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RESEARCH ARTICLE

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Work-related allergy and asthma associated with cleaning agents in health workers in Southern African tertiary hospitals

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Abstract

Background: Health workers (HWs) are exposed to diverse cleaning agents in large hospitals. This study determined the prevalence of work-related symptoms, allergic sensitization, and lung function abnormalities in HWs of two tertiary hospitals in Southern Africa.

Methods: A cross-sectional study of 699 HWs (South Africa: SAH, *n* = 346; Tanzania: TAH, *n* = 353) was conducted. Health outcomes were assessed using a standardized ECRHS questionnaire, immunological tests (specific IgE antibody to common aero-allergens and to occupational allergens: natural rubber latex [NRL] Hev b5 and Hev b6.02, chlorhexidine, and ortho-phthalaldehyde [OPA]), spirometry [pre-and post-bronchodilator], methacholine challenge, and fractional exhaled nitric oxide (FeNO).

Results: A large proportion of participants (78%) were women. Median age was 42 years, with 76% nurses, 12% cleaners, and 5% administrative workers. Current smoking was more common in SAHWs (12%) than TAHWs (1%). The overall prevalence of doctor-diagnosed asthma was 7%. Atopy was present in 43% of HWs, while 4% were sensitized to OPA, 2% to NRL, and 1% to chlorhexidine. Prevalence of work-related ocular-nasal symptoms (16%) was higher than skin (12%) and chest (7%) symptoms. TAHWs had significantly lower mean lung volumes, higher degrees of significant airflow obstruction and impaired lung function. The prevalence of bronchial hyperresponsiveness in SAHWs (14%) was high. Overall, 23% of HWs had abnormal FeNO; 6% having high (>50 ppb) levels. FeNO was positively associated with sensitization to occupational allergens, primarily OPA and NRL.

Conclusions: HWs from both hospitals had similar prevalence of work-related respiratory symptoms. Sensitization to OPA and NRL appears to be contributing to allergic airway inflammation in these HWs.

KEYWORDS

airway obstruction, allergy, cleaning agents, health workers, NSBH, work-related asthma

1 | INTRODUCTION

Although health workers compose only 1.8% of the total workforce in South Africa and 0.3% in Tanzania, they play a critical role in the delivery of health care to the general population by virtue of it being an essential service.[1] Health workers (HWs) are exposed to relatively higher concentrations of a wide range of chemicals used for cleaning and disinfection in hospital settings, and more so during COVID-19 pandemic.[2,3] Several studies have demonstrated an association between exposure to cleaning agents used in various clinical settings (instrument cleaning and surface disinfection) and adverse health effects, commonly in the form of rhinitis, asthma, and contact dermatitis.[4–6] In the past few years, increased use of ortho-phthalaldehyde (OPA) and chlorhexidine has resulted in an increase in reports of allergy and asthma affecting patients and health workers in hospital settings, as the incidence of latex allergy has declined globally.

Historically, glutaraldehyde has been used for over 40 years as a high-level disinfectant in healthcare settings and was linked to various health effects such as occupational asthma and allergic contact dermatitis.[7,8] Due to these health effects, OPA was introduced as a safer alternative to glutaraldehdye in some healthcare settings. However, in recent times, OPA has also been reported to cause occupational asthma and anaphylaxis in HWs as well as in patients undergoing instrument procedures.[9] Most of these studies have been case reports involving a small number of participants. In a Japanese study among 70 HWs responsible for endoscope disinfection, 24% had work-related skin, respiratory, or eye symptoms due to OPA.[10] Work-related symptoms due to OPA were also reported in another group of 80 female HWs from endoscopy units.[11] However, both of these two studies did not investigate the specific immunological basis for the OPA associated asthma.[10,11] In a more recent US study, 5 (4%) HWs had positive responses to skin prick tests (SPT) with OPA solution but none had detectable specific serum IgE and IgG.[12] Other cleaning agents such as quaternary ammonium compounds and bleach products have also been implicated in the causation or aggravation of work-related rhinoconjuctivitis and asthma in HWs.[8,13–15]

Exposure to cleaning chemicals is commonly encountered in HWs for hand or wound disinfection to comply with infection control standards in hospitals. Chlorhexidine, one of the most commonly encountered chemicals used in hand hygiene products, is also used for disinfection of wounds and patients' skin before various medical procedures. Chlorhexidine is a known sensitizer and irritant to both the skin and airways.[16] There have been some published reports of asthma, rhinitis, urticaria, anaphylaxis, and dermatitis due to chlorhexidine, mostly in patients and a few also reported in HWs.[17–21]

Natural rubber latex (NRL) gloves have been used in healthcare settings for many years and have contributed to work-related skin and respiratory symptoms in HWs.[22] The most common NRL allergens associated with latex allergy in HWs are Hev b 5, Hev b 6.01, and Hev b 6.02.[23–25] Although the incidence of sensitization to these allergens has decreased to 1% in countries that have promoted latex avoidance, HWs in developing countries continue to use significant amounts of powdered NRL gloves due to financial considerations.[26] While the prevalence of NRL allergy among HWs has ranged between 3% and 31% globally,[26–28] the prevalence of NRL sensitization among HWs in South Africa has ranged between 5% and 21%, the most recent study was conducted a decade ago.[29–34] However, the prevalence of NRL sensitization and allergy in Tanzania has not been documented.

