Original Article

The Safety of the Direct Drug Provocation Test in Beta-Lactam Hypersensitivity in Children: A Systematic Review and Meta-Analysis

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What is already known about this topic? Many recent studies and recommendations reported the efficacy and safety of direct drug provocation tests (DPTs) without prior skin tests in children with a history of benign cutaneous nonimmediate hypersensitivity reaction to beta-lactams (BLs).

What does this article add to our knowledge? The prevalence of any reaction and severe reaction confirmed by direct DPT without skin test prior to delabeling BL-hypersensitivity reaction (HSR) in children was found to be 5.23% and 0.036%, respectively. Three severe HSRs occurred during the direct DPT, 2 of which were reported from studies that included high-risk patients.

How does this study impact current management guidelines? Direct DPT for delabeling of BL-HSR among children with nonsevere immediate and nonimmediate HSRs can be performed safely. Risk stratification is mandatory to perform before conducting this procedure. Even though severe reactions are very uncommon, they still occur.

BACKGROUND: Direct drug provocation test (DPT) without prior skin testing (ST) has been investigated in children suspected of being at risk for beta-lactam (BL) hypersensitivity reaction (HSR). However, no systematic review and meta-analysis has investigated the efficacy and safety of direct DPT for BL-HSR in children.

OBJECTIVE: To investigate the prevalence of BL-HSR by direct DPT and the safety of direct DPT in children.

METHODS: We searched MEDLINE, EMBASE, Web of Science, and CINAHL from their inception to July 23, 2022, for studies that performed direct DPT in children with suspected BL-HSR, or for studies that performed DPT in all cases with ST results, but they ignored the ST results. The true prevalence was defined as the proportion of children who experienced an HSR during direct DPT. Safety was determined according to the proportion of children who developed a dangerous reaction following DPT.

RESULTS: Twenty-eight studies with 8,334 direct challenges were included. Fifteen studies included patients who presented with either immediate or nonimmediate HSR, and the majority of the index reactions were nonsevere. Amoxicillin/amoxicillin-clavulanic acid was the most commonly used during the DPT. The pooled prevalence of confirmed BL-HSR was 5.23% (95% CI 4.17−6.39; I^2 = 72%). Immediate and nonimmediate HSR were reported in 0.8% (95% CI 0.43−1.25; I^2 = 55.1%) and 3.69% (95% CI 2.66-4.87; I^2 = 79.77%), respectively. Severe reactions were found in 3 cases with the frequency of 0.036% (95% CI 0.012−0.112; I^2 = 0%).

CONCLUSIONS: The prevalence of BL-HSR by direct DPT was 5.23%, and the frequency of severe reactions from direct DPT

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Abbreviations used
BL- Beta-lactam
DHR- Drug hypersensitivity reaction
DPT- Drug provocation test
HSR- Hypersensitivity reaction
IHR- Immediate hypersensitivity reaction
NIHR- Nonimmediate hypersensitivity reaction
SCAR- Severe cutaneous adverse reaction
SSLRs- Serum sickness—like reactions
ST- Skin test

was very low (0.036%). Our findings support direct DPT as a safe and effective delabeling tool in children with suspected nonsevere BL-HSR. **© 2022 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2023;11:506-18)**

Key words: *Prevalence; Beta-lactam hypersensitivity reaction; Direct drug provocation test; Drug hypersensitivity; Children; Systematic review; Meta-analysis*

INTRODUCTION

Drug hypersensitivity reaction (DHR), either immediate (IHR; occurring ≤1 hour after administration) or nonimmediate (NIHR; occuring from 1 hour to several days after administration),[1] most notably to beta-lactam (BL) antibiotics has caused a high level of public health concern during past decades owing to the high rate of false labeling, which has resulted in several negative sequelae, including the antimicrobial stewardship outcomes.[2,3] Both adults and children can be inaccurately labeled as BL-allergic. Viral exanthem rashes during childhood are common, and they can cause nonspecific rash or urticaria similar to those observed in DHRs.[4,5] Therefore, a drug allergy workup plays an important role as a tool for delabeling patients at suspected risk of DHR.

The diagnostic approach in patients with suspected DHR comprises a sequence of steps. Although clinical history taking is generally performed first, it was reported to be unreliable as a single diagnostic tool.[6] Skin tests (STs), including skin prick test and intradermal test (which is performed after negative skin prick test), followed by drug provocation test (DPT) are part of a classical workup for delabeling DHR. It is commonly accepted that DPT should be performed only after a negative ST and if there are no contraindications.[1] This is due to the potentially severe reaction that can occur following a DPT, even though these severe reactions are rare.[7]

The true prevalence of BL hypersensitivity reaction (HSR) in children as confirmed by drug allergy workup usually ranges from 5% to 15%.[7-9] However, STs in children during the diagnostic workup were shown to have limited diagnostic value,[9-11] and ST is painful for children—especially young children. Thus, various direct DPT protocols without ST were developed and studied to investigate their effectiveness and safety—particularly in children presenting with nonimmediate index HSRs to BLs.[12-23] The findings of many of those studies revealed the effectiveness and safety of direct DPT without prior ST in children with a history of benign cutaneous NIHR and recommendations were made for this subgroup.[5,7,24-26]

Given the scarcity of systematic reviews and meta-analyses of the efficacy and safety of direct DPT, this systematic review and meta-analysis aimed to investigate the prevalence of BL-HSR by direct DPT and the safety of direct DPT for BL-HSR in children.

METHODS

Protocol and registration

This systematic review and meta-analysis was conducted and reported in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[27] We registered the study protocol in the PROSPERO systematic review registry (registration ID CRD 42022321394). Because this study was a systematic review and meta-analysis, it was considered exempt from ethics approval, and written informed consent was not obtained from the included study subjects.

Data sources and search strategy

We searched MEDLINE, EMBASE, Web of Science, and CINAHL from their inception to July 23, 2022, and we limited our search to articles about humans that were published in English. A search of the published literature was conducted by 2 independent authors (P.K. and W.S.) using a structured search strategy described in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). A search was also performed to identify relevant articles via Google Scholar. Lastly, we reviewed the reference lists of identified publications for additional eligible publications.

Study screening and selection

After the removal of duplicates, we began the study selection process by screening titles and the abstracts of articles retrieved from the search. For articles that were determined to be potentially relevant, the full text of the article was reviewed. The full text was also reviewed if a decision could not be made from reading the title and abstract alone. Two investigators (P.K. and W.S.) independently screened the titles and abstracts of retrieved articles and disagreements in study selection were resolved by consensus.

Study eligibility criteria

We included studies reporting the prevalence of BL-HSR confirmed by DPT and the frequency of severe reactions subsequent to DPT in children aged 18 years or younger. The inclusion criteria were (1) studies that performed direct DPT to BLs, or (2) studies that performed DPTs in all cases with/without ST results, but they ignored the ST results, or (3) comparative studies from which only a subgroup of children who underwent direct DPTs without prior STs were included in our meta-analyses. We excluded studies with inconsistent determinant indicators (eg, considered the result of ST and/or serum-specific immunoglobulin E before performing DPT), no full text available, conference abstract, and duplicate published studies. We also excluded case reports and case series.

