

DR ANCA MIRELA CHIRIAC (Orcid ID : 0000-0002-1558-1966)
DR NAJAH BEN FADHEL (Orcid ID : 0000-0001-9558-0666)

Article type : Research Letter

Follow-up of patients with negative drug provocation tests to betalactams

Negative predictive value of drug provocation tests to betalactams

Anca Mirela CHIRIAC^{a,b}, Antonino ROMANO^{c,d}, Najah BEN FADHEL^a, Francesco GAETA^c,
Nicolas MOLINARI^{e,f,g}, Michela MAGGIOLETTI^c, Pascal DEMOLY^{a,b}

^aCentre hospitalier universitaire de Montpellier, hôpital Arnaud-de-Villeneuve, département de pneumologie et addictologie, univ Montpellier, 34295 Montpellier, France

^bSorbonne université, INSERM, institut Pierre-Louis d'épidémiologie et de santé publique, équipe EPAR, 75013 Paris, France

^cAllergy Unit, Complesso Integrato Columbus, Rome, Italy;

^dIRCCS Oasi Maria S.S., Troina, Italy;

^e Department of Clinical Information, Clinical Research Unit, University Hospital of Montpellier, Montpellier, France;

^f Montpellier University, Montpellier, France;

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.13314

This article is protected by copyright. All rights reserved.

^g IMAG, UMR 5149, University Hospital of Montpellier, Montpellier, France.

Corresponding author:

Dr Anca Mirela CHIRIAC

a-chiriac@chu-montpellier.fr

Allergy Unit, Arnaud de Villeneuve Hospital, University Hospital of Montpellier

371, Avenue du Doyen Gaston Giraud

34295 Montpellier Cedex 5

Montpellier, France

Key words: betalactam, drug allergy, drug provocation test, negative predictive value, number needed to harm

To the Editor,

Drug allergy work-up in betalactam (BL) allergy is probably the most-developed drug-allergy evaluation at present [1]. During the last few years, the debate on whether one-day or several-day (prolonged) drug provocation test (DPT) should be performed in non-immediate reactions (i.e., occurring >1h after the last administered dose) in order to increase sensitivity has been ongoing and groups working in drug allergy diagnosis have been deploying *pro* and *con* arguments and studies in favour of either option [2-5]. The most acceptable way to validate a negative DPT is by studying its negative predictive value (NPV) in patients who are re-challenged to the negatively tested drug, in real-life therapeutic conditions [6,7]. Because therapeutic conditions imply underlying infectious

disease (and therefore, a differential diagnosis responsible of cutaneous eruptions, independent of medication), performing a follow-up of tested patients including retest if necessary is advisable, under the hypothesis that not all reactions occurring upon retaking the drug are drug-related.

The number needed to harm (NNH) is a measure of the harm caused by an intervention. More specifically, it is a measure of how many people need to be exposed to an intervention, (e.g., DPT) in order for one person to have a particular adverse effect (e.g., a DHR): the larger the value of the number needed to harm, the lower the risk of the adverse effect. In the specific case of DPT, prolonged DPT deliver courses of antibiotics in subjects that are otherwise healthy and this intervention may have additional drawbacks at a higher overall level (e.g., microbial resistance, economic costs). If the NNH is high, and considering that prolonged DPT pick up merely mild reactions (as confirmed by the studies performing prolonged DPT [2-4]), prolonged DPT might not be an effective intervention as compared to one-day DPT.

Between December 2014 and June 2016, a multicentre (NCT02844712) study was conducted in two allergy units, Hôpital Arnaud de Villeneuve (Montpellier, France) and Complesso Integrato Columbus (Rome, Italy). Patients with a complete and negative allergy work-up for a BL were contacted and asked to answer a questionnaire regarding re-administration of a negatively tested BL, as previously described [6]. Both centres perform one-day DPT in both immediate and in mild/moderate non-immediate suspicions of BL drug hypersensitivity reactions (DHR), in a similar manner (including contraindications for DPT). Data were expressed either as numbers and percentage (with 95% CIs) or as medians (with interquartile range). Comparisons were made using chi-square tests for categorical variables. Clinical risk factors for developing a reaction upon subsequent re-challenge in real-life were searched using multivariate logistic regression.

