



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003070
Article Type:	Research
Date Submitted by the Author:	17-Apr-2013
Complete List of Authors:	Einsiedel, Lloyd; Flinders University, Northern Territory Rural Clinical School Fernandes, Liselle; Flinders University, NTRCS Joseph, Sheela; Flinders University, NTRCS Brown, Alex; Baker IDI Heart and Diabetes Institute, Centre for Indigenous Vascular and Diabetes Research Woodman, Richard; Flinders University, General Practice
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Global health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, MICROBIOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Nephrology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

Only

1
2
3
4 2 *Non-communicable diseases and infection in an Indigenous Australian*
5
6 3 *population: increased risk during a rapid epidemiological transition*
7
8
9 4

10
11 5 Lloyd Einsiedel¹, Liselle Fernandes¹, Sheela Joseph¹, Alex Brown² and
12
13
14 6 Richard J Woodman¹
15
16
17 7
18
19
20 8
21
22

23 9 (1) Flinders University/Northern Territory Rural Clinical School, Alice Springs Hospital, 0870,
24
25 10 Northern Territory, Australia
26
27

28 11 (2) Head, Centre for Indigenous Vascular Research, Baker IDI Heart and Diabetes
29
30 12 Institute, Alice Springs Hospital, 0870, Northern Territory, Australia.
31
32
33
34 13
35
36
37

38 14 § Corresponding author:
39
40

41 15 Lloyd Einsiedel. Alice Springs Hospital, Department of Medicine, Darwin, Northern
42
43 16 Territory, Australia. Tel: + 61 08 89519607, Fax: + 61 08 89538385, E-mail:
44
45 17 lloyd.einsiedel@health.sa.gov.au
46
47
48
49 18

50
51
52 19 Running title: Infection risk in Indigenous Australians
53
54

55 20 Keywords: Epidemiologic transition, Infection, Indigenous Health, Australia
56
57
58
59
60

1
2
3 2 Word count:
4

5
6 3 Abstract: 293
7

8 4 Text: 3489
9

10 5 References: 40
11

12
13
14 6 Conflict-of-interest : None reported
15

16
17 7 Funding statement:
18

19 8 This study received funding from the Northern Territory Rural Clinical School, which is
20
21 9 an initiative of the Australian Department of Health and Ageing.
22

23
24 10 Contributorship: LE designed the study, collected the data, assisted with statistical
25
26 11 analysis and prepared the manuscript, LF and SJ collected the data, AB assisted in
27
28 12 manuscript preparation and RW was responsible for statistical analysis and assisted in
29
30 13 manuscript preparation.
31
32

33 14 Data sharing: Data relate to Indigenous Australians and cannot be shared without specific
34
35 15 approval from the relevant Indigenous communities and the responsible HREC.
36
37 16 Obtaining such approval will require detail of all individuals seeking access and each
38
39 17 research project for which the inclusion of this data is proposed.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Abstract**
4

5 Objectives: We hypothesize that rising prevalence rates of non-communicable diseases
6 (NCDs) increases infection risk and worsens outcomes among socially disadvantaged
7
8 Indigenous Australians undergoing a rapid epidemiological transition.
9

10 Design: Pathology, imaging and discharge morbidity codes were retrospectively reviewed
11 for a period of 5 years prior to admission with a blood stream infection (BSI), 1st January
12 2003 to 30th June 2007.
13

14 Participants: 558 Indigenous and 55 non-Indigenous community residents of central
15
16 Australia.
17

18 Outcome measures: The effects of NCDs on risk of infection and death were determined
19 after stratifying by ethnicity.
20

21 Results: Mean annual BSI incidence rates were far higher among Indigenous residents
22 (Indigenous, 970 per 100,000; non-Indigenous, 48 per 100,000 person-years; IRR=20.33;
23 95% CI=20.31-20.35, $p<0.001$). Indigenous patients were also more likely to have
24 previous bacterial infections (68.7% versus 34.6%; respectively, $p<0.001$), diabetes
25 (44.3% versus 20.0%; $p<0.001$), harmful alcohol consumption (37.0% versus 12.7%;
26 $p<0.001$) and other communicable diseases (HTLV-1, 45.2%; strongyloidiasis, 36.1%;
27 HBV, 12.9%). Among Indigenous patients, diabetes increased odds of current
28 *Staphylococcus aureus* BSI (OR=1.6, 95% CI=1.0-2.5) and prior skin infections (adjusted
29 OR=2.1, 95% CI=1.4-3.3). Harmful alcohol consumption increased odds of current
30 *Streptococcus pneumoniae* BSI (OR=1.57, 95% CI=1.02-2.40) and of previous BSI
31 (OR=1.7, 95% CI=1.1-2.5), skin infection (OR=1.7, 95% CI=1.1-2.6) or pneumonia
32 (OR=4.3, 95% CI=2.8-6.7). Twenty-six percent of Indigenous patients died at a mean
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 (SD) age of 47±15 years. Complications of diabetes and harmful alcohol consumption
4
5
6 3 predicted 28-day mortality (non-rheumatic heart disease, HR=2.9; 95% CI=1.4-6.2;
7
8 4 chronic renal failure, HR=2.6, 95%CI=1.0-6.5; chronic liver disease, HR=3.3,
9
10 5 95%CI=1.6-6.7).
11
12 6 Conclusion: In a socially disadvantaged population undergoing a rapid epidemiologic
13
14 7 transition, NCDs further increase risk of infection and BSI related mortality. Complex
15
16 8 interactions between communicable diseases and NCDs demand an integrated approach
17
18 9 to management, which must include the empowerment of affected populations to promote
19
20 10 behavioural change.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 2 material on which our analysis is based.
4
5
6 3
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 Introduction

3 Prevalence rates of non-communicable diseases (NCDs), such as diabetes, are rising
4 rapidly in developing countries, adding to a pre-existing burden of infectious diseases in
5 populations that are undergoing rapid demographic changes^{1,2}. A similar burden of
6 communicable diseases and NCDs affects marginalized Indigenous people living in
7 poverty within developed countries^{3,4}. Among Indigenous Australians, for example,
8 NCDs are the major contributors to racial disparities in mortality and to a life expectancy
9 that remains 17 years less than that of their non-Indigenous peers³. In central Australia,
10 rising prevalence rates of NCDs affect an Indigenous population in which a high burden
11 of infectious diseases persists. Incidence rates of sepsis⁵, blood stream infections⁶ and
12 childhood pneumonia, and prevalence rates of bronchiectasis⁷ are the highest reported
13 worldwide. Strongyloidiasis and chronic viral infections, such as with hepatitis B virus
14 (HBV) and the Human T-Lymphotropic Virus 1 (HTLV-1), are also common⁶.
15 Population-based infection-related mortality rates for Indigenous adults in central
16 Australia therefore remain higher than those of some African countries prior to the
17 current HIV pandemic and the median age of in-hospital death is only 48 years⁸.

18
19 Interactions between communicable diseases and NCDs have been little studied;
20 however, an appreciable effect of NCDs on infection rates is likely where pathogen
21 exposure is frequent. Diabetes, for example, contributes to the risk of serious bacterial
22 infections including *Streptococcus pneumoniae*⁹ and *Staphylococcus aureus*¹⁰, which are
23 common pathogens in overcrowded Indigenous Australian communities⁶. The NCD
24 burden may therefore have a substantial impact on infection rates and outcomes where

1
2
3 2 these two epidemics coincide. Such an interaction could reverse health gains in
4
5 3 populations undergoing a rapid epidemiologic transition and exacerbate health
6
7 4 inequalities among disadvantaged subgroups within developed countries. The recent
8
9 5 description in New Zealand of an increasing divergence in infection-related
10
11 6 hospitalization rates according to social status is consistent with this possibility and
12
13 7 challenges health transition theory ¹¹.
14
15
16
17
18
19

20 9 Central Australia is well placed to study interactions between poverty, NCDs and
21
22 10 infectious diseases. Most Indigenous residents live in remote communities in conditions
23
24 11 of considerable socio-economic disadvantage, leaving only a minority within the major
25
26 12 regional township of Alice Springs. The latter have ready access to a well-resourced
27
28 13 medical facility, Alice Springs Hospital (ASH), which has sophisticated diagnostic
29
30 14 capabilities and provides specialist medical care to a region of 1,000,000 km². Indigenous
31
32 15 residents of Alice Springs dwell in either overcrowded ‘town camps’, which have poor
33
34 16 amenities and limited refuse disposal, or are integrated with the majority of the non-
35
36 17 Indigenous population within the township’s suburbs. The Indigenous population of this
37
38 18 region also has among the highest blood stream infection incidence rates reported ⁶.
39
40 19 Living conditions that increase the risk of pathogen exposure and high background rates
41
42 20 of focal infections, which provide portals of entry for bacterial invasion, are likely to
43
44 21 precede these life-threatening infections. Blood stream infection incidence rates therefore
45
46 22 provide measurable end-points to which environmental and host factors contribute.
47
48
49
50
51
52

53 23
54
55
56
57
58
59
60

1
2
3 2 Here we report the infectious and non-communicable disease burden among community
4
5
6 3 residents of central Australia who presented with a blood stream infection and determine
7
8 4 risk factors for infection and death after stratifying by ethnicity.
9
10 5
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

2 **Methods**

3 We conducted a retrospective review of all positive blood cultures collected from adult
4 patients (age \geq 15 years) admitted to ASH between 1st January 2001 and 31st June 2007. In
5 July 2007 the Australian Federal Government suspended racial discrimination legislation
6 and implemented an ‘Emergency Response’ that resulted in considerable uncertainty
7 among Indigenous residents¹². This raised concerns that the central Australian resident
8 population could change as people moved interstate to escape these restrictions and no
9 data was collected after this date. Data collected included organism, ethnicity, dates of
10 birth, dates of death, indigenous status and place of residence. For patients who presented
11 between 1st January 2003 and 31st June 2007 we also obtained ICD 10 morbidity codes
12 and the results of microbiological and radiological investigations for each admission for 5
13 years prior to the final BSI presentation. NCDs were derived from ICD-10 morbidity
14 codes for diabetes, harmful alcohol consumption, >stage 2 chronic kidney disease,
15 ischaemic heart disease, chronic liver disease and malignancy. Bronchiectasis was
16 diagnosed radiologically using American College of Chest Physician criteria. Heart
17 failure and valvular heart disease, including rheumatic heart disease (RHD), were
18 diagnosed by trans-thoracic echocardiography. Ischaemic heart disease and cardiac
19 failure were combined (‘non-rheumatic heart disease’) for statistical analysis.

21 *Definitions*

22 Residence

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

1
2
3 2 Nursing home residents were included in calculations of BSI incidence rates, but
4
5 3 excluded from further analysis because the primary study objective was to determine risk
6
7
8 4 factors for infection and death among community residents.
9

10 5

11 6 Infections

12
13 7 A blood culture from which a pathogen was isolated was defined as a 'BSI episode'.
14
15 8 Repeated culture of the same organism from blood culture was regarded as a separate
16
17 9 'episode' only if blood samples were drawn more than one month apart. Blood stream
18
19 10 infections were defined as community-acquired if a pathogen was isolated from blood
20
21 11 cultures drawn within 48 hours of admission and nosocomial if isolated from blood
22
23 12 cultures drawn after this time. Foci of infection were determined where possible from
24
25 13 ICD-10 morbidity codes in association with pathology and imaging results for each
26
27 14 admission for five years prior to the final BSI during the study period. A diagnosis of
28
29 15 pneumonia was made if there was radiological evidence of consolidation and this was
30
31 16 attributed to the pathogen isolated from blood cultures if the same organism was also
32
33 17 isolated from sputum or the blood culture isolate was an organism typically associated
34
35 18 with pneumonia, such as *Streptococcus pneumoniae*. Blood stream infections excluded
36
37 19 infections with potential contaminants including coagulase negative staphylococci,
38
39 20 bacillus spp., coryneforms and viridans streptococci unless grown from more than one
40
41 21 BC in a 24 hour period, as were *Acinetobacter sp* in the absence of an identifiable focus.
42
43
44
45
46
47
48
49
50

51 22

52
53 23 The study was approved by the Central Australian Human Research Ethics Committee.
54

55 24
56
57
58
59
60

1
2
3 2 *Statistics.*
4

5
6 3 All associations were assessed using data obtained for the final BSI admission within the
7
8 4 study period. Univariate analysis for categorical data was performed using Chi-squared
9
10 5 statistics and Fishers Exact where appropriate. Multivariate analysis was performed using
11
12 6 binary logistic regression. Short (28-day) and long-term survival analysis following the
13
14 7 final BSI episode in the study period was performed using the log-rank statistic for
15
16 8 univariate analysis and Cox regression for multivariate analysis. We calculated the annual
17
18 9 population-based incidence rates for 2001-2006 for the combined Alice Springs and
19
20 10 Anangu Pitjantjatjara Yankunyatjara (APY) land areas using the total number of BSI
21
22 11 presentations each year as the numerator. The denominator used was the estimated Adult
23
24 12 resident population obtained from Australian Bureau of Statistics 2006 census data for
25
26 13 the Alice Springs region combined with that of the neighbouring APY land areas. To
27
28 14 enable analysis according to place of residence this population was further divided into
29
30 15 that of i) the Alice Springs urban area excluding town camps (Indigenous 2898, non-
31
32 16 Indigenous 18471), ii) Alice Springs town camps, including that of a closely affiliated
33
34 17 neighbouring community (Indigenous, 1482), and iii) the Alice Springs rural area
35
36 18 (Indigenous, 8925; non-Indigenous, 2775), which included that for the APY land areas
37
38 19 (Indigenous= 1302, non-Indigenous=294).
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2

3 **Results**

4 *Patient demographics*

5 558 Indigenous and 55 non-indigenous adult community residents presented to ASH with
6 a BSI between January 2003 and July 2007. Detailed demographic, clinical and
7 microbiological data are described in Table 1. Indigenous patients were younger
8 (Indigenous, 44.7±15.2; non-Indigenous, 57.5±21.1; p<0.001), more likely to be female
9 (Indigenous, 58.1%; non-Indigenous, 41.8%; p<0.03) and to live in a town camp or
10 remote community (Indigenous, 84.0%; non-Indigenous, 0; p<0.001). Non-
11 communicable diseases including diabetes (Indigenous, 44.3%; non-Indigenous, 20.0%;
12 p<0.001) and harmful alcohol consumption (Indigenous, 37.0%; non-Indigenous, 12.7%;
13 p<0.001) were more common among Indigenous patients, while non-Indigenous patients
14 were more likely to have ischaemic heart disease (Indigenous, 3.4%; non-Indigenous,
15 31.6%; p<0.001), malignancy (Indigenous, 2.3%; non-Indigenous, 20.0%; p<0.001), to
16 be receiving palliative care (Indigenous, 1.8%; non-Indigenous, 9.1%; p=0.001) and to
17 have a history of intravenous drug use (Indigenous, 0; non-Indigenous, 5.5%; p=0.001).
18 Forty-seven (8.4%) Indigenous and 5 (9.3%) non-indigenous BSI episodes were
19 nosocomial (Table 1).

20

21 *Population-based incidence rates 2001-2006*

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 CI, 20.31-20.35; $p < 0.001$). Incidence rates for Indigenous town camp residents
3 (4,042/100,000 person-years) were nearly 70 times higher than amongst non-Indigenous
4 urban residents (60/100,000 person years) (IRR=67.9, 95% CI=67.8-67.9, $p < 0.001$) and
5 greater than 3 times that of either urban dwelling Indigenous adults (IRR=3.87, 95%
6 CI=3.86-3.87, $p < 0.001$) or those from remote communities (IRR=3.42, 95% CI=3.42-
7 3.42, $p < 0.001$) (Fig 1).

9 *Microbial Aetiology*

10 *Escherichia coli* and *S.aureus* were the most common pathogens causing BSI in both
11 ethnic groups. Methicillin-resistant *S.aureus* (Indigenous, 53 (5.2%); non-Indigenous, 1
12 (0.9%); $p < 0.001$) and *S.pneumoniae* (Indigenous, 136 (13.2%); non-Indigenous, 8
13 (5.9%); $p < 0.001$) were more common among Indigenous patients (Table 1).

14
15 Risk factors for BSI were determined for pathogens contributing more than 5% of all BSI
16 episodes (Table 2). Diabetes was more common among Indigenous patients with a
17 *S.aureus* BSI during their final BSI admission (20.2% versus 13.5%; OR=1.6 (1.04, 2.53;
18 $p = 0.03$) (Table 2). In contrast, increased risk of *Streptococcus pneumoniae* BSI was
19 associated with harmful alcohol consumption, while risk was reduced among patients
20 with diabetes or those receiving haemodialysis (Table 2). Risk of BSI with other major
21 pathogens (*E.coli*, *Klebsiella pneumoniae* or *Streptococcus pyogenes*) was not increased
22 by any NCD (Table 2).

