Self-reported beta-lactam allergy in government and private hospitals in Cape Town, South Africa

C Day,[1] FCP (SA), MMed (Med); **M Deetlefs,**[1] MB ChB, Dip Allerg (SA); **A O'Brien,**[2] medical student; **J Smith,**[2] medical student; **M Boyd,**[3] medical student; **N Embling,**[2] medical student; **S Patel,**[2] medical student; **K Moody,**[2] medical student; **T Ramabele,**[2] medical student; **A Budge,**[4] MB ChB; **T Tarwa,**[5] medical student; **O Jim,**[2] medical student; **T Maharaj,**[2] medical student; **S Pandy,**[2] medical student; **J-M Abrahams,**[1] BNurs; **A Panieri,**[2] MB ChB; **S Verhage,**[2] MB ChB; **M van der Merwe,**[2] MB ChB; **A Geragotellis,**[2] medical student; **W Amanjee,**[2] medical student; **C Joseph,**[2] medical student; **Z Zhao,**[2] medical student; **S Moosa,**[2] medical student; **M Bunting,**[2] medical student; **Y Pulani,**[2] medical student; **P Mukhari,**[2] medical student; **M de Paiva,**[2] medical student; **G Deyi,**[2] medical student; **R P Wonkam,**[2] medical student; **N Mancotywa,**[2] medical student; **A Dunge,**[2] medical student; **T Msimanga,**[2] medical student; **A Singh,**[2] medical student; **O Monnaruri,**[2] medical student; **B Molale,**[2] medical student; **T A G Butler,**[4] MB BCh, Dip HIV Man (SA); **K Browde,**[6] FC Paed (SA), MMed (Paed); **C Muller,**[7] MB ChB; **J van der Walt,**[7] FCFP (SA), Cert Allergy (SA); **R Whitelaw,**[3] MB ChB; **D Cronwright,**[3] MB ChB; **S Sinha,**[2] MB ChB; **U Binase,**[2] MB ChB; **I Francis,**[3] FCP (SA), MMed (Med); **D Boakye,**[3] FCP (SA), MMed (Med); **S Dlamini,**[8] Cert Infect Dis (SA), PhD; **M Mendelson,**[8] MRCP, PhD; **J Peter,**[1,7] FCP, PhD

[1] *Division of Allergology and Clinical Immunology, Department of Medicine, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Faculty of Health Sciences, University of Cape Town, South Africa*
[3] *Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[4] *Department of Paediatrics, Faculty of Health Sciences, University of Cape Town, South Africa*
[5] *Molecular Mycobacteriology Research Unit, Division of Medical Microbiology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, South Africa*
[6] *Division of Allergology and Clinical Immunology, Department of Paediatrics, Red Cross War Memorial Children's Hospital and Faculty of Health Sciences, University of Cape Town, South Africa*
[7] *Allergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa*
[8] *Division of Infectious Diseases and HIV Medicine, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*

Corresponding author: *J Peter (jonny.peter@uct.ac.za)*

Background. Up to a quarter of inpatients in high-income countries (HICs) self-report beta-lactam allergy (BLA), which if incorrect, increases the use of alternative antibiotics, worsening individual health outcomes and driving bacterial resistance. In HICs, up to 95% of self-reported BLAs are incorrect. The epidemiology of BLA in low- and middle-income African countries is unknown.
Objectives. To describe the epidemiology and de-labelling outcomes of self-reported BLA in hospitalised South African (SA) patients.
Methods. Point-prevalence surveys were conducted at seven hospitals (adult, paediatric, government and privately funded, district and tertiary level) in Cape Town, SA, between April 2019 and June 2021. Ward prescription records and in-person interviews were conducted to identify and risk-stratify BLA patients using the validated PEN-FAST tool. De-labelling was attempted at the tertiary allergy clinic at Groote Schuur Hospital.
Results. A total of 1 486 hospital inpatients were surveyed (1 166 adults and 320 children). Only 48 patients (3.2%) self-reported a BLA, with a higher rate in private than in government-funded hospitals (6.3% v. 2.8%; p=0.014). Using the PEN-FAST tool, only 10.4% (n=5/48) of self-reported BLA patients were classified as high risk for true penicillin hypersensitivity. Antibiotics were prescribed to 70.8% (n=34/48) of self-reported BLA patients, with 64.7% (n=22/34) receiving a beta-lactam. Despite three attempts to contact patients for de-labelling at the allergy clinic, only 3/36 underwent *in vivo* testing, with no positive results, and 1 patient proceeded to a negative oral challenge.
Conclusion. Unlike HICs, self-reported BLA is low among inpatients in SA. The majority of those who self-reported BLA were low risk for type 1 hypersensitivity, but outpatient de-labelling efforts were largely unsuccessful.