A total of 950 patients, 208 (21.9%) from Rome and 742 (78.1%) from Montpellier, answered and returned the questionnaire. The index reaction had been immediate in 152 (16%) of patients, and non-immediate (or of unknown chronology) for the remaining 798 patients (84%).

Amongst them, 371 patients (39.0%) retook the same negatively tested drug (re-challenged subjects, 53 from the immediate group (34.8%) and 318 (39.8%) from the non-immediate group). This drug was amoxicillin or amoxicillin/clavulanic acid in most cases (76.5%), followed by cefuroxime (10.8%), oral 3rd generation cephalosporins (cefixime and cefpodoxime, 4.8%), cefaclor (2.1%) and others (5.8%). Female patients were predominant (270, 72.8%). Median age was 27 years (IQR: 9-43).

The index reaction of the re-challenged group was mostly non-immediate¹ (318 cases, 85.7%*). The clinical manifestations consisted of urticaria/angioedema (160, 43.1%), maculo-papular exanthema (MPE) (120, 32.3%), anaphylaxis (57, 15.3%) or other and unknown symptoms (34, 9.1%). In about one tenth of the patients (11.2%), the negatively tested drug was an alternative to their proven allergy to another BL.

Of the 371 patients, 46 (12.4%) described a reaction upon re-exposure, of which 16 (34.7%) were considered as non-compatible with a DHR (e.g., digestive symptoms, mycosis). Hence, of 371 patients, only 30 (8%) were considered potentially hypersensitive (Figure 1) and were offered re-testing. Their initial reaction was mostly non-immediate or of non-specified chronology (27 cases, 90%), and cutaneous (16 cases, 53.3% urticaria/angioedema; 10 cases, 33.3%, MPE), while four patients (13.3%) had had anaphylaxis. Upon re-exposure (Table E1), 6 patients (20%) described anaphylaxis, and all the others, cutaneous symptoms (either MPE, 40% or urticaria/angioedema, 40%). The chronology of the reactions upon re-exposure was the same as the one of the index reaction (10 cases, 33%), faster (6 cases, 20%) or unmatched due to missing data (13 cases, 43%).

Eleven patients (36.7%, including 2 with anaphylaxis upon re-exposure) were re-tested (skin tests, one-day DPT) and proved to be not allergic. Four (13.3%) declined re-testing, and 15 (50%) did not answer several reminders to complete allergy work-up. For the purpose of the study, these 19 patients

¹ If the cut-off between immediate and non-immediate reactions were set at 6 hours after the last drug intake, 61% of the 371 patients would still be in the category of non-immediate reactors.

were considered as potentially hypersensitive, and NPV was calculated at 94.8% (95%CI 92.1-96.8). In the subgroups of immediate and non-immediate index reaction, the NPV was 94.3% and 94.9%, respectively.

We found no difference in terms of sex, asthmatic or atopic status, chronology and clinical manifestations of the index reaction, between patients who had been re-challenged in real-life (371 patients) and those who had not re-taken the drug (579 patients). There were however more non-allergic than allergic patients in the re-challenged group (33.9% versus 18%, $p<0.0001$) and more aminopenicillins than any other BL (84.7% versus 62.3%, $p<0.0001$).

While using the same variables as above, in multivariate logistic analysis performed within the re-challenged patients group, we identified no risk factors of developing a reaction upon re-challenge in real-life conditions.

In this study, the NPV of DPT was high and concordant with previous studies [6-8]. Recommendations regarding DPT performance [9] leave room for interpretation, as for the number of steps and their positioning over time. False-negative DPT may result from too short exposure, and this reasoning would firstly apply to non-immediate DHR. In our studied population of 371 patients, the majority (85%, or 61% according to whether the cut-off between immediate and non-immediate DHR is set at 1h or 6h respectively) had had a non-immediate index reaction. We have recently proven, with data issued from a 20-year experience in DPT, that patients can react as late as 48 hours (or later, in rare cases, up to 8 days), after a full therapeutic dose of BL, administered via a one-day DPT for non-immediate reactions [5]. It can therefore be presumed that a one-day DPT allows at least a 48-hour stimulation of immune cells. Moreover, in the same study, when the chronology of the index reaction (e.g., Day 1, Day 2, etc. of treatment) was matched with the delay of reaction after the last dose administered during DPT (e.g. Day 1, Day 2, etc...), the percentage of match was above 96%. These observations go against the hypothesis of the too short exposure. Additional causes of false-negative DPT have been hypothesized (e.g., missing co-factors, too long a time interval from the index reaction) [8] and they may apply to our cohort, although none can be thoroughly confirmed.

