

# **Prevalence of latex allergy may be vastly overestimated when determined by in vitro assays.**

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## **Abstract**

**BACKGROUND:** The prevalence of latex-specific IgE computed from the results of serologic assays is commonly thought to reflect, to a greater or lesser extent, the prevalence of latex allergy and its implied risk.

**OBJECTIVE:** The study examines how imperfect test specificity of in vitro assays influences the precision of latex allergy prevalence that it estimates.

**METHODS:** Various models encompassing a range of hypothetical test sensitivity and specificity values are investigated to gauge their influence on the estimate of latex allergy prevalence. The models examine these interactions in situations of high or low allergy prevalence.

**RESULTS:** Serologic latex diagnostic assays with test specificity within the range of those of commercially available assays can greatly overestimate prevalence where the true prevalence is low (eg, of the order of one in 100 or one in 1,000). A formula to correct for errors in prevalence estimates arising from imperfect test sensitivity and specificity of an in vitro assay is presented.

**CONCLUSION:** While serologic assays for latex IgE pose few hazards to the patient and are useful for confirming the diagnosis of latex allergy, the test results may vastly overestimate the true prevalence of latex allergy and its associated risks in situations where latex allergy is actually rare.

Full paper follows ...

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## INTRODUCTION

While there have been increasing reports of latex allergy in recent years,<sup>1–3</sup> it is not clear to what extent this reflects an actual rise in its incidence, and how much can be attributed to latex allergy being more commonly recognized than before. It is useful to monitor the shifts in the incidence of latex allergy over time to understand the epidemiology and risk factors associated with it. To set baselines for its current prevalence, screening tests to diagnose latex allergy should be performed on representative samples for various sectors of the population. Whereas a detailed study of the clinical history of the subject is important in diagnosing allergy, this may not always be possible when screening large populations. Skin-prick tests are con-

sidered the most reliable tests to diagnose latex allergy<sup>4–8</sup> and they are often taken as the 'gold standard' against which other assays are compared.<sup>5,7</sup> Very few researchers would classify a patient with a negative skin test result as being unequivocally allergic to latex, irrespective of his clinical history. In fact, many studies adopt the premise that the skin prick test (sometimes supplemented by clinical history) defines the true positive reaction. In such cases, the presence or absence of an immediate allergic skin reaction would—by definition—represent a test result with 100% sensitivity and close to 100% specificity. (Specificity may fall short of 100% if wheal formation were induced by a non-allergic reaction.) The utility of the skin prick test notwithstanding, in vitro serologic tests are often undertaken with or without verification of latex allergy by skin prick or other clinical assessment<sup>9–13</sup> to avoid the possible systemic reactions to skin prick testing and provocation tests. In the United States no skin prick

test reagent has been licensed by the Food and Drug Administration.

## TRUE AND FALSE POSITIVE OUTCOMES OF SEROLOGIC ASSAYS

It is not unusual for in vitro serologic test outcomes to be at variance with the clinical assessment of latex allergy.<sup>4,14,15</sup> An in vitro latex allergy test that generates a positive/negative outcome is liable to two major sources of error. A *false negative* error occurs when the assay fails to diagnose an allergic test subject as such. A *false positive* error occurs when the assay misdiagnoses a non-allergic test subject as being allergic. The latter could be due either to the assay being flawed, giving rise to a positive test outcome even when no IgE is present, or it could be an irrelevant positive test result where IgE is detected in a sensitized but asymptomatic subject. The propensity of an assay to false negative or false positive outcomes is gauged by its test sensitivity and test specificity respectively.

Test sensitivity and test specificity of an assay are calculated as:

Sensitivity (%)

$$= \frac{\text{No of TP detected by the assay}}{\text{Total number of TP + FN present in the test sample}} \times 100$$

Specificity (%)

$$= \frac{\text{No of TN detected by the assay}}{\text{Total number of TN + FP present in the test sample}} \times 100$$

where TN = true negative, FP = false positive, and No = number. While the prevalence of latex-specific IgE is thought to reflect the prevalence of actual latex allergy, deficiencies in di-

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agnostic sensitivity and specificity—particularly the latter—can distort test results. As will be discussed below, overestimates of the true latex allergy prevalence becomes especially significant where prevalence is low. The effect of test specificity on the accuracy of diagnostic screening is commonly covered in publications on diagnostic test interpretation. As the wellbeing of the patient being tested is of primary concern, many texts (eg, Galen and Gambino,<sup>16</sup> Motulsky<sup>17</sup>) emphasize the predictive value of the tests under conditions of imperfect specificity and discuss how low prevalence could lead to wrong interpretation of an in vitro test result. Less well discussed is the converse: how the inappropriate use of test results can lead to erroneous estimation of prevalence. While most researchers are prepared for some degree of mismatching when relating in vitro test results to the clinical reaction, they may fail to recognize that such overestimates may become quite large.

