

# The diagnosis and management of antibiotic allergy in children: Systematic review to inform a contemporary approach

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## ABSTRACT

**Background** Adverse drug reactions (ADRs) to antibiotics are commonly reported among children, with some representing genuine drug allergies. Accurate diagnostic tests are required. Drug provocation testing (DPT) is accepted as the gold standard investigation among children with suspected antibiotic allergy. We conducted this review to ascertain the strength of current evidence for using DPT as the first-line investigation for suspected antibiotic allergy among children.

**Methods** Medline was searched in June 2014 for publications investigating antibiotic allergy among children.

**Results** 865 publications were retrieved and 76 studies selected. ADRs are most common among children of 0–4 years, however only some reveal drug allergies. The best evidence demonstrates that around 0.21% of general paediatric outpatients demonstrate positive antibiotic intradermal (ID) testing or DPTs, while 6.8% of children attending emergency departments for suspected  $\beta$ -lactam allergy may fulfil DPT reactions. Four studies used DPT-based protocols to investigate suspected antibiotic allergy, with two of these conducting ID testing and DPTs across all participants.  $\beta$ -lactam and clarithromycin ID testing had sensitivities of 66.7% and 75%, with positive predictive values of 36% and 33%, respectively, when compared with DPT data.

**Conclusions** Our literature review found four (6%) publications that performed DPTs to subjects' index antibiotic across all participants. No rigorous evidence supports using skin prick, ID or in vitro diagnostic testing; indeed, the testing regimens, extracts and positivity criteria used are inconsistent. We recommend that suspected non-serious antibiotic allergy should be primarily investigated using DPT-based clinical protocols. Data examining their safety, acceptability and diagnostic performance are required.

## INTRODUCTION

Adverse drug reactions (ADRs) to antibiotics are commonly reported among children and young people. Allergic mechanisms are frequently suspected and alternative agents routinely prescribed. Altered antibiotic choices may impact on the health of both the individual and wider society, where antibiotic resistance and increasing health costs are becoming more burdensome.<sup>1</sup>

A substantial proportion of children develop rashes, urticaria, angio-oedema and respiratory symptoms while unwell, frequently while taking antibiotics.<sup>2</sup> Thus many children are diagnosed with 'suspected antibiotic allergy'. This is understandable, since 51 (36.7%) of the anaphylactic deaths in the UK over a 6 year period were due to medication.

Sixteen (31.4%) of these deaths resulted from antibiotics, including a 5-year-old child.<sup>3</sup> However, only a small proportion of ADRs result from reproducible allergic immunological mechanisms. One meta-analysis found that up to 24% of inpatient ADRs were characterised as 'allergic and or idiosyncratic' reactions, without requiring further investigation for more detailed determination.<sup>4</sup> Despite this, prevailing caution has allowed a substantial proportion of children experiencing ADRs to be labelled with 'suspected antibiotic allergy', without further investigation or confirmation.

Identifying and managing suspected antibiotic allergy has now become a clinical imperative, as current practice requires that we have reliable systems in place to mitigate iatrogenic harm and manage risks associated with healthcare interventions. In September 2014, the National Institute of Health and Care Excellence recommended that individuals warrant referral to specialist services if "they are likely to need  $\beta$ -lactam antibiotics frequently in the future".<sup>5</sup> It can be argued that all children then qualify for investigation as many antibiotic courses may be required over a lifetime, usually in an acute setting. The National Institute of Health and Care Excellence guideline emphasises the need for all healthcare workers to recognise, record and make referrals for suspected antibiotic allergy, while the antibiotic prescription rate among UK general practices is soaring.<sup>6</sup> The few specialist paediatric allergy services in the UK are widely dispersed and have limited capacity to cope with increased demand for the investigation of suspected drug allergy.<sup>7</sup>