Drug provocation test is an intervention and, as for any intervention, it is important to balance the benefits with the potential harms and incorporate both in the decision-making process. In our study, if we consider the one-day DPT as the “reference” intervention and the re-challenge in real-life conditions as a prolonged DPT (the “exposure”), the NNH is 16.6 (calculation available in Table E2). Thus, we would have to perform 16 prolonged DPT in order to capture one reaction. Antimicrobial stewardship is a major current issue in the public health field, and as allergists, we respond to it mostly by antibiotic allergy delabelling [10]. Considering NNH when prescribing prolonged exposures outside a therapeutic context, is consistent with the approach of administering an antibiotic in order to ensure it has minimal impact on subsequent resistance.

Some considerations regarding the debate around one-day or several-day DPT are summarized in Table 1. In the light of these issues, we believe that several-day DPT has not proven its superiority over one-day DPT, for non-immediate reactions. Additionally, the literature regarding follow-up of patients with prolonged DPT to BL in non-immediate DHR concerns paediatric populations and the NPV is very similar to the one found in our study (97% for Ponvert et al [7], 93.3% for Misiroglu et al [8] and 96.4% for Tonson La Tour et al [11]).

It is important to underline that since our previous NPV study [6] of one-day DPT, the number of patients who took the same negatively tested drug has increased from 24.3% to 39%. Although our study was not designed to capture the reasons for it, we can presume it is partly due to education of patients and doctors over time. Ratzon et al [3] noticed a 100% rate of re-administration of the negatively tested BL in prolonged DPT in a paediatric population, versus 75% in one-day DPT ($p=0.02$). In this study, the calculated NNH was 9.

Our study has several limitations: (i) NPV was not evaluated in patients with severe T-cell-mediated reactions, because in this population, DPT is contraindicated; (ii) only 39% of the patients were exposed to a therapeutic course of the negatively tested drug and only 37% of the individuals with recurrent adverse reactions, despite initial negative testing, were re-tested (the others did not complete the allergy evaluation up to present despite several reminders); (iii) the retrospective retrieval of

information via a questionnaire may introduce inaccurate data, since patient recollection of their alleged DHR may be poor. Nevertheless, having re-confirmed a good NPV in a population of predominantly non-immediate reactions, we believe that the adequate cumulative dose to trigger the hypersensitivity reaction is more important than the timing of exposure alone. Moreover, we could not identify clinical predictors of a reaction upon re-exposure. Therefore, unless better, evidence-based justification of prolonged-DPT is provided, we support one-day DPT in suspicions of non-immediate DHR to BL (while observing contraindications of DPT).

Contribution: AMC, MM, AR and PD designed the study. AMC, MM, FG and NBF participated in the collection of data. AMC, NBF and NM analysed the data and performed the statistical analysis. AMC, MM and FG wrote the initial manuscript. AR, PD and NM revised the manuscript. All authors participated in the interpretation of the results and approved the final version of the manuscript. AMC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This study was founded by the University Hospital of Montpellier, via the *Contrat Fort Chercheur* Funds and by the *COBIOPHAD project* (Horizon2020 project, supported by the European Commission, grant # 688448).

Acknowledgements: We thank our collaborators from the Clinical Research Department in Montpellier, for their assistance throughout the study, especially Laetitia FERRANDO, our clinical research technician, for assisting us with data collection.

Conflict of interest: The authors declare no conflicts of interest for this work.