To illustrate the point, let us say that the prevalence of latex allergy is estimated using a test kit with a sensitivity of 95% and a specificity of 90%. Let us suppose that the true prevalence of latex allergy in the population being studied is 5%. The number of true positive outcomes of the assay is then given by  $5 \times (\text{Sensitivity})\% = 4.75$  per hundred. Besides these true positives, there will be other positive outcomes derived from the tests. These are the false positives; ie, non-allergic subjects wrongly diagnosed as being allergic because the specificity of the test is imperfect. If the test diagnoses non-allergics correctly 90% of the time, then it misdiagnoses the other 10% of the time. In this hypothetical population, non-allergics make up 95% of the sample. The number of false positives will therefore be  $95 \times (100 - \text{specificity})\% = 9.5$  per hundred. It is evident from this example that the number of false positives can in fact be *double* that of the true positives. The total number of positives, both true and false, comes to 14.25 per hundred. If the value is then taken as the prevalence of latex allergy, the es-

timate would be off—not by 10% as the test specificity figure might superficially suggest to some—but by 285%, ie, an almost 3-fold overestimate as compared with the true prevalence of 5 per hundred.

How did this vast inflation in the prevalence estimate come about? Because of the relative scarcity of allergic patients, the number of patients tested who are in fact nonallergic is large (95 out of 100 in the above example). In this example where specificity is 90%, even 10% of the 95 nonallergic patients amounts to a very significant number when compared with the 5 patients who are truly allergic.

The apparent prevalence (AP) based on the diagnostic test outcomes in a series of assays is calculated as:

Equation 1

$$AP = \frac{TP \times Sen}{100} + \frac{(100 - TP)(100 - Spe)}{100}$$

True positives      False positives

where AP = Apparent prevalence (%)

TP = True prevalence (%)

Sen = Test sensitivity (%)

Spe = Test specificity (%)

The total number of positive outcomes (apparent prevalence) are derived both from allergic test subjects who are correctly diagnosed as positive (true positives) and from non-allergic test subjects who are incorrectly diagnosed as positive (false positives). It is when the number of false positives is large in comparison with the number of true positives that serious errors arise in estimates of prevalence.

#### CORRECTING FOR IMPERFECT TEST SENSITIVITY AND SPECIFICITY

Given the sensitivity and specificity of an in vitro diagnostic, the true preva-

lence (TP) can be obtained from the test data (apparent prevalence) using the following correction formula that is derived from Equation 1:

Equation 2

$$TP = \frac{(AP + Spe - 100)100}{(Sen + Spe - 100)}$$

where  $Sen + Spe \neq 100$

where TP = True prevalence (%)

AP = Apparent prevalence (%)

Sen = Test sensitivity (%)

Spe = Test specificity (%)

The above correction is more useful where the prevalence is not too low (eg, exceeding 10%). As prevalence decreases, the estimated true prevalence becomes increasingly sensitive to small variances in the apparent prevalence. Thus, where latex allergy is very rare, even slight changes in the apparent prevalence give rise to quite massive changes in the estimated true prevalence. The correction formula also requires the test sensitivity and, especially, the test specificity to be determined with good accuracy. The last point is significant considering that test specificity can vary considerably between laboratories for the same assay, depending on the exact experimental protocol employed. For example, values as high as 97%<sup>18</sup> and as low as 33%<sup>4</sup> have been reported for the AlaSTAT latex immunoassay.

