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Non-communicable diseases and infection in an Indigenous Australian population: increased risk during a rapid epidemiological transition

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Data sharing: Data relate to Indigenous Australians and cannot be shared without specific approval from the relevant Indigenous communities and the responsible HREC. Obtaining such approval will require detail of all individuals seeking access and each research project for which the inclusion of this data is proposed.

Abstract

Objectives: We hypothesize that rising prevalence rates of non-communicable diseases (NCDs) increases infection risk and worsens outcomes among socially disadvantaged Indigenous Australians undergoing a rapid epidemiological transition.

Design: Pathology, imaging and discharge morbidity codes were retrospectively reviewed for a period of 5 years prior to admission with a blood stream infection (BSI), 1st January 2003 to 30th June 2007.

Participants: 558 Indigenous and 55 non-Indigenous community residents of central Australia.

Outcome measures: The effects of NCDs on risk of infection and death were determined after stratifying by ethnicity.

Results: Mean annual BSI incidence rates were far higher among Indigenous residents (Indigenous, 970 per 100,000; non-Indigenous, 48 per 100,000 person-years; IRR=20.33; 95% CI=20.31-20.35, p<0.001). Indigenous patients were also more likely to have previous bacterial infections (68.7% versus 34.6%; respectively, p<0.001), diabetes (44.3% versus 20.0%; p<0.001), harmful alcohol consumption (37.0% versus 12.7%; p<0.001) and other communicable diseases (HTLV-1, 45.2%; strongyloidiasis, 36.1%; HBV, 12.9%). Among Indigenous patients, diabetes increased odds of current *Staphylococcus aureus* BSI (OR=1.6, 95% CI=1.0-2.5) and prior skin infections (adjusted OR=2.1, 95% CI=1.4-3.3). Harmful alcohol consumption increased odds of current *Streptococcus pneumoniae* BSI (OR=1.57, 95% CI=1.02-2.40) and of previous BSI (OR=1.7, 95% CI=1.1-2.5), skin infection (OR=1.7, 95% CI=1.1-2.6) or pneumonia (OR=4.3, 95% CI=2.8-6.7). Twenty-six percent of Indigenous patients died at a mean

(SD) age of 47±15 years. Complications of diabetes and harmful alcohol consumption predicted 28-day mortality (non-rheumatic heart disease, HR=2.9; 95% CI=1.4-6.2; chronic renal failure, HR=2.6, 95%CI=1.0-6.5; chronic liver disease, HR=3.3, 95%CI=1.6-6.7).

Conclusion: In a socially disadvantaged population undergoing a rapid epidemiologic transition, NCDs further increase risk of infection and BSI related mortality. Complex interactions between communicable diseases and NCDs demand an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change.

Article Summary

Article Focus

- Remote dwelling, Indigenous Australians are undergoing a rapid epidemiological transition, which is accompanied by a rapidly rising burden of non-communicable diseases (NCDs).
- In this setting of social disadvantage and frequent pathogen exposure, NCDs may increase risk of infection and infection-related death.

Key Messages

- We reveal substantial racial disparities in rates of infection and of NCDs, reflecting the dual burden of disease that affects this Indigenous population.
- NCDs increased risk of blood stream infections with some pathogens, previous infections that provide portals of entry for life-threatening invasive disease and infection-related mortality.
- Complex interactions between communicable diseases and NCDs demand an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change.

Strengths and limitations of this study

- This hospital-based study only includes patients who were admitted with a blood stream infection. We are therefore unable to determine the actual risk of blood stream infections that is attributable to NCDs or to comment on background rates of other infections, which might be treated in the community.
- The major strength of our study lies in the demography of the study population, which is served by a single hospital, and the extensive nature of the clinical

material on which our analysis is based.

Introduction

Prevalence rates of non-communicable diseases (NCDs), such as diabetes, are rising rapidly in developing countries, adding to a pre-existing burden of infectious diseases in populations that are undergoing rapid demographic changes[1,2]. A similar burden of communicable diseases and NCDs affects marginalized Indigenous people living in poverty within developed countries [3,4]. Among Indigenous Australians, for example, NCDs are the major contributors to racial disparities in mortality and to a life expectancy that remains 17 years less than that of their non-Indigenous peers[3]. In central Australia, rising prevalence rates of NCDs affect an Indigenous population in which a high burden of infectious diseases persists. Incidence rates of sepsis [5], blood stream infections [6] and childhood pneumonia, and prevalence rates of bronchiectiasis[7] are the highest reported worldwide. Strongyloidiasis and chronic viral infections, such as with hepatitis B virus (HBV) and the Human T-Lymphotropic Virus 1 (HTLV-1), are also common [6]. Population-based infection-related mortality rates for Indigenous adults in central Australia therefore remain higher than those of some African countries prior to the current HIV pandemic and the median age of in-hospital death is only 48 years [8].

Interactions between communicable diseases and NCDs have been little studied; however, an appreciable effect of NCDs on infection rates is likely where pathogen exposure is frequent. Diabetes, for example, contributes to the risk of serious bacterial infections including *Streptococcus pneumoniae*[9] and *Staphylococcus aureus* [10], which are common pathogens in overcrowded Indigenous Australian communities [6]. The NCD burden may therefore have a substantial impact on infection rates and outcomes where

these two epidemics coincide. Such an interaction could reverse health gains in populations undergoing a rapid epidemiologic transition and exacerbate health inequalities among disadvantaged subgroups within developed countries. The recent description in New Zealand of an increasing divergence in infection-related hospitalization rates according to social status is consistent with this possibility and challenges health transition theory [11].

Central Australia is well placed to study interactions between poverty, NCDs and infectious diseases. Most Indigenous residents live in remote communities in conditions of considerable socio-economic disadvantage, leaving only a minority within the major regional township of Alice Springs. The latter have ready access to a well-resourced medical facility, Alice Springs Hospital (ASH), which has sophisticated diagnostic capabilities and provides specialist medical care to a region of 1,000,000 km^2. Indigenous residents of Alice Springs dwell in either overcrowded 'town camps', which have poor amenities and limited refuse disposal, or are integrated with the majority of the non-Indigenous population within the township's suburbs. The Indigenous population of this region also has among the highest blood stream infection incidence rates reported [6]. Living conditions that increase the risk of pathogen exposure and high background rates of focal infections, which provide portals of entry for bacterial invasion, are likely to precede these life-threatening infections. Blood stream infection incidence rates therefore provide measurable end-points to which environmental and host factors contribute.

Here we report the infectious and non-communicable disease burden among community residents of central Australia who presented with a blood stream infection and determine risk factors for infection and death after stratifying by ethnicity.

Methods

We conducted a retrospective review of all positive blood cultures collected from adult patients (age≥15 years) admitted to ASH between 1st January 2001 and 31st June 2007. In July 2007 the Australian Federal Government suspended racial discrimination legislation and implemented an 'Emergency Response' that resulted in considerable uncertainty among Indigenous residents [12]. This raised concerns that the central Australian resident population could change as people moved interstate to escape these restrictions and no data was collected after this date. Data collected included organism, ethnicity, dates of birth, dates of death, indigenous status and place of residence. For patients who presented between 1st January 2003 and 31st June 2007 we also obtained ICD 10 morbidity codes and the results of microbiological and radiological investigations for each admission for 5 years prior to the final BSI presentation. NCDs were derived from ICD-10 morbidity codes for diabetes, harmful alcohol consumption, >stage 2 chronic kidney disease, ischaemic heart disease, chronic liver disease and malignancy. Bronchiectasis was diagnosed radiologically using American College of Chest Physician criteria. Heart failure and valvular heart disease, including rheumatic heart disease (RHD), were diagnosed by trans-thoracic echocardiography. Ischaemic heart disease and cardiac failure were combined ('non-rheumatic heart disease') for statistical analysis.

Definitions

Residence

Place of residence was categorized as i) remote (>100 km from Alice Springs), ii) Alice Springs town camp and iii) urban (resident in Alice Springs, but not in a town camp).

Nursing home residents were included in calculations of BSI incidence rates, but excluded from further analysis because the primary study objective was to determine risk factors for infection and death among community residents.

Infections

A blood culture from which a pathogen was isolated was defined as a 'BSI episode'. Repeated culture of the same organism from blood culture was regarded as a separate 'episode' only if blood samples were drawn more than one month apart. Blood stream infections were defined as community-acquired if a pathogen was isolated from blood cultures drawn within 48 hours of admission and nosocomial if isolated from blood cultures drawn after this time. Foci of infection were determined where possible from ICD-10 morbidity codes in association with pathology and imaging results for each admission for five years prior to the final BSI during the study period. A diagnosis of pneumonia was made if there was radiological evidence of consolidation and this was attributed to the pathogen isolated from blood cultures if the same organism was also isolated from sputum or the blood culture isolate was an organism typically associated with pneumonia, such as *Streptococcus pneumoniae*. Blood stream infections excluded infections with potential contaminants including coagulase negative staphylococci, bacillus spp., coryneforms and viridans streptococci unless grown from more than one BC in a 24 hour period, as were *Acinetobacter sp* in the absence of an identifiable focus.

The study was approved by the Central Australian Human Research Ethics Committee.

Statistics.

All associations were assessed using data obtained for the final BSI admission within the study period. Univariate analysis for categorical data was performed using Chi-squared statistics and Fishers Exact where appropriate. Multivariate analysis was performed using binary logistic regression. Short (28-day) and long-term survival analysis following the final BSI episode in the study period was performed using the log-rank statistic for univariate analysis and Cox regression for multivariate analysis. We calculated the annual population-based incidence rates for 2001-2006 for the combined Alice Springs and Anangu Pitjantjatjara Yankunyatjara (APY) land areas using the total number of BSI presentations each year as the numerator. The denominator used was the estimated Adult resident population obtained from Australian Bureau of Statistics 2006 census data for the Alice Springs region combined with that of the neighbouring APY land areas. To enable analysis according to place of residence this population was further divided into that of i) the Alice Springs urban area excluding town camps (Indigenous 2898, non-Indigenous 18471), ii) Alice Springs town camps, including that of a closely affiliated neighbouring community (Indigenous, 1482), and iii) the Alice Springs rural area (Indigenous, 8925; non-Indigenous, 2775), which included that for the APY land areas (Indigenous= 1302, non-Indigenous=294).

Results

Patient demographics

558 Indigenous and 55 non-indigenous adult community residents presented to ASH with a BSI between January 2003 and July 2007. Detailed demographic, clinical and microbiological data are described in Table 1. Indigenous patients were younger (Indigenous, 44.7±15.2; non-Indigenous, 57.5±21.1; p<0.001), more likely to be female (Indigenous, 58.1%; non-Indigenous, 41.8%; p<0.03) and to live in a town camp or remote community (Indigenous, 84.0%; non-Indigenous, 0; p<0.001). Non-communicable diseases including diabetes (Indigenous, 44.3%; non-Indigenous, 20.0%; p<0.001) and harmful alcohol consumption (Indigenous, 37.0%; non-Indigenous, 12.7%; p<0.001) were more common among Indigenous patients, while non-Indigenous patients were more likely to have ischaemic heart disease (Indigenous, 3.4%; non-Indigenous, 31.6%; p<0.001), malignancy (Indigenous, 2.3%; non-Indigenous, 20.0%; p<0.001), to be receiving palliative care (Indigenous, 1.8%; non-Indigenous, 9.1%; p=0.001) and to have a history of intravenous drug use (Indigenous, 0; non-Indigenous, 5.5%; p=0.001). Forty-seven (8.4%) Indigenous and 5 (9.3%) non-indigenous BSI episodes were nosocomial (Table 1).

Population-based incidence rates 2001-2006

The overall population-based BSI incidence rate for the Alice Springs area between 2001 and 2006 was more than 20 times higher for Indigenous adults (970 per 100,000 person-years) than for non-Indigenous adults (48 per 100,000 person-years) (IRR=20.33; 95%

CI, 20.31-20.35; p<0.001). Incidence rates for Indigenous town camp residents (4,042/100,000 person-years) were nearly 70 times higher than amongst non-Indigenous urban residents (60/100,000 person years) (IRR=67.9, 95% CI=67.8-67.9, p<0.001) and greater than 3 times that of either urban dwelling Indigenous adults (IRR=3.87, 95% CI=3.86-3.87, p<0.001) or those from remote communities (IRR=3.42, 95% CI=3.42-3.42, p<0.001) (Fig 1).

Microbial Aetiology

Escherichia coli and *S.aureus* were the most common pathogens causing BSI in both ethnic groups. Methicillin-resistant *S.aureus* (Indigenous, 53 (5.2%); non-Indigenous, 1 (0.9%); p<0.001) and *S.pneumoniae* (Indigenous, 136 (13.2%); non-Indigenous, 8 (5.9%); p<0.001) were more common among Indigenous patients (Table 1).

Risk factors for BSI were determined for pathogens contributing more than 5% of all BSI episodes (Table 2). Diabetes was more common among Indigenous patients with a *S.aureus* BSI during their final BSI admission (20.2% versus 13.5%; OR=1.6 (1.04, 2.53; p=0.03) (Table 2). In contrast, increased risk of *Streptococcus pneumoniae* BSI was associated with harmful alcohol consumption, while risk was reduced among patients with diabetes or those receiving haemodialysis (Table 2). Risk of BSI with other major pathogens (*E.coli*, *Klebsiella pneumoniae or Streptococcus pyogenes*) was not increased by any NCD (Table 2).

Concurrent infections

During their final BSI admission, Indigenous patients more often had an additional focus of bacterial infection unrelated to the presenting BSI (Indigenous, n=69 (12.4%); non-Indigenous, n=2 (3.6%); p=0.05) (Table 1). Infections with HTLV-1 (45.2%), *S.stercoralis* (36.1%) and hepatitis B virus (anti-HBc, 62.5%; HBsAg, 12.9%) were also more common among Indigenous patients (Table 1). *Sarcoptes scabiei* infestations were only found in Indigenous patients (n=20; 4.0%) (Table 1).

Previous infections

Excluding Indigenous patients who were at increased risk of recurrent infection (haemodialysis, 83; bronchiectasis, 27) and those residing outside the Alice Springs region who could not be followed-up (17), 296 of 431 (68.7%) Indigenous adults were admitted with an acute infection during the five years prior to the final BSI admission (Table 3). Significantly more common among Indigenous patients were pneumonia, previous BSI, skin abscesses and wound infections (Table 3). Predisposing factors for previous infection-related admissions included diabetes (previous skin infections), harmful alcohol consumption (previous skin infections, pneumonia and BSI) and stage 3-4 chronic kidney disease (any previous infection) (Table 4).

Mortality

28 day mortality

Overall 28-day mortality rates following a BSI were 11.7% and 11.4% for Indigenous and non-Indigenous adults, respectively. Mortality rates among Indigenous patients were highest for town camp residents (Fig 2) and varied according to pathogen. Among the

major pathogens causing BSI, most often fatal within the first 28 days was *K.pneumoniae* infection (40.0%) followed by *S.pneumoniae* (9.6%) *S.aureus* (8.0%), and *E.coli* (5.0%) (χ^2=39.1, 4df; p<0.001). Case fatality rates according to focus of infection were pneumonia (21.5%), pyelonephritis (8.9%) and skin infections (7.2%) (χ^2=14.5, 3df; p=0.002).

1. Community-acquired BSI amongst Indigenous patients

Non-communicable diseases including chronic liver disease, non-rheumatic heart disease and chronic kidney disease were independent predictors of death (Table 5). Relative to patients with *E.coli* BSI, both *S.aureus* (HR=2.7, 95% CI=1.0-7.3; p=0.05) and *S.pneumoniae* (HR=13.4, 95% CI=4.6-39.2; p<0.001) were independently associated with an increased risk of death (Table 5).

2. Nosocomial BSI amongst Indigenous patients

In univariate analysis, place of residence (p=0.04) was a predictor of short-term mortality. Within the first 28 days of admission, town camp residents were more likely to die (7 of 11=64%) relative to other township (0 of 6=0.0%) or remote residents (14 of 30=46.7%) (p=0.039). In multivariate analysis, place of residence remained an independent predictor (p<0.001) and there was also an increased risk in those with non-rheumatic heart disease (HR=4.6, 95% CI=1.2,17.6; p=0.03), a primary focus of pneumonia (HR=6.0, 95% CI=1.5, 24.5) and those with a previous BSI (HR=3.8, 95% CI=1.4, 10.3; p-0.008).

