, Brisbane, QLD, AUS.
6. Department of Clinical Immunology, Pathwest Laboratory Medicine, Queen Elizabeth II Medical Centre, WA, Australia.
7. Institute for Immunology & Infectious Diseases, Murdoch University, WA, AUS.
8. Department of Medicine, Vanderbilt Medical Center, TN, USA.

Corresponding Author:

Dr Jason Trubiano

Infectious Diseases Physician

Austin Health

PO BOX 5555 Heidelberg, VIC, Australia 3084

P: (03) 94965000

F: (03) 94966676

E: jason.trubiano@austin.org.au

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ABSTRACT*Background*

Antibiotic allergies are frequently reported and have significant impacts upon appropriate prescribing and clinical outcomes. We surveyed infectious diseases physicians, allergists, clinical immunologists and hospital pharmacists to evaluate antibiotic allergy knowledge and service delivery in Australia and New Zealand.

Methods

An online multi-choice questionnaire was developed and endorsed by representatives of the Australasian Society of Clinical Immunology and Allergy (ASCIA), Australasian Society of Infectious Diseases (ASID) and Society of Hospital Pharmacists Australia (SHPA). The 37-item survey was distributed in April 2015 to members of ASCIA, ASID, SHPA and Royal Australasian College of Physicians.

Results

Of 277 respondents, 94% currently use or would utilise antibiotic allergy testing (AAT) and reported seeing up to 10 patients/week labelled as antibiotic-allergic. Forty-two per cent were not aware of or did not have AAT available. Most felt that AAT would aid antibiotic selection, antibiotic appropriateness and antimicrobial stewardship (79%, 69% and 61%, respectively). Patients with histories of immediate hypersensitivity were more likely to be referred than those with delayed hypersensitivities (76% vs. 41%, $p=0.0001$). Lack of specialist physicians (20%) and personal experience (17%) were barriers to service delivery. A multidisciplinary approach was the preferred AAT model (53%). Knowledge gaps were identified, with the majority over-estimating rates of penicillin/cephalosporin (78%), penicillin/carbapenem (57%) and penicillin/monobactam (39%) cross-reactivity.

Conclusions

A high burden of antibiotic allergy labelling and demand for AAT is complicated by a relative lack availability or awareness of AAT services in Australia and New Zealand. Antibiotic allergy education and deployment of AAT, accessible to community and hospital-based clinicians, may improve clinical decisions and reduce antibiotic allergy impacts. A collaborative approach involving ID physicians, pharmacists and allergists/immunologists is required.

KEYWORDS:

Antibiotic allergy, adverse drug reactions, antibiotic allergy testing, antimicrobial stewardship, skin testing

BACKGROUND:

Despite 10% of the population reporting a penicillin “allergy”, less than 1% of the population are confirmed as being truly penicillin allergic by formal testing¹⁻⁵. In Australia, the prevalence of antimicrobial allergy labels in hospitalised inpatients is 18% and higher in populations with more frequent antibiotic use (e.g. immunocompromised hosts)^{6, 7}. Antimicrobial allergy labels are associated with broad spectrum antibiotic usage, antimicrobial resistance, inappropriate prescribing, morbidity and mortality^{4, 7, 8}. The majority of antibiotic allergy labels reflect either pharmacologically predictable side effects or mild non-immunologically mediated drug reactions that are amendable to rechallenge or symptomatic management as necessary^{9, 10}. Antibiotic allergy testing (AAT), which combines skin prick testing (SPT), intradermal testing (IDT) and ingestion (usually oral) challenge, has a high negative-predictive value and can therefore accurately de-label patients previously suspected to have an allergy on clinical criteria alone^{1, 11, 12}. In an era of increasing antimicrobial resistance, a strategic approach for clinicians to confirm and reliably document antibiotic allergy labels is required.

AIMS:

To identify the need for and potential barriers to development of coordinated multidisciplinary AAT programs in Australia & New Zealand we surveyed current knowledge and approaches to antibiotic allergy testing among allergists, clinical immunologists, infectious diseases physicians, general physicians, and hospital pharmacists.

METHODS:*Studied population*

We targeted healthcare providers most closely involved with the diagnosis and management of antibiotic allergies and adverse drug reaction reporting in Australian and New Zealand. These included allergists/clinical immunologists, infectious diseases physicians, general physicians and hospital pharmacists.