S Afr Med J 2023;113(2):69-74. https://doi.org/10.7196/SAMJ.2023.v113i2.16760

Beta-lactams are the commonest antibiotic class reported to cause allergy, yet globally there is a large burden of patients mislabelled as having a beta-lactam allergy (BLA).[1] In high-income countries (HICs), 6 - 25% of the population are labelled as having a BLA, but only 1 - 10% of the population have a true BLA. In keeping with this low prevalence, the prevalence of life-threatening anaphylaxis caused by beta-lactams is estimated to be 0.02 - 0.04%, a rate unchanged in the past 60 years.[1-3] While the epidemiology of BLA in HICs is well described, there are no published epidemiological data available on BLA in Africa or other low- and middle-income countries (LMICs).[4] An HIC is defined by the World Bank as a nation with a gross national income (GNI) per capita of ≥USD12 696 in 2020, whereas an LMIC is defined as one with a GNI of USD1 046 - 4 095.[5] South Africa (SA) is classed as an upper middle-income economy, with a GNI per capita of USD4 096 - 12 695.[6]

Being labelled with a BLA is potentially harmful to patients, with detrimental effects including the risk of antibiotic failure,[1] increased duration of hospital stay,[7] increased rates of postoperative

sepsis[8,9] and adverse reactions to prescribed alternative antibiotics.[1] In addition to increased patient risk, there is extra financial cost to the healthcare system with the increased cost of broad-spectrum antibiotics, longer duration of hospital admission, and increased rates of readmission.[10,11] Globally BLA drives antibiotic resistance (ABR) owing to the increased use of broader-spectrum antibiotics than the penicillins, which results in increased risks of infection with vancomycin-resistant enterococci,[7] methicillin-resistant *Staphylococcus aureus*[12] and Clostridiodes *difficile*.[1,13] In 2019, 4.95 million people worldwide died with an antibiotic-resistant bacterial infection, and 1.3 million of those deaths were a direct result of bacteria being resistant to antibiotics.[14] The burden of ABR is highest in low-income countries (LICs).[4,14,15] Western sub-Saharan Africa has the highest all-age death rate attributable to ABR (27.3 deaths per 100 000; 95% confidence interval (CI) 20.9 - 35.3).[14] The high mortality due to ABR in sub-Saharan Africa makes de-labelling BLA a public health and antibiotic stewardship priority.

The success of programmatic antibiotic allergy testing incorporated into antibiotic stewardship programmes has been increasingly reported with the use of clinical decision tools that can be used by allergists and non-allergists.[16] Direct de-labelling of inpatients is safe and effective, with rates of negative testing being comparable to the outpatient setting.[17] The need to establish the true prevalence and incidence of BLA in LMICs is of paramount importance to improve our management of BLA in settings with the highest burden of infectious diseases.[4]

Methods

We conducted a multicentre point-prevalence survey of hospitalised patients. Between 4 April 2019 and 14 June 2021, a total of 1 486 hospital inpatients were surveyed at five government-funded hospitals and two privately funded hospitals in Cape Town, SA. The government-funded hospitals were Groote Schuur Hospital (GSH, tertiary level), Red Cross War Memorial Children's Hospital (RXH, paediatric tertiary level), and three secondary-level hospitals – Victoria Hospital Wynberg (VHW), New Somerset Hospital (NSH) and Mitchell's Plain Hospital (MPH). The two privately funded hospitals were Christiaan Barnard Memorial Hospital (CBMH) and University of Cape Town Private Academic Hospital (UCTPAH) (Fig. 1 and Table 1; see Appendix 1 (available online at https://www.samedical.org/file/1959) for descriptions of the hospitals).

The study was approved by the Human Ethics Research Committee of the University of Cape Town (ref. no. HREC 417/2019) and the institutional hospital committees, including the Netcare Research Operations Committee. The delay in conducting the final surveys was due to the COVID–19 pandemic, as six of the surveys were performed between the second and third COVID-19 waves in SA.

A medical team trained in using the PEN-FAST tool for BLA risk stratification (developed by Trubiano *et al.*[16]) surveyed all hospitalised patients. If the patient reported a BLA, the PEN-FAST classification was done immediately with the patient or guardian. In addition, the patient's folder was reviewed for documentation of BLA (in the doctor's notes and nursing notes, and on the prescription charts), and antibiotic use was recorded. All patients who reported a BLA were contacted after discharge and offered allergy testing (de-labelling) at the nearby Groote Schuur Hospital allergy clinic. A direct challenge was performed for low-risk patients in the clinic. Patients at moderate and high risk first had skin-prick testing and intradermal testing, followed by an oral challenge if the skin-prick tests and intradermal tests were negative. The PEN-FAST BLA phenotype clinical decision tool has a high negative predictive value of 96.3% (95% CI 94.1 - 97.8).[16,18] The major criteria for the PEN-FAST tool are the allergy event having occurred within the preceding 5 years (2 points), and anaphylaxis, angio-oedema or severe cutaneous delayed reactions (2 points). A single minor criterion of whether the allergic reaction required treatment scores 1 point. The PEN-FAST tool has a validated area under the curve of 0.805 (for a cut-off of 3 points, chosen to classify patients as low risk of penicillin allergy).[16] The novel PEN-FAST BLA clinical decision mobile app was used by the investigators to classify patients as low risk (1 - 5%), moderate risk (20%) or high risk (50%) of a positive penicillin allergy test.