3. Nosocomial and Community acquired BSI amongst non-Indigenous patients

In multivariate analysis, only non-rheumatic heart disease was an independent predictor of short-term mortality amongst non-indigenous patients with a community-acquired BSI (HR=12.5, 95% CI=1.0, 150.3; p<0.05). There were 3 deaths within 28 days amongst 12 non-indigenous patients with non-rheumatic heart disease and 3 deaths amongst 56 patients without non-rheumatic heart disease. Numbers of nosocomial BSI amongst non-indigenous patients were too few (n=5) to attempt survival analysis.

Long-term mortality

One-hundred and forty-five (26.0%) Indigenous and 15 (27.3%) non-Indigenous patients died during the 2,056 years of follow-up at a mean ± SD age of 47±15 and 68±21 years (p<0.001), respectively. Amongst Indigenous patients, mortality rates were again highest amongst those from town camps (Log-rank χ^2=5.05, p=0.08) (Fig 2).

Among Indigenous patients, NCDs (non-rheumatic heart disease, chronic kidney disease, chronic liver disease and malignancy) and BSI with *S.aureus* and *S.pneumoniae* were independent predictors of long-term mortality following community-acquired BSI (Table 5). Residence in a town camp (town camp, 7 of 11; local residence, 0 of 6; remote areas, 14 of 30; χ^2=6.5, 2df; p=0.04) and BSI with *K.pneumoniae* BSI (HR=4.0, 95% CI=1.5, 11.2; p=0.007) were the only univariate predictors of long-term mortality for nosocomial BSI's amongst Indigenous patients.

There were no independent predictors of long-term mortality for non-Indigenous patients with community acquired infections and too few non-indigenous patients with nosocomial BSI's (n=5) to perform long-term survival analysis.

Discussion

The Indigenous adult population of central Australia has among the highest BSI incidence rates worldwide. Relative to their non-Indigenous peers, rates for Indigenous adults were 20-fold higher overall and 70-fold higher among Indigenous town camp residents. A high burden of other infections, particularly repeated respiratory and skin infections, provide portals of entry for life-threatening invasive bacterial disease. Nearly 70% of Indigenous patients required admission for an acute infection in the preceding five years, 24.4% experienced a prior BSI and a second unrelated bacterial infection was found in 12.4% of patients. Chronic viral and parasitic infections were also common. Among Indigenous adults who were tested, more than 60% had been infected with Hepatitis B virus, 13% remained HBsAg positive, nearly half were HTLV-1 seropositive and 36% were *S.stercoralis* seropositive. A similar burden of infection is experienced by Indigenous children amongst whom frequent co-infection with bacterial pathogens and parasites [13] contributes to 'failure-to-thrive' [14]. In our adult cohort, 26.0% of Indigenous patients died during the study period at a mean age of only 47 years. Although we were unable to attribute cause of death in the present study, 60% of Indigenous deaths at ASH are infection-related [8].

High prevalence rates of non-communicable diseases were also found in our Indigenous cohort. These included diabetes, harmful alcohol consumption, chronic lung disease and end-stage kidney disease, all of which increase the risk of bacterial infection [10,15, 9, 16]. Invasive pneumococcal disease (IPD), for example, is three, 5.6 and 7-11 times more

common among patients with diabetes[9], chronic lung disease[9] and alcohol dependence [9,17], respectively. Alcohol dependence and diabetes also increase risk of a BSI requiring intensive care nearly six-fold and haemodialysis increases risk several hundred fold [16], largely due to prolonged central venous access [18]. In the present study, rates of diabetes among Indigenous adults were nearly three times reported background rates [19]. Diabetes was associated with *S.aureus* BSI and with previous skin infections, but not with *S.pneumoniae* BSI. Stage 3-4 chronic kidney disease, which is most often a complication of diabetes in our patient population[20], increased risk of previous infections. Harmful alcohol consumption was associated with *S.pneumoniae* BSI and with previous infections. Non-communicable diseases, including non-rheumatic heart disease, chronic kidney disease and chronic liver disease, were also major predictors of mortality after a BSI. However, once invasive infections were established, *S.aureus* and *S.pneumoniae* predicted death independently of any underlying medical condition.

The present study has compared risk of non-communicable diseases among patients presenting with a BSI and cannot determine the population-based risks attributable to these conditions. Nevertheless, racial disparities in NCD prevalence are unlikely to fully account for the BSI incidence rate ratios reported here, nor do regional differences in their prevalence [19] explain IPD incidence rates that are twice as high among Indigenous residents of central Australia relative to those of the tropical north [21]. In the USA, higher IPD incidence rates among Black Americans [9,22] are more robustly associated with poverty than race [22]. An increased risk of *S.aureus* infection has also been reported among those of lower socio-economic position [23-25] and infection-related hospital

admissions in New Zealand are associated with social deprivation [11]. The socioeconomic circumstances of Indigenous Australians are therefore likely to further increase the infection risks associated with non-communicable diseases.

Social disadvantage predisposes to non-communicable diseases [26, 27] while increasing pathogen exposure and limiting opportunities to implement behavioural strategies that ameliorate risk [28]. In some Indigenous Australian communities the average number of people living per house is 17 [29] and non-functioning health hardware leads to environmental conditions that are detrimental to householders [30]. Overcrowded housing [31] and an inability to maintain adequate skin hygiene [30] contribute to high rates of pyoderma. More than 40% of Indigenous patients in the present study were previously admitted with skin infections, which are the most common primary focus for *S.aureus* bacteraemia in this population[32]. Scabies, a recognized cause of *S.aureus* and Streptococcal pyoderma [31,33], affected 4% of our cohort. Streptococcal pyoderma underlies most cases of RHD in the Northern Territory [29] and this was confirmed echocardiographically in 2% of our Indigenous cohort. Similarly, the transmission of respiratory pathogens is promoted by household crowding [34] and nearly 40% of Indigenous adults were admitted previously with pneumonia. Environmental contamination [14], inadequate sanitation and unhygienic food preparation areas [30] contribute to infection with enteric pathogens and *S.stercoralis*. The risks of complicated strongyloidiasis, crusted scabies [35] and bronchiectasis [7] are further increased by HTLV-1 infection; however, no attempt has been made to control transmission of this virus among Indigenous Australians. Previously we have shown that Indigenous adults are less likely

to engage with a conventional medical paradigm [36] and delays in seeking care for uncomplicated urinary tract infections may contribute to the very high rates of *E.coli* BSI reported here.

The retrospective design of this study results in a number of limitations. Firstly, residents of remote communities frequently stay in town camps and this is not recorded by ASH. The effect of town camp residence may therefore be underestimated if large numbers of remote residents acquire infection during these visits. Although foci of infection were determined by reviewing the results of microbiology and imaging for each presentation, these varied between patients according to the practice of the treating physician. The number of patients with concurrent bacterial infections and medical conditions, such as RHD, may therefore be underestimated. Similarly, seropositivity rates for infections, such as HBV and HTLV-1, could only be determined for a subset of patients. A further limitation is the identification of NCDs and previous infections using ICD-10 codes; however, coding errors are unlikely to vary systematically according to ethnicity or place of residence. Finally, the present study has demonstrated an increased risk of infection and death associated with town camp residence. This occurred despite better access to health care relative to remote residents and little difference in crude measures of socioeconomic deprivation[3]. For community-acquired BSIs, risk of death was strongly associated with NCDs; however, these conditions did not fully account for the increased risk following a nosocomial BSI. Unmeasured socioeconomic factors might contribute to increased mortality among town camp residents; however, recent research linking health outcomes to perceived racism [37] may also be relevant to this marginalized population.

The disease burden among the Indigenous population of central Australia is similar to that of many developing countries where NCD prevalence rates are rising rapidly in a setting of persistently high infection rates [1,38]. Recently, the validity of conventional health transition theory has been challenged by findings that infection-related hospitalization rates are increasing among the most socially disadvantaged community members in a developed country [11]. The present study provides a possible explanation for this observation and further suggests that, in contrast to the orderly epidemiological transition envisaged by Omran (1971)[39], life expectancy may fall where social deprivation persists in the face of a rising prevalence of non-communicable diseases. High BSI incidence rates among Indigenous Australians were associated with a heavy burden of other infections that provide portals of entry for invasive bacterial disease. Improving life expectancy in this setting will require public health initiatives to reduce pathogen exposure in addition to controlling the burgeoning non-communicable disease burden. Diabetes, harmful alcohol consumption and organ damage resulting from these conditions increased both the likelihood of infection and the subsequent risk of death. Both conditions are included in proposed international management strategies to control the non-communicable disease crisis [27]. However, our findings also illustrate the complexity of interactions between communicable and non-communicable diseases and support calls for an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change [40].

Contributions:

LE designed the study, collected the data, assisted with statistical analysis and prepared the manuscript, LF and SJ collected the data, AB assisted in manuscript preparation and RW was responsible for statistical analysis and assisted in manuscript preparation.

Table 1 Demographics and comorbidities for indigenous and non-indigenous BSI patients 2003-2007.

	Indigenous (n=558)	**Non-indigenous (n=55)**	**p-value for difference**
Age, yrs (±SD)	44.7±15.2	57.5±21.1	<0.001
Gender (M/F)	234/324	31/23	0.03
(%)	(42/58)	(57/43)	
Residence			
Urban	89 (16.0)	55 (100.0)	
Town Camp	136 (24.4)	0 (0.0)	
Remote Community	333 (59.7)	0 (0.0)	<0.001
Co-morbidities[a]			
Diabetes	247 (44.3)	11 (20.0)	<0.001
Harmful Alcohol Consumption	205 (37.0)	7 (12.7)	<0.001
Chronic Kidney Disease			
Stage 3-4	34 (6.1)	5 (9.1)	0.39
Stage 5	83 (14.9)	3 (5.5)	0.06
Chronic liver disease[b]	53 (9.6)	6 (10.9)	0.74
Bronchiectasis	27 (4.8)	0	0.10
Congestive Cardiac failure	15 (2.7)	3 (5.5)	0.25
Ischaemic heart disease	9 (1.6)	7 (15.2)	<0.001
Valvular Heart Disease	27 (4.8)	3 (5.5)	0.84

Rheumatic heart disease	12 (2.0)	0 (0.0)	0.27
Palliative care	10 (1.8)	5 (9.1)	0.001
Malignancy	13 (2.3)	11 (20.0)	<0.001
IVDU	0 (0.0)	3 (5.5)	0.001
Community Acquired	510 (91.6)	49 (90.7)	0.84
Primary focus of infection			
No focus	250 (44.8)	20 (36.4)	0.37
Pneumonia[c]	110 (19.7)	6 (10.9)	0.08
Skin abscess	66 (11.8)	5 (9.1)	0.65
Pyelonephritis[d]	63 (11.3)	5 (9.1)	0.56
Other	53 (9.5)	18 (32.7)	<0.001
Enteritis	15 (2.7)	1 (1.8)	0.71
Bone/joint	1 (0.2)	0.0 (0.0)	0.61
Additional Infections[e]			
Acute bacterial infections	69 (12.4)	2 (3.6)	0.05
Pneumonia	18 (3.2)	0 (0.0)	0.39
Urinary tract	20 (3.6)	1 (1.8)	0.49
Skin	27 (4.8)	1 (1.8)	0.31
Enteritis	4 (0.7)	0	0.53
Chronic Viral infections			
HTLV-1[f]	137 (45.2)	0 (0.0)	<0.001
Hepatitis B virus[f]			
HBsAg	49 (12.9)	1 (6.7)	0.70

Anti-HBc	193 (62.5)	3 (27.3)	<0.001
Parasites			
Strongyloidiasis[f]	78 (36.1)	0 (0.0)	0.001
Scabies	20 (4.0)	0 (0.0)	0.24
Mortality			
28 days	62 (11.1)	7 (12.7)	0.72
All deaths	145 (26.0)	15 (27.3)	0.84
Age of death (years)	47±15	68±21	<0.001
Major BSI Pathogens[g]	1029	110	
Enterobacteriaceae	370 (36.0)	38 (34.5)	0.56
Escherichia coli	246 (23.9)	28 (25.5)	0.37
Klebsiella pneumoniae	57 (5.54)	2 (1.82)	0.09
Staphylococcus aureus	191 (18.6)	20 (18.2)	0.83
MRSA	53 (5.15)	1 (0.91)	<0.001
Streptococcus pneumoniae	136 (13.2)	8 (5.88)	<0.001
Streptococcus pyogenes	68 (6.61)	8 (7.27)	0.42
Haemophilus influenzae	22 (2.14)	0	0.14
Enteric pathogens[h]	29 (2.81)	1 (0.91)	0.27

a. comorbidities determined from IC-10 discharge morbidity codes

b. Chronic liver disease attributed to alcohol (Indigenous, 43; non-Indigenous, 5), chronic hepatitis B (Indigenous, 10; non-Indigenous, 0) and chronic hepatitis C (Indigenous, 0; non-Indigenous, 3).

c. Chest X-rays performed for 457 Indigenous patients.

d. Respiratory cultures performed for 150 Indigenous patients.

e. Urine cultures performed for 310 Indigenous patients.

e. Alternative bacterial pathogen isolated.

f. Indigenous patients tested: HTLV-1, 309; HBsAg, 388; HBcAb, 309; Strongyloides stercoralis serology, 235. Denominators exclude 6 Indigenous patients with indeterminate HTLV-1 Western blot results and 19 Indigenous patients with borderline Strongyloides serology whose infective status could not be determined.

f. Major BSI pathogens responsible for all recorded episodes 2001-2007.

g. Includes Salmonella spp., Shigella spp., Campylobacter spp.

Abbreviations: CHB, chronic hepatitis B virus; HCV, hepatitis C virus; IVDU, intravenous drug use.

Table 2. Demographic and non-communicable disease associations for the major BSI pathogens among Indigenous adults.

		S.aureus			*S.pneumonia*			*K.Pneumonia*			*E.Coli*		
	n	**No (%)**	**Yes (%)**	**p-value[1]**	**No (%)**	**Yes (%)**	**p-value[1]**	**No (%)**	**Yes (%)**	**p-value[1]**	**No (%)**	**Yes (%)**	**p-value[1]**
Residence													
Urban	89	86.5	13.5		89.9	10.1		96.6	3.4		76.4	23.6	
Town Camp	136	88.2	11.8		83.1	16.9		91.9	8.1		73.5	26.5	
Remote	333	80.5	19.5	0.08	89.2	10.8	0.15	94.6	5.4	0.30	73.0	27.0	0.81
Diabetes													
No	310	86.5	13.6		83.9	16.1		93.9	6.1		74.1	25.8	
Yes	247	79.8	20.2	**0.035**	92.7	7.3	**0.002**	94.7	5.3	0.66	72.9	27.1	0.73
CRF													
No	524	83.4	16.6		87.6	12.4		94.3	5.7		73.7	26.3	
Yes	34	82.4	17.7	0.87	91.2	8.8	0.54	94.1	5.9	0.97	73.5	26.5	0.99

HD													
No	475	84.2	15.8		86.3	13.7		94.1	5.9		70.5	29.5	
Yes	83	78.3	21.7	0.18	96.4	3.6	**0.01**	95.2	4.8	0.70	92.6	8.4	**<0.001**
CLD													
No	505	82.4	17.6		87.7	12.3		93.9	6.1		73.5	26.5	
Yes	53	92.5	7.6	0.06	88.7	11.3	0.84	98.1	1.9	0.20	75.6	24.5	0.75
Alcohol													
No	349	82.2	17.8		92.0	8.0		95.1	4.9		75.1	24.9	
Yes	205	84.9	15.1	0.42	80.5	19.5	**<0.001**	93.1	6.8	0.33	71.7	28.3	0.38

Major BSI pathogens recorded during the 5 years period prior to the final BSI admission. Abbreviations: Alcohol, harmful alcohol consumption; CRF, stage 3 or 4 chronic renal disease; HD, stage 5 renal disease; CLD, chronic liver disease.