The aim of this study was to determine the prevalence of work-related respiratory and skin symptoms, allergic sensitization and lung function abnormalities (airway obstruction, bronchial hyperresponsiveness, and airway inflammation) in HWs exposed to cleaning agents in two large tertiary academic hospitals in Southern Africa. Other separate communications focus on detailed environmental exposure characterization and risk factors for asthma in these HWs, one of which is already published elsewhere.[35]

2 | MATERIALS AND METHODS

2.1 | Study design, population, and sampling

A cross-sectional study of 699 HWs was conducted in two large tertiary academic hospitals (346 from a South African hospital [SAH] and 353 from Tanzanian hospital [TAH]) during the period July 2014–March 2015 for the SAH and between September 2017 and March 2018 for the TAH). These two hospitals were chosen since they are one of the largest in both countries. Cleaning agents are extensively used to comply with strict infection prevention control standards to prevent health care-associated nosocomial infections. Apart from increasing the statistical power of the study to investigate associations with health outcomes, it was envisaged that the differing exposure contexts between the two hospitals would provide an opportunity to perform comparisons across hospitals. Following meetings with several key stakeholders and walk-through inspections by the investigators of both hospitals, specific departments were identified as potentially high-risk exposure settings for cleaning agents. Health workers in these departments used significant amounts of cleaning agents at a frequency much higher than other departments. The departments identified in the SAH included outpatient clinics, intensive care units (ICUs), operating theaters, emergency units, ENT ward, vascular radiology, and the hemodialysis unit. The outpatient clinics, ICUs, operating theaters, emergency unit, Central Sterile Services Department (CSSD), and hemodialysis unit were identified in the TAH.

All permanently employed HWs in the high-risk departments constituted the sampling frame of the study. Doctors were excluded from the sampling frame since, unlike other staff that worked consistently in their same department for long periods of time, they were more likely to work in multiple different exposure settings across the hospital. A list of all permanently employed HWs in the high-risk departments was obtained from their respective managers. Study participants were selected from these departments using stratified random sampling according to job title, choosing up to five HWs from each high-risk department. For departments with more than five HWs with the same job title, a random sample of five workers was selected. For departments having less than five workers, all workers were selected to participate in the study. The overall response rate was 53%, with a higher response rate in the TAH (63%) compared with the SAH (46%). Ethics approval was obtained from the Institutional Review Boards of the respective institutions. Informed consent was obtained from all individual participants included in the study.

2.2 | Questionnaire

A total of 697 participants completed the questionnaire interviews (344 from SAH and 353 from TAH). Each participant answered a modified questionnaire for the investigation of asthma as contained in the Protocol for the European Community Respiratory Health Survey.[36] The study questionnaire also included validated questions from the NIOSH-specific questionnaire for cleaning agents in the healthcare setting.[37] The questionnaire was administered by trained interviewers in English language for South African health workers (SAHWs) and in Swahili language for Tanzanian health workers (TAHWs). The translated Swahili questionnaire was back-translated to ensure validity and repeatability.

2.3 | Immunological assessment

Blood samples were collected from 682 participants (339 SAHWs and 343 TAHWs). Specific IgE antibody reactivity to common aeroallergens and to specific occupational allergens was evaluated. The quantification of specific IgE sIgE antibodies to occupational allergens: recombinant NRL components (*Hevea brasiliensis*: Hev b5, Hev b6.02), chlorhexidine, and OPA was performed using the UniCAP system (Phadia™ Laboratory Systems, ThermoFisher Scientific Corp). The cross-reacting carbohydrate determinant (CCD) horseradish peroxidase (HRP) was also assessed. Immunological assessment for chlorhexidine was only done on sera of SAHWs since chlorhexidine-containing chemicals were not used in the TAH. Individuals with atopy were defined as those having a positive Phadiatop test. Individuals with sensitization to specific occupational allergens tested were identified based on sIgE ≥ 0.35 KU/L.

Commercial ImmunoCAPs containing Phadiatop (Phad), chlorhexidine (C8), rHev b5 (K218), and rHev b6.02 (K220) allergens were obtained from ThermoFisher Scientific. Serum samples were tested at the National Institute for Occupational Health (NIOH) Immunology laboratory using the Phadia250 machine supplied by ThermoFisher Scientific according to the manufacturer's manual. This instrument uses the fluorescent enzyme immunoassay (FEIA) technique in an automated process. Briefly, serum is added to the allergen of interest covalently coupled to ImmunoCAP. If specific IgE is present in the serum being tested, it will bind to the antigen and form an antigen–antibody complex. After washing away nonspecific IgE, a fluorescent-labeled anti-human immunoglobulin is added that binds to the unwashed antigen–antibody complex. The degree of fluorescence is quantified as specific IgE concentrations by the machine software.

Since the OPA test was not readily available commercially, it required further development. OPA was coupled to albumin using a modification of the ELISA method by Suzukawa et al.,[38] Anderson et al.,[39] and Johnson et al.[40] A 4% (40 mg in 1 ml) solution of bovine serum albumin (BSA) (GE Healthcare Life Sciences) was prepared in phosphate-buffered saline (PBS) (Roche) and a 2.2% (22 mg in 1 ml) solution of OPA (Sigma) was prepared in sterile water. Equal amounts (500 µl) of BSA and OPA solutions were mixed resulting in a final concentration of 2% BSA and 1.1% OPA.

This mixture was labeled with Biotin and separated on a Sephadex G-25 column using the Biotin labeling kit from Roche according to the manufacturer's instructions. Briefly, 6.7 µl of Biotin-7-NHS was added to the BSA/OPA mix and incubated for 2 h at 15–25°C while stirring. The Sephadex G-25 column was prepared by adding 5 ml of blocking solution to the column and allowed to flow through. Thereafter, the column was rinsed six times with 5 ml of PBS. The biotin labeled protein mixture was added to the column. This was then eluted with 3.5 ml of PBS and 40 drops of labeled protein was collected and used as the allergen.

The ImmunoCAPs were then washed and placed in a 2 ml Eppendorf with a pipette tip. These were then centrifuged to get rid of the glycerol for 2 min 1450 g. ImmunoCAPs were washed and centrifuged four times with 50 µl ImmunoCAP Washing solution. Washed ImmunoCAPs were placed in a microtiter plate and 50 µl of biotinylated allergen was added into each ImmunoCAP. After 30 min the ImmunoCAPs was put into a carrier and loaded into the Phadia250 machine. Specific IgE antibodies to prepared OPA allergens were then measured using the UNICAP 250 machine according to manufacturer's procedure.