Descriptive statistics were performed

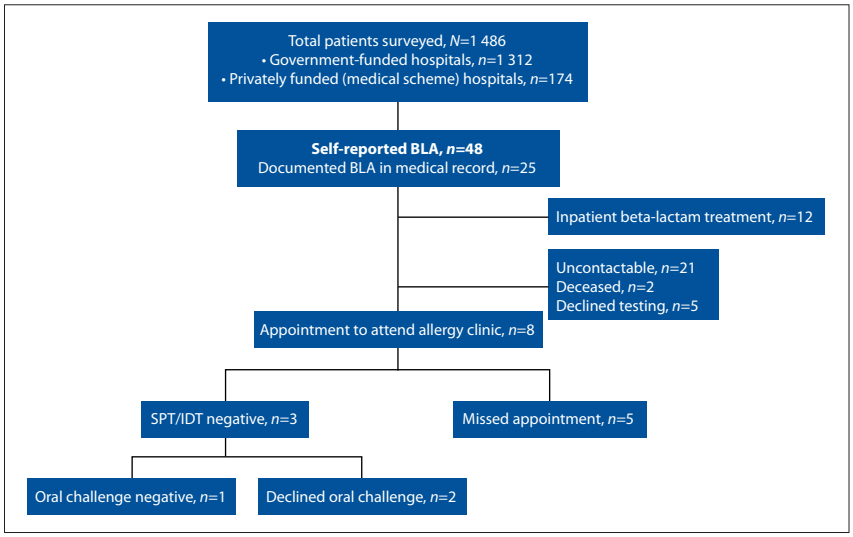

Fig. 1. Consort diagram. (BLA = beta-lactam allergy; SPT = skin-prick testing; IDT = intradermal testing.)

Table 1. Summary of all patients surveyed, stratified by hospital funding base

	All (*N*=1 486), *n* (%)*	Government-funded hospitals (*n*=1 312), *n* (%)*	Privately funded hospitals (*n*=174), *n* (%)*
Bed capacity, *N*	2 301	1 929	372
Bed occupancy, %	64	68	47†
Female	785 (52.8)	703 (53.6)	81 (47)
Age (years), median (IQR)	40 (25 - 60)	39 (24 - 57)	16 (1 - 58)
Unable to speak to patient/parent	303 (20.4)	264 (20.1)	40 (23.0)
BLA reported	48 (3.2)	37 (2.8)	11 (6.3)

IQR = interquartile range; BLA = beta-lactam allergy.
*Except where otherwise indicated.
†The low bed occupancy in these hospitals was the result of COVID-19 restrictions at the time of the survey.

using counts and proportions for categorical data, and medians and interquartile ranges (IQRs) for continuous variables. All statistical analyses were conducted using Stata version 14 (StataCorp, USA).

Results

A total of 1 486 hospital inpatients (1 166 adults aged ≥18 years and 320 children aged <18 years) were surveyed in seven hospitals in Cape Town during the study period (Fig. 1, Tables 1 and 2; Supplementary Table 1, https://www.samedical.org/file/1959). Of these, 52.8% were female, and the median (IQR) age was 40 (25 - 60) years. Overall, 48 patients (3.2%) self-reported a BLA, with a significantly higher rate of self-reported BLA in the privately funded hospitals compared with the government-funded hospitals (2.8% v. 6.3%, respectively; p=0.014). None of the facilities had 100% bed capacity at the time of the surveys (GSH n=721/893; 80.7%, RXH n=189/300; 63.0%, VHW n=107/206; 51.9%, NSH n=200/330; 60.6%, MPH n=95/200; 47.5%, CBMH n=129/248; 52.0%, and UCTPAH n=45/124; 36.3%). Six of the seven surveys were performed between March 2021 and July 2021, and the decreased bed occupancy in these facilities was probably due to the COVID-19 pandemic and decreased utilisation of non-urgent clinical services.