References

- [1] Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009;64(2):183-193.
- [2] Hjortlund J, Mortz CG, Skov PS, Eller E, Poulsen JM, Borch JE, et al. One-week oral challenge with penicillin in diagnosis of penicillin allergy. *Acta Derm Venereol* 2012;92(3):307-312.
- [3] Ratzon R, Reshef A, Efrati O, Deutch M, Forschmidt R, Cukierman-Yaffe T, et al. Impact of an extended challenge on the effectiveness of β -lactam hypersensitivity investigation. *Ann Allergy Asthma Immunol* 2016;116(4):329-33.
- [4] Mori F, Cianferoni A, Barni S, Pucci N, Rossi ME, Novembre E. Amoxicillin allergy in children: five-day drug provocation test in the diagnosis of nonimmediate reactions. *J Allergy Clin Immunol Pract*. 2015;3(3):375-80.
- [5] Chiriac AM, Rerkpattanapipat T, Bousquet PJ, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. *Allergy*. 2017; 72(4):552-61.
- [6] Demoly P, Romano A, Botelho C, Bousquet-Rouanet L, Gaeta F, Silva R, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2010;65(3):327-332.
- [7] Ponvert C, Weilenmann C, Wassenberg J, Walecki P, Bourgeois ML, de Blic J, et al. Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. *Allergy* 2007;62(1):42-46.
- [8] Misirlioglu ED, Toyran M, Capanoglu M, Kaya A, Civelek E, Kocabas CN. Negative predictive value of drug provocation tests in children. *Pediatr Allergy Immunol* 2014;25(7):685-90.

[9] Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58(9):854-863.

[10] Trubiano JA, Stone CA, Grayson ML, Urbancic K, Slavin MA, Thursky KA et al. The 3 Cs of Antibiotic Allergy-Classification, Cross-Reactivity, and Collaboration. *J Allergy Clin Immunol Pract* 2017;5(6):1532-1542. Erratum in: *J Allergy Clin Immunol Pract* 2018;6(1):323.

[11] Tonson la Tour A, Michelet M, Eigenmann PA, Caubet JC. Natural History of Benign Nonimmediate Allergy to Beta-Lactams in Children: A Prospective Study in Retreated Patients After a Positive and a Negative Provocation Test. *J Allergy Clin Immunol Pract* 2017: S2213-2198(17)30789-4. doi: 10.1016/j.jaip.2017.10.008. [Epub ahead of print]

[12] Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. *Allergy* 2014;69(4):420-437.

Legends

Figure 1. Flow chart of the study

BL, betalactam; DHR, drug hypersensitivity reaction; MPE, maculo-papular exanthema

In italics, the patients who were retested.

“Other” designates undefined cutaneous reactions, rhino-conjunctivitis, or unknown reactions.

“Non-compatible” designates reactions upon retreatment that are not compatible with a DHR (e.g., mycosis, vomiting).

Table 1. PROs and CONs of one-day and several-day DPT

BL, betalactam; *DHR*, drug hypersensitivity reaction; *DPT*, drug provocation test; *NPV*, negative predictive value

Table E1. Table E1. The clinical characteristics of the patients who reacted upon re-challenge in real-life situations.

The patients are numbered according to their centre.

Ampi, ampicillin; Amox, amoxicillin; AO, angioedema; Clavulanic, clavulanic acid; F, female; M, male;

MPE, maculopapular exanthema; ND, not determined; U, urticarial

Table E2. Calculation of the number needed to harm (NNH)