The IgE test was validated to determine the measurement of uncertainty using the EP15 method and was found to be 0.617253664 kAU/L. Furthermore, the test is done routinely and is part of monthly proficiency testing. Quality controls are also performed with every batch of testing as part of the laboratory quality assurance. According to the manufacturer, a large number of studies have been performed in which the clinical performance of ImmunoCAP specific IgE tests in allergy diagnosis has been evaluated. Clinical performance expressed as sensitivity, ranged from 84% to 95%, and specificity, ranging from 85% to 94%, and has been reported from multicenter studies including several hundred patients

tested for a range of different allergens. Whilst these indicators were not determined in this study we deemed it to be acceptable based on reported studies.

2.4 | Spirometry and bronchodilator responsiveness (BDR) testing

There were 328 participants from the TAH who performed spirometry and bronchodilator responsiveness (BDR) tests. In this group, BDR testing was conducted since there was no pulmonary function laboratory infrastructure to perform methacholine challenge testing (MCT) (see next section). In the SAH, spirometry and BDR tests were performed on 25 participants for whom MCT was contraindicated (e.g., FEV_1 below 1.5 L or 70% predicted, or pregnant and breastfeeding women). Spirometry was conducted according to guidelines of the American Thoracic Society/European Respiratory Society (ATS/ERS)[41] using EasyOne World spirometer (NDD Medical Technologies) at the TAH, and Jaeger Aerosol Provocation System (APS) Pro apparatus at the SAH, according to the manufacturer's instructions. Special instructions were given to health workers to abstain from smoking tobacco (at least 2 h before), or taking any antiasthmatic inhalers (12 h before) or oral asthma medications (48 h before) before the test. The Global Lung Function Initiative (GLI) 2012 reference values using "other" ethnic groups were used for grading the degree of impairment of spirometry.[42] A change in FEV_1 of ≥ 200 ml and ≥12% at 10 min after the administration of bronchodilator (400 μg of salbutamol) was considered to be a significant bronchial response. Only spirometric tests with ATS quality Grade A, B, and C were included in the analysis of BDR test data.[43]

2.5 | Methacholine challenge tests

Methacholine challenge testing (MCT) was only performed in the South African study site due to logistical and safety considerations. The tests were conducted in a pulmonary function laboratory that was well equipped with appropriate resuscitation facilities. Among 318 participants who were eligible for MCT, 239 performed interpretable PD_{20} methacholine results, while 52 participants had ≥10% decrease in FEV_1 after administration of saline diluent and were therefore not considered for further testing using MCT. MCT was discontinued in two participants who requested the test to be stopped. As explained above, 25 participants underwent postbronchodilator spirometry instead, since MCT was contraindicated. MCT was conducted under the supervision of an experienced technologist according to an abbreviated protocol used in epidemiological surveys. The Medic Aid Pro Nebulizer dosimeter method involved a protocol of increasing numbers of breaths to achieve pre-defined cumulative doses of methacholine.[44] The doses were delivered by the Jaeger APS MedicAid Side Stream APS-Nebulizer according to the manufacturer's instructions, commencing with the lowest dose of 0.026 mg. The dose was increased to a maximum of 2.048 mg methacholine if a positive endpoint (fall in FEV_1 of 20% or more) was not obtained. The results of the MCT were interpreted as follows: borderline defined as 0.4 mg < $PD_{20}M$ < 1.0 mg; mild = 0.08 mg < $PD_{20}M$ < 0.4 mg; moderate/severe = $PD_{20}M$ < 0.08 mg. Borderline values for $PD_{20}M$ were considered negative in the definition of nonspecific bronchial hyperresponsiveness (NSBH). These cut-offs for the APS system are based on the results from a validation study performed on 40 hyperresponsive bakery workers that confirmed a satisfactory correlation between the APS cumulative $PD_{20}M$ method and the standard VMAX (Sensormedics) method (34). A urine pregnancy test was offered to women before the administration of methacholine, while pregnant women and nursing mothers were excluded from testing.

2.6 | Fractional exhaled nitric oxide (FeNO)

A total of 654 participants performed FeNO tests (334 from SAH and 320 from TAH). A hand-held portable exhaled nitric oxide sampling device (NIOX MINO® Airway Inflammation Monitor (NIOX MINO); Aerocrine AB) was used. Under the guidance of clinical personnel, all HWs inhaled NO-free air close to total lung capacity and exhaled for 10 s at a flow rate of 50 ml/s according to the manufacturer's instructions. Two technically adequate measurements were performed in line with the current American Thoracic Society/European Respiratory Society recommendations.[45] A third maneuver was performed if the difference between the first two measurements was more than 10 ppb. The FeNO test was done during the work shift before spirometry/MCT. Special instructions were provided to workers to ensure that tested individuals did not smoke tobacco, eat or drink (at least 1 h before) before the test. Ambient NO and temperature were also recorded. FeNO results were interpreted as follows: low < 25 ppb; elevated for values 25–50 ppb; and high for values > 50 ppb.[46]

2.7 | Statistical analysis

All data analysis was performed using statistical package STATA version 14. Frequencies of categorical variables were compared between the two hospitals using χ^2 test or Fisher's exact test where appropriate. Numerical variables were summarized using median and interquartile range (IQR) since not all variables followed a normal distribution. Numerical variables were compared between the two hospitals using Wilcoxon sum rank test. A p value < 0.05 was regarded as statistically significant. Multivariate linear and logistic regression models adjusted for atopy and smoking were used to evaluate the association between asthma-related outcomes and sensitization to occupational allergens. The two covariates (atopy and smoking) were selected a priori and they also had consistent associations with asthma-related outcomes. For linear regression analyses, log-transformed values of FeNO were used, with geometric

mean ratios and 95% confidence intervals (CI). A negative binomial regression analysis was used for the association between asthma symptom score (a count outcome variable) and occupational sensitization. The results of the negative binomial regression models were reported as mean ratios with 95% CIs. For logistic regression models, results were reported as odds ratio (OR) with 95% CIs.

