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 β-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. β-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.[1]

A substantial proportion of children develop rashes, urticaria, angio-oedema and respiratory symptoms while unwell, frequently while taking antibiotics.[2] 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.[3] 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.[4] 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 β-lactam antibiotics frequently in the future".[5] 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.[6] 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.[7]

Allergic reactions to antibiotics may be caused by a variety of mechanisms and raise a considerable diagnostic challenge.[8] 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).[9]

Drug provocation tests (DPTs) are recommended as the first-line gold standard investigation among children with mild allergic reactions and rashes to β-lactams.[10] 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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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 Pustolosis
			* Serum Sickness Syndrome
			* Drug-induced dermatoses (eg lupus spectrum)
			# Stevens Johnson Syndrome & # Toxic Epidermal Necrolysis

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).[6]

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

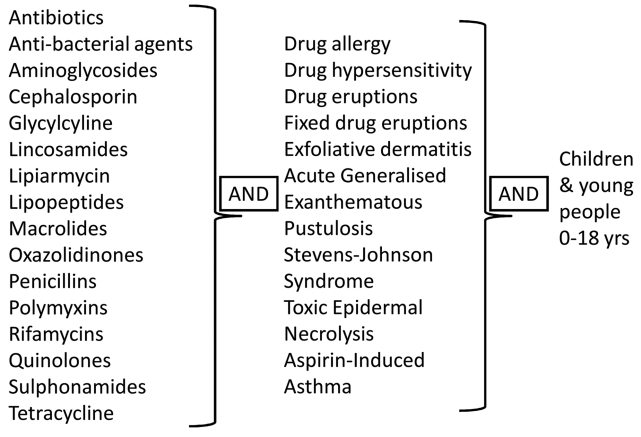

Figure 2 Search strategy.

The Medline search retrieved 865 publications and items were selected in accordance with a selection protocol (figure 3).[11] This required that selected publications investigated only children (≤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.[12–14] 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.[15] The Swedish Medical Products Agency received 5771 reports of

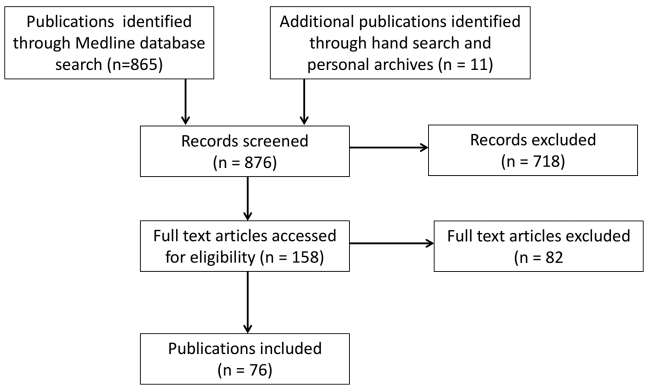

Figure 3 Flow chart of study selection process.

ADRs over 14 years, with 681 (27.2%) of non-vaccine drug doses implicating antibiotics.[16] 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 β-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 (β-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.[17]

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, $p<0.0001$).[18]

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 β-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.[19 20]

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 β-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%. β-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.[21 22] 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.[21] 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 tem 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.[22] 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 β-lactam and clarithromycin are very low at 36% and 33%, respectively.[23 24] 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.[21–24] 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,[25] 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.[8] The two papers conducting ID testing among erythema multiforme and serum

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

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.[24 34–36] One study suggested that food allergy was a risk factor for β-lactam allergy among 161 Portuguese children (p=0.047).[37] Kidon and See[38] 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%).[39] 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.[40] 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.[15 16] The likely prevalence of positive skin testing and DPTs to antibiotics among general paediatric outpatients is around 0.21%,[17] whereas DPT-proven reproducibility among children with suspected antibiotic allergy ranges between 6.3% and 24%.[21 23 24] 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 β-lactam and clarithromycin, respectively.[23 24] 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

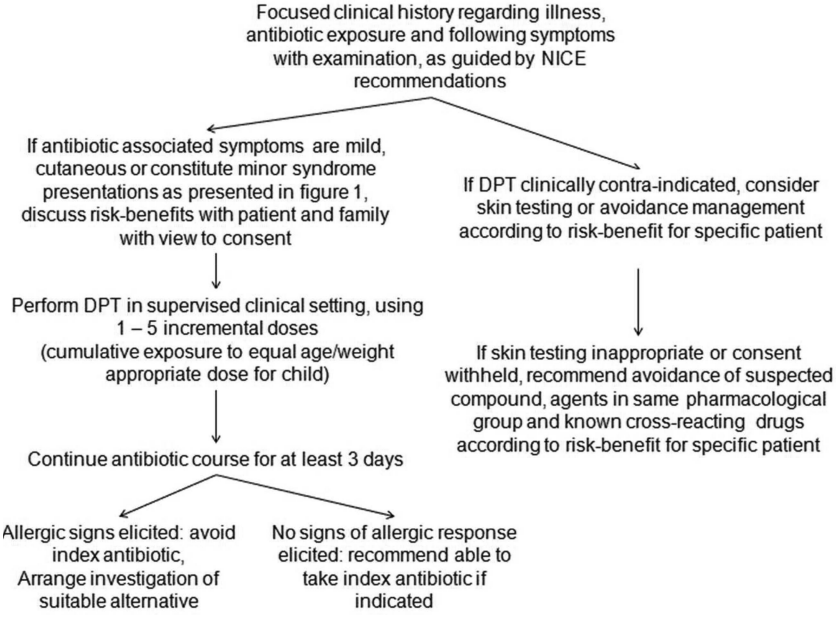

Figure 4 Evidence-led approach to the diagnosis and management of antibiotic allergy in children.