24 *Concurrent infections*

1
2
3 2 During their final BSI admission, Indigenous patients more often had an additional focus
4
5 3 of bacterial infection unrelated to the presenting BSI (Indigenous, n=69 (12.4%); non-
6
7 4 Indigenous, n=2 (3.6%); p=0.05) (Table 1). Infections with HTLV-1 (45.2%),
8
9 5 *S.stercoralis* (36.1%) and hepatitis B virus (anti-HBc, 62.5%; HBsAg, 12.9%) were also
10
11 6 more common among Indigenous patients (Table 1). *Sarcoptes scabiei* infestations were
12
13 7 only found in Indigenous patients (n=20; 4.0%) (Table 1).
14
15
16
17
18
19

20 *Previous infections*

21
22 10 Excluding Indigenous patients who were at increased risk of recurrent infection
23
24 11 (haemodialysis, 83; bronchiectasis, 27) and those residing outside the Alice Springs
25
26 12 region who could not be followed-up (17), 296 of 431 (68.7%) Indigenous adults were
27
28 13 admitted with an acute infection during the five years prior to the final BSI admission
29
30 14 (Table 3). Significantly more common among Indigenous patients were pneumonia,
31
32 15 previous BSI, skin abscesses and wound infections (Table 3). Predisposing factors for
33
34 16 previous infection-related admissions included diabetes (previous skin infections),
35
36 17 harmful alcohol consumption (previous skin infections, pneumonia and BSI) and stage 3-
37
38 18 4 chronic kidney disease (any previous infection) (Table 4).
39
40
41
42
43
44

45 *Mortality*

46 *28 day mortality*

47
48 21 Overall 28-day mortality rates following a BSI were 11.7% and 11.4% for Indigenous
49
50 22 and non-Indigenous adults, respectively. Mortality rates among Indigenous patients were
51
52 23 highest for town camp residents (Fig 2) and varied according to pathogen. Among the
53
54 24
55
56
57
58
59
60

1
2
3 major pathogens causing BSI, most often fatal within the first 28 days was *K.pneumoniae*
4 infection (40.0%) followed by *S.pneumoniae* (9.6%) *S.aureus* (8.0%), and *E.coli* (5.0%)
5 ($\chi^2=39.1$, 4df; $p<0.001$). Case fatality rates according to focus of infection were
6 pneumonia (21.5%), pyelonephritis (8.9%) and skin infections (7.2%) ($\chi^2=14.5$, 3df;
7 $p=0.002$).

8 *1. Community-acquired BSI amongst Indigenous patients*

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

14 *2. Nosocomial BSI amongst Indigenous patients*

15 In univariate analysis, place of residence ($p=0.04$) was a predictor of short-term mortality.
16 Within the first 28 days of admission, town camp residents were more likely to die (7 of
17 11=64%) relative to other township (0 of 6=0.0%) or remote residents (14 of 30=46.7%)
18 ($p=0.039$). In multivariate analysis, place of residence remained an independent predictor
19 ($p<0.001$) and there was also an increased risk in those with non-rheumatic heart disease
20 (HR=4.6, 95% CI=1.2,17.6; $p=0.03$), a primary focus of pneumonia (HR=6.0, 95%
21 CI=1.5, 24.5) and those with a previous BSI (HR=3.8, 95% CI=1.4, 10.3; $p=0.008$).

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

1
2
3 2 In multivariate analysis, only non-rheumatic heart disease was an independent predictor
4
5 3 of short-term mortality amongst non-indigenous patients with a community-acquired BSI
6
7 4 (HR=12.5, 95% CI=1.0, 150.3; $p<0.05$). There were 3 deaths within 28 days amongst 12
8
9 5 non-indigenous patients with non-rheumatic heart disease and 3 deaths amongst 56
10
11 6 patients without non-rheumatic heart disease. Numbers of nosocomial BSI amongst non-
12
13 7 indigenous patients were too few ($n=5$) to attempt survival analysis.
14
15
16
17
18
19

20 9 *Long-term mortality*

21
22 10 One-hundred and forty-five (26.0%) Indigenous and 15 (27.3%) non-Indigenous patients
23
24 11 died during the 2,056 years of follow-up at a mean \pm SD age of 47 ± 15 and 68 ± 21 years
25
26 12 ($p<0.001$), respectively. Amongst Indigenous patients, mortality rates were again highest
27
28 13 amongst those from town camps (Log-rank $\chi^2=5.05$, $p=0.08$) (Fig 2).
29
30
31
32
33

34 15 Among Indigenous patients, NCDs (non-rheumatic heart disease, chronic kidney disease,
35
36 16 chronic liver disease and malignancy) and BSI with *S.aureus* and *S.pneumoniae* were
37
38 17 independent predictors of long-term mortality following community-acquired BSI (Table
39
40 18 5). Residence in a town camp (town camp, 7 of 11; local residence, 0 of 6; remote areas,
41
42 19 14 of 30; $\chi^2=6.5$, 2df; $p=0.04$) and BSI with *K.pneumoniae* BSI (HR=4.0, 95% CI=1.5,
43
44 20 11.2; $p=0.007$) were the only univariate predictors of long-term mortality for nosocomial
45
46 21 BSI's amongst Indigenous patients.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 There were no independent predictors of long-term mortality for non-Indigenous patients
4
5
6 3 with community acquired infections and too few non-indigenous patients with
7
8 4 nosocomial BSI's (n=5) to perform long-term survival analysis.
9
10
11 5
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2

3 Discussion

4 The Indigenous adult population of central Australia has among the highest BSI
5 incidence rates worldwide. Relative to their non-Indigenous peers, rates for Indigenous
6 adults were 20-fold higher overall and 70-fold higher among Indigenous town camp
7 residents. A high burden of other infections, particularly repeated respiratory and skin
8 infections, provide portals of entry for life-threatening invasive bacterial disease. Nearly
9 70% of Indigenous patients required admission for an acute infection in the preceding
10 five years, 24.4% experienced a prior BSI and a second unrelated bacterial infection was
11 found in 12.4% of patients. Chronic viral and parasitic infections were also common.
12 Among Indigenous adults who were tested, more than 60% had been infected with
13 Hepatitis B virus, 13% remained HBsAg positive, nearly half were HTLV-1 seropositive
14 and 36% were *S.stercoralis* seropositive. A similar burden of infection is experienced by
15 Indigenous children amongst whom frequent co-infection with bacterial pathogens and
16 parasites¹³ contributes to 'failure-to-thrive'¹⁴. In our adult cohort, 26.0% of Indigenous
17 patients died during the study period at a mean age of only 47 years. Although we were
18 unable to attribute cause of death in the present study, 60% of Indigenous deaths at ASH
19 are infection-related⁸.

20

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

1
2
3 2 common among patients with diabetes⁹, chronic lung disease⁹ and alcohol dependence
4
5 3 ^{9,17}, respectively. Alcohol dependence and diabetes also increase risk of a BSI requiring
6
7
8 4 intensive care nearly six-fold and haemodialysis increases risk several hundred fold ¹⁶,
9
10 5 largely due to prolonged central venous access ¹⁸. In the present study, rates of diabetes
11
12 6 among Indigenous adults were nearly three times reported background rates ¹⁹. Diabetes
13
14 7 was associated with *S.aureus* BSI and with previous skin infections, but not with
15
16 8 *S.pneumoniae* BSI. Stage 3-4 chronic kidney disease, which is most often a complication
17
18 9 of diabetes in our patient population²⁰, increased risk of previous infections. Harmful
19
20 10 alcohol consumption was associated with *S.pneumoniae* BSI and with previous
21
22 11 infections. Non-communicable diseases, including non-rheumatic heart disease, chronic
23
24 12 kidney disease and chronic liver disease, were also major predictors of mortality after a
25
26 13 BSI. However, once invasive infections were established, *S.aureus* and *S.pneumoniae*
27
28 14 predicted death independently of any underlying medical condition.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 2 admissions in New Zealand are associated with social deprivation ¹¹. The socioeconomic
4
5 3 circumstances of Indigenous Australians are therefore likely to further increase the
6
7 4 infection risks associated with non-communicable diseases.
8
9 5

10 6 Social disadvantage predisposes to non-communicable diseases ^{26, 27} while increasing
11 7 pathogen exposure and limiting opportunities to implement behavioural strategies that
12 8 ameliorate risk ²⁸. In some Indigenous Australian communities the average number of
13 9 people living per house is 17 ²⁹ and non-functioning health hardware leads to
14 10 environmental conditions that are detrimental to householders ³⁰. Overcrowded housing ³¹
15 11 and an inability to maintain adequate skin hygiene ³⁰ contribute to high rates of
16 12 pyoderma. More than 40% of Indigenous patients in the present study were previously
17 13 admitted with skin infections, which are the most common primary focus for *S.aureus*
18 14 bacteraemia in this population³². Scabies, a recognized cause of *S.aureus* and
19 15 Streptococcal pyoderma ^{31,33}, affected 4% of our cohort. Streptococcal pyoderma
20 16 underlies most cases of RHD in the Northern Territory ²⁹ and this was confirmed
21 17 echocardiographically in 2% of our Indigenous cohort. Similarly, the transmission of
22 18 respiratory pathogens is promoted by household crowding ³⁴ and nearly 40% of
23 19 Indigenous adults were admitted previously with pneumonia. Environmental
24 20 contamination ¹⁴, inadequate sanitation and unhygienic food preparation areas ³⁰
25 21 contribute to infection with enteric pathogens and *S.stercoralis*. The risks of complicated
26 22 strongyloidiasis, crusted scabies ³⁵ and bronchiectasis ⁷ are further increased by HTLV-1
27 23 infection; however, no attempt has been made to control transmission of this virus among
28 24 Indigenous Australians. Previously we have shown that Indigenous adults are less likely
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 to engage with a conventional medical paradigm³⁶ and delays in seeking care for
4
5 3 uncomplicated urinary tract infections may contribute to the very high rates of *E.coli* BSI
6
7
8 4 reported here.
9

10 5
11
12 6 The retrospective design of this study results in a number of limitations. Firstly, residents
13
14 7 of remote communities frequently stay in town camps and this is not recorded by ASH.
15
16 8 The effect of town camp residence may therefore be underestimated if large numbers of
17
18 9 remote residents acquire infection during these visits. Although foci of infection were
19
20 10 determined by reviewing the results of microbiology and imaging for each presentation,
21
22 11 these varied between patients according to the practice of the treating physician. The
23
24 12 number of patients with concurrent bacterial infections and medical conditions, such as
25
26 13 RHD, may therefore be underestimated. Similarly, seropositivity rates for infections, such
27
28 14 as HBV and HTLV-1, could only be determined for a subset of patients. A further
29
30 15 limitation is the identification of NCDs and previous infections using ICD-10 codes;
31
32 16 however, coding errors are unlikely to vary systematically according to ethnicity or place
33
34 17 of residence. Finally, the present study has demonstrated an increased risk of infection
35
36 18 and death associated with town camp residence. This occurred despite better access to
37
38 19 health care relative to remote residents and little difference in crude measures of
39
40 20 socioeconomic deprivation³. For community-acquired BSIs, risk of death was strongly
41
42 21 associated with NCDs; however, these conditions did not fully account for the increased
43
44 22 risk following a nosocomial BSI. Unmeasured socioeconomic factors might contribute to
45
46 23 increased mortality among town camp residents; however, recent research linking health
47
48 24 outcomes to perceived racism³⁷ may also be relevant to this marginalized population.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2
4
5 3 The disease burden among the Indigenous population of central Australia is similar to
6
7
8 4 that of many developing countries where NCD prevalence rates are rising rapidly in a
9
10 5 setting of persistently high infection rates ^{1,38}. Recently, the validity of conventional
11
12 6 health transition theory has been challenged by findings that infection-related
13
14 7 hospitalization rates are increasing among the most socially disadvantaged community
15
16 8 members in a developed country ¹¹. The present study provides a possible explanation for
17
18 9 this observation and further suggests that, in contrast to the orderly epidemiological
19
20 10 transition envisaged by Omran (1971)³⁹, life expectancy may fall where social
21
22 11 deprivation persists in the face of a rising prevalence of non-communicable diseases.
23
24
25 12 High BSI incidence rates among Indigenous Australians were associated with a heavy
26
27 13 burden of other infections that provide portals of entry for invasive bacterial disease.
28
29
30 14 Improving life expectancy in this setting will require public health initiatives to reduce
31
32 15 pathogen exposure in addition to controlling the burgeoning non-communicable disease
33
34 16 burden. Diabetes, harmful alcohol consumption and organ damage resulting from these
35
36 17 conditions increased both the likelihood of infection and the subsequent risk of death.
37
38 18 Both conditions are included in proposed international management strategies to control
39
40 19 the non-communicable disease crisis ²⁷. However, our findings also illustrate the
41
42 20 complexity of interactions between communicable and non-communicable diseases and
43
44 21 support calls for an integrated approach to management, which must include the
45
46 22 empowerment of affected populations to promote behavioural change ⁴⁰.
47
48
49
50
51
52
53 23
54
55
56
57
58
59
60

1
2
3 **2 Contributions:**
4

5 LE designed the study, collected the data, assisted with statistical analysis and prepared
6
7
8 the manuscript, LF and SJ collected the data, AB assisted in manuscript preparation and
9
10
11 RW was responsible for statistical analysis and assisted in manuscript preparation.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Table 1 Demographics and comorbidities for indigenous and non-indigenous BSI patients
4
5
6 2003-2007.
7

	Indigenous (n=558)	Non- indigenous (n=55)	p-value for difference
Age, yrs (\pm SD)	44.7 \pm 15.2	57.5 \pm 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

1				
2				
3	Rheumatic heart disease	12 (2.0)	0 (0.0)	0.27
4				
5	Palliative care	10 (1.8)	5 (9.1)	0.001
6				
7				
8	Malignancy	13 (2.3)	11 (20.0)	<0.001
9				
10	IVDU	0 (0.0)	3 (5.5)	0.001
11				
12				
13	Community Acquired	510 (91.6)	49 (90.7)	0.84
14				
15	Primary focus of infection			
16				
17	No focus	250 (44.8)	20 (36.4)	0.37
18				
19	Pneumonia ^c	110 (19.7)	6 (10.9)	0.08
20				
21	Skin abscess	66 (11.8)	5 (9.1)	0.65
22				
23	Pyelonephritis ^d	63 (11.3)	5 (9.1)	0.56
24				
25	Other	53 (9.5)	18 (32.7)	<0.001
26				
27	Enteritis	15 (2.7)	1 (1.8)	0.71
28				
29	Bone/joint	1 (0.2)	0.0 (0.0)	0.61
30				
31				
32				
33				
34	Additional Infections^e			
35				
36	Acute bacterial infections	69 (12.4)	2 (3.6)	0.05
37				
38	Pneumonia	18 (3.2)	0 (0.0)	0.39
39				
40	Urinary tract	20 (3.6)	1 (1.8)	0.49
41				
42	Skin	27 (4.8)	1 (1.8)	0.31
43				
44	Enteritis	4 (0.7)	0	0.53
45				
46				
47				
48	Chronic Viral infections			
49				
50	HTLV-1 ^f	137 (45.2)	0 (0.0)	<0.001
51				
52	Hepatitis B virus ^f			
53				
54	HBsAg	49 (12.9)	1 (6.7)	0.70
55				
56				
57				
58				
59				
60				

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			
Enterobacteriaceae	370 (36.0)	38 (34.5)	0.56
<i>Escherichia coli</i>	246 (23.9)	28 (25.5)	0.37
<i>Klebsiella pneumoniae</i>	57 (5.54)	2 (1.82)	0.09
<i>Staphylococcus aureus</i>	191 (18.6)	20 (18.2)	0.83
MRSA	53 (5.15)	1 (0.91)	<0.001
<i>Streptococcus pneumoniae</i>	136 (13.2)	8 (5.88)	<0.001
<i>Streptococcus pyogenes</i>	68 (6.61)	8 (7.27)	0.42
<i>Haemophilus influenzae</i>	22 (2.14)	0	0.14
Enteric pathogens ^h	29 (2.81)	1 (0.91)	0.27

2 a. comorbidities determined from IC-10 discharge morbidity codes

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

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

- 1
2
3
4 2 d. Respiratory cultures performed for 150 Indigenous patients.
5
6 3 e. Urine cultures performed for 310 Indigenous patients.
7
8 4 e. Alternative bacterial pathogen isolated.
9
10 5 f. Indigenous patients tested: HTLV-1, 309; HBsAg, 388; HBcAb, 309; Strongyloides
11
12 6 stercoralis serology, 235. Denominators exclude 6 Indigenous patients with indeterminate
13
14 7 HTLV-1 Western blot results and 19 Indigenous patients with borderline Strongyloides
15
16 8 serology whose infective status could not be determined.
17
18 9 f. Major BSI pathogens responsible for all recorded episodes 2001-2007.
19
20 10 g. Includes Salmonella spp., Shigella spp., Campylobacter spp.
21
22 11 Abbreviations: CHB, chronic hepatitis B virus; HCV, hepatitis C virus; IVDU,
23
24 12 intravenous drug use.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

	n	<i>S.aureus</i>			<i>S.pneumonia</i>			<i>K.Pneumonia</i>			<i>E.Coli</i>		
		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

1														
2														
3														
4														
5	HD													
6														
7	No	475	84.2	15.8		86.3	13.7		94.1	5.9		70.5	29.5	
8														
9	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
10														
11	CLD													
12														
13														
14	No	505	82.4	17.6		87.7	12.3		93.9	6.1		73.5	26.5	
15														
16	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
17														
18	Alcohol													
19														
20														
21	No	349	82.2	17.8		92.0	8.0		95.1	4.9		75.1	24.9	
22														
23	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
24														
25														
26														
27														
28														
29														
30														
31														
32														
33														
34														
35														
36														
37														
38														
39														
40														
41														
42														
43														
44														
45														
46														
47														
48														
49														

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	Non-Indigenous	p-value
	n=431 (%)	(n=52)	
Any	296 (68.7)	18 (34.6)	<0.001
BSI	105 (24.4)	4 (7.7)	0.007
<i>Respiratory Tract</i>	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
<i>Skin/Soft Tissue</i>	154 (35.7)	7 (13.5)	0.001
<i>Infections</i>			
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
<i>Pyelonephritis</i>	77 (17.9)	4 (7.7)	0.06
<i>Bone/joint</i>	11 (2.6)	0 (0.0)	0.24
<i>Enteritis</i>	21 (4.9)	1 (1.9)	0.33
<i>Scabies</i>	14 (3.3)	0 (0.0)	0.19
<i>Other</i>	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	BSI (n=553)	Skin^b (n=470)	Pneumonia^c (n=443)
	Odds ratio	Odds ratio	Odds ratio	Odds ratio
	(95% CI)	(95% CI)	(95% CI)	(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)

1
2
3 a. Previous infections during 5 years prior to the final BSI in the study period. Adjusted
4
5 for other risk factors in table.
6

7
8 b. Excluding patients receiving haemodialysis.
9

10 c. Excluding patients receiving haemodialysis and those with bronchiectasis
11

12 Abbreviations: BSI, blood stream infections; CRF, chronic renal failure excluding
13 patients receiving haemodialysis.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

	n	Deaths		28 day survival		Long-term survival	
		(28 days)	(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							
<i>E.coli</i>	143	5	22	1.0		1.0	
<i>S.aureus</i>	83	7	18	2.7 (1.0-7.3)	0.05	1.8 (1.1-3.0)	0.03
<i>K.pneumoniae</i>	29	12	15	2.3 (0.7-7.5)	0.17	1.4 (0.7-2.7)	0.17
<i>S.pneumoniae</i>	67	5	17	13.4 (4.6-39.2)	<0.001	4.8 (2.5-9.5)	<0.001
<i>Other</i>	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.