Survey tool

A 37-item multiple-choice survey was developed to assess the key antibiotic allergy domains: (a) prevalence, (b) testing practices (c) benefits to antimicrobial stewardship (AMS), (d) models of care and (e) clinician knowledge. Stakeholders represented clinical practice, research and supportive care sectors. Consultation and endorsement was sought from the Australasian Society of Clinical Immunology and Allergy (ASCIA) and Australasian Society of Infectious Diseases (ASID). Clarity and presentation of the survey were evaluated and refined by pre-testing of the questionnaire by two infectious diseases physicians, two pharmacists and one allergist/clinical immunologist prior to distribution. The survey was delivered electronically via an on-line portal (Survey Monkey, Palo Alto,

CA, USA) by the ASCIA, ASID, Society of Hospital Pharmacists of Australia (SHPA) and the Royal Australasian College of Physicians (RACP). Local ethics approval by the research ethics committee of the administering institution (Peter MacCallum Cancer Centre, VIC) was obtained prior to survey distribution (Number 15/06L).

Survey distribution

An invitation and link to the survey was distributed via online modalities only, including RACP weekly e-bulletin (n = 13,016), SHPA e-bulletin (n = 2550), ASCIA e-bulletin (n = 320), ASID weekly e-bulletin (n = 778) and Ozbug mailing list (n = 800). Ozbug is a moderated and closed mailing list for infectious diseases physicians and microbiologists in Australia and New Zealand¹³. Survey recipients may have been members of multiple listed societies or groups. The online survey was open between 15th March and 2nd April 2015, and one electronic reminder was sent to each group midway through the survey period. Anonymity of respondents and associated healthcare facilities was preserved.

Analysis

Responses were included if greater than 10% of survey questions were completed by a single participant. An overall percentage response rate could not be accurately obtained due to the overlapping nature of the surveyed societies and memberships. Survey responses were collated and analysed via Stata v13 (Statacorp, College Station Texas). Categorical variables were summarized using frequency and percentage and compared between groups using a chi-square test. Continuous variables were summarized using mean and standard deviation (SD) or median and inter-quartile range as appropriate and compared using a paired t-test or Wilcoxon signed-rank test as appropriate. A *p*-value of <0.05 was deemed statistically significant.

RESULTS:

A total of 277 persons completed the survey. **Table 1** summarises the baseline demographics of respondents. Fifty-eight percent (160/277), were members of the RACP. All Australian states, territories and areas of New Zealand were represented in the survey respondents. There were more respondents with less than 10 years experience than those with greater than 10 years clinical experience (57% [157/277] vs. 43% [120/277], *p* = 0.002). (**Table 1**)

(a) Antibiotic allergy label prevalence

Penicillin allergy label prevalence (8-10% in published literature^{5, 7}) was correctly estimated by 30% (83/277) of respondents. The majority of respondents (204/277, 74%) indicated that they reviewed 0-5

patients per week with a penicillin allergy, with a further 21% (58/277) reviewing 6-10 patients per week.

(b) Allergy testing practices

Whilst 32% (67/208) indicated they already employed allergy testing, 42% (118/277) of respondents were either unaware of or did not have AAT services available to them (**Figure 1**). Antibiotic allergy services were available equally to those with < 10 years or \geq 10 years clinical experience ($p=0.63$). Varied skin testing practices were available to respondents (**Figure 1**). The allergy phenotypes referred for AAT are demonstrated in **Table 2**, which shows more respondents refer patients with immediate compared with delayed hypersensitivities (76% [110/144] vs. 41% [59/144], $p=0.001$). Gold-standard allergy testing (SPT/IDT plus provocation challenge) was available to 58% (91/156) of respondents. Sixty-five percent (157/240) would be comfortable to use penicillin following negative gold-standard allergy testing, whilst 35% (83/240) remained unsure or would not employ.

(c) Benefits of antibiotic allergy testing to antimicrobial stewardship

When asked if AAT would benefit AMS, 74% (158/213) responded in the affirmative. The removal of an antibiotic allergy label was felt to aid antibiotic selection (78%, 165/212), antibiotic appropriateness (69%, 147/212), medication safety (69%, 146/212), AMS services (61%, 129/212) and all of the aforementioned (29%, 61/121). Four percent (8/212) of respondents felt there would be no measurable benefit to removal of an antibiotic allergy label. A beside point-of-care antibiotic allergy tool to assist management of patients with "labels" was thought to be of benefit to 71% (153/214) of respondents.