3 | RESULTS

3.1 | Study population

The demographic characteristics of the study population are summarized in Table 1. The majority of study participants were women (78%), had a median age of 42 years (IQR: 32–51 years), and had worked in the healthcare industry for 14 years (median: 14 years; IQR: 6–28 years). A significant number of study participants (76%) were nursing professionals (registered nurses, enrolled nurses, and nurse assistants or health attendants), but a small proportion of cleaners (12%) and administrative workers (5%) were also included. South African HWs were significantly older, with a higher mean BMI (although comparable with their respective general populations), and a higher prevalence of current smoking and past history of tuberculosis compared with their counterparts. However, a history of repeated childhood chest infections was significantly higher among the Tanzanian HWs ($p = 0.001$).

3.2 | Immunological characteristics

The prevalence of atopy (positive Phadiatop test) was higher (47%) in South African HWs ($p = 0.047$) (Table 2). Among the 5% sensitized to one or more occupational allergens, OPA sensitization prevalence was higher (4%) than for natural rubber latex (Hev b5 or Hev b6.02) (2%), although no significant differences in allergen-specific sensitization were observed between the two hospitals. However, the prevalence of chlorhexidine sensitization was only 1% among SAHWs. Workers who were atopic were more likely to be sensitized to occupational allergens ($p < 0.001$). Except for one non-atopic participant sensitized to OPA, all HWs sensitized to occupational allergens were atopic.

3.3 | Symptoms

While the prevalence of doctor-diagnosed asthma was 7%, with no significant difference between the two hospitals (Table 3), the majority (60%) of these individuals reported adult-onset asthma. A two-fold higher prevalence of SAHWs (17%) had an asthma symptom score ≥ 2 compared with their Tanzanian counterparts (9%). Overall, the prevalence of work-related ocular-nasal symptoms in the past 12 months (16%) was also higher than that of work-related skin (12%) and asthma (7%) symptoms (Table 4). The prevalence of work-related skin symptoms was significantly higher among HWs in the SAH compared with the TAH ($p < 0.001$) (Table 4). There were 16 (2%) workers from both hospitals who reported job changes due to work-related chest symptoms. The agents commonly attributed for these work-related chest symptoms included the general dust, NRL, and OPA/glutaraldehyde.

3.4 | Pulmonary function tests (spirometry, MCT, and FeNO)

The results of the pulmonary function tests are summarized in Table 5. Overall, TAHWs had significantly lower lung volumes and a higher prevalence of airflow obstruction than their SAH counterparts ($p < 0.001$). While 29% of workers had an FEV_1 of less than the lower limit of normal (LLN), 11% had evidence of airflow obstruction (pre-bronchodilator FEV_1/FVC ratio less than LLN). In the South African group, 14% of workers had evidence of BHR (positive on methacholine challenge test: a PD_{20} methacholine < 0.4 mg, or significant bronchial reversibility postbronchodilator) while in the Tanzanian group, 8% of HWs had evidence of bronchial responsiveness on the basis of significant postbronchodilator reversibility.

The median FeNO levels (interquartile range: 11–24) were slightly higher among SAHWs compared with the Tanzanian counterparts. Overall, across all hospitals, 23% had abnormal FeNO levels with 6% having high (>50 ppb) levels. The proportion of HWs with high FeNO, was slightly higher in the South African group. Atopic individuals ($p = 0.002$) and those who have never smoked ($p = 0.045$) were more likely to have high FeNO levels.

3.5 | Asthma-related outcomes associated with sensitization to occupational allergens

In the entire group of HWs, increasing FeNO was positively associated with sensitization to OPA (Geometric mean [GM] ratio = 1.49; 95% CI: 1.15–1.93) and natural rubber latex (GM ratio = 1.82; 95% CI: 1.19–2.78) in unadjusted linear regression models (Table 6). FeNO ≥ 25 ppb (OR = 2.27; 95% CI: 1.08–4.79) was also strongly associated with sensitization to at least one occupational allergen (OPA, chlorhexidine, or natural rubber latex) in the adjusted models. However, while there was a generally positive association between work-related respiratory symptoms and sensitization to occupational allergens, these were not statistically significant.

4 | DISCUSSION

The health and well-being of HWs, a large proportion of whom are nurses, is crucial in ensuring health care for the population. The findings of this study demonstrated that HWs in two tertiary academic hospitals in southern Africa experience an appreciable proportion of work-related airway and skin symptoms associated

TABLE 1 Demographic characteristics of health workers in two Southern African tertiary hospitals

Demographic characteristics	Overall	SAH *n* (%)	TAH *n* (%)	*p* Value (χ^2 test)
Participants (*n*)	**697**	**344**	**353**	
Age (years) [median (IQR)]	42 (32–51)	46 (33–51)	39 (31–51)	0.009[a]
Gender (%F:M)	77:23	84:16	71:29	<0.001
BMI [median (IQR)]	29 (26–34)	31 (27–37)	28 (25–32)	<0.001[a]
Smoking status: *n* (%)				<0.001
Current smokers	42 (6)	40 (12)	2 (1)	
Ex-smokers	48 (7)	48 (14)	0 (0)	
Never smokers	607 (87)	256 (74)	351 (99)	
Job title: *n* (%)				<0.001
Registered nurse	283 (41)	132 (38)	151 (43)	
Nurse assistant/Health attendant	168 (24)	59 (17)	109 (31)	
Enrolled nurse	75 (11)	48 (14)	27 (8)	
Cleaner	85 (12)	45 (13)	40 (11)	
Clerk	38 (5)	13 (4)	25 (7)	
Technician	34 (5)	33 (10)	1 (0)	
Porter	14 (2)	14 (4)	0 (0)	
Total years in healthcare industry [median (IQR)]	14 (6–28)	20 (8–28)	11 (4–27)	<0.001[a]
Total years in the current job [median (IQR)]	4 (2–9)	4 (1–11)	4 (2–8)	0.862[a]
Past history of lung disease (self-reported): *n* (%)				
Previous treatment for chronic bronchitis	44 (6)	42 (12)	2 (1)	<0.001
Repeated childhood chest infections	76 (11)	24 (7)	52 (15)	0.001
Previous treatment for tuberculosis	32 (5)	22 (6)	10 (3)	0.025
Family history of allergy	353 (51)	219 (64)	134 (38)	<0.001
Cleaning activities at home in the last 12 months:	660 (95)	342 (99)	318 (90)	<0.001
Less than 1 day per week	96 (14)	17 (5)	79 (22)	<0.001
1 or more days per week	601 (86)	327 (95)	274 (78)	