1 References

- 2 1. Maher D, Smeeth, L., Sekajugo, J. Health transition in Africa: practical policy
3 proposals for primary care. *Bull WHO*. 2010;88:943-948.
- 4 2. Gracey M, King, M. Indigenous Health part 1: determinants and disease patterns.
5 *Lancet*. 2009;374:65-75.
- 6 3. Australian Bureau of Statistics. *The health and welfare of Australia's Aboriginal
7 and Torres Strait Islander peoples*. Canberra. 2005.
- 8 4. Zhao Y, Dempsey, K. Causes of inequality in life expectancy between indigenous
9 and non-indigenous people in the Northern Territory, 1981-2000: a decomposition
10 study. *Med J Aust*. 2006;184:490-494.
- 11 5. Davis J, Cheng, AC., McMillan, M., Humphrey, AB., Stephens, DP., Anstey,
12 NM. Sepsis in the tropical Top End of Australia's Northern Territory: disease
13 burden and impact on Indigenous Australians. *Med J Aust*. 2011;194:519-524.
- 14 6. Einsiedel L, Woodman, RJ. Two Nations: racial disparities in bloodstream
15 infections recorded at Alice Springs Hospital, central Australia, 2001-2005. *Med J
16 Aust*. 2010;192:567-571.
- 17 7. Einsiedel L, Fernandes, L., Spelman, T., Steinfors, D., Gotuzzo, E. Bronchiectasis
18 is associated with Human T Lymphotropic Virus 1 infection in an Indigenous
19 Australian population. *Clin Infect Dis*. 2012;54(1):43-50.
- 20 8. Einsiedel L, Fernandes, L., Woodman, R. Racial disparities in infection-related
21 mortality at Alice Springs Hospital, central Australia, 2000-2005. *Med J Aust*.
22 2008;188:568-571.

- 1
2
3
4 1 9. Kway M, Rose, CE., Fry, AM., Singleton, JA., Moore, Z., Zell, ER., Whitney,
5
6 2 CG. The influence of chronic illness on the incidence of invasive pneumococcal
7
8 3 disease in adults. *Clin Infect Dis.* 2005;192:377-386.
9
10 4 10. Joshi N, Caputo, GM., Weitekamp, MR., Karchmer, AW. Infections in diabetic
11
12 5 patients. *N. Engl. J. Med.* 1999;341(25):1906-1912.
13
14 6 11. Baker M, Barnard, LT., Kvalsvig, A., Verrall, A., Zhang, J., Keall, M., Wilson,
15
16 7 N., Wall, T., Howden-Chapman, P. Increasing incidence of serious infectious
17
18 8 diseases and inequalities in New Zealand: a national epidemiological study.
19
20 9 *Lancet.* 2012;379:1112-1119.
21
22 10 12. Anaya J. *Report of the Special Rapporteur on the situation of human rights and*
23
24 11 *fundamental freedoms of indigenous peoples, James Anaya, on the situation of*
25
26 12 *indigenous people in Australia:* United Nations;2010.
27
28 13 13. d'Espaignet E, Kennedy, K., Paterson, B., Measey, M. *Health Status in the*
29
30 14 *Northern Territory 1998.* Darwin: Epidemiology, Primary Care and Coordinated
31
32 15 Care Branch;1998.
33
34 16 14. McDonald E, Bailie, R., Grace, J., Brewster, D. An ecological approach to health
35
36 17 promotion in remote Australian Aboriginal communities. *Health Promotion*
37
38 18 *International.* 2010;25(1):42-53.
39
40 19 15. O'Brien J, Lu, B., Ali, NA., Martin, GS., Aberegg, SK., Marsh, CB., Lemeshow,
41
42 20 S., Douglas, IS. Alcohol dependence is independently associated with sepsis,
43
44 21 septic shock and hospital mortality among adult intensive care unit patients. *Crit.*
45
46 22 *Care Med.* 2007;35(2):345-350.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

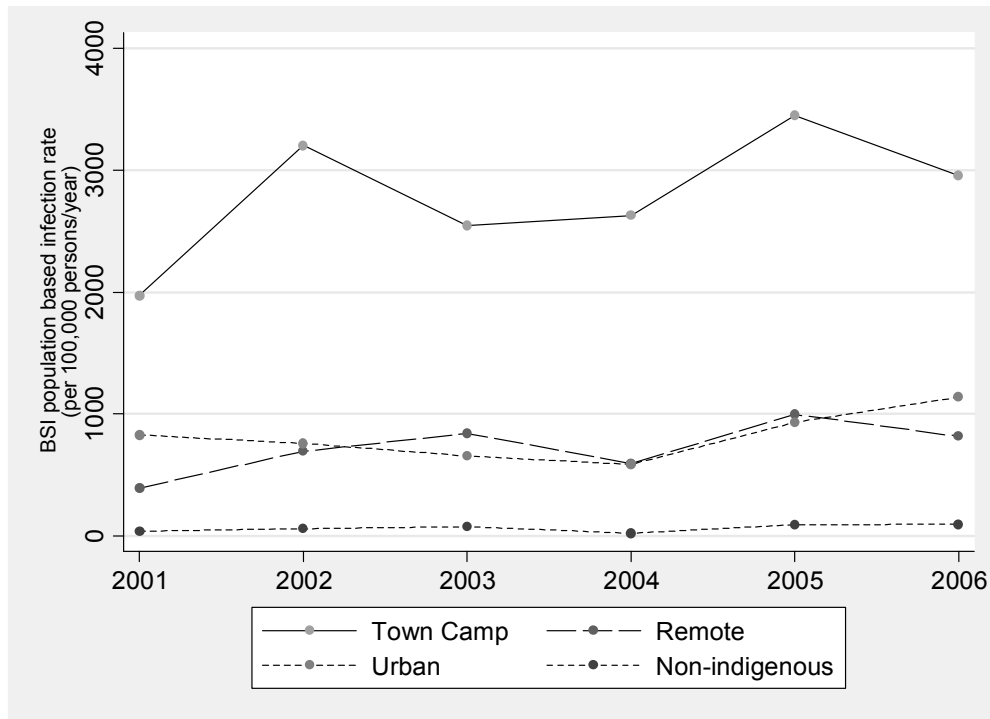
- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 1 **16.** Laupland K, Gregson, DB., Zygun, DA., Doig, CJ., Mortis, G., Church, DL.
2 Severe blood stream infections: a population-based assessment. *Crit Care Med.*
3 2004;32:992-997.
- 4 **17.** Nuori J, Butler, JC., Farley, MM., Harrison, LH., McGeer, A., Kolczak, MS.,
5 Breiman, RF. Cigarette smoking and invasive pneumococcal disease. *N Engl J*
6 *Med.* 2000;342:681-689.
- 7 **18.** Dopirak M, Hill, C., Oleksiw, M., Dumigan, D., Arvai, J., English, E., Carusillo,
8 E., Malo-Schlegel, S., Richo, J., Traficanti, K., Welch, B., Cooper, B.
9 Surveillance of hemodialysis-associated primary bloodstream infections: the
10 experience of ten hospital-based centers. *Infect Control Hosp Epidemiol.*
11 2002;23:721-724.
- 12 **19.** Zhao Y, Connors, C., Wright, J., Guthridge, S. Estimating chronic disease
13 prevalence among the remote Aboriginal population of the Northern Territory
14 using multiple data sources. *Aust NZ J Public Health.* 2008;32:307-313.
- 15 **20.** Hoy W, Davey, RL., Sharma, S., Hoy, PW., Smith, JM., Kondalsamy-
16 Chennakesavan, S. Chronic disease profiles in remote Aboriginal settings and
17 implications for health services planning. *Aust NZ J Public Health.* 2010;34:11-
18 18.
- 19 **21.** Moberley S, Krause, V., Cook, H., Mulholland, K., Carapetis, J., Torzillo, P.,
20 Andrews, R. Failure to vaccinate or failure of vaccine? Effectiveness of the 23-
21 valent pneumococcal polysaccharide vaccine program in Indigenous adults in the
22 Northern Territory of Australia. *Vaccine.* 2010;28:2296-2301.

- 1
2
3 1 22. Flory J, Joffe, M., Fishman, NO., Edelstein, PH., Metlay, JP. Socioeconomic risk
4
5 factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiol Infect.*
6
7 2009;137:717-726.
8
9
10 4 23. Tong S, Bishop, E., Lilliebridge, R., Cheng, A., Spasova-Penkova, Z., Holt, D.,
11
12 Giffard, P., McDonald, M., Currie, B., Boutlis, C. Community Associated strains
13
14 of Methicillin-Resistant *Staphylococcus aureus* and Methicillin-Susceptible
15
16 *S.aureus* in Indigenous Northern Australia: Epidemiology and Outcomes. *J Infect*
17
18 *Dis.* 2009;199:1461-1470.
19
20
21 9 24. Huggan P, Wells, JE., Browne, M., Richardson, A., Murdoch, DR., Chambers,
22
23 ST. Population-based epidemiology of *Staphylococcus aureus* bloodstream
24
25 infection in Canterbury, New Zealand. *Int Med J.* 2010;40:117-125.
26
27
28 12 25. Bagger J, Zindrou, D., Taylor, KM. Post-operative infection with Methicillin-
29
30 resistant *Staphylococcus aureus* and socioeconomic background. *Lancet.*
31
32 2004;363:706-708.
33
34
35 15 26. Marmot M, Friel, S., Bell, R., Houweling, T., Taylor, S. Closing the gap in a
36
37 generation: health equity through action on the social determinants of health.
38
39 *Lancet.* 2008;372(November 8):1661-1669.
40
41
42 18 27. Beaglehole R, Bonita, R., Horton, R., Adams, C., Alleyne, G., Asaria, P. et al for
43
44 the Lancet NCD action group and the NCD alliance. Priority actions for the non-
45
46 communicable disease crisis. *Lancet.* 2011;377:1438-1447.
47
48
49 21 28. Bailie R, Stevens, MR., McDonald, E., Halpin, S., Brewster, D., Robinson, G.,
50
51 Guthridge, S. Skin infection, housing and social circumstances in children living
52
53
54
55
56
57
58
59
60

- 1
2
3 1 in remote Indigenous communities: testing conceptual and methodological
4
5 2 approaches. *BMC public health*. 2005;5.
6
7
8 3 **29.** McDonald M, Towers, RJ., Andrews, RM., Bengler, N., Currie, BJ., Carapetis, JR.
9
10 4 Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian
11
12 5 Aboriginal communities where acute rheumatic fever is hyperendemic. *Clin Infect*
13
14 6 *Dis*. 2006;43:683-689.
15
16
17 7 **30.** Bailie R, Runcie, MJ. Household infrastructure in Aboriginal communities and
18
19 8 the implications for health improvement. *Med J Aust*. 2001;175:363-366.
20
21
22 9 **31.** Currie B, Carapetis, JR. Skin infections and infestations in Aboriginal
23
24 10 communities in northern Australia. *Aust J Dermatol*. 2000;41:139-145.
25
26
27 11 **32.** Hewagama S, Spelman, T., Einsiedel, L. Staphylococcus aureus bacteraemia at
28
29 12 Alice Springs Hospital, central Australia, 2003-2006. *Int Med J*. 2012;42:505-
30
31 13 512.
32
33
34 14 **33.** Carapetis J, Wolff, DR., Currie, BJ. Acute rheumatic fever and rheumatic heart
35
36 15 disease in the Top End of Australia's Northern Territory. *Med J Aust*. 1996;164(5
37
38 16 February):146-149.
39
40
41 17 **34.** Jacoby P, Carvillo, K., Hall, S., Riley, T., Bowman, J., Leach, A., Lehmann, D.,
42
43 18 Kalgoorlie Otitis Media Research Project Team. Crowding and other strong
44
45 19 predictors of upper respiratory carriage of otitis media related bacteria in
46
47 20 Australian Aboriginal and non-Aboriginal children. *Paed Inf Dis J*.
48
49 21 2011;30(6):480-485.
50
51
52
53
54
55
56
57
58
59
60

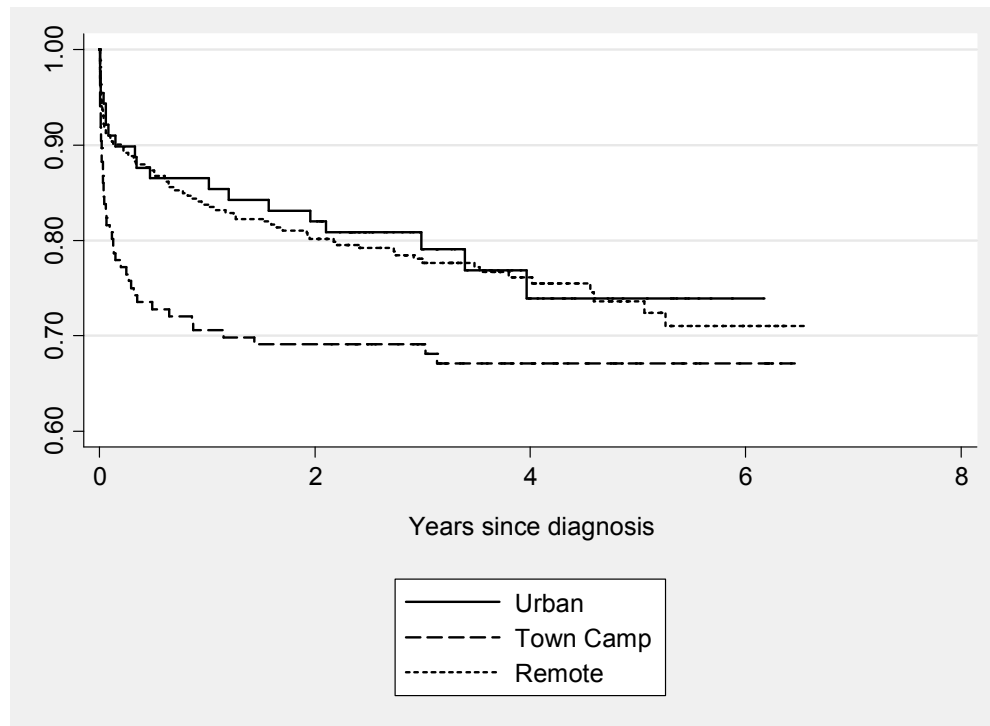
- 1
2
3 1 35. Verdonck K, Gonzalez, E., Van Dooren, S., Vandamme, A., Vanham, G.,
4
5 2 Gotuzzo, E. Human T-lymphotropic virus 1: recent knowledge about an ancient
6
7 3 infection. *Lancet Infect Dis.* 2007;7:266-281.
8
9
10 4 36. Einsiedel L, van Iersel, E., Macnamara, R., Spelman, T., Heffernan, M., Bray, L,
11
12 5 Morris, H., Porter, B., Davis, A. Self-Discharge by adult Aboriginal patients at
13
14 6 Alice Springs Hospital, central Australia: insights from a prospective cohort
15
16 7 study. *Aust Health Rev.* 2012.
17
18
19 8 37. Priest N, Paradies, Y., Stevens, M., Bailie, R. Exploring relationships between
20
21 9 racism, housing and child illness in remote indigenous communities. *J Epidemiol*
22
23 10 *Community Health* 2012;66:440-447.
24
25
26 11 38. Boutayeb A, Boutayeb, B. The burden of non-communicable diseases in
27
28 12 developing countries. *Int J Equity in Health.* 2005;4(1):2.
29
30
31 13 39. Omran A. A theory of the epidemiology of population change. *Milbank Mem*
32
33 14 *Fund Q.* 1971;49:509-538.
34
35
36 15 40. De Maeseneer J, Roberts RG, Demarzo M, et al. Tackling NCDs: a different
37
38 16 approach is needed. *The Lancet.* 2012;379(9829):1860-1861.
39
40
41 17
42
43 18
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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.