(d) Antibiotic allergy models of care

Twenty-six percent (55/209) felt there were no barriers to AAT, whilst 12% (26/209) recorded no demand for services. Barriers to AAT are summarised in **Figure 2**, with an absence of specialist clinicians being the most commonly reported. There was a non-significant trend for those with < 10 years experience to become new users of AAT services ($p=0.08$). A referral process involving a combined immunology/infectious diseases stream was preferred (47%, 90/192). Alternative favourable AAT models included referral to or by the following mechanism: (i) automated referral (25%, 47/192), (ii) pharmacist (38%, 72/192), (iii) AMS physician (45%, 88/192), (iv) allergist (45%, 86/192), (v) infectious diseases (37%, 71/192). Preferred delivery of AAT was through clinical immunology/allergy departments (53%, 112/213), a 'partnership between infectious diseases, pharmacy and immunology' (39%, 84/213), AMS programs (5%, 10/213) or infectious diseases physicians (2.3%, 5/213). More infectious diseases physicians (45%; 35/78) and pharmacists (62%; 36/58) preferred and saw the benefits of a partnership model than allergists/immunologists (17%; 9/52) ($p=0.001$).

(e) Clinician knowledge regarding antibiotic allergy

The responses to questions regarding the prevalence of penicillin allergy and mechanisms of cross-reactivity are summarised in **Table 3**. There was no difference in understanding of penicillin and beta-lactam cross-reactivity comparing those with < 10 and \geq 10 years experience (**Figure 3**). In patients with a history of **immediate penicillin hypersensitivity**, only 15% (37/241) would consider ceftriaxone, 41% (101/241) meropenem and 63% (152/241) aztreonam safe to administer in this clinical scenario, despite low rates of cross-reactivity (**Table 3**). Twenty four percent (57/237) of respondents would administer benzylpenicillin in the setting of community acquired pneumonia, 67% (159/237) preferring ceftriaxone, in a patient with a childhood history of **mild delayed hypersensitivity** (i.e. maculopapular exanthema [MPE]) to penicillin. Seven percent (16/237) would employ moxifloxacin in this scenario. In the case of methicillin-sensitive *Staphylococcus aureus* bloodstream infection in a patient with a history of childhood MPE, a 1st generation cephalosporin was the treatment of choice (47%, 112/237), followed by flucloxacillin (26%, 62/237), flucloxacillin following desensitisation (11%, 26/237), clindamycin (7%, 6/237) and vancomycin (6%, 15/237) therapy.

DISCUSSION:

In the current era of increasing antimicrobial resistance, opportunities to improve antibiotic prescribing are essential. Attention has turned to antibiotic allergy de-labelling to enhance AMS programs¹⁴. Before de-labelling can be incorporated into AMS, assessments of current Australian and New Zealand antibiotic allergy service provisions and stakeholder knowledge are required to identify the barriers to implementing multi-disciplinary AAT services. We surveyed Australian and New Zealand clinicians and pharmacists to examine the current and future requirements of AAT programs and attitudes toward antibiotic allergy.

Our survey highlights a demand for AAT amongst key stakeholders irrespective of clinical experience, contrasted with significant operational barriers. Whilst antibiotic allergies encountered by infectious diseases physicians are being increasingly found to impact on antibiotic selection, antibiotic appropriateness and antimicrobial resistance^{6, 8, 15}, less than half infectious diseases specialists had AAT available, likely reflective of poor access. When available, testing to a vast array of β -lactams, including the implicated antibiotic, was offered. There appears a desire to refer patients with a history of immediate hypersensitivity over delayed, potentially reflecting a perception of less robust options for the management and diagnosis for T-cell mediated reactions. This is interesting as antibiotics contribute almost 50% of severe cutaneous adverse reactions¹⁶, and both *in vivo* (skin testing) and *ex vivo* diagnostics are continually improving¹⁷⁻¹⁹. In addition clinical phenotyping and risk stratification is even more important for many serious delayed reactions to avoid future morbidity and mortality related to re-exposure to a suspect drug or one that is structurally related. Most respondents were optimistic that overall AAT could aid AMS and, if more easily accessible, would employ AAT in their AMS programs.