Allergic reactions to antibiotics may be caused by a variety of mechanisms and raise a considerable diagnostic challenge.<sup>8</sup> The World Health Organisation (WHO) defines ADRs as being either Predictable (type A) or Unpredictable (type B). The Unpredictable type are subclassified into pharmacological drug intolerance, idiosyncratic pharmacodynamic reactions and allergic reactions. Immediate, type 1 hypersensitivity and IgE-mediated drug allergic reactions commonly cause urticaria, angio-oedema and potentially airway and systemic compromise, whereas non-immediate syndromes may manifest either as localised cutaneous responses, or systemic signs associated with more serious syndromes (figure 1).<sup>9</sup>

Drug provocation tests (DPTs) are recommended as the first-line gold standard investigation among children with mild allergic reactions and rashes to  $\beta$ -lactams.<sup>10</sup> However, clinical pathways using patients' histories, skin prick testing (SPT) and intradermal (ID) testing have not been validated against DPT outcome data. Rigorous appraisal of



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**Figure 1** Clinical presentation patterns of antibiotic allergy. \*Proceed to drug provocation testing only among patients with minor syndrome presentations and when clinical risk benefit favourable. #Avoid drug provocation testing. Caution also with skin testing according to risk-benefit. Further guidance regarding syndrome characteristics available from National Institute for Health and Care Excellence (NICE).<sup>6</sup>

	Immediate	Non-immediate	Non-immediate suspected serious
	Time-scale from first administration		
	< 1 hour	> 1 hour	> 1 hour
Possible associated symptoms & signs	Urticaria, angio-oedema, airway & systemic compromise	Maculopapular exanthema	Lymph node, joint, mucous membrane involvement, bullae, cytopenia, hepatitis, nephritis & vasculitis
Specific syndromes include	* IgE-mediated anaphylaxis	* Fixed drug eruption, non-bullous	# Drug Rash with Eosinophilia and Systemic Symptoms
	* Non-IgE-mediated anaphylactoid reactions	* Erythema multiforme	* Acute Generalised Exanthematous Pustulosis
			* Serum Sickness Syndrome
			* Drug-induced dermatoses (eg lupus spectrum)
			# Stevens Johnson Syndrome & # Toxic Epidermal Necrolysis

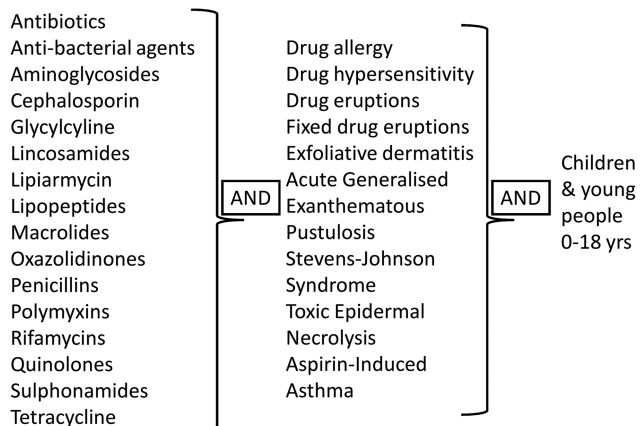
published studies is required to identify accurate, safe and acceptable diagnostic investigations and management strategies, to address this public health concern.

We performed a systematic review of the literature in order to identify best practice principles for diagnosing and managing antibiotic allergy among children and address the following questions:

1. What is the prevalence of antibiotic allergy among children?
2. What are the most accurate clinical investigations for the diagnosis of antibiotic allergy among children, using DPT as the diagnostic gold standard?
3. Do any clinical features of a child's reaction or comorbid risk factors obviate or modify the need for investigation?
4. How long does antibiotic allergy last in children and when should follow-up assessments be planned after diagnosis?

## METHODOLOGY

We systematically searched Medline from inception in 1948 until June 2014. The search strategy combined terms for all major groups of antibiotics through subject headings, and antibiotic syndromes while requiring that children were included (figure 2). Further publications were sourced through hand searches of the literature. No limits were set for language of



**Figure 2** Search strategy.

publication, and where articles were not accessible, contact was attempted with authors.