Abbreviations: F, female; IQR, interquartile range; M, male; SAH, South African hospital; TAH, Tanzanian hospital.
[a]Wilcoxon sum-rank test.

with cleaning agents similar to their counterparts in other regions of the world. As has been reported in most studies of work-related rhinitis and asthma,[47] the prevalence of work-related ocular-nasal symptoms was twice as common as asthma symptoms in this study. Furthermore, in this current study, lifetime prevalence of work-related ocular–nasal (23%) and asthma symptoms (12%) was higher than that reported in South African dental HWs (14% and 4%, respectively).[34] Moreover, in this current study, the prevalence of work-related asthma symptoms (WRAS) in the past 12 months (7%) was higher than that reported in a US study of HWs (3.3%) and on the upper end of the range compared to the Saudi Arabian study of HWs (5.7%), both using a similar definition of WRAS.[48,49] Although the authors did not comment on the adequacy of workplace control measures in the two studies,[48,49] the inadequate controls observed in the current study (manuscript under review; unreferenced) could partly explain the relatively higher prevalence of WRAS. Furthermore, 16 (2%) workers with WRAS in the current study had to change their jobs due to these symptoms, underscoring the negative

TABLE 2 Allergic sensitization profiles of health workers in two Southern African tertiary hospitals

Allergic sensitization profiles	Overall	SAH *n* (%)	TAH *n* (%)	*p* Value (χ^2 test)
Participants (*n*)	682	339	343	
Atopy (positive Phadiatop test)	296 (43)	160 (47)	136 (40)	0.047
OPA	26 (4)	12 (4)	14 (4)	0.712
Chlorhexidine	NA	3 (1)	ND	NA
Latex (Hev b5 or Hev b6.02)	11 (2)	7 (2)	4 (1)	0.352
Latex Hev b5	3 (0)	3 (1)	0 (0)	0.122[a]
Latex Hev b6.02	8 (1)	4 (1)	4 (1)	1.000[a]
Sensitization to at least one occupational allergen (OPA, Chlorhexidine or Latex)[b]	34 (5)	19 (6)	15 (4)	0.460

Note: Horseradish peroxidase (HRP): 19 (6).

Abbreviations: NA, Not applicable; ND, Not done; OPA, ortho-phthalaldehyde; SAH, South African hospital; TAH, Tanzanian hospital.

[a]Fisher's exact test.

[b]Sensitization to at least one occupational allergen (OPA, chlorhexidine, or latex) and HRP negative (in relation to latex).

consequences associated with continued exposure for work-related asthma.[50,51]

The overall prevalence of work-related skin symptoms (lifetime = 19% and in the past 12 months = 12%) in the current study is consistent with results from previous studies (11%–28%) among workers exposed to cleaning agents in other parts of the world.[52–55] Unlike upper and lower airway symptoms that were similar across both study groups, a higher prevalence of work-related skin symptoms was reported in SAHWs. However, there was no correlation between the presence of respiratory and skin symptoms, suggesting multiple co-existing exposures having irritant and allergenic effects. This could partially be explained by the significantly higher frequency of handwashing at work among South African HWs (58 times per day), compared to Tanzanian HWs (20 times per day) and the different hand hygiene products used. The SAHWs commonly used chlorhexidine-containing products and alcohols compared to the TAHWs using diluted all-purpose cleaner and alcohols. Chlorhexidine is a well-known skin irritant and allergen capable of causing both IgE-mediated (urticaria) and delayed type (contact dermatitis) hypersensitivity skin reactions.[16,56]

In this study, the overall atopy prevalence (43%) was very similar to that observed in a US study of HWs (45%).[12] In the latter study, 4% (*n* = 129) of HWs had positive SPTs with OPA solution, which was similar to the findings in the current study. Interestingly, sIgE and IgG antibodies were not detected in any of the blood samples tested in the US HWs. Since only sIgE to OPA was assessed in the current study, it is probable that a higher prevalence of OPA sensitization could have been obtained had SPT been used. Furthermore, the prevalence of work-related symptoms associated with OPA (4%) was similar to the prevalence of OPA sensitization (4%), although they were not significantly correlated in multivariate models. As expected, the prevalence of work-related symptoms associated with OPA was much higher (9%–24%) in the two Japanese studies, which focussed only on HWs exposed to OPA in the endoscopy units, rather than the entire hospital.[10,11]

Despite 20% of SAHWs reporting work-related symptoms associated with chlorhexidine, only three (1%) HWs had evidence of chlorhexidine sensitization. The low prevalence of chlorhexidine sensitization in this study is similar to the findings by Garvey et al.[17] Four cases of occupational IgE-mediated allergy to chlorhexidine were diagnosed among 53 HWs in a UK hospital.[19] Wittczak et al. also reported three Polish HW cases of occupational chlorhexidine allergy.[20] In contrast, cases of chlorhexidine allergy have frequently been reported among patients[21] and the coexistence of chlorhexidine and NRL allergy has also been observed.[19,57]

South African studies of NRL sensitization in HWs have reported a prevalence ranging between 5% and 20.8% (20, 21, 22, and 23–25). However, in this current study, the prevalence was only 2%, which was much lower compared to a previous study[31] conducted more than a decade ago in the same SAH, which reported a 9% prevalence. The decline in the prevalence of NRL sensitization in this hospital setting over this period is most likely related to latex avoidance measures implemented in the hospital, and more specifically the substitution of powdered latex gloves with less-powdered/powder-free low protein gloves. Despite the lower frequency of NRL sensitization in this study, 12% of HWs reported a history of work-related symptoms associated with NRL. Furthermore, SAHWs (4%) were more likely to be diagnosed with NRL allergy, compared to their Tanzanian counterparts (1%).