Of the 48 self-reported BLA patients, 60.4% were female, and the median (IQR) age was 59 years (38 - 68) years (Table 3; Supplementary Table 2, https://www.samedical.org/file/1959). No BLA was reported in patients aged <18 years. There were 12 patients (0.8%) who reported non-beta-lactam antibiotic allergies. The majority (n=35; 72.9%) of the participants reported that the allergic event had taken place <10 years previously. Most (64.6%; n=31) could recall the details of the allergic event, but 12.5% (n=6) reported a BLA based on family history alone. In total, 64.6% of patients (n=31) were classified as low risk and 22.9% (n=11) as moderate risk for positive penicillin testing, while only 10.4% of patients (n=5) were classified as high risk. Eight patients reported anaphylaxis and 10 reported angio-oedema (6 of whom had laryngeal angio-oedema). The most commonly reported symptom was a mild/self-limiting skin rash in 25.0% of patients (n=12). In total, 30 patients (62.5%) required treatment for the BLA, but only 10 (20.8%) required adrenaline.

A BLA was documented on 52.1% (n=25) of the inpatient prescription charts, with significantly higher rates of documentation in the privately funded facilities (n=9; 81.8%) compared with the government-funded facilities (n=16; 43.2%) (p=0.02) (Table 4; Supplementary Table 3, https://www.samedical.org/file/1959). A total of 34 (70.8%) of the reported BLA patients were prescribed antibiotics, of whom 22 (64.7%) still received a beta-lactam-containing antibiotic (beta-lactam/beta-lactamase inhibitor combination (amoxicillin-clavulanate or piperacillin-tazobactam) n=6; aminopenicillin n=5; cephalosporin n=9; carbapenem n=2).

The 11 patients (32.4%) who were prescribed a beta-lactam/aminopenicillin, either alone or in combination with clavulanate, completed treatment with no allergic reaction. Seven of these patients who received a beta-lactam/aminopenicillin had no documentation of the reported BLA in the prescription charts or patient notes. Ten of these 11 patients were classified as low risk by PEN-FAST scoring; however, one patient's risk was high, with previous anaphylaxis and laryngeal angio-oedema. The remaining 14 patients (41.2%) were prescribed lincosamides (n=5), aminoglycosides (n=3), fluoroquinolones/quinolones (n=2), macrolides (n=2) and nitroimidazole (n=1).

Over a quarter of the patients were prescribed more than one antibiotic. As per antibiotic stewardship requirements, 15 patients (44.1%) had the indication for the antibiotic documented on the antibiotic chart. The difference between the government-funded and privately funded hospitals was not significant (n=10 (37.0%) in the government-funded hospitals and n=5 (71.4%) in the privately funded hospitals; p=0.1). The most common indication for antibiotic therapy was pneumonia (n=4), followed by bloodstream infection (n=2), and gynaecological/obstetric, urinary tract and abdominal infection (n=1 each). In 5 cases, the indication for an antibiotic was documented as 'not defined'.

The median (IQR) duration of admission for the government-funded hospital patients was 6 (4 - 15) days, with longer admission durations at GSH and MPH compared with NSH and VHW (Table 3; Supplementary Table 2, https://www.samedical.org/file/1959). Data for admission, length of stay and readmission rates were not available for the privately funded hospitals.

A total of 8 patients who were contactable after discharge had a clinic appointment made, with 21 patients lost to follow-up (not including 2

Table 2. Summary of all patients surveyed, stratified by hospital funding base and age group

Age (years)	All (N=1 486), n (%)	Reported BLA, n (%)	Government-funded hospitals (n=1 312), n (%)	GSH (n=721), n (%)	VHW (n=107), n (%)	RXH (n=189), n (%)	MPH (n=95), n (%)	NSH (n=200), n (%)	Privately funded hospitals (n=174), n (%)	CBMH (n=129), n (%)	UCTPAH (n=45), n (%)
<1	147 (9.9)	0	124 (9.5)	0	8 (7.5)	81 (42.9)	10 (10.5)	25 (12.5)	23 (13.2)	23 (17.8)	0
1 - 5	89 (6)	0	84 (6.4)	7 (1.0)	7 (6.5)	63 (33.3)	7 (7.4)	0	5 (2.9)	3 (1.7)	2 (4.4)
6 - 11	43 (2.9)	0	39 (3.0)	5 (0.7)	0	34 (18.0)	0	0	4 (2.3)	0	4 (8.8)
12 - 18	29 (2.0)	0	26 (2.0)	12 (1.7)	0	11 (5.8)	0	3 (1.5)	3 (1.7)	2 (1.1)	1 (2.2)
>18	1 166 (78.5)	48 (3.2)	1 027 (78.3)	685 (95.0)	92 (86.0)	0	78 (82.1)	172 (86.0)	139 (79.9)	101 (78.3)	38 (84.4)
Unknown	12 (0.8)	0	12 (0.9)	12 (1.7)	0	0	0	0	0	0	0

BLA = beta-lactam allergy; GSH = Groote Schuur Hospital; VHW = Victoria Hospital Wynberg; RXH = Red Cross War Memorial Children's Hospital; MPH = Mitchell's Plain Hospital; NSH = New Somerset Hospital; CBMH: Christiaan Barnard Memorial Hospital; UCTPAH = University of Cape Town Private Academic Hospital.