Table 3. Infections recorded for Indigenous and non-Indigenous adults during the 5 years prior to the final BSI presentation[a]

	Indigenous n=431 (%)	Non-Indigenous (n=52)	p-value
Any	296 (68.7)	18 (34.6)	<0.001
BSI	105 (24.4)	4 (7.7)	0.007
Respiratory Tract	179 (41.5)	3 (5.8)	<0.001
Pneumonia	164 (38.1)	4 (7.7)	<0.001
>3 episodes	32 (7.4)	0 (0.0)	0.04
Exacerbation BE	13 (6.0)	0 (0.0)	0.20
Skin/Soft Tissue Infections	154 (35.7)	7 (13.5)	0.001
Abscess	88 (20.5)	0 (0.0)	<0.001
Cellulitis	47 (10.9)	7 (13.7)	0.55
Wound infection	42 (9.7)	0 (0.0)	0.02
Pyelonephritis	77 (17.9)	4 (7.7)	0.06
Bone/joint	11 (2.6)	0 (0.0)	0.24
Enteritis	21 (4.9)	1 (1.9)	0.33
Scabies	14 (3.3)	0 (0.0)	0.19
Other	6 (1.4)	0 (0.0)	0.39

a. Excluding haemodialysis patients (n=83 indigenous, 3 non-indigenous), patients with bronchiectasis (n=27) and those residing outside the Alice Springs urban and rural districts for whom data were not available (Indigenous, 18; non-Indigenous, 0).

Abbreviations: BSI, blood stream infections; BE, bronchiectasis.

Table 4: Multivariate adjusted odds ratios for previous infections among Indigenous patients[a]

	Any infection (n=470)[b] Odds ratio (95% CI)	**BSI (n=553) Odds ratio (95% CI)**	**Skin[b] (n=470) Odds ratio (95% CI)**	**Pneumonia[c] (n=443) Odds ratio (95% CI)**
Residence				
Urban	1.00	1.00	1.00	1.00
Town camp	1.2 (0.6-2.4)	1.8 (0.9-3.4)	1.3 (0.7-2.5)	1.3 (0.7-2.6)
Remote	0.8 (0.5-1.4)	1.3 (0.7-2.3)	1.2 (0.7-2.2)	0.8 (0.4-1.4)
Age (10 yrs)	0.9 (0.8-1.0)	1.1 (0.9-1.2)	0.9 (0.8-1.0)	1.0 (0.9-1.2)
Gender (0=F, 1=M)	1.0 (0.7-1.5)	1.3 (0.9-1.9)	1.0 (0.7-1.6)	1.0 (0.7-1.6)
Diabetes	1.4 (0.9-2.2)	1.1 (0.7-1.7)	**2.1 (1.4-3.3)**	1.1 (0.7-1.7)
CRF	**3.0 (1.1-8.2)**	1.7 (0.8-3.8)	1.5 (0.7-3.2)	1.6 (0.7-3.7)
Alcohol	**2.8 (1.8-4.4)**	**1.7 (1.1-2.5)**	**1.7 (1.1-2.6)**	**4.3 (2.8-6.7)**

a. Previous infections during 5 years prior to the final BSI in the study period. Adjusted for other risk factors in table.

b. Excluding patients receiving haemodialysis.

c. Excluding patients receiving haemodialysis and those with bronchiectasis

Abbreviations: BSI, blood stream infections; CRF, chronic renal failure excluding patients receiving haemodialysis.

Table 5: Multivariate analysis of factors associated with 28 day and long-term survival for 510 Indigenous patients following a Community-acquired Blood Stream Infection[a].

				28 day survival		Long-term survival	
	n	**Deaths (28 days)**	**Deaths (all)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Residence							
Urban	63	7	20	1.00		1.0	
Town Camp	125	20	37	1.7 (0.7-4.1)		1.2 (0.7-2.2)	
Remote	302	22	67	0.9 (0.4-2.0)	0.12	0.9 (0.5-1.5)	0.28
Age (10yrs)				1.04 (0.8-1.3)	0.70	1.0 (0.9-1.1)	0.99
Gender (0=F,1=M)	298F/212M	23/26	65/59	1.5 (0.8-2.7)	0.17	1.3 (0.9-2.0)	0.13
CLD (0=No, 1=Yes)	41	11	20	**3.3 (1.6-6.7)**	**0.001**	**2.5 (1.5-4.2)**	**<0.001**
Non-RHD	37	9	16	**2.9 (1.4-6.2)**	**0.005**	**2.1 (1.2-3.6)**	**0.01**
CRF	28	6	11	**2.6 (1.0-6.5)**	**0.04**	**2.3 (1.2-4.3)**	**0.01**

Malignancy	11	3	10	2.9 (0.9-9.9)	0.09	**6.0 (3.0-12.4)**	**<0.001**
Organism[b]							
E.coli	143	5	22	1.0		1.0	
S.aureus	83	7	18	**2.7 (1.0-7.3)**	**0.05**	**1.8 (1.1-3.0)**	**0.03**
K.pneumoniae	29	12	15	2.3 (0.7-7.5)	0.17	1.4 (0.7-2.7)	0.17
S.pneumoniae	67	5	17	**13.4 (4.6-39.2)**	**<0.001**	**4.8 (2.5-9.5)**	**<0.001**
Other	188	20	52	1.8 (0.5-6.3)	0.37	1.5 (0.8-3.0)	0.22

a. Excluded from analysis: 48 Nosocomial infections.

b. Pathogens isolated from blood cultures

Abbreviations: BSI, blood stream infection; CCF; CLD, chronic liver disease; CRF, chronic renal failure; Non-RHD, ischaemic heart disease and cardiac failure.

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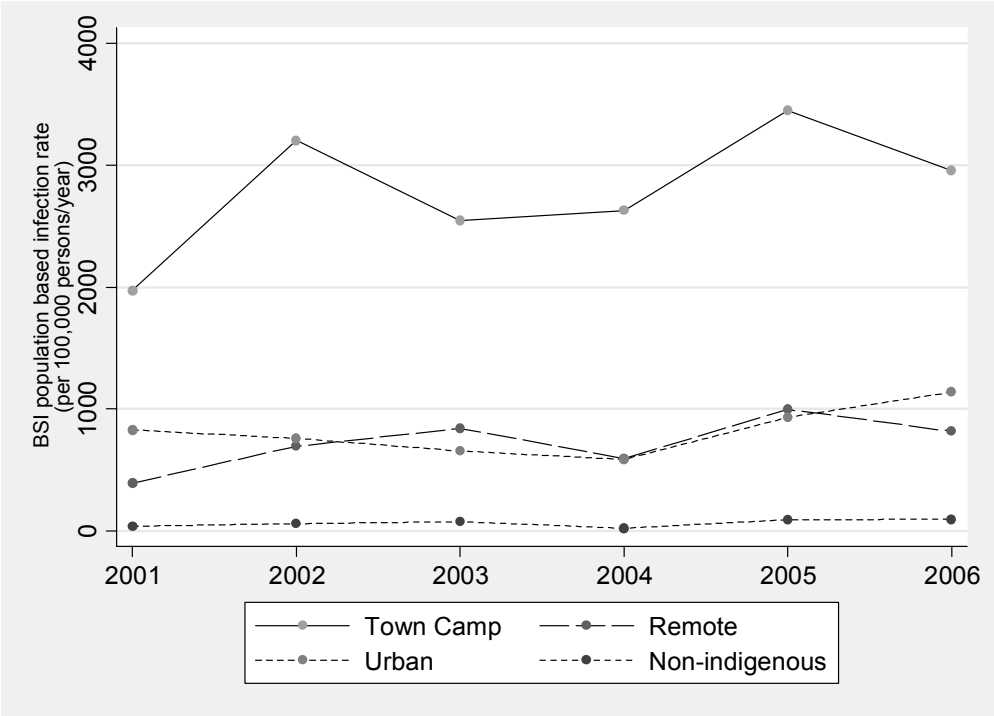
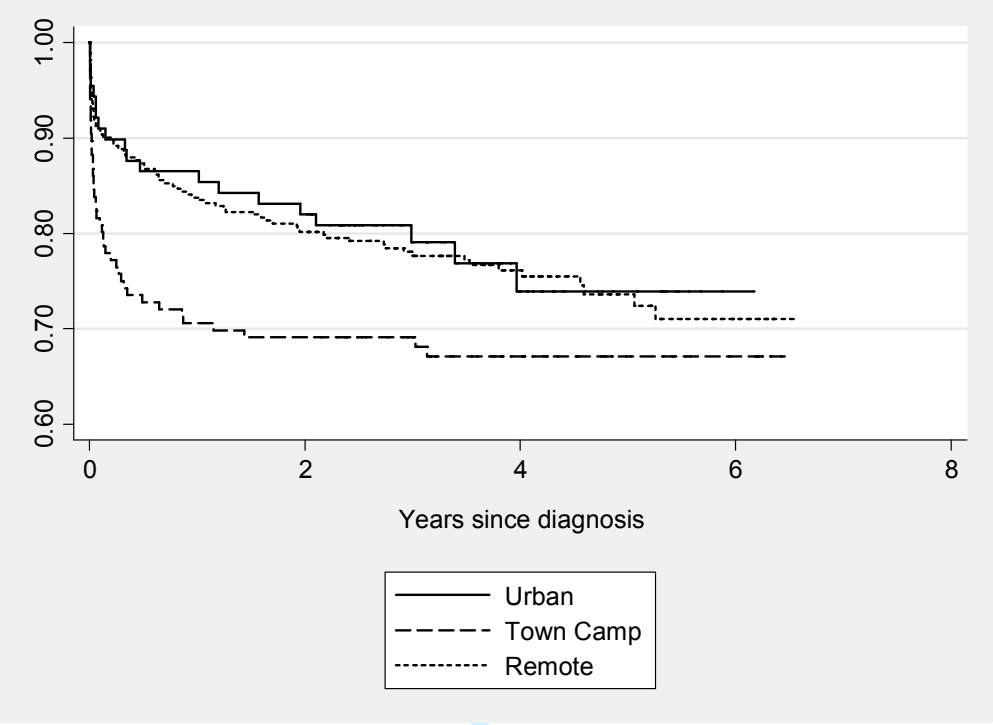
Figure 1. Blood stream infection incidence rates according to ethnicity and place of residence.



Blood Stream infection incidence rates according to ethnicity and place of residence. Town Camp, Indigenous residents of Town Camp; Urban, Indigenous residents of township who do not reside in a town camp; Remote, Indigenous residents of remote Indigenous communities. Non-Indigenous residents of Alice Springs region.

Fig 2 Survival of Indigenous adults according to place of residence



Survival following the final BSI recorded during the study period according to place of residence. Urban, residence within the township, but not in a town camp; Town Camp, residence in a town camp within the township; Remote, residence in a remote Indigenous community.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Non-communicable diseases, infection and survival in a retrospective cohort of Indigenous and non-Indigenous adults in central Australia.

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Non-communicable diseases, infection and survival in a retrospective cohort of Indigenous and non-Indigenous adults in central Australia.

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Abstract

Objectives: We hypothesize that rising prevalence rates of non-communicable diseases (NCDs) increases infection risk and worsens outcomes among socially disadvantaged Indigenous Australians undergoing a rapid epidemiological transition.

Design: Pathology, imaging and discharge morbidity codes were retrospectively reviewed for a period of 5 years prior to admission with a blood stream infection (BSI), 1st January 2003 to 30th June 2007.

Participants: 558 Indigenous and 55 non-Indigenous community residents of central Australia.

Outcome measures: The effects of NCDs on risk of infection and death were determined after stratifying by ethnicity.

Results: Mean annual BSI incidence rates were far higher among Indigenous residents (Indigenous, 937 per 100,000; non-Indigenous, 64 per 100,000 person-years; IRR=14.6; 95% CI=14.61-14.65, p<0.001). Indigenous patients were also more likely to have previous bacterial infections (68.7% versus 34.6%; respectively, p<0.001), diabetes (44.3% versus 20.0%; p<0.001), harmful alcohol consumption (37.0% versus 12.7%; p<0.001) and other communicable diseases (HTLV-1, 45.2%; strongyloidiasis, 36.1%; HBV, 12.9%). Among Indigenous patients, diabetes increased odds of current *Staphylococcus aureus* BSI (OR=1.6, 95% CI=1.0-2.5) and prior skin infections (adjusted OR=2.1, 95% CI=1.4-3.3). Harmful alcohol consumption increased odds of current *Streptococcus pneumoniae* BSI (OR=1.57, 95% CI=1.02-2.40) and of previous BSI (OR=1.7, 95% CI=1.1-2.5), skin infection (OR=1.7, 95% CI=1.1-2.6) or pneumonia (OR=4.3, 95% CI=2.8-6.7). Twenty-six percent of Indigenous patients died at a mean

(SD) age of 47±15 years. Complications of diabetes and harmful alcohol consumption predicted 28-day mortality (non-rheumatic heart disease, HR=2.9; 95% CI=1.4-6.2; chronic renal failure, HR=2.6, 95%CI=1.0-6.5; chronic liver disease, HR=3.3, 95% CI=1.6-6.7).

Conclusion: In a socially disadvantaged population undergoing a rapid epidemiologic transition, NCDs are associated with an increased risk of infection and BSI related mortality. Complex interactions between communicable diseases and NCDs demand an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change.

Article Summary

Article Focus

- Remote dwelling, Indigenous Australians are undergoing a rapid epidemiological transition, which is accompanied by a rising burden of non-communicable diseases (NCDs).
- In this setting of social disadvantage and frequent pathogen exposure, NCDs may increase risk of infection and infection-related death.

Key Messages

- We reveal substantial racial disparities in rates of infection and of NCDs, reflecting the dual burden of disease that affects this Indigenous population.
- NCDs were associated with an increased risk of blood stream infections with some pathogens, previous infections that provide portals of entry for life-threatening invasive disease and infection-related mortality.
- Complex interactions between communicable diseases and NCDs demand an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change.

Strengths and limitations of this study

- This hospital-based study only includes patients who were admitted with a blood stream infection. We are therefore unable to determine the actual risk of blood stream infections that is attributable to NCDs or to comment on background rates of other infections that might be treated in the community.
- The major strength of our study lies in the demography of the study population, which is served by a single hospital, and the extensive nature of the clinical

material on which our analysis is based.

Introduction

Complex interactions between the demographic, economic and sociologic determinants of disease result in changing patterns of health and disease over time[1]. The development of modern social and economic structures, for example, has been associated with a reduction in infectious diseases and nutritional deficiencies and a corresponding rise in non-communicable diseases (NCDs) that are associated with ageing and lifestyle factors[1]. In many developing countries the rapidity of this 'epidemiologic transition' has resulted in a dramatic increase in NCD prevalence among populations that have a substantial pre-existing infectious disease burden[2,3]. This phenomenon proceeds at different rates according to the socioeconomic status of particular sub-groups within a given population and may reinforce established health inequalities [4,5].

Among Indigenous people, forced displacement, the collapse of Indigenous economies and the destruction of socio-political structures have been the shared experience of colonization [6]. Indigenous people living within developed countries continue to live in poverty and experience a 'protracted' epidemiologic transition [4] that is associated with a double burden of communicable and non-communicable diseases[7,8] similar to that of many developing countries [2]. In central Australia, for example, diabetes and other NCDs are the major contributors to racial disparities in mortality [8] and to a life expectancy that remains 14 years less for Indigenous Australian men relative to their non-Indigenous peers[9]. A high burden of infectious diseases persists in this Indigenous population. Incidence rates of sepsis [10], blood stream infections [11] and childhood pneumonia [12], and prevalence rates of bronchiectiasis[13] are the highest reported worldwide. Strongyloidiasis

and chronic viral infections, such as with hepatitis B virus (HBV) and the Human T-Lymphotropic Virus 1 (HTLV-1), are also common [11]. Population-based infection-related mortality rates for Indigenous adults in central Australia therefore remain higher than those of some African countries prior to the current HIV pandemic and the median age of in-hospital death is only 48 years [14].