We identified significant knowledge gaps among surveyed clinicians and pharmacists that did not correlate with years of clinical experience. Compounding either a true or perceived absence of AAT, is a potential misunderstanding of antibiotic allergy, previously noted in the US²⁰. Whilst historical estimates of IgE mediated cephalosporin and penicillin cross-reactivity were 15-25%, more contemporary studies suggest the true rate of cross-reactivity to be <2% and potentially lower for third and later generation cephalosporins²¹⁻²³. Recent studies suggest the rate of immediate carbapenem and penicillin allergy cross-reactivity to be also extremely low (<1%)^{24, 25}. This contrasts with our surveyed stakeholders, 78% of whom suggested a cephalosporin cross-reactivity rate > 2% and 58%, a meropenem cross-reactivity of > 1%. Furthermore, despite most childhood-onset MPE being secondary to viral exanthema or antibiotic/viral interaction^{26, 27} rather than antibiotic exposure, clinicians and pharmacists were reluctant to administer a preferred penicillin therapy in these patients with community-acquired pneumonia and *Staphylococcus aureus* bloodstream infection. Despite the high negative predictive value of penicillin skin prick testing and oral challenge¹, 35% of respondents were still unsure or unwilling to prescribe penicillin in the setting of a negative testing. Investment in updating undergraduate and continuing medical and pharmacy antibiotic allergy education would enhance clinical knowledge and potentially improve antibiotic utilization amongst key stakeholders²⁸.

Study limitations include the diversity of the surveyed population, including the fact that some responses were obtained from non-practicing clinicians. Notwithstanding this limitation, 85% of respondents were current prescribers of antibiotics and actively engaged in clinical care. An accurate estimate of overall response rates could not be obtained due to overlap across the studied membership bases. As with all studies employing voluntary survey participation, the potential for selection bias is recognised. It is possible respondents represented a biased sample of those with an interest in AAT. Nonetheless, this survey provides the first attempt at understanding current AAT practices and service provision in Australia and New Zealand

Although models of antibiotic allergy care have been proposed,²⁸⁻³⁰ a standardised or multidisciplinary approach to AAT testing in Australia and New Zealand does not currently exist. We have demonstrated one of the preferred models to be a partnership between allergists, clinical immunologists, pharmacists and infectious diseases physicians. Similar multidisciplinary models in cancer patient AMS programs, engaging relevant clinicians, have lead to significant improvements in quality of care and mortality benefits³¹. Improved knowledge of antibiotic allergy and the role ATT will help promote allergy services as a safe and effective service.

CONCLUSION:

Despite a high antibiotic allergy label prevalence and demand for AAT services, current implementation barriers include lack of access to appropriate specialist healthcare providers to carry out AAT as well as cost of delivery. A collaborative model of infectious diseases physicians, pharmacists and allergists/clinical immunologists would enable targeted AAT delivery to those that require it, improving antibiotic utilisation, choice and drug safety. Current knowledge gaps suggest that education of clinicians and pharmacists and engagement of allergy and infectious diseases networks will be needed to provide the change necessary to fuel such multidisciplinary service models.

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ABBREVIATIONS:

AAT – Antibiotic allergy testing

AMS – Antimicrobial Stewardship

ASCIA – Australasian Society of Clinical Immunology and Allergy

ASID – Australasian Society of Infectious Diseases

IDT – Intradermal testing

RACP – Royal Australasian College of Physicians

SHPA – Society of hospital pharmacists Australia

SPT – Skin prick testing

TABLES:

Table 1: Baseline demographics of survey respondents.