Outcome measurement

The prevalence of confirmed DHR was defined as the proportion of children who developed a reaction after DPT. The index event of DHR was classified as IHR or NIHR. Subgroup-specific prevalence was calculated and compared, as follows: (1) geographic region (Europe, Asia/Asia Pacific, or North America), (2) duration of challenge (single day vs multiple days), and (3) type of step challenge (single step vs multiple steps). Safety was defined as the number of children who developed severe reactions if they had at least 1 of the

following reactions following DPT: for IHRs—palmoplantar/genital/ear/head itching, conjunctival redness, hypotension symptoms (eg, dizziness, fainting, need to lie down), cough, sneezing, wheezing, dyspnea, dysphonia, dysphagia; and for NIHRs—intense facial involvement, atypical target lesions, bullous lesions, widespread dark-red erythema, extensive pustulosis, painful skin, mucosal involvement, generalized lymphadenopathy, elevated liver enzymes, impaired renal function tests, fever greater than 38.5°C, alterations in blood cell counts (ie, anemia, granulocytopenia, thrombocytopenia, neutrophilia, eosinophilia), hypocomplementemia, hepatitis, nephritis, or pneumonitis.[24] For other reactions, severe reactions were classified according to the description by authors.

Data extraction

The data were independently extracted by 2 reviewers (P.K. and W.S.) and compared. Disagreements were resolved by discussion and subsequent consensus. The following information was retrieved from each study: (1) year of publication; (2) country and geographic region; (3) study design (prospective or retrospective); (4) challenge setting (allergy or nonallergy clinic); (5) type of index reaction (IHR or NIHR); (6) type of challenge drug (culprit or alternative); (7) drug challenge; (8) challenge steps during DPT (single dose or graded); (9) days of challenge (single or multiple days); (10) the period during which patients were followed for nonimmediate reactions; and (11) the number of participants undergoing a DPT as well as the number and type of subsequent severe reactions. If the required information was not readily available from published reports, we requested the raw data from the authors.

Risk of bias assessment

Two authors (P.K. and W.S.) independently assessed the methodological quality of the included studies, and consensus was reached by discussion with a third party (P.P.) in case of disagreements. The quality of each study was assessed using an adaptation of a tool developed for prevalence studies.[28,29] For each of the included studies, the following 6 questions were asked: (1) whether the study's target population represented the national population in relation to relevant variables; (2) whether the sample frame represented the target population; (3) whether random or consecutive selection was used to select the sample; (4) whether the likelihood of nonresponse bias was minimal (<25% follow-up losses and/or participants not undergoing direct DPT); (5) whether an acceptable definition of BL-HSR was used in the study (or if DHR were described in detail); and (6) whether the same data collection and assessment method were used for all participants.

Data synthesis and analysis

All statistical analyses were performed using Stata 17 (StataCorp LLC, College Station, TX) or R version 4.1.2 (R Foundation, Vienna, Austria). A 2-tailed *P* value less than .05 was regarded as being statistically significant. The true prevalence of confirmed DHR was calculated as the number of patients who experienced a reaction during or following a DPT divided by the total number of patients included. The proportion of children who developed a severe reaction during or following a DPT was calculated using the same method. We calculated the pooled estimate of the prevalence of drug reaction using the metaprop command in Stata. The random effects model was used to manage and compensate for significant heterogeneity among the 28 included studies. The uncertainty of the pooled prevalence is presented with 95% CI. Freeman-Tukey double arcsine transformation or generalized linear mixed models were used to appropriately stabilize the variance when studies had 0 prevalence, as appropriate.[30,31] Subgroup analyses were performed for geographic region, duration of challenge (single day vs multiple days), and type of step challenge (single step vs multiple steps). Heterogeneity was assessed using the I^2 statistic, which ranges from 0% to 100%. A higher value indicates a greater degree of variability across the study results. Therefore, I^2 values of more than 75% indicating substantial heterogeneity.[30] The results of all meta-analyses are visualized as forest plots, and funnel plots were generated to detect publication bias. The Egger test of bias was used to assess for publication bias and a *P* value less than .05 indicates significant publication bias.[32]

RESULTS

Study selection

The search results are summarized in Figure 1. Of the 521 records identified from the 4 databases, 359 were screened after the removal of 162 duplicate records. Of those 359 articles, 34 articles were fully read, and 25 of those were included in the systematic review. Another 451 studies were identified via Google Scholar and a search of reference lists in identified studies, but only 3 studies were eligible. A total of 28 studies were finally included in the present study.

Study characteristics

A summary of the study characteristics of the 28 included studies is shown in Table I, and details specific to the inclusion and exclusion criteria for each of those studies are described in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). Data extraction from all participants was performed in 21 studies, and partial extraction that included only a subgroup of children who underwent a direct DPT without prior ST was performed in another 7 studies.[15,33-38] Most studies included patients presenting with HSR to BLs, but 3 studies[12,39,40] included patients by using a low-risk criteria of having a low probability of BL-HSR. The low-risk criteria referred to reactions that were not likely to represent a severe HSR, or nonallergic reaction, or patients with family history of penicillin allergy that led to drug avoidance. Almost all studies excluded or not included patients with severe life-threatening reactions, namely (severe) anaphylaxis (except in 2 studies),[33,38] severe cutaneous adverse drug reaction (SCAR; ie, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, or acute generalized exanthematous pustulosis), internal organ involvement (nephritis, pneumonitis, hepatitis), and vasculitis (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org).

Most studies (18 studies)[12,13,17,18,20-23,34,36,39-46] had a prospective study design and were conducted in an allergy clinic (22 studies).[13,14,17,18,20-23,33-38,41-48] Approximately half of studies (15 studies) included patients with either IHR or NIHR,[13,19,20,33,34,36-38,40-42,44,45,47,49] whereas 12 studies included only patients who presented with NIHR.[12,14,15,17,18,21-23,35,39,43,48] One study solely included children with a clinical presentation compatible with serum sickness–like reactions (SSLRs).[46] Culprit drugs were used in almost all studies (89.3%), except for 3 studies that used an alternative drug in some circumstances.[19,34,35] Amoxicillin with or