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.[41] This may explain considerable changes in prevalence data detected over time.[41 42] 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.[43–45] 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.[46]

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.[47] 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).[19] The index antibiotic preparation should be used where possible, to best support positive diagnosis of an allergic syndrome.[19–21] 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.[24] 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.[34 39] Unlike common food allergens, antibiotic molecules are typically low molecular weight and haptenisation 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.[48] 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.[49]

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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Table 1. Studies investigating adverse drug reaction prevalence using population-based designs amongst children

First author Year	*Study type Country, language*	*No. of study subjects, age*	*Inclusion criteria*	*Antibiotic DPT protocol*	*Skin testing protocol*	*Results*	*Quality score (of 7)*
Bourgeois, 2009	Retrospective review of National Center for Health Statistics, USA, English	6,445,252 visits over 11 yr period were related to Adverse Reactions to Drugs	Interrogation of A&E and out-patient visit data listing related Adverse Reactions to Drugs	Not undertaken by study authors	Not undertaken by study authors	Mean number of medical visits annually for adverse drug reactions in USA was 585,922. 253,101 (43% (CI 36 – 51%)) of these visits related to children 0 – 4 yrs. Antibiotics were most frequently implicated agents, amongst 28% (CI 22 – 35%), and more commonly amongst younger age group.	3
Kimland, 2005	Retrospective clinical case series from database of records, Sweden, English	5,771, 0 – 16 yrs	Cases of adverse drug reactions reported to Swedish Medical Products Agency	Not undertaken	Not undertaken	385 reports completed per year over 15 years, for 1.7 million Swedish children. Most common symptoms were site reaction (24%), fever (12%) and exanthema (7%). Most common groups of drugs were vaccines (64%) and systemic antibiotics (10%; 149 (6%) Amox, 134 (5%) Cefaclor, 45 (2%) Pen A, 38 (2%) Co-Trimoxazole out of 2501 non-vaccines). 13% of reports required in-patient treatment, or resulted in disability of death (8 fatal (0.14%); none antibiotic related). 61% were 0 – 4 yrs.	3
Orhan, 2008	Retrospective questionnaire Turkey, English	2,855, 6 – 9 yrs	School attending general paediatric population	Not undertaken by study authors	Not undertaken by study authors	81 (3%) of parents reported drug allergy , 48 (59%) of who implicated beta-lactams, 9 (11%) to Co-Trim. 14 (17%) reported multi-system reactions to beta-lactams.	3

Broides, 2010	Retrospective clinical database review, Israel, English	26,665 records (n=11,069 Jewish, 15,586 Bedouin)	Patient records listing beta-lactam allergy	None reported	None reported	344 diagnosed beta-lactam allergic. 226 (2%) were Jewish; 118 (1%) were Bedouin, $p < 0.001$, although no adjustment made for relative prescription or cultural exposures. Boys more common than girls (135 (60%) of Jewish, 81 (69%) Bedouin respectively, $p < 0.01$). Although higher incidence of tonsillitis found amongst Jewish children and greater Amox prescription amongst Bedouin children.	2
Lange, 2008	Retrospective questionnaire Denmark, English	1,447, 0 – 18 yrs	Questionnaire amongst acute and elective paediatric admissions	Not conducted by study authors	Not conducted by study authors	Lifetime prevalence of adverse drug reactions 108 (8%), six of these being severe with three reported anaphylaxis. 61 (4%) reported symptoms consistent with allergic mechanism, and 52 (85%) of these were to antibiotics.	2
Ibia, 2000	Retrospective clinical database review, USA, English	5,923 records reviewed, 0 – 16 yrs	Suspected antibiotic allergy	Not undertaken	Not undertaken	3,996 (68%) received antibiotics, of which 472 (12%) were documented to have a rash whilst being treated. Rashes were recorded in 12% receiving Cefaclor, 7% Pen, 9% Sulfonamides, 3% other Cephs: precise number of patients not given	1
Tan, 2009	Cross-sectional questionnaire study amongst general	4480, 7 – 16yrs	Questionnaire requesting adverse drug reaction history	Not undertaken by study authors	Not undertaken by study authors	5% of children reported adverse responses to drugs, 57% of whom specified beta-lactams. Multiple drug adverse reactions reported by 4%. Only 7% were referred for further	1

	population, Singapore, English					investigations.	
Oshikoya2007	Retrospective clinical case series from medical records & prospective investigation of clinical adverse drug reactions, Nigeria, English	3,139 records assessed retrospectively, 682 admitted prospectively. 44 children identified, 0 -12 yrs	Suspected adverse drug reactions	Not undertaken	Not undertaken	14 (32%) demonstrated EM, two fixed drug eruption, two SJS and one anaphylaxis (2%; to Ceftriaxone)	1
Le, 2006	Retrospective clinical case series, USA, English	1,087, upper age limit not reported	Adverse drug reactions reported within paediatric department	Not undertaken	Not undertaken	371 (40.4%) of 919 adverse drug reaction subjects were under 5 yrs of age. Low severity of adverse drug reactions predominated (89%), resulting mostly from antibiotics. Adverse drug reactions occurring in theatre or presenting to A&E were more severe, and more frequently involved anti-convulsant/neoplastic agents	1
Kidon, 2004	Retrospective case control study from medical records database, Singapore, English	222 with adverse drug reaction cases, 0 – 17 yrs, 450 control children admitted	Adverse drug reaction reported in medical records	Not undertaken	Not undertaken	151 (68%) attributed to antibiotics (100 (45%) being beta-lactams). Multiple regression analysis comparing clinical characteristic of all drug reactions (including non-antibiotics) found that having asthma and other chronic diseases significantly raised the risk of developing an adverse responses whilst being treated.	1

Padilla Serrato, 2006	Questionnaire amongst asthmatic children, Mexico, Spanish	90 children	Evaluated children on asthma summer camp for adverse drug reactions	Not undertaken	Not undertaken	Eight (9%) had history of reacting to drugs: four (4%) to Pen, one (1%) to Trimethoprim-Sulphomethaxazole	0

Table 2. Studies investigating suspected immediate and non-immediate non-serious antibiotic allergic children

First author Year	*Study type Country, language*	*No. of study subjects, age*	*Inclusion criteria*	*Antibiotic DPT protocol*	*Skin / sensitisation testing protocol*	*Results*	*Quality score (out of 7)*
Rubio, 2012	Retrospective clinical case series, comparing children to adults with proven drug allergy, France, English	3,275 total, including subset of 658 children aged 0 – 18 yrs	Suspected drug allergy	Single blinded incremental dosing DPTs conducted with index drug, when skin testing negative, no report of FU courses for antibiotics	SPT & ID testing in line with European guidance.	The prevalence of +ve tests was 10.6% (CI 8.3 – 13.0) for children, and significantly different to prevalence amongst adults of 16.5% (CI 15.2 – 17.8) ($p<0.0001$). Amongst sub-types of index reactions, this was mainly observed amongst beta-lactams, and the difference was significant for maculopapular rashes, but not urticaria/angioedema, nor anaphylaxis. 31 (9.6%) of beta-lactam histories amongst children were associated with +ve investigations	5
Rebelo-Gomes, 2008	Prospectively introduced clinical protocol, Portugal, English	1,426 completed survey 0 – 16 yrs N=67 suspected drug allergy, 0 – 16 yrs	Questionnaire amongst families attending paediatric out-patient clinic. Suspected drug allergy identified then investigated	Incremental DPT, without FU course stipulated for antibiotics. All underwent DPT, however to alternative drug where +ve skin test elicited.	Skin testing amongst all suspected antibiotic allergy: SPT & ID to PPL, MDM, Amox, Pen G, Cephs, Co-Trimoxazole. Serum sIgE to beta-lactams	From questionnaire, 143 (10%) reported adverse responses to drugs, with 67 (6%) parents reporting an allergy. 37 (3%) already had a diagnosis of drug allergy. 60 attended for further review, of whom 34 were suitable for investigation and underwent DPT. Index reactions were to antibiotics in 25 (74%): Amox in 5, Co-Amox in 6, Cephs 3, Co-Trimoxazole in 3, Macrolide in 3, more than one beta-lactam 4, beta-lactam + other drug in 1. One (4%) skin	5