The Medline search retrieved 865 publications and items were selected in accordance with a selection protocol (figure 3).<sup>11</sup> This required that selected publications investigated only children ( $\leq 18$  years of age) or described a specific group thereof within the sample. Reviews, animal models and case reports of less than five subjects were excluded. A hand search was also performed.

Evidence was graded according to a pragmatic score, based closely on the Newcastle-Ottawa Quality Score, as no quality appraisal tool has been published relating to drug allergy evidence.<sup>12–14</sup> Publications were awarded greater weight of evidence for using DPTs (+1), skin testing (+1), population-based samples (+1), >99 subjects (+1), reporting of incomplete testing or follow-up (+1), adjustment for age, sex (+1) and appropriate statistics (+1). Studies of the same quality score were ranked such that larger samples contributed more weight of evidence. Meta-analysis was not appropriate due to heterogeneity in study design. We report studies qualitatively and present individual study data in tables.

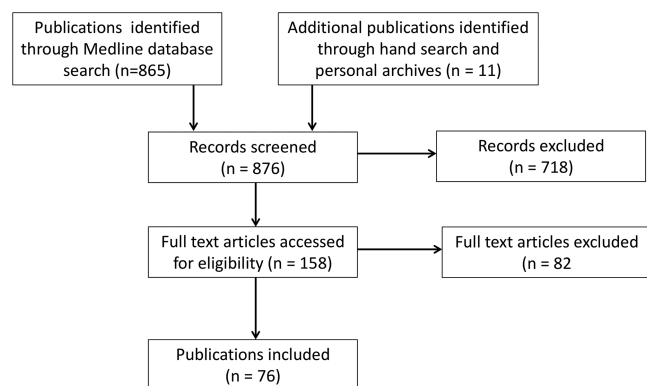
## RESULTS

Eight hundred and sixty-five publications were retrieved, with 11 added from hand searches, of which 158 passed screening and resulted in 76 studies being selected for this review.

### Question 1: What is the prevalence of antibiotic allergy among children?

Eleven studies surveyed the prevalence of suspected antibiotic allergy among children and four of these were conducted among the general population, however none used any confirmatory investigations, limiting their value (see online supplementary table S1).

The largest survey used the US National Centre for Health Statistics to trawl 11 years worth of outpatient and accident and emergency department (ED) visit data for ADRs. Of 585 932 annual attendances, 253 101 (43%) related to children 0–4 years of age. Antibiotics accounted for 28% of ADR visits across age groups, with further increases among those of 0–4 years.<sup>15</sup> The Swedish Medical Products Agency received 5771 reports of



**Figure 3** Flow chart of study selection process.

ADRs over 14 years, with 681 (27.2%) of non-vaccine drug doses implicating antibiotics.<sup>16</sup> The remaining studies assessing institution records or parental reported histories found that 57–85% of ADRs were reportedly due to antibiotics.

All studies using investigations to determine antibiotic allergy recruited participants from hospital, raising the risks of selection bias. One study in Switzerland investigated suspected  $\beta$ -lactam allergy using a DPT-based protocol among consecutive presentations to their ED, and elicited positive reactions among 6.8% of patients. A Portuguese study investigated likely antibiotic allergic patients among 1426 general paediatric outpatients, who returned questionnaires. Three of the 25 suspected antibiotic allergy subjects had either positive ID or DPTs to index antibiotics ( $\beta$ -lactams, co-trimoxazole and macrolides), yielding 12% prevalence of positive tests among those with likely antibiotic allergy and 0.21% diagnoses among general paediatric attendees.<sup>17</sup>

The majority of other case series sampled data from allergy department referrals, further raising selection bias. A large case series reporting investigations among 3275 French drug allergy referrals found that children had a significantly lower rate of positive ID or DPT results when compared with adults, especially after maculopapular rashes (10.6% positive tests among children vs 16.5% among adults,  $p < 0.0001$ ).<sup>18</sup>

These studies suggest that children aged up to 4 years present most commonly to drug allergy clinics, suggesting that young children may be more susceptible to antibiotic allergy. However, parents of younger children may pay greater attention to adverse reactions and seek more robust medical investigation, leading to bias. Additionally, none of these studies adjusted for how commonly antibiotics were used by the populations investigated.