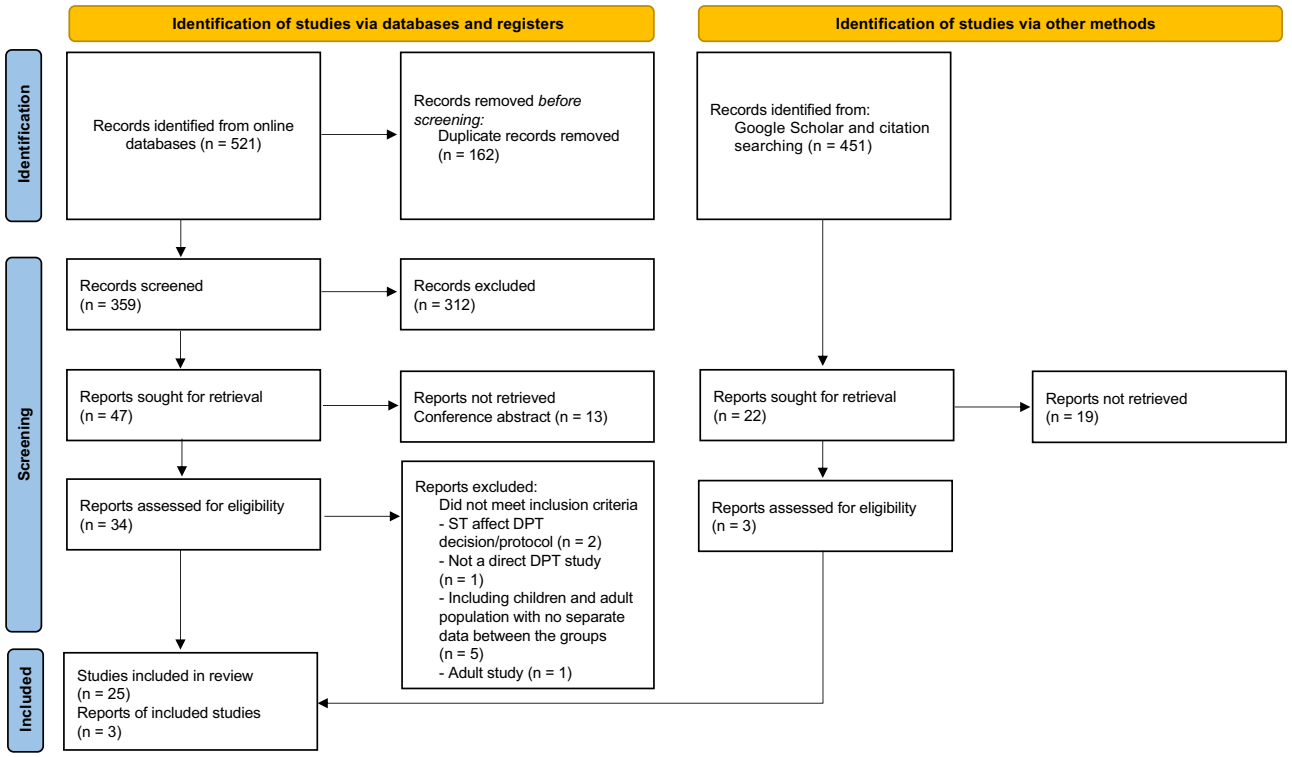

FIGURE 1. Flow diagram describing the study selection process.

without clavulanic acid was the most commonly reported culprit drugs used during the DPT. There was wide variation in the drug challenge protocols used among studies in terms of dosing (data not shown), type of step challenge, and the number of challenge days (Table I). Single-dose challenge was used in 7 studies,[12,17,22,35,39,40,47] whereas the other two-thirds of studies used a graded challenge test (2−5 steps) during the first day of challenge.[13-15,18-21,23,33,34,36,37,41-46,48,49] Another study used 1- or 2-step oral challenges based on a patient's history.[38] Challenge days starting from a single day (reported in 12 studies)[13,15,19,20,36,38-40,44,46,47,49] to 3 to 6 days[12,18,21,23,33-35,37,42,43,45,48] or prolonged as index days (plus another 1−2 days, or with a maximum of 7−8 days).[14,17,22,41]

Frequency of DHRs confirmed by direct DPT, and severe reactions

A total of 8,334 direct DPTs to BLs were included in the present study (51.1%, 40.6%, and 8.3% of DPT were from Europe, North America, and Asia/Asia Pacific, respectively). Confirmed BL-HSRs were found in 494 reactions, with an estimated pooled prevalence of 5.23% (95% CI 4.17−6.39; I^2 = 72%) (Figure 2, *A*). Among the positive reactions, 111 reactions were IHRs with an estimated pooled prevalence of 0.8% (95% CI 0.43−1.25; I^2 = 55.1%). Ninety-two of these (82.9%) were reported from 10 studies that included either IHR and NIHR,[13,19,20,33,37,41,42,44,45,49] 19 IHRs (17.1%) were from 9 studies that included only patients with NIHR and SSLRs.[14,15,17,21,23,39,43,46,48] The NIHRs were reported in 383 positive reactions with an estimated pooled prevalence of 3.69% (95% CI 2.66−4.87; I^2 = 79.77%) (Figure 2, *B, C*).

The information regarding to chronology between index and DPT reactions were available in 6 IHRs (464 IHR index reactions from 3,808 DPTs),[13,20,34,37,41,47] and 18 NIHR studies (4,997 NIHR index reactions from 5,743 DPTs).[12-15,17,18,20-23,35,37,39,41,43,46-48] The concordance rate of chronology between index and DPT reactions was 52.2% (12 of 23 reactions), and 76.9% (240 of 312 reactions) for immediate and nonimmediate reactors, respectively (Tables E3 and E4; available in this article's Online Repository at www.jaci-inpractice.org).

Severe reactions occurred in 3 patients from 3 studies,[14,18,33] including anaphylaxis (n = 1); rash, fever, and liver enzymes elevation (n = 1); and SSLRs (n = 1), for an overall frequency of 0.036% (95% CI 0.012−0.112; I^2 = 0%) (Table II).

Subgroup analyses by geographic region, duration of challenge, and type of step challenge

When stratified by geographic region (Figure 3, *A*), Europe had a significantly higher prevalence of confirmed BL-HSRs at 7.26% (95% CI 5.67−9.01) compared with 3.03% (95% CI 1.57−4.87) in North America, and 3.46% (95% CI 1.98−5.29) in Asia and the Asia-Pacific (P = .001). When stratified by the duration of challenge (Figure 3, *B*), the estimated pooled prevalence for the multiple-day challenge was 6.80% (95% CI 5.16−8.63), which was significantly higher than that of the single-day challenge (3.32%; 95% CI 2.07−4.81) (P = .004). When stratified by the type of step of challenge (Figure 3, *C*), there was no significant difference between single-step and multiple-step challenges (P = .388).