						test of the 25 potential antibiotic allergies was +ve to Ceftriaxone, so this case underwent DPT to Amox, and passed. Two (8%) DPTs were positive to index antibiotics (Amox & Co-Trimoxazole) in different cases.	
Hershkovich, 2009	Prospectively introduced clinical protocol, with FU repeat testing 1 – 5 months later amongst participants with negative tests from first visit, Israel, English	166, 0 – 16 yrs	Suspected beta lactam allergy, excluding anaphylaxis and non-IgE syndromes	If skin testing negative after first or FU visit, one single oral dose of index antibiotic given, with 1 hr monitoring and phone call 72 hrs later. FU repeat investigation 1 – 5 months after first visit: DPT repeated	SPT & ID: PPL, BP, MDM, MDM of Amp & Cloxacillin, (+ Cefuroxime & Cefamezin if indicated). FU repeat investigation 1 – 5 months after first visit: SPT & ID to index antibiotic	150 children had suspected reaction to Pen, Amox or Co-Amox, and 16 to Cephs. Four participants demonstrated +ve skin testing, six demonstrated +ve DPT; 10 diagnosed beta lactam allergic and not investigated further. 98 of the remaining 156 completed second round FU assessment, with one demonstrating +ve skin test to Pen, and another developing a maculopapular rash 30 minutes after FU DPT single dose. A subsequent questionnaire completed by 71 participants showed that 59 (83%) had received beta-lactams, and one developed a rash after Amox. Therefore, 3% re-sensitisation rate after negative investigation	5
Ponvert, 2011 *	Retrospective clinical case series, France, English	1,865, 0 – 18 yrs	Suspected beta-lactam allergy	Incremental DPTs undertaken if no history of SSS, SJS or TEN. If skin testing +ve, DPT	SPT & ID: Amox, Amp, Aztreonam, BP, Cefadroxil, Cefazolin, Cefixime, Cefotaxime,	1431 (77%%) completed investigations. 227 (16%) were diagnosed allergic to beta-lactams: 50 (31%) of the 162 reporting immediate reactions, and in 177 (17%) of the 1087 reporting non-immediate	4

				undertaken to alternative. Incremental DPT of index antibiotic administered, with FU course for 3 – 10 days.	Ceftazidime, Ceftriaxone, Cefuroxime, Cephaloridin, Cephalotin, Cephamandole, Imipenem, Oxacillin, Pen A, Piperacillin & Ticarcillin	reactions. Skin testing diagnosed 76% and 15% of immediate and non-immediate reactions respectively.	
Herve, 1998	Prospectively introduced clinical protocol France, French	112, 0 – 15 yrs	Suspected Amox allergy	If skin testing negative, incremental Amox DPT up to therapeutic dose, without further course, and FU phone call 4 days later	SPT & ID: PPL, MDM, Amox, Co-Amox Serum RAST, ELISA, Farr and histamine release testing to Pen	Of 112, 39 (35%) demonstrated +ve skin testing, 6 (5%) +ve serological testing. 52 (78%) of 67 participants completed DPT, with 6 of these (12%) demonstrating +ve reaction consisting of self-limiting rash.	4
Caubet, 2011	Prospectively introduced clinical protocol with consecutive recruitment of suspected cases from A&E, Switzerland, English	88, 0 – 16 yrs	Suspected beta-lactam allergy, excluding clinically diagnostic viral-induced rash, SJS, DRESS & anaphylaxis	All participants underwent oral DPT with therapeutic drug, in split doses initially if skin test positive, and continued for 48 hours	SPT and ID to PPL, MDM, Amox + the relevant Ceph if implicated in history. Serum sIgE to Pen G, Pen V & Amox.	History of rash starting average of 3.8 days after first dose index reaction. 11 (13%) of 88 patients tested demonstrated +ve ID tests. All had sIgE <0.35. 6 (6.8%) demonstrated positive oral DPT with rash (one at 30 minutes, five ranging between 7 – 12 hours after first dose). Only four of the six reacting on DPT had positive ID tests: Sensitivity for ID testing 66.7%, specificity 91.5%. (Amongst patients with urticaria: sensitivity 75% & specificity 92%; amongst delayed maculopapular rash: sensitivity 50% & specificity 87%)	4

Atanaskovic-Markovic 2012 *	Prospectively introduced clinical protocol, Serbia, English	279 completed investigation; 2 – 14 yrs	Suspected multiple drug allergy	Single day DPT, if skin testing negative	SPT and ID to PPL, MDM, BP & Amox	179 reported reactions to more than one class of antibiotic, 245 reported reactions to beta-lactams, and 167 to non beta-lactam antibiotics. 606 reactions reported, 80 of which immediate symptoms. 15 demonstrated SPT positivity, and a different 2 demonstrated DPT positivity to only one antibiotic and were negative on DPT to other drug. 7 demonstrated +ve investigations to two drug groups, however five involved one antibiotic and one non-antibiotic combinations, and the only participant reacting to two antibiotics demonstrated delayed reactions to BP and Co-trimoxazole	4
Mori, 2010	Retrospective clinical case series, Italy, English	64, 1-17yrs	Suspected Clarithr allergy	Incremental single blinded DPT to Clarithr, with 5 day FU course, amongst all cases. Delayed DPT responses were investigated with double-blind DPT protocol	SPT & ID to Clarithr	All SPTs were negative, however nine (14%) participants demonstrated +ve responses to ID testing. All participants also completed the DPT, with four (6%) demonstrating +ve responses (urticaria / angioedema within 20 minutes for two, and delayed maculopapular rashes after 3 days in two further participants, which was confirmed as per double-blind protocol). Clarithr ID testing demonstrated 75% sensitivity and 90% specificity	4

