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Cover photo: The Australian Institute of Tropical Medicine in 1916 (photo courtesy of James Cook University)

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EDITORIAL

The increasing impact of non-communicable diseases

The contents of the Annals has generally reflected the traditional emphasis on infectious and vector-borne disease in the discipline of tropical medicine. A subject analysis for the Annals' first 15 years of publication (1995-2009) showed that communicable conditions comprised 58.6% of the content, with far lower proportions of non-communicable diseases (NCDs).[1] (Amongst the latter, reflecting an Australian specialty, snakebite and marine envenomation topics made up a large proportion, namely 9.5% of content). This imbalance is slowly changing: the Annals has recently carried articles on NCDs, such as the physical health impacts of tropical cyclones,[2] nutritional interventions in children,[3] and obesity in developing countries;[4] and most of the annual Townsville Health Research Week abstracts that are published in the Annals, deal with NCDs.[5]

There is increasing recognition that non-communicable diseases (NCDs), such as heart disease, cancer, diabetes, and chronic lung and mental diseases, previously considered to be largely a problem of developed countries, are becoming major health problems in developing nations as well. It has been predicted that NCDs will account for 80% of the global burden of disease by 2020, and will be responsible for 70% of deaths in in developing countries, up from less than 50% today.[6] At the same time, communicable diseases continue to be a major cause of mortality in developing countries. As a more inclusive indicator of disease burden than mortality, disability-adjusted life years (DALYs) are often employed. This measure of lost years of healthy life is the combination of years of life lost through premature death, and years lived with disability.

A revealing analysis of the global and regional burden of disease at the beginning of the century was published in 2006.[7] Childhood deaths comprised nearly 20% of the total in 2001, with 99% of these in low- and middle-income countries. Causes of death in children were predominantly (>50%) infectious: acute respiratory infections, measles, malaria and HIV/AIDS. The ten leading contributors to the global health burden were, however, a mixture of communicable and NCDs: perinatal conditions, lower respiratory tract infections, ischaemic heart disease, cerebrovascular disease, HIV/AIDS, diarrhoeal disease, unipolar major depression, malaria, chronic obstructive pulmonary disease, and tuberculosis.[7] Cancer and diabetes are other NCDs that have substantial global disease burdens.[6] In the decade 1990-2001, there was a moderate (20%) reduction in disease burden due to communicable, maternal, perinatal, and nutritional conditions. The joint effects of health risk factors was evident, with 45% of global mortality and 36% of global disease burden attributable to combinations of diseases.[7] In developing countries there is a large overlap in diseases such as tuberculosis, HIV, malaria and severe viral infections, with NCDs, producing this 'double burden of disease'. Tuberculosis in particular is strongly linked to other communicable diseases and NCDs that influence the immune system. Comorbid NCD risk factors for tuberculosis include diabetes, smoking, malnutrition, and chronic lung disease.[8] Globalisation has contributed to the growing burden of NCDs, as it has direct effects on risks to populations and indirect effects on national economies and health systems.[9] The globalisation of the production and marketing campaigns of tobacco and alcohol industries provide major challenges for health policy makers and public health practitioners. Likewise, unhealthy food and leisure choices and habits have also become globalised, contributing to the obesity pandemic.[4]

The World Health Organization has published NCD country profiles for 2014, and these make for interesting reading.[10] For example, in Australia, a high income country, premature mortality from NCDs (that is, the probability of dying between ages of 30 and 70 years from the four main NCDs, namely cancers, diabetes, cardiovascular, and chronic respiratory diseases), is 9%; for South Africa, an upper middle income country, but one with many pressing health and socioeconomic problems,[11] it is three times higher, at 27%; for Fiji, also upper middle income, it is 31%.[10] The prevalences of major risk factors (smoking, alcohol consumption, raised blood pressure and obesity), and public health policies and measures in place to reduce or control NCDs in each country are also listed.[10]

In this issue of the Annals, the theme of NCDs (and sometimes their interaction with communicable diseases) is carried by articles on smoking and metabolic syndrome, military health, impact of NCDs and other factors on tuberculosis transmission on Pacific island countries, and Indigenous prison mortality. Not to neglect infectious diseases, there is also a review of treatment of typhoid fever, and case reports of Q fever and Whipple's disease.

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References

1. Smith DR, Goldsmid JM, Leggat PA, Frean J. Celebrating Volume 10 of the Annals, Part 1: Historical development and content analysis, 1995-2009. Ann Australas Coll Trop Med 2009; 10: 2-7.
2. Mitchell RD, Aitken P, Franklin RC. The physical health impacts of tropical cyclones. Ann Australas Coll Trop Med 2014; 15: 2-8.
3. Wood B. Vitamin A, zinc, iron and iodine interventions in children under five years of age. Ann Australas Coll Trop Med 2014; 15: 8-11.
4. Dixit R. Obesity in developing countries. Ann Australas Coll Trop Med 2015; 16: 18-26.
5. James Cook University. Townsville Health Symposium. Ann Australas Coll Trop Med 2015; 16: 1-20.
6. Boutayeb A. The double burden of communicable and non-communicable diseases in developing countries. Trans Royal Soc Trop Med Hyg 2006; 100: 191-9.
7. Lopez A, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367: 1747-57.
8. Bates M, Marais BJ, Zumla A. Tuberculosis comorbidity with communicable and noncommunicable diseases. Cold Spring Harb Perspect Med 2015; 5: a017889.
9. Beaglehole R, Yach D. Globalisation and the prevention and control of non-communicable disease: the neglected chronic diseases of adults. Lancet 2003; 362: 903-8.
10. World Health Organization. Noncommunicable Diseases Country Profiles 2014. Geneva: WHO; 2014.
11. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman S, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet 2009; 374: 934-47.

SMOKING AND METABOLIC SYNDROME IN A RURAL MALAYSIAN POPULATION

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Abstract

Tobacco smoking is a well-established risk factor for coronary artery disease, amongst many other conditions. Coronary artery disease is one of most common causes of mortality and morbidity worldwide; this study investigated its association with smoking and metabolic syndrome. It was a retrospective hospital-based study of 259 male patients in a rural Malaysian population. Smoking was significantly associated with coronary artery disease, with increased waist circumference, and with high serum triglycerides. Diabetes mellitus was the best predictor for developing metabolic syndrome followed by smoking, but age, body mass index and ethnicity were not significantly associated with metabolic syndrome. Smoking was the strongest risk factor for developing coronary artery disease and was significantly associated with metabolic syndrome. The prevalence of coronary artery disease was higher in smokers with diabetes mellitus and metabolic syndrome.

Key words: Smoking, coronary artery disease, increased waist circumference, metabolic syndrome

Introduction

The metabolic syndrome (MetS) is a constellation of central obesity and various metabolic abnormalities, and carries an increased risk for diabetes and cardiovascular diseases. It is estimated that the prevalence of MetS in adults is 20-25% worldwide.[1]

Smoking is a strong risk factor for genesis of atherosclerosis[2] and endothelial dysfunction[3] and is reported to be associated with high serum lipids, high triglycerides, low high-density lipoprotein cholesterol (HDL-C),[4-6] and also for causing insulin resistance and hyperinsulinemia.[7,8] Thus, smoking might be an important modifiable risk factor for metabolic syndrome (MetS) and coronary artery disease (CAD). The role of tobacco in the pathophysiology of MetS is thought due to the actions of nicotine, a major harmful component of cigarette smoke. Nicotine acts through nicotinic acetylcholine receptors, widely expressed in the central and peripheral nervous systems. Nicotine action is mediated by several mechanisms. Either directly or indirectly, it augments the release of several important neurotransmitters and hormones, including dopamine, serotonin, glutamate, and γ-aminobutyric acid and acetylcholine in the central and peripheral nervous systems, and arginine vasopressor, corticotrophin releasing hormone, adrenocorticotropic hormone, and growth hormone, epinephrine and norepinephrine from the adrenal medulla, and cortisol from the adrenal cortex.[9-11] Nicotine also acts on the hypothalamic-pituitary-adrenal axis[12] and finally, on the renin angiotensin-aldosterone system.[13]

Positive correlation between smoking and MetS has been seen in some but not all studies.[14,15] One study in Turkish women even found a protective effect of smoking on MetS.[16] Different definitions of MetS and individual baseline information of the study population might explain inconsistent results on this issue. The prevalence of smoking among Malaysian adult males is 46.5% based on the latest National Health and Morbidity Surveys (2006).[17] An association of smoking and MetS is not appreciated by the general population and smoking has been promoted as a weight control. Such concepts are an added excuse to continue smoking. Our study looked for an association between smoking and MetS.

Subjects and methods

This was a retrospective cross-sectional study with a sample size (n=257) determined using Epi Info 6 for population surveys (CDC, Atlanta, USA). The study period was from January 2010 to June 30, 2011. Subjects were selected using clustered systematic randomizing and comprised patients attending a rural district hospital in Malaysia, who were referred by medical officers and other practitioners, or referred back from secondary and tertiary level hospitals for continued care.

Fifteen patients were recruited every week, by randomly selecting patients from two out-patient clinics. Inclusion criteria were males, age 13 years and above. Exclusion criteria were patients with known causes of obesity such as Cushing's and pseudo-Cushing's syndrome, and known causes of dyslipidaemia such as chronic renal failure, nephrotic syndrome, hypothyroidism, and HIV patients on antiviral drugs.

The research purpose was explained and consent was obtained from all patients aged 18 years and above, and from parents of those aged less than 18 years. All subjects were interviewed and examined by the investigators. Questions were asked about smoking history, alcohol intake, occupation, family income, exercise (mild: active with household chores; moderate activity: 30 minute walk, jog, swimming three days per week, etc; strenuous exercise: manual labour). Interviewers also assessed knowledge of healthy food and lifestyle, and hazards of being obese (defined as body mass index (BMI) ≥27). Coronary artery disease was defined by patients' records of coronary artery angiography, angioplasty, coronary artery bypass graft, symptoms of angina, unstable angina, myocardial infarction plus ECG and raised cardiac biomarkers, with or without echocardiogram changes, and response to coronary vasodilators. Smokers were defined as those who stated they actively smoked cigarettes, either intermittently or continuously. Non-smokers were defined as those who stated they never smoked.

MetS was defined according to the US National Cholesterol Education Programme Adult Panel III,[18] with reference to Asian cut-off criteria for waist circumference. Measurements of the BMI (kg/m^2), waist circumference (WC) (cm) and blood pressure (mmHg) were carried out by the same assigned staff. Measurement of WC was standardized at the midpoint between the lower costal cartilage and the highest point of iliac crest with the patient exhaling completely. Blood samples for fasting plasma glucose (FPG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), were taken in the early morning after an overnight fast. Subject classifications were high waist circumference (defined as WC ≥90 cm); normal weight (BMI 18.5-22.9), overweight (BMI 23-26.9) and obese (BMI ≥27); hypertension (systolic BP ≥130 mmHg, or diastolic BP ≥85 mmHg); raised fasting plasma glucose (FPG = 5.6 mmol/L-6.99 mmol/L; diabetes mellitus (FPG ≥7 mmol/L); low HDL-C (<1.03 mmol/L), high TG (≥1.7 mmol/L), high TC (≥5.2 mmol/L) and high LDL-C (≥2.4 mmol/L). Isolated high TC, TG, LDL-C and HDL-C accompanying otherwise normal lipid profiles were recorded. Statistical analyses were done with SPSS version 16 (SPSS Inc, Chicago, Il, USA). Student's t-test was used to compare means and the chi-squared test to identify associations. Wilcoxon signed rank test was used for non-normally distributed variables where applicable. P values <0.05 were considered significant.

