

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence of latex sensitisation and allergy and associated risk factors amongst health care workers using hypoallergenic latex gloves at King Edward VIII hospital, KwaZulu-Natal South Africa: A cross sectional study
AUTHORS	Phaswana, Shumani; Naidoo, Saloshni

VERSION 1 - REVIEW

REVIEWER	Prof Dick Heederik, Head Division Environmental Epidemiology IRAS Utrecht University The Netherlands
REVIEW RETURNED	01-Apr-2013

GENERAL COMMENTS	<p>General</p> <p>This is a well written cross-sectional study among latex glove exposed health care workers. There is only one major issue which might be considered in the analysis. Because there are some differences with regard to age and employment duration between exposed and controls, it would be of interest to give some emphasis to an analysis including exposed only for some of the exposure variables.</p> <p>Introduction</p> <p>A clear distinction should be made between sensitization (can be asymptomatic) and allergy (symptomatic). Details about the specific hospitals in SA where latex allergy or sensitization has been studied can be limited. This is not of great interest to international readers. It is sufficient to explain that latex allergy or sensitization is prevalent in SA and has been observed in several studies. In addition, details about SA legislation is not necessarily interesting for international readers either. Please bring back the information to what is relevant and interesting for international readers. The message of the introduction, that intervention measures (producing powder free gloves) might not be fully effective is the key message. This message should not be snowed under by unnecessary details.</p> <p>A reference should be given to evidence based analyses of the latex literature (for instance de la Montagne in OEM http://www.ncbi.nlm.nih.gov/pubmed/16469822) and the recent European Respiratory Society guidelines for management of occupational asthma, which both contain clear statements regarding latex allergy prevention (http://www.ncbi.nlm.nih.gov/pubmed/22654083 and http://www.ncbi.nlm.nih.gov/pubmed/22379148).</p> <p>Line 127: while it is important to diagnose etc., , add, "in an early stage of disease" and refer to surveillance.</p> <p>Methods</p>
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	<p>Line 151: when was this policy fully implemented? Line 152: remained sensitive or remained sensitized? The 6% background prevalence seems relatively high also in comparison with other studies. To what extent does cross-reactivity with other agents possibly play a role? Line 164: degrees of the field worker can be removed. Reduce level of detail. Line 184: remove who trained the field technicians Line 218: why was departmental glove use omitted? The analysis involves logistic regression analysis. This is appropriate but could be expanded by the use of generalized additive models which can produce splines which may help in visualizing relationships for some of the continuous exposure variables.</p> <p>Results Sometimes, statements are incomplete for instance like in line 262. Working as an enrolled nurse ... etc. compared to which other job titles? ORs involve always relative comparisons. Line 274: what is meant with personal history? Personal history of latex allergy? Other? Line 277: do not only focus on statistical significance. Give ORs as well. Line 280: estimates of the OR above 2. How should an association with glove use during the last seven days be interpreted? Is the idea that recent use influences symptomatology?</p> <p>Discussion Section starting with line 303: a healthy worker effect seems more plausible. This is a cross-sectional study and associations should be interpreted with care. The fact that HCWs with allergy/sensitization work more often with powder free gloves is indicative of reversed causality because of symptoms. Thus, there is a complex interplay between the HWE which worked over a long period, probably especially in the early years of the older employees, when powder free gloves were not available, reversed causality and exposure reduction by the introduction of powder free gloves. This complex interplay should be emphasized. Some of the associations seem clear indicators of these different effects. It should also be emphasized, although latex is one of the best studied allergens, no exposure response studies have been published with measured latex allergen levels. In combination with the observations that allergen content can vary, this may lead to discrepancies in the literature with regard to the role of duration of employment as a surrogate of exposure. Some of the major limitations in the latex literature should be emphasized.</p> <p>Atopy. the role of atopy is complex, because some individuals might also have become atopic after having been latex sensitized. similarly, cross-reactivity between allergens may lead to inflated associations. Cohort studies are necessary to disentangle this phenomenon. Again, this is a limitation of a cross-sectional study and should be emphasized briefly. there is no need for a detailed comparison with other studies. This is basically an uninteresting comparison of methodological problems.</p>
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REVIEWER	Prof. Cândida Tomaz Health Sciences Research Center University of Beira Interior,
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	Covilhã, Portugal
	No competing interests to declare
REVIEW RETURNED	03-Jun-2013