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003070.R1
Article Type:	Research
Date Submitted by the Author:	02-Jun-2013
Complete List of Authors:	Einsiedel, Lloyd; Flinders University, Northern Territory Rural Clinical School Fernandes, Liselle; Flinders University, NTRCS Joseph, Sheela; Flinders University, NTRCS Brown, Alex; Baker IDI Heart and Diabetes Institute, Centre for Indigenous Vascular and Diabetes Research Woodman, Richard; Flinders University, General Practice
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Global health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, MICROBIOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Nephrology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

only

1
2
3 2 Non-communicable diseases, infection and survival in a retrospective cohort
4 of Indigenous and non-Indigenous adults in central Australia.
5
6
7
8

9 Lloyd Einsiedel¹, Liselle Fernandes¹, Sheela Joseph¹, Alex Brown² and
10
11 Richard J Woodman¹
12
13

14
15
16
17
18
19
20 9 (1) Flinders University/Northern Territory Rural Clinical School, Alice Springs Hospital, 0870,
21 Northern Territory, Australia
22
23

24
25
26 11 (2) Head, Centre for Indigenous Vascular Research, Baker IDI Heart and Diabetes
27 Institute, Alice Springs Hospital, 0870, Northern Territory, Australia.
28
29
30

31
32
33
34
35 14 § Corresponding author:
36

37
38
39 15 Lloyd Einsiedel. Alice Springs Hospital, Department of Medicine, Darwin, Northern
40 Territory, Australia. Tel: + 61 08 89519607, Fax: + 61 08 89538385, E-mail:
41
42
43 17 lloyd.einsiedel@health.sa.gov.au
44
45

46
47
48
49 19 Running title: Infection risk in Indigenous Australians
50

51
52
53 20 Keywords: Non-communicable diseases, diabetes, alcohol, infection, Indigenous health,
54
55 21 Australia
56
57
58
59
60

1
2
3 2 Word count:

4
5 3 Abstract: 293

6
7 4 Text: 3758

8
9 5 References: 47

10
11
12
13 6

14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 **Abstract**
4

5 Objectives: We hypothesize that rising prevalence rates of non-communicable diseases
6 (NCDs) increases infection risk and worsens outcomes among socially disadvantaged
7
8 Indigenous Australians undergoing a rapid epidemiological transition.
9

10 Design: Pathology, imaging and discharge morbidity codes were retrospectively reviewed
11 for a period of 5 years prior to admission with a blood stream infection (BSI), 1st January
12 2003 to 30th June 2007.
13

14 Participants: 558 Indigenous and 55 non-Indigenous community residents of central
15 Australia.
16

17 Outcome measures: The effects of NCDs on risk of infection and death were determined
18 after stratifying by ethnicity.
19

20 Results: Mean annual BSI incidence rates were far higher among Indigenous residents
21 (Indigenous, 937 per 100,000; non-Indigenous, 64 per 100,000 person-years; IRR=14.6;
22 95% CI=14.61-14.65, $p<0.001$). Indigenous patients were also more likely to have
23 previous bacterial infections (68.7% versus 34.6%; respectively, $p<0.001$), diabetes
24 (44.3% versus 20.0%; $p<0.001$), harmful alcohol consumption (37.0% versus 12.7%;
25 $p<0.001$) and other communicable diseases (HTLV-1, 45.2%; strongyloidiasis, 36.1%;
26 HBV, 12.9%). Among Indigenous patients, diabetes increased odds of current
27 *Staphylococcus aureus* BSI (OR=1.6, 95% CI=1.0-2.5) and prior skin infections (adjusted
28 OR=2.1, 95% CI=1.4-3.3). Harmful alcohol consumption increased odds of current
29 *Streptococcus pneumoniae* BSI (OR=1.57, 95% CI=1.02-2.40) and of previous BSI
30 (OR=1.7, 95% CI=1.1-2.5), skin infection (OR=1.7, 95% CI=1.1-2.6) or pneumonia
31 (OR=4.3, 95% CI=2.8-6.7). Twenty-six percent of Indigenous patients died at a mean
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 (SD) age of 47±15 years. Complications of diabetes and harmful alcohol consumption
4
5
6 3 predicted 28-day mortality (non-rheumatic heart disease, HR=2.9; 95% CI=1.4-6.2;
7
8 4 chronic renal failure, HR=2.6, 95%CI=1.0-6.5; chronic liver disease, HR=3.3, 95%
9
10 5 CI=1.6-6.7).

11
12 6 Conclusion: In a socially disadvantaged population undergoing a rapid epidemiologic
13
14 7 transition, NCDs are associated with an increased risk of infection and BSI related
15
16 8 mortality. Complex interactions between communicable diseases and NCDs demand an
17
18 9 integrated approach to management, which must include the empowerment of affected
19
20 10 populations to promote behavioural change.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 2 material on which our analysis is based.
4
5
6 3
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 Introduction

3 Complex interactions between the demographic, economic and sociologic determinants
4 of disease result in changing patterns of health and disease over time¹. The development
5 of modern social and economic structures, for example, has been associated with a
6 reduction in infectious diseases and nutritional deficiencies and a corresponding rise in
7 non-communicable diseases (NCDs) that are associated with ageing and lifestyle factors¹.
8 In many developing countries the rapidity of this 'epidemiologic transition' has resulted
9 in a dramatic increase in NCD prevalence among populations that have a substantial pre-
10 existing infectious disease burden^{2,3}. This phenomenon proceeds at different rates
11 according to the socioeconomic status of particular sub-groups within a given population
12 and may reinforce established health inequalities^{4,5}.

13
14 Among Indigenous people, forced displacement, the collapse of Indigenous economies
15 and the destruction of socio-political structures have been the shared experience of
16 colonization⁶. Indigenous people living within developed countries continue to live in
17 poverty and experience a 'protracted' epidemiologic transition⁴ that is associated with a
18 double burden of communicable and non-communicable diseases^{7,8} similar to that of
19 many developing countries². In central Australia, for example, diabetes and other NCDs
20 are the major contributors to racial disparities in mortality⁸ and to a life expectancy that
21 remains 14 years less for Indigenous Australian men relative to their non-Indigenous
22 peers⁹. A high burden of infectious diseases persists in this Indigenous population.
23 Incidence rates of sepsis¹⁰, blood stream infections¹¹ and childhood pneumonia¹², and
24 prevalence rates of bronchiectasis¹³ are the highest reported worldwide. Strongyloidiasis

1
2
3 and chronic viral infections, such as with hepatitis B virus (HBV) and the Human T-
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

7
8 Interactions between communicable diseases and NCDs have been little studied;
9 however, an appreciable effect of NCDs on infection rates is likely where pathogen
10 exposure is frequent. Diabetes, for example, contributes to the risk of serious bacterial
11 infections including *Streptococcus pneumoniae*¹⁵ and *Staphylococcus aureus* ¹⁶, which
12 are common pathogens in overcrowded Indigenous Australian communities ¹¹. The NCD
13 burden may therefore have a substantial impact on infection rates and outcomes where
14 these two epidemics coincide. Such an interaction could reverse health gains in
15 populations undergoing a rapid epidemiologic transition and exacerbate health
16 inequalities among disadvantaged subgroups within developed countries. The recent
17 description in New Zealand of an increasing divergence in infection-related
18 hospitalization rates according to social status is consistent with this possibility and
19 challenges health transition theory ¹⁷.

20
21 Central Australia is well placed to study interactions between poverty, NCDs and
22 infectious diseases. Most Indigenous residents live in remote communities in conditions
23 of considerable socio-economic disadvantage, leaving a minority within the major
24 regional township of Alice Springs. The latter have ready access to a well-resourced

1
2
3 2 medical facility, Alice Springs Hospital (ASH), which has sophisticated diagnostic
4
5 3 capabilities and provides specialist medical care to a region of 1,000,000 km². Indigenous
6
7 4 residents of Alice Springs dwell in either overcrowded ‘town camps’, which have poor
8
9 5 amenities and limited refuse disposal, or are integrated with the majority of the non-
10
11 6 Indigenous population within the township’s suburbs. Indigenous adults living in town
12
13 7 camps and remote communities are often unemployed, have limited education and poor
14
15 8 health literacy¹⁸. Among Indigenous adult residents of town camps, nearly half have 8
16
17 9 years or less schooling, labour participation rates are less than 20% and only 12% are
18
19 10 employed ¹⁹. Despite an extremely complex regulatory framework and numerous
20
21 11 Government attempts to minimize risk, harmful alcohol consumption in this setting
22
23 12 remains common ²⁰.
24
25
26
27
28
29
30
31

32 14 The Indigenous population of central Australia also has among the highest blood stream
33
34 15 infection incidence rates reported ¹¹. Living conditions that increase the risk of pathogen
35
36 16 exposure ²¹ and high background rates of focal infections, which provide portals of entry
37
38 17 for bacterial invasion, are likely to precede these life-threatening infections. Blood stream
39
40 18 infection incidence rates therefore provide measurable end-points to which environmental
41
42 19 and host factors contribute. Here we report the infectious and non-communicable disease
43
44 20 burden among community residents of central Australia who presented with a blood
45
46 21 stream infection and determine risk factors for infection and death after stratifying by
47
48 22 ethnicity.
49
50
51
52

53 23
54
55
56
57
58
59
60

2 **Methods**

3 We conducted a retrospective review of all positive blood cultures collected from adult
4 patients (age \geq 15 years) admitted to ASH between 1st January 2001 and 31st June 2007. In
5 July 2007 the Australian Federal Government suspended racial discrimination legislation
6 and implemented an 'Emergency Response' that resulted in considerable uncertainty
7 among Indigenous residents²². This raised concerns that the central Australian resident
8 population could change as people moved interstate to escape these restrictions and no
9 data was collected after this date. Data collected included organism, ethnicity, dates of
10 birth, dates of death, indigenous status and place of residence. For patients who presented
11 between 1st January 2003 and 31st June 2007 we also obtained ICD 10 morbidity codes
12 and the results of microbiological and radiological investigations for each admission for 5
13 years prior to the final BSI presentation. NCDs were derived from ICD-10 morbidity
14 codes for diabetes, harmful alcohol consumption, >stage 2 chronic kidney disease,
15 ischaemic heart disease, chronic liver disease and malignancy. Bronchiectasis was
16 diagnosed radiologically using American College of Chest Physician criteria. Heart
17 failure and valvular heart disease, including rheumatic heart disease (RHD), were
18 diagnosed by trans-thoracic echocardiography. Ischaemic heart disease and cardiac
19 failure were combined ('non-rheumatic heart disease') for statistical analysis.

21 *Definitions*

22 Residence

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

1
2
3 2 Nursing home residents were included in calculations of BSI incidence rates, but
4
5 3 excluded from further analysis because the primary study objective was to determine risk
6
7 4 factors for infection and death among community residents.
8
9 5

6 Infections

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

22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 The study was approved by the Central Australian Human Research Ethics Committee
4
5 3 (www.health.nt.gov.au/Agency/Advisory_Groups_and_Taskforces/Human_Research_Et
6
7
8 4 hics_Committee/index.aspx).
9

10
11 5

12
13 6 *Statistics.*

14
15 7 All associations were assessed using data obtained for the final BSI admission within the
16
17 8 study period. Univariate analysis for categorical data was performed using Chi-squared
18
19 9 statistics and Fishers Exact where appropriate. Multivariate analysis was performed using
20
21 10 binary logistic regression. Short (28-day) and long term survival analysis following the
22
23 11 final BSI episode in the study period was performed using the log-rank statistic for
24
25 12 univariate analysis and Cox regression for multivariate analysis. We calculated the annual
26
27 13 population-based incidence rates for 2001-2006 for the combined Alice Springs and
28
29 14 Anangu Pitjantjatjara Yankunyatjara (APY) land areas using the total number of BSI
30
31 15 presentations each year as the numerator. The denominator used was the estimated Adult
32
33 16 resident population obtained from Australian Bureau of Statistics 2006 census data for
34
35 17 the Alice Springs region combined with that of the neighbouring APY land areas. To
36
37 18 enable analysis according to place of residence this population was further divided into
38
39 19 that of i) the Alice Springs urban area excluding town camps (Indigenous 2898, non-
40
41 20 Indigenous 18471), ii) Alice Springs town camps, including that of a closely affiliated
42
43 21 neighbouring community (Indigenous, 1482), and iii) the Alice Springs rural area
44
45 22 (Indigenous, 8925; non-Indigenous, 2775), which included that for the APY land areas
46
47 23 (Indigenous= 1302, non-Indigenous=294).
48
49
50
51
52
53
54
55
56
57
58
59
60

2

3 **Results**

4 *Patient demographics*

5 558 Indigenous and 55 non-indigenous adult community residents presented to ASH with
6 a BSI between January 2003 and July 2007. Detailed demographic, clinical and
7 microbiological data are described in Table 1. Indigenous patients were younger
8 (Indigenous, 44.7±15.2; non-Indigenous, 57.5±21.1; p<0.001), more likely to be female
9 (Indigenous, 58.1%; non-Indigenous, 41.8%; p<0.03) and to live in a town camp or
10 remote community (Indigenous, 84.0%; non-Indigenous, 0; p<0.001). Non-
11 communicable diseases including diabetes (Indigenous, 44.3%; non-Indigenous, 20.0%;
12 p<0.001) and harmful alcohol consumption (Indigenous, 37.0%; non-Indigenous, 12.7%;
13 p<0.001) were more common among Indigenous patients, while non-Indigenous patients
14 were more likely to have ischaemic heart disease (Indigenous, 3.4%; non-Indigenous,
15 31.6%; p<0.001), malignancy (Indigenous, 2.3%; non-Indigenous, 20.0%; p<0.001), to
16 be receiving palliative care (Indigenous, 1.8%; non-Indigenous, 9.1%; p=0.001) and to
17 have a history of intravenous drug use (Indigenous, 0; non-Indigenous, 5.5%; p=0.001).
18 Forty-seven (8.4%) Indigenous and 5 (9.3%) non-indigenous BSI episodes were
19 nosocomial (Table 1).

20

21 *Population-based incidence rates 2001-2006*

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

1
2
3 14.65; $p < 0.001$). Incidence rates for Indigenous town camp residents (2,794/100,000
4 person-years) were more than 40 times higher than those of non-Indigenous urban
5 residents (64/100,000 person years) (IRR=43.6, 95% CI=43.57-43.65, $p < 0.001$) and at
6 least three times higher than those of urban dwelling Indigenous adults (IRR=3.421, 95%
7 CI=3.418-3.423, $p < 0.001$) or those from remote communities (IRR=3.87, 95% CI=3.864-
8 3.868, $p < 0.001$) (Fig 1).
9

10 *Microbial Aetiology*

11 *Escherichia coli* and *S.aureus* were the most common pathogens causing BSI in both
12 ethnic groups. Methicillin-resistant *S.aureus* (Indigenous, 53 (5.2%); non-Indigenous, 1
13 (0.9%); $p < 0.001$) and *S.pneumoniae* (Indigenous, 136 (13.2%); non-Indigenous, 8
14 (5.9%); $p < 0.001$) were more common among Indigenous patients (Table 1).
15

16 Risk factors for BSI were determined for pathogens contributing more than 5% of all BSI
17 episodes (Table 2). Diabetes was more common among Indigenous patients with a
18 *S.aureus* BSI during their final BSI admission (20.2% versus 13.5%; OR=1.6 (1.04, 2.53;
19 $p = 0.03$) (Table 2). In contrast, increased risk of *Streptococcus pneumoniae* BSI was
20 associated with harmful alcohol consumption, while risk was reduced among patients
21 with diabetes or those receiving haemodialysis (Table 2). Risk of BSI with other major
22 pathogens (*E.coli*, *Klebsiella pneumoniae* or *Streptococcus pyogenes*) was not increased
23 by any NCD (Table 2).
24

25 *Concurrent infections*

1
2
3 2 During their final BSI admission, Indigenous patients more often had an additional focus
4
5 3 of bacterial infection unrelated to the presenting BSI (Indigenous, n=69 (12.4%); non-
6
7 4 Indigenous, n=2 (3.6%); p=0.05) (Table 1). Infections with HTLV-1 (45.2%),
8
9 5 *S.stercoralis* (36.1%) and hepatitis B virus (anti-HBc, 62.5%; HBsAg, 12.9%) were also
10
11 6 more common among Indigenous patients (Table 1). *Sarcoptes scabiei* infestations were
12
13 7 only found in Indigenous patients (n=20; 4.0%) (Table 1).
14
15
16
17
18
19

20 *Previous infections*

21
22 10 Excluding Indigenous patients who were at increased risk of recurrent infection
23
24 11 (haemodialysis, 83; bronchiectasis, 27) and those residing outside the Alice Springs
25
26 12 region who could not be followed-up (17), 296 of 431 (68.7%) Indigenous adults were
27
28 13 admitted with an acute infection during the five years prior to the final BSI admission
29
30 14 (Table 3). Significantly more common among Indigenous patients were pneumonia,
31
32 15 previous BSI, skin abscesses and wound infections (Table 3). Predisposing factors for
33
34 16 previous infection-related admissions included diabetes (previous skin infections),
35
36 17 harmful alcohol consumption (previous skin infections, pneumonia and BSI) and stage 3-
37
38 18 4 chronic kidney disease (any previous infection) (Table 4).
39
40
41
42
43
44

45 *Mortality*

46 *28 day mortality*

47
48 21 Overall 28-day mortality rates following a BSI were 11.7% and 11.4% for Indigenous
49
50 22 and non-Indigenous adults, respectively. Mortality rates among Indigenous patients were
51
52 23 highest for town camp residents (Fig 2) and varied according to pathogen. Among the
53
54
55
56
57
58
59
60

1
2
3 major pathogens causing BSI, most often fatal within the first 28 days was *K.pneumoniae*
4 infection (40.0%) followed by *S.pneumoniae* (9.6%) *S.aureus* (8.0%), and *E.coli* (5.0%)
5 ($\chi^2=39.1$, 4df; $p<0.001$). Case fatality rates according to focus of infection were
6 pneumonia (21.5%), pyelonephritis (8.9%) and skin infections (7.2%) ($\chi^2=14.5$, 3df;
7 $p=0.002$).