In summary, the best evidence suggests that 0.21% of unselected general paediatric outpatients demonstrate positive tests for antibiotic allergy, whereas 6.8% of children attending ED for suspected  $\beta$ -lactam allergy develop allergic signs on DPT.

### Question 2: What are the most accurate clinical investigations for the diagnosis of antibiotic allergy among children, using DPT as the diagnostic gold standard?

Consensus has established that DPT is the gold standard investigation for drug allergy, since varying mechanisms may be attributed and reproducibility is one of the key diagnostic criteria.<sup>19 20</sup>

Four publications performed DPT to the index antibiotic among all children included in their studies. Two of these also used skin testing among their sample, allowing its performance to be ascertained. However, among 41 (54%) of the selected studies, positive skin testing was assumed to indicate antibiotic allergy, preventing comparison with the gold standard (see online supplementary tables S2 and S3).

Caubet *et al* reported the best quality publication comparing skin testing to DPT results for index antibiotics across their sample. The authors consented 88 of 108 consecutive presentations of suspected  $\beta$ -lactam allergy presenting to their Swiss ED. Each participant underwent skin prick and ID testing, followed by DPT with a 48 h continuing course. Eleven (13%) of the 88 patients demonstrated positive ID testing, none reacted to SPT or serum-specific IgE. Six (6.8%) demonstrated positive oral DPT with non-serious rashes, one at 30 min and five producing cutaneous signs between 7 h and 12 h later. Only four of the six reacting on DPT had positive ID tests, leaving seven children with false-positive ID results and therefore giving a positive predictive value of only 36.4%.  $\beta$ -lactam ID testing had a sensitivity of 66.7%, and specificity of 91.5% with respect to DPT.

One other study performed skin and DPT to clarithromycin after previous suspected reactions among 64 children in Florence, Italy. Mori *et al* demonstrated that nine (14%) demonstrated positive ID responses, and yet only four (6%) resulted in positive DPTs. Urticaria and angio-oedema arose within 20 min of DPT Clarithromycin dosing for two participants, and delayed maculopapular rashes developed after 3 days in two others. The authors' clarithromycin ID testing protocol demonstrated 75% sensitivity, 90% specificity and 33.3% positive predictive value with respect to DPT.

Two other studies performed DPTs across all subjects to their index antibiotics, supporting the use of DPTs as first-line investigations for antibiotic allergy in children.<sup>21 22</sup> The same team from Florence investigated consecutive referrals with co-amoxiclav suspension ADRs by performing DPTs to co-amoxiclav itself and sodium benzoate, the suspension preservative.<sup>21</sup> Eight (9%) of the 89 consecutive suspected co-amoxiclav allergy referrals demonstrated positive DPT reactions to co-amoxiclav itself, while 10 (11%) reacted to sodium benzoate and three (3%) failed both DPTs. Therefore, 21 (24%) demonstrated a reproducible allergic response to sodium benzoate or co-amoxiclav. A Dutch team performed DPTs to index agents among 33 children with suspected antibiotic allergy and reported that four (12%) produced mild skin reactions after index DPT, confirming reproducible allergy.<sup>22</sup> No studies demonstrated that investigation using SPT alone or serum antibiotic antibodies was reliable or useful.

In conclusion, positive predictive values for ID testing to  $\beta$ -lactam and clarithromycin are very low at 36% and 33%, respectively.<sup>23 24</sup> The four studies which reported using DPTs as their principle diagnostic tool resulted in positive signs among 6.3–23.6% of suspected antibiotic allergy cases.<sup>21–24</sup> Where DPTs elicited signs, these were usually cutaneous and mild, often arising more than 1 h post administration (see online supplementary table S2).

### Question 3: Do any clinical features of a child's reaction or comorbid risk factors obviate or modify the need for investigation?