TABLE I. Characteristics of the 28 included studies

Study	Study design	Population	Clinic type	Index reaction	Drug type tested	Drug(s) tested	Type of step challenge	Challenge duration	Time of observation for NIHR
Chambel et al, 2010* (only direct DPT data were included in our analysis)	Prospective	Children (<15 y)	Allergy	IHR + NIHR	Culprit (59.6%) or alternative (28.1%) or both (12.3%)	Amoxicillin, amoxicillin-clavulanic acid, benzylpenicillin, cephalosporins, flucloxacillin	Graded	5 d	Within 48 h after a 5-d challenge
Moral et al, 2011* (only direct DPT data were included in our analysis)	Prospective	Children (<15 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin, amoxicillin-clavulanic acid, cephalosporins, penicillin	3-step graded	Single day	NA
Mori et al, 2015* (only direct DPT data were included in our analysis)	Retrospective	Children (<15 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin	3-step graded	5 d	Within 48 h after a 5-d challenge
Mill et al, 2016	Prospective	Children	Allergy	IHR+NIHR	Culprit	Amoxicillin	2-step graded	Single day	Up to 1 wk after a single-d challenge
Vezir et al, 2016	Prospective	Children	Allergy	NIHR	Culprit	Amoxicillin (3.4%), amoxicillin-clavulanic acid (73.1%), ampicillin-sulbactam (2.5%), cephalosporins (20.2%), penicillin (0.8%)	2-/3-step graded	5 d	NA
Vyles et al, 2017	Prospective	Children (3.5−18Y)	Nonallergy (performed under physicians who were trained by allergist)	Low-risk criteria (IHR + NIHR)	Culprit	Amoxicillin	Single-dose	Single day	NA
Ibáñez et al, 2018	Prospective	Children (≤14 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin (66.8%), amoxicillin-clavulanic acid (30.1%), penicillin V (2.6%), penicillin G (0.5%),	3-step graded	Prolonged as index days for NIHR	NA
Labrosse et al, 2018	Prospective	Children (<18 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin	3-step graded	5 d	At the end of a 5-d challenge
Arnold et al, 2019† (only direct DPT data were included in our analysis)	Retrospective	Children (0−16 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin (70%), amoxicillin-clavulanic acid (2%), cephalexin (10%), flucloxacillin (2%), penicillin (16%)	2-step graded	5 d	NA
García Rodríguez et al, 2019	Retrospective	Children (<14 y)	Allergy	NIHR (>6 h)	Culprit	Amoxicillin (55.7%), amoxicillin-clavulanic acid (39.2%), Other BLs (ie, phenoxymethylpenicillin/ cefuroxime) (5.1%)	3-step graded	Prolonged as index days	NA
Jaoui et al, 2019	Prospective	Children	Allergy	NIHR (>1 h)	Culprit	Amoxicillin (69.3%) amoxicillin-clavulanic acid (23.7%), cephalosporins (7%)	Single-dose	Prolonged as index days + 1−2 d, maximum 8 d	Within 48 h after the end of the DPT (prolonged as index days plus 1−2 d, maximum 8 d)
Pouessel et al, 2019	Prospective	Children	Allergy	NIHR	Culprit	Amoxicillin (70%), amoxicillin-clavulanic acid (15%), cefpodoxim (12%), cefixim (2%)	2-step graded	3 d	Two wk after DPT
Allen et al, 2020	Prospective	Children (1−17 y)	Nonallergy (performed under physician who were trained MS in allergy)	Low-risk criteria (NIHR)	Culprit	Amoxicillin, flucloxacillin, penicillin V	Single-dose	5 d	Day 6 after a 5-d challenge
Krusenstjerna-Hafstrøm et al, 2020	Retrospective	Children	NA	IHR + NIHR	Culprit or amoxicillin	Amoxicillin (58%) amoxicillin-clavulanic acid (1%), ampicillin (1%), dicloxacillin (3%), penicillin G/V (36%)	2-step graded	Single day	Day 7 after a single-d challenge
Kulhas Celik et al, 2020	Prospective	Children	Allergy	NIHR (>1 h)	Culprit	Amoxicillin (2.5%), amoxicillin-clavulanic acid (76.9%), penicillin V (2.5%), ampicillin-sulbactam (1.4%), cephalosporins (16.6%)	≤5-step graded	6 d	At the end of a 6-d challenge

Labrosse et al, 2020	Prospective	Children (0−18 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin	3-step graded	Single day	48 h after a single-d challenge
Petersen et al, 2020	Prospective	Children (0−18 y)	Allergy	IHR + NIHR	Culprit	Amoxicillin (49.5%) amoxicillin-clavulanic acid (4.9%), dicloxacillin (5.6%), penicillin V (40%)	2-step graded	5 d	During DPT or the following 48 h
Wang et al, 2020	Retrospective	Children	Allergy	IHR + NIHR	Culprit	Amoxicillin	Single-dose	Single day	NA
Delli colli et al, 2021	Prospective	Children	Allergy	SSLR	Culprit	Amoxicillin (88%), amoxicillin-clavulanic acid (6.7%), cefprozil (2.7%), cephalexin (2.7%)	2-step graded	Single day	Weeks to 1 mo after a single-d challenge
Exius et al, 2021	Prospective	Children	Allergy	IHR + NIHR	Culprit	Amoxicillin	2-step graded	Single day	Day 7 after a single-d challenge
Gateman et al, 2021*	Retrospective	Children (≥18 m) + adults (only children were included in our analysis)	Nonallergy (performed under family physician and nurse practitioner)	NIHR	Culprit	Amoxicillin	2-step graded	Single day	Same day or week after a single-d challenge
Goh et al, 2021*	Retrospective	Children (≤18 y)	Allergy	IHR + NIHR (only NIHR group underwent a direct DPT and included in our analysis)	Culprit (except in 1 patient with SJS in which an alternative drug challenge was performed)	Amoxicillin (47.5%), amoxicillin-clavulanic acid (37.5%), cloxacillin (1%), cephalosporins (14%)	Single-dose	5 d	At the end of a 5-d challenge
Koosakulchai et al, 2021	Prospective	Children (<15 y)	Allergy	NIHR (>1−6 h)	Culprit	Amoxicillin (75.9%), amoxicillin-clavulanic acid (24.1%)	2-step graded	5 d	Day 7 after a 5-d challenge
Prieto et al, 2021	Prospective	Children (0-14Y)	Allergy	NIHR (>6H)	Culprit	Amoxicillin (70.1%), amoxicillin-clavulanic acid (26.8%), penicillin (0.5%), ampicillin (0.5%), cefuroxime (2%)	Single-dose	Prolonged as index days, max 7 days	NA
Antoon et al, 2022	Prospective	Children	Nonallergy (performed DPT by a pharmacist)	Low-risk criteria (NIHR)	NA	Amoxicillin	Single-dose	Single day	60 min
Guðnadóttir et al, 2022	Retrospective	Children (5 mo−18 y)	Nonallergy (participated by pediatric allergist)	IHR + NIHR	Culprit	Amoxicillin (44.9%), amoxicillin-clavulanic acid (40.8%), cephalosporins (4%), other penicillin (7.8%), others (2.5%)	2-step graded	Single day	Within 24 h after a single-d challenge
Liccioli et al, 2022	Retrospective	Children	Allergy	NIHR (>1 h)	Culprit	Amoxicillin (9.6%), amoxicillin-clavulanic acid (90.4%)	3-step graded	5 d	Within 48 h after the last dose
Nguyen et al, 2022* (only direct DPT data were included in our analysis)	Retrospective	Children (0−19 y)†	Allergy	IHR + NIHR	Culprit	Amoxicillin (74%), amoxicillin-clavulanic acid (10.4%), penicillin (9.1%), others (6.5%)	1- or 2-step	Single day	NA

NA, Not applicable; *NIHR,*Nonimmediate hypersensitivity reaction; *SJS,* Stevens-Johnson syndrome.
*Only a subgroup of patients who met the inclusion criteria for our study was included.
†This study included pediatric patients between 0 and 19 y.