Results

Of 257 subjects recruited, 21% (54) were smokers. The highest percentage of smokers was in age group ≥70 years, followed by age groups 30-39 and 40-49 years. However, a large percentage of smokers were age <50 years. Prevalence of smoking was highest in Chinese and Indians, and lowest in Malays. Non-smokers were more frequently overweight whereas smokers were more frequently obese (Table 1).

Table 1. Prevalences of age, ethnicity, overweight and obesity status in smokers and non-smokers

	Smokers (n=54)	Non-smokers (n=203)
Age groups	%	%
<20	0	3.9
20-29	6.3	7.4
30-39	26.9	9.4
40-49	26.4	19.2
50-59	16.9	31.5
60-69	21.6	21.1
≥70	30.8	7.4
Ethnicity		
Malay	17.6	43.8
Chinese	23.3	27.6
Indian	23.7	28.6
BMI		
Overweight (BMI 18.5-22.9)	29.6	33.5
Obesity (BMI≥ 27)	51.9	40.9

Smokers had significantly higher CAD, MetS, WC, and TG; they were older, more obese both generally and centrally, and were more frequently hypertensive (both systolic and diastolic) and hyperglycemic, than non-smokers (Table 2). Mean HDL-C was lower in smokers (Table 3).

Table 2. Prevalences of coronary artery disease, metabolic syndrome, and metabolic syndrome components in smokers and non-smokers

		Smokers (n=54)	Non-smokers (n=199)	P	OR	CI
	Number	%	%			
CAD	78	75.9	18.1	<0.001	14.2	6.89-29.0
MetS	148	72.2	53.7	0.01	2.24	1.16-4.82
High WC	148	72.2	53.7	0.01	2.24	1.16-4.32
High triglycerides	114	59.3	40.4	0.01	2.42	1.17-3.95
High BP	148	68.5	54.7	0.06	1.80	0.95-3.41
Raised FPG	155	68.5	58.1	0.16	1.57	0.83-2.97
Low HDL-C	124	53.7	46.8	0.34	0.70	0.34-1.47
DM	119	57.2	44.3	0.22	1.46	0.79-2.66
BMI ≥27	152	66.7	57.1	0.21	0.67	0.36-1.25

OR = odds ratio; CI = confidence interval

Table 3. Physiological and biochemical characteristics of smokers and non-smokers

	Smokers (n=53) mean ± SD	Non-smokers (n=199) mean ± SD
Age	53.5 ± 13.4	52.3 ± 13.8
BMI	27.2 ± 5.71	26.4 ± 5.84
WC	97.8 ± 13.9	92.8 ± 8.00
Systolic BP	141.0 ± 22.7	134.5 ±19.5
Diastolic BP	85.4 ± 10.8	82.6 ± 11.1
FBG	7.17 ± 2.89	7.09 ± 3.09
Triglycerides	2.37 ± 2.37	1.84 ± 1.59
HDL-C	1.07 ± 0.44	1.20 ± 0.85

BMI = body mass index (body weight in kg/height in meter^2); WC = waist circumference; FBG = fasting blood glucose LDL-C = low density lipoprotein, HDL-C = high density lipoprotein; SD=standard deviation

High WC, raised FPG and hypertension were independent risk factors for developing MetS in smokers by multiple logistic regression analysis (Table 4). DM was identified as independent factor for developing MetS in males and smoking was borderline independent significance (Table 5).

Table 4. Association of smoking with metabolic syndrome components by multivariate logistic regression analysis

	Wald statistic	P	OR	95% CI
High WC	5.96	0.01	120.3	2.57-5634.2
Raised fasting plasma glucose	4.21	0.04	34.0	1.17-992.0
High BP	4.01	0.04	19.5	1.07-358.1
High triglycerides	2.95	0.08	14.6	0.686-308.9
Low HDL-C	3.38	0.07	43.5	0.78-2436.8

Table 5. Predictors of metabolic syndrome by multivariate logistic regression analysis

	Wald statistic	P	OR	95% CI
DM	20.2	<0.001	3.82	2.13-6.83
Smoking	3.69	0.05	2.04	0.99-4.24
Age	5.20	0.02	0.97	0.95-0.99
BMI	15.6	<0.001	0.88	0.83-0.94
Ethnicity 1 (Malay)	0.00	0.93	0.97	0.48-1.96
Ethnicity 2 (Chinese)	2.69	0.10	1.88	0.88-4.01

Smokers with DM (S+/DM+) had the highest percentage of CAD and the highest odds ratio, followed by smokers without DM (S+/DM-). Diabetes

without smoking (S-/DM+) was not associated with CAD, and the non-diabetic, non-smokers (S-/DM-) had significantly less CAD (Table 6). Likewise, smoking with and without MetS (S+/MetS+ and S+/MetS-) were significantly associated with CAD, with S+/MetS+ having the highest odds ratio. There was no association between nonsmoking with MetS (S-/MetS+) and CAD, and nonsmokers without MetS (S-/MetS-) were significantly less likely to develop CAD (Table 7).

Table 6. Associations between smoking, diabetes mellitus, and coronary artery disease

	% of CAD	P	OR	95% CI
S+/DM+	82.9	<0.001	18.4	6.82-49.4
S+/DM-	68	0.00	7.49	3.14-17.9
S-/DM+	21.7	0.25	0.78	0.50-1.21
S-/DM-	15.5	0.00	0.36	0.23-0.56

S+ = smokers; S- = non-smokers

Table 7. Associations between smoking, metabolic syndrome, and coronary artery disease

	% of CAD	P	OR	95% CI
S+/MetS+ (29/39)	74.4	<0.001	10.0	4.56-21.9
S+/MetS- (10/15)	66.7	<0.001	5.12	1.69-15.5
S-/MetS+ (31/110)	26.2	0.51	0.94	0.49-1.43
S-/MetS- (9/94)	9.6	<0.001	0.14	0.07-0.31

Discussion

Our finding of a significant association between smoking and MetS (Table 2) is consistent with previous reports that active smoking is associated with development of MetS and is dose dependent.[19-23] Our study recruited only males, and is thus consistent with the report that an association between smoking and MetS is only observed in men,[15] although we cannot comment on this association in women. Significant association of smoking with increased waist circumference, insulin resistance and elevated triglycerides was observed by us and others.[24-27] However, this is contrary to a general concept that smokers have lower WC than non-smokers,[28] and this misconception may keep smokers concerned about weight gain from stopping smoking.[29] Smokers should be advised that smoking causes visceral fat accumulation and increases the risk of MetS and CAD. Among middle-aged smokers of both sexes, waist circumference increased in a dose dependent fashion with smoking, particularly in women.[30,31]

Our finding supports Kishida *et al*[32] that smoking seems to accelerate visceral fat accumulation and promote obesity-related disorders. Medical research has focused on visceral adiposity as a target for the management of MetS. High WC is also noted to be an independent risk factor for developing MetS, among other components in smokers (Table 4). Although obesity (defined as BMI ≥27) was not significantly associated with smoking in our study (Table 2), there is a higher BMI trend in smokers (Table 1). Our study supports reports that smoking decreases body weight in the short term due to increased energy expenditure and reduced appetite.[14,33-34] However, heavy, chronic smokers tend to have greater body weight than do light smokers or non-smokers, which likely reflects a clustering of risky behaviors (e.g. low degree of physical activity, poor diet, and smoking) that is conducive to weight gain. The acute response of decreased appetite and increase body metabolism might lead to the false impression that smoking controls weight, whereas chronic changes increase appetite and decrease metabolic rate. Our study and others have highlighted the fact that smoking causes increases in both general and central obesity. Thus smoking is not a tool to decrease body weight. Peeters *et al* reported that the co-occurrence of overweight and smoking has substantial consequence for health,[35] and according to the Framingham study, the life expectancy of obese smokers was 13 years less than that of normal-weight non-smokers.

We did not find hypertension to be significantly higher in smokers than non-smokers, consistent with Raihan *et al*,[33] who stated that various studies since 1971, relating smoking and blood pressure, had given varying results. Recent studies suggested that smoking causes vasomotor dysfunction as the result of reduction of nitrous oxide (NO), which functions as a vasoregulatory molecule that could have hypotensive action. While the exact mechanism and pathophysiology of such effects in cigarette smoking are still not well understood,[36,37] our findings differ from others who showed smoking had significant association with hypertension.[38,39] We did note smoking and hypertension to be independent predictors for MetS (Tables 4, 5).

Raised fasting plasma glucose was not significantly associated with smoking, although there was a trend for higher levels in smokers, consistent with previous findings.[33] DM also did not appear to be significantly associated with smoking, differing from reports showing that smoking had significant associations with DM.[40-41] However, raised FPG was noted to be an independent predictor of MetS in smokers (Table 4).

Significant association of high TG with smoking, and a trend of low HDL-C in our study is consistent with other studies.[5,15,42] The association of cigarette smoking with high TG can be explained by the elevated plasma free fatty acids (FFAs) caused by decreased lipoprotein lipase activity,[34] increased 3-hydroxy-3-methylglutaryl-CoA reductase activity, and increased glucose-6-phosphate dehydrogenase activity with smoking.[14] These FFAs stimulate the hepatic synthesis and secretion of cholesterol, which increases production of very low-density lipoproteins (VLDL) and serum TG concentrations, and decreases HDL concentrations.[5,43,44] However, low HDL-C was non-significantly associated with smoking in our study. It may be that there are different determinants of HDL-C, especially genetic, than for TG.

Our findings of significant association with CAD of smoking alone, smoking plus DM, and smoking plus MetS, are consistent with reports by others.[45] The direct effect of nicotine and carbon monoxide on the blood vessels and oxygen carrying capacity, the important role of nicotine and its metabolites on insulin resistance,[11,12] the anti-estrogenic effect, and increased level of stress hormones like cortisol[46-47] resulting from cigarette smoking, are strong independent risk factors for cardiovascular disease as well as for non-insulin-dependent diabetes mellitus.[43,48] The synergistic effect of DM and smoking on development of CAD is seen in Table 5, with DM noted to be the most predictive factor for developing MetS in males in our study.

The very high prevalence of MetS in smokers in our study seems to be mainly contributed by high WC and high TG. Passive smoking also appears to be associated with MetS,[15] and this factor should also be considered in population studies of MetS. The pathophysiology of MetS in smokers is described in many reports.[9,10,11,12] Smoking possibly has a pseudo-Cushing's effect like alcohol and therefore perhaps smokers should either be excluded from MetS studies, or such studies should stratified for smoking. Larger population studies need to be carried to validate these proposals.