8 *1. Community-acquired BSI amongst Indigenous patients*

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

14 *2. Nosocomial BSI amongst Indigenous patients*

15 In univariate analysis, place of residence ($p=0.04$) was a predictor of short-term mortality.
16 Within the first 28 days of admission, town camp residents were more likely to die (7 of
17 11=64%) relative to other township (0 of 6=0.0%) or remote residents (14 of 30=46.7%)
18 ($p=0.039$). In multivariate analysis, place of residence remained an independent predictor
19 ($p<0.001$) and there was also an increased risk in those with non-rheumatic heart disease
20 (HR=4.6, 95% CI=1.2,17.6; $p=0.03$), a primary focus of pneumonia (HR=6.0, 95%
21 CI=1.5, 24.5) and those with a previous BSI (HR=3.8, 95% CI=1.4, 10.3; $p=0.008$).

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

1
2
3 2 In multivariate analysis, only non-rheumatic heart disease was an independent predictor
4
5 3 of short-term mortality amongst non-indigenous patients with a community-acquired BSI
6
7
8 4 (HR=12.5, 95% CI=1.0, 150.3; $p<0.05$). There were 3 deaths within 28 days amongst 12
9
10 5 non-indigenous patients with non-rheumatic heart disease and 3 deaths amongst 56
11
12 6 patients without non-rheumatic heart disease. Numbers of nosocomial BSI amongst non-
13
14 7 indigenous patients were too few ($n=5$) to attempt survival analysis.
15
16
17
18
19

20 9 *Long-term mortality*

21
22 10 One-hundred and forty-five (26.0%) Indigenous and 15 (27.3%) non-Indigenous patients
23
24 11 died during the 2,056 years of follow-up at a mean \pm SD age of 47 ± 15 and 68 ± 21 years
25
26 12 ($p<0.001$), respectively. Amongst Indigenous patients, mortality rates were again highest
27
28 13 amongst those from town camps (Log-rank $\chi^2=5.05$, $p=0.08$) (Fig 2).
29
30
31
32
33

34 15 Among Indigenous patients, NCDs (non-rheumatic heart disease, chronic kidney disease,
35
36 16 chronic liver disease and malignancy) and BSI with *S.aureus* and *S.pneumoniae* were
37
38 17 independent predictors of long-term mortality following community-acquired BSI (Table
39
40 18 5). Residence in a town camp (town camp, 7 of 11; local residence, 0 of 6; remote areas,
41
42 19 14 of 30; $\chi^2=6.5$, 2df; $p=0.04$) and BSI with *K.pneumoniae* BSI (HR=4.0, 95% CI=1.5,
43
44 20 11.2; $p=0.007$) were the only univariate predictors of long-term mortality for nosocomial
45
46 21 BSI's amongst Indigenous patients.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 There were no independent predictors of long-term mortality for non-Indigenous patients
4
5
6 3 with community acquired infections and too few non-indigenous patients with
7
8 4 nosocomial BSI's (n=5) to perform long-term survival analysis.
9
10
11 5
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2

3 Discussion

4 The Indigenous adult population of central Australia has among the highest BSI
5 incidence rates worldwide. Relative to their non-Indigenous peers, rates for Indigenous
6 adults were nearly 15-fold higher overall and 40-fold higher among Indigenous town
7 camp residents. A high burden of other infections, particularly repeated respiratory and
8 skin infections, provide portals of entry for life-threatening invasive bacterial disease.
9 Nearly 70% of Indigenous patients required admission for an acute infection in the
10 preceding five years, 24.4% experienced a prior BSI and a second unrelated bacterial
11 infection was found in 12.4% of patients. Chronic viral and parasitic infections were also
12 common. Among Indigenous adults who were tested, more than 60% had been infected
13 with Hepatitis B virus, 13% remained HBsAg positive, nearly half were HTLV-1
14 seropositive and 36% were *S.stercoralis* seropositive. A similar burden of infection is
15 experienced by Indigenous children amongst whom frequent co-infection with bacterial
16 pathogens and parasites²³ contributes to 'failure-to-thrive'²⁴. In our adult cohort, 26.0%
17 of Indigenous patients died during the study period at a mean age of only 47 years.
18 Although we were unable to attribute cause of death in the present study, 60% of
19 Indigenous deaths at ASH are infection-related¹⁴.

20

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

1
2
3 2 common among patients with diabetes¹⁵, chronic lung disease¹⁵ and alcohol dependence
4
5 15,27, respectively. Alcohol dependence and diabetes also increase risk of a BSI requiring
6
7
8 4 intensive care nearly six-fold and haemodialysis increases risk several hundred fold²⁶,
9
10 5 largely due to prolonged central venous access²⁸. In the present study, rates of diabetes
11
12 6 among Indigenous adults were nearly three times reported background rates²⁹. Diabetes
13
14 7 was associated with *S.aureus* BSI and with previous skin infections, but not with
15
16 8 *S.pneumoniae* BSI. Stage 3-4 chronic kidney disease, which is most often a complication
17
18 9 of diabetes in our patient population³⁰, was associated with any previous infection.
19
20 10 Harmful alcohol consumption was associated with *S.pneumoniae* BSI and with previous
21
22 11 infection-related admissions. Non-communicable diseases, including non-rheumatic heart
23
24 12 disease, chronic kidney disease and chronic liver disease, were also major predictors of
25
26 13 mortality after a BSI. However, once invasive infections were established, *S.aureus* and
27
28 14 *S.pneumoniae* predicted death independently of any underlying medical condition.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

16 The present study has compared risk of non-communicable diseases among patients
17 presenting with a BSI and cannot determine the population-based risks attributable to
18 these conditions. Nevertheless, racial disparities in NCD prevalence are unlikely to fully
19 account for the BSI incidence rate ratios reported here, nor do regional differences in
20 their prevalence²⁹ explain IPD incidence rates that are twice as high among Indigenous
21 residents of central Australia relative to those of the tropical north³¹. In the USA, higher
22 IPD incidence rates among Black Americans^{15,32} are more robustly associated with
23 poverty than race³². An increased risk of *S.aureus* infection has also been reported
24 among those of lower socio-economic position³³⁻³⁵ and infection-related hospital

1
2
3 2 admissions in New Zealand are associated with social deprivation¹⁷. The socioeconomic
4
5 3 circumstances of Indigenous Australians are therefore likely to further increase the
6
7 4 infection risks associated with non-communicable diseases.
8
9 5

10 6 Social disadvantage predisposes to non-communicable diseases^{36, 37} while increasing
11 7 pathogen exposure and limiting opportunities to implement behavioural strategies that
12 8 ameliorate risk³⁸. In some Indigenous Australian communities the average number of
13 9 people living per house is 17³⁹ and non-functioning health hardware leads to
14 10 environmental conditions that are detrimental to householders²¹. Overcrowded housing⁴⁰
15 11 and an inability to maintain adequate skin hygiene²¹ contribute to high rates of
16 12 pyoderma. More than 40% of Indigenous patients in the present study were previously
17 13 admitted with skin infections, which are the most common primary focus for *S.aureus*
18 14 bacteraemia in this population⁴¹. Scabies, a recognized cause of *S.aureus* and
19 15 Streptococcal pyoderma^{40,42}, affected 4% of our cohort. Streptococcal pyoderma
20 16 underlies most cases of RHD in the Northern Territory³⁹ and this was confirmed
21 17 echocardiographically in 2% of our Indigenous cohort. Similarly, the transmission of
22 18 respiratory pathogens is promoted by household crowding⁴³ and nearly 40% of
23 19 Indigenous adults were admitted previously with pneumonia. Environmental
24 20 contamination²⁴, inadequate sanitation and unhygienic food preparation areas²¹
25 21 contribute to infection with enteric pathogens and *S.stercoralis*. The risks of complicated
26 22 strongyloidiasis, crusted scabies⁴⁴ and bronchiectasis¹³ are further increased by HTLV-1
27 23 infection; however, no attempt has been made to control transmission of this virus among
28 24 Indigenous Australians. These effects are compounded by poor health literacy and
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2 Indigenous adults are less likely to engage with a conventional medical paradigm¹⁸.
4
5
6 3 Delays in seeking care for uncomplicated urinary tract infections may therefore
7
8 4 contribute to the very high gram negative BSI incidence rates reported here.
9
10 5

11
12 6 The retrospective design of this study results in a number of limitations. Firstly, only
13
14 7 limited demographic information is collected by ASH and the Indigenous population is
15
16 8 relatively mobile. Residents of remote communities, for example, frequently stay in town
17
18 9 camps and this is not recorded by ASH. The effect of town camp residence may therefore
19
20 10 be underestimated if large numbers of remote residents acquire infection during these
21
22 11 visits. Although foci of infection were determined by reviewing the results of
23
24 12 microbiology and imaging for each presentation, these varied between patients according
25
26 13 to the practice of the treating physician. The number of patients with concurrent bacterial
27
28 14 infections and medical conditions, such as RHD, may therefore be underestimated.
29
30 15 Similarly, seropositivity rates for infections, such as HBV and HTLV-1, could only be
31
32 16 determined for a subset of patients. A further limitation is the identification of NCDs and
33
34 17 previous infections using ICD-10 codes; however, coding errors are unlikely to vary
35
36 18 systematically according to ethnicity or place of residence. The use of ICD-10 codes
37
38 19 does, however, limit our ability to study factors that are more difficult to define and
39
40 20 which might also influence infection risk, such as nutrition and health literacy. Finally,
41
42 21 the present study has demonstrated an increased risk of infection and death associated
43
44 22 with town camp residence. This occurred despite better access to health care relative to
45
46 23 remote residents and little difference in crude measures of socioeconomic deprivation⁷.
47
48 24 For community-acquired BSIs, risk of death was strongly associated with NCDs;
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 however, these conditions did not fully account for the increased risk following a
4 nosocomial BSI. Unmeasured socioeconomic factors might contribute to increased
5 mortality among town camp residents; however, recent research linking health outcomes
6 to perceived racism⁴⁵ may also be relevant to this marginalized population.
7
8
9
10
11
12
13

14
15 The disease burden among the Indigenous population of central Australia is similar to
16 that of many developing countries where NCD prevalence rates are rising rapidly in a
17 setting of persistently high infection rates^{2,46}. Recently, the validity of conventional
18 health transition theory has been challenged by findings that infection-related
19 hospitalization rates are increasing among the most socially disadvantaged community
20 members in a developed country¹⁷. The present study provides a possible explanation for
21 this observation and further suggests that, in contrast to the orderly epidemiological
22 transition envisaged by Omran (1971)¹, life expectancy may fall where social deprivation
23 persists in the face of a rising prevalence of non-communicable diseases. High BSI
24 incidence rates among Indigenous Australians were associated with a heavy burden of
25 other infections that provide portals of entry for invasive bacterial disease. Improving life
26 expectancy in this setting will require public health initiatives to reduce pathogen
27 exposure in addition to controlling the burgeoning non-communicable disease burden.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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 crisis³⁷. However, our findings also illustrate the complexity
of interactions between communicable and non-communicable diseases and support calls

1
2
3 2 for an integrated approach to disease management ⁴⁷. The intimate association between
4
5
6 3 these conditions and human behaviour renders the empowerment of affected populations
7
8 4 to adopt protective health-related strategies critical to the success of any management
9
10 5 program ⁴⁷.
11
12
13 6
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **2 Contributions:**
4

5 LE designed the study, collected the data, assisted with statistical analysis and prepared
6 the manuscript, LF and SJ collected the data, AB assisted in manuscript preparation and
7
8 RW was responsible for statistical analysis and assisted in manuscript preparation.
9
10
11
12

13
14
15 **7 Acknowledgments:**
16

17 We wish to thank Dr S.Guthridge, Department of Health Gains Planning, Northern
18 Territory Government, for providing the population data.
19
20
21

22
23 **10 Conflict-of-interest** :_None reported
24

25
26 **11 Funding statement:**
27

28 This study received funding from the Northern Territory Rural Clinical School, which is
29 an initiative of the Australian Department of Health and Ageing.
30
31

32
33 **14 Data sharing:** Data relate to Indigenous Australians and cannot be shared without
34 specific approval from the relevant Indigenous communities and the responsible HREC.
35
36 Obtaining such approval will require detail of all individuals seeking access and each
37
38 research project for which the inclusion of this data is proposed.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (\pm SD)	44.7 \pm 15.2	57.5 \pm 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

1				
2				
3	Rheumatic heart disease	12 (2.0)	0 (0.0)	0.27
4				
5	Palliative care	10 (1.8)	5 (9.1)	0.001
6				
7				
8	Malignancy	13 (2.3)	11 (20.0)	<0.001
9				
10	IVDU	0 (0.0)	3 (5.5)	0.001
11				
12				
13	Community Acquired	510 (91.6)	49 (90.7)	0.84
14				
15	Primary focus of infection			
16				
17	No focus	250 (44.8)	20 (36.4)	0.37
18				
19	Pneumonia ^c	110 (19.7)	6 (10.9)	0.08
20				
21	Skin abscess	66 (11.8)	5 (9.1)	0.65
22				
23	Pyelonephritis ^d	63 (11.3)	5 (9.1)	0.56
24				
25	Other	53 (9.5)	18 (32.7)	<0.001
26				
27	Enteritis	15 (2.7)	1 (1.8)	0.71
28				
29	Bone/joint	1 (0.2)	0.0 (0.0)	0.61
30				
31				
32				
33				
34	Additional Infections^e			
35				
36	Acute bacterial infections	69 (12.4)	2 (3.6)	0.05
37				
38	Pneumonia	18 (3.2)	0 (0.0)	0.39
39				
40	Urinary tract	20 (3.6)	1 (1.8)	0.49
41				
42	Skin	27 (4.8)	1 (1.8)	0.31
43				
44	Enteritis	4 (0.7)	0	0.53
45				
46				
47				
48	Chronic Viral infections			
49				
50	HTLV-1 ^f	137 (45.2)	0 (0.0)	<0.001
51				
52	Hepatitis B virus ^f			
53				
54	HBsAg	49 (12.9)	1 (6.7)	0.70
55				
56				
57				
58				
59				
60				

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			
<i>Enterobacteriaceae</i>	370 (36.0)	38 (34.5)	0.56
<i>Escherichia coli</i>	246 (23.9)	28 (25.5)	0.37
<i>Klebsiella pneumoniae</i>	57 (5.54)	2 (1.82)	0.09
<i>Staphylococcus aureus</i>	191 (18.6)	20 (18.2)	0.83
MRSA	53 (5.15)	1 (0.91)	<0.001
<i>Streptococcus pneumoniae</i>	136 (13.2)	8 (5.88)	<0.001
<i>Streptococcus pyogenes</i>	68 (6.61)	8 (7.27)	0.42
<i>Haemophilus influenzae</i>	22 (2.14)	0	0.14
Enteric pathogens ^h	29 (2.81)	1 (0.91)	0.27

2 a. comorbidities determined from IC-10 discharge morbidity codes

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

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

- 1
2
3 2 d. Respiratory cultures performed for 150 Indigenous patients.
4
5
6 3 e. Urine cultures performed for 310 Indigenous patients.
7
8 4 e. Alternative bacterial pathogen isolated.
9
10 5 f. Indigenous patients tested: HTLV-1, 309; HBsAg, 388; HBcAb, 309; Strongyloides
11
12 6 stercoralis serology, 235. Denominators exclude 6 Indigenous patients with indeterminate
13
14 7 HTLV-1 Western blot results and 19 Indigenous patients with borderline Strongyloides
15
16 8 serology whose infective status could not be determined.
17
18 9 f. Major BSI pathogens responsible for all recorded episodes 2001-2007.
19
20 10 g. Includes Salmonella spp., Shigella spp., Campylobacter spp.
21
22 11 Abbreviations: CHB, chronic hepatitis B virus; HCV, hepatitis C virus; IVDU,
23
24 12 intravenous drug use.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

	n	<i>S.aureus</i>			<i>S.pneumonia</i>			<i>K.Pneumonia</i>			<i>E.Coli</i>		
		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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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
<i>Respiratory Tract</i>	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
<i>Skin/Soft Tissue</i>	154 (35.7)	7 (13.5)	0.001
<i>Infections</i>			
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
<i>Pyelonephritis</i>	77 (17.9)	4 (7.7)	0.06
<i>Bone/joint</i>	11 (2.6)	0 (0.0)	0.24
<i>Enteritis</i>	21 (4.9)	1 (1.9)	0.33
<i>Scabies</i>	14 (3.3)	0 (0.0)	0.19
<i>Other</i>	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	BSI (n=553)	Skin^b (n=470)	Pneumonia^c (n=443)
	Odds ratio	Odds ratio	Odds ratio	Odds ratio
	(95% CI)	(95% CI)	(95% CI)	(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)

1
2
3 a. Previous infections during 5 years prior to the final BSI in the study period. Adjusted
4
5 for other risk factors in table.
6

7
8 b. Excluding patients receiving haemodialysis.
9

10 c. Excluding patients receiving haemodialysis and those with bronchiectasis
11

12 Abbreviations: BSI, blood stream infections; CRF, chronic renal failure excluding
13 patients receiving haemodialysis.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

		Deaths		28 day survival		Long-term survival	
	n	(28 days)	(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							
<i>E.coli</i>	143	5	22	1.0		1.0	
<i>S.aureus</i>	83	7	18	2.7 (1.0-7.3)	0.05	1.8 (1.1-3.0)	0.03
<i>K.pneumoniae</i>	29	12	15	2.3 (0.7-7.5)	0.17	1.4 (0.7-2.7)	0.17
<i>S.pneumoniae</i>	67	5	17	13.4 (4.6-39.2)	<0.001	4.8 (2.5-9.5)	<0.001
<i>Other</i>	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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **References**