Atanaskovic-Markovic 2005 *	Retrospective clinical case series, Yugoslavia, English	1170, 0 - 14 yrs	Suspected Pen & / or Ceph immediate allergy	SBPC DPT performed if skin testing negative, single day exposure	SPT & ID: PPL, MDM, BP, Pen A, Amox, Amp, Cefalexin, Cefaclor, ceftriaxone & Cefotaxime. Serum sIgE to penicilloyl G, penicilloyl V, amoxicilloyl, ampicilloyl > 0.35kU/l +ve.	252 (42%) of children reacting to skin / DPT demonstrated positive sIgE to at least one agent. Skin and DPT positivity conflated into one category throughout study design – cannot distinguish utility of either investigation. All sIgE positive subjects demonstrated skin or DPT positivity.	3
Jost, 2006	Retrospective clinical case series 1979 – 1992, with prospectively introduced clinical protocol for consecutive referrals 1993 – 2003, USA, English	359 prospective referrals, 0 – 18 yrs 562, retrospective cases, ages unreported	Suspected beta-lactam allergy	Not undertaken	SPT & ID: Major determinant benzylpenicilloyl polylysine, Pen G, sodium penicilloate (Pen A) Switch of benzylpenicilloyl polylysine manufacturer in 2001	23 (6%) of 359 prospective participants demonstrated +ve skin testing, with 22 in 1993 and 1 in 2002. 154 (27%) of retrospective case series demonstrated +ve skin testing, with decreasing trend from 1979 until all testing negative from 1994.	3
Ponvert, 1999 *	Retrospective clinical case series France, English	325, 0 – 18 yrs	Suspected beta-lactam allergy	Incremental DPTs undertaken if no history of SSS, SJS or TEN. If skin testing +ve, DPT undertaken to alternative. Incremental DPT of index antibiotic	SPT & ID: Amox, Amp, BP, Cefazolin, Cefotaxime, Ceftazidime, Ceftriaxone, Cephaloridin, Cephalotin, Cephamandole, Oxacillin & Ticarcillin	24 (7%) demonstrated +ve ID tests, & 15 (5%) +ve DPTs. The likelihood of beta-lactam allergy was significantly higher for anaphylaxis (42.9% versus 8.3% in other reactions) and immediate reactions (25% versus 10% in accelerated and delayed reactions). 68 (21%) were diagnosed as beta-lactam allergic, with 39 (12%) through skin and DPT investigations, and	3

				administered, with FU course for 5 – 7 days.		29 (9%) due to SSS and toxidermia history. 8 (12%) were sensitized to several classes of beta-lactams: the proportion being higher amongst children with anaphylaxis (26.7% versus 7.5% of other reactions) and in children reporting immediate reactions (33.3% versus 8.5% of delayed reactions).	
Chandra, 1980	Prospective cross-sectional study, New Zealand, English	300 with suspected penicillin, "children" - age not reported	Suspected beta-lactam allergy	DPT undertaken in selected subset of 56 skin test negative participants, but procedure not reported	Benzylpenicilloyl-polylysine, MDM (sodium benzylpen G, sodium D-benzylpenicilloate). RAST to benzylpenicilloyl and phenoxymethyl penicilloyl	48 (16%) of 300 suspected penicillin allergic children demonstrated positive skin tests, and five of these received penicillin on a subsequent occasion and developed acute urticaria. Out of 56 undergoing DPT, two developed "slight erythematous, non-itchy rash". 42 of the children who demonstrated positive skin tests were investigated one year later, and 14 showed negative responses on both skin testing and DPT. Trend towards quicker trigger time and faster progression to investigation being related to higher likelihood of positive skin tests, although no P-trend given.	3
Graff-Lonnevig, 1988	Prospectively introduced clinical protocol, Sweden, English	298, 0 – 15 yrs	Suspected beta-lactam allergy	Course of oral Pen V twice daily for 10 days, at least first dose supervised.	SPT using BP & Pen V. No ID testing undertaken. Serum RAST to Pen	30 (10%) of 297 undertaking DPT demonstrated a reaction, however 22 of these after day 6. Further questionnaire administered to 222 children 1 – 4 yrs after DPT received replies	3

					metabolites, penicilloyl V and G amongst 277 children	indicating that 110 (50%) had received Penicillin and 7 of these demonstrated rash after at least 6 days of treatment. One child received Penicillin after a positive DPT, and demonstrated no adverse effects. 3 subjects showed borderline RAST results. 14(11%) of children with index urticaria reactions and 15 (42%) of angioedema or joint swelling reactions demonstrated +ve DPT, whereas none of those after index exanthematous reaction.	
Ponvert, 2007 *	Retrospective questionnaire France, English	256 parents invited	Negative skin and DPT testing to beta-lactams	Incremental DPTs undertaken if no history of SSS, SJS or TEN. If skin testing +ve, DPT undertaken to alternative. Incremental DPT of index antibiotic administered, with FU course for 5 – 7 days.	SPT & ID: BP, Amox, Amp, Cefazolin & Ceftriaxone	141 (55%) questionnaires returned. 93 (66%) of these had been treated with beta-lactam antibiotics, and 7 (8%) reported allergic reactions. Of the six of these attending for investigations, one was diagnosed with delayed rash reaction after Co-Amox challenge and also Cefaclor SSS, after two adverse responses since previously negative skin testing. If non-attender was also allergic, authors report maximum of 2% subsequent reaction to any beta-lactams after preceding skin test and DPTs were negative.	3
Pichichero 1998	Retrospective clinical case series, USA,	247, 0 – 18 yrs	Paediatrician suspected beta-lactam allergy	If skin test negative, single dose oral Pen	SPT & ID: PPL, BP, MDM, Amp, Cefazolin	53 (22%) of initial skin tests were +ve, with 5 (2%) of DPTs +ve, leading to 58 (23%) being	3