In this current study, pulmonary function tests revealed significantly lower lung volumes among Tanzanian HWs compared with their South African counterparts. One possible explanation for this finding is the high frequency of repeated childhood chest infections reported in the Tanzanian HWs. Repeated childhood chest

TABLE 3 Asthma history and respiratory symptoms reported by health workers in two Southern African tertiary hospitals

Symptoms	Overall	SAH *n* (%)	TAH *n* (%)	*p* Value (χ^2 test)
Participants (*n*)	697	344	353	
Asthma history:				
Ever attacks of breathlessness at rest with wheezing	33 (5)	13 (4)	20 (6)	0.241
Ever asthma	52 (8)	28 (8)	24 (7)	0.501
Ever asthma attack	55 (8)	26 (8)	29 (8)	0.748
Doctor-diagnosed asthma:	48 (7)	29 (8)	19 (5)	0.112
≤16 years	19 (3)	9 (2)	10 (3)	0.135
>16 years	29 (4)	20 (6)	9 (2)	
Current use of asthma medication	39 (6)	21 (6)	18 (5)	0.564
Asthma attack in the past 12 months	31 (5)	16 (5)	15 (4)	0.797
Current use of asthma medication OR	44 (6)	24 (7)	20 (6)	0.477
Asthma attack in the past 12 months				
Asthma-like symptoms	219 (31)	154 (45)	65 (18)	<0.001
Short of breath while wheezing in the last 12 months	67 (10)	38 (11)	29 (8)	0.214
Woken up with chest tightness in the last 12 months	85 (12)	51 (15)	34 (10)	0.039
Attack of shortness of breath at rest during daytime in the last 12 months	51 (7)	18 (5)	33 (9)	0.035
Attack of shortness of breath following running or exercise in the last 12 months	154 (22)	128 (37)	26 (7)	<0.001
Woken up by an attack of shortness of breath in the last 12 months	48 (7)	26 (8)	22 (6)	0.503
More symptomatic (≥ 2 asthma-like symptoms)	91 (13)	58 (17)	33 (9)	0.003
Less symptomatic (0–1 asthma-like symptom)	606 (87)	286 (83)	320 (91)	
Asthma symptom score				<0.001
0	478 (69)	190 (55)	288 (82)	
1	128 (18)	96 (28)	32 (9)	
2	42 (6)	31 (9)	11 (3)	
3	17 (2)	11 (3)	6 (2)	
4	18 (3)	10 (3)	8 (2)	
5	14 (2)	6 (2)	8 (2)	
Upper airway symptoms				
Presence of ocular–nasal symptoms ever	306 (44)	167 (49)	139 (39)	0.015

Abbreviations: SAH, South African hospital; TAH, Tanzanian hospital.

infections have been reported to be a risk factor for lower adult FEV_1 due to early insults on lung development.[58] Another possible explanation for the observed differences could be related to exposure to biomass fuel as it was used for cooking by a large proportion of individuals in a recent Tanzanian study.[59] The influence of other socioeconomic factors that influence lung development such as nutrition and perinatal factors (low birth weight, preterm delivery) could not be assessed in this study, but could potentially explain these differences. It also needs to be borne in mind that the GLI multiethnic reference values may not be totally generalizable at this stage to African populations given the paucity of studies on the continent.[60,61] However, these factors are unlikely to influence the

TABLE 4 Work-related symptoms reported by health workers in two Southern African tertiary hospitals

Symptoms	Overall	SAH *n* (%)	TAH *n* (%)	*p* Value (χ^2 test)
Participants (*n*)	697	344	353	
Work-related asthma symptoms:				
Episode of high exposure at work causing tight chest, shortness of breath, wheeze, or cough	3 (0)	2 (1)	1 (0)	0.043
Work-related asthma symptoms (ever)	83 (12)	38 (11)	45 (13)	0.488
Work-related asthma symptoms in the past 12 months[a]	65 (9)	28 (8)	37 (11)	0.288
Work-related asthma symptoms in the past 12 months[b]	48 (7)	20 (6)	28 (8)	0.270
Doctor-diagnosed work-related asthma (ever)	15 (2)	8 (2)	7 (2)	0.755
Job change due to work-related chest symptoms	16 (2)	10 (3)	6 (2)	0.287
Work-related upper airway symptoms:				
Work-related ocular–nasal symptoms (ever)	163 (23)	80 (23)	83 (24)	0.936
Work-related ocular–nasal symptoms in the past 12 months[a]	146 (21)	70 (20)	76 (22)	0.702
Work-related ocular–nasal symptoms in the past 12 months[b]	109 (16)	48 (14)	61 (17)	0.227
Doctor-diagnosed work-related ocular–nasal symptoms (ever)	19 (3)	9 (3)	10 (3)	0.861
Work-related skin symptoms:				
Work-related skin symptoms (ever)	130 (19)	95 (28)	35 (10)	<0.001
Work-related skin symptoms in the past 12 months[a]	103 (15)	76 (22)	27 (8)	<0.001
Work-related skin symptoms in the past 12 months[b]	80 (12)	61 (18)	19 (5)	<0.001
Doctor-diagnosed work-related skin condition (ever)	20 (3)	16 (5)	4 (1)	0.005

Abbreviations: SAH, South African hospital; TAH, Tanzanian hospital.

[a]Symptoms (asthma/ocular–nasal/skin) experienced at work in the last 12 months.