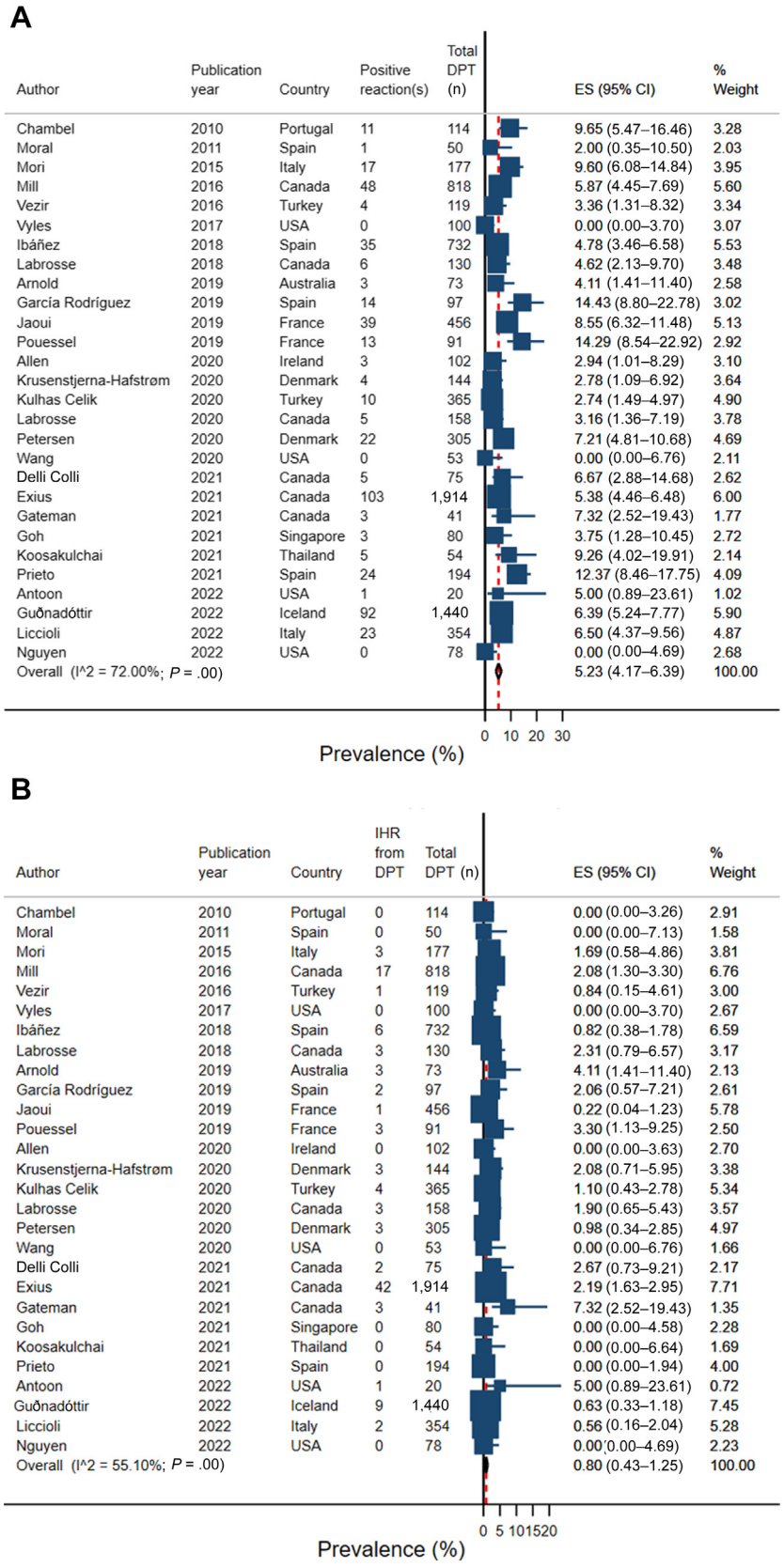

FIGURE 2. The estimated pooled prevalence of BL drug allergy confirmed by direct DPT in children. (**A**) The overall prevalence of IHRs or NIHRs to BLs. (**B**) The prevalence of IHRs to BLs. (**C**) The prevalence of NIHRs to BLs. *ES,* Effect size; *USA,* United States of America.

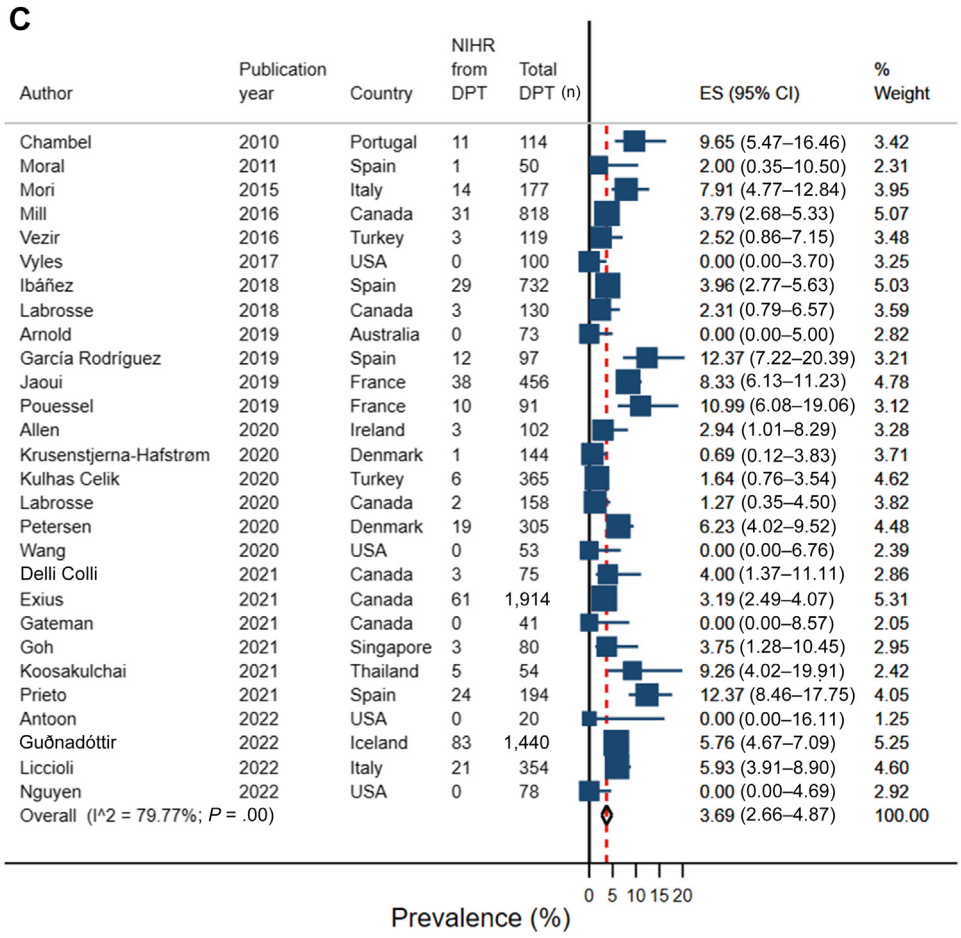

FIGURE 2. (continued).