	English			challenge, with 5 – 10 day FU course of *index* antibiotic	& Ceftriaxone (panel not completed in all subjects) Skin testing repeated 4 weeks after DPT	diagnosed allergic. Of the 189 with negative skin tests, 26 (14%) then demonstrated +ve skin test one month later, and were also recommended to avoid Pen. 163 participants with negative skin tests and DPTs later received any beta-lactam treatment, and three (2%) demonstrated mild reactions	
Martin-Munoz, 1999	Retrospective clinical case series, Spain, English	239, children	Referred for evaluation of drug allergy, excluding anaphylaxis, SJS, Severe systemic reactions / illness	Where skin testing negative, DPT undertaken. Protocol not accessible	Protocol not accessible	Reactions attributed to beta-lactam antibiotics in 50% & Sulphonamides in 9%. DPT undertaken when skin testing negative demonstrated 4% reactions	3
Minguez, 1998	Retrospective clinical case series, Spain, English	219, children – age not reported	Suspected beta-lactam allergy	Oral or intramuscular incremental DPT, without FU course, only if non-serious index reported	SPT: Pen G, PPL, Amox, Amp, IV preparation of Co-Amox. ID and patch test to above agents only if delayed index response. CAP undertaken, not specified	20 (9%) of 219 referrals were diagnosed as beta-lactam allergic (11 by SPT, 1 by sIgE, 2 by DPT and 6 owing to serious index reaction, 2 of which on more than one occasion). All 3 children undergoing ID and patch testing gave negative results	3
Chambel, 2010	Prospectively introduced clinical protocol, Portugal, Spanish	161, 0 – 14 yrs	Suspected beta-lactam allergy	DPT to either index antibiotic, or an alternative where skin tests +ve or if parents wished. Incremental	47 children underwent skin testing by choice: SPT & ID: PPL, MDM, Pen, Amox, Co-Amox & Cefuroxime. 106 underwent	33 (21%) reported immediate index reaction. 11 (13%) of children demonstrated a +ve DPT to index beta-lactam when skin testing not performed, and 1 (3%) +ve DPT to index where index skin testing negative. 47 children underwent optional skin testing, which was +ve to ID	3

				dosing, with 5 day FU course at home.	serum sIgE to Amox, Pen G & Pen V	in 8 (17%) cases (two of whom were also sIgE +ve). Having a +ve DPT to either index or alternative antibiotic was associated with food allergy	
Bierman, 1969	Retrospective clinic case series, USA, English	160, 0 – 14 yrs	Inpatient, with physician diagnosis of penicillin allergy	Penicillin re-administered where tests negative and treatment still clinically warranted whilst admitted.	BP & PPL SPT. ID with patient's own serum, then either BP or PPL.	17 (11%) +ve skin tests, and three acute, four intermediate (2 – 48hrs) and 10 late reactions demonstrated after continued penicillin administration. DPT reactions included coughing, laryngeal oedema and hypotension when DPTs undertaken at the time of acute illness. Overall, 34 (21%) demonstrated +ve signs.	3
Romano, 2008	Retrospective clinical case series, Italy, English	148, 2 – 14yrs	Suspected allergy to Cephs	Incremental oral or intramuscular DPT to index Ceph in one day for immediate index reactions, and weekly doses for non-immediate reactions. FU courses for one week amongst immediate index reactors with negative skin test & DPT	SPT & ID: PPL, MDM, BP & Cephs - manufacturer swap in 2005 Patch and serum sIgE CAP to penicilloyl G & V, ampicilloyl, amoxicilloyl and Cefaclor amongst 43 children with immediate index reactions (cut-off > 0.35kU/l)	43 (29%) reported immediate reactions (anaphylaxis, urticaria, angioedema & rash) and 34 demonstrated +ve skin test. 105 (71%) had non-immediate reactions (urticaria & EM predominated) one of whom had +ve ID test, but all had negative patch and delayed skin test reading results.	3
Cetinkaya, 2004	Prospectively	147, 6 – 14 yrs	Children admitted to hospital with	Not undertaken	SPT & ID to PPL & MDM	SPT demonstrated one positive response to PPL, and ID	3

	introduced clinical protocol, Turkey, English		upper respiratory tract infection who had tolerated three beta-lactam courses		(including BP)	demonstrated 11 PPL responses and three MDM responses: 15 children demonstrated at least one positive skin test. One participant demonstrated a mild systemic reaction after PPL ID testing and received adrenaline and antihistamine injections.	
Mori, 2014	Retrospective clinical case series, Italy, English	136 children	Suspected Macrolide allergy	DPTs undertaken but protocol not reported, nor amongst how many participants	SPT & ID: ENDA protocol referenced, but no protocol details reported	Only 66 participants completed investigations, 3 (5%) demonstrated positive SPT (in two) and ID testing (in one). One participant had history of anaphylaxis to both Azithr & Clarithr, suggesting co-reactivity	3
Atanaskovic-Markovic, 2009 *	Prospectively introduced clinical protocol, Serbia, English	124, 3 – 14 yrs	Suspected beta-lactam allergy with +ve skin tests	Single day Imipenem-cilastatin intramuscular or intravenous incremental challenge amongst children with negative skin testing to Imipenem-cilastatin	SPT and ID to PPL, MDM, BP, Amp, Amox & Meropenem	1 of 124 (1%) reacted to ID Imipenem/Cilastatin (a 5yr boy with 6mm wheal). None of 123 participants undergoing intramuscular or intravenous challenge to Imipenem/Cilastatin demonstrated clinical reaction.	3
Atanaskovic-Markovic, 2008 *	Prospectively introduced clinical protocol, Serbia, English	108, 3 – 14 yrs (beta-lactam cases) compared to 20 healthy children	Suspected beta-lactam allergy with +ve skin tests	Single day Meropenem DPT amongst children with negative skin testing to Meropenem	SPT and ID to PPL, MDM, BP, Amp, Amox & Meropenem. Serum sIgE to penicilloyl G, penicilloyl V, amoxicilloyl, ampicilloyl >	1 of 108 (1%) beta-lactam cases demonstrated positive (5mm) ID Meropenem, whereas no beta-lactam cases reacted to SPT Meropenem. All 107 beta-lactam cases undergoing Meropenem DPT were negative. No controls reacted to Meropenem ID, however none	3

					0.35kU/l +ve.	underwent DPT either. 14 of 108 cases +ve to PenG and/or PenV sIgE	
Kavadas, 2013	Retrospective clinical case series, Canada, English	42, 0 – 18 yrs	Suspected beta lactam allergy, excluding anaphylaxis, SSS, SJS, TEN and participants who had alternative suitable antibiotic choices	Index antibiotic given (oral or intravenous), if skin testing negative in all but one case. Further protocol not reported.	SPT & ID: Amino, Azithr, Cotrimoxazole, Cefazolin, Ceftriaxon, Cefuroxime, Clindamycin, Cefazolin, Ceftazidime, Cotrimoxazole, Erythromycin, Levofloxacin, Vanc	One SPT was +ve, 11 demonstrated positive skin testing results (6 Cotrimoxazole, 1 Erythromycin, 1 Vanc, 1 Ceftriaxone, 2 Azithr). Some participants undertook more than one challenge, and 3 of 42 DPTs were +ve. One ID +ve participant underwent DPT, because index reaction involved hypotension	3
Ahmed, 2012	Retrospective clinical case series, with further record examination for later prescription of Cephs USA, English	173, 0 - 18 yrs	Suspected beta-lactam allergy and subsequent course of Cephs	None conducted, rather medical records inspected for subsequent administration of Cephs	Benzylpenicilloyl polylysine, penicillin G potassium, penicilloate & Amox	21 (12%) demonstrated positive skin testing, none of whom demonstrated signs on later Cephs exposure. One 4 year old boy with history of delayed rash with amoxicillin developed angioedema 5 days after oral Cephalexin.	2
Rosh, 1968	Case control study, USA, English	172, 0 – 16yrs	73 cases with suspected Pen allergy, 99 controls without	DPT as open course of Pen, Methicillin or Oxacillin amongst 10 subjects	ID: BP/Pen G, PPL-12, PPL-12C. Serum haemagglutination with BP	6 (8%) of cases demonstrated +ve IDs, 5 of whom also had +ve serum response to BP. One of these underwent DPT, and reacted to Pen with urticaria. Two cases without +ve skin tests passed Pen DPTs. 6 (6%) of controls demonstrated +ve ID tests to PPLs.	2
Kamada, 1991	Prospectively introduced clinical	120 children	Suspected multiple antibiotic allergy	Not undertaken	Pen G (benzyl penicilloyl polylysine),	31 (21%) of the participants demonstrated +ve skin testing	2