GENERAL COMMENTS	<p>This is a very interesting study about latex allergy prevalence, with an accurate description of the methods, results and discussion, supported by a correct statistical analysis. Despite the limitations reported by the authors, regarding to the misclassification of exposure and atopy respectively, I think that this study can be accepted to be published in BMJ Open.</p> <p>Minor comments:</p> <p>Page-10, line 188, please indicate the concentration (%) of histamine solution</p> <p>Page 11, line 206 the sentence is confusing</p> <p>Page 15, line 310, Smith is in lower case</p>
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VERSION 1 – AUTHOR RESPONSE

General

COMMENT: This is a well written cross-sectional study among latex glove exposed health care workers. There is only one major issue which might be considered in the analysis. Because there are some differences with regard to age and employment duration between exposed and controls, it would be of interest to give some emphasis to an analysis including exposed only for some of the exposure variables.

ANSWER: This was explored in the analysis and analysis of the exposed group only for variables such as age, duration of employment and type of gloves did not differ significantly compared to analysis of the whole group.

Introduction

COMMENT: A clear distinction should be made between sensitization (can be asymptomatic) and allergy (symptomatic).

ANSWER: A clear distinction has been made between latex sensitisation and latex allergy on page7
Line 104-107 “HCWs using these gloves are exposed via direct dermal contact and are at risk for developing latex sensitization which maybe asymptomatic and if exposure continues they can later develop latex allergy which presents with clinical manifestations”

COMMENT: Details about the specific hospitals in SA where latex allergy or sensitization has been studied can be limited. This is not of great interest to international readers. It is sufficient to explain that latex allergy or sensitization is prevalent in SA and has been observed in several studies.

ANSWER: Details on specific Hospitals in South Africa has been limited. The following sentences have been removed.

“Latex allergy comprised an estimated 1.4 % of all occupational diseases reported by the Surveillance of Work Related and Occupational Respiratory Diseases of South Africa programme (SORDSA) between 1996 and 1998.¹⁸ In 2000 De Beers and De Villiers documented a high prevalence (20.8%) of latex sensitisation among theatre and laboratory staff (n=277) employed at Tygerberg hospital in the Western Cape Province.¹⁵ Potter and colleagues conducted a latex allergy screening survey among Groote Schuur hospital employees. They reported latex sensitisation of 11.9% among 969 respondents with the majority of sensitised HCWs being nursing staff (64%) followed by doctors (10%), technologists (8%), paramedics (7%) and cleaners (6%).¹⁶ A 2001 survey at the Red Cross childrens hospital in Cape Town reported a latex sensitisation prevalence of 7% amongst the HCWs working in clinical and laboratory areas of the hospital.”

COMMENT: In addition, details about SA legislation is not necessarily interesting for international readers either. Please bring back the information to what is relevant and interesting for international readers. The message of the introduction, that intervention measures (producing powder free gloves) might not be fully effect is the key message. This message to not be snowed under by unnecessary details.

ANSWER: the following specifics about South African legislation have been removed.

“In South Africa the health and safety of workers is regulated by the Occupational Health and Safety Act No 85 of 1993 (OHSA).²⁵ The accompanying Hazardous Chemical Substances Regulations No?? (HCS) of OHSA has tasked the employer with ensuring health and safety in the workplace by applying the hierarchy of hygiene controls in addressing workplace hazardous chemicals.²⁵ In South African hospitals the procurement of latex gloves is based on the cost of gloves and the stock is obtained from various providers who meet the South African Bureau of Standards (SABS) specifications for latex gloves.”

COMMENT: A reference should be given to evidence based analyses of the latex literature (for instance de la Montagne in OEM <http://www.ncbi.nlm.nih.gov/pubmed/16469822>) and the recent European Respiratory Society guidelines for management of occupational asthma, which both contain clear statements regarding latex allergy prevention (<http://www.ncbi.nlm.nih.gov/pubmed/22654083> and <http://www.ncbi.nlm.nih.gov/pubmed/22379148>).

ANSWER: references have been given as suggested.

Reference 24-26 cited in Line 112-114

24. LaMontagne AD, Radi S, Elder DS, Abramson MJ and Sim M. Primary prevention of latex related sensitisation and occupational asthma: a systematic review. Occupational and environmental medicine. 2006; 63: 359-64.

25. Heederik D, Henneberger PK, Redlich CA and Asthma ERSTFotMoW-r. Primary prevention: exposure reduction, skin exposure and respiratory protection. European respiratory review : an official journal of the European Respiratory Society. 2012; 21: 112-24.