- 2 1. Omran A. A theory of the epidemiology of population change. *Milbank Mem*
3 *Fund Q.* 1971;49:509-538.
- 4 2. Maher D, Smeeth, L., Sekajugo, J. Health transition in Africa: practical policy
5 proposals for primary care. *Bull WHO.* 2010;88:943-948.
- 6 3. Gracey M, King, M. Indigenous Health part 1: determinants and disease patterns.
7 *Lancet.* 2009;374:65-75.
- 8 4. Frenk J, Bobadilla, JL., Sepulveda J., et al. Health transition in middle-income
9 countries: new challenges for health care. *Health Policy and Planning.*
10 1989;4(1):29-39.
- 11 5. Heuveline P, Guillot, M., Gwatkin, DR. The uneven tide of the health transition.
12 *Soc Sci Med.* 2002;55:313-322.
- 13 6. United Nations. *State of the World's Indigenous Peoples.* New York: The United
14 Nations Department of Economic and Social Affairs; 2009.
- 15 7. Australian Bureau of Statistics. *The health and welfare of Australia's Aboriginal*
16 *and Torres Strait Islander peoples.* Canberra; 2005.
- 17 8. Zhao Y, Dempsey, K. Causes of inequality in life expectancy between indigenous
18 and non-indigenous people in the Northern Territory, 1981-2000: a decomposition
19 study. *Med J Aust.* 2006;184:490-494.
- 20 9. Australian Bureau of Statistics. *The Health and Welfare of Australia's Aboriginal*
21 *and Torres Strait Islander Peoples.* Canberra: Australia; 2010.
22 www.censusdata.abs.gov.au/census_services/getproduct/census/2011/community
23 [profile/IARE701002?opendocument&navpos=230](http://www.censusdata.abs.gov.au/census_services/getproduct/census/2011/community)
- 24 10. Davis J, Cheng, AC., McMillan, M., et al. Sepsis in the tropical Top End of
25 Australia's Northern Territory: disease burden and impact on Indigenous
26 Australians. *Med J Aust.* 2011;194:519-524.
- 27 11. Einsiedel L, Woodman, RJ. Two Nations: racial disparities in bloodstream
28 infections recorded at Alice Springs Hospital, central Australia, 2001-2005. *Med J*
29 *Aust.* 2010;192:567-571.
- 30 12. O'Grady K, Taylor-Thompson, D., Chang, A., et al. Rates of radiologically
31 confirmed pneumonia as defined by the World Health Organisation in Norther
32 Territory Indigenous children. *Med J Aust.* 2010;192(10):592-595.
- 33 13. Einsiedel L, Fernandes, L., Spelman, T., et al. Bronchiectasis is associated with
34 Human T Lymphotropic Virus 1 infection in an Indigenous Australian population.
35 *Clin Infect Dis.* 2012;54(1):43-50.
- 36 14. Einsiedel L, Fernandes, L., Woodman, R. . Racial disparities in infection-related
37 mortality at Alice Springs Hospital, central Australia, 2000-2005. *Med J Aust.*
38 2008;188:568-571.
- 39 15. Kway M, Rose, CE., Fry, AM., et al. The influence of chronic illness on the
40 incidence of invasive pneumococcal disease in adults. *Clin Infect Dis.*
41 2005;192:377-386.
- 42 16. Joshi N, Caputo, GM., Weitekamp, MR., et al. Infections in diabetic patients. *N.*
43 *Engl. J. Med.* 1999;341(25):1906-1912.

- 1 17. Baker M, Barnard, LT., Kvalsvig, A., et al. Increasing incidence of serious
2 infectious diseases and inequalities in New Zealand: a national epidemiological
3 study. *Lancet*. 2012;379:1112-1119.
- 4 18. Einsiedel L, van Iersel, E., Macnamara, R., et al. Self-Discharge by adult
5 Aboriginal patients at Alice Springs Hospital, central Australia: insights from a
6 prospective cohort study. *Aust Health Rev*. 2012.
- 7 19. Australian Bureau of Statistics. *2011 Census of population and Housing.*
8 *Aboriginal and Torres Strait Islander (Indigenous) Profile*. Canberra; 2013.
9 2002.0.
10 www.abs.gov.au/AUSSTATS/abs@.nsf/lookup/4704.0Chapter218Oct+2010
- 11 20. Skov S, Chikrizhs, TN., Li SQ., et al. How much is too much? Alcohol
12 consumption and related harm in the Northern Territory. *Med J Aust*.
13 1010;193:269-272.
- 14 21. Bailie R, Runcie, MJ. Household infrastructure in Aboriginal communities and
15 the implications fro health improvement. *Med J Aust*. 2001;175:363-366.
- 16 22. Anaya J. *Report of the Special Rapporteur on the situation of human rights and*
17 *fundamental freedoms of indigenous peoples, James Anaya, on the situation of*
18 *indigenous people in Australia*. United Nations; 2010.
- 19 23. d'Espaignet E, Kennedy, K., Paterson, B., et al. *Health Status in the Northern*
20 *Territory 1998*. Darwin: Epidemiology, Primary Care and Coordinated Care
21 Branch;1998.
- 22 24. McDonald E, Bailie, R., Grace, J., et al. An ecological approach to health
23 promotion in remote Australian Aboriginal communities. *Health Promotion*
24 *International*. 2010;25(1):42-53.
- 25 25. O'Brien J, Lu, B., Ali, NA., Martin, GS., et al. Alcohol dependence is
26 independently associated with sepsis, septic shock and hospital mortality among
27 adult intensive care unit patients. *Crit. Care Med*. 2007;35(2):345-350.
- 28 26. Laupland K, Gregson, DB., Zygun, DA., Doig, CJ., et al. Severe blood stream
29 infections: a population-based assessment. *Crit Care Med*. 2004;32:992-997.
- 30 27. Nuori J, Butler, JC., Farley, MM., Harrison, LH., et al. Cigarette smoking and
31 invasive pneumococcal disease. *N Engl J Med*. 2000;342:681-689.
- 32 28. Dopirak M, Hill, C., Oleksiw, M., Dumigan, D., et al. Surveillance of
33 hemodialysis-associated primary bloodstream infections: the experience of ten
34 hospital-based centers. *Infect Control Hosp Epidemiol*. 2002;23:721-724.
- 35 29. Zhao Y, Connors, C., Wright, J., et al. Estimating chronic disease prevalence
36 among the remote Aboriginal population of the Northern Territory using multiple
37 data sources. *Aust NZ J Public Health*. 2008;32:307-313.
- 38 30. Hoy W, Davey, RL., Sharma, S., Hoy, PW., et al. Chronic disease profiles in
39 remote Aboriginal settings and implications for health services planning. *Aust NZ*
40 *J Public Health*. 2010;34:11-18.
- 41 31. Moberley S, Krause, V., Cook, H., Mulholland, K., et al. Failure to vaccinate of
42 failure of vaccine? Effectiveness of the 23-valent pneumococcal polysaccharide
43 vaccine program in Indigenous adults in the Northern Territory of Australia.
44 *Vaccine*. 2010;28:2296-2301.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 1 32. Flory J, Joffe, M., Fishman, NO., Edelstein, PH., et al. Socioeconomic risk factors
2 for bacteraemic pneumococcal pneumonia in adults. *Epidemiol Infect.*
3 2009;137:717-726.
- 4 33. Tong S, Bishop, E., Lilliebridge, R., Cheng, A., et al. Community Associated
5 strains of Methicillin-Resistant Staphylococcus aureus and Methicillin-
6 Susceptible S.aureus in Indigenous Northern Australia: Epidemiology and
7 Outcomes. *J Infect Dis.* 2009;199:1461-1470.
- 8 34. Huggan P, Wells, JE., Browne, M., Richardson, A., et al. Population-based
9 epidemiology of Staphylococcus aureus bloodstream infection in Canterbury,
10 New Zealand. *Int Med J.* 2010;40:117-125.
- 11 35. Bagger J, Zindrou, D., Taylor, KM. Post-operative infection with Methicillin-
12 resistant Staphylococcus aureus and socioeconomic background. *Lancet.*
13 2004;363:706-708.
- 14 36. Marmot M, Friel, S., Bell, R., Houweling, T., et al. Closing the gap in a
15 generation: health equity through action on the social determinants of health.
16 *Lancet.* 2008;372(November 8):1661-1669.
- 17 37. Beaglehole R, Bonita, R., Horton, R., Adams, C., et al for the Lancet NCD action
18 group and the NCD alliance. Priority actions for the non-communicable disease
19 crisis. *Lancet.* 2011;377:1438-1447.
- 20 38. Bailie R, Stevens, MR., McDonald, E., Halpin, S., et al. Skin infection, housing
21 and social circumstances in children living in remote Indigenous communities:
22 testing conceptual and methodological approaches. *BMC public health.* 2005;5.
- 23 39. McDonald M, Towers, RJ., Andrews, RM., Bengler, N., et al. Low rates of
24 streptococcal pharyngitis and high rates of pyoderma in Australian Aboriginal
25 communities where acute rheumatic fever is hyperendemic. *Clin Infect Dis.*
26 2006;43:683-689.
- 27 40. Currie B, Carapetis, JR. Skin infections and infestations in Aboriginal
28 communities in northern Australia. *Aust J Dermatol.* 2000;41:139-145.
- 29 41. Hewagama S, Spelman, T., Einsiedel, L. Staphylococcus aureus bacteraemia at
30 Alice Springs Hospital, central Australia, 2003-2006. *Int Med J.* 2012;42:505-
31 512.
- 32 42. Carapetis J, Wolff, DR., Currie, BJ. Acute rheumatic fever and rheumatic heart
33 disease in the Top End of Australia's Northern Territory. *Med J Aust.* 1996;164(5
34 February):146-149.
- 35 43. Jacoby P, Carvillo, K., Hall, S., Riley, T., et al. Crowding and other strong
36 predictors of upper respiratory carriage of otitis media related bacteria in
37 Australian Aboriginal and non-Aboriginal children. *Paed Inf Dis J.*
38 2011;30(6):480-485.
- 39 44. Verdonck K, Gonzalez, E., Van Dooren, S., Vandamme, A., et al. Human T-
40 lymphotropic virus 1: recent knowledge about an ancient infection. *Lancet Infect*
41 *Dis.* 2007;7:266-281.
- 42 45. Priest N, Paradies, Y., Stevens, M., Bailie, R. Exploring relationships between
43 racism, housing and child illness in remote indigenous communities. *J Epidemiol*
44 *Community Health* 2012;66:440-447.
- 45 46. Boutayeb A, Boutayeb, B. The burden of non-communicable diseases in
46 developing countries. *int J Equity in Health.* 2005;4(1):2.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 1 47. De Maeseneer J, Roberts RG, Demarzo M, et al. Tackling NCDs: a different
2 approach is needed. *The Lancet*. 2012;379(9829):1860-1861.
3
4

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 | ~~The a~~ Association of non-communicable diseases, ~~with blood stream~~
3 | infection ~~incidence~~ and survival in a retrospective cohort of ~~I~~indigenous and
4 | non-Indigenous ~~adults in central Australia in central Australians~~.

6 | Lloyd Einsiedel¹, Liselle Fernandes¹, Sheela Joseph¹, Alex Brown² and

7 | Richard J Woodman¹

10 | (1) Flinders University/Northern Territory Rural Clinical School, Alice Springs Hospital, 0870,
11 | Northern Territory, Australia

12 | (2) Head, Centre for Indigenous Vascular Research, Baker IDI Heart and Diabetes
13 | Institute, Alice Springs Hospital, 0870, Northern Territory, Australia.

15 | § Corresponding author:

16 | Lloyd Einsiedel. Alice Springs Hospital, Department of Medicine, Darwin, Northern
17 | Territory, Australia. Tel: + 61 08 89519607, Fax: + 61 08 89538385, E-mail:
18 | lloyd.einsiedel@health.sa.gov.au

20 | Running title: Infection risk in Indigenous Australians

21 | Keywords: ~~—Epidemiologic transition~~Non-communicable diseases, [diabetes](#), [alcohol](#),

22 | [i](#)nfection, Indigenous [h](#)Health, Australia

2

2 Word count:

3 Abstract: 293

4 Text: ~~3758491~~

5 References: ~~470~~

6 Conflict-of-interest : None reported

7 Funding statement:

8 This study received funding from the Northern Territory Rural Clinical School, which is
9 an initiative of the Australian Department of Health and Ageing.

2 Abstract

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

6 Design: Pathology, imaging and discharge morbidity codes were retrospectively reviewed
7 for a period of 5 years prior to admission with a blood stream infection (BSI), 1st January
8 2003 to 30th June 2007.

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

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

13 Results: Mean annual BSI incidence rates were far higher among Indigenous residents
14 (Indigenous, 93770 per 100,000; non-Indigenous, 6448 per 100,000 person-years;
15 IRR=14.620.33; 95% CI=14.6120.31-14.6520.35, $p<0.001$). Indigenous patients were
16 also more likely to have previous bacterial infections (68.7% versus 34.6%; respectively,
17 $p<0.001$), diabetes (44.3% versus 20.0%; $p<0.001$), harmful alcohol consumption (37.0%
18 versus 12.7%; $p<0.001$) and other communicable diseases (HTLV-1, 45.2%;
19 strongyloidiasis, 36.1%; HBV, 12.9%). Among Indigenous patients, diabetes increased
20 odds of current *Staphylococcus aureus* BSI (OR=1.6, 95% CI=1.0-2.5) and prior skin
21 infections (adjusted OR=2.1, 95% CI=1.4-3.3). Harmful alcohol consumption increased
22 odds of current *Streptococcus pneumoniae* BSI (OR=1.57, 95% CI=1.02-2.40) and of
23 previous BSI (OR=1.7, 95% CI=1.1-2.5), skin infection (OR=1.7, 95% CI=1.1-2.6) or
24 pneumonia (OR=4.3, 95% CI=2.8-6.7). Twenty-six percent of Indigenous patients died

1
2
3
4
5
6
7
8 at a mean (SD) age of 47±15 years. Complications of diabetes and harmful alcohol
9
10 consumption predicted 28-day mortality (non-rheumatic heart disease, HR=2.9; 95%
11
12 CI=1.4-6.2; chronic renal failure, HR=2.6, 95%CI=1.0-6.5; chronic liver disease,
13
14 HR=3.3, 95%_CI=1.6-6.7).
15
16 Conclusion: In a socially disadvantaged population undergoing a rapid epidemiologic
17
18 transition, NCDs are associated with an further-increased risk of infection-risk of
19
20 infection and BSI related mortality. Complex interactions between communicable
21
22 diseases and NCDs demand an integrated approach to management, which must include
23
24 the empowerment of affected populations to promote behavioural change.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

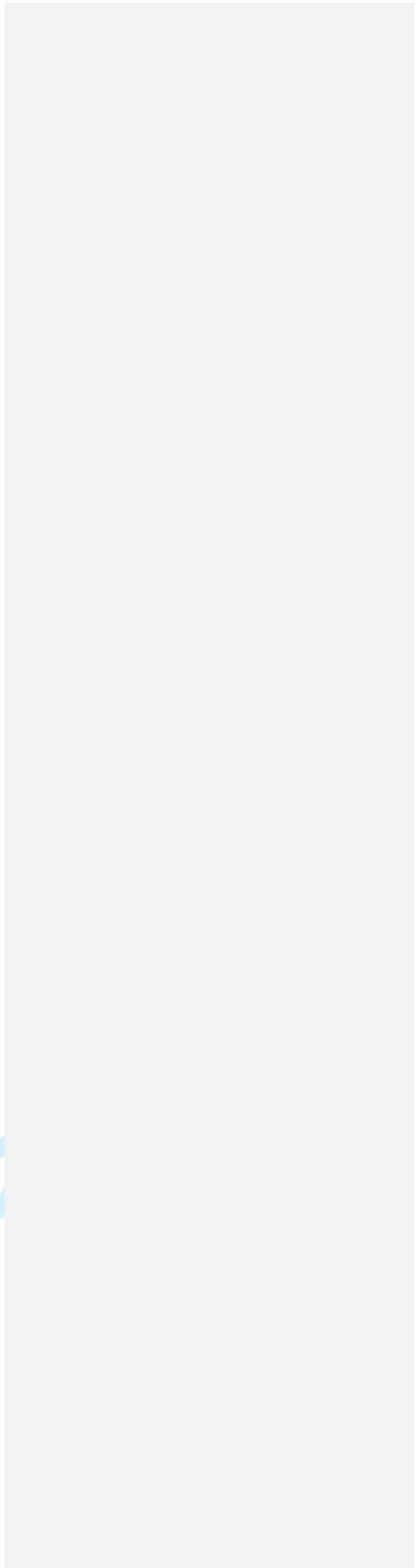
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

6

2 material on which our analysis is based.

3

For peer review only



2 Introduction

3 Complex interactions between the demographic, economic and sociologic determinants
4 of disease result in changing patterns of health and disease over time¹. The development
5 of modern social and economic structures, for example, has been ~~is~~ associated with a
6 reduction in infectious diseases and nutritional deficiencies and a corresponding rise in
7 non-communicable diseases (NCDs) that are associated with ~~due to~~ ageing and ~~lifestyle~~
8 factors¹. In many developing countries ~~The~~ rapidity of this ~~phenomenon has been~~
9 termed the 'epidemiologic transition' (Omran) ~~has resulted in a~~ -In developing countries,
10 rapid demographic change has dramatic ~~been associated with marked increases in~~ NCD
11 the pPrevalence rates ~~of of~~ non-communicable diseases (NCDs), such as diabetes,
12 among ~~in~~ populations that have with a substantial pre-existing infectious disease ~~are rising~~
13 rapidly in developing countries, adding to a pre-existing burden of infectious diseases in
14 populations that are undergoing rapid demographic changes^{2,3}. This phenomenon
15 proceeds at different rates according to the socioeconomic status of particular sub-groups
16 within a given population and may reinforce established health inequalities^{4,5}.