	protocol, USA, English				MDM, beta lactam analogue		
Birkebaek, 1992	Retrospective clinic case series, Denmark, Danish	109, 0-16 yrs	Suspected penicillin allergy	DPT to penicillin, if skin and sIgE tests negative	Skin testing not undertaken in substantial proportion. Serum sIgE Pen	107 children underwent Pen DPT and only one (1%) demonstrated urticaria five hours after dose. Two were +ve for sIgE Pen.	2
Kamboj, 2010	Retrospective clinical case series, USA, English	96 children	Suspected antibiotic allergy	Protocol inaccessible	Protocol inaccessible	4 (4%) demonstrated +ve skin testing, and 4 (4%) +ve DPTs. 87 (91%) tolerated skin testing and DPT	2
Perez-Rodriguez, 2006	Retrospective clinical case series, Spain, English	91, 4 – 16 yrs	Suspected beta-lactam allergy	DPT if skin testing negative, protocol not reported	SPT (& ID if > 12 yrs): Major and minor determinants, Pen G, index antibiotic	Skin and DPT investigations were repeated after 15 days. Only one "positive result" reported, without detailing whether through skin or DPT, or whether repeated 15 days later	2
Mori, 2012	Prospectively introduced clinical protocol, Italy, English	89, 2 – 9 yrs	Suspected Co-Amox allergy	Single blinded incremental oral DPT to Co-Amox, Sodium Benzoate (excipient) and placebo, in randomized order, and continued for 5 day FU course. Delayed DPT responses were investigated with double-blind DPT protocol	SPT & ID: beta-lactam reagents – individual preparations not reported	Eight (9%) demonstrated +ve DPT to Co-Amox, but negative to Sodium Benzoate. 10 (11%) +ve to Sodium Benzoate but negative to Co-Amox, and three (3%) were +ve to both Co-Amox and Sodium Benzoate DPTs. No participants reacted to placebo DPT. 10 (11%) of participants had idiopathic urticaria, two of whom reacted to both Co-Amox and Sodium Benzoate on DPT. 10 (91%) of 11 participants with delayed DPT responses were confirmed on double-blind DPT.	2
Huang, 1998	Prospectively introduced	86, 0 – 6 yrs	Suspected antibiotic allergy	Single dose DPT to index	SPT & ID: benzylpenicillo	One (1%) participant demonstrated +ve skin test, and	2

	clinical protocol, USA, English			antibiotic without FU course amongst skin test negative participants - and then further single dose DPT when child next became unwell	yl polylysine, Penicilloic acid & Pen G Serum RAST to penicilloyl G & V amongst 52 participants	none of remaining 85 participants developed +ve DPT to index antibiotic whilst well. 65 participants became unwell in the following two years and chose to receive the same antibiotic using either the same (n=3) preparation or dye-free (n=62), eight (12%) of the latter whom demonstrated a mild rash, which did not preclude completion of course	
Romano, 1997	Retrospective clinical case series, Italy, English	82, 3 – 12 yrs	Suspected beta-lactam allergy	Incremental doses of either oral Amox or Amp at weekly intervals, no FU course, if skin testing negative & index reaction occurred < 1yr ago	SPT & ID: PPL, MDM, Pen G, Amp. Serum RAST to Pen G, Pen C, Amp & Amox	Four (5%) were +ve to skin tests (two to index allergen, one to Pen G, one to PPL & Pen C: SPT and ID not reported, although one of these was +ve RAST to Pen G & V). 11 children with immediate reaction histories and 38 with delayed morbilliform rashes underwent DPT, and all were negative.	2
Moral, 2011	Prospectively introduced clinical protocol, Spain, English	78, 0 – 14 yrs	Suspected beta-lactam allergy	Oral incremental DPT if no sensitisation detected	SPT & ID amongst higher risk index reactions: PPL, MDM, Pen and index antibiotic Serum sIgE to Pen G, Amox	56 (72%) were termed low risk, and 50 of these proceeded directly to DPT with only one (2%) demonstrating mild delayed rash (not urticaria) twice after repeated DPT. None of the 17 children undergoing skin testing prior to DPT demonstrated +ve results on either skin or DPT testing.	2
Langley, 2002	Retrospective clinical case series, Canada,	74, mean age 7.4yrs	Suspected beta-lactam allergy	For skin test negative participants, a single dose of	SPT & ID: benzylpenicilloyl-polylysin, Pen G,	No SPT were +ve, 3 (4%) demonstrated +ve ID response and no reactions were observed amongst 69 who proceeded to	2

	English			index beta lactam administered orally and monitored for one hour		DPT.	
Seitz, 2012	Retrospective clinical case series, Germany, English	43, 5 – 16 yrs	Suspected drug allergy	Incremental dosage to index drug, no report of FU courses for antibiotics.	SPT & ID: reagents not reported. Serum sIgE BPO, phenoxymethyl penicilloyl, amoxicilloyl & ampicilloyl	24 (56%) reported immediate reactions, 10 due to beta-lactams and 8 due to macrolides: none of these 18 reacted to either skin tests or DPT. 19 (44%) reported non-immediate reactions, 12 due to beta-lactams, 6 due to macrolides and 1 to Clindamyin: and one of these demonstrated delayed skin test +ve response for Amox & Amp	2
Navarro, 1985	Retrospective clinical case series, Spain, English	16, 2 – 9 yrs	Adverse reaction to intravenous Pen G	DPT protocol inaccessible	SPT & ID: Major determinant & MDM	Eight participants demonstrated a +ve response to either skin testing or DPT.	2
Berroa, 2013	Retrospective clinic case series, Spain, English	14, 0 – 14 yrs	Suspected beta-lactam non-immediate allergy	Where skin testing negative, DPT to original oral beta-lactam preparation for one week	PPL, MDM, BP & Amox. Serum sIgE to Pen and Amox.	All skin testing was negative, and 7 (50%) demonstrated maculopapular rash on DPT	2
Novembre, 2009	Retrospective clinical case series, Italy, English	13, 3 – 14 yrs	Referral with suspected anaphylaxis to beta lactams	DPT in accordance with guidance, protocol not reported	SPT & ID: PPL, MDM, Amox, Cefaclor. Serum sIgE to penicilloyl G, Penicilloyl V, Ampicilloyl &	13 (5%) reported anaphylactic reactions (8 to Cefaclor, 2 to Ceftriaxone, 2 to Amox, 1 to BP). The eight Cefaclor anaphylaxis participants all demonstrated +ve responses to Cefaclor on skin testing. Two had Cefaclor +ve sIgE. One of	2