Conclusions

Our study shows that smoking is significantly associated with MetS. In addition to its known direct effect on the endothelial function of blood vessels, smoking also has an effect on metabolism and is an independent risk factor for CAD, with additional risks if coupled with DM and MetS. Although our study was hospital based and included only men, it does show that smoking is associated with MetS, high WC and CAD, and is a modifiable factor to prevent and treat MetS.

References

4. International Diabetes Foundation. The IDF Consensus Worldwide Definition of the Metabolic Syndrome. Brussels: IDF Communications; 2006.
5. Kannel WB. Update on the role of cigarette smoking in coronary artery disease. Am Heart J 1981; 101: 319-28.
6. Heitzer T, Yla-Herttuala S, Luoma J, *et al.* Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia: role of oxidized LDL. Circulation 1996; 9: 1346-53.
7. Kong C, Nimmo L, Elatrozy T, *et al.* Smoking is associated with increased hepatic lipase activity, insulin resistance, dyslipidaemia and early atherosclerosis in type 2 diabetes. Atherosclerosis 2001; 156: 373-8.
8. Connelly PW, Petrasovits A, Stachenko S, *et al.* Prevalence of high plasma triglyceride combined with low HDL-C levels and its association with smoking, hypertension, obesity, diabetes, sedentariness and LDL-C levels in the Canadian population. Can J Cardiol 1999; 15: 428-33.
9. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. Br Med J 1989; 298: 784-8.
10. Facchini FS, Hollenbeck CB, Jeppesen J, *et al.* Insulin resistance and cigarette smoking. Lancet 1992; 339: 1128-30.
11. Ronnemaa T, Ronnemaa EM, Puukka P, *et al.* Smoking is independently associated with high plasma insulin levels in nondiabetic men. Diabetes Care 1996; 19: 1229-32.
12. Audrain-McGovern J and Benowitz NL. Cigarette smoking, nicotine, and body weight. Clin Pharmacol Ther 2011; 90: 164-8.
13. Kalamida D, Poulas K, Avramopoulou V, *et al.* Muscle and neuronal nicotinic acetylcholine receptors. Structure, function and pathogenicity. FEBS J 2007; 274: 3799-845.
14. Rohleder N and Kirschbaum C. The hypothalamic-pituitary- adrenal (HPA) axis in habitual smokers. Int J Psychophysiol 2006; 59: 236-43.
15. Laustiola KE, Lassila R, and Nurmi AK. Enhanced activation of the renin-angiotensin-aldosterone system in chronic cigarette smokers: a study of monozygotic twin pairs discordant for smoking. Clin Pharmacol Ther 1988; 44: 426-30.
16. Balhara YP. Tobacco and metabolic syndrome. Indian J Endocrinol Metab 2012; 16: 81-87. doi: 10.4103/2230-8210.91197
17. Cena H, Fonte ML, Turconi G. Relationship between smoking and metabolic syndrome. Nutrition Reviews 2011; 69: 745-753. doi: 10.1111/j.1753-4887.2011.00446.x
18. Wei P JIA. The impact of cigarette smoking on metabolic syndrome. Biomed Environ Sci 2013; 26: 947-952. doi: 10.3967/ bes2013.029
19. Onat A, Ozhan H, Esen AM, *et al.* Prospective epidemiologic evidence of a 'protective' effect of smoking on metabolic syndrome and diabetes among Turkish women – without associated overall health benefit. Atherosclerosis 2007; 193: 380-388. doi: 10.1016/j.atherosclerosis.2006.07.002
20. Lim HK, Ghazali SM, Kee CC, *et al.* Epidemiology of smoking among Malaysian adult males: prevalence and associated factors. BMC Public Health 2013; 13: 8. doi: 10.1186/1471-2458-13-8
21. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. Circulation 2002; 106: 3143-3421.
22. Sun K, Liu J, Ning G. Active smoking and risk of metabolic syndrome: a meta-analysis of prospective studies. PLoS One 2012; 7: e47791. doi: 10.1371/journal.pone.0047791
23. Geslain-Biquez C, Vol S, Tichet J, *et al.* The metabolic syndrome in smokers. The DESIR study. Diabetes Metab 2003, 29: 226-34.
24. Eliasson B, Attvall S, Taskinen MR, *et al.* The insulin resistance syndrome in smokers is related to smoking habits. Arterioscler Thromb 1994; 14: 1946-50.
25. Cena H, Tesone A, Niniano R, *et al.* Prevalence rate of metabolic syndrome in a group of light and heavy smokers. Diabetol Metab Syndr 2013, 5: 28. doi: 10.1186/1758-5996-5-28
26. Oh SW, Yoon YS, Lee ES, *et al.* Association between cigarette smoking and metabolic syndrome. Diabetes Care August 2005; 28: 2064-6.
27. Bamia C, Trichopoulou A, Lenas D, *et al.* Tobacco smoking in relation to body fat mass and distribution in a general population sample. Int J Obes Relat Metab Disord 2004; 28: 1091-6.
28. Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. III. Effects of cigarette smoking. JAMA 1989; 261: 1169-73.
29. Barrett-Connor E, Khaw K. Cigarette smoking and increased central adiposity. Ann Intern Med 1989; 111: 783-7.
30. Chiolero A, Faeh D, Paccaud F, *et al.* Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr 2008; 87: 801-9.
31. Ferrara CM, Kumar M, Nicklas B, *et al.* Weight gain and adipose tissue metabolism after smoking cessation in women. Int J Obes 2001; 25: 1322-6.
32. Gorber SC, Tromblay M, Moher D, *et al.* A comparison of direct vs. self-report measures for assessing height, weight and body mass index; a systematic review. Obes Rev 2007; 8: 307-26. doi:10.1111/j.1467-789X.2007.00347
33. Clair C, Chiolero A, Faeh D, *et al.* Dose-dependent positive association between cigarette smoking, abdominal obesity and body fat: cross-sectional data from a population-based survey. BMC Public Health 2011; 11: 23.
34. Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. Effects of cigarette smoking. JAMA 1989; 26:1169-73.
35. Kishida K, Funahashi T, Matsuzawa Y, *et al.* Visceral adiposity as a target for the management of the metabolic syndrome. Ann Med 2011; 44: 233-41.
36. Raihan K, Azmawati MN. Cigarette smoking and cardiovascular risk factor among male youth population. Malaysian J Public Health Med 2013; 13: 28-36.
37. Audrain-McGovern J, Benowitz NL. Cigarette smoking, nicotine, and body weight. Clin Pharmacol Ther 2011; 90: 164-8.
38. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A,Bonneux L. NEDCOM, the Netherlands Epidemiology and Demography Compression of Morbidity Research Group. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. Ann Intern Med 2003; 138:24-32.
39. Magnus HF, Tom IL, Turid LH, Torstein V. Life style related to blood pressure and body weight in adolescence: cross-sectional data from the Young-HUNT study, Norway. BMC Public Health 2008; 8: 111-20.
40. John A. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004; 43: 1731-7.
41. Elliott JM, Simpson FO. Cigarettes and accelerated hypertension. N Z Med J 1980; 91: 447-9.
42. Dyer AR, Stamler J, Shekelle RB, *et al.* Pulse pressure. II. Factors associated with follow-up values in three Chicago epidemiologic studies. J Chronic Dis 1982; 35: 275-82.
43. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 1995; 310: 555-9.
44. Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men: the Zutphen Study. Am J Epidemiol 1989; 130: 1101-8.
45. Watari M, Uetani M, Suwazono Y, *et al.* A longitudinal study of the influence of smoking on the onset of obesity at a telecommunications company in Japan. Prev Med 2006; 43: 107-12.
46. Criqui MH, Wallace RB, Heiss G, *et al.* Cigarette smoking and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program Prevalence Study. Circulation 1980, 62: IV70-IV76.
47. Mjos OD. Lipid effects of smoking. Am Heart J 1988; 115: 272-5.
48. Will JC, Galuska DA, Ford ES, *et al.* Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. Int J Epidemiol 2001, 30: 540-46.
49. Tanko LB. Novel association between bioaviable estradiol and adipokines in elderly women with different phenotypes of obesity: implication for atherogenesis. Circulation 2004; 110: 2246-52.
50. Cryer PE, Haymond MW, Santiago JV, *et al.* Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976; 295: 573-7.
51. Kannel WB. Cigarettes, coronary occlusion, and myocardial infarction. JAMA 1981; 246: 871-2.

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COMPARISON BETWEEN INDIGENOUS MORTALITY RATES IN A PROVINCIAL QUEENSLAND PRISON WITH THE GENERAL INDIGENOUS POPULATION

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Abstract

There has been much concern about the gap in disadvantage and mortality between Indigenous and non-Indigenous Australians. One focus of this concern has been black deaths in custody. This has been considered to be particularly relevant as Indigenous people are vastly over-represented in Australian prisons. This author recently attended an Aboriginal protest rally and was disturbed by the discordance between the emphasis given to black deaths in custody and this author's own experience as a part-time general practitioner in the male wing of a provincial Queensland prison over the previous 5.75 years. In response, an analysis was performed comparing the Indigenous male mortality in this prison with the expected mortality of an Indigenous male population of the same size and age structure. The mortality of prisoners is much lower than expected. The reasons for the improved survival of Indigenous prisoners, and its implications, are briefly discussed.

Key words: Prison, mortality rates, indigenous Australians, Queensland

Introduction

Indigenous speakers at a recent protest rally attended by the author, clearly regarded black deaths in custody as the most dramatic manifestation of the many sources of disadvantage and discrimination faced by Indigenous people and focused much of their attention on this issue. However, this author has the impression from work in Indigenous communities and in a prison, that this focus is misplaced. Black deaths in custody would not seem to represent inadequate care of Indigenous people in custody, but rather reflects underlying disadvantage and dysfunction resulting in a disproportionate number of Indigenous people in custody. A focus on deaths in custody would seem to detract from attention to underlying real causes of disadvantage and the ability to address these. Accordingly, this author has analysed black deaths in custody occurring on his watch and has compared this with the mortality rate in the general Indigenous community.

Methods

It was estimated that the author had the equivalent of 1748 person-years observation of male Indigenous prisoners during 5.75 years from the time of commencement of work at the prison in 2009 to the time of the last revision of this paper in 2015. Obtaining a precise value rather than an estimate would have required access to daily Indigenous prisoner numbers over this time. This was not available to the author. Instead, at various times over the period 2009 to the present, there were 7 different estimates available of total male prisoner numbers at this prison from a variety of publicly-available and internal sources. An exponential growth curve was fitted to the data. It gave an average prisoner number growth rate of 5.18%. The number of prisoner years of observation, over the 5.75 years up until the date of last revision of this paper, could then be calculated by integration. There was also information showing that the number of Indigenous prisoners had remained very close to 62% of all prisoners throughout this period. This then gives the person-years of observation of Indigenous male prisoners. The ages of the Indigenous prisoners were obtained from a snapshot available to the author in November 2014. It is assumed that this age structure has remained constant.