[b]Symptoms (asthma/ocular–nasal/skin) experienced at work in the last 12 months that improve when away from work OR worsen on return to work.

higher prevalence of airway obstruction observed in the TAHs, despite a very low prevalence of current smokers (1%) suggesting that tobacco exposures were unlikely to be responsible for the obstructive lung disease burden observed. Compared with other Tanzanian working populations exposed to dusty jobs, the prevalence of airway obstruction in this study was relatively similar or slightly lower.[62–66]

In this study, the overall prevalence of bronchial hyperresponsiveness was higher in the SAHWs (14%) compared with TAHWs (8%). This could be explained by the use of a more sensitive test (MCT), compared to the pre- and post-BD spirometry used in the TAH. A case–control study among cleaning workers reported similar proportions of bronchial reversibility between asthmatic workers (cases) and controls but a higher prevalence of nonspecific bronchial hyperresponsiveness (PD_{20} < 1 mg = 55%) among cases.[67] Higher prevalence of NSBH was also reported in a previous study of HWs (PC_{20} ≤ 4 mg/ml = 48% and ≤8 mg/ml = 55%).[68] Even when the cut point for methacholine was raised to PD20 < 1 mg (as opposed to PD20 < 0.4 mg) in the current study, the prevalence of NSBH was still lower compared with the previous studies. However, the current study included more participants who completed methacholine challenge test (*n* = 239) as compared to the previous studies (*n* = 118; *n* = 22).[67,68] Larger studies are needed to have a better estimation of NSBH in HWs exposed to cleaning agents.

In the current study, overall FeNO levels were comparable to the other workplace-based studies in Tanzania and South Africa in nonhealthcare settings.[65,69–72] The median FeNO levels in the current study (17 ppb) were similar to those of supermarket bakery workers (median = 15 ppb), cement factory workers (median = 15 ppb), and coffee factory workers (geometric mean = 17.4 ppb).[65,69,70] However, the 6% prevalence of high FeNO (>50 ppb) indicative of allergic airway inflammation in the current study, was lower than previous South African studies of workers exposed to predominantly high molecular weight protein agents (poultry farm: 7%, spice mill: 8%, supermarket bakeries: 11%).[69,71,72] Furthermore, in the current study, increasing levels of FeNO were consistently associated with sensitization to any one of the occupational allergens tested, suggesting a possible role of OPA and NRL in underying allergic airway inflammation in these HWs.

To the best of our knowledge, this is the first study of HWs in southern Africa to have undertaken an extensive epidemiological study on the immunological assessment of HWs to OPA and chlorhexidine. Previous studies have reported only on work-related symptoms without more objective measures of work-related allergy, airway inflammation, and hyperresponsiveness as inthe current study. Despite these strengths, there are some limitations since the immunological assessment of sensitization to glutaraldehyde was not

TABLE 5 Pulmonary function indices of health workers in two Southern African tertiary hospitals

Pulmonary function indices[a,b]	Overall	SAH *n* (%)	TAH *n* (%)	*p* Value (χ^2 test)
Participants (*n*)	646	318	328	
FVC L [median (IQR)]	3.02 (2.47–3.53)	3.23 (2.80–3.68)	2.68 (2.21–3.35)	<0.001[c]
FEV_1 L [median (IQR)]	2.42 (1.96–2.88)	2.66 (2.30–3.07)	2.16 (1.78–2.65)	<0.001[c]
FEV_1/FVC, % [median (IQR)]	82 (77–86)	83 (80–87)	81 (76–85)	<0.001[c]
FVC % pred. [median (IQR)]	91 (79–103)	99 (90–108)	82 (73–94)	<0.001[c]
FEV_1% pred. [median (IQR)]	89 (76–101)	99 (89–108)	79 (70–90)	<0.001[c]
FVC < 80% pred.	168 (26)	24 (8)	144 (44)	<0.001
FVC < LLN (*n*,%)	172 (27)	24 (8)	148 (45)	<0.001
FEV_1 < 80% pred. (*n*,%)	205 (32)	33 (10)	172 (52)	<0.001
FEV_1 < LLN (*n*,%)	185 (29)	26 (8)	159 (49)	<0.001
FEV_1/FVC < LLN (*n*,%)	73 (11)	20 (6)	53 (16)	<0.001
FEV_1/FVC < 70% (*n*,%)	50 (8)	14 (4)	36 (11)	0.002
Bronchial hyperresponsiveness (BHR)				
≥12% and ≥200 ml FEV_1 increase postbronchodilator		*n* = 20 5 (25)	*n* = 177 14 (8)	NA
≥10% FEV_1 decrease postsaline diluent (*n* = 291)		52 (18)	ND	NA
Methacholine challenge test: PD_{20} methacholine < 0.4 mg (*n* = 239)		31 (13)	ND	NA
BHR[d]		*n* = 259 36 (14)	*n* = 177 14 (8)	NA
Fractional exhaled nitric oxide (FeNO)	*n* = 654	*n* = 334	*n* = 320	
FeNO (ppb) [median (IQR)]	17 (11–24)	17 (12–25)	15 (10–22)	0.003[c]
Low <25 ppb	504 (77)	251 (75)	253 (79)	0.487
Elevated 25–50 ppb	111 (17)	61 (18)	50 (16)	
High > 50 ppb	39 (6)	22 (7)	17 (5)	

Abbreviations: % pred, % predicted; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; L, litres; LLN, Lower limit of normal; NA, not applicable; ND, not done; PD20 methacholine, provocative dose of methacholine causing a ≥ 20% fall in FEV1; SAH, South African hospital; TAH, Tanzanian hospital.

[a]Pre-bronchodilator values, unless stated otherwise

[b]Global lung function initiative (GLI) reference values used

[c]Wilcoxon sum rank test

[d]BHR defined as (PD20methacholine < 0.4 mg) OR (≥ 12% and ≥200 ml increase in FEV1 after bronchodilator).

done due to the lack of commercially available tests for the Tanzanian group. Furthermore, methacholine challenge tests could not be conducted in the TAH due to logistical and safety reasons. Hence, a more comprehensive picture of HWs in this hospital could not be obtained relative to their South African counterparts. Nevertheless, the study has provided important insights into work-related asthma in southern African HWs exposed to OPA and NRL. Furthermore, since the health outcome status of nonrespondents was not known, the possibility of sampling bias affecting the results cannot be ruled out given the response rate (overall: 53%) obtained in this study.