Risk of bias assessment

The level of risk of different types of bias among overall studies is summarized in Figure 4, and the level of risk of different types of bias for each of the 28 included studies is shown in Table E5 and Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org). More than half of the included studies had a high risk of bias specific to the study population being representative of the national population. However, most studies had a low risk of bias relative to the study population being representative of the target population, consecutive or random sampling, nonresponse bias, outcome definition, and consistency of data collection and assessment.

Assessment of publication bias

The results of Egger method test did not show a significant difference of bias for the overall prevalence of BL-HSR (n = 28; bias = 0.004; 95% CI −0.31 to 0.32; $P = .978$). There was also no significant difference of bias for the prevalence of IHR, NIHR, and severe HSR to BL (Table E6; available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This systematic review and meta-analysis evaluated the prevalence and safety of direct DPT among children with suspected HSR to BLs using data from the 28 included primary studies. Our results showed an estimated pooled prevalence of true BL-HSRs of 5.23% and supported that direct DPT without prior ST is safe to perform for delabeling BL-HSRs in children presenting with nonsevere IHR or NIHR. However, careful risk stratification should be performed before conducting the test because, although very uncommon, severe reactions still do occur.

The prevalence of true BL-HSRs in our study ranged from 0% to 15% with substantial heterogeneity, and this rate is similar to several previous studies that performed sequential drug allergy workup in children.[4,9,10,37,50-52] In our analysis, the prevalence of NIHRs as a result of provocation testing was higher than IHRs. This may be explained by the fact that only half of the included studies included patients presenting with IHR. More importantly, the time interval between index reactions and tests should be taken into the account, because sensitization decreases overtime, particularly for IHRs.[53] However, natural tolerance has also been reported among children with a nonsevere NIHR.[54]

Interestingly, the majority of IHRs (82.9%) as a result from direct DPT were from studies that included either IHR or NIHR index reactions; however, another one-fifth of those IHRs were from studies that included patients presented with NIHR or SSLR. In our study, we were able to identify 6

TABLE II. Types of reactions among patients with severe hypersensitivity reactions as a result from direct DPT

Types of reactions	n (meta-analysis frequency; 95% CI; I^2)
Direct DPT (n)	8,334
Severe hypersensitivity reactions	3 (0.036%; 0.012%−0.112%; 0%)
Anaphylaxis*	1 (0.012%; 0.002%−0.085%; 0%)
Rash + fever + liver enzymes elevation†	1 (0.012%; 0.002%−0.085%; 0%)
SSLR‡	1 (0.012%, 0.002%- 0.085%; 0%)

BUN, Blood urea nitrogen; *Cr,* creatinine; *SGOT,* serum glutamic-oxaloacetic transaminase; *SGPT,* serum glutamate pyruvate transaminase.

*Anaphylaxis: This patient presented with an index reaction of anaphylaxis and experienced anaphylaxis during the DPT.

†Rash + fever + hepatitis: a 14-y-old boy with clinical history of angioedema 12 h after the last dose of amoxicillin-clavulanic acid who developed maculopapular rash, fever, increased atypical lymphocyte, and hepatitis (absolute eosinophil count 221 cell/mm^3, atypical lymphocyte 5%, SGOT 101 U/L, SGPT 84 U/L, BUN 7.3 mg%, Cr 0.54 mg%) on the fourth day after amoxicillin-clavulanic acid challenge test.

‡SSLR: a 5-y-old boy with a clinical history of 2 episodes of urticaria after 2−3 d of amoxicillin (clavulanic acid) taken and another episode of urticaria and mild arthralgia after finishing a course of amoxicillin-clavulanic acid who developed macular rash, fever, arthralgia, and neutrophilia at day 4 after DPT to amoxicillin-clavulanic acid.

studies[13,20,34,37,41,47] that included IHR patients and a chronology between index and DPT reactions being described. Immediate index reaction accounted for 12.2% (464 of 3,808 reactions) of all reactions (no anaphylaxis included), and positive direct DPTs were found in 23 of 464 (5%) reactions (12 IHRs, and 11 NIHRs), without any severe reaction in this subgroup population. The concordance between chronology of index and DPT reactions was only 52.2% for IHRs (data from those 6 studies), whereas a better match (76.9%) for NIHRs (data from 18 studies) were found. Recently, a large study from Chiriac, et al[55] reported the results of 3,046 children and adult whom underwent DPTs (preceded by STs in all cases) to BLs. They showed a higher rate of concordance between chronology of the index reaction and provocation test among immediate reactors (94.2%) compared with nonimmediate reactors (71.1%). The concordance rate for NIHRs was similar between our result and previous reported, whereas the concordance rate for IHRs was much lower in our study; this could be explained by the fact that almost all included children presented with nonsevere IHR; therefore, lower risk of positive reactions, and only a limited number of children/studies included for this subanalysis owing to the lack of chronology reported from most IHR-included studies.

According to several updated recommendations and reviews,[5,7,16,24-26,56] ST is not mandatory in the DHR workup algorithm in some low-risk children who present with NIHRs, but the debate continues relative to children with IHRs.[57] However, a large study from Mill et al[20] included 818 children with suspected amoxicillin HSRs (12% with immediate index HSRs) and they performed a direct DPT to amoxicillin in all children. They reported that only 48 patients (5.9%) developed reactions, and all reactions were mild with hive or a maculopapular rash. Thereafter and during the past 5 years, several centers performed a direct DPT in children with a nonsevere allergic reaction to BLs (both IHRs and NIHRs) and demonstrated the safety of direct DPT. However, it should be noted that the majority of those studies excluded patients with a history of (severe) anaphylaxis, and when it was included, the numbers were extremely low.