Non-immediate antibiotic allergy syndromes, such as Toxic Epidermal Necrolysis (TEN) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), carry significant mortality rates: cautious investigation is warranted (see online supplementary table S3, figure 1). Seven of the nine studies investigating non-immediate suspected serious antibiotic reactions did not investigate cases. One study reported cases reacting to more than one drug of entirely unrelated classes,<sup>25</sup> suggesting that looking for antibiotic agent-specific causes for these immune responses may be less justified if the problem relates more to constitutional vulnerability or latent virus reactivation.<sup>8</sup> The two papers conducting ID testing among erythema multiforme and serum

sickness-like syndrome presentations did not report unsafe adverse effects.<sup>26 27</sup> Three publications described drug eruption series, with one conducting DPTs to co-trimoxazole among five (14%) participants without reporting systemic responses.<sup>28</sup> The remaining studies which assessed non-immediate suspected serious reactions reported likely culprit agents including antibiotics, without reference to their investigation.<sup>25 29–33</sup>

Some studies investigated potential risk factors for immediate antibiotic allergy, however none of these were strong enough to obviate the need for investigation. Three studies highlighted that anaphylaxis, urticaria and angio-oedema index responses were associated with a higher likelihood of positive DPT or ID responses when compared with non-specific rashes, however did not preclude investigation.<sup>24 34–36</sup> One study suggested that food allergy was a risk factor for  $\beta$ -lactam allergy among 161 Portuguese children ( $p=0.047$ ).<sup>37</sup> Kidon and See<sup>38</sup> found that having asthma predisposed towards failing drug DPTs, however was unable to correct for their increased medication requirement.

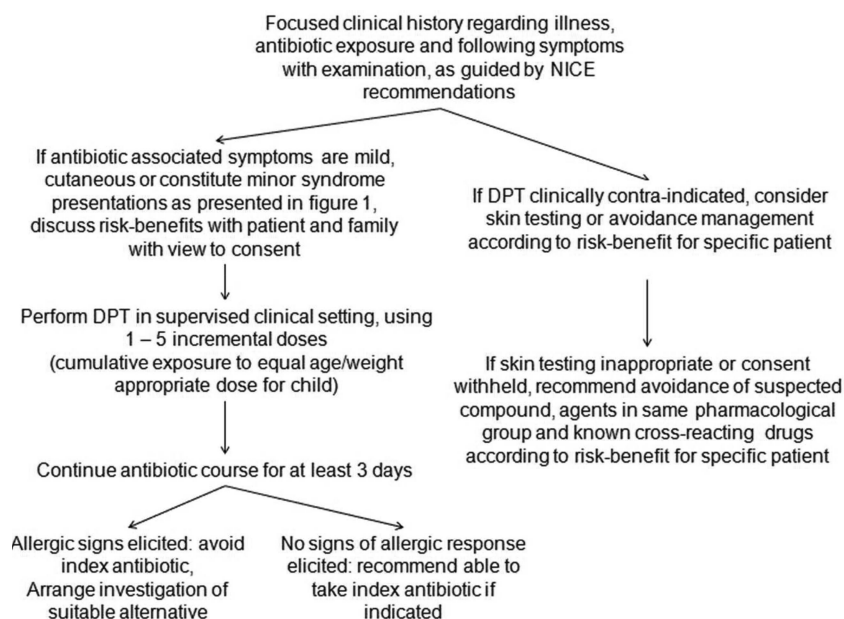
Overall, it is prudent to take a cautious approach among children describing multiple signs which are consistent with an allergic reaction to antibiotics. If the first dose of an antibiotic course induced immediate anaphylaxis with breathing difficulty or airway signs, or patients fulfil criteria for non-immediate serious syndromes, DPTs may be contraindicated (figures 1 and 4).

#### Question 4: How long does antibiotic allergy last in children and when should follow-up assessments be planned after diagnosis?

No single study has followed the natural history of DPT-proven antibiotic allergy with subsequent investigation.