17
18 Among Indigenous people, forced displacement, the collapse of Indigenous economies
19 and the destruction of socio-political structures have been the shared experience of
20 colonization⁶. Indigenous people living within developed countries continue to live in
21 poverty and experience a 'protracted' epidemiologic transition⁴ that is associated with a
22 double burden of communicable and non-communicable diseases^{7,8} similar to that of
23 many developing countries². A similar double burden of communicable and non-
24 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 mortality⁸ and to a life expectancy that remains ~~147~~ years less ~~for Indigenous Australian men relative to than that of~~ their non-Indigenous peers⁹. ~~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 sepsis¹⁰, blood stream infections¹¹ and childhood pneumonia¹² ~~(ref)~~, and prevalence rates of bronchiectasis¹³ 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 common¹¹. 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 years¹⁴.

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 communities¹¹. 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

1
2
3
4
5
6
7
8
9 2 description in New Zealand of an increasing divergence in infection-related
10 3 hospitalization rates according to social status is consistent with this possibility and
11 4 challenges health transition theory¹⁷.

12
13
14
15
16 6 Central Australia is well placed to study interactions between poverty, NCDs and
17 7 infectious diseases. Most Indigenous residents live in remote communities in conditions
18 8 of considerable socio-economic disadvantage, leaving a minority within the major
19 9 regional township of Alice Springs. The latter have ready access to a well-resourced
20 10 medical facility, Alice Springs Hospital (ASH), which has sophisticated diagnostic
21 11 capabilities and provides specialist medical care to a region of 1,000,000 km². Indigenous
22 12 residents of Alice Springs dwell in either overcrowded 'town camps', which have poor
23 13 amenities and limited refuse disposal, or are integrated with the majority of the non-
24 14 Indigenous population within the township's suburbs. Indigenous adults living in town
25 15 camps and remote communities are often unemployed, have limited education (ABS) and
26 16 poor health literacy¹⁸ (ref). ~~A~~For example, among Indigenous adult residents of town
27 17 camps, nearly half 60% have less than 8 years or less of schooling, labour participation
28 18 rates are less than 20% and only 12% are employed¹⁹ (ABS 2013). ~~Despite an extremely
29 19 complex regulatory framework and numerous a variety of Government
30 20 attempts interventions to minimize risk, harmful alcohol consumption in this setting
31 21 remains common²⁰ (ref).~~

32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49 23 The Indigenous population of central Australia~~this region~~ also has among the highest
50 24 blood stream infection incidence rates reported¹¹. Living conditions that increase the risk
51
52
53
54
55
56
57
58
59
60

10

1
2
3
4
5
6
7
8 of pathogen exposure ²¹(ref) and high background rates of focal infections, which provide
9 portals of entry for bacterial invasion, are likely to precede these life-threatening
10 infections. Blood stream infection incidence rates therefore provide measurable end-
11 points to which environmental and host factors contribute.
12
13
14
15
16
17

18 Here we report the infectious and non-communicable disease burden among community
19 residents of central Australia who presented with a blood stream infection and determine
20 risk factors for infection and death after stratifying by ethnicity.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 **Methods**

3 We conducted a retrospective review of all positive blood cultures collected from adult
4 patients (age \geq 15 years) admitted to ASH between 1st January 2001 and 31st June 2007. In
5 July 2007 the Australian Federal Government suspended racial discrimination legislation
6 and implemented an 'Emergency Response' that resulted in considerable uncertainty
7 among Indigenous residents²². This raised concerns that the central Australian resident
8 population could change as people moved interstate to escape these restrictions and no
9 data was collected after this date. Data collected included organism, ethnicity, dates of
10 birth, dates of death, indigenous status and place of residence. For patients who presented
11 between 1st January 2003 and 31st June 2007 we also obtained ICD 10 morbidity codes
12 and the results of microbiological and radiological investigations for each admission for 5
13 years prior to the final BSI presentation. NCDs were derived from ICD-10 morbidity
14 codes for diabetes, harmful alcohol consumption, >stage 2 chronic kidney disease,
15 ischaemic heart disease, chronic liver disease and malignancy. Bronchiectasis was
16 diagnosed radiologically using American College of Chest Physician criteria. Heart
17 failure and valvular heart disease, including rheumatic heart disease (RHD), were
18 diagnosed by trans-thoracic echocardiography. Ischaemic heart disease and cardiac
19 failure were combined ('non-rheumatic heart disease') for statistical analysis.

21 *Definitions*

22 Residence

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

1
2
3
4
5
6
7
8
9 2 Nursing home residents were included in calculations of BSI incidence rates, but
10 3 excluded from further analysis because the primary study objective was to determine risk
11 4 factors for infection and death among community residents.
12
13

14 5 15 6 Infections

17 7 A blood culture from which a pathogen was isolated was defined as a 'BSI episode'.
18 8 Repeated culture of the same organism from blood culture was regarded as a separate
19 9 'episode' only if blood samples were drawn more than one month apart. Blood stream
20 10 infections were defined as community-acquired if a pathogen was isolated from blood
21 11 cultures drawn within 48 hours of admission and nosocomial if isolated from blood
22 12 cultures drawn after this time. Foci of infection were determined where possible from
23 13 ICD-10 morbidity codes in association with pathology and imaging results for each
24 14 admission for five years prior to the final BSI during the study period. A diagnosis of
25 15 pneumonia was made if there was radiological evidence of consolidation and this was
26 16 attributed to the pathogen isolated from blood cultures if the same organism was also
27 17 isolated from sputum or the blood culture isolate was an organism typically associated
28 18 with pneumonia, such as *Streptococcus pneumoniae*. Blood stream infections excluded
29 19 infections with potential contaminants including coagulase negative staphylococci,
30 20 bacillus spp., coryneforms and viridans streptococci unless grown from more than one
31 21 BC in a 24 hour period, as were *Acinetobacter sp* in the absence of an identifiable focus.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 Yankunytjara (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).

2

3 **Results**

4 *Patient demographics*

5 558 Indigenous and 55 non-indigenous adult community residents presented to ASH with
6 a BSI between January 2003 and July 2007. Detailed demographic, clinical and
7 microbiological data are described in Table 1. Indigenous patients were younger
8 (Indigenous, 44.7±15.2; non-Indigenous, 57.5±21.1; p<0.001), more likely to be female
9 (Indigenous, 58.1%; non-Indigenous, 41.8%; p<0.03) and to live in a town camp or
10 remote community (Indigenous, 84.0%; non-Indigenous, 0; p<0.001). Non-
11 communicable diseases including diabetes (Indigenous, 44.3%; non-Indigenous, 20.0%;
12 p<0.001) and harmful alcohol consumption (Indigenous, 37.0%; non-Indigenous, 12.7%;
13 p<0.001) were more common among Indigenous patients, while non-Indigenous patients
14 were more likely to have ischaemic heart disease (Indigenous, 3.4%; non-Indigenous,
15 31.6%; p<0.001), malignancy (Indigenous, 2.3%; non-Indigenous, 20.0%; p<0.001), to
16 be receiving palliative care (Indigenous, 1.8%; non-Indigenous, 9.1%; p=0.001) and to
17 have a history of intravenous drug use (Indigenous, 0; non-Indigenous, 5.5%; p=0.001).
18 Forty-seven (8.4%) Indigenous and 5 (9.3%) non-indigenous BSI episodes were
19 nosocomial (Table 1).

20

21 *Population-based incidence rates 2001-2006*

22 ~~The overall population based BSI incidence rate for the Alice Springs area between 2001~~
23 ~~and 2006 was more than 20 times higher for Indigenous adults (970 per 100,000 person-~~
24 ~~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=14.62, 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 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).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

11 *Concurrent infections*

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

18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

19 *Previous infections*

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

1
2
3
4
5
6
7
8 previous BSI, skin abscesses and wound infections (Table 3). Predisposing factors for
9 previous infection-related admissions included diabetes (previous skin infections),
10 harmful alcohol consumption (previous skin infections, pneumonia and BSI) and stage 3-
11 4 chronic kidney disease (any previous infection) (Table 4).
12
13
14
15

16 6

17 7 *Mortality*

18 8 *28 day mortality*

19 Overall 28-day mortality rates following a BSI were 11.7% and 11.4% for Indigenous
20 and non-Indigenous adults, respectively. Mortality rates among Indigenous patients were
21 highest for town camp residents (Fig 2) and varied according to pathogen. Among the
22 major pathogens causing BSI, most often fatal within the first 28 days was *K.pneumoniae*
23 infection (40.0%) followed by *S.pneumoniae* (9.6%) *S.aureus* (8.0%), and *E.coli* (5.0%)
24 ($\chi^2=39.1$, 4df; $p<0.001$). Case fatality rates according to focus of infection were
25 pneumonia (21.5%), pyelonephritis (8.9%) and skin infections (7.2%) ($\chi^2=14.5$, 3df;
26 $p=0.002$).
27
28
29
30
31
32
33
34
35
36
37
38

39 18 *I. Community-acquired BSI amongst Indigenous patients*

40 Non-communicable diseases including chronic liver disease, non-rheumatic heart disease
41 and chronic kidney disease were independent predictors of death (Table 5). Relative to
42 patients with *E.coli* BSI, both *S.aureus* (HR=2.7, 95% CI=1.0-7.3; $p=0.05$) and
43 *S.pneumoniae* (HR=13.4, 95% CI=4.6-39.2; $p<0.001$) were independently associated
44 with an increased risk of death (Table 5).
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 \pm 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 $\chi^2=5.05$, $p=0.08$) (Fig 2).

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

9
10 There were no independent predictors of long-term mortality for non-Indigenous patients
11 with community acquired infections and too few non-indigenous patients with
12 nosocomial BSI's (n=5) to perform long-term survival analysis.

13

2

3 Discussion

4 The Indigenous adult population of central Australia has among the highest BSI
5 incidence rates worldwide. Relative to their non-Indigenous peers, rates for Indigenous
6 adults were ~~nearly 15420-~~fold higher overall and ~~470-fold-fold~~ higher among Indigenous
7 town camp residents. A high burden of other infections, particularly repeated respiratory
8 and skin infections, provide portals of entry for life-threatening invasive bacterial disease.
9 Nearly 70% of Indigenous patients required admission for an acute infection in the
10 preceding five years, 24.4% experienced a prior BSI and a second unrelated bacterial
11 infection was found in 12.4% of patients. Chronic viral and parasitic infections were also
12 common. Among Indigenous adults who were tested, more than 60% had been infected
13 with Hepatitis B virus, 13% remained HBsAg positive, nearly half were HTLV-1
14 seropositive and 36% were *S.stercoralis* seropositive. A similar burden of infection is
15 experienced by Indigenous children amongst whom frequent co-infection with bacterial
16 pathogens and parasites²³ contributes to 'failure-to-thrive'²⁴. In our adult cohort, 26.0%
17 of Indigenous patients died during the study period at a mean age of only 47 years.
18 Although we were unable to attribute cause of death in the present study, 60% of
19 Indigenous deaths at ASH are infection-related¹⁴.

20

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 common among patients with diabetes¹⁵, chronic lung disease¹⁵ and alcohol dependence
3 ^{15,27}, respectively. Alcohol dependence and diabetes also increase risk of a BSI requiring
4 intensive care nearly six-fold and haemodialysis increases risk several hundred fold ²⁶,
5 largely due to prolonged central venous access ²⁸. In the present study, rates of diabetes
6 among Indigenous adults were nearly three times reported background rates ²⁹. Diabetes
7 was associated with *S.aureus* BSI and with previous skin infections, but not with
8 *S.pneumoniae* BSI. Stage 3-4 chronic kidney disease, which is most often a complication
9 of diabetes in our patient population³⁰, was associated with any previous infection.
10 Harmful alcohol consumption was associated with *S.pneumoniae* BSI and with previous
11 infection-related admissions. Non-communicable diseases, including non-rheumatic heart
12 disease, chronic kidney disease and chronic liver disease, were also major predictors of
13 mortality after a BSI. However, once invasive infections were established, *S.aureus* and
14 *S.pneumoniae* predicted death independently of any underlying medical condition.

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

admissions in New Zealand are associated with social deprivation¹⁷. 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 risk³⁸. In some Indigenous Australian communities the average number of people living per house is 17³⁹ and non-functioning health hardware leads to environmental conditions that are detrimental to householders²¹. Overcrowded housing⁴⁰ and an inability to maintain adequate skin hygiene²¹ 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 population⁴¹. 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 Territory³⁹ and this was confirmed echocardiographically in 2% of our Indigenous cohort. Similarly, the transmission of respiratory pathogens is promoted by household crowding⁴³ and nearly 40% of Indigenous adults were admitted previously with pneumonia. Environmental contamination²⁴, inadequate sanitation and unhygienic food preparation areas²¹ contribute to infection with enteric pathogens and *S.stercoralis*. The risks of complicated strongyloidiasis, crusted scabies⁴⁴ and bronchiectasis¹³ 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~~ 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

1
2
3
4
5
6
7
8
9 2 remote residents and little difference in crude measures of socioeconomic deprivation⁷.
10 3 For community-acquired BSIs, risk of death was strongly associated with NCDs;
11 4 however, these conditions did not fully account for the increased risk following a
12 5 nosocomial BSI. Unmeasured socioeconomic factors might contribute to increased
13 6 mortality among town camp residents; however, recent research linking health outcomes
14 7 to perceived racism⁴⁵ may also be relevant to this marginalized population.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

9 The disease burden among the Indigenous population of central Australia is similar to
10 that of many developing countries where NCD prevalence rates are rising rapidly in a
11 setting of persistently high infection rates^{2,46}. Recently, the validity of conventional
12 health transition theory has been challenged by findings that infection-related
13 hospitalization rates are increasing among the most socially disadvantaged community
14 members in a developed country¹⁷. The present study provides a possible explanation for
15 this observation and further suggests that, in contrast to the orderly epidemiological
16 transition envisaged by Omran (1971)¹, life expectancy may fall where social deprivation
17 persists in the face of a rising prevalence of non-communicable diseases. High BSI
18 incidence rates among Indigenous Australians were associated with a heavy burden of
19 other infections that provide portals of entry for invasive bacterial disease. Improving life
20 expectancy in this setting will require public health initiatives to reduce pathogen
21 exposure in addition to controlling the burgeoning non-communicable disease burden.
22 Diabetes, harmful alcohol consumption and organ damage resulting from these conditions
23 increased both the likelihood of infection and the subsequent risk of death. Both
24 conditions are included in proposed international management strategies to control the

1
2
3
4
5
6
7
8
9 2 non-communicable disease crisis³⁷. However, our findings also illustrate the complexity
10 3 of interactions between communicable and non-communicable diseases and support calls
11 4 for an integrated approach to disease management⁴⁷. The intimate association between
12 5 these conditions and human behaviour renders, ~~which must include~~ the empowerment of
13 6 affected populations to adopt protective health-related strategies behaviours critical to the
14 7 success of any management program that reduce risk⁴⁷. ~~(National Aboriginal Health~~
15 8 ~~Strategy)~~, ~~which must include the empowerment of affected populations to promote~~
16 9 behavioural change⁴⁰.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2 **Contributions:**

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

7 **Acknowledgments:**

8 We wish to thank Dr S.Guthridge, Department of Health Gains Planning, Northern
9 Territory Government, for providing the population data.