NNH, number needed to harm

The debate between the two protocols of DPT is on whether we...	One-day DPT Addresses all types of suspected DHR	Several-day DPT Addresses non-immediate suspected DHR
...increase sensitivity in non-immediate suspected DHR	It has a very satisfactory NPV (>90%), reproduced in several studies.	Few data are available regarding NPV for prolonged DPT. In paediatric populations where it was studied, the NPV is similar to that of one-day DPT (>90%).
...reassure patients/doctors	The gap in awareness/knowledge could be filled by enhanced education <i>Of note: non-immediate reactions following a negative one-day DPT are described as mild/moderate.</i>	Patients and doctors might be (falsely) re-assured by the reproducibility of the initial lapse of time. <i>Of note: non-immediate reactions following a negative several-day DPT are described as mild/moderate.</i>
...capture late reactions	A therapeutic dose of BL administered on Day 1 may induce DHR as far as 48h after the intake (and up to 8 days, in extreme cases).	Many reports of prolonged-DPT do not include a wash-out period after Day 1 dose, therefore, at least some reactions occurring on Day 2 or onwards can presumably be due to the Day 1 dose.
...capture severe reactions (i.e., anaphylactic)	No intervention has been efficacious in detecting the risk of an anaphylactic reaction upon re-exposure after a negative drug allergy work-up including DPT. International experts agree that “consideration may be given to retesting individuals with particularly severe previous reactions to a BL” [12]. Further large studies are still needed to determine the utility of a boost test.	Prolonged exposures do not address immediate reactions, therefore, it cannot be presumed to capture anaphylactic reactions.
...capture old/new sensitization	The percentage of subjects with reactions upon re-challenge in real-life approaches the incidence in general population, so new sensitization following a negative DPT cannot be excluded.	It cannot be excluded that a reaction occurring on Day 2 or onwards may be due to new sensitization during prolonged DPT, instead of old sensitization.
...consider the number needed to harm	A one-day therapeutic dose is administered, keeping the unnecessary (in otherwise healthy individuals) exposure to	About a dozen patients should be tested with a prolonged DPT in order to capture one mild/moderate non-immediate

	its minimum.	reaction.
...think larger than our domain	One-day DPT addresses the need for pragmatic and effective interventions.	Considering the concern for antimicrobial stewardship, bacterial resistance as well as economic costs of prolonged or full-therapeutic courses should be taken into account when considering prolonged DPT.

Table 1. PROs and CONs of one-day and several-day DPT.

BL, betalactam; *DHR*, drug hypersensitivity reaction; *DPT*, drug provocation test; *NPV*, negative predictive value

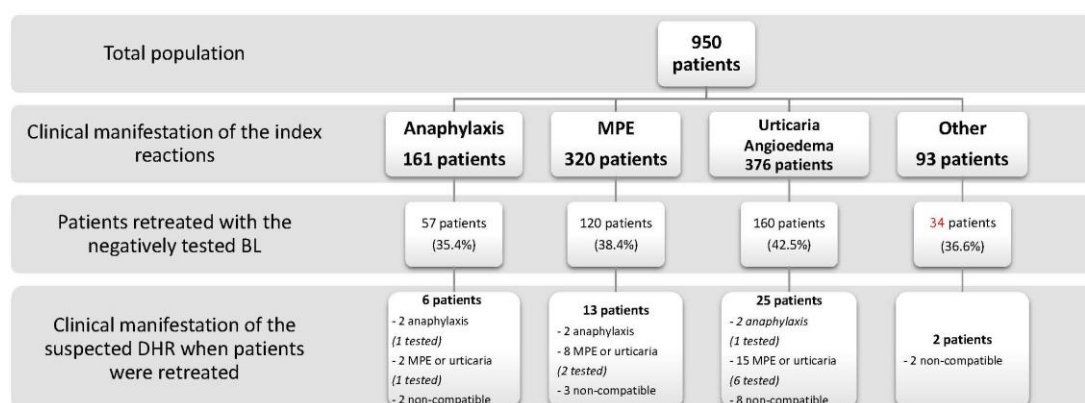
Figure 1. Flow chart of the study.

BL, betalactam; DHR, drug hypersensitivity reaction; MPE, maculo-papular exanthema

In italics, the patients who were retested.

"Other" designates undefined cutaneous reactions, rhino-conjunctivitis, or unknown reactions.

"Non-compatible" designates reactions upon retreatment that are not compatible with a DHR (e.g., mycosis, vomiting).