General male Indigenous age-specific death rates are available from the Australian Bureau of Statistics.[1] It was assumed that these had remained constant over the period of observation. This age-structured death rate was used to calculate the expected number of male Indigenous deaths at the prison over the period of observation. In effect, these are the calculations to obtain a standardised mortality ratio (SMR)[2]. The actual number of male Indigenous deaths was assumed to follow a Poisson process with this expected number of deaths. This allows a calculation of the p-value based on the assumption that the death rate at this prison is the same as the mortality of Indigenous males in general. The actual number of male Indigenous deaths at the prison over this period was obtained by my personal recollection, confirmed by other long serving health staff: there were none. There were, however, two deaths of Indigenous men, who had recently been in custody in the prison and who had been moved to the local hospital in the final stages of terminal illnesses. These recollections are almost certainly accurate as a death in custody is a very major event for health staff.

Results

There were several choices for male Indigenous age-specific mortality available – figures for Queensland, figures for the Northern Territory and combined figures for all states and territories with larger Indigenous populations. It was noted that states with a longer history of white occupation tended to have appreciably lower Indigenous mortality rates than those of the Northern Territory, with Queensland having mortality rates slightly better than the combined rates. It is speculated that the lower figures in Queensland are weighted by the proportion of Indigenous people who live in the longer-occupied area of South East Queensland and who may therefore have better mortality rates, akin to those of New South Wales. Since the prison in question mainly serves prisoners from North Queensland with an appreciable number of Indigenous prisoners originating from the Northern Territory, it could be expected that the rates applicable to this population may be between the figures for Queensland as a whole and for the Northern Territory.

The expected death rate for the 1748 person-years of observation of the male Indigenous prisoners, on the assumption that they have the same mortality as the general Indigenous population, is given by:

$$\sum_{\text{each age group}} \text{general male Indigenous mortality in each age group} \times \text{proportion in this age group} \times 1748$$

Low and high expected death rates are obtained using Queensland and Northern Territory figures respectively. This gives a low figure of 6.19 and a high figure of 11.29. Assuming a Poisson distribution for the actual number of deaths, the probability of the observed death rate of zero (giving an SMR of 0) is between $e^{-11.29}$ and $e^{-6.19}$ or between 0.000013 and 0.00204. This therefore constitutes evidence that is highly statistically significant that in this prison, male Indigenous prisoners fare better than the general male Indigenous population.

There is however a moot point about whether it is appropriate to include the two men who died in hospital, as deaths in this prison's custodial care. Both these men were in the final stages of terminal illnesses unrelated to their incarceration. The exact status of one of the men at the time of death cannot be reliably ascertained by this author. It is known that one of the two was formally released from custody for his final hours in palliative care, but

the planned release of the other man in similar circumstances was to occur about the time of his death and he may still have formally been in the prison's custody at the time of death. Since any change in the custodial status of these men was due only to their impending death, it may be argued that, regardless of their official custodial status, these deaths should be counted as deaths in this prison's custody. Counting these 2 deaths, the Poisson distribution gives a probability of 2 or fewer deaths when the expected number is 11.29 or 6.19, to be 0.00095 or 0.0538 respectively, depending on whether NT or Queensland mortality data are used. Whilst use of Queensland Indigenous male mortality rate gives a probability just short of 'statistical significance', it seems fair to assert that the data is reasonably convincing in showing that the mortality of male Indigenous prisoners is less than the mortality of male Indigenous people in general. The best guess estimate from these very limited data, is that imprisonment reduces mortality by a factor of 6.19/2 to 11.29/2, or in other words Indigenous male prisoners are between about 3 and 6 times less likely to die than those not in prison.

Discussion

Limitations of the methodology

There are a number of issues relevant to the calculations here:

1. Perhaps the most important consideration is the issue of a post hoc fallacy. This arises when observers are in a position to observe a number of situations, the most unusual of the situations is noted and then a statistical analysis is performed limited to only that situation, with the statistics confirming it is indeed particularly unusual and therefore by definition 'statistically significant'. It could be argued here that this paper was written only because an unusual event had occurred of no deaths in custody and since this was the event that was analysed, a post hoc fallacy will apply. However, the period that was chosen was simply the full length of this observer's presence at the prison until after the protest meeting that stimulated this analysis. The post hoc fallacy would then only be relevant if one had the philosophical viewpoint that there are many prisons where a prison doctor might have the propensity to write an analysis such as this, but the analysis arose only from this prison simply because the results here were so unusual. This viewpoint does not seem very reasonable. To put it perhaps too simply, the post hoc fallacy is of little relevance because it is unlikely that most Australian prison doctors have the interest and the background to write a paper on Indigenous prisoner mortality, but refrain from doing so only because they can see that their results will not be remarkable.

2. A related issue is that this analysis concerns just one prison and so excludes consideration not only of mortality in other prisons but also deaths in other custodial situations such as watchhouses. In other words, granted that one accepts the argument in 1. that the data can be accepted almost as a random sample, it is possible that some of the risk of mortality for the people in the sample may be specific to features of the particular prison. However, it seems reasonable to assume that the contrasts between the life of prisoners in different prisons will be far smaller than the contrast between life in and out of prison, so the results from this one prison very likely indicate an effect of prisons in general.

3. Another reason why deaths in custody may be less than expected from overall mortality rates, is that a degree of physical fitness is required to commit some of the crimes for which people are being incarcerated, so this would be an argument to suggest that prisoners might be expected to have a better mortality rate than people outside who will include those physically incapable of committing a crime. My experience, referred to below, gives me the impression that such a healthy survivor effect for people in prisons is of minimal relevance and indeed the converse is much more likely to be the case.

4. The Indigenous mortality rates for each state are based on relatively small numbers in each age group and so are less certain than mortality rates based on large populations. This will add very slightly to uncertainty in the findings here. Additionally, assumptions discussed in the methods section, such as the constancy of the age structure of Indigenous prisoners over the period of observation, will not be precisely true and so such assumptions will also add slightly to uncertainty in the findings here.

5. It would seem reasonable to expect that prisoners come in with poorer physical health than non-imprisoned members of the Indigenous community of the same age, as abuse of alcohol and other drugs and violence can be expected to be more common for people who end up in prison. My experience as a doctor in various Indigenous communities over a number of years as well as my experience in a prison with a majority of Indigenous prisoners, also shows that abstinence from tobacco smoking (since May 2014), improved compliance with medications and a healthier diet are other advantages which Indigenous prisoners have, compared to the disadvantages of their likely lifestyle after release. In short, prisoners are forced to live much healthier lives than many of them would otherwise choose to live on the outside.

6. A smaller issue that will lead to a minor underestimate of the differences between the mortality of Indigenous prisoners and non-prisoners is that the male Indigenous age-specific death rates that are used, apply not just to the 97% of Indigenous males over 15 years of age who are not in custody but also include the approximately 3% who are in custody.

Some of the items in the list above could suggest that the protective effect of custody on Indigenous mortality shown in this analysis may have been overestimated and other items could suggest an underestimation. However the most important source of inaccuracy would seem to be that discussed in item 5, and this implies that this study will considerably underestimate the protective effect of imprisonment on the type of people who come to prison.

A complete tally of Indigenous male mortality in all Australian prisons has been undertaken and shows that the crude Indigenous death rate in custody (of 0.19 per 100 person-years) is now slightly lower than the crude non-Indigenous death rate in custody.[3] An analysis of the death rate of ex-prisoners has also been undertaken.[4] Summary figures available from this study involve quite a number of approximations and do not adjust Indigenous ex-prisoner mortality for age, only giving results for all ex-prisoners combined, in broad age strata. To the extent that one can compare populations that differ geographically and in time and generally in age structure, a comparison of these two studies suggests that the Indigenous ex-prisoner mortality rate in the year after release is increased more than 4-fold (two estimates are available of indigenous ex-prisoner mortality, of which the lower is 8.61 per 1000 person-years).[4]

To properly allow for the likelihood that those at highest risk of choosing the most unhealthy lifestyles outside prison, are protected from such choices by imprisonment, a more accurate study could be envisaged where the age-adjusted mortality of Indigenous prisoners throughout Australia is compared with their age-adjusted mortality post-release with due allowance for other difficulties in assessing the mortality of ex-prisoners.[5] The study here, takes full account of age but compares Indigenous male prisoners to Indigenous men in general, not to Indigenous male ex-prisoners. It is also based on a very limited amount of observation. It can therefore provide only weaker evidence of the protective effect of imprisonment. As even this study provides reasonably convincing evidence for a protective effect of imprisonment, it reinforces the conclusion from previous studies that imprisonment almost certainly lowers Indigenous mortality.[3,4,5]

Ethical note

Due to the sensitivity of the issue, this author has encountered reluctance from several personnel who would have had the authorisation to organise a wider study of this type. However, the author considered this study to be important because a misplaced focus on an issue that can be revealed to be a non-problem, namely, deaths in custody, has an opportunity cost in terms of lives that could be saved elsewhere. Accordingly, this study proceeded without being submitted for scrutiny to either the relevant custodial system or health system and associated ethics committees. However, this study should be regarded as ethical as it involved no interventions and no disclosure of any data which could identify any individual and no disclosure regarding imprisonment that goes substantially beyond data publicly available.[1,6]

Implication of these findings

There has long been concern about black deaths in custody.[7] It would be entirely appropriate for the Indigenous community to be outraged if there were deaths occurring as a result of racially motivated neglect, criminal neglect, or indeed, outright murder. It seems reasonable to suspect that there may have been a few such deaths in recent history and for these, outrage is an appropriate response by the Indigenous community, and this outrage should be fully supported by the non-Indigenous community. However, the Black Deaths in Custody Royal Commission 'established that Aboriginal people in custody do not die at a greater rate than non-Aboriginal people in custody'.[7] The excess of Indigenous deaths that occur in custody simply reflects the excess of Indigenous people in custody. One response to the excess of Indigenous deaths in custody is a call to reduce the incarceration rate of Indigenous people. Unfortunately, whilst some Indigenous people are in prison as a result of situations such as non-payment of fines that would not result in imprisonment for more affluent people, many are in prison for serious violent crime largely inflicted on their own community.[6] Non-imprisonment or early release of violent offenders back into Indigenous communities seems likely to add to community disruption and dysfunction, so may well be counterproductive. The work here goes further and shows that some of the offenders themselves would suffer premature death as a result of early release from prison as they are likely to resume the self-destructive lifestyle from which they are largely protected by imprisonment.

Indigenous disadvantage is very real and has many components. For example, it seems likely to this author that current pro-development Government policies in remote areas, by overriding Indigenous sovereignty and land rights, will be perpetuating hopelessness. Much Indigenous disadvantage also seems to be the result of vicious cycles set in train by the earlier process of colonisation of Australia with subsequent welfare responses that have been dis-empowering. There is much to be done to overcome this disadvantage. Focusing on the wrong issue, black deaths in custody, diverts attention from real causes of disadvantage. Furthermore, if calls for reduced Indigenous imprisonment were heeded but without major social changes in other areas, the calculations here show that the direct result would be an increase in premature Indigenous deaths.