26. Baur X and Sigsgaard T. The new guidelines for management of work-related asthma. The European respiratory journal. 2012; 39: 518-9.

COMMENT: Line 127: while it is important to diagnose etc., , add, "in an early stage of disease" and refer to surveillance.

ANSWER: "In the early stages of the disease" has been added on page7 lines 108-109

Methods

COMMENT: Line 151: when was this policy fully implemented?

ANSWER: The policy was implemented in 2001 and this has been included on page 8 line 133

COMMENT: Line 152: remained sensitive or remained sensitized?

ANSWER: "remained sensitised" now on page 8 line 134

COMMENT: The 6% background prevalence seems relatively high also in comparison with other studies. To what extent does cross-reactivity with other agents possibly play a role?

ANSWER: the 6% background prevalence was estimated based on the study by Smith (2005) which showed that about 70% of healthcare workers remained latex specific SPT 5 years following a complete ban on powdered latex gloves. It is however possible that cross reactivity with other agents such as fruits play an important role as well. Unfortunately budgetary constraints did not allow us to study these aspects.

COMMENT: Line 164: degrees of the field worker can be removed. Reduce level of detail.

ANSWER: the degrees of fieldworker have been removed from line 146

COMMENT: Line 184: remove who trained the field technicians

ANSWER: the details of who trained the fieldworker have been removed

"by the Chief Pulmonary Technician at Inkosi Albert Luthuli Central hospital (A Quaternary Hospital in KwaZulu-Natal)"

COMMENT: Line 218: why was departmental glove use omitted?

ANSWER: "Departmental glove consumption was omitted as this only indicated annual distribution of gloves per department and not necessarily employees' exposure since enrolled nursing assistants

and enrolled nurses are rotated through different departments in any given year.” has been added on pages 11 and 12 lines 199-202

COMMENT: The analysis involves logistic regression analysis. This is appropriate but could be expanded by the use of generalized additive models which can produce splines which may help in visualizing relationships for some of the continuous exposure variables.

ANSWER: “Fractional polynomial and a fractional plot was used to visualise the dose-response relationship of these continuous exposure variables.” has been inserted on page 12 line 205-206

Results

COMMENT: Sometimes, statements are incomplete for instance like in line 262. Working as an enrolled nurse ... etc. compared to which other job titles? ORs involve always relative comparisons.

ANSWER: “In comparison with unexposed workers”, has been inserted on page 14 Line 247

COMMENT: Line 274: what is meant with personal history? Personal history of latex allergy? Other?

ANSWER: “There was no significant association between reported personal history of allergy disease,” has been inserted on page 14 line 260

COMMENT: Line 277: do not only focus on statistical significance. Give ORs as well.

ANSWER: OR have been inserted on page 14 line 263. Avocado (OR: 12.3; 95% CI: 5.1-29.6) and others (OR: 5.1; 95% CI: 2.1-11.8)

COMMENT: Line 280: estimates of the OR above 2.

ANSWER: “had estimates of the OR above 2” has been inserted on page15 line 267

COMMENT: How should an association with glove use during the last seven days be interpreted? Is the idea that recent use influences symptomatology?

ANSWER: the idea was indeed to establish association between recent glove use and presence of latex glove related symptoms. “Further analysis of duration of employment and number of pairs of gloves using fractional polynomial failed to demonstrate a dose-response relationship with either latex sensitisation or latex allergy” has been inserted on page 15 lines 274-276

Discussion

COMMENT: Section starting with line 303: a healthy worker effect seems more plausible. This is a cross-sectional study and associations should be interpreted with care. The fact that HCWs with allergy/sensitization work more often with powder free gloves is indicative of reversed causality because of symptoms. Thus, there is a complex interplay between the HWE which worked over a

long period, probably especially in the early years of the older employees, when powder free gloves were not available, reversed causality and exposure reduction by the introduction of powder free gloves. This complex interplay should be emphasized. Some of the associations seem clear indicators of these different effects.

ANSWER: “The healthy worker effect is a possible explanation of this finding. Prior to availability of hypoallergenic latex gloves, workers who had developed latex allergy may have left employment or they may have changed their career path and moved into a more administrative or managerial role with no contact with latex gloves” has been inserted on page 16 lines 293-296

“The fact that HCWs with latex sensitisation or allergy work more often with powder free latex gloves is indicative of reverse causality because of symptoms.” has been inserted in Line 310-311

COMMENT: It should also be emphasized, although latex is one of the best studied allergens, no exposure response studies have been published with measured latex allergen levels. In combination with the observations that allergen content can vary, this may lead to discrepancies in the literature with regard to the role of duration of employment as a surrogate of exposure. Some of the major limitations in the latex literature should be emphasized.