Interactions between communicable diseases and NCDs have been little studied; however, an appreciable effect of NCDs on infection rates is likely where pathogen exposure is frequent. Diabetes, for example, contributes to the risk of serious bacterial infections including *Streptococcus pneumoniae*[15] and *Staphylococcus aureus* [16], which are common pathogens in overcrowded Indigenous Australian communities [11]. The NCD burden may therefore have a substantial impact on infection rates and outcomes where these two epidemics coincide. Such an interaction could reverse health gains in populations undergoing a rapid epidemiologic transition and exacerbate health inequalities among disadvantaged subgroups within developed countries. The recent description in New Zealand of an increasing divergence in infection-related hospitalization rates according to social status is consistent with this possibility and challenges health transition theory [17].

Central Australia is well placed to study interactions between poverty, NCDs and infectious diseases. Most Indigenous residents live in remote communities in conditions of considerable socio-economic disadvantage, leaving a minority within the major regional township of Alice Springs. The latter have ready access to a well-resourced

medical facility, Alice Springs Hospital (ASH), which has sophisticated diagnostic capabilities and provides specialist medical care to a region of 1,000,000 km^2. Indigenous residents of Alice Springs dwell in either overcrowded 'town camps', which have poor amenities and limited refuse disposal, or are integrated with the majority of the non-Indigenous population within the township's suburbs. Indigenous adults living in town camps and remote communities are often unemployed, have limited education and poor health literacy[18]. Among Indigenous adult residents of town camps, nearly half have 8 years or less schooling, labour participation rates are less than 20% and only 12% are employed [19]. Despite an extremely complex regulatory framework and numerous Government attempts to minimize risk, harmful alcohol consumption in this setting remains common [20].

The Indigenous population of central Australia also has among the highest blood stream infection incidence rates reported [11]. Living conditions that increase the risk of pathogen exposure [21] and high background rates of focal infections, which provide portals of entry for bacterial invasion, are likely to precede these life-threatening infections. Blood stream infection incidence rates therefore provide measurable end-points to which environmental and host factors contribute. Here we report the infectious and non-communicable disease burden among community residents of central Australia who presented with a blood stream infection and determine risk factors for infection and death after stratifying by ethnicity.

Methods

We conducted a retrospective review of all positive blood cultures collected from adult patients (age≥15 years) admitted to ASH between 1st January 2001 and 31st June 2007. In July 2007 the Australian Federal Government suspended racial discrimination legislation and implemented an 'Emergency Response' that resulted in considerable uncertainty among Indigenous residents [22]. This raised concerns that the central Australian resident population could change as people moved interstate to escape these restrictions and no data was collected after this date. Data collected included organism, ethnicity, dates of birth, dates of death, indigenous status and place of residence. For patients who presented between 1st January 2003 and 31st June 2007 we also obtained ICD 10 morbidity codes and the results of microbiological and radiological investigations for each admission for 5 years prior to the final BSI presentation. NCDs were derived from ICD-10 morbidity codes for diabetes, harmful alcohol consumption, >stage 2 chronic kidney disease, ischaemic heart disease, chronic liver disease and malignancy. Bronchiectasis was diagnosed radiologically using American College of Chest Physician criteria. Heart failure and valvular heart disease, including rheumatic heart disease (RHD), were diagnosed by trans-thoracic echocardiography. Ischaemic heart disease and cardiac failure were combined ('non-rheumatic heart disease') for statistical analysis.

Definitions

Residence

Place of residence was categorized as i) remote (>100 km from Alice Springs), ii) Alice Springs town camp and iii) urban (resident in Alice Springs, but not in a town camp).

Nursing home residents were included in calculations of BSI incidence rates, but excluded from further analysis because the primary study objective was to determine risk factors for infection and death among community residents.

Infections

A blood culture from which a pathogen was isolated was defined as a 'BSI episode'. Repeated culture of the same organism from blood culture was regarded as a separate 'episode' only if blood samples were drawn more than one month apart. Blood stream infections were defined as community-acquired if a pathogen was isolated from blood cultures drawn within 48 hours of admission and nosocomial if isolated from blood cultures drawn after this time. Foci of infection were determined where possible from ICD-10 morbidity codes in association with pathology and imaging results for each admission for five years prior to the final BSI during the study period. A diagnosis of pneumonia was made if there was radiological evidence of consolidation and this was attributed to the pathogen isolated from blood cultures if the same organism was also isolated from sputum or the blood culture isolate was an organism typically associated with pneumonia, such as *Streptococcus pneumoniae*. Blood stream infections excluded infections with potential contaminants including coagulase negative staphylococci, bacillus spp., coryneforms and viridans streptococci unless grown from more than one BC in a 24 hour period, as were *Acinetobacter sp* in the absence of an identifiable focus.

The study was approved by the Central Australian Human Research Ethics Committee (www.health.nt.gov.au/Agency/Advisory_Groups_and_Taskforces/Human_Research_Ethics_Committee/index.aspx).

Statistics.

All associations were assessed using data obtained for the final BSI admission within the study period. Univariate analysis for categorical data was performed using Chi-squared statistics and Fishers Exact where appropriate. Multivariate analysis was performed using binary logistic regression. Short (28-day) and long term survival analysis following the final BSI episode in the study period was performed using the log-rank statistic for univariate analysis and Cox regression for multivariate analysis. We calculated the annual population-based incidence rates for 2001-2006 for the combined Alice Springs and Anangu Pitjantjatjara Yankunyatjara (APY) land areas using the total number of BSI presentations each year as the numerator. The denominator used was the estimated Adult resident population obtained from Australian Bureau of Statistics 2006 census data for the Alice Springs region combined with that of the neighbouring APY land areas. To enable analysis according to place of residence this population was further divided into that of i) the Alice Springs urban area excluding town camps (Indigenous 2898, non-Indigenous 18471), ii) Alice Springs town camps, including that of a closely affiliated neighbouring community (Indigenous, 1482), and iii) the Alice Springs rural area (Indigenous, 8925; non-Indigenous, 2775), which included that for the APY land areas (Indigenous= 1302, non-Indigenous=294).

Results

Patient demographics

558 Indigenous and 55 non-indigenous adult community residents presented to ASH with a BSI between January 2003 and July 2007. Detailed demographic, clinical and microbiological data are described in Table 1. Indigenous patients were younger (Indigenous, 44.7±15.2; non-Indigenous, 57.5±21.1; p<0.001), more likely to be female (Indigenous, 58.1%; non-Indigenous, 41.8%; p<0.03) and to live in a town camp or remote community (Indigenous, 84.0%; non-Indigenous, 0; p<0.001). Non-communicable diseases including diabetes (Indigenous, 44.3%; non-Indigenous, 20.0%; p<0.001) and harmful alcohol consumption (Indigenous, 37.0%; non-Indigenous, 12.7%; p<0.001) were more common among Indigenous patients, while non-Indigenous patients were more likely to have ischaemic heart disease (Indigenous, 3.4%; non-Indigenous, 31.6%; p<0.001), malignancy (Indigenous, 2.3%; non-Indigenous, 20.0%; p<0.001), to be receiving palliative care (Indigenous, 1.8%; non-Indigenous, 9.1%; p=0.001) and to have a history of intravenous drug use (Indigenous, 0; non-Indigenous, 5.5%; p=0.001). Forty-seven (8.4%) Indigenous and 5 (9.3%) non-indigenous BSI episodes were nosocomial (Table 1).

Population-based incidence rates 2001-2006

The overall population-based BSI incidence rate for the Alice Springs area between 2001 and 2006 was nearly 15 higher for Indigenous adults (937 per 100,000 person-years) than for non-Indigenous adults (64 per 100,000 person-years) (IRR=14.6; 95% CI, 14.61,

14.65; p<0.001). Incidence rates for Indigenous town camp residents (2,794/100,000 person-years) were more than 40 times higher than those of non-Indigenous urban residents (64/100,000 person years) (IRR=43.6, 95% CI=43.57-43.65, p<0.001) and at least three times higher than those of urban dwelling Indigenous adults (IRR=3.421, 95% CI=3.418-3.423, p<0.001) or those from remote communities (IRR=3.87, 95% CI=3.864-3.868, p<0.001) (Fig 1).

Microbial Aetiology

Escherichia coli and *S.aureus* were the most common pathogens causing BSI in both ethnic groups. Methicillin-resistant *S.aureus* (Indigenous, 53 (5.2%); non-Indigenous, 1 (0.9%); p<0.001) and *S.pneumoniae* (Indigenous, 136 (13.2%); non-Indigenous, 8 (5.9%); p<0.001) were more common among Indigenous patients (Table 1).

Risk factors for BSI were determined for pathogens contributing more than 5% of all BSI episodes (Table 2). Diabetes was more common among Indigenous patients with a *S.aureus* BSI during their final BSI admission (20.2% versus 13.5%; OR=1.6 (1.04, 2.53; p=0.03) (Table 2). In contrast, increased risk of *Streptococcus pneumoniae* BSI was associated with harmful alcohol consumption, while risk was reduced among patients with diabetes or those receiving haemodialysis (Table 2). Risk of BSI with other major pathogens (*E.coli*, *Klebsiella pneumoniae or Streptococcus pyogenes*) was not increased by any NCD (Table 2).

Concurrent infections

During their final BSI admission, Indigenous patients more often had an additional focus of bacterial infection unrelated to the presenting BSI (Indigenous, n=69 (12.4%); non-Indigenous, n=2 (3.6%); p=0.05) (Table 1). Infections with HTLV-1 (45.2%), *S.stercoralis* (36.1%) and hepatitis B virus (anti-HBc, 62.5%; HBsAg, 12.9%) were also more common among Indigenous patients (Table 1). *Sarcoptes scabiei* infestations were only found in Indigenous patients (n=20; 4.0%) (Table 1).

Previous infections

Excluding Indigenous patients who were at increased risk of recurrent infection (haemodialysis, 83; bronchiectasis, 27) and those residing outside the Alice Springs region who could not be followed-up (17), 296 of 431 (68.7%) Indigenous adults were admitted with an acute infection during the five years prior to the final BSI admission (Table 3). Significantly more common among Indigenous patients were pneumonia, previous BSI, skin abscesses and wound infections (Table 3). Predisposing factors for previous infection-related admissions included diabetes (previous skin infections), harmful alcohol consumption (previous skin infections, pneumonia and BSI) and stage 3-4 chronic kidney disease (any previous infection) (Table 4).

Mortality

28 day mortality

Overall 28-day mortality rates following a BSI were 11.7% and 11.4% for Indigenous and non-Indigenous adults, respectively. Mortality rates among Indigenous patients were highest for town camp residents (Fig 2) and varied according to pathogen. Among the

major pathogens causing BSI, most often fatal within the first 28 days was *K.pneumoniae* infection (40.0%) followed by *S.pneumoniae* (9.6%) *S.aureus* (8.0%), and *E.coli* (5.0%) (χ^2=39.1, 4df; p<0.001). Case fatality rates according to focus of infection were pneumonia (21.5%), pyelonephritis (8.9%) and skin infections (7.2%) (χ^2=14.5, 3df; p=0.002).

1. Community-acquired BSI amongst Indigenous patients

Non-communicable diseases including chronic liver disease, non-rheumatic heart disease and chronic kidney disease were independent predictors of death (Table 5). Relative to patients with *E.coli* BSI, both *S.aureus* (HR=2.7, 95% CI=1.0-7.3; p=0.05) and *S.pneumoniae* (HR=13.4, 95% CI=4.6-39.2; p<0.001) were independently associated with an increased risk of death (Table 5).

2. Nosocomial BSI amongst Indigenous patients

In univariate analysis, place of residence (p=0.04) was a predictor of short-term mortality. Within the first 28 days of admission, town camp residents were more likely to die (7 of 11=64%) relative to other township (0 of 6=0.0%) or remote residents (14 of 30=46.7%) (p=0.039). In multivariate analysis, place of residence remained an independent predictor (p<0.001) and there was also an increased risk in those with non-rheumatic heart disease (HR=4.6, 95% CI=1.2,17.6; p=0.03), a primary focus of pneumonia (HR=6.0, 95% CI=1.5, 24.5) and those with a previous BSI (HR=3.8, 95% CI=1.4, 10.3; p-0.008).

3. Nosocomial and Community acquired BSI amongst non-Indigenous patients

In multivariate analysis, only non-rheumatic heart disease was an independent predictor of short-term mortality amongst non-indigenous patients with a community-acquired BSI (HR=12.5, 95% CI=1.0, 150.3; p<0.05). There were 3 deaths within 28 days amongst 12 non-indigenous patients with non-rheumatic heart disease and 3 deaths amongst 56 patients without non-rheumatic heart disease. Numbers of nosocomial BSI amongst non-indigenous patients were too few (n=5) to attempt survival analysis.

Long-term mortality

One-hundred and forty-five (26.0%) Indigenous and 15 (27.3%) non-Indigenous patients died during the 2,056 years of follow-up at a mean ± SD age of 47±15 and 68±21 years (p<0.001), respectively. Amongst Indigenous patients, mortality rates were again highest amongst those from town camps (Log-rank χ^2=5.05, p=0.08) (Fig 2).

Among Indigenous patients, NCDs (non-rheumatic heart disease, chronic kidney disease, chronic liver disease and malignancy) and BSI with *S.aureus* and *S.pneumoniae* were independent predictors of long-term mortality following community-acquired BSI (Table 5). Residence in a town camp (town camp, 7 of 11; local residence, 0 of 6; remote areas, 14 of 30; χ^2=6.5, 2df; p=0.04) and BSI with *K.pneumoniae* BSI (HR=4.0, 95% CI=1.5, 11.2; p=0.007) were the only univariate predictors of long-term mortality for nosocomial BSI's amongst Indigenous patients.

There were no independent predictors of long-term mortality for non-Indigenous patients with community acquired infections and too few non-indigenous patients with nosocomial BSI's (n=5) to perform long-term survival analysis.

Discussion

The Indigenous adult population of central Australia has among the highest BSI incidence rates worldwide. Relative to their non-Indigenous peers, rates for Indigenous adults were nearly 15-fold higher overall and 40-fold higher among Indigenous town camp residents. A high burden of other infections, particularly repeated respiratory and skin infections, provide portals of entry for life-threatening invasive bacterial disease. Nearly 70% of Indigenous patients required admission for an acute infection in the preceding five years, 24.4% experienced a prior BSI and a second unrelated bacterial infection was found in 12.4% of patients. Chronic viral and parasitic infections were also common. Among Indigenous adults who were tested, more than 60% had been infected with Hepatitis B virus, 13% remained HBsAg positive, nearly half were HTLV-1 seropositive and 36% were *S.stercoralis* seropositive. A similar burden of infection is experienced by Indigenous children amongst whom frequent co-infection with bacterial pathogens and parasites [23] contributes to 'failure-to-thrive' [24]. In our adult cohort, 26.0% of Indigenous patients died during the study period at a mean age of only 47 years. Although we were unable to attribute cause of death in the present study, 60% of Indigenous deaths at ASH are infection-related [14].

High prevalence rates of non-communicable diseases were also found in our Indigenous cohort. These included diabetes, harmful alcohol consumption, chronic lung disease and end-stage kidney disease, all of which increase the risk of bacterial infection [16,25, 15, 26]. Invasive pneumococcal disease (IPD), for example, is three, 5.6 and 7-11 times more

common among patients with diabetes[15], chronic lung disease[15] and alcohol dependence [15,27], respectively. Alcohol dependence and diabetes also increase risk of a BSI requiring intensive care nearly six-fold and haemodialysis increases risk several hundred fold [26], largely due to prolonged central venous access [28]. In the present study, rates of diabetes among Indigenous adults were nearly three times reported background rates [29]. Diabetes was associated with *S.aureus* BSI and with previous skin infections, but not with *S.pneumoniae* BSI. Stage 3-4 chronic kidney disease, which is most often a complication of diabetes in our patient population[30], was associated with any previous infection. Harmful alcohol consumption was associated with *S.pneumoniae* BSI and with previous infection-related admissions. Non-communicable diseases, including non-rheumatic heart disease, chronic kidney disease and chronic liver disease, were also major predictors of mortality after a BSI. However, once invasive infections were established, *S.aureus* and *S.pneumoniae* predicted death independently of any underlying medical condition.