These conclusions could be extrapolated to other areas such as mandatory alcohol treatment programs. When risk to life is high, human rights have to be balanced against other considerations,[8] particularly the protective effect of holding people in a custodial arrangement. Since not all prisoners in this study had a prior lifestyle that was particularly unhealthy, one would expect that the protective effect of a custodial arrangement would be even greater for those taking part in a mandatory alcohol treatment program. This study can then be seen as allowing calculation of a lower bound on the person years of life that would be saved by such a program and this should inform any debate on the costs of such a program in terms of human rights.

References

1. Australian Bureau of Statistics. Table 19: Age-specific death rates, Indigenous status, selected states and territories, 2008-2012. ABS 3302.0. Deaths, Australia, 2012. Available at: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3302.0Main+Features12012 (accessed 29 October 2015).
2. Julious S, Nicholl J, George S. Why do we continue to use standardized mortality ratios for small area comparisons? J Public Health Med 2001; 23(1): 40-46.
3. Mathew Lyneham, Andy Chan. Deaths in custody in Australia to 30 June 2011. Twenty years of monitoring by the National Deaths in Custody Program since the Royal Commission into Aboriginal Deaths in Custody. Australian Institute of Criminology Reports, Monitoring Report 20, May 2013. Available at: http://www.aic.gov.au (accessed 12 April 2015).
4. Kinner S, Preen D, Kariminia A, Butler T, Andrews J, Stoové M, Law M. Counting the cost: estimating the number of deaths among recently released prisoners in Australia. Med J Aust 2011; 195(2): 64-8.
5. Kinner S, Forsyth S, Williams G. Systematic review of record linkage studies of mortality in ex-prisoners: why (good) methods matter. Addiction 2012; 108: 38-49.
6. Australian Bureau of Statistics. Prisoners in Australia. ABS 4157.0. Available at: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4517.0main+features352013 (accessed 6 December 2014).
7. Black Deaths in Custody Royal Commission Report, 1987. Available at: http://www.austlii.edu.au/au/other/IndigLRes/rciadic/national/vol1/1to done2.html (accessed 2 December 2014).
8. Pearson N. On the human right to misery, mass incarceration and early death. University of Sydney, Dr Charles Perkins Memorial Oration 2001. Available at: http://sydney.edu.au/koori/news/pearson.pdf (accessed 15 December 2014).

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CLIMATE CHANGE, OVERCROWDING AND NON-COMMUNICABLE DISEASES: THE 'TRIPLE WHAMMY' OF TUBERCULOSIS TRANSMISSION RISK IN PACIFIC ATOLL COUNTRIES

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Abstract

The atoll nations of Kiribati, Marshall Islands and Tuvalu are home to the highest rates of tuberculosis in the Pacific region. These countries also have very high rates of poverty, overcrowding and non-communicable diseases such as smoking and diabetes mellitus, which are all well-established risk factors for tuberculosis transmission. In addition, these three countries are among the most vulnerable in the world to the impacts of climate change, due to, *inter alia*, their very low elevation and extreme susceptibility to sea-level rise and extreme weather events such as cyclones, droughts and storm surges. Tuberculosis transmission rates have been linked to climate activity, such as changing seasons, yet tuberculosis has not hitherto been seriously discussed in the international literature as an infectious disease considered susceptible to climate change. This paper highlights the unique and unprecedented convergence of social and environmental risk factors for tuberculosis transmission risk in these three Pacific atoll countries, which demonstrate that tuberculosis is indeed a 'climate-sensitive' disease warranting international support for climate policy and public health intervention.

Key words: Pacific Islands, climate change, tuberculosis, non-communicable diseases

Introduction

The small island developing states (SIDS) of the Pacific region are among the most vulnerable in the world to the impacts of climate change, including the likely detrimental effects on human health.[1–4] The pathways by which climate change threatens population health may be considered in terms of direct (or primary), indirect (or secondary) and disseminated, diffuse or tertiary effects.[5–7] The priority 'climate-sensitive' health risks identified by Pacific island countries (PICs) in the vulnerability and adaptation assessment process led by the World Health Organization (WHO) between 2010 and 2013 include such direct effects (e.g. health impacts of extreme weather events and heat-related illnesses); indirect effects (including compromised water and food security and safety, and increasing burden of water- and food-borne diseases; increasing incidence of vector-borne diseases, zoonoses and respiratory illnesses; and disorders of the eyes, ears, skin and other body systems); and diffuse effects (disorders of mental/psycho-social health; increasing burden of non-communicable diseases; health system problems and population pressures).[8,9] Climate-sensitive health risks for PICs correspond largely with risks reported for other geographical areas.[10–13] In the Pacific, however, there exists a contemporary confluence of demographic, socio-economic and environmental risk factors that highlights some specific diseases hitherto overlooked in the climate change and health literature. One of these diseases is tuberculosis (TB) – a scourge since ancient times, still present in many developing countries, including the extremely climate-sensitive Pacific atoll nations of Kiribati, Marshall Islands and Tuvalu, where the prevalence of TB is among the highest in the world.[14]

TB is a mycobacterial infection spread by respiratory droplets. Recent progress in case detection, diagnostics, treatment and follow-up care notwithstanding, TB is still responsible for approximately 8.6 million new infections and 1.3 million deaths annually worldwide.[15,16] TB transmission risk is linked to conditions favouring exposure to infected individuals (e.g. poverty, overcrowding)[17,18] and impairment of the immune response of exposed individuals (e.g. HIV infection, alcohol abuse, malnutrition and immunosuppressive drugs).[19] Diabetes mellitus also compromises immune function, and is thus associated with increased TB infection and mortality.[20,21] Smoking and indoor air pollution are significant additional TB risk factors.[22] Risk factors for TB have been studied in depth in the relevant literature. One of the more holistic models of transmission considers population-wide determinants such as globalisation, urbanisation, poverty, and weak social, economic and environmental policies; and 'proximate' risk factors that affect individuals, such as malnutrition, HIV infection, lung diseases, diabetes mellitus and smoking.[18,23] The roles of the physical environment and meteorological factors, and the potential impact of climate change on TB transmission have been surprisingly absent from much of this literature. Despite Hippocrates of Cos – often referred to as the 'Father of Medicine' – having noted the relationship between variations in climate and patterns of disease, including 'phthisis' (TB) over two millennia ago,[24] and century-old reports discussing the impact of different types of climate on recovery of patients with TB,[25–27] specific consideration of the seasonality and climate-sensitivity of TB seems only to have returned to serious consideration relatively recently.[28–31] Given this correlation between climatic factors and TB activity, it seems reasonable to assume that globalization and the manifestations of climate change, in particular the prospect of more frequent and/or severe environmental disasters, may increase TB transmission risk, primarily by increasing the exposure of infectious individuals to others,[32,33] or via interplay with established risk factors such as HIV.[34]

This paper explores some important environmental and social determinants of TB transmission risk, that are considered in relation to the case study of three low-lying atoll countries in the Pacific region: Kiribati, Marshall Islands and Tuvalu. In doing so, well-understood TB risk factors such as overcrowding and smoking are placed in the context of 21st century health and development challenges facing Pacific communities, most particularly the effects of climate change and the 'epidemic' of non-communicable diseases (NCDs).[35] We postulate that a convergence of established and novel risk factors is occurring that may increase TB transmission risk for these island nations, if appropriate adaptation and mitigation strategies and socio-economic policies for poverty reduction are not implemented promptly and effectively.

Methods

We performed a retrospective descriptive analysis of secondary data from the three study countries related to TB infection rates, the prevalence of diabetes and other NCD risk factors, and population, demographic and geo-political information relevant to climate change. The primary sources of this information were census and survey data from each country, as well as the Demographic and Health Surveys conducted by the Secretariat for the Pacific Community (SPC, the regional technical agency based in New Caledonia) and the WHO STEPwise Surveillance of NCD Risk Factors (STEPS) surveys. In addition, the available literature on the epidemiology and social and environmental determinants of TB was reviewed, to assess the possible impact of converging risk factor pathways on TB transmission risk in the three study countries. Finally, a conceptual model was developed, drawing upon aspects of earlier models,[18] to explain this unique convergence of TB risk factors occurring in the Pacific atoll context.

Results

The table presents the descriptive analysis of the key risk factors related to TB and climate change impacts in the three Pacific atoll study countries.

Indicator	Kiribati	Tuvalu	Marshall Islands	Data source
Burden of TB				
TB Prevalence (/100 000) Incidence (/100 000) Case notifications (/100 000) Mortality (/100 000)	628 (10th highest in world) 429 343 (1st in Pacific) 17	377 (31st highest in world) 241 193 (4th in Pacific) 37	1080 (2nd highest in world) 572 276 (3rd in Pacific) 111	2012 TB data taken from the WHO Global Tuberculosis Report 2013 (WHO, 2013a)
Population size				
Population (2011 estimates unless otherwise stated) Proportion living in urban settings	103,758 (2010) 49%	11,206 47%	54,999 65%	Kiribati: Kiribati Census of Population and Housing (Government of Kiribati, 2011) Marshall Islands, Tuvalu: SPC-Statistics for Development Division 20111
Upstream determinants				
Population density (persons/square kilometre) Projected population density (national average persons/square kilometre, by 2030)	127 (national) (80th in world) 3184 (South Tarawa in 2010) 170	431 (national)(30th in world) 1900 (Funafuti in 2002) 480	304 (national)(44th in world) 2619 (Majuro in 2008) ~ 41,700 (Ebeye in 2011) 345	Kiribati: Current pop. density: Kiribati census 2005. Projected pop. density SPC-Statistics for Development Division 20111 Tuvalu: SPC-Statistics for Development Division 20111 Marshall Islands: SPC-Statistics for Development Division 20111
Annual net population growth rate	1.8%	0.5%	0.7%	SPC- Statistics for Development Division1
Gross Domestic Product per capita in USD	2,907	7,103	3,327	SPC- National Minimum Development Indicators2
Basic needs poverty rate*	21.8	26.3	52.7	SPC- National Minimum Development Indicators2
Youth literacy (%)	98.5%	98.6%	98%	SPC- National Minimum Development Indicators2
Proximate risk factors				
Diabetes mellitus in adults aged 20-79 Prevalence (year)	28.77% (2013)	14.53% (2013)	34.89% (2013)	International Diabetes Federation Diabetes Atlas, Sixth Edition (IDF, 2013)
TB-diabetes co-incidence (Specific location, where specified)	37%	9.5%	45% (Ebeye)	Kiribati: CDC-SPC-MHMS study (Viney et al, unpublished data) Tuvalu: Personal communication- Ms Temilo Seono (National TB Programme Co-ordinator) Marshall Islands: Nasa et al, 2014
Prevalence of overweight and obesity in adults (aged 15-64 years)	Males: 41.7% Females: 58.9%	Males: 76.3% Females: 87.9% ("overweight or obese")	Males: 37.9% Females: 52.2%	Kiribati and Marshall Islands: PICT NCD Risk Factor STEPS reports, 2005-2010 Tuvalu: Tuvalu DHS 2007
Smoking rates (Proportion adults who are daily smokers, aged 15 years and above)	54.8% (males 71.5%, females 39.2%)	37.9% (males 54.6%, females 22.7%)	19.8% (males 34.7%, females 4.2%)	Kiribati: WHO 2011 (from Kiribati STEPS, 2006) Tuvalu: WHO 2011 (from Tuvalu census 2002) Marshall Islands: WHO 2011 (from RMI STEPS 2002)
Prevalence of HIV infection Incident HIV diagnoses (2011)	0.018 2	0.052 0	0.030 1	SPC HIV epidemiological update 2012
Total fertility rate (births/woman) Crude birth rate (/1000 population)	Urban 3.5 Rural 4.1 Urban 30.7 Rural 28.8	Urban 4.2 Rural 3.7 22.9	Urban 4.1 Rural 5.2 31.1	Kiribati: SPC Kiribati DHS 2009 Tuvalu: TFR from Tuvalu DHS 2007, CBR from Tuvalu census 2002 Marshall Islands: TFR from RMI DHS 2007, CBR from SPC-Statistics for Development Division 2011 (last census 1999)
Household composition (i.e. level of overcrowding) Average number of people/household Proportion of households with ≥9 people	Urban 7.3 Rural 5.3 Urban 30% Rural 11%	Urban (Funafuti) 6.2 Rural (outer islands) 5.8 Funafuti: 31% Outer islands 6%	Urban 7.6 Rural 6.6 Urban >30% Rural ~25%	Kiribati: SPC Kiribati DHS 2009 Tuvalu: Tuvalu DHS 2007 Marshall Islands: RMI DHS 2007
Use of solid fuel for cooking (at household level) Use of stove/fire with no chimney/hood (as proportion of all households using solid fuel)	68.8% 98.2%	21.0% 77.9%	36.3% 93.7%	Kiribati: Kiribati DHS 2009 Tuvalu: Tuvalu DHS 2007 Marshall Islands: RMI DHS 2007
Environmental				
Maximum elevation (in metres)	81 (Banaba) (231st in world); majority of inhabited atolls <3	5 (243rd in world)	10 (242nd in world)	www.wikipedia.com