					Cefaclor	these eight demonstrated +ve skin testing to Amox also, however all of the remaining seven tolerated Amox DPT.	
Tortajada, 2008	Retrospective clinical case series, Spain, English	10, 4 – 12 yrs	History of reaction to Co-Amox	DPT to Co-Amox & Clavulanic Acid:	Penicilloyl G & V, Amox, Amp & Cefaclor. Serum sIgE to Penicilloyl G & V, Amox, Amp & Cefaclor	Each of these were positive to both Co-Amox and Clavulanic Acid alone on DPT	2
Schauf, 1985	Questionnaire 2 years after RCT of neonatal Pen G injection intervention to prevent Group B Streptococcal sepsis, USA, English	420 parents of neonatal RCT participants interviewed over the phone	200 neonates were Pen G recipients, and 220 placebo	Not undertaken	Serum RAST IgG (n=107) and IgE (n=6) to major Benzyl Penicilloyl	220 (52%) received a beta-lactam < 2 yrs of age, 109 amongst neonatal pen recipients and 111 amongst placebo. 10 (9%) of 109 neonatal Pen recipients versus 12 (11%) of 111 placebo recipients reported possible beta-lactam allergy: no association between neonatal Pen injection & either suspected allergy or RAST results.	1
Balaban, 2002	Retrospective clinic case series, Bosnia Herzogovinia, English	132, 0 - 16 yrs	Physician diagnosed urticaria	Not undertaken	Not undertaken	17 (13%) took antibiotics and 6 (5%) took antibiotics & antipyretics directly before urticaria developed.	1
Lesniak, 2013	Retrospective clinical case series, Poland, Polish	846, 0 – 18 yrs	Clinical presentations of adverse drug reactions	Not undertaken	Not undertaken	19% of cases were attributed to antibiotics. 402 (48%) cases presented as rashes alone, although 44 (5%) diagnosed as anaphylaxis, 46 (5%) non-immune anaphylaxis and one (0%) as SJS.	1
Picard, 2012	Telephone questionnaire	200 parents	Parents of children with negative Pen	Not undertaken during this	Not undertaken during this	170 (85%) of parents answered questions: 130 (76%) had	1

	Canada, English		skin test & DPT	study	study	received antibiotics since investigations, 59 (45%) had received Pen A, 24 (18%) had refused Pen A because they feared adverse response.	
Khoo, 2000	Retrospective clinical case series, Singapore, English	111, 0 – 12 yrs	Fixed drug eruption	Not undertaken	Not undertaken	Suspected drug was Aminopenicillin in 59%, Co-Trimoxazole in 19%.	1
Miller, 2011	Retrospective questionnaire USA, English	100, 0 – 18 yrs	Parental reported antibiotic allergy	Not undertaken	Not undertaken	Possible immune-related reaction described in 58%, non-immune-related reaction described in 27%	1
Anibarro, 1992	Retrospective clinical case series, Spain, Spanish	72, 0 - 18 yrs	Suspected drug allergy	None conducted	None conducted	29 (40%) had history of immediate reactions, and Sulphonamide fixed drug reactions was most common non-immediate allergy	1
Morelli, 1999	Retrospective clinical case series, USA, English	35, 1 – 16 yrs	Physician diagnosed fixed drug eruption	For selection of cases, repeat administration of Trimethoprim-Methoxazole. Full protocol not described.	Not undertaken	18 (51%) were attributed to Trimethoprim-Sulfamethoxazole, 4 (11%) to Sulphonamide alone, 1 (3%) to Amp, 1 (3%) to Amox & 1 (3%) to Erythromycin. 19 (54%) had recurrence of FDE. 5 children underwent re-challenge with Trimethoprim-Sulphamethoxazole, and demonstrated a reaction.	1
Mattheij, 2012	Prospectively introduced clinical protocol, Netherlands, English	33, 0 – 16 yrs	Suspected antibiotic allergy	Open oral DPT undertaken to index antibiotic, not reported if FU course	Not undertaken	4 (12%) of 33 demonstrated positive response by mild skin reactions on DPT.	1

Park, 2000	Retrospective clinical case series from allergy department referrals, Canada, English	97, 0 – 13 yrs	Suspected multiple antibiotic allergy	Not undertaken	Not undertaken	Suspected multiple antibiotic allergy constituted 11% of all referrals to drug allergy service. 83 (86%) reacted to a Pen derivative, 78 (80%) to Sulphonamide, 69 (71%) to a Cephs, 34 (35%) to Macrolides	0
Khaled, 2012	Retrospective clinical case series, Tunisia, English	90, 0 – 16 yrs	Diagnosed with cutaneous eruption whilst receiving drugs	Not undertaken	Not undertaken	52 (58%) presented with maculopapular rash, 15 (17%) urticaria, 13 (14%) fixed drug eruption, 2 (2%) EM. 50 (56%) were attributed to antibiotics	0
Strannegard, 1987	Case control study, Sweden, English	30 cases, 4 – 12 yrs with Rheumatic Fever, & 29 controls with acute PSGN	18 received mean 1.8 yrs of Pen G depot injections for bacterial prophylaxis	Not undertaken	Serum RAST IgE to Penicilloyl determinant	Two (11%) of Pen G recipients demonstrated raised IgE to Pen G & V, without their demonstrating adverse reactions to depot Pen injections.	0
Wills, 1998	Retrospective clinical case series, Australia, English	53 children	Children with Cystic Fibrosis	Not undertaken	Not undertaken	18 (34%) had experienced a suspected reaction, with intravenous antibiotics producing more suspected reactions than oral, in that 9.5% of intravenous antibiotic courses produced adverse effects	0
Rallis, 2006	Retrospective clinical case series, Ireland, English	47, 0 – 15 yrs	ENT patients with cutaneous adverse drug reactions	Not undertaken	Not undertaken	Urticaria, maculopapular rash, fixed drug eruption and EM were most common reactions. Drugs included Co-Amox, Cephs, Clarithr, Clindamycin & Erythromycin	0
Adegbidi, 2012	Retrospective clinical case	35, 0 – 16 yrs	Suspected drug induced rash	Not conducted	Not conducted	21 patients (60%) were advised to avoid particular drug: 14 of	0

	series, Benin, French	the 21 were antibiotic (11 Sulphonamides, 2 Penicillin, 1 Ceftriaxone). Clinical patterns: fixed drug eruption 16/35 (46%), maculopapular rash 6/35 (17%), SJS 6/35 (17%), urticaria 3/35 (9%), TENS 1/35 (3%)