The present study has compared risk of non-communicable diseases among patients presenting with a BSI and cannot determine the population-based risks attributable to these conditions. Nevertheless, racial disparities in NCD prevalence are unlikely to fully account for the BSI incidence rate ratios reported here, nor do regional differences in their prevalence [29] explain IPD incidence rates that are twice as high among Indigenous residents of central Australia relative to those of the tropical north [31]. In the USA, higher IPD incidence rates among Black Americans [15,32] are more robustly associated with poverty than race [32]. An increased risk of *S.aureus* infection has also been reported among those of lower socio-economic position [33-35] and infection-related hospital

admissions in New Zealand are associated with social deprivation [17]. The socioeconomic circumstances of Indigenous Australians are therefore likely to further increase the infection risks associated with non-communicable diseases.

Social disadvantage predisposes to non-communicable diseases [36, 37] while increasing pathogen exposure and limiting opportunities to implement behavioural strategies that ameliorate risk [38]. In some Indigenous Australian communities the average number of people living per house is 17 [39] and non-functioning health hardware leads to environmental conditions that are detrimental to householders [21]. Overcrowded housing [40] and an inability to maintain adequate skin hygiene [21] contribute to high rates of pyoderma. More than 40% of Indigenous patients in the present study were previously admitted with skin infections, which are the most common primary focus for *S.aureus* bacteraemia in this population[41]. Scabies, a recognized cause of *S.aureus* and Streptococcal pyoderma [40,42], affected 4% of our cohort. Streptococcal pyoderma underlies most cases of RHD in the Northern Territory [39] and this was confirmed echocardiographically in 2% of our Indigenous cohort. Similarly, the transmission of respiratory pathogens is promoted by household crowding [43] and nearly 40% of Indigenous adults were admitted previously with pneumonia. Environmental contamination [24], inadequate sanitation and unhygienic food preparation areas [21] contribute to infection with enteric pathogens and *S.stercoralis*. The risks of complicated strongyloidiasis, crusted scabies [44] and bronchiectasis [13] are further increased by HTLV-1 infection; however, no attempt has been made to control transmission of this virus among Indigenous Australians. These effects are compounded by poor health literacy and

Indigenous adults are less likely to engage with a conventional medical paradigm [18]. Delays in seeking care for uncomplicated urinary tract infections may therefore contribute to the very high gram negative BSI incidence rates reported here.

The retrospective design of this study results in a number of limitations. Firstly, only limited demographic information is collected by ASH and the Indigenous population is relatively mobile. Residents of remote communities, for example, frequently stay in town camps and this is not recorded by ASH. The effect of town camp residence may therefore be underestimated if large numbers of remote residents acquire infection during these visits. Although foci of infection were determined by reviewing the results of microbiology and imaging for each presentation, these varied between patients according to the practice of the treating physician. The number of patients with concurrent bacterial infections and medical conditions, such as RHD, may therefore be underestimated. Similarly, seropositivity rates for infections, such as HBV and HTLV-1, could only be determined for a subset of patients. A further limitation is the identification of NCDs and previous infections using ICD-10 codes; however, coding errors are unlikely to vary systematically according to ethnicity or place of residence. The use of ICD-10 codes does, however, limit our ability to study factors that are more difficult to define and which might also influence infection risk, such as nutrition and health literacy. Finally, the present study has demonstrated an increased risk of infection and death associated with town camp residence. This occurred despite better access to health care relative to remote residents and little difference in crude measures of socioeconomic deprivation[7]. For community-acquired BSIs, risk of death was strongly associated with NCDs;

however, these conditions did not fully account for the increased risk following a nosocomial BSI. Unmeasured socioeconomic factors might contribute to increased mortality among town camp residents; however, recent research linking health outcomes to perceived racism [45] may also be relevant to this marginalized population.

The disease burden among the Indigenous population of central Australia is similar to that of many developing countries where NCD prevalence rates are rising rapidly in a setting of persistently high infection rates [2,46]. Recently, the validity of conventional health transition theory has been challenged by findings that infection-related hospitalization rates are increasing among the most socially disadvantaged community members in a developed country [17]. The present study provides a possible explanation for this observation and further suggests that, in contrast to the orderly epidemiological transition envisaged by Omran (1971)[1], life expectancy may fall where social deprivation persists in the face of a rising prevalence of non-communicable diseases. High BSI incidence rates among Indigenous Australians were associated with a heavy burden of other infections that provide portals of entry for invasive bacterial disease. Improving life expectancy in this setting will require public health initiatives to reduce pathogen exposure in addition to controlling the burgeoning non-communicable disease burden. Diabetes, harmful alcohol consumption and organ damage resulting from these conditions increased both the likelihood of infection and the subsequent risk of death. Both conditions are included in proposed international management strategies to control the non-communicable disease crisis [37]. However, our findings also illustrate the complexity of interactions between communicable and non-communicable diseases and support calls

for an integrated approach to disease management [47]. The intimate association between these conditions and human behaviour renders the empowerment of affected populations to adopt protective health-related strategies critical to the success of any management program [47].

Contributions:

LE designed the study, collected the data, assisted with statistical analysis and prepared the manuscript, LF and SJ collected the data, AB assisted in manuscript preparation and RW was responsible for statistical analysis and assisted in manuscript preparation.

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Conflict-of-interest :_None reported

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Data sharing: Data relate to Indigenous Australians and cannot be shared without specific approval from the relevant Indigenous communities and the responsible HREC. Obtaining such approval will require detail of all individuals seeking access and each research project for which the inclusion of this data is proposed.

Table 1 Demographics and comorbidities for indigenous and non-indigenous BSI patients 2003-2007.

	Indigenous (n=558)	**Non-indigenous (n=55)**	**p-value for difference**
Age, yrs (±SD)	44.7±15.2	57.5±21.1	<0.001
Gender (M/F)	234/324	31/23	0.03
(%)	(42/58)	(57/43)	
Residence			
Urban	89 (16.0)	55 (100.0)	
Town Camp	136 (24.4)	0 (0.0)	
Remote Community	333 (59.7)	0 (0.0)	<0.001
Co-morbidities[a]			
Diabetes	247 (44.3)	11 (20.0)	<0.001
Harmful Alcohol Consumption	205 (37.0)	7 (12.7)	<0.001
Chronic Kidney Disease			
Stage 3-4	34 (6.1)	5 (9.1)	0.39
Stage 5	83 (14.9)	3 (5.5)	0.06
Chronic liver disease[b]	53 (9.6)	6 (10.9)	0.74
Bronchiectasis	27 (4.8)	0	0.10
Congestive Cardiac failure	15 (2.7)	3 (5.5)	0.25
Ischaemic heart disease	9 (1.6)	7 (15.2)	<0.001
Valvular Heart Disease	27 (4.8)	3 (5.5)	0.84

Rheumatic heart disease	12 (2.0)	0 (0.0)	0.27
Palliative care	10 (1.8)	5 (9.1)	0.001
Malignancy	13 (2.3)	11 (20.0)	<0.001
IVDU	0 (0.0)	3 (5.5)	0.001
Community Acquired	510 (91.6)	49 (90.7)	0.84
Primary focus of infection			
No focus	250 (44.8)	20 (36.4)	0.37
Pneumonia[c]	110 (19.7)	6 (10.9)	0.08
Skin abscess	66 (11.8)	5 (9.1)	0.65
Pyelonephritis[d]	63 (11.3)	5 (9.1)	0.56
Other	53 (9.5)	18 (32.7)	<0.001
Enteritis	15 (2.7)	1 (1.8)	0.71
Bone/joint	1 (0.2)	0.0 (0.0)	0.61
Additional Infections[e]			
Acute bacterial infections	69 (12.4)	2 (3.6)	0.05
Pneumonia	18 (3.2)	0 (0.0)	0.39
Urinary tract	20 (3.6)	1 (1.8)	0.49
Skin	27 (4.8)	1 (1.8)	0.31
Enteritis	4 (0.7)	0	0.53
Chronic Viral infections			
HTLV-1[f]	137 (45.2)	0 (0.0)	<0.001
Hepatitis B virus[f]			
HBsAg	49 (12.9)	1 (6.7)	0.70

Anti-HBc	193 (62.5)	3 (27.3)	<0.001
Parasites			
Strongyloidiasis[f]	78 (36.1)	0 (0.0)	0.001
Scabies	20 (4.0)	0 (0.0)	0.24
Mortality			
28 days	62 (11.1)	7 (12.7)	0.72
All deaths	145 (26.0)	15 (27.3)	0.84
Age of death (years)	47±15	68±21	<0.001
Major BSI Pathogens[g]	1029	110	
Enterobacteriaeciae	370 (36.0)	38 (34.5)	0.56
Escherichia coli	246 (23.9)	28 (25.5)	0.37
Klebsiella pneumoniae	57 (5.54)	2 (1.82)	0.09
Staphylococcus aureus	191 (18.6)	20 (18.2)	0.83
MRSA	53 (5.15)	1 (0.91)	<0.001
Streptococcus pneumoniae	136 (13.2)	8 (5.88)	<0.001
Streptococcus pyogenes	68 (6.61)	8 (7.27)	0.42
Haemophilus influenzae	22 (2.14)	0	0.14
Enteric pathogens[h]	29 (2.81)	1 (0.91)	0.27

a. comorbidities determined from IC-10 discharge morbidity codes

b. Chronic liver disease attributed to alcohol (Indigenous, 43; non-Indigenous, 5), chronic hepatitis B (Indigenous, 10; non-Indigenous, 0) and chronic hepatitis C (Indigenous, 0; non-Indigenous, 3).

c. Chest X-rays performed for 457 Indigenous patients.

d. Respiratory cultures performed for 150 Indigenous patients.

e. Urine cultures performed for 310 Indigenous patients.

e. Alternative bacterial pathogen isolated.

f. Indigenous patients tested: HTLV-1, 309; HBsAg, 388; HBcAb, 309; Strongyloides stercoralis serology, 235. Denominators exclude 6 Indigenous patients with indeterminate HTLV-1 Western blot results and 19 Indigenous patients with borderline Strongyloides serology whose infective status could not be determined.

f. Major BSI pathogens responsible for all recorded episodes 2001-2007.

g. Includes Salmonella spp., Shigella spp., Campylobacter spp.

Abbreviations: CHB, chronic hepatitis B virus; HCV, hepatitis C virus; IVDU, intravenous drug use.

Table 2. Demographic and non-communicable disease associations for the major BSI pathogens among Indigenous adults.

		S.aureus			*S.pneumonia*			*K.Pneumonia*			*E.Coli*		
	n	**No (%)**	**Yes (%)**	**p-value[1]**	**No (%)**	**Yes (%)**	**p-value[1]**	**No (%)**	**Yes (%)**	**p-value[1]**	**No (%)**	**Yes (%)**	**p-value[1]**
Residence													
Urban	89	86.5	13.5		89.9	10.1		96.6	3.4		76.4	23.6	
Town Camp	136	88.2	11.8		83.1	16.9		91.9	8.1		73.5	26.5	
Remote	333	80.5	19.5	0.08	89.2	10.8	0.15	94.6	5.4	0.30	73.0	27.0	0.81
Diabetes													
No	310	86.5	13.6		83.9	16.1		93.9	6.1		74.1	25.8	
Yes	247	79.8	20.2	**0.035**	92.7	7.3	**0.002**	94.7	5.3	0.66	72.9	27.1	0.73
CRF													
No	524	83.4	16.6		87.6	12.4		94.3	5.7		73.7	26.3	
Yes	34	82.4	17.7	0.87	91.2	8.8	0.54	94.1	5.9	0.97	73.5	26.5	0.99

HD													
No	475	84.2	15.8		86.3	13.7		94.1	5.9		70.5	29.5	
Yes	83	78.3	21.7	0.18	96.4	3.6	**0.01**	95.2	4.8	0.70	92.6	8.4	**<0.001**
CLD													
No	505	82.4	17.6		87.7	12.3		93.9	6.1		73.5	26.5	
Yes	53	92.5	7.6	0.06	88.7	11.3	0.84	98.1	1.9	0.20	75.6	24.5	0.75
Alcohol													
No	349	82.2	17.8		92.0	8.0		95.1	4.9		75.1	24.9	
Yes	205	84.9	15.1	0.42	80.5	19.5	**<0.001**	93.1	6.8	0.33	71.7	28.3	0.38

Major BSI pathogens recorded during the 5 years period prior to the final BSI admission. Abbreviations: Alcohol, harmful alcohol consumption; CRF, stage 3 or 4 chronic renal disease; HD, stage 5 renal disease; CLD, chronic liver disease.

Table 3. Infections recorded for Indigenous and non-Indigenous adults during the 5 years prior to the final BSI presentation[a]

	Indigenous n=431 (%)	Non-Indigenous (n=52)	p-value
Any	296 (68.7)	18 (34.6)	<0.001
BSI	105 (24.4)	4 (7.7)	0.007
Respiratory Tract	179 (41.5)	3 (5.8)	<0.001
Pneumonia	164 (38.1)	4 (7.7)	<0.001
>3 episodes	32 (7.4)	0 (0.0)	0.04
Exacerbation BE	13 (6.0)	0 (0.0)	0.20
Skin/Soft Tissue Infections	154 (35.7)	7 (13.5)	0.001
Abscess	88 (20.5)	0 (0.0)	<0.001
Cellulitis	47 (10.9)	7 (13.7)	0.55
Wound infection	42 (9.7)	0 (0.0)	0.02
Pyelonephritis	77 (17.9)	4 (7.7)	0.06
Bone/joint	11 (2.6)	0 (0.0)	0.24
Enteritis	21 (4.9)	1 (1.9)	0.33
Scabies	14 (3.3)	0 (0.0)	0.19
Other	6 (1.4)	0 (0.0)	0.39

a. Excluding haemodialysis patients (n=83 indigenous, 3 non-indigenous), patients with bronchiectasis (n=27) and those residing outside the Alice Springs urban and rural districts for whom data were not available (Indigenous, 18; non-Indigenous, 0).

Abbreviations: BSI, blood stream infections; BE, bronchiectasis.

Table 4: Multivariate adjusted odds ratios for previous infections among Indigenous patients[a]

	Any infection (n=470)[b] Odds ratio (95% CI)	**BSI (n=553) Odds ratio (95% CI)**	**Skin[b] (n=470) Odds ratio (95% CI)**	**Pneumonia[c] (n=443) Odds ratio (95% CI)**
Residence				
Urban	1.00	1.00	1.00	1.00
Town camp	1.2 (0.6-2.4)	1.8 (0.9-3.4)	1.3 (0.7-2.5)	1.3 (0.7-2.6)
Remote	0.8 (0.5-1.4)	1.3 (0.7-2.3)	1.2 (0.7-2.2)	0.8 (0.4-1.4)
Age (10 yrs)	0.9 (0.8-1.0)	1.1 (0.9-1.2)	0.9 (0.8-1.0)	1.0 (0.9-1.2)
Gender (0=F, 1=M)	1.0 (0.7-1.5)	1.3 (0.9-1.9)	1.0 (0.7-1.6)	1.0 (0.7-1.6)
Diabetes	1.4 (0.9-2.2)	1.1 (0.7-1.7)	**2.1 (1.4-3.3)**	1.1 (0.7-1.7)
CRF	**3.0 (1.1-8.2)**	1.7 (0.8-3.8)	1.5 (0.7-3.2)	1.6 (0.7-3.7)
Alcohol	**2.8 (1.8-4.4)**	**1.7 (1.1-2.5)**	**1.7 (1.1-2.6)**	**4.3 (2.8-6.7)**

a. Previous infections during 5 years prior to the final BSI in the study period. Adjusted for other risk factors in table.

b. Excluding patients receiving haemodialysis.

c. Excluding patients receiving haemodialysis and those with bronchiectasis

Abbreviations: BSI, blood stream infections; CRF, chronic renal failure excluding patients receiving haemodialysis.

Table 5: Multivariate analysis of factors associated with 28 day and long-term survival for 510 Indigenous patients following a Community-acquired Blood Stream Infection[a].