Our study showed the estimated frequency of severe HSRs from direct DPTs to BLs of 0.036% with no heterogeneity. This finding is similar to the result from a previous meta-analysis[28] that reported the frequency of severe HSRs to penicillin among both children and adults to be 0.06% (95% CI 0.01−0.13; I^2 = 57.9%). When they assessed the risk of developing severe reactions, they found no association between the performance of direct DPTs in low-risk patients and sequential DHR workup. In addition, a previous systematic review that assessed the efficacy and safety of direct DPT to penicillin in adults found 41 of 1,202 positive reactions (3.41%), and all were mild IHRs or NIHRs.[58] Thus, we can conclude that severe reactions caused by direct DPTs are rare in low-risk patients with either IHRs or NIHRs. However, it is important to note that patients with severe life-threatening DHRs, particularly SCARs and internal organ involvement, are contraindicated from undergoing DPTs without prior STs[1,24]; this is normally one of the exclusion criteria in almost all studies.

There is 1 severe IHR case (anaphylaxis) as a result from direct DPT reported from a study that included 5 patients with anaphylaxis.[33] Another severe NIHR (SSLR) was reported from a study that included 2 patients presented with SSLR.[14] The last severe NIHR (rash, fever, and liver enzymes elevation) reported from 1 study that included only patients presenting with nonsevere NIHRs.[18] In summary, 2 out of 3 reported severe reactions are from studies that included high-risk patients. Therefore, a careful history, physical examination, and risk stratification are mandatory before performing this procedure. Even though severe reactions are very uncommon, they still occur.

In this study, 5 included studies[13,14,20,41,46] investigated children presenting with SSLR. Two of those studies[20,41] reported positive reactions from DPT compatible with SSLR, but all were mild self-limiting reactions, whereas another study[14] reported 1 severe SSLR (macular rash, fever, arthralgia, and neutrophilia) (Figure E1). In children, presentation of SSLR (rash, malaise, fever, lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, and arthralgia/arthritis) can be similar to viral infection, and therefore, DPT can be used for the diagnosis. An SSLR is not like a classical serum sickness. It usually presents with milder phenotype, without hypocomplementemia, and internal organ involvement. However, it should be noted that some reports[24] classified SSLR as a high-risk reaction, and therefore, classical DHR workup (including ST) may be preferred over direct DPT.

Concerning the subgroup analysis, we found a significantly higher frequency of BL-HSRs in Europe than in Asia/Asia-Pacific and North America, but no significant difference between Asia/Asia-Pacific and North America. This finding raises the possibility that genetic and epigenetic factors might mediate the risk of BL-HSRs. There is strong evidence that genetics and ethnicity play important roles as predisposing factors to SCARs to antiepileptic, allopurinol, and antiviral drugs.[59] However, the effect of genetic variants in BL-HSR was inconclusive,[60,61] and further studies are needed to determine the depth, breadth, and relevance of these associations. Another explanation could be differences in risk assessment and patient selection to undergo a DPT. In North America, the tendency toward ordering or

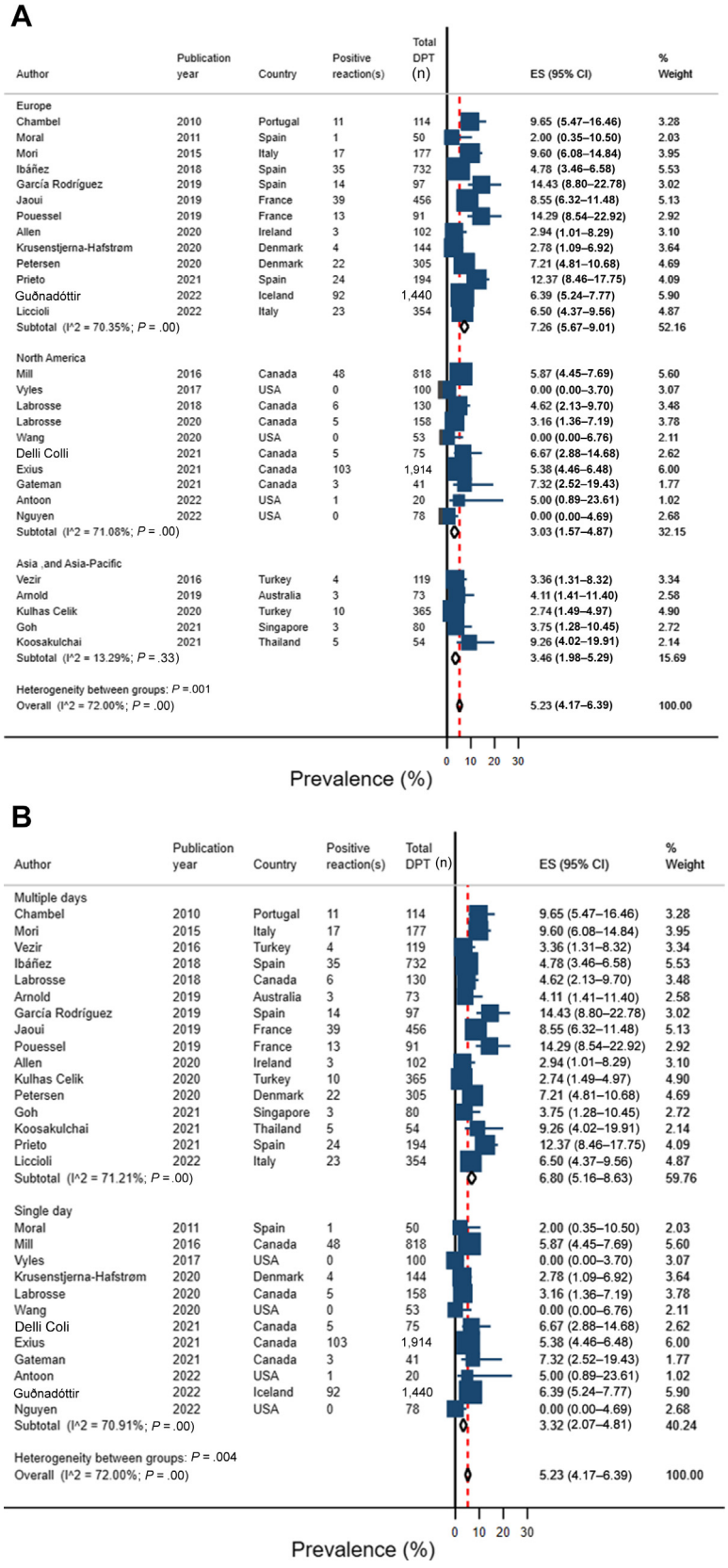

FIGURE 3. (**A**) Subgroup analysis by geographic region (Europe vs Asia, and Asia-Pacific vs North America). (**B**) Subgroup analysis by duration of challenge (single day vs multiple days). (**C**) Subgroup analysis by type of step challenge (single step vs multiple steps). *ES,* Effect size; *USA,* United States of America.