Table 3. Summary of self-reported BLA, stratified by hospital funding base and age group

	All (*N*=48), *n* (%)*	Government-funded hospitals (*n*=37), *n* (%)*	Privately funded hospitals (*n*=11), *n* (%)*
Female	29 (60.4)	22 (59.4)	8 (72.7)
Age (years), median (IQR)	59 (38 - 68)	59 (38 - 68)	58 (52 - 63)
PEN-FAST[16]			
Low risk	31 (64.6)	24 (64.9)	7 (63.6)
Moderate risk	11 (22.9)	8 (21.6)	3 (27.3)
High risk	5 (10.4)	4 (10.8)	1 (9)
Unknown	1 (2.1)	1 (2.7)	0
Questions from PEN-FAST[16]			
Penicillin allergy reported	48 (100)	37 (100)	11 (100)
≤5 years since reaction	9 (18.8)	5 (13.5)	4 (36.3)
Anaphylaxis or angio-oedema	10 (20.8)	7 (18.9)	3 (27.2)
Severe cutaneous adverse reaction	7 (14.6)	6 (16.2)	1 (9.1)
Required treatment	30 (62.5)	24 (64.9)	6 (54.5)
Reaction >10 years	35 (72.9)	28 (75.7)	7 (63.6)
Patient can recall event	31 (64.6)	22 (59.5)	9 (81.8)
Family history only	6 (12.5)	4 (10.8)	2 (18.2)
Required adrenaline	10 (20.8)	8 (21.6)	2 (18.2)
Hospital admission and re-admission details			
Duration of admission (days), median (IQR)	6 (4 - 15)	6 (4 - 15)	Unknown
Duration of admission not known	12 (24.5)	1 (2.6)	11 (100)
Number of re-admissions in following 6 months, median (IQR)	0 (0 - 2)	0 (0 - 2)	Unknown

BLA = beta-lactam allergy; IQR = interquartile range.
*Except where otherwise indicated.

deaths and 5 patients who declined further investigation) (Table 5). However, only 3/8 patients returned to the GSH allergy clinic for evaluation; 5 patients missed their clinic follow-up and were subsequently not contactable. All 3 patients had negative epidermal testing, but 2 of them declined an oral challenge. Ultimately only 1 patient proceeded to direct oral challenge, which was negative.

Discussion

Spurious BLA labels are potentially dangerous to patients and pose a public health emergency in terms of healthcare costs and driving ABR. This article is the first to report the epidemiology of BLA in SA and Africa. Our major finding was a prevalence of reported BLA in hospitalised patients of only 3.2%, a rate considerably lower than HIC rates. The self-reported BLA rates were lower in the government-funded hospitals than in the privately funded hospitals. The second main finding was that, despite several attempts and assistance, very few participants in our study with a BLA label returned to our clinic for allergy de-labelling.

The lowest rate of self-reported BLA from HIC inpatient settings is 9.9% of 1 738 patients enrolled over a 1-year period in Montreal, Canada.[11] The rate in our study was less than half of this low-end rate. Furthermore, >60% of our small number of self-reported cases of BLA were considered low risk for true BLA, meaning that the prevalence of confirmed beta-lactam hypersensitivity may in fact be even lower in our SA population. There are several possible factors that may explain both a lower rate of BLA labels and a possible lower rate of true beta-lactam hypersensitivity in our population. Antibiotic prescribing patterns differ across the world, and involve a complex interplay of social, patient, provider and economic factors.[19] The majority of BLA labels are the result of viral or drug-related exanthems in childhood.[2] However, difficulties in accessing healthcare in SA (particularly in rural areas), resulting in fewer antibiotics being given,[19] may limit childhood exposure to BLA allergens and so contribute to less identification of true BLA in our setting.

Drug-related (and viral) exanthems, considered to be the predominant driver of incorrect BLA labels, are predominantly T-cell mediated, the majority of which are HLA restricted. A recent genome-wide association study (GWAS) linked *HLA-B55:01* with penicillin allergy label. Interestingly, this allele has relatively low frequencies in black African populations. This finding contrasts with another recent GWAS among confirmed cases of immediate hypersensitivity to beta-lactams, which identified *HLA-DRB1*10:01* as a risk allele. *HLA-DRB1*10:01* is carried twice as frequently in individuals of African ancestry as in individuals of Caucasian ancestry.[20] Other genetic studies in European populations with confirmed beta-lactam hypersensitivity have linked polymorphisms in cytokine genes (*TNFA*, *IL-13*, *IL-4*, *IL-4R*),[21] which are also likely to be population specific. It is therefore possible that compared with Caucasian populations, African populations may have a similar or higher risk for true immediate beta-lactam hypersensitivity, but less likelihood of mild delayed reactions, the major drivers of incorrect BLA labelling in childhood. Finally, skin colour may affect the detection of maculopapular exanthems in individuals with Fitzpatrick skin types IV, V and VI,[22] as erythema and fine rashes are more difficult to detect in pigmented skin. Taken together, there may be several genetic and biological factors that explain self-reported BLA prevalence in black African populations.