				28 day survival		Long-term survival	
	n	**Deaths (28 days)**	**Deaths (all)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Residence							
Urban	63	7	20	1.00		1.0	
Town Camp	125	20	37	1.7 (0.7-4.1)		1.2 (0.7-2.2)	
Remote	302	22	67	0.9 (0.4-2.0)	0.12	0.9 (0.5-1.5)	0.28
Age (10yrs)				1.04 (0.8-1.3)	0.70	1.0 (0.9-1.1)	0.99
Gender (0=F,1=M)	298F/212M	23/26	65/59	1.5 (0.8-2.7)	0.17	1.3 (0.9-2.0)	0.13
CLD (0=No, 1=Yes)	41	11	20	**3.3 (1.6-6.7)**	**0.001**	**2.5 (1.5-4.2)**	**<0.001**
Non-RHD	37	9	16	**2.9 (1.4-6.2)**	**0.005**	**2.1 (1.2-3.6)**	**0.01**
CRF	28	6	11	**2.6 (1.0-6.5)**	**0.04**	**2.3 (1.2-4.3)**	**0.01**

Malignancy	11	3	10	2.9 (0.9-9.9)	0.09	**6.0 (3.0-12.4)**	**<0.001**
Organism[b]							
E.coli	143	5	22	1.0		1.0	
S.aureus	83	7	18	**2.7 (1.0-7.3)**	**0.05**	**1.8 (1.1-3.0)**	**0.03**
K.pneumoniae	29	12	15	2.3 (0.7-7.5)	0.17	1.4 (0.7-2.7)	0.17
S.pneumoniae	67	5	17	**13.4 (4.6-39.2)**	**<0.001**	**4.8 (2.5-9.5)**	**<0.001**
Other	188	20	52	1.8 (0.5-6.3)	0.37	1.5 (0.8-3.0)	0.22

a. Excluded from analysis: 48 Nosocomial infections.

b. Pathogens isolated from blood cultures

Abbreviations: BSI, blood stream infection; CCF; CLD, chronic liver disease; CRF, chronic renal failure; Non-RHD, ischaemic heart disease and cardiac failure.

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NThe aAssociation of non-communicable diseases, with blood stream infection incidence and survival in a retrospective cohort of Iindigenous and non-Indigenous adults in central Australia in central Australians.

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Abstract

Objectives: We hypothesize that rising prevalence rates of non-communicable diseases (NCDs) increases infection risk and worsens outcomes among socially disadvantaged Indigenous Australians undergoing a rapid epidemiological transition.

Design: Pathology, imaging and discharge morbidity codes were retrospectively reviewed for a period of 5 years prior to admission with a blood stream infection (BSI), 1st January 2003 to 30th June 2007.

Participants: 558 Indigenous and 55 non-Indigenous community residents of central Australia.

Outcome measures: The effects of NCDs on risk of infection and death were determined after stratifying by ethnicity.

Results: Mean annual BSI incidence rates were far higher among Indigenous residents (Indigenous, 9377~~0~~ per 100,000; non-Indigenous, 64~~48~~ per 100,000 person-years; IRR=14.6~~20.33~~; 95% CI=14.61~~20.31~~-14.65~~20.35~~, p<0.001). Indigenous patients were also more likely to have previous bacterial infections (68.7% versus 34.6%; respectively, p<0.001), diabetes (44.3% versus 20.0%; p<0.001), harmful alcohol consumption (37.0% versus 12.7%; p<0.001) and other communicable diseases (HTLV-1, 45.2%; strongyloidiasis, 36.1%; HBV, 12.9%). Among Indigenous patients, diabetes increased odds of current *Staphylococcus aureus* BSI (OR=1.6, 95% CI=1.0-2.5) and prior skin infections (adjusted OR=2.1, 95% CI=1.4-3.3). Harmful alcohol consumption increased odds of current *Streptococcus pneumoniae* BSI (OR=1.57, 95% CI=1.02-2.40) and of previous BSI (OR=1.7, 95% CI=1.1-2.5), skin infection (OR=1.7, 95% CI=1.1-2.6) or pneumonia (OR=4.3, 95% CI=2.8-6.7). Twenty-six percent of Indigenous patients died

at a mean (SD) age of 47±15 years. Complications of diabetes and harmful alcohol consumption predicted 28-day mortality (non-rheumatic heart disease, HR=2.9; 95% CI=1.4-6.2; chronic renal failure, HR=2.6, 95%CI=1.0-6.5; chronic liver disease, HR=3.3, 95% CI=1.6-6.7).

Conclusion: In a socially disadvantaged population undergoing a rapid epidemiologic transition, NCDs are associated with an ~~further~~ increased risk of infection ~~risk of infection~~ and BSI related mortality. Complex interactions between communicable diseases and NCDs demand an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change.

5

Article Summary

Article Focus

- Remote dwelling, Indigenous Australians are undergoing a rapid epidemiological transition, which is accompanied by a ~~rapidly~~ rising burden of non-communicable diseases (NCDs).
- In this setting of social disadvantage and frequent pathogen exposure, NCDs may increase risk of infection and infection-related death.

Key Messages

- We reveal substantial racial disparities in rates of infection and of NCDs, reflecting the dual burden of disease that affects this Indigenous population.
- NCDs were associated with an increased risk of blood stream infections with some pathogens, previous infections that provide portals of entry for life-threatening invasive disease and infection-related mortality.
- Complex interactions between communicable diseases and NCDs demand an integrated approach to management, which must include the empowerment of affected populations to promote behavioural change.

Strengths and limitations of this study

- This hospital-based study only includes patients who were admitted with a blood stream infection. We are therefore unable to determine the actual risk of blood stream infections that is attributable to NCDs or to comment on background rates of other infections that~~, which~~ might be treated in the community.
- The major strength of our study lies in the demography of the study population, which is served by a single hospital, and the extensive nature of the clinical

material on which our analysis is based.

Introduction

Complex interactions between the demographic, economic and sociologic determinants of disease result in changing patterns of health and disease over time[1]. The development of modern social and economic structures, for example, has beenis associated with a reduction in infectious diseases and nutritional deficiencies and a corresponding rise in non-communicable diseases (NCDs) that are associated with due to ageing andor lifestyle factors[1]. In many developing countries Ththe rapidity of thisis phenomenon has been termed the 'epidemiologic transition' (Omran)has resulted in a . In developing countries, rapid demographic change has dramatic been associated with marked increases in NCD the pPrevalence rates of of non-communicable diseases (NCDs), such as diabetes, amongin populations that have with a substantial pre-existing infectious disease are rising rapidly in developing countries, adding to a pre-existing burden of infectious diseases in populations that are undergoing rapid demographic changes[2,3]. This phenomenon proceeds at different rates according to the socioeconomic status of particular sub-groups within a given population and may reinforce established health inequalities [4,5].

Among Indigenous people, forced displacement, the collapse of Indigenous economies and the destruction of socio-political structures have been the shared experience of colonization [6]. Indigenous people living within developed countries continue to live in poverty and experience a 'protracted' epidemiologic transition [4] that is associated with a double burden of communicable and non-communicable diseases[7,8] similar to that of many developing countries [2]. A similar double burden of communicable and non-communicable diseases and NCDs affects marginalized Indigenous people living in

~~poverty within developed countries [3,4]. In central Australia, Among Indigenous Australians,~~ for example, diabetes and other NCDs ~~NCDs~~ are the major contributors to racial disparities in mortality [8] and to a life expectancy that remains 14~~7~~ years less for Indigenous Australian men relative to ~~than that of~~ their non-Indigenous peers [9]. ~~A In central Australia, rising prevalence rates of NCDs affect an Indigenous population in which a~~ high burden of infectious diseases persists in this Indigenous population. Incidence rates of sepsis [10], blood stream infections [11] and childhood pneumonia [12] ~~(ref)~~, and prevalence rates of bronchiectiasis[13] are the highest reported worldwide. Strongyloidiasis and chronic viral infections, such as with hepatitis B virus (HBV) and the Human T-Lymphotropic Virus 1 (HTLV-1), are also common [11]. Population-based infection-related mortality rates for Indigenous adults in central Australia therefore remain higher than those of some African countries prior to the current HIV pandemic and the median age of in-hospital death is only 48 years [14].

Interactions between communicable diseases and NCDs have been little studied; however, an appreciable effect of NCDs on infection rates is likely where pathogen exposure is frequent. Diabetes, for example, contributes to the risk of serious bacterial infections including *Streptococcus pneumoniae*[15] and *Staphylococcus aureus* [16], which are common pathogens in overcrowded Indigenous Australian communities [11]. The NCD burden may therefore have a substantial impact on infection rates and outcomes where these two epidemics coincide. Such an interaction could reverse health gains in populations undergoing a rapid epidemiologic transition and exacerbate health inequalities among disadvantaged subgroups within developed countries. The recent

description in New Zealand of an increasing divergence in infection-related hospitalization rates according to social status is consistent with this possibility and challenges health transition theory [17].

Central Australia is well placed to study interactions between poverty, NCDs and infectious diseases. Most Indigenous residents live in remote communities in conditions of considerable socio-economic disadvantage, leaving a minority within the major regional township of Alice Springs. The latter have ready access to a well-resourced medical facility, Alice Springs Hospital (ASH), which has sophisticated diagnostic capabilities and provides specialist medical care to a region of 1,000,000 km^2. Indigenous residents of Alice Springs dwell in either overcrowded 'town camps', which have poor amenities and limited refuse disposal, or are integrated with the majority of the non-Indigenous population within the township's suburbs. Indigenous adults living in town camps and remote communities are often unemployed, have limited education ~~(ABS)~~ and poor health literacy~~-~~[18]~~(ref)~~. A~~For example, a~~mong Indigenous adult residents of town camps, nearly half~~60%~~ have ~~less than~~ 8 years or less ~~of~~ schooling, labour participation rates are less than 20% and only 12% are employed [19] ~~(ABS 2013)~~. Despite an extremely complex regulatory framework and numerous ~~a variety of~~ Government attempts~~interventions~~ to minimize risk, harmful alcohol consumption in this setting remains common [20]~~(ref)~~.

The Indigenous population of central Australia~~this region~~ also has among the highest blood stream infection incidence rates reported [11]. Living conditions that increase the risk

of pathogen exposure [21] ~~(ref)~~ and high background rates of focal infections, which provide portals of entry for bacterial invasion, are likely to precede these life-threatening infections. Blood stream infection incidence rates therefore provide measurable end-points to which environmental and host factors contribute.

Here we report the infectious and non-communicable disease burden among community residents of central Australia who presented with a blood stream infection and determine risk factors for infection and death after stratifying by ethnicity.

Methods

We conducted a retrospective review of all positive blood cultures collected from adult patients (age≥15 years) admitted to ASH between 1st January 2001 and 31st June 2007. In July 2007 the Australian Federal Government suspended racial discrimination legislation and implemented an 'Emergency Response' that resulted in considerable uncertainty among Indigenous residents [22]. This raised concerns that the central Australian resident population could change as people moved interstate to escape these restrictions and no data was collected after this date. Data collected included organism, ethnicity, dates of birth, dates of death, indigenous status and place of residence. For patients who presented between 1st January 2003 and 31st June 2007 we also obtained ICD 10 morbidity codes and the results of microbiological and radiological investigations for each admission for 5 years prior to the final BSI presentation. NCDs were derived from ICD-10 morbidity codes for diabetes, harmful alcohol consumption, >stage 2 chronic kidney disease, ischaemic heart disease, chronic liver disease and malignancy. Bronchiectasis was diagnosed radiologically using American College of Chest Physician criteria. Heart failure and valvular heart disease, including rheumatic heart disease (RHD), were diagnosed by trans-thoracic echocardiography. Ischaemic heart disease and cardiac failure were combined ('non-rheumatic heart disease') for statistical analysis.

Definitions

Residence

Place of residence was categorized as i) remote (>100 km from Alice Springs), ii) Alice Springs town camp and iii) urban (resident in Alice Springs, but not in a town camp).

Nursing home residents were included in calculations of BSI incidence rates, but excluded from further analysis because the primary study objective was to determine risk factors for infection and death among community residents.

Infections

A blood culture from which a pathogen was isolated was defined as a 'BSI episode'. Repeated culture of the same organism from blood culture was regarded as a separate 'episode' only if blood samples were drawn more than one month apart. Blood stream infections were defined as community-acquired if a pathogen was isolated from blood cultures drawn within 48 hours of admission and nosocomial if isolated from blood cultures drawn after this time. Foci of infection were determined where possible from ICD-10 morbidity codes in association with pathology and imaging results for each admission for five years prior to the final BSI during the study period. A diagnosis of pneumonia was made if there was radiological evidence of consolidation and this was attributed to the pathogen isolated from blood cultures if the same organism was also isolated from sputum or the blood culture isolate was an organism typically associated with pneumonia, such as *Streptococcus pneumoniae*. Blood stream infections excluded infections with potential contaminants including coagulase negative staphylococci, bacillus spp., coryneforms and viridans streptococci unless grown from more than one BC in a 24 hour period, as were *Acinetobacter sp* in the absence of an identifiable focus.

The study was approved by the Central Australian Human Research Ethics Committee (www.health.nt.gov.au/Agency/Advisory_Groups_and_Taskforces/Human_Research_Ethics_Committee/index.aspx).

Statistics.

All associations were assessed using data obtained for the final BSI admission within the study period. Univariate analysis for categorical data was performed using Chi-squared statistics and Fishers Exact where appropriate. Multivariate analysis was performed using binary logistic regression. Short (28-day) and long term survival analysis following the final BSI episode in the study period was performed using the log-rank statistic for univariate analysis and Cox regression for multivariate analysis. We calculated the annual population-based incidence rates for 2001-2006 for the combined Alice Springs and Anangu Pitjantjatjara Yankunyatjara (APY) land areas using the total number of BSI presentations each year as the numerator. The denominator used was the estimated Adult resident population obtained from Australian Bureau of Statistics 2006 census data for the Alice Springs region combined with that of the neighbouring APY land areas. To enable analysis according to place of residence this population was further divided into that of i) the Alice Springs urban area excluding town camps (Indigenous 2898, non-Indigenous 18471), ii) Alice Springs town camps, including that of a closely affiliated neighbouring community (Indigenous, 1482), and iii) the Alice Springs rural area (Indigenous, 8925; non-Indigenous, 2775), which included that for the APY land areas (Indigenous= 1302, non-Indigenous=294).

Results

Patient demographics

558 Indigenous and 55 non-indigenous adult community residents presented to ASH with a BSI between January 2003 and July 2007. Detailed demographic, clinical and microbiological data are described in Table 1. Indigenous patients were younger (Indigenous, 44.7±15.2; non-Indigenous, 57.5±21.1; p<0.001), more likely to be female (Indigenous, 58.1%; non-Indigenous, 41.8%; p<0.03) and to live in a town camp or remote community (Indigenous, 84.0%; non-Indigenous, 0; p<0.001). Non-communicable diseases including diabetes (Indigenous, 44.3%; non-Indigenous, 20.0%; p<0.001) and harmful alcohol consumption (Indigenous, 37.0%; non-Indigenous, 12.7%; p<0.001) were more common among Indigenous patients, while non-Indigenous patients were more likely to have ischaemic heart disease (Indigenous, 3.4%; non-Indigenous, 31.6%; p<0.001), malignancy (Indigenous, 2.3%; non-Indigenous, 20.0%; p<0.001), to be receiving palliative care (Indigenous, 1.8%; non-Indigenous, 9.1%; p=0.001) and to have a history of intravenous drug use (Indigenous, 0; non-Indigenous, 5.5%; p=0.001). Forty-seven (8.4%) Indigenous and 5 (9.3%) non-indigenous BSI episodes were nosocomial (Table 1).