1. http://www.spc.int/sdd/
2. http://www.spc.int/nmdi/

*The proportion of the population living in poverty (as defined by the Millennium Development Goals (http://www.un.org/millenniumgoals/poverty.shtml)

As can be seen from the table, Kiribati, Marshall Islands and Tuvalu are relatively poor, extremely low-lying, urbanized and population-dense countries, meaning that the manifestations of climate change, particularly sea-level rise, are having – and will continue to have – profound effects on their respective societies and economies. These three countries have among the highest prevalence rates of TB and diabetes mellitus in the world. Between 15 and 35% of the adult population in these countries have diabetes, and up to 45% of TB patients have concomitant diabetes, which is of great concern in these countries experiencing the 'triple burden' of NCDs, communicable diseases and climate change.[36,37] A number of other social and environmental risk factors for TB are summarised in the table. The very high population densities of each country's capital atoll (South Tarawa in Kiribati, Majuro in the Marshall Islands and Funafuti in Tuvalu) and the extreme levels of overcrowding on Ebeye island in the Marshall Islands warrant special attention. An examination of these multiple, convergent risk factors in the three study countries suggests that there are plausible pathways by which climate change may interact with other, established TB risk factors and consequently act as an indirect driver of TB transmission risk (Figure 1).

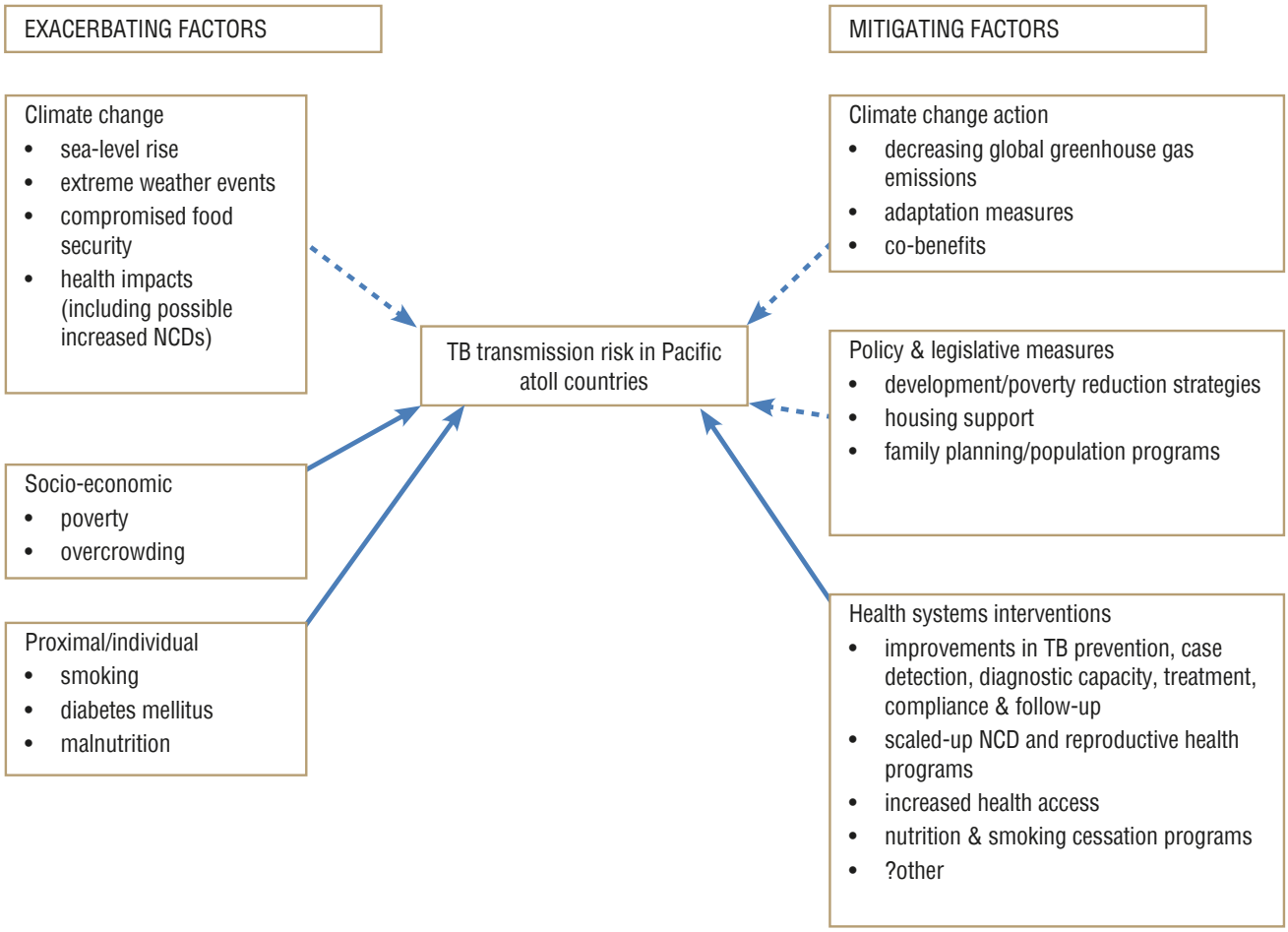

Figure 1. Schematic representation of risk factors for tuberculosis transmission in Pacific atoll countries and opportunities for intervention (NB. solid lines indicate where current research supports links; dashed lines indicate new/hypothetical links)

Discussion

Pacific island atoll countries such as Kiribati, Marshall Islands and Tuvalu have very high burdens of both TB itself, and some of the critical risk factors – such as overcrowding and NCDs – that contribute to TB transmission. TB rates have remained high in all three countries over time, despite increased investment in disease prevention and control, improved management, active TB case-finding strategies and highly sensitive and specific diagnostic tools.[38] All three countries of these countries are also extremely vulnerable to the biopsychosocial effects of climate change. These effects potentially amplify the role of TB determinants and risk factors through environmental, economic and social pathways (Figure 1). Thus, Kiribati, Marshall Islands and Tuvalu are likely unique in the Pacific - and possibly global - context, in sharing environmental and social characteristics that potentially increase the risk of TB, not to mention other infectious diseases, due to climate change-related phenomena such as sea-level rise. A few of the most important of these converging TB risk factors will be discussed in more detail below in relation to the three study countries.

Poverty

Poverty increases the risk of TB infection and worsens an individual's prognosis.[39,40] Evidence for this is suggested in the Pacific, where high rates of TB are observed in atoll countries with lower per capita income levels (Table). Conversely, the largest reductions in the burdens of TB over recent decades have been achieved in two PICs (Commonwealth of the Northern Mariana Islands and New Caledonia) which are both classified as high-income countries and whose level of economic development has ensured a better standard of living - including access to health care - across all income groups.

Overcrowding

Another significant concern in relation to TB risk is overcrowding. Urbanised areas in the capital atolls of each country (respectively, South Tarawa, Majuro and Funafuti) are becoming increasingly crowded. This has been identified as a significant risk factor for TB transmission, both in terms of overall population density[41] and household-level overcrowding,[42] whereby the number of persons per room is strongly associated with TB transmission risk.[43]

Population growth

High fertility rates compound the problem of population density and household-level overcrowding in all three countries.[44,45] To ensure sustainable development in Kiribati, Marshall Islands and Tuvalu, population growth must slow. This is especially important in the context of rural-urban migration and climate change, which increase both demand for and availability of land.[46] In parallel, measures targeting women's education and family planning must be implemented in parallel with economic development, and improved housing and infrastructure. All of these may be considered to be intrinsic – or at least related – to climate change adaptation. There has been significant attention, and some action to date, on adaptation in the Pacific, and in Kiribati in particular. One such adaptation measure, which is relatively extreme but deemed necessary by the leadership within the government of Kiribati, is the re-location of *i-Kiribati* citizens to neighbouring islands or countries, as one measure to reduce population density in South Tarawa (Anote Tong, President of Kiribati, personal communication, 2013).

Smoking and diabetes

Smoking and diabetes are important proximate risk factors for TB in the Pacific context; smoking is also a well-known risk factor for a range of other NCDs including heart disease and certain cancers.[47,48] Smoking and diabetes increase the risk of TB synergistically[20,22] and approximately 29% of all TB in 22 high-burden endemic countries is attributable to these two proximate risk factors.[18] Seven of the ten highest diabetes-prevalence countries globally are in the Pacific, with Marshall Islands and Kiribati respectively the third and fourth highest.[49] Both countries are implementing TB-diabetes collaborative control activities in response to the identified link between the two diseases, with patients with diabetes recognised as having a threefold risk of developing TB.[20,50,51] Case-control studies conducted in Kiribati show that TB patients appear three times more likely to have diabetes than people without TB (Viney *et al*, unpublished data, 2014) and in the Marshall Islands approximately 45% of TB patients had concomitant diabetes (Nasa *et al*, 2014). Global efforts to detect, diagnose and control diabetes are therefore likely to have a positive impact on TB control.[52,53] All three study countries also have high rates of daily cigarette smoking – see table. Thus, localised strategies to prevent and reduce the burden of diabetes and smoking appear likely to reduce the burden of TB in the Pacific.