Abbreviations: ALTE – Acute Life Threatening Event, Amino – Aminoglycoside, Amox – Amoxicillin, Amp – Ampicillin, aOR – adjusted Odds Ratio, Azithr – Azithromycin, BP – Benzyl Penicillin, Cephs – Cephalosporins, Clarithr – Clarithromycin, Co-Amox – Amoxicillicin with Clavulanic Acid, DPT – Drug Provocation Test, EM – Erythema Multiforme, FU – follow-up, ID – Intra-Dermal MDM – Minor Determinant Mixture, Pen – Penicillin, PPL – penicilloyl penicilloate, PSGN - Post-Streptococcal Glomerulonephritis, RCT – Randomised Controlled Trial, SJS – Stevens Johnson Syndrome, SSS – Serum Sickness-like Syndrome, TEN – Toxic Epidermal Necrolysis, Vanc – Vancomycin

Table 3. Studies investigating suspected non-immediate serious antibiotic allergic children

First author Year	*Study type Country, language*	*No. of study subjects, age*	*Inclusion criteria*	*Antibiotic DPT protocol*	*Skin testing protocol*	*Results*	*Quality score (out of 7)*
Raucci, 2013	Case control study of SJS, Italy, English	29 SJS cases, 1,362 controls who attended A&E for neurological disorder, 0 – 15 yrs	Presentation to A&E with muco-cutaneous condition, which was diagnosed as SJS or TEN on discharge	Not undertaken	Not undertaken	Participants selected from multicentre Italian 13 year long surveillance study. SJS cases were more frequently exposed to drugs with aOR 2.4 (1.0 – 6.1): anticonvulsants aOR 26.8 (8.4 – 86.0) & antibiotics aOR 3.3 (1.5 – 7.2)	3
Blanca-Lopez, 2009	Retrospective clinic case series, Spain, English	39, 0-14 yrs	Suspected Amox & Co-Amox non-immediate allergy with osteo-articular involvement & SSS	Incremental oral Amox DPT, if skin testing negative, with following 5 day course	ID only to PPL, MDM, BP & Amox. Serum sIgE to BP and Amox	1 (3%) of 39 demonstrated a positive skin test. 19 (50%) of 38 demonstrated a positive oral DPT, ranging 1 to 8 days after starting challenge (median 7 days), with 10 reported to develop wheals, 12 with itching & at least 4 with joint swelling (says seven with osteo-articular reactions in text)	2
King, 2003	Retrospective clinical case series from medical records database, Australia, English	150, 0 – 16 yrs	Search for diagnostic codes relating to potential SSS, with FU call to parents for corroborating history, to identify rash with joint involvement presenting to emergency facility	Not undertaken	Not undertaken	70 (47%) attributed to Cefaclor, 10 (7%) combinations of antibiotics including Cefaclor, 66 (44%) other antibiotics, 4 (3%) other combinations of antibiotics.	1
Forman, 2002	Retrospective clinical case	61 children, mean age	All records listing bullous EM, SJS or	Not undertaken	Not undertaken	30 with bullous EM, 28 with SJS, three with TEN. 16 (26%) were	0

	series, Canada, English	4.8 yrs	TEN over 10 yr period			likely due to Sulphonamides, 16 (26%) due to Penicillins, 8 (13%) to Cephs & 4 (7%) to Erythromycin	
Ginsburg, 1982	Retrospective clinical case series, USA, English	51, 0 – 14 yrs	Suspected SJS admitted during 22 yr period	Not undertaken	Not undertaken	14 to Sulphonomides, 11 to Benzyl Penicillin G, 2 to Doxycyxline	0
Dore, 2007	Retrospective clinical case series, USA, English	32, 0 – 17 yrs	Patients referred to a burn centre for exfoliative eruptions consistent with diagnosis of EM, SJS / TEN (biopsy confirmed)	Not undertaken	Not undertaken	Of these 32, 10 were EM (3 to Amox, 1 Co-Amox, 1 Azithr/Ibuprofen, 1 Ceftin), 18 were SJS (1 to Amox, 1 Azithr, 4 Azithr/Ibuprofen, 1 Cefixime/Ibuprofen, 1 Clarithr/Ibuprofen, 2 Trimeth-Sulfamethoxazole) and 4 were TEN (1 to Azithr/Ibuprofen)	0
Zhang, 2008	Retrospective clinical case series, China, Chinese	20 children	Diagnosed with Acute Generalised Exanthematous Pustulosis	Not undertaken	Not undertaken	Six were receiving Pen, three Cephs & two Sulphonamides.	0
Ferrandiz-Pulido, 2010	Retrospective clinical case series, Spain, English	14, 1 – 14 yrs	All patients leaving teaching hospital with diagnosis of SJS or TEN over 10 yrs	Not undertaken	Not undertaken	Eight cases of SJS and six TEN. All possible trigger agents are listed for each case, with three of eight SJS, and two of six TEN including antibiotics.	0
Chopra, 1989	Retrospective case series, Canada, English	11, 0 – 10 yrs	Suspected Amox allergy with serious systemic reactions	Not undertaken	Major and minor determinant mixtures of BP and minor	10 had SSS and one EM. Negative skin testing for the only patient investigated and all 10 RAST tests were negative.	0

Abbreviations: Amox – Amoxicillin, Azithr – Azithromycin, BP – Benzyl Penicillin, Cephs – Cephalosporins, Co-Amox – Amoxicillicin with Clavulanic Acid, DPT – Drug Provocation Test, EM – Erythema Multiforme, ID – Intra-Dermal, MDM – Minor Determinant Mixture, Pen – Penicillin, PPL – penicilloyl penicilloate, PSGN, SJS – Stevens Johnson Syndrome, SSS – Serum Sickness-like Syndrome, TEN – Toxic Epidermal Necrolysis