#### INFLUENCE OF TEST SPECIFICITY AND TRUE PREVALENCE ON THE PRECISION OF THE PREVALENCE ESTIMATE

The true prevalence of latex allergy in a sample and the specificity of the test employed have an important bearing on the precision of the calculated (apparent) prevalence. Examination of Equation 1 shows that as true prevalence decreases and approaches zero, the apparent prevalence approaches a value equal to  $(100 - \text{specificity})$ . Even in the extreme case where the true prevalence were zero (ie, if everyone in the sample were truly non-all-

gic), substituting for true prevalence (TP) = 0 in Equation 1 will give an apparent prevalence (AP) of (100 – specificity). These false positives are unavoidable so long as the test specificity falls short of 100%. In the general case, the calculated apparent prevalence does not fall below (100 – specificity) which is essentially the proportion of false positives that an assay generates. Hence, any estimation of prevalence would have to begin from this ‘false positive’ baseline.

To appreciate how these important characteristics might affect estimates of latex allergy prevalence, the apparent prevalence is calculated in Tables 1 to 3 for various true prevalence situations using sensitivity and specificity values similar to those claimed by the manufacturers of three latex diagnostics that are commercially available. The three latex immunoassays endorsed by the US Food and Drug Administration are the Upjohn-Pharmacia CAP assay<sup>19</sup> (sensitivity = 74.8% and specificity = 93.8%), the DPC AlaSTAT assay<sup>20</sup> (sensitivity = 86.9 and specificity = 85.2) and the Hycor Latex Allergen Specific IgE EIA<sup>21</sup> (sensitivity = 91.4 and specificity = 96.0). Starting from a prevalence of 100%, the apparent prevalence decreases as the true prevalence decreases, but the declining trend in the former flattens out as the true prevalence approaches zero. Values close to (100 – specificity), ie, 6.2%, 14.8% and 4.0% for the three assays are encountered irrespective of whether the

Table 2. Outcomes of in Vitro Tests as Influenced by Diagnostic Sensitivity and Specificity Values Similar to those Claimed by the DPC AlaSTAT Assay\*

True Prevalence (%)	True Positives (per hundred)	False Positives (per hundred)	Total Positives (per hundred)	Underestimate or Overestimate
100	86.90	0	86.90	0.87 ×
50	43.45	7.40	50.85	1.02 ×
20	17.38	11.84	29.22	1.46 ×
10	8.69	13.32	22.01	2.20 ×
5	4.35	14.06	18.41	3.68 ×
1	0.87	14.65	15.52	15.52 ×
0.5	0.43	14.73	15.16	30.32 ×
0.1	0.09	14.78	14.88	148.80 ×
0	0	14.80	14.80	–

\* Sensitivity = 86.9% and specificity = 85.2%. The manufacturer of AlaSTAT has also cited 93.8% sensitivity and 80.6% specificity in another trial.

Table 3. Outcomes of in Vitro Tests as Influenced by Diagnostic Sensitivity and Specificity Values\* Similar to those Claimed by the Hycor Latex Allergen Specific IgE EIA

True Prevalence (%)	True Positives (per hundred)	False Positives (per hundred)	Total Positives (per hundred)	Underestimate or Overestimate
100	91.40	0	91.40	0.91 ×
50	45.70	2.00	47.70	0.95 ×
20	18.28	3.20	21.48	1.07 ×
10	9.14	3.60	12.74	1.27 ×
5	4.57	3.80	8.37	1.67 ×
1	0.91	3.96	4.87	4.87 ×
0.5	0.46	3.98	4.44	8.88 ×
0.1	0.09	4.00	4.09	40.90 ×
0	0	4.00	4.00	–

\* Sensitivity = 91.4% and specificity = 96.0%.

true prevalence is 1%, 0.1% or 0% (Tables 1, 2, and 3). Thus, as test specificity decreases, the assay becomes increasingly prone to over-estimating the true allergy prevalence. Consequently, the smaller the true prevalence is, the greater would be the *proportional* inflation due to the imperfect

test specificity. For example, if the true prevalence were 10%, the overestimate would be 2.2-fold when calculated using the AlaSTAT sensitivity and specificity values. When the true prevalence falls to 1%, the over-estimate increases to over 15-fold, and this increases further to almost 150-fold when true prevalence is one in 1,000 (Table 2). This trend is also true when calculating prevalence using the sensitivity and specificity values for the other two diagnostics, Pharmacia and Hycor.