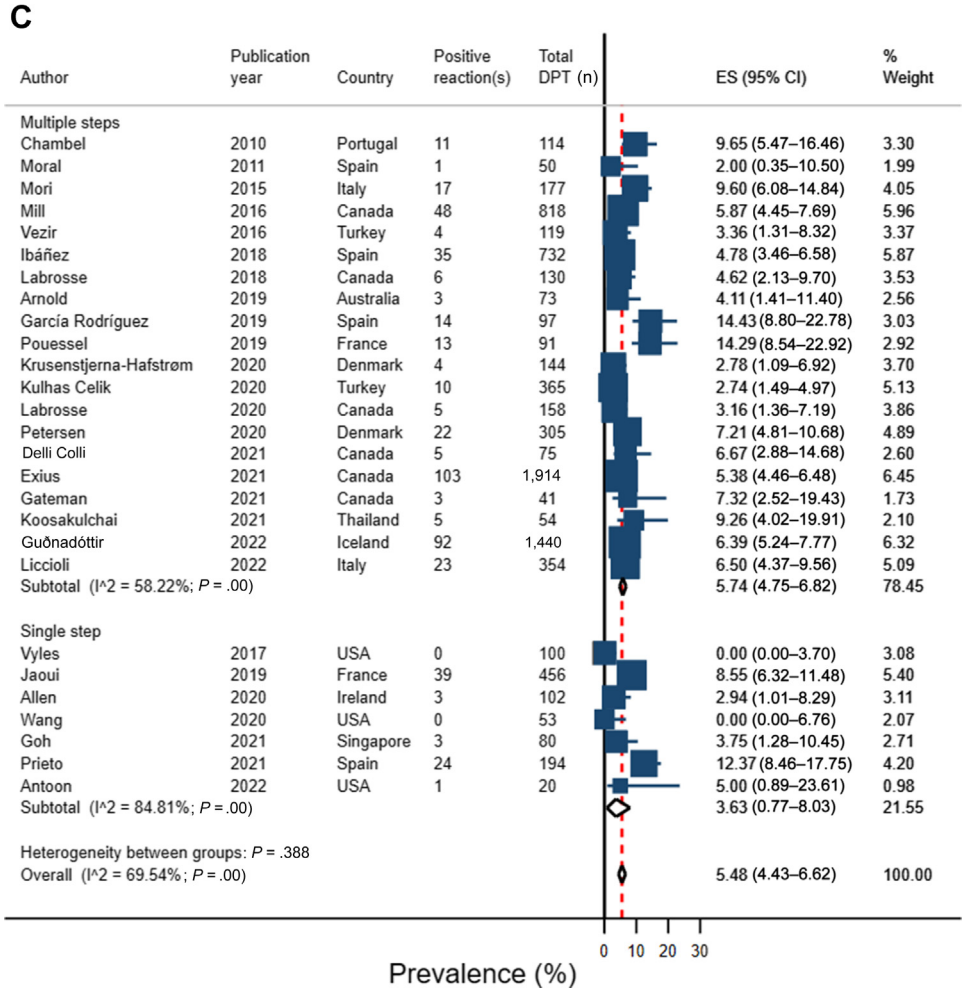

FIGURE 3. (continued).

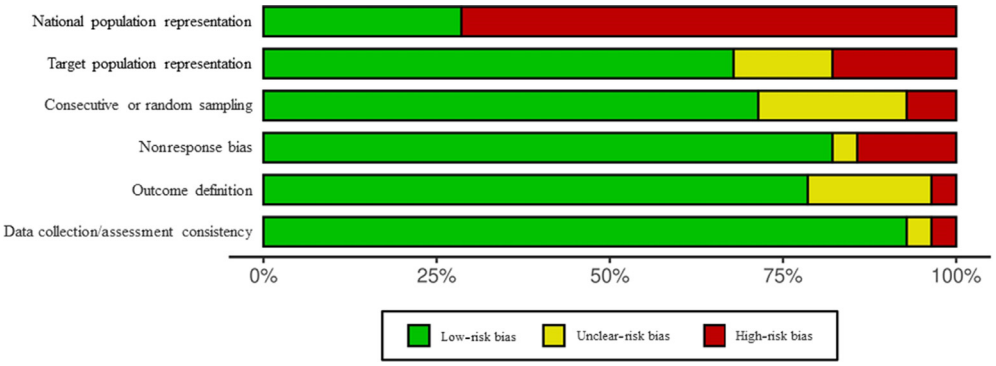

FIGURE 4. Level of risk of different types of bias among overall studies.

offering a provocation test may be less than in Europe, and only patients with low risk were selected to undergo DPT.

There was a significantly higher positive provocation rate using a prolonged challenge test (3—8 days) than a single-day protocol. Several studies suggested using a prolonged challenge protocol to increase the performance of DPTs in the diagnosis of NIHRs to BLs.[9,37,42,51,62-64] A recent study from Liccioli et al[48] reported that, among 23 children who had positive DPT

outcome by using a 5-day prolonged protocol, 11 (47.8%) developed a reaction at home on the fifth day of DPT. In contrast, some studies did not find any additional value of a prolonged challenge, and reported higher cost, antimicrobial stewardship, and bacterial resistance to be notable drawbacks of prolonged challenge protocols.[14,65-67] Chiriac et al[65] reported that, among 950 patients who underwent a 1-day DPT for suspicion of IHR or NIHR, the negative predictive value of the test was 94.8% (94.3% for IHR, and 94.9% for NIHR), and the number needed to harm was 16.6, which means that an additional 16 prolonged DPTs were needed to capture 1 reaction. Van Gasse et al[67] reported prolonged challenge to be of limited added value because 43.5 prolonged DPTs were needed to capture 1 additional reaction among patients with NIHR to amoxicillin (clavulanic acid). Nevertheless, there is currently no consensus regarding the standardization of challenge protocols (doses, steps, and duration of the DPT).

This study has limitations that merit mention. First, although most included studies were prospective in design, there was significant heterogeneity across studies. Second, most included studies collected their data from single centers, which increased the risk of bias that the study population may not be generalizable. Third, the chronology between the index reaction and the DPT was unavailable in many studies, so we were unable to analyze or determine any concordance in the chronology between the index reaction and the provocation test from all studies. Finally, because this study only evaluated the pediatric population and was focused on direct DPT, partial selection of data in some studies might lead to a selection bias. Of note, a pediatric population in this study generally referred to patients aged 18 years or younger, although some centers may perform drug allergy workup in adolescents as an adult.

The main strength of this study is a comprehensive search from 4 different medical research databases plus an additional search from Google Scholar. Sensitivity analysis was also performed to identify subgroups that might associate with different outcomes. We also found a low risk of bias in three-quarters of the included studies specific to target population representation, consecutive or random sampling, nonresponse bias, outcome definition, and consistency of data collection and assessment.

In conclusion, the prevalence of BL-HSRs by direct DPTs was 5.23%, and the frequency of severe reactions from direct DPTs was a very low 0.036%. Our findings support direct DPT as a safe and effective delabeling tool in children with suspected nonsevere immediate and nonimmediate BL-HSR.

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