BLA labels were significantly more common in patients attending private compared with government-funded hospitals. SA is the most inequitable country in Africa, with a Gini coefficient of 0.63 in 2015, an inequality reflected in its public as opposed to private healthcare. Race and socioeconomic status are major factors.[23-25] The population sector utilising privately funded healthcare in SA

Table 4. Summary of antibiotic use in patients with self-reported BLA, stratified by hospital funding base

	All (*N*=48), *n* (%)	Government-funded hospitals (*n*=37), *n* (%)	Privately funded hospitals (*n*=11), *n* (%)
BLA documented on antibiotic script	25 (52.1)	16 (43.2)	9 (81.8)
On antibiotic	34 (70.8)	27 (73.0)	7 (63.6)
Indication for antibiotics on script	14/34 (41.1)	9/27 (33.0)	5 (71.4)
Not defined	5/15 (33.3)	2/10 (20.0)	3/5 (60.0)
Pneumonia	4/15 (26.6)	3/10 (30.0)	1/5 (20.0)
Bloodstream	2/15 (13.3)	2/10 (20.0)	0
Gynaecological/obstetric	1/15 (6.7)	1/10 (10.0)	0
Abdominal infection	1/15 (6.7)	0	1/5 (20.0)
Urinary tract infection	1/15 (6.7)	1/10 (10.0)	0
Type of antibiotics			
Beta-lactam antibiotics	22/34 (64.7)	17/27 (63.0)	5/7 (71.4)
Beta-lactam/beta-lactamase inhibitor (amoxicillin-clavulanate or piperacillin-tazobactam)	6/34 (17.6)	4/27 (14.8)	2/7 (28.6)
Aminopenicillin	5/34 (14.7)	4/27 (14.8)	1/7 (14.3)
Carbapenem	2/34 (5.9)	1/27 (3.7)	1/7 (14.3)
Cephalosporin	9/34 (26.5)	8/27 (29.6)	1/7 (14.3)
Non-beta-lactam antibiotics	14/34 (41.2)	9/27 (33.3)	5/7 (71.4)
Fluoroquinolone/quinolone	2/34 (5.9)	2/27 (7.4)	0
Glycopeptide	1/34 (2.9)	0	1/7 (14.3)
Lincosamide	5/34 (14.7)	2/27 (7.4)	3/7 (42.9)
Macrolide	2/34 (5.9)	2/27 (7.4)	0
Nitroimidazole	1/34 (2.9)	1/27 (3.7)	0
Aminoglycoside	3/34 (6.3)	2/27 (7.4)	1/7 (14.3)
Antibiotic unknown	5/34 (14.7)	5/27 (18.5)	0
More than one antibiotic	9/34 (26.5)	5/27 (18.5)	4/7 (57.1)

BLA = beta-lactam allergy.

Table 5. BLA de-labelling efforts at the tertiary Groote Schuur Hospital allergy clinic

	All (*N*=48), n (%)	Government-funded hospitals (*n*=37), *n* (%)	Privately funded hospitals (*n*=11), *n* (%)
Uncontactable	21 (43.8)	16 (43.2)	5 (45.4)
Contacted but now living in a different province	5 (10.4)	5 (13.5)	0
Contacted and declined testing	5 (10.4)	3 (8.1)	2 (18.2)
Deceased	2 (4.2)	1 (2.7)	1 (9.1)
BL antibiotic given in ward	12 (25.0)	9 (24.3)	3 (27.2)
Intradermal testing and SPT negative, declined oral challenge	2 (4.2)	2 (2.7)	0
Intradermal testing and SPT negative, oral challenge negative	1 (2.1)	1 (2.7)	0

BLA = beta-lactam allergy; BL = beta-lactam; SPT = skin-prick testing.

resembles that of an HIC in that the predominant racial group is white (European ancestry),[24] with a higher income. The population that accesses government-funded healthcare has a high proportion of individuals of black African, Indian or mixed ancestry. The difference in BLA rates between government and private hospital inpatients may therefore reflect both differences in access to healthcare in childhood, with different levels of antibiotic exposure, and genetic and skin pigment biological factors related to populations of origin.[22] Further qualitative and basic science research is required to understand these differences.