## TEST OUTCOMES IN HIGH-PREVALENCE AND LOW-PREVALENCE GROUPS

From the above, it can be seen that the precision of the serologic assay would vary with the true prevalence of the test sample. If the test sample were made up mainly of latex-allergic patients, for example, the percentage of

Table 1. Outcomes of in Vitro Tests as Influenced by Diagnostic Sensitivity and Specificity Values\* Similar to those Claimed by the Upjohn-Pharmacia CAP Assay

True Prevalence (%)	True Positives (per hundred)	False Positives (per hundred)	Total Positives (per hundred)	Underestimate or Overestimate
100	74.80	0	74.80	0.75 ×
50	37.40	3.10	40.50	0.81 ×
20	14.96	4.96	19.92	1.00 ×
10	7.48	5.58	13.06	1.31 ×
5	3.74	5.89	9.63	1.93 ×
1	0.75	6.14	6.89	6.89 ×
0.5	0.37	6.17	6.54	13.08 ×
0.1	0.07	6.19	6.26	62.60 ×
0	0	6.20	6.20	–

\* Sensitivity = 74.8% and specificity = 93.8%.



positives would be very high and the error would correspondingly be small and less important. On the other hand, overestimate of the prevalence takes on increasing significance as negative outcomes dominate the test results. For example, inflation in the prevalence figure would be markedly greater in a random sampling of hospital workers, the vast majority of whom would still be expected to be non-allergic despite their being a high-risk group. Needless to say, the margin of overestimate for a low-risk group would be far wider. Tests on the last group, where the impact of overestimating latex allergy prevalence is greatest, include those made on samples collected from a cross-section of the general population. For example, Ownby et al reported a prevalence of 6.4% for latex-specific IgE in volunteer blood donors using the AlaSTAT assay.<sup>10</sup> This is below even the 14.8% 'false positive' baseline (Table 2) that might be expected from the AlaSTAT assay (using the manufacturer's specificity value) in the extreme case where the true prevalence of latex allergy is zero. As stated above, estimates of test specificity for the same assay can vary between laboratories; hence, it is likely that the authors' assay had a test specificity better than that claimed by the manufacturer (for example, by repeating test results or confirming tests with inhibitory assays). Unless the test specificity had been 100%, nevertheless, the true prevalence of latex allergy in the blood donors could have been substantially below the estimate of 6.4% for IgE prevalence. As a comparison, it is noteworthy that an estimate based on skin tests (where test specificity is equal, or close to 100% by its nature) places the prevalence of latex allergy in the general Finnish<sup>1</sup> and French<sup>22</sup> populations at an order of one in 1,000.

Where the prevalence of sensitivity to latex had been computed from serologic assays in various studies appearing in the literature,<sup>9-13</sup> the authors were careful to state that the test results estimated the prevalence of latex-specific IgE antibodies rather than latex

allergy. But while no claims were made that the IgE data estimated allergy prevalence, neither did the reports highlight the fact that the relationship between allergy prevalence and IgE prevalence broke down as the former declined. The consequence of this was left unstated as well. Attention was not drawn to the fact that latex IgE prevalence estimated for the general population, for example, might have little bearing on the potential risks associated with latex allergy. There are no good data to indicate to what extent a sensitized but asymptomatic subject might be more liable to latex allergy in the future without further exposure to latex.

#### 'RARE EVENT PREDICTION ERROR' OF IN VITRO ASSAYS

The potential inflation of prevalence estimates is of course not confined to latex allergy. Sometimes referred to in Bayesian statistics as a 'rare event prediction error,' it applies to any estimate of occurrences that are relatively rare using a test method where the test specificity is imperfect. It would therefore apply to the results of any clinical assay that is used to estimate prevalence in the general low risk population. The potential error is far less serious (though not necessarily negligible) in the cases where high test specificity is achievable. To put matters into perspective, consider the example where the true prevalence of a clinical condition being investigated were one in a thousand (0.1%), and the test sensitivity and specificity of the assay were 100% and 99% respectively. It can be shown by substituting into Equation 1 that the apparent prevalence estimated from the test result (without using the correction in Equation 2) is still eleven times that of the true prevalence. Similarly, if the true prevalence were one in ten thousand, the apparent prevalence is a hundred times that of the true prevalence.

#### CONCLUSION

In vitro latex diagnostic tests based on latex-specific IgE pose few hazards to the patient, and they do a good job

when used for the purpose they are designed (ie, to confirm the diagnosis of latex allergy in patients). Where latex allergy is rare (eg, in the general population), however, latex IgE assays may vastly overestimate the true prevalence of latex allergy and its associated risks.

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