Climate change

These three low-lying atoll countries are among the most vulnerable in the world to the impacts of, *inter alia*, sea-level rise (bringing with it the prospect of forced relocation) and the potential for compromised water and food security. Food security - which exists 'when all people at all times have access to sufficient, safe, nutritious food to maintain a healthy and active life'- is a complex development issue which has already had a profound negative impact on the health of Pacific island populations.[54] Compromised food security can result in over-nutrition, with resultant increase in individual and population level overweight and obesity, and subsequent development of type 2 diabetes.[55] The fragility of food security is compounded in atolls due to the lack of arable land for agriculture and the related scarcity of fresh water.[56] Water, sanitation and hygiene (WASH) problems already place a heavy burden on *i-Kiribati* communities, as the absence of groundwater sources enforces a reliance on rainwater harvesting and wells to aquifers, which frequently become contaminated with pathogens causing diarrhoea.[57] This, along with the lack of improved sanitation facilities in most households and the common practice of open defecation (including in the lagoon side of the atolls), particularly in children, contributes to high rates of diarrhoeal disease, which then feeds into a vicious cycle of malnutrition, immune suppression and increased transmission of infections.[58] There is little research on the association of TB and climate change, and TB has been hitherto all but absent from the various published lists of diseases thought likely to be susceptible to climate change. We argue that traditional schemas for upstream determinants and risk factors for TB should incorporate the wider effects of climate change and consideration of the ecology of fragile island environments. These islands have a unique suite of vulnerabilities which impacts on the health of their populations, but may also provide opportunities for intervention. The latter mainly relate to interventions to reduce poverty, smoking and NCD rates, as well as reducing greenhouse gas emissions and enabling the so-called 'co-benefits' of climate change mitigation, which have positive effects on individual and population health.

Other opportunities for health protection include mainstreaming climate change adaptation and mitigation measures with health systems strengthening. Guidelines exist on building climate-resilient health systems, which incorporates the full spectrum of health sector activities, from research, governance, financing, emergency preparedness and capacity-building to provision of essential services, technology and infrastructure.[59] Poorly-resourced health systems such as those in Kiribati, Marshall Islands and Tuvalu are at close to maximal capacity at present, yet still struggle to achieve adequate health access and outcomes. These difficulties are very likely to be exacerbated by climate change, as with other major development challenges, thus any support to the health sector in these and other countries facing similar challenges may be considered not just relevant, but vital to climate change adaptation.

Conclusion

In the Pacific atoll countries of Kiribati, Marshall Islands and Tuvalu there is a unique convergence of risk factors for TB that is coupled with the already devastating effects of climate change in these highly vulnerable communities. Therefore, we argue that, in the Pacific atoll context at least, TB must be considered a climate-sensitive disease. Efforts towards addressing the causes and effects of climate change in these small, poor, overcrowded, low-lying atoll countries must take into account the broad range of health impacts that climate change entails, and the health sector should provide leadership in addressing these impacts via a 'Health in all policies' approach to adaptation and mitigation. In addition, efforts towards improved TB control should incorporate wider contextual issues such as social, economic and environmental factors driving disease transmission, and consider the unprecedented pressures that climate change places on TB and other, hitherto overlooked, climate-sensitive diseases. Policies and interventions to improve the socioeconomic status of communities (including poverty reduction strategies and provision of adequate housing); increasing access to, and quality of, health services (particularly those related to TB, NCDs and reproductive health); and addressing the drivers and impacts of climate change, will benefit population health, and have the potential to reduce TB transmission risk in the face of climate change in Pacific atolls and other vulnerable communities elsewhere in the developing world.

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References

1. Pachauri RK, Allen MR, Barros VR, Broome J, Cramer W, Christ R, *et al.* Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Available at: http://epic.awi.de/37530/ (accessed 28 October 2015)
2. Mimura N. Vulnerability of island countries in the South Pacific to sea level rise and climate change. Clim Res 1999; 12: 137-43.
3. Russell L. Poverty, climate change and health in Pacific island countries. Menzies Centre for Health Policy, 2011. Available at: http://ses.library.usyd.edu.au/handle/2123/9202 (accessed 28 October 2015)
4. Woodward A, Hales S, Weinstein P. Climate change and human health in the Asia Pacific region: who will be most vulnerable? Clim Res 1998; 11: 31-8.
5. Butler CD, Harley D. Primary, secondary and tertiary effects of eco-climatic change: the medical response. Postgrad Med J 2010; 86: 230-4.
6. McMichael AJ, Powles JW, Butler CD, Uauy R. Food, livestock production, energy, climate change, and health. Lancet 2007; 370: 1253-63.
7. McMichael AJ. Globalization, Climate Change, and Human Health. N Engl J Med 2013; 368: 1335-43.
8. McIver L, Hanna L. Fragile paradise - health and climate change in the South Pacific. In: Butler CD, Dixon J, Capon AG (eds). Health of People, Places and Planet: Reflections based on Tony McMichael's four decades of contribution to epidemiological understanding. Canberra: ANU Press; 2015.
9. Hanna L, McIver L. Small island states - canaries in the coal mine of climate change and health. In: Butler CD (ed). Climate Change and Global Health. Wallingford, UK: CABI; 2014.
10. Haines A, Kovats RS, Campbell-Lendrum D, Corvalan C. Climate change and human health: Impacts, vulnerability and public health. Lancet 2006; 367: 2101-9.
11. McMichael AJ, Woodruff RE, Hales S. Climate change and human health: present and future risks. Lancet 2006; 367: 859-69.
12. McMichael AJ. Climate change and human health: risks and responses. Geneva: World Health Organization; 2003.

13. Patz J, Campbell-Lendrum D, Holloway T, Foley J. Impact of regional climate change on human health. Nature 2005; 438: 310-7.
14. Secretariat of the Pacific Community, 2010. Tuberculosis surveillance in the Pacific Island countries and territories. Noumea, New Caledonia.
15. Donald PR, van Helden PD. The global burden of tuberculosis — combating drug resistance in difficult times. N Engl J Med 2009; 360: 2393-5.
16. World Health Organization. Global Tuberculosis Report 2013. Geneva: WHO; 2013. p. 306.
17. Munch Z, Van Lill SWP, Booysen CN, Zietsman HL, Enarson DA, Beyers N. Tuberculosis transmission patterns in a high-incidence area: a spatial analysis. Int J Tuberc Lung Dis 2003; 7: 271-7.
18. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med 2009; 68: 2240-6.
19. Lawn SD, Zumla AI. Tuberculosis. Lancet 2011; 378: 57-72.
20. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008; 5: e152.
21. Baker M, Das D, Venugopal K, Howden-Chapman P. Tuberculosis associated with household crowding in a developed country. J Epidemiol Community Health 2008; 62: 715-21.
22. Lin H-H, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med 2007; 4: e20.
23. Marais BJ, Lönnroth K, Lawn SD, *et al.* Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. Lancet Infect Dis 2013; 3099: 1-13.
24. Falagas ME, Bliziotis IA, Kosmidis J, Daikos GK. Unusual climatic conditions and infectious diseases: observations made by Hippocrates. Enferm Infecc Microbiol Clin 2010; 28: 716-8.
25. Peers R. The influence of climate upon tuberculosis; with remarks on the climate of Colfax, California. Cal State J Med 1908; VII: 106-10.
26. Grant R. Tuberculosis and climate. J Natl Med Assoc 1917; 10: 18-21.
27. Trask J. Climate and tuberculosis: the relation of climate to recovery. Public Health Rep 1917; 32: 318-24.
28. Douglas AS, Strachan DP, Maxwell JD. Seasonality of tuberculosis: the reverse of other respiratory diseases in the UK. Thorax 1996; 51: 944-6.
29. Fares A. Seasonality of tuberculosis. J Glob Infect Dis 2011; 3: 46-55.
30. Naranbat N, Nymadawa P, Schopfer K, Rieder HL. Seasonality of tuberculosis in an Eastern-Asian country with an extreme continental climate. Eur Respir J 2009; 34: 921-5.
31. Yang X, Duan Q, Wang J, Zhang Z, Jiang G. Seasonal variation of newly notified pulmonary tuberculosis cases from 2004 to 2013 in Wuhan, China. PLoS One 2014; 9: e108369.
32. Schipper L, Pelling M. Disaster risk, climate change and international development: scope for, and challenges to, integration. Disasters 2006; 30: 19-38.
33. Weiss R, McMichael A. Social and environmental risk factors in the emergence of infectious diseases. Nat Med 2004; 10: S70-6.
34. Abayomi A, Cowan MN. The HIV/AIDS epidemic in South Africa: convergence with tuberculosis, socioecological vulnerability, and climate change patterns. S Afr Med J 2014; 104: 583.
35. Tuitama LT, Young-soo S, Clark H, Tukuitonga C, Beaglehole R. Acting on the Pacific crisis in non-communicable diseases. Lancet 2014; 384: 1823-4.
36. Barrett B, Charles JW, Temte JL. Climate change, human health, and epidemiological transition. Prev Med (Baltim) 2014; 70: 69-75.
37. World Health Organization. WHO Multi-Country Cooperation Strategy for the Pacific (2013-2017). Manila: WHO; 2013.
38. Viney K, O'Connor J, Wiegandt A, Lambert M, Cox H, Downing S. Tuberculosis trends in the Pacific: 2000-2006. Pacific Health Dialog 2010; 16(1): 157-171.
39. Spence D, Hotchkiss J, Williams C, Davies P. Tuberculosis and poverty. BMJ 1993; 307: 759-61.
40. Oxlade O, Murray M. Tuberculosis and poverty: why are the poor at greater risk in india? PLoS One 2012; 7: 1-8.
41. Gninafon M, Trébucq A, Rieder HL. Epidemiology of tuberculosis in Benin. Int J Tuberc Lung Dis 2011; 15: 61-6.
42. Baker M, Das D, Venugopal K, Howden-Chapman P. Tuberculosis associated with household crowding in a developed country. J Epidemiol Community Health 2008; 62: 715-21.
43. Clark M, Riben P, Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. Int J Epidemiol 2002; 31: 940-5.
44. Ware H. Demography, migration and conflict in the Pacific. J Peace Res 2005; 42: 435-54.
45. Taylor R, Bampton D, Lopez AD. Contemporary patterns of Pacific Island mortality. Int J Epidemiol 2005; 34: 207-14.
46. Connell J. Environmental change, economic development, and emigration in Tuvalu. 1999; 22: 1-20.
47. Lienhardt C, Fielding K, Sillah JS, *et al.* Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa. Int J Epidemiol 2005; 34: 914-23.
48. Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. N Engl J Med 2014; 370: 60-8.
49. Danaei G, Finucane MM, Lu Y, *et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. Lancet 2011; 378: 31-40.
50. Stevenson CR, Forouhi NG, Roglic G, *et al.* Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health 2007; 7: 234.
51. Marais BJ, Lönnroth K, Lawn SD, *et al.* Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. Lancet Infect Dis 2013; 13: 436-48.
52. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008; 5: e152.
53. Alisjahbana B, Sahiratmadja E, Nelwan EJ, *et al.* The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis 2007; 45: 428-35.
54. Asian Development Bank. Food Security and Climate Change in the Pacific - Rethinking the Options. Manila: ADB; 2011.
55. Beaglehole R, Bonita R, Horton R, *et al.* Priority actions for the non-communicable disease crisis. Lancet 2011; 377: 1438-47.
56. Food and Agriculture Organization. Climate change and food security in Pacific island countries. Rome: FAO; 2008.
57. McIver L, Woodward A, Davies S, Tibwe T, Iddings S. Assessment of the health impacts of climate change in Kiribati. Int J Environ Res Public Health 2014; 11(5): 5224-40.
58. Wu J, Yunus M, Streatfield PK, Emch M. Association of climate variability and childhood diarrhoeal disease in rural Bangladesh, 2000-2006. Epidemiol Infect 2014; 142(9): 1859-68.
59. Panic M, Ford JD. A review of national-level adaptation planning with regards to the risks posed by climate change on infectious diseases in 14 OECD nations. Int J Environ Res Public Health 2013; 10: 7083-109.