Indeed most interest has focused on finding out whether negative investigation results remain consistently negative. One Israeli study repeated ID testing and DPTs among 98 children up to 5 months after their first investigations were negative. One subject demonstrated a positive response to penicillin ID testing the second time around, and another developed a maculopapular rash 30 min after the single dose DPT, resulting in two further diagnoses (2%).<sup>39</sup> The second American study conducted ID testing 1 month after initial skin and DPT investigations were negative, reporting that 26 (14%) then tested ID positive.<sup>40</sup>

**Figure 4** Evidence-led approach to the diagnosis and management of antibiotic allergy in children.



Neither study assessed whether their postinvestigation prevalence was higher than those among healthy control children.

## DISCUSSION

We have performed the first systematic review to appraise evidence for the diagnosis and management of antibiotic allergy in children.

Younger children present more commonly with ADRs, with 43–61% of episodes originating in 0–4-year-olds.<sup>15 16</sup> The likely prevalence of positive skin testing and DPTs to antibiotics among general paediatric outpatients is around 0.21%,<sup>17</sup> whereas DPT-proven reproducibility among children with suspected antibiotic allergy ranges between 6.3% and 24%.<sup>21 23 24</sup> The conduct of DPTs among children with non-serious reactions was safe. Indeed the majority produced delayed cutaneous reactions which are of questionable clinical significance and need not preclude antibiotic usage in a medical emergency. We recommend that suspected non-serious antibiotic allergy should be primarily investigated using DPT-based clinical protocols.

Despite DPT-based diagnosis becoming increasingly common throughout the UK, our literature review finds only four (6%) papers that performed DPTs to subjects' index antibiotic across all participants with mild reaction histories. No rigorous evidence supports skin and in vitro diagnostic testing; two studies compared ID testing with DPT data across participants. These demonstrated a sensitivity of 66.7% and 75%, with positive predictive values of 36% and 33% for ID testing to  $\beta$ -lactam and clarithromycin, respectively.<sup>23 24</sup> These data raise the question of whether skin testing should be undertaken to investigate antibiotic allergy among children at all.

We ensured that a wide range of literature was retrieved using broad search terms and not limiting according to language. Nonetheless, not all publications were retrievable, even after attempting contact with study authors.

Heterogeneity in study design and investigation protocols prevented meta-analysis and assessment of publication bias. The majority of hospital-based case series were vulnerable to selection bias, although better quality publications highlighted prospective introduction of protocols to reduce this (see online supplementary table S2). Nonetheless, since the first publication in 1964, an

**Figure 5** Benefits and drawbacks of investigating allergy to antibiotics using drug provocation testing.

Benefits	Drawbacks
Age and dose appropriate protocols	Risk of administering systemic doses (asthma must be well controlled)
Acceptable for most paediatric patients	Difficult to interpret subjective symptoms
Good safety record	DPT to only one agent possible over a few days
Negative responses are painless	Should not be undertaken whilst taking antihistamines
Low risk of false positive diagnosis	Low risk of false negative diagnostic outcomes as co-factors typically absent at time of DPT
Antibiotic course may be extended for late reactions	If positive, subsequent DPT required to identify safe alternatives
	Mild symptoms and signs may develop on subsequent doses
	Requires supervised clinical setting; once validated protocols may allow secondary and primary care
	Low risk of re-sensitisation to antibiotic with DPT

increased variety of antibiotics has become available and laboratory techniques for detecting sensitisation have changed enormously.<sup>41</sup> This may explain considerable changes in prevalence data detected over time.<sup>41–42</sup> Where outlined, some DPT protocols did not require ongoing course completion to ascertain delayed reactions. We were unable to construct a receiver operating characteristic curve analysis to compare investigations, as too few study designs would have been eligible for inclusion therein.