Population-based incidence rates 2001-2006

~~The overall population-based BSI incidence rate for the Alice Springs area between 2001 and 2006 was more than 20 times higher for Indigenous adults (970 per 100,000 person-years) than for non-Indigenous adults (48 per 100,000 person years) (IRR=20.33; 95%~~

~~CI, 20.31-20.35; p<0.001). Incidence rates for Indigenous town camp residents (4,042/100,000 person years) were nearly 70 times higher than amongst non-Indigenous urban residents (60/100,000 person years) (IRR=67.9, 95% CI=67.8-67.9, p<0.001) and greater than 3 times that of either urban dwelling Indigenous adults (IRR=3.87, 95% CI=3.86-3.87, p<0.001) or those from remote communities (IRR=3.42, 95% CI=3.42-3.42, p<0.001) (Fig 1).~~The overall population-based BSI incidence rate for the Alice Springs area between 2001 and 2006 was nearly 15 ~~more than 14 times~~ higher for Indigenous adults (937 per 100,000 person-years) than for non-Indigenous adults (64 per 100,000 person-years) (IRR=14.6~~2~~; 95% CI, 14.61, 14.65; p<0.001). Incidence rates for Indigenous town camp residents (2,794/100,000 person-years) were more than 40 times higher than those of~~amongst~~ non-Indigenous urban residents (64/100,000 person years) (IRR=43.6, 95% CI=43.57-43.65, p<0.001) and at least three~~greater than 3~~ times higher than those~~at~~ of urban dwelling Indigenous adults ~~either urban dwelling indigenous adults~~ (~~(~~IRR=3.421, 95% CI=3.418-3.423, p<0.001) or those ~~those~~ from remote communities (IRR=3.87, 95% CI=3.864-3.868, p<0.001) (Fig 1).

Microbial Aetiology

Escherichia coli and *S.aureus* were the most common pathogens causing BSI in both ethnic groups. Methicillin-resistant *S.aureus* (Indigenous, 53 (5.2%); non-Indigenous, 1 (0.9%); p<0.001) and *S.pneumoniae* (Indigenous, 136 (13.2%); non-Indigenous, 8 (5.9%); p<0.001) were more common among Indigenous patients (Table 1).

Risk factors for BSI were determined for pathogens contributing more than 5% of all BSI episodes (Table 2). Diabetes was more common among Indigenous patients with a *S.aureus* BSI during their final BSI admission (20.2% versus 13.5%; OR=1.6 (1.04, 2.53; p=0.03) (Table 2). In contrast, increased risk of *Streptococcus pneumoniae* BSI was associated with harmful alcohol consumption, while risk was reduced among patients with diabetes or those receiving haemodialysis (Table 2). Risk of BSI with other major pathogens (*E.coli*, *Klebsiella pneumoniae or Streptococcus pyogenes*) was not increased by any NCD (Table 2).

Concurrent infections

During their final BSI admission, Indigenous patients more often had an additional focus of bacterial infection unrelated to the presenting BSI (Indigenous, n=69 (12.4%); non-Indigenous, n=2 (3.6%); p=0.05) (Table 1). Infections with HTLV-1 (45.2%), *S.stercoralis* (36.1%) and hepatitis B virus (anti-HBc, 62.5%; HBsAg, 12.9%) were also more common among Indigenous patients (Table 1). *Sarcoptes scabiei* infestations were only found in Indigenous patients (n=20; 4.0%) (Table 1).

Previous infections

Excluding Indigenous patients who were at increased risk of recurrent infection (haemodialysis, 83; bronchiectasis, 27) and those residing outside the Alice Springs region who could not be followed-up (17), 296 of 431 (68.7%) Indigenous adults were admitted with an acute infection during the five years prior to the final BSI admission (Table 3). Significantly more common among Indigenous patients were pneumonia,

previous BSI, skin abscesses and wound infections (Table 3). Predisposing factors for previous infection-related admissions included diabetes (previous skin infections), harmful alcohol consumption (previous skin infections, pneumonia and BSI) and stage 3-4 chronic kidney disease (any previous infection) (Table 4).

Mortality

28 day mortality

Overall 28-day mortality rates following a BSI were 11.7% and 11.4% for Indigenous and non-Indigenous adults, respectively. Mortality rates among Indigenous patients were highest for town camp residents (Fig 2) and varied according to pathogen. Among the major pathogens causing BSI, most often fatal within the first 28 days was *K.pneumoniae* infection (40.0%) followed by *S.pneumoniae* (9.6%) *S.aureus* (8.0%), and *E.coli* (5.0%) (χ^2=39.1, 4df; p<0.001). Case fatality rates according to focus of infection were pneumonia (21.5%), pyelonephritis (8.9%) and skin infections (7.2%) (χ^2=14.5, 3df; p=0.002).

1. Community-acquired BSI amongst Indigenous patients

Non-communicable diseases including chronic liver disease, non-rheumatic heart disease and chronic kidney disease were independent predictors of death (Table 5). Relative to patients with *E.coli* BSI, both *S.aureus* (HR=2.7, 95% CI=1.0-7.3; p=0.05) and *S.pneumoniae* (HR=13.4, 95% CI=4.6-39.2; p<0.001) were independently associated with an increased risk of death (Table 5).

2. Nosocomial BSI amongst Indigenous patients

In univariate analysis, place of residence (p=0.04) was a predictor of short-term mortality. Within the first 28 days of admission, town camp residents were more likely to die (7 of 11=64%) relative to other township (0 of 6=0.0%) or remote residents (14 of 30=46.7%) (p=0.039). In multivariate analysis, place of residence remained an independent predictor (p<0.001) and there was also an increased risk in those with non-rheumatic heart disease (HR=4.6, 95% CI=1.2,17.6; p=0.03), a primary focus of pneumonia (HR=6.0, 95% CI=1.5, 24.5) and those with a previous BSI (HR=3.8, 95% CI=1.4, 10.3; p-0.008).

3. Nosocomial and Community acquired BSI amongst non-Indigenous patients

In multivariate analysis, only non-rheumatic heart disease was an independent predictor of short-term mortality amongst non-indigenous patients with a community-acquired BSI (HR=12.5, 95% CI=1.0, 150.3; p<0.05). There were 3 deaths within 28 days amongst 12 non-indigenous patients with non-rheumatic heart disease and 3 deaths amongst 56 patients without non-rheumatic heart disease. Numbers of nosocomial BSI amongst non-indigenous patients were too few (n=5) to attempt survival analysis.

Long-term mortality

One-hundred and forty-five (26.0%) Indigenous and 15 (27.3%) non-Indigenous patients died during the 2,056 years of follow-up at a mean ± SD age of 47±15 and 68±21 years (p<0.001), respectively. Amongst Indigenous patients, mortality rates were again highest amongst those from town camps (Log-rank χ^2=5.05, p=0.08) (Fig 2).

Among Indigenous patients, NCDs (non-rheumatic heart disease, chronic kidney disease, chronic liver disease and malignancy) and BSI with *S.aureus* and *S.pneumoniae* were independent predictors of long-term mortality following community-acquired BSI (Table 5). Residence in a town camp (town camp, 7 of 11; local residence, 0 of 6; remote areas, 14 of 30; χ^2=6.5, 2df; p=0.04) and BSI with *K.pneumoniae* BSI (HR=4.0, 95% CI=1.5, 11.2; p=0.007) were the only univariate predictors of long-term mortality for nosocomial BSI's amongst Indigenous patients.

There were no independent predictors of long-term mortality for non-Indigenous patients with community acquired infections and too few non-indigenous patients with nosocomial BSI's (n=5) to perform long-term survival analysis.

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Discussion

The Indigenous adult population of central Australia has among the highest BSI incidence rates worldwide. Relative to their non-Indigenous peers, rates for Indigenous adults were nearly 1542~~0~~ -fold higher overall and 4~~7~~0-fold ~~-fold~~ higher among Indigenous town camp residents. A high burden of other infections, particularly repeated respiratory and skin infections, provide portals of entry for life-threatening invasive bacterial disease. Nearly 70% of Indigenous patients required admission for an acute infection in the preceding five years, 24.4% experienced a prior BSI and a second unrelated bacterial infection was found in 12.4% of patients. Chronic viral and parasitic infections were also common. Among Indigenous adults who were tested, more than 60% had been infected with Hepatitis B virus, 13% remained HBsAg positive, nearly half were HTLV-1 seropositive and 36% were *S.stercoralis* seropositive. A similar burden of infection is experienced by Indigenous children amongst whom frequent co-infection with bacterial pathogens and parasites [23] contributes to 'failure-to-thrive' [24]. In our adult cohort, 26.0% of Indigenous patients died during the study period at a mean age of only 47 years. Although we were unable to attribute cause of death in the present study, 60% of Indigenous deaths at ASH are infection-related [14].

High prevalence rates of non-communicable diseases were also found in our Indigenous cohort. These included diabetes, harmful alcohol consumption, chronic lung disease and end-stage kidney disease, all of which increase the risk of bacterial infection [16,25, 15, 26]. Invasive pneumococcal disease (IPD), for example, is three, 5.6 and 7-11 times more

common among patients with diabetes[15], chronic lung disease[15] and alcohol dependence [15,27], respectively. Alcohol dependence and diabetes also increase risk of a BSI requiring intensive care nearly six-fold and haemodialysis increases risk several hundred fold [26], largely due to prolonged central venous access [28]. In the present study, rates of diabetes among Indigenous adults were nearly three times reported background rates [29]. Diabetes was associated with *S.aureus* BSI and with previous skin infections, but not with *S.pneumoniae* BSI. Stage 3-4 chronic kidney disease, which is most often a complication of diabetes in our patient population[30], was associated with any previous infection. Harmful alcohol consumption was associated with *S.pneumoniae* BSI and with previous infection-related admissions. Non-communicable diseases, including non-rheumatic heart disease, chronic kidney disease and chronic liver disease, were also major predictors of mortality after a BSI. However, once invasive infections were established, *S.aureus* and *S.pneumoniae* predicted death independently of any underlying medical condition.

The present study has compared risk of non-communicable diseases among patients presenting with a BSI and cannot determine the population-based risks attributable to these conditions. Nevertheless, racial disparities in NCD prevalence are unlikely to fully account for the BSI incidence rate ratios reported here, nor do regional differences in their prevalence [29] explain IPD incidence rates that are twice as high among Indigenous residents of central Australia relative to those of the tropical north [31]. In the USA, higher IPD incidence rates among Black Americans [15,32] are more robustly associated with poverty than race [32]. An increased risk of *S.aureus* infection has also been reported among those of lower socio-economic position [33-35] and infection-related hospital

admissions in New Zealand are associated with social deprivation [17]. The socioeconomic circumstances of Indigenous Australians are therefore likely to further increase the infection risks associated with non-communicable diseases.

Social disadvantage predisposes to non-communicable diseases [36, 37] while increasing pathogen exposure and limiting opportunities to implement behavioural strategies that ameliorate risk [38]. In some Indigenous Australian communities the average number of people living per house is 17 [39] and non-functioning health hardware leads to environmental conditions that are detrimental to householders [21]. Overcrowded housing [40] and an inability to maintain adequate skin hygiene [21] contribute to high rates of pyoderma. More than 40% of Indigenous patients in the present study were previously admitted with skin infections, which are the most common primary focus for *S.aureus* bacteraemia in this population[41]. Scabies, a recognized cause of *S.aureus* and Streptococcal pyoderma [40,42], affected 4% of our cohort. Streptococcal pyoderma underlies most cases of RHD in the Northern Territory [39] and this was confirmed echocardiographically in 2% of our Indigenous cohort. Similarly, the transmission of respiratory pathogens is promoted by household crowding [43] and nearly 40% of Indigenous adults were admitted previously with pneumonia. Environmental contamination [24], inadequate sanitation and unhygienic food preparation areas [21] contribute to infection with enteric pathogens and *S.stercoralis*. The risks of complicated strongyloidiasis, crusted scabies [44] and bronchiectasis [13] are further increased by HTLV-1 infection; however, no attempt has been made to control transmission of this virus among Indigenous Australians. These effects are compounded by poor health literacy ~~; less than~~

~~30% of Indigenous adults understood the reason for hospital admission~~ and ~~Previously we have shown that~~ Indigenous adults are less likely to engage with a conventional medical paradigm [18]. D~~and d~~elays in seeking care for uncomplicated urinary tract infections may therefore contribute to the very high gram negative BSI incidence rates reported here.

The retrospective design of this study results in a number of limitations. Firstly, only limited ~~-~~demographic information is collected by ASH and the Indigenous population is relatively mobile. R~~r~~esidents of remote communities, for example, frequently stay in town camps ~~-~~and this is not recorded by ASH. The effect of town camp residence may therefore be underestimated if large numbers of remote residents acquire infection during these visits. Although foci of infection were determined by reviewing the results of microbiology and imaging for each presentation, these varied between patients according to the practice of the treating physician. The number of patients with concurrent bacterial infections and medical conditions, such as RHD, may therefore be underestimated. Similarly, seropositivity rates for infections, such as HBV and HTLV-1, could only be determined for a subset of patients. A further limitation is the identification of NCDs and previous infections using ICD-10 codes; however, coding errors are unlikely to vary systematically according to ethnicity or place of residence. The use of ICD-10 codes does, however, limit our ability to study factors that are more difficult to define and which might also influence infection risk, such as nutrition and health literacy. Finally, the present study has demonstrated an increased risk of infection and death associated with town camp residence. This occurred despite better access to health care relative to

remote residents and little difference in crude measures of socioeconomic deprivation[7]. For community-acquired BSIs, risk of death was strongly associated with NCDs; however, these conditions did not fully account for the increased risk following a nosocomial BSI. Unmeasured socioeconomic factors might contribute to increased mortality among town camp residents; however, recent research linking health outcomes to perceived racism [45] may also be relevant to this marginalized population.

The disease burden among the Indigenous population of central Australia is similar to that of many developing countries where NCD prevalence rates are rising rapidly in a setting of persistently high infection rates [2,46]. Recently, the validity of conventional health transition theory has been challenged by findings that infection-related hospitalization rates are increasing among the most socially disadvantaged community members in a developed country [17]. The present study provides a possible explanation for this observation and further suggests that, in contrast to the orderly epidemiological transition envisaged by Omran (1971)[1], life expectancy may fall where social deprivation persists in the face of a rising prevalence of non-communicable diseases. High BSI incidence rates among Indigenous Australians were associated with a heavy burden of other infections that provide portals of entry for invasive bacterial disease. Improving life expectancy in this setting will require public health initiatives to reduce pathogen exposure in addition to controlling the burgeoning non-communicable disease burden. Diabetes, harmful alcohol consumption and organ damage resulting from these conditions increased both the likelihood of infection and the subsequent risk of death. Both conditions are included in proposed international management strategies to control the

non-communicable disease crisis [37]. However, our findings also illustrate the complexity of interactions between communicable and non-communicable diseases and support calls for an integrated approach to disease management [47]. The intimate association between these conditions and human behaviour renders ~~, which must include~~ the ~~-~~empowerment of affected populations to adopt protective health-related strategies~~behaviours~~ critical to the success of any management program ~~that reduce risk~~ [47]~~, (National Aboriginal Health Strategy).~~ ~~, which must include the empowerment of affected populations to promote behavioural change~~ [40]~~.~~

Contributions:

LE designed the study, collected the data, assisted with statistical analysis and prepared the manuscript, LF and SJ collected the data, AB assisted in manuscript preparation and RW was responsible for statistical analysis and assisted in manuscript preparation.

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Table 1 Demographics and comorbidities for indigenous and non-indigenous BSI patients 2003-2007.