Baseline demographics	Total N = 277
Medical training college	170 (61)
Royal Australasian College of Physicians	160 (58)
Royal Australasian College of Surgeons	2 (1)
Royal Australian College of General Practitioners	4 (1)
Royal College of Pathologists	4 (1)
Member of Society of Hospital Pharmacists	92 (33)
Member of Australasian Society of Infectious Diseases	101 (37)
Member of Australasian Society of Clinical Immunology & Allergy	81 (32)
Primary area of practice	
Infectious diseases	97 (35)
Pharmacy	87 (31)
Allergy/Clinical Immunology	61 (22)
General medicine or general practice	10 (4)
Other/not-specified	22 (8)
Clinical experience	
<10 years	157 (57)
Hospital Setting	
Private Hospital	22 (8)
Public Hospital	218 (79)
Currently involved in clinical practice that requires the prescribing of antibiotics	234 (85)

Table 2: Antibiotic allergy phenotypes referred for testing

Allergy phenotypes referred for testing, n (%)				
<i>Q. For what reactions would you perform or suggest referral for skin prick or intradermal allergy testing?</i>				
	Immediate	Delayed		All reactions
	IgE	SCAR	MPE	
Infectious diseases physicians (n = 48)	32 (67)	7 (15)	17 (35)	6 (13)
Pharmacists (n= 28)	22 (79)	5 (18)	7 (25)	4 (14)
Allergists/Immunologists (n = 53)	47 (89)	1 (2)	17 (32)	3 (6)
Other (n = 15) ^a	9 (60)	3 (20)	2 (7)	7 (47)
Total (n = 144)	110 (76)	16 (11)	43 (30)	20 (14)

^a Includes general practitioners, general physicians, microbiologists

Definitions: SCAR, severe cutaneous adverse reactions; MPE, maculopapular exanthema; SCAR, severe cutaneous adverse reactions, MPE, maculopapular exanthems.

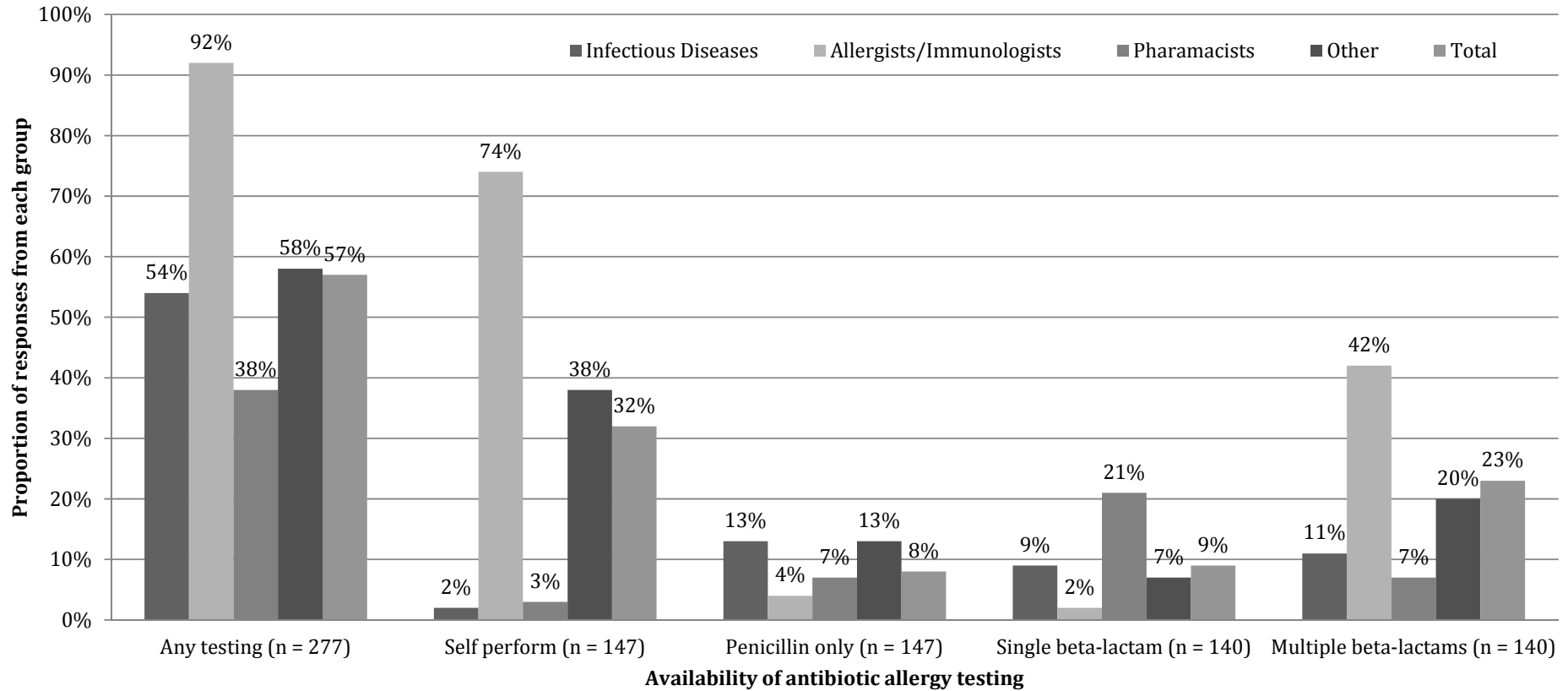
Table 3: Knowledge of Antibiotic Allergy Cross-Reactivity