2 Table 1 Demographics and comorbidities for indigenous and non-indigenous BSI patients
3 2003-2007.

	Indigenous (n=558)	Non- indigenous (n=55)	p-value for difference
Age, yrs (\pm SD)	44.7 \pm 15.2	57.5 \pm 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

28

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	
<i>Enterobacteriaceae</i>	370 (36.0)	38 (34.5)	0.56
<i>Escherichia coli</i>	246 (23.9)	28 (25.5)	0.37
<i>Klebsiella pneumoniae</i>	57 (5.54)	2 (1.82)	0.09
<i>Staphylococcus aureus</i>	191 (18.6)	20 (18.2)	0.83
MRSA	53 (5.15)	1 (0.91)	<0.001
<i>Streptococcus pneumoniae</i>	136 (13.2)	8 (5.88)	<0.001
<i>Streptococcus pyogenes</i>	68 (6.61)	8 (7.27)	0.42
<i>Haemophilus influenzae</i>	22 (2.14)	0	0.14
Enteric pathogens ^h	29 (2.81)	1 (0.91)	0.27

2 a. comorbidities determined from IC-10 discharge morbidity codes

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

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

- 1
2
3
4
5
6
7
8
9 2 d. Respiratory cultures performed for 150 Indigenous patients.
10
11 3 e. Urine cultures performed for 310 Indigenous patients.
12
13 4 e. Alternative bacterial pathogen isolated.
14
15 5 f. Indigenous patients tested: HTLV-1, 309; HBsAg, 388; HBcAb, 309; Strongyloides
16
17 6 stercoralis serology, 235. Denominators exclude 6 Indigenous patients with indeterminate
18
19 7 HTLV-1 Western blot results and 19 Indigenous patients with borderline Strongyloides
20
21 8 serology whose infective status could not be determined.
22
23 9 f. Major BSI pathogens responsible for all recorded episodes 2001-2007.
24
25 10 g. Includes Salmonella spp., Shigella spp., Campylobacter spp.
26
27 11 Abbreviations: CHB, chronic hepatitis B virus; HCV, hepatitis C virus; IVDU,
28
29 12 intravenous drug use.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

	n	<i>S.aureus</i>			<i>S.pneumonia</i>			<i>K.Pneumonia</i>			<i>E.Coli</i>		
		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

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
<i>Respiratory Tract</i>	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
<i>Skin/Soft Tissue</i>	154 (35.7)	7 (13.5)	0.001
<i>Infections</i>			
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
<i>Pyelonephritis</i>	77 (17.9)	4 (7.7)	0.06
<i>Bone/joint</i>	11 (2.6)	0 (0.0)	0.24
<i>Enteritis</i>	21 (4.9)	1 (1.9)	0.33
<i>Scabies</i>	14 (3.3)	0 (0.0)	0.19
<i>Other</i>	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	BSI (n=553)	Skin^b (n=470)	Pneumonia^c (n=443)
	Odds ratio	Odds ratio	Odds ratio	Odds ratio
	(95% CI)	(95% CI)	(95% CI)	(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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

For peer review only

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.

	n	Deaths		28 day survival		Long-term survival	
		(28 days)	(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							
<i>E.coli</i>	143	5	22	1.0		1.0	
<i>S.aureus</i>	83	7	18	2.7 (1.0-7.3)	0.05	1.8 (1.1-3.0)	0.03
<i>K.pneumoniae</i>	29	12	15	2.3 (0.7-7.5)	0.17	1.4 (0.7-2.7)	0.17
<i>S.pneumoniae</i>	67	5	17	13.4 (4.6-39.2)	<0.001	4.8 (2.5-9.5)	<0.001
<i>Other</i>	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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 References

- 2 1. Omran A. A theory of the epidemiology of population change. *Milbank Mem*
3 *Fund Q.* 1971;49:509-538.
- 4 2. Maher D, Smeeth, L., Sekajugo, J. Health transition in Africa: practical policy
5 proposals for primary care. *Bull WHO.* 2010;88:943-948.
- 6 3. Gracey M, King, M. Indigenous Health part 1: determinants and disease patterns.
7 *Lancet.* 2009;374:65-75.
- 8 4. Frenk J, Bobadilla, JL., Sepulveda J., Cervantes, ML. Health transition in middle-
9 income countries: new challenges for health care. *Health Policy and Planning.*
10 1989;4(1):29-39.
- 11 5. Heuveline P, Guillot, M., Gwatkin, DR. The uneven tide of the health transition.
12 *Soc Sci Med.* 2002;55:313-322.
- 13 6. [United Nations.](#) *State of the World's Indigenous Peoples.* New York: The United
14 Nations Department of Economic and Social Affairs; 2009.
- 15 7. [Australian Bureau of Statistics.](#) *The health and welfare of Australia's Aboriginal*
16 *and Torres Strait Islander peoples.* Canberra; 2005.
- 17 8. Zhao Y, Dempsey, K. Causes of inequality in life expectancy between indigenous
18 and non-indigenous people in the Northern Territory, 1981-2000: a decomposition
19 study. *Med J Aust.* 2006;184:490-494.
- 20 9. [Australian Bureau of Statistics.](#) *The Health and Welfare of Australia's Aboriginal*
21 *and Torres Strait Islander Peoples.* Canberra: Australia; 2010.
22 www.censusdata.abs.gov.au/census_services/getproduct/census/2011/community
23 [profile/IARE701002?opendocument&navpos=230](http://www.censusdata.abs.gov.au/census_services/getproduct/census/2011/community)
- 24 10. Davis J, Cheng, AC., McMillan, M., Humphrey, AB., Stephens, DP., Anstey,
25 NM. Sepsis in the tropical Top End of Australia's Northern Territory: disease
26 burden and impact on Indigenous Australians. *Med J Aust.* 2011;194:519-524.
- 27 11. Einsiedel L, Woodman, RJ. Two Nations: racial disparities in bloodstream
28 infections recorded at Alice Springs Hospital, central Australia, 2001-2005. *Med J*
29 *Aust.* 2010;192:567-571.
- 30 12. O'Grady K, Taylor-Thompson, D., Chang, A., Torzillo, P., Morris, P., Mackenzie,
31 G., Wheaton, G., Bauert, P., De Campo, M., De Campo, J., Ruben, A. Rates of
32 radiologically confirmed pneumonia as defined by the World Health Organisation
33 in Northern Territory Indigenous children. *Med J Aust.* 2010;192(10):592-595.
- 34 13. Einsiedel L, Fernandes, L., Spelman, T., Steinfort, D., Gotuzzo, E. Bronchiectasis
35 is associated with Human T Lymphotropic Virus 1 infection in an Indigenous
36 Australian population. *Clin Infect Dis.* 2012;54(1):43-50.
- 37 14. Einsiedel L, Fernandes, L., Woodman, R. . Racial disparities in infection-related
38 mortality at Alice Springs Hospital, central Australia, 2000-2005. *Med J Aust.*
39 2008;188:568-571.
- 40 15. Kway M, Rose, CE., Fry, AM., Singleton, JA., Moore, Z., Zell, ER., Whitney,
41 CG. The influence of chronic illness on the incidence of invasive pneumococcal
42 disease in adults. *Clin Infect Dis.* 2005;192:377-386.
- 43 16. Joshi N, Caputo, GM., Weitekamp, MR., Karchmer, AW. Infections in diabetic
44 patients. *N. Engl. J. Med.* 1999;341(25):1906-1912.

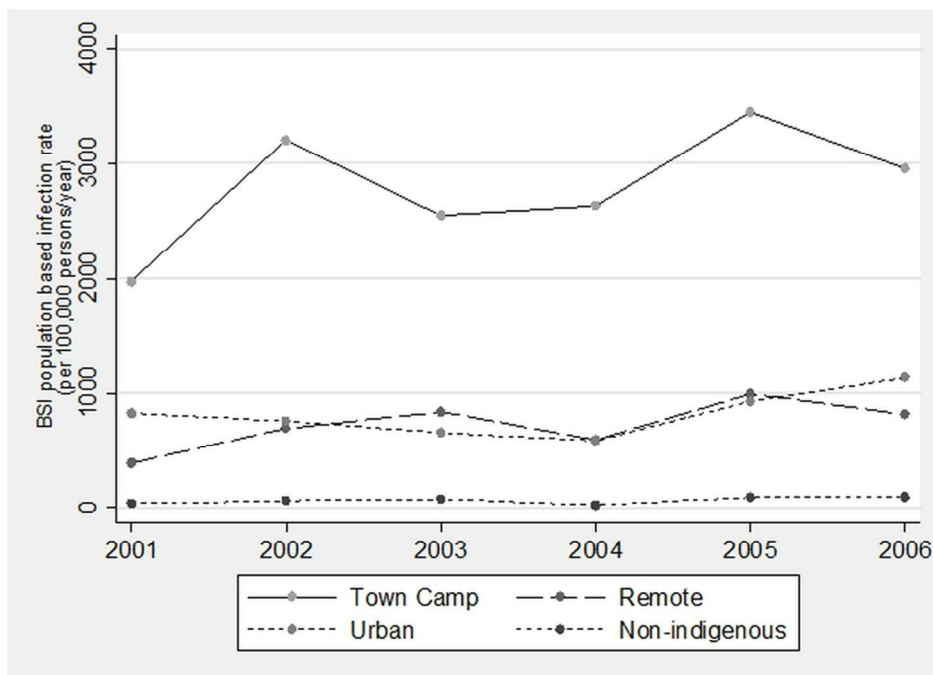
17. Baker M, Barnard, LT., Kvalsvig, A., Verrall, A., Zhang, J., Keall, M., Wilson, N., Wall, T., Howden-Chapman, P. Increasing incidence of serious infectious diseases and inequalities in New Zealand: a national epidemiological study. *Lancet*. 2012;379:1112-1119.
18. Einsiedel L, van Iersel, E., Macnamara, R., Spelman, T., Heffernan, M., Bray, L, Morris, H., Porter, B., Davis, A. Self-Discharge by adult Aboriginal patients at Alice Springs Hospital, central Australia: insights from a prospective cohort study. *Aust Health Rev*. 2012.
19. [Australian Bureau of Statistics](http://www.abs.gov.au/AUSSTATS/abs@.nsf/lookup/4704.0Chapter218Oct+2010). 2011 Census of population and Housing. Aboriginal and Torres Strait Islander (Indigenous) Profile. Canberra; 2013. 2002.0.
20. Skov S, Chikrizhs, TN., Li SQ., Pircher, S., Whetton, S. How much is too much? Alcohol consumption and related harm in the Northern Territory. *Med J Aust*. 2010;193:269-272.
21. Bailie R, Runcie, MJ. Household infrastructure in Aboriginal communities and the implications for health improvement. *Med J Aust*. 2001;175:363-366.
22. Anaya J. Report of the Special Rapporteur on the situation of human rights and fundamental freedoms of indigenous peoples, James Anaya, on the situation of indigenous people in Australia. United Nations; 2010.
23. d'Espaignet E, Kennedy, K., Paterson, B., Measey, M. *Health Status in the Northern Territory 1998*. Darwin: Epidemiology, Primary Care and Coordinated Care Branch;1998.
24. McDonald E, Bailie, R., Grace, J., Brewster, D. An ecological approach to health promotion in remote Australian Aboriginal communities. *Health Promotion International*. 2010;25(1):42-53.
25. O'Brien J, Lu, B., Ali, NA., Martin, GS., Aberegg, SK., Marsh, CB., Lemeshow, S., Douglas, IS. Alcohol dependence is independently associated with sepsis, septic shock and hospital mortality among adult intensive care unit patients. *Crit Care Med*. 2007;35(2):345-350.
26. Laupland K, Gregson, DB., Zygun, DA., Doig, CJ., Mortis, G., Church, DL. Severe blood stream infections: a population-based assessment. *Crit Care Med*. 2004;32:992-997.
27. Nuori J, Butler, JC., Farley, MM., Harrison, LH., McGeer, A., Kolczak, MS., Breiman, RF. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med*. 2000;342:681-689.
28. Dopirak M, Hill, C., Oleksiw, M., Dumigan, D., Arvai, J., English, E., Carusillo, E., Malo-Schlegel, S., Richo, J., Traficanti, K., Welch, B., Cooper, B. Surveillance of hemodialysis-associated primary bloodstream infections: the experience of ten hospital-based centers. *Infect Control Hosp Epidemiol*. 2002;23:721-724.
29. Zhao Y, Connors, C., Wright, J., Guthridge, S. Estimating chronic disease prevalence among the remote Aboriginal population of the Northern Territory using multiple data sources. *Aust NZ J Public Health*. 2008;32:307-313.
30. Hoy W, Davey, RL., Sharma, S., Hoy, PW., Smith, JM., Kondalsamy-Chennakesavan, S. Chronic disease profiles in remote Aboriginal settings and

- 1 implications for health services planning. *Aust NZ J Public Health*. 2010;34:11-18.
- 2
- 3 31. Moberley S, Krause, V., Cook, H., Mulholland, K., Carapetis, J., Torzillo, P.,
- 4 Andrews, R. Failure to vaccinate or failure of vaccine? Effectiveness of the 23-
- 5 valent pneumococcal polysaccharide vaccine program in Indigenous adults in the
- 6 Northern Territory of Australia. *Vaccine*. 2010;28:2296-2301.
- 7 32. Flory J, Joffe, M., Fishman, NO., Edelstein, PH., Metlay, JP. Socioeconomic risk
- 8 factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiol Infect*.
- 9 2009;137:717-726.
- 10 33. Tong S, Bishop, E., Lilliebridge, R., Cheng, A., Spasova-Penkova, Z., Holt, D.,
- 11 Giffard, P., McDonald, M., Currie, B., Boutlis, C. Community Associated strains
- 12 of Methicillin-Resistant *Staphylococcus aureus* and Methicillin-Susceptible
- 13 *S.aureus* in Indigenous Northern Australia: Epidemiology and Outcomes. *J Infect*
- 14 *Dis*. 2009;199:1461-1470.
- 15 34. Huggan P, Wells, JE., Browne, M., Richardson, A., Murdoch, DR., Chambers,
- 16 ST. Population-based epidemiology of *Staphylococcus aureus* bloodstream
- 17 infection in Canterbury, New Zealand. *Int Med J*. 2010;40:117-125.
- 18 35. Bagger J, Zindrou, D., Taylor, KM. Post-operative infection with Methicillin-
- 19 resistant *Staphylococcus aureus* and socioeconomic background. *Lancet*.
- 20 2004;363:706-708.
- 21 36. Marmot M, Friel, S., Bell, R., Houweling, T., Taylor, S. Closing the gap in a
- 22 generation: health equity through action on the social determinants of health.
- 23 *Lancet*. 2008;372(November 8):1661-1669.
- 24 37. Beaglehole R, Bonita, R., Horton, R., Adams, C., Alleyne, G., Asaria, P. et al for
- 25 the Lancet NCD action group and the NCD alliance. Priority actions for the non-
- 26 communicable disease crisis. *Lancet*. 2011;377:1438-1447.
- 27 38. Bailie R, Stevens, MR., McDonald, E., Halpin, S., Brewster, D., Robinson, G.,
- 28 Guthridge, S. Skin infection, housing and social circumstances in children living
- 29 in remote Indigenous communities: testing conceptual and methodological
- 30 approaches. *BMC public health*. 2005;5.
- 31 39. McDonald M, Towers, RJ., Andrews, RM., Bengler, N., Currie, BJ., Carapetis, JR.
- 32 Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian
- 33 Aboriginal communities where acute rheumatic fever is hyperendemic. *Clin Infect*
- 34 *Dis*. 2006;43:683-689.
- 35 40. Currie B, Carapetis, JR. Skin infections and infestations in Aboriginal
- 36 communities in northern Australia. *Aust J Dermatol*. 2000;41:139-145.
- 37 41. Hewagama S, Spelman, T., Einsiedel, L. *Staphylococcus aureus* bacteraemia at
- 38 Alice Springs Hospital, central Australia, 2003-2006. *Int Med J*. 2012;42:505-
- 39 512.
- 40 42. Carapetis J, Wolff, DR., Currie, BJ. Acute rheumatic fever and rheumatic heart
- 41 disease in the Top End of Australia's Northern Territory. *Med J Aust*. 1996;164(5
- 42 February):146-149.
- 43 43. Jacoby P, Carvillo, K., Hall, S., Riley, T., Bowman, J., Leach, A., Lehman, D.,
- 44 Kalgoolie Otitis Media Resarch Project Team. Crowding and other strong
- 45 predictors of upper respiratory carriage of otitis media related bacteria in

- 1
2
3
4
5
6
7
8
9 1 Australian Aboriginal and non-Aboriginal children. *Paed Inf Dis J*.
10 2 2011;30(6):480-485.
11 3 44. Verdonck K, Gonzalez, E., Van Dooren, S., Vandamme, A., Vanham, G.,
12 4 Gotuzzo, E. Human T-lymphotropic virus 1: recent knowledge about an ancient
13 5 infection. *Lancet Infect Dis*. 2007;7:266-281.
14 6 45. Priest N, Paradies, Y., Stevens, M., Bailie, R. Exploring relationships between
15 7 racism, housing and child illness in remote indigenous communities. *J Epidemiol*
16 8 *Community Health* 2012;66:440-447.
17 9 46. Boutayeb A, Boutayeb, B. The burden of non-communicable diseases in
18 10 developing countries. *Int J Equity in Health*. 2005;4(1):2.
19 11 47. De Maeseneer J, Roberts RG, Demarzo M, et al. Tackling NCDs: a different
20 12 approach is needed. *The Lancet*. 2012;379(9829):1860-1861.
21 13
22 14

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

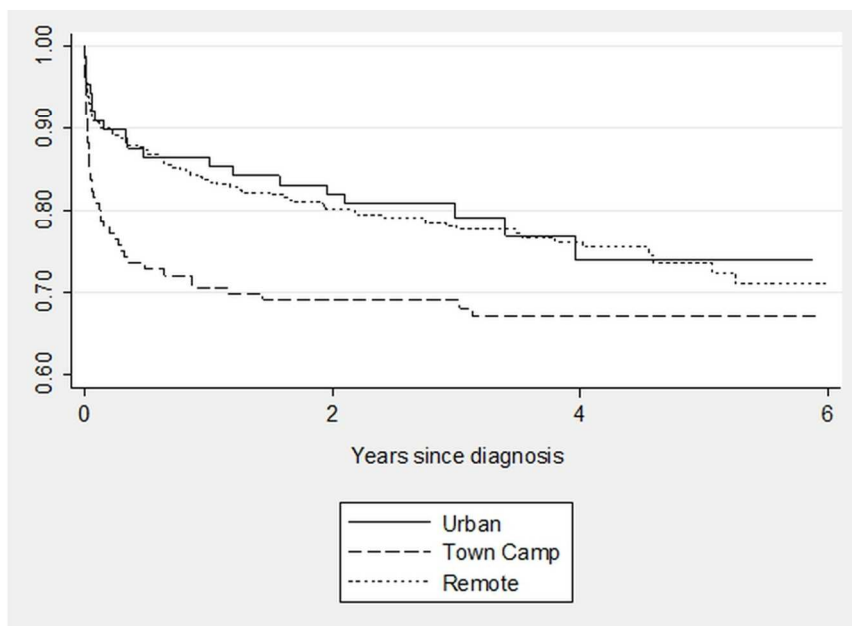


Blood Stream infection incidence rates according to ethnicity and place of residence. Town Camp, Indigenous residents of Town Camp; Urban, Indigenous residents of township who do not reside in a town camp; Remote, Indigenous residents of remote Indigenous communities. Non-Indigenous residents of Alice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

92x90mm (300 x 300 DPI)

only

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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.