	Indigenous (n=558)	**Non-indigenous (n=55)**	**p-value for difference**
Age, yrs (±SD)	44.7±15.2	57.5±21.1	<0.001
Gender (M/F)	234/324	31/23	0.03
(%)	(42/58)	(57/43)	
Residence			
Urban	89 (16.0)	55 (100.0)	
Town Camp	136 (24.4)	0 (0.0)	
Remote Community	333 (59.7)	0 (0.0)	<0.001
Co-morbidities[a]			
Diabetes	247 (44.3)	11 (20.0)	<0.001
Harmful Alcohol Consumption	205 (37.0)	7 (12.7)	<0.001
Chronic Kidney Disease			
Stage 3-4	34 (6.1)	5 (9.1)	0.39
Stage 5	83 (14.9)	3 (5.5)	0.06
Chronic liver disease[b]	53 (9.6)	6 (10.9)	0.74
Bronchiectasis	27 (4.8)	0	0.10
Congestive Cardiac failure	15 (2.7)	3 (5.5)	0.25
Ischaemic heart disease	9 (1.6)	7 (15.2)	<0.001
Valvular Heart Disease	27 (4.8)	3 (5.5)	0.84

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Rheumatic heart disease	12 (2.0)	0 (0.0)	0.27
Palliative care	10 (1.8)	5 (9.1)	0.001
Malignancy	13 (2.3)	11 (20.0)	<0.001
IVDU	0 (0.0)	3 (5.5)	0.001
Community Acquired	510 (91.6)	49 (90.7)	0.84
Primary focus of infection			
No focus	250 (44.8)	20 (36.4)	0.37
Pneumonia[c]	110 (19.7)	6 (10.9)	0.08
Skin abscess	66 (11.8)	5 (9.1)	0.65
Pyelonephritis[d]	63 (11.3)	5 (9.1)	0.56
Other	53 (9.5)	18 (32.7)	<0.001
Enteritis	15 (2.7)	1 (1.8)	0.71
Bone/joint	1 (0.2)	0.0 (0.0)	0.61
Additional Infections[e]			
Acute bacterial infections	69 (12.4)	2 (3.6)	0.05
Pneumonia	18 (3.2)	0 (0.0)	0.39
Urinary tract	20 (3.6)	1 (1.8)	0.49
Skin	27 (4.8)	1 (1.8)	0.31
Enteritis	4 (0.7)	0	0.53
Chronic Viral infections			
HTLV-1[f]	137 (45.2)	0 (0.0)	<0.001
Hepatitis B virus[f]			
HBsAg	49 (12.9)	1 (6.7)	0.70

Anti-HBc	193 (62.5)	3 (27.3)	<0.001
Parasites			
Strongyloidiasis[f]	78 (36.1)	0 (0.0)	0.001
Scabies	20 (4.0)	0 (0.0)	0.24
Mortality			
28 days	62 (11.1)	7 (12.7)	0.72
All deaths	145 (26.0)	15 (27.3)	0.84
Age of death (years)	47±15	68±21	<0.001
Major BSI Pathogens[g]	1029	110	
Enterobacteriaeciae	370 (36.0)	38 (34.5)	0.56
Escherichia coli	246 (23.9)	28 (25.5)	0.37
Klebsiella pneumoniae	57 (5.54)	2 (1.82)	0.09
Staphylococcus aureus	191 (18.6)	20 (18.2)	0.83
MRSA	53 (5.15)	1 (0.91)	<0.001
Streptococcus pneumoniae	136 (13.2)	8 (5.88)	<0.001
Streptococcus pyogenes	68 (6.61)	8 (7.27)	0.42
Haemophilus influenzae	22 (2.14)	0	0.14
Enteric pathogens[h]	29 (2.81)	1 (0.91)	0.27

a. comorbidities determined from IC-10 discharge morbidity codes

b. Chronic liver disease attributed to alcohol (Indigenous, 43; non-Indigenous, 5), chronic hepatitis B (Indigenous, 10; non-Indigenous, 0) and chronic hepatitis C (Indigenous, 0; non-Indigenous, 3).

c. Chest X-rays performed for 457 Indigenous patients.

d. Respiratory cultures performed for 150 Indigenous patients.

e. Urine cultures performed for 310 Indigenous patients.

e. Alternative bacterial pathogen isolated.

f. Indigenous patients tested: HTLV-1, 309; HBsAg, 388; HBcAb, 309; Strongyloides stercoralis serology, 235. Denominators exclude 6 Indigenous patients with indeterminate HTLV-1 Western blot results and 19 Indigenous patients with borderline Strongyloides serology whose infective status could not be determined.

f. Major BSI pathogens responsible for all recorded episodes 2001-2007.

g. Includes Salmonella spp., Shigella spp., Campylobacter spp.

Abbreviations: CHB, chronic hepatitis B virus; HCV, hepatitis C virus; IVDU, intravenous drug use.

Table 2. Demographic and non-communicable disease associations for the major BSI pathogens among Indigenous adults.

		S.aureus			*S.pneumonia*			*K.Pneumonia*			*E.Coli*		
		No	**Yes**	**p-value[1]**	**No**	**Yes**	**p-value[1]**	**No**	**Yes**	**p-value[1]**	**No**	**Yes**	**p-value[1]**
	n	**(%)**	**(%)**		**(%)**	**(%)**		**(%)**	**(%)**		**(%)**	**(%)**	
Residence													
Urban	89	86.5	13.5		89.9	10.1		96.6	3.4		76.4	23.6	
Town Camp	136	88.2	11.8		83.1	16.9		91.9	8.1		73.5	26.5	
Remote	333	80.5	19.5	0.08	89.2	10.8	0.15	94.6	5.4	0.30	73.0	27.0	0.81
Diabetes													
No	310	86.5	13.6		83.9	16.1		93.9	6.1		74.1	25.8	
Yes	247	79.8	20.2	**0.035**	92.7	7.3	**0.002**	94.7	5.3	0.66	72.9	27.1	0.73
CRF													
No	524	83.4	16.6		87.6	12.4		94.3	5.7		73.7	26.3	
Yes	34	82.4	17.7	0.87	91.2	8.8	0.54	94.1	5.9	0.97	73.5	26.5	0.99

													32
HD													
No	475	84.2	15.8		86.3	13.7		94.1	5.9		70.5	29.5	
Yes	83	78.3	21.7	0.18	96.4	3.6	**0.01**	95.2	4.8	0.70	92.6	8.4	**<0.001**
CLD													
No	505	82.4	17.6		87.7	12.3		93.9	6.1		73.5	26.5	
Yes	53	92.5	7.6	0.06	88.7	11.3	0.84	98.1	1.9	0.20	75.6	24.5	0.75
Alcohol													
No	349	82.2	17.8		92.0	8.0		95.1	4.9		75.1	24.9	
Yes	205	84.9	15.1	0.42	80.5	19.5	**<0.001**	93.1	6.8	0.33	71.7	28.3	0.38

Major BSI pathogens recorded during the 5 years period prior to the final BSI admission. Abbreviations: Alcohol, harmful alcohol consumption; CRF, stage 3 or 4 chronic renal disease; HD, stage 5 renal disease; CLD, chronic liver disease.

Table 3. Infections recorded for Indigenous and non-Indigenous adults during the 5 years prior to the final BSI presentation[a]

	Indigenous n=431 (%)	Non-Indigenous (n=52)	p-value
Any	296 (68.7)	18 (34.6)	<0.001
BSI	105 (24.4)	4 (7.7)	0.007
Respiratory Tract	179 (41.5)	3 (5.8)	<0.001
Pneumonia	164 (38.1)	4 (7.7)	<0.001
>3 episodes	32 (7.4)	0 (0.0)	0.04
Exacerbation BE	13 (6.0)	0 (0.0)	0.20
Skin/Soft Tissue Infections	154 (35.7)	7 (13.5)	0.001
Abscess	88 (20.5)	0 (0.0)	<0.001
Cellulitis	47 (10.9)	7 (13.7)	0.55
Wound infection	42 (9.7)	0 (0.0)	0.02
Pyelonephritis	77 (17.9)	4 (7.7)	0.06
Bone/joint	11 (2.6)	0 (0.0)	0.24
Enteritis	21 (4.9)	1 (1.9)	0.33
Scabies	14 (3.3)	0 (0.0)	0.19
Other	6 (1.4)	0 (0.0)	0.39

a. Excluding haemodialysis patients (n=83 indigenous, 3 non-indigenous), patients with bronchiectasis (n=27) and those residing outside the Alice Springs urban and rural districts for whom data were not available (Indigenous, 18; non-Indigenous, 0).

Abbreviations: BSI, blood stream infections; BE, bronchiectasis.

Table 4: Multivariate adjusted odds ratios for previous infections among Indigenous patients[a]

	Any infection (n=470)[b] Odds ratio (95% CI)	**BSI (n=553) Odds ratio (95% CI)**	**Skin[b] (n=470) Odds ratio (95% CI)**	**Pneumonia[c] (n=443) Odds ratio (95% CI)**
Residence				
Urban	1.00	1.00	1.00	1.00
Town camp	1.2 (0.6-2.4)	1.8 (0.9-3.4)	1.3 (0.7-2.5)	1.3 (0.7-2.6)
Remote	0.8 (0.5-1.4)	1.3 (0.7-2.3)	1.2 (0.7-2.2)	0.8 (0.4-1.4)
Age (10 yrs)	0.9 (0.8-1.0)	1.1 (0.9-1.2)	0.9 (0.8-1.0)	1.0 (0.9-1.2)
Gender (0=F, 1=M)	1.0 (0.7-1.5)	1.3 (0.9-1.9)	1.0 (0.7-1.6)	1.0 (0.7-1.6)
Diabetes	1.4 (0.9-2.2)	1.1 (0.7-1.7)	**2.1 (1.4-3.3)**	1.1 (0.7-1.7)
CRF	**3.0 (1.1-8.2)**	1.7 (0.8-3.8)	1.5 (0.7-3.2)	1.6 (0.7-3.7)
Alcohol	**2.8 (1.8-4.4)**	**1.7 (1.1-2.5)**	**1.7 (1.1-2.6)**	**4.3 (2.8-6.7)**

a. Previous infections during 5 years prior to the final BSI in the study period. Adjusted for other risk factors in table.

b. Excluding patients receiving haemodialysis.

c. Excluding patients receiving haemodialysis and those with bronchiectasis

Abbreviations: BSI, blood stream infections; CRF, chronic renal failure excluding patients receiving haemodialysis.

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Table 5: Multivariate analysis of factors associated with 28 day and long-term survival for 510 Indigenous patients following a Community-acquired Blood Stream Infection[a].

				28 day survival		Long-term survival	
	n	**Deaths (28 days)**	**Deaths (all)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Residence							
Urban	63	7	20	1.00		1.0	
Town Camp	125	20	37	1.7 (0.7-4.1)		1.2 (0.7-2.2)	
Remote	302	22	67	0.9 (0.4-2.0)	0.12	0.9 (0.5-1.5)	0.28
Age (10yrs)				1.04 (0.8-1.3)	0.70	1.0 (0.9-1.1)	0.99
Gender (0=F,1=M)	298F/212M	23/26	65/59	1.5 (0.8-2.7)	0.17	1.3 (0.9-2.0)	0.13
CLD (0=No, 1=Yes)	41	11	20	**3.3 (1.6-6.7)**	**0.001**	**2.5 (1.5-4.2)**	**<0.001**
Non-RHD	37	9	16	**2.9 (1.4-6.2)**	**0.005**	**2.1 (1.2-3.6)**	**0.01**
CRF	28	6	11	**2.6 (1.0-6.5)**	**0.04**	**2.3 (1.2-4.3)**	**0.01**

Malignancy	11	3	10	2.9 (0.9-9.9)	0.09	**6.0 (3.0-12.4)**	**<0.001**
Organism[b]							
E.coli	143	5	22	1.0		1.0	
S.aureus	83	7	18	**2.7 (1.0-7.3)**	**0.05**	**1.8 (1.1-3.0)**	**0.03**
K.pneumoniae	29	12	15	2.3 (0.7-7.5)	0.17	1.4 (0.7-2.7)	0.17
S.pneumoniae	67	5	17	**13.4 (4.6-39.2)**	**<0.001**	**4.8 (2.5-9.5)**	**<0.001**
Other	188	20	52	1.8 (0.5-6.3)	0.37	1.5 (0.8-3.0)	0.22

a. Excluded from analysis: 48 Nosocomial infections.

b. Pathogens isolated from blood cultures

Abbreviations: BSI, blood stream infection; CCF; CLD, chronic liver disease; CRF, chronic renal failure; Non-RHD, ischaemic heart disease and cardiac failure.

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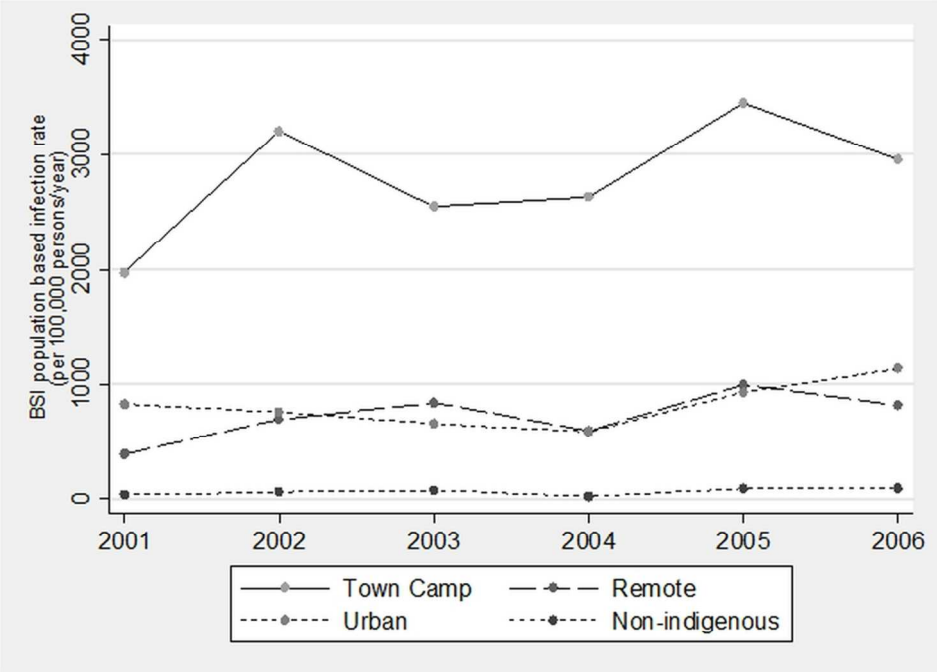
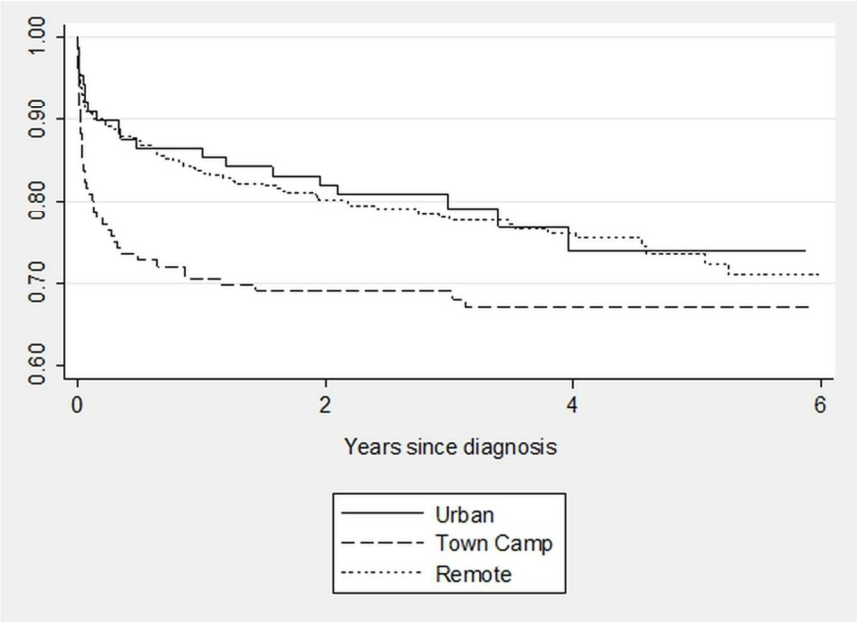
Figure 1. Blood stream infection incidence rates according to ethnicity and place of residence.



Blood Stream infection incidence rates according to ethnicity and place of residence. Town Camp, Indigenous residents of Town Camp; Urban, Indigenous residents of township who do not reside in a town camp; Remote, Indigenous residents of remote Indigenous communities. Non-Indigenous residents of Alice Springs region.

92x90mm (300 x 300 DPI)

Fig 2. Survival of Indigenous adults following a blood stream infection according to place of residence.



Survival following the final BSI recorded during the study period according to place of residence. Urban, residence within the township, but not in a town camp; Town Camp, residence in a town camp within the township; Remote, residence in a remote Indigenous community. Median follow-up time for all Indigenous subjects was 3.23 years and for Urban, Town camp and Remote subjects was 2.99, 3.04 and 3.38 years, respectively.

90x94mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.