#Patient	Sex	Drug	Index Reaction	Chronology Index Reaction	Reaction upon re-exposure	Chronology upon re-exposure	Re-tested
Rome_15	F	Ampi	MPE	1h-6h	MPE	1h-6h	No
Rome_47	F	Amox+Clavulanic	MPE	1h-6h	MPE	1h-6h	No
Rome_69	F	Amox+Clavulanic	U	1h-6h	MPE	1h-6h	No
Rome_206	F	Amox+Clavulanic	U	>24h	MPE	ND	No
Mtpl_1	F	Amox+Clavulanic	U	ND	Anaphylaxis	1h-6h	Yes
Mtpl_2	F	Amox	U	1h - 6h	U	1h-6h	Yes
Mtpl_45	M	Amox	MPE	< 1h	U	>24h	No
Mtpl_55	M	Cefpodoxime	U	6h-24h	U	1h-6h	No
Mtpl_76	M	Cefuroxime	Anaphylaxis	> 24h	U	1h-6h	Yes
Mtpl_91	F	Amox+Clavulanic	U	1h - 6h	AO	1h-6h	No
Mtpl_94	F	Amox+Clavulanic	U	ND	U	1h-6h	Yes
Mtpl_159	F	Amox	U	1h-6h	U	1h-6h	Yes
Mtpl_160	F	Amox+Clavulanic	U	> 24h	U/AO	1h-6h	No
Mtpl_173	F	Amox	MPE	ND	U	6h-24h	Yes
Mtpl_216	F	Amox	U	> 24h	MPE	6h-24h	Yes
Mtpl_225	F	Amox	U	< 1h	Anaphylaxis	<1h	No
Mtpl_229	F	Amox+Clavulanic	Anaphylaxis	6h-24h	Anaphylaxis	ND	No
Mtpl_237	F	Amox	U	1h - 6h	U	1h-6h	No
Mtpl_243	F	Amox+Clavulanic	U	< 1h	MPE	ND	No
Mtpl_295	F	Amox	Anaphylaxis	ND	Anaphylaxis	1h-6h	Yes
Mtpl_316	F	Amox+Clavulanic	U	ND	MPE	1h-6h	Yes
Mtpl_374	M	Amox	AO + MPE	> 24h	AO	>24h	No
Mtpl_441	F	Amox	MPE	ND	Anaphylaxis	<1h	No
Mtpl_445	F	Amox	U	6h-24h	MPE	6h-24h	No
Mtpl_557	F	Amox	Anaphylaxis	> 24h	MPE	6h-24h	No
Mtpl_560	M	Amox+Clavulanic	MPE	> 24h	MPE	1h-6h	No
Mtpl_588	M	Amox+Clavulanic	U	> 24h	MPE	ND	Yes
Mtpl_600	M	Amox	MPE	ND	MPE	1h-6h	No
Mtpl_609	F	Cefaclor	MPE	ND	AO	<1h	Yes
Mtpl_737	F	Amox	MPE	ND	Anaphylaxis	1h-6h	No

Table E1. The clinical characteristics of the patients who reacted upon re-challenge in real-life situations.

LEGEND

The patients are numbered according to their centre;

Ampi, ampicillin;

Amox, amoxicillin;

AO, angioedema;

Clavulanic, clavulanic acid;

F, female;

M, male;

MPE, maculopapular exanthema;

ND, not determined;

U, urticaria

Table E2. Calculation of the number needed to harm (NNH)

A) Patients that have had a prolonged exposure in our series = patients that re-took the drug for several days, in real-life conditions

	Re-challenge in real-life conditions
	« exposure »
Reaction +	24*
Reaction -	341
Total	365

$\text{Risk}_{\text{reference}} = 0$ (i.e., all these patients are negative in one-day DPT)

$\text{Risk}_{\text{exposure}} = 24/365 = 0.06$

$\text{NNH} = 1/(\text{Risk}_{\text{exposure}} - \text{Risk}_{\text{reference}}) = 1/0.06 = 16.6$

* 30 patients (with compatible DHR after negative allergy work-up), minus 6 patients (with anaphylaxis and chronology <6h after the drug administration, they stopped the administration on Day1 of exposure, due to the reaction) = 24 patients with reactions upon prolonged exposure, of a total of 365 exposures

B) Example of calculation of NNH for the article of Ratzon *et al* 2016

	5-day DPT
	« exposure »
Reaction +	3
Reaction -	23
Total	26

$\text{Risk}_{\text{reference}} = 0$ (i.e., all these patients are negative in one-day DPT)

$\text{Risk}_{\text{exposure}} = 3/26 = 0.11$

$\text{NNH} = 1/(\text{Risk}_{\text{exposure}} - \text{Risk}_{\text{reference}}) = 1/0.11 = 9$