Statement or question regarding antibiotic allergy	Evidence-based response *	% of specialty staff with correct response				% of all respondents with correct response
		ID physicians	Pharmacists	Allergists/ Immunologists	Other ^a	
<i>The major cause of cross-reactivity between amoxicillin and cephalixin allergy is the beta-lactam ring</i>	False	48	38	36	48	42
<i>What is the rate of immediate 3rd generation cephalosporin allergy in a patient with penicillin allergy?</i>	<1-2%	6	18	48	35	21
<i>What is the rate of immediate carbapenem allergy in a patient with penicillin allergy?</i>	<1%	46	31	50	28	40
<i>What is the rate of immediate monobactam allergy in a patient with penicillin allergy?</i>	<1%	79	46	63	41	61

*Evidence based responses based upon references: ^{23, 24, 32}

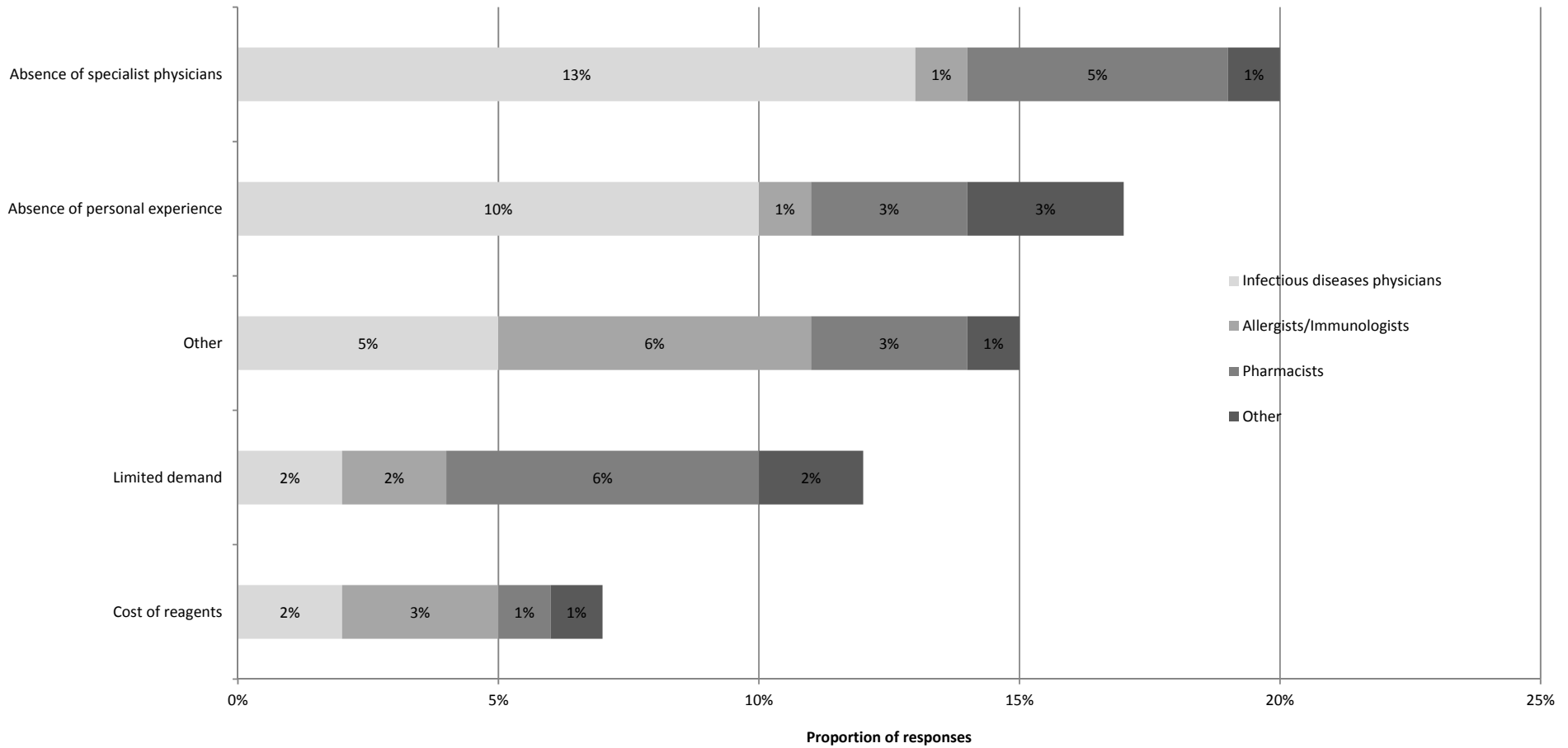
^a Includes general practitioners, general physicians, microbiologists