Another important finding was that, despite several attempts to contact patients and assist them to attend our allergy clinic, only 1 of 48 patients completed an oral challenge for de-labelling. Many factors may contribute to this difficulty, including patient-perceived lack of importance of carrying a BLA label, fear of the testing and procedures or the time involved, changes in contact details and a mobile patient population, or even lack of resources to return for clinic visits.[19,24,26] This inability to have patients return and attend allergy clinics or for elective procedures has been highlighted even in HICs, and was undoubtedly aggravated across the world by the COVID-19 pandemic. In paediatric patients, recommendations now exclude the use of skin-prick tests as a possible barrier to care advocating for direct oral de-labelling.[27] These data indicate that the only viable option for BLA de-labelling in LMICs is likely to be direct de-labelling or challenges in low-risk patients by non-allergists. The development, validation and implementation of risk-

stratification tools to guide non-allergists will be critical to this effort. A comprehensive framework for incorporation of BLA de-labelling in LMICs/LICs has recently been outlined.[4] The inclusion of several hospitals across different levels of the health system in the present study, and inclusion of private and government-funded hospitals, improved the generalisability of these data. However, the fact that the study was performed in only one SA city is a limitation. The COVID-19 pandemic meant that there was a several months' gap between the initial survey at GSH in April 2019 and the other surveys in the study, and it also limited bed occupancy at the time of surveys in several hospitals, which may have affected results. The lack of reported BLA in patients aged <18 years may reflect low bed occupancy rates at RXH at the time of the survey, and the high percentage of paediatric patients in the cohort aged <1 year may also be a factor limiting the generalisability of paediatric data.

Conclusion

This study provides the first data on the epidemiology of BLA in Africa and demonstrates that the overall prevalence of BLA is much lower than that reported in HICs. Furthermore, disparity of our results across health sectors highlights several of the complex social and biological determinants of both true and incorrectly labelled BLA. The inability to confirm BLA in the majority of cases through skin testing and direct oral challenge in the allergy clinic illustrates the difficulties of incorporating BLA de-labelling strategies in antibiotic stewardship programmes in LMICs, which demands a different solution to that in HICs, by shifting the site of testing to the bedside and to non-allergists. Epidemiological data from other LMICs are required to confirm our findings and help LMIC policymakers decide on the importance of targeting BLA de-labelling in local antibiotic stewardship efforts. Affordable strategies for direct de-labelling or inpatient challenge are supported by these data.

Dedication. In memory of Tokoloho (Tuks) Ramabele.

Declaration. None.

Acknowledgements. None.

Author contributions. JP, MM and SD devised the proposal and protocol. CD organised hospital surveys and analysed data. CD and JP wrote and edited the manuscript. MD conducted all allergy testing. MBo assisted with data cleaning, and AOB assisted with communication with the survey team. All authors reviewed the manuscript. The following authors conducted surveys. *One survey:* JP, MM, SD, AG, WA, CJ, ZZ, SM, MBu, YP, PM, MdP, GD, RPW, NM, AD, TMs, AS, OM, BM, TAGB, KB, CM, JvdW, RW, DC, SS, UB, IF, DB. *Two surveys:* J-MA, AB, TT, OJ, TMa, SP, AP, SV, MvdM, MD. *Three surveys:* NE, SP, KM, TR. *Four surveys:* AOB, JS. *Six surveys:* CD.

Funding. None.

Conflicts of interest. None.