In conclusion, this study demonstrates that HWs in these two tertiary hospitals experience an appreciable proportion of work-related airway symptoms of similar prevalence. While TAHWs had comparatively lower lung volumes and higher degrees of airflow obstruction, SAHWs had higher degrees of nonspecific bronchial responsiveness. The study has also confirmed that the prevalence of NRL sensitization is declining in South Africa, most likely due to

TABLE 6 Asthma-related outcomes associated with occupational sensitization in health workers from both hospitals

	Prevalence (%)		Sensitization to OPA	Sensitization to NRL[b,c]	Sensitization to at least one occupational allergen (OPA, chlorhexidine, or NRL)[c]
Prevalence (%) (n = 682)			26 (4)	10 (2)	34 (5)
Ocular–nasal symptoms	306 (44)	Crude OR (CI)	2.05 (0.92–4.58)	1.25 (0.36–4.35)	**2.09 (1.03–4.24)***
		Adjusted OR (CI)	1.31 (0.57–3.01)	0.73 (0.21–2.59)	1.28 (0.61–2.67)
WRONS	109 (16)	Crude OR (CI)	2.04 (0.84–4.98)	1.35 (0.28–6.42)	2.01 (0.91–4.44)
		Adjusted OR (CI)	1.84 (0.73–4.63)	1.14 (0.24–5.57)	1.77 (0.77–4.05)
Asthma symptom score[a]		Crude MR (CI)	1.05 (0.49–2.25)	1.37 (0.43–4.33)	1.16 (0.60–2.24)
		Adjusted MR (CI)	0.83 (0.39–1.78)	1.04 (0.33–3.21)	0.89 (0.46–1.73)
Asthma symptom score (≥2 vs. 0–1)	91 (13)	Crude OR (CI)	0.54 (0.13–2.31)	0.73 (0.09–5.79)	0.62 (0.19–2.08)
		Adjusted OR (CI)	0.37 (0.09–1.62)	0.45 (0.06–3.62)	0.40 (0.12–1.36)
WRAS	48 (7)	Crude OR (CI)	1.81 (0.52–6.26)	NC	1.32 (0.39–4.50)
		Adjusted OR (CI)	1.33 (0.37–4.77)	NC	1.01 (0.29–3.56)
BHR (n = 446)	57 (13)	Crude OR (CI)	1.38 (0.39–4.93)	4.67 (0.76–28.55)	1.47 (0.48–4.47)
		Adjusted OR (CI)	1.27 (0.34–4.72)	4.33 (0.68–27.47)	1.35 (0.42–4.33)
FeNO, ppb[b] (n = 654)		Crude GMR (CI)	**1.49 (1.15–1.93)****	**1.82 (1.19–2.78)****	**1.57 (1.25–1.97)*****
		Adjusted GMR (CI)	1.25 (0.97–1.61)	**1.54 (1.02–2.33)***	**1.34 (1.07–1.69)***
FeNO ≥ 25 (n = 654)	150 (23)	Crude OR (CI)	**3.90 (1.74–8.75)****	**4.32 (1.15–16.29)***	**4.18 (2.03–8.59)*****
		Adjusted OR (CI)	2.06 (0.90–4.74)	2.28 (0.60–8.76)	**2.27 (1.08–4.79)***
FeNO ≥ 50 (n = 654)	41 (6)	Crude OR (CI)	**3.10 (1.01–9.50)***	4.50 (0.91–22.43)	**3.94 (1.52–10.21)****
		Adjusted OR (CI)	1.70 (0.54–5.39)	3.10 (0.59–16.42)	2.41 (0.89–6.53)

Note: Data presented as OR (95% CI) unless otherwise indicated; BHR defined as (PD_{20}methacholine < 0.4 mg) OR (≥12% and ≥ 200 ml increase in FEV_1 after bronchodilator); each OR/MR/GMR represents a separate regression model in unadjusted and adjusted (atopy and smoking) models.

Abbreviations: BHR, bronchial hyperresponsiveness; CI, confidence interval; GMR, geometric mean ratio; MR, mean ratio; NC, not calculable; NRL, natural rubber latex; OPA, ortho-phthalaldehyde; OR, odds ratio; WRAS, work-related asthma symptoms (asthma symptoms experienced at work in the past 12 months that gets better when away from work OR worsen on return to work; WRONS, work-related ocular–nasal symptoms (ocular–nasal symptoms experienced at work in the past 12 months that improve when away from work OR worsen on return to work.

[a]MR (95% CI).

[b]GMR (95% CI).

[c]Sensitization to latex and horseradish peroxidase negative.

*p value < 0.05; **p value < 0.01; ***p value < 0.001.

preventive measures implemented for NRL allergy. Furthermore, sensitization to occupational allergens (OPA and NRL) appear to be contributing to underlying airway inflammation in these HWs.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Leena Nylander-French declares that she has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

Hussein H. Mwanga and Mohamed F. Jeebhay were responsible for the conceptualization of the study. Hussein H. Mwanga and

Roslynn Baatjies were responsible for the fieldwork. Tanusha Singh conducted a laboratory analysis of the serum samples. Hussein H. Mwanga was responsible for data collection, data management, analysis, and write-up under the supervision of Roslynn Baatjies and Mohamed F. Jeebhay. Hussein H. Mwanga was responsible for the preparation of the first draft of the manuscript. All authors contributed to and reviewed the manuscript before submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS APPROVAL AND INFORMED CONSENT

Ethics approval was obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town (HREC Ref: 212/2013), Muhimbili University of Health and Allied Sciences (MUHAS) Institutional Review Board, and University of Michigan Medical School Institutional Review Board (HUM00083115). Informed consent was obtained from all individual participants included in the study.

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