Figure 1: The availability of antibiotic allergy testing services to key stakeholders in Australia and New Zealand



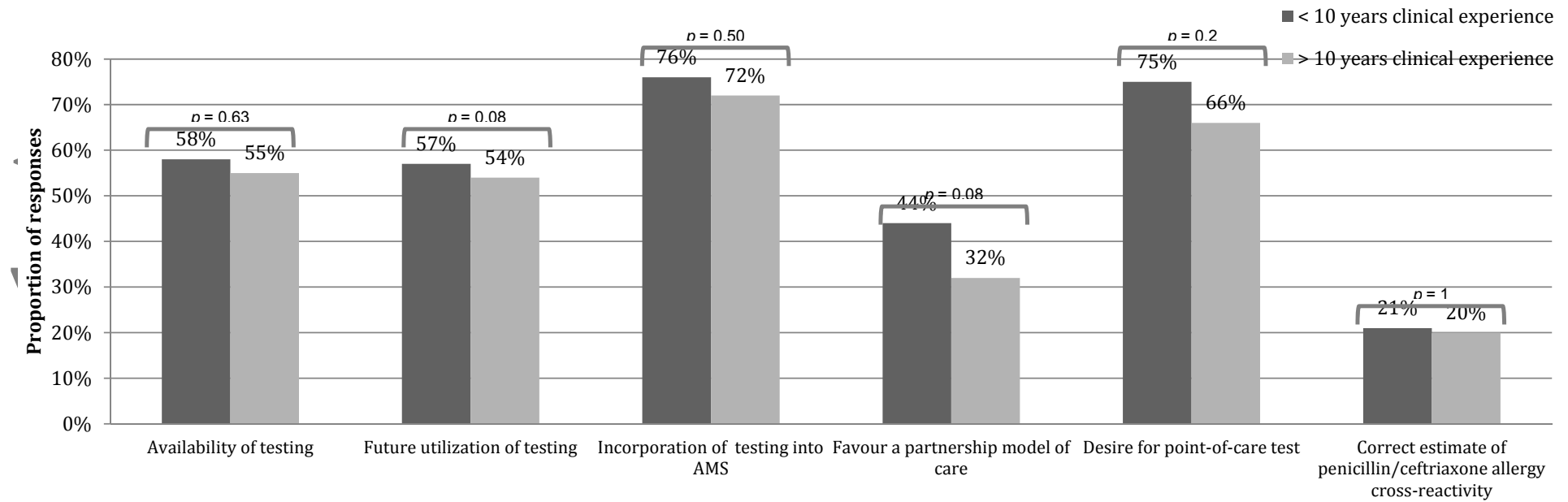
Legend: The availability of antibiotic allergy testing (y-axis, %) for various antibiotics (x-axis) is demonstrated. The percentage value is representative of the proportion of each stakeholder group. The total number of responses for each variable is displayed on the x-axis.

Figure 2: Identifiable barriers to antibiotic allergy testing



Respondents = 211

Figure 3: The impact of clinical experience on the utilization of antibiotic allergy testing and antibiotic allergy knowledge



Legend: A comparison of antibiotic allergy testing utilisation and knowledge for those with less than 10 and greater than 10 years of clinical experience.