### Context of findings

Early consensus guidelines for investigating antibiotic allergy proposed that positive SPT and ID results fulfilled diagnostic criteria for antibiotic allergy, based on two early case series which sporadically used DPT.<sup>43–45</sup> It has since become clear that skin testing is of limited accuracy with 8.4–13.7% of ID negative adults demonstrating symptoms on DPT.<sup>46</sup>

Additionally, in clinical practice, we determine the patient's status towards the suspected antibiotic and towards suitable alternatives. Therefore, the majority of ID testing panels include a range of reagents at varying concentrations.<sup>47</sup> This is unacceptable to a large proportion of paediatric patients, particularly since their discomfort can prevent adequate investigation. There appears to be little reason to continue to use ID testing to antibiotics among children.

We recommend that suspected non-serious antibiotic allergy should be primarily investigated using DPT-based clinical protocols, as has become routine among large centres in the UK and abroad (figure 4). Incremental DPTs should be undertaken with expert clinical supervision for the first cumulative dose, to ensure appropriate surveillance of symptoms and signs, and excellent management of allergic reactions (figure 5).<sup>19</sup> The index antibiotic preparation should be used where possible, to best support positive diagnosis of an allergic syndrome.<sup>19–21</sup> Intravenous DPT may be undertaken only where paediatric intensive care facilities are available. A 3 day course of the suspected antibiotic should be continued after negative DPTs, to allow elicitation of non-immediate responses and reduce concomitant bacterial resistance.<sup>24</sup> Delayed cutaneous reactions that are mild and last for less than 24 h may not be clinically concerning (with the exception of erythema multiforme and the

suspected serious syndromes listed in figure 1) and may not preclude administration of the same antibiotic should there be sufficient clinical indication.

Although DPTs are the clinical gold standard and are safe among well children, they still have some limitations. For example, DPT results may still have the capacity to produce false-negative results.<sup>34–39</sup> Unlike common food allergens, antibiotic molecules are typically low molecular weight and haptens may be required to facilitate immune activation. There may be many cofactors that facilitate this process; for example, studies investigating food challenges have highlighted that intercurrent illnesses, poor control of comorbid atopic disease and exposure to other drugs may reduce the threshold at which patients demonstrate allergic responses.<sup>48</sup> Necessarily, the majority of children who experience ADRs to antibiotics are unwell when they develop suspected allergic responses. There is currently no evidence investigating what proportion of children passing their DPT may later experience an allergic recurrence at the time of future illness. These factors should not be recreated when preparing for a DPT to test reproducibility as this may compromise safety.<sup>49</sup>

DPT-based protocols also require that only one antibiotic is investigated for several days at a time, increasing the time taken for each investigation. Positive DPT responses will typically require that a second DPT be undertaken during another visit to identify a suitable alternative antibiotic, with consequences for resource allocation.

As we move towards adopting DPT-based diagnosis for children with suspected antibiotic allergy, it is imperative for us to collate high quality data regarding children undergoing DPTs, their conduct and safety. There is also a need to design carefully controlled multicentre follow-up studies to ascertain their long-term validity. Cost-benefit analyses associated with DPT-based challenge regimens are also indicated, given the prevalence of suspected antibiotic allergy and the scarce resources available for allergy services. The safety of DPT-based protocols require robust investigation before it would become appropriate to consider advocating this practice more widely, with the aim to improve accessibility to the appropriate investigation of antibiotic allergy in children.

In the interim, we recommend that suspected non-serious antibiotic allergy should be primarily investigated using DPT-based clinical protocols in tertiary drug allergy centres.

**Contributors** TM and GdT conceived the four premise questions. TM performed the systematic review and drafted the article. ATF and GL provided feedback. All authors designed the pragmatic management recommendations.

**Competing interests** GdT was on the National Institute for Clinical Excellence Guideline Group for "Drug Allergy: diagnosis and management of drug allergy in adults, children and young people" published September 2014. GdT joint led and wrote the Royal College of Paediatrics and Child Health (RCPCH) Care Pathway for Children with Drug Allergies, ADC 2011. GdT currently leads the Paediatric Drug Allergy service which conducts challenges and skin testing at the Children's Allergies Department, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust. GL has received research funding from ALK Abello and sponsorship from Novartis, Sodilac and Nestle.

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