ANSWER: “Although latex is one of the best studied allergens, no exposure response studies have been published with measured latex allergen levels. In addition, studies have demonstrated variation in allergen content of different gloves. These may lead to discrepancies in the literature with regard to the role of duration of employment as a surrogate measure of exposure” has been inserted on page 16 lines 304-308

COMMENT: Atopy. The role of atopy is complex, because some individuals might also have become atopic after having been latex sensitized. Similarly, cross-reactivity between allergens may lead to inflated associations. Cohort studies are necessary to disentangle this phenomenon. Again, this is a limitation of a cross-sectional study and should be emphasized briefly. There is no need for a detailed comparison with other studies. This is basically an uninteresting comparison of methodological problems.

ANSWER: Watts and colleagues reported that the risk of latex sensitisation was increased by 14 times in the presence of personal atopy and 4 times in the presence of a family history atopy among 122 American HCWs studied.¹⁰ Contrary to Watts and co-workers findings, the risk of latex sensitisation did not increase with a reporting of family history of atopy in our study population” has been removed and been replaced by

“The role of atopy is complex because some individuals might also have become atopic after having been latex sensitised and cross sectional study is not suitable in establishing this association.” Has been inserted on page 18 lines 340-342

“Fruit allergy prior to latex exposure could have contributed to the association observed in our study” has been inserted on page 18 lines 351-352

“Some of the observed associations in the study may be as a result of a complex interplay that between the healthy worker effect, reverse causality and exposure reduction by the introduction of powder free latex gloves. These interactions can be better explored and understood in a longitudinal study” has been inserted under the section discussing the limitation of the study on page 18 lines 377-380

Minor comments:

COMMENT: Page-10, line 188, please indicate the concentration (%) of histamine solution

ANSWER: 0.61% concentration of phenol has been inserted on page 10 Line 169

COMMENT: Page 11, line 206 the sentence is confusing

ANSWER: the sentence has been revised and now reads as follows “The Chi-square and the Kruskal-Wallis test were used to test for significant associations between categorical and continuous variables and the dependent variables under study on bivariate analysis, respectively” page 11, Line 186-188

COMMENT: Page 15, line 310, Smith is in lower case

ANSWER: Smith is upper case now page 16 Line 303

VERSION 2 – REVIEW

REVIEWER	D Heederik IRAS Utrecht University
REVIEW RETURNED	08-Sep-2013

GENERAL COMMENTS	<ul style="list-style-type: none"> - binary (in binary logistic regression) can be removed (line 189) - line 274-276 fractional polynomials. Why have splines not been supplied? The relation with duration of exposure seems to increase and then decrease again (from tables with descriptive statistics). A penalized spline is able to capture this and is expected to be statistically significant when the degrees of freedom is kept limited (<2-3) given the results in table 4. - line 293 the healthy worker effect is a likely explanation for the observation with duration (likely instead of possible). - table 4. Some of the ORs for duration or the confidence intervals cannot be correct (OR 0.9 c.i. 0.8-0.8).
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VERSION 2 – AUTHOR RESPONSE

Comments: Please state any competing interests or state 'None declared': none declared

Answer: "none declared" has been inserted under conflict of interest

Comment: binary (in binary logistic regression) can be removed (line 189)

Answer: "binary" has been removed in line 189

Comments: - line 274-276 fractional polynomials. Why have splines not been supplied? The relation with duration of exposure seems to increase and then decrease again (from tables with descriptive statistics). A penalized spline is able to capture this and is expected to be statistically significant when the degrees of freedom is kept limited (<2-3) given the results in table 4.

Answer: splines have been supplied as Figure 1 on page 29. Duration of employment showed significant ($p= 0.000$) dose-response relationship when analysed using using penalised spline with degree of freedom =2 (Figure1)

Comments:- line 293 the healthy worker effect is a likely explanation for the observation with duration (likely instead of possible).

Answer: "possible" has been replace with "likely" in line 293

Comment:- table 4. Some of the ORs for duration or the confidence intervals cannot be correct (OR 0.9 c.i. 0.8-0.8).

Answer: the ci in table 4 has been corrected as (0.8-0.9)