1. Stone CA Jr, Trubiano J, Coleman DT, Rukasin CR, Phillips EJ. The challenge of de-labeling penicillin allergy. Allergy 2020;75(2):273-288. https://doi.org/10.1111/all.13848
2. Castells M, Khan DA, Phillips EJ. Penicillin allergy. N Engl J Med 2019;381(24):2338-2351. https://doi.org/10.1056/NEJMra1807761
3. Gonzalez-Estrada A, Radojicic C. Penicillin allergy: A practical guide for clinicians. Cleve Clin J Med 2015;82(5):295-300. https://doi.org/10.3949/ccjm.82a.14111
4. Krishna MT, Vedanthan PK, Vedanthan R, et al. Is spurious penicillin allergy a major public health concern only in high-income countries? BMJ Glob Health 2021;6(5):e005437. https://doi.org/10.1136/bmjgh-2021-005437
5. World Bank. World Bank country and lending groups: Country classification. 2022. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519#High_income (accessed 1 October 2022).
6. World Bank. The world by income and region. 2022. https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html#:~:text=The%20World%20Bank%20classifies%20economies,%2Dmiddle%2C%20and%20high%20income (accessed 1 October 2022).
7. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin 'allergy' in hospitalised patients: A cohort study. J Allergy Clin Immunol 2014;133(3):790-796. https://doi.org/10.1016/j.jaci.2013.09.021
8. Savic LC, Khan DA, Kopac P, et al. Management of a surgical patient with a label of penicillin allergy: Narrative review and consensus recommendations. Br J Anaesth 2019;123(1):e82-e94. https://doi.org/10.1016/j.bja.2019.01.026
9. Lam PW, Tarighi P, Elligsen M, et al. Self-reported beta-lactam allergy and the risk of surgical site infection: A retrospective cohort study. Infect Control Hosp Epidemiol 2020;41(4):438-443. https://doi.org/10.1017/ice.2019.374
10. Mattingly TJ, Fulton A, Lumish RA, et al. The cost of self-reported penicillin allergy: A systematic review. J Allergy Clin Immunol Pract 2018;6(5):1649-1654.e4. https://doi.org/10.1016/j.jaip.2017.12.033
11. Picard M, Bégin P, Bouchard H, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. J Allergy Clin Immunol Pract 2013;1(3):252-257. https://doi.org/10.1016/j.jaip.2013.01.006
12. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: Population based matched cohort study. BMJ 2018;361:k2400. https://doi.org/10.1136/bmj.k2400
13. Turner NA, Wrenn R, Sarubbi C, et al. Evaluation of a pharmacist-led penicillin allergy assessment program and allergy delabeling in a tertiary care hospital. JAMA Netw Open 2021;4(5):e219820. https://doi.org/10.1001/jamanetworkopen.2021.9820
14. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet 2022;339(10325):629-655. https://doi.org/10.1016/S0140-6736(21)02724-0
15. Pierce J, Apisarnthanarak A, Schellack N, et al. Global antimicrobial stewardship with a focus on low- and middle-income countries: A position statement for the International Society for Infectious Diseases. Int J Infect Dis 2020;96:621-629. https://doi.org/10.1016/j.ijid.2020.05.126
16. Trubiano JA, Vogrin S, Chua KYL, et al. Development and validation of a penicillin allergy clinical decision rule. JAMA Intern Med 2020;180(5):745-752. https://doi.org/10.1001/jamainternmed.2020.0403
17. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: A systematic review and meta-analysis. Allergy 2017;72(9):1288-1296. https://doi.org/10.1111/all.13168
18. Piotin A, Godet J, Trubiano JA, et al. Predictive factors of amoxicillin immediate hypersensitivity and validation of PEN-FAST clinical decision rule. Ann Allergy Asthma Immunol 2022;128(1):27-32. https://doi.org/10.1016/j.anai.2021.07.005
19. Manderson L. Prescribing, care and resistance: Antibiotic use in urban South Africa. Humanit Soc Sci Commun 2020;7:77. https://doi.org/10.1057/s41599-020-00564-1
20. Nicoletti P, Carr DF, Barrett S, et al. Beta-lactam-induced immediate hypersensitivity reactions: A genome-wide association study of a deeply phenotyped cohort. J Allergy Clin Immunol 2021;147(5):1830-1837.e15. https://doi.org/10.1016/j.jaci.2020.10.004
21. Gueant J-L, Romano A, Cornejo-Garcia JA, Guéant-Rodriguez R-M, Gaeta F, Blanca M. Genetic associations in beta-lactam allergy. Clin Transl Allergy 2014;4(Suppl 3):P68. https://doi.org/10.1186/2045-7022-4-S3-P68
22. Lehloenya RJ, Phillips EJ, Pasieka HB, Peter J. Recognizing drug hypersensitivity in pigmented skin. Immunol Allergy Clin North Am 2022;42(2):219-238. https://doi.org/10.1016/j.iac.2022.01.005
23. Harris B, Goudge J, Ataguba JE, et al. Inequities in access to health care in South Africa. J Public Health Policy 2011;32(1):S102-S123. https://doi.org/10.1057/jphp.2011.35
24. Mhlanga D, Garidzirai R. The influence of racial differences in the demand for healthcare in South Africa: A case of public healthcare. Int J Environ Res Public Health 2020;17(14):5043. https://doi.org/10.3390/ijerph17145043
25. Van Rensburg HCJ. South Africa's protracted struggle for equal distribution and equitable access – still not there. Hum Resour Health 2014;12:26. https://doi.org/10.1186/1478-4491-12-26
26. Gordon T, Booysen F, Mbonigaba J. Socio-economic inequalities in the multiple dimensions of access to healthcare: The case of South Africa. BMC Public Health 2020;20:289. https://doi.org/10.1186/s12889-020-8368-7
27. Schroer B, Macy E. Another step forward in the optimisation of penicillin allergy delabeling strategies in children. J Allergy Clin Immunol Pract 2021;9(11):4067-4068. https://doi.org/10.1016/j.jaip.2021.08.011

Accepted 3 October 2022.