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CAMELS, COMBAT MEDICINE AND COMMUNICABLE DISEASES – EXPERIENCES ON OPERATION SLIPPER

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Abstract

Between November 2013 and May 2014, the author deployed to the Middle East as the Senior Medical Officer (SMO) for Australian Defence Force (ADF) personnel in the Middle East and Afghanistan. He was responsible for ensuring that adequate healthcare was provided to more than 1 200 personnel located across an enormous area, stretching from Afghanistan in the north to Tanzania in the south, and from Bahrain in the west to the Indian Ocean in the east. This was professionally very challenging, and involved the management of a wide range of health threats, including improvised explosive devices and rabies in Afghanistan, heat illness, Middle East respiratory syndrome (MERS) and vehicle accidents in the Middle East, and tropical diseases such as yellow fever and malaria along the east African coast. The deployment was also personally challenging, with the requirement to travel extensively and negotiate with a wide range of individuals and organisations, at a time when national involvement in the Middle East was being significantly reduced.

Key words: Australian Defence Force, military medicine, Middle East, public health, tropical medicine, occupational medicine

Introduction

In November 2013, the author (Fig. 1) was fortunate to deploy to the Middle East as the Senior Medical Officer for the ADF in the Middle East Area of Operations (MEAO). This position is a multi-faceted one, involving a variety of roles including being the medical advisor to a two-star general and his staff, a staff officer on a deployed headquarters, and the technical supervisor for health personnel deployed across thousands of kilometres. Tasks undertaken included constantly reviewing health support arrangements to ADF personnel across the MEAO (involving a combination of civilian, Australian and Coalition health facilities), constantly assessing potential health threats and mitigating these wherever possible, overseeing the day-to-day management of casualties, and providing health planning input for any future activities. This was professionally challenging, and drew on a wide spectrum of medicine, including tropical medicine, public health, medical administration, occupational medicine and military medicine.

Figure 1. The author in adverse environmental conditions in Kabul, 2014.

These challenges were further complicated by an extremely dynamic operational environment, with the draw-down of Australian personnel from Tarin Kowt in Afghanistan, continuing maritime operations in the Arabian Gulf and Indian Ocean, presidential elections in Afghanistan, support to the UN in South Sudan, and the planned reduction of NATO/ISAF troop numbers in Afghanistan throughout 2014. It would be fair to say that developing and maintaining situational awareness was a key requirement of the position, and that invariably this meant travelling extensively and often! As could be expected from the size and geopolitical contrasts within the region, there was a wide range of potential health threats that needed to be considered. These are discussed below.

Motor vehicle trauma

Motor vehicle trauma was (and remains) a significant health threat, particularly in Bedouin Arabian Gulf countries. While the road infrastructure is world class in most of the Gulf States, fatality rates (in terms of fatalities per hundred million vehicle kilometres and fatalities per hundred thousand vehicles) are up to ten times greater than in countries such as the US and UK.[1] The largest single cause of accidents was classed as careless driving, contributing more than 36.5% of all casualties and fatalities in motor vehicle accidents.[1] This was reinforced by visits to the local trauma hospital in Dubai (the El Rashid Hospital), which was impressive for not only the trauma facilities, but also the volume of trauma patients treated. One particular issue raised was the morbidity and mortality associated with camel versus vehicle (Fig. 2), with the size and mass of the camel resulting in a higher proportion of serious injuries compared to the Australian version.

Figure 2. Vehicular hazard near Dubai.

(Reproduced from Image by Andrey, sourced from http://holidayexperiences.net/photos-of-the-hour-from-dubai-15/)

Malaria

The assessment and management of the malaria risk throughout the MEAO was extremely variable. For example, malaria in Afghanistan (predominantly *P. vivax* malaria) was characterised by a number of variables including irrigation, temperature, altitude and season (generally May to November). This meant that protection measures for troops varied considerably between different national forces, with 27 different combinations of drugs and other measures for 28 different troop-contributing nations.[2] Despite this, the rate of malaria was relatively low, with 85 cases of malaria in British, German and US troops since 2002.[2] This was in contrast to the risk assessment for personnel visiting locations such as Dar Es Salaam in Tanzania, where exposures were short (such as port visits), but the risk and mortality (predominantly from *P. falciparum* malaria) were much higher.[3]

Rabies

While rabies is a well-recognised hazard on the Indian subcontinent, causing in excess of 20 000 deaths per annum, troops in Afghanistan from the majority of troop-contributing nations are not routinely vaccinated against rabies pre-exposure, unless they are identified as being at higher risk (such as dog handlers). This relies on soldiers reporting immediately if they are bitten, and seeking appropriate post-exposure prophylaxis. This sort of behavioural response does occasionally fail, and the death of a U.S. Army soldier was reported in late August 2011, related to a dog bite in Afghanistan in January 2011.[4]

Yellow Fever

Yellow fever is a mosquito-transmitted viral haemorrhagic fever, endemic to sub-Saharan Africa and tropical South America. It has been known to be fatal in 20-50% of patients with severe disease, but is preventable by vaccination.[5] In late December 2013, increased tension in South Sudan resulted in assistance being required to the UN mission in that country. Current guidance is that yellow fever vaccination is recommended for travel to South Sudan.[6] The management of this issue required consideration of a number of factors, including the limited world-wide availability of the vaccine, the delay between vaccination and effectiveness (minimum 10 days), the requirement to access vaccination from accredited yellow fever vaccination centres, and potential travel implications for any unvaccinated personnel attempting to enter countries (including Australia) that have restrictions on people arriving from yellow fever endemic countries. Throw in the Christmas-New Year public holiday period, and effective risk management becomes paramount!

Leishmaniasis

Leishmaniasis is a sandfly-borne disease caused by protozoa of the genus *Leishmania*. Cutaneous leishmaniasis is endemic to Afghanistan, and has the potential to cause chronic lesions and skin ulcers. This is a particular issue in Kabul, where 24.6% of the population have either active leishmaniasis lesions or scars.[7] There is no chemoprophylaxis for this condition, and sandfly bite avoidance is the main protection. Management of this risk is complicated by a general lack of awareness of the condition, and perceived low mortality and morbidity compared to other conditions.

Middle East respiratory syndrome

Middle East respiratory syndrome (MERS) is a viral respiratory illness first reported in Saudi Arabia in 2012, caused by a coronavirus called MERS-CoV. It has a case fatality rate of approximately 35%.[8] Dromedary camels are suspected to be the primary source of infection for humans, although the exact routes of direct or indirect exposure are not fully understood. Current guidance involves travellers at high risk avoiding exposure to camels, and all other travellers practising good hand and food hygiene when camels are present.[8] While ADF members by definition would not be high risk, consideration of rest and recreation activities, such as visits to camel farms, was required.

Environmental hazards

In such a large and diverse region, environmental hazards included heat-related illness (particularly in the UAE), dust and smoke, noise (particularly given proximity to aircraft and airfields) and hypothermia (particularly in Afghanistan). This required education, monitoring and protective equipment as appropriate.

Combat-related injuries

Combat-related injury, while only a small percentage of overall injury sustained by a deployed force, remains an important consideration from both a morale and psychological perspective. While Australia has sustained 40 deaths and 291 wounded in action during its recent involvement in the MEAO, the level of combat-related injuries was appreciably lower during November 2013 to May 2014, due to the draw-down in numbers and change in role of coalition troops.[9] Nonetheless, training for this condition remains important, especially with regard to responding to battlefield trauma, including the use of the combat tourniquet.

Personal perspectives on deployment

This deployment represented the highlight of over 30 years in the ADF, including previous deployments to northern Iraq in 1991 and East Timor in 2001. The multi-faceted nature of the role was continually challenging, and the dynamic situation meant that nothing could be assumed. This required extensive travelling around the region to develop and maintain situational awareness of health threats and health support arrangements. The major challenge of changing health threats is that there are a lot of them, and they all require time and effort to manage and mitigate. As many of them involve behavioural modification or training, there is an opportunity cost involved, such that increasing the time for one threat then reduces the effectiveness of training for other threats. In addition, there is then a challenge in how this risk management process can be effectively communicated to a non-medical command structure, which requires an understanding of how the military works.

Other aspects of the deployment were equally demanding. While strong friendships are developed, living in close confines for extended periods, long working hours, missing family support and sleep deprivation can all have negative mental health consequences. Maintaining an awareness of how those around you are travelling becomes an important responsibility for everyone to attempt to reduce the mental health consequences of deployment.

A particular highlight for the author was the opportunity to work with the Afghan National Army (ANA) health services in Kandahar in reviewing their rehabilitation services. Given that by 2014, the ANA was bearing the brunt of combat-related injuries, including traumatic amputations, this was having a resulting impact on the number of patients requiring amputation by their health facilities. This was further complicated by the lack of dedicated rehabilitation personnel and facilities in country, and various options were considered to address this.

Conclusion

To be an effective SMO for a deployed force, a wide range of skills and capabilities are required, both professional and personal. Professional requirements include a broad range of medical practice, including tropical medicine, travel medicine, occupational medicine, public health and medical administration, particularly as they apply to the military setting. While it is one thing to have knowledge in areas such as tropical and travel medicine, it is another thing to apply this in a dynamic operational setting. Effective risk management is vital to the effective performance of the SMO role, drawing all these elements together. Personal requirements include the ability to provide leadership to more junior health staff (even if they do not report to you directly), communication skills (especially with command and staff officers, and other coalition partners), the ability to be an effective team player (especially in the headquarters environment), and most importantly, a good sense of humour. While all these skills take time to develop, there is immense satisfaction in being able to apply them in a dynamic and challenging part of the world (and one which is likely to remain so for some considerable time).

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References

1. Bener A, Crundall D. Road traffic accidents in the United Arab Emirates compared to Western countries. Advances in Transportation Studies 2005; Section A6: 5-12.
2. Croft AM, Darbyshire AH, Jackson CJ, van Thiel PP. Malaria prevention measures in coalition troops in Afghanistan. JAMA 2007; 297: 2197-200.
3. World Health Organization. Malaria country profile – United Republic of Tanzania. World Malaria Report. Geneva, WHO; 2010. Available from: www.who.int/malaria (accessed October 2014).
4. Centers for Disease Control and Prevention. Imported human rabies in a U.S. Army soldier – New York, 2011. MMWR Morb Mortal Wkly Rep 2012; 61(17): 302-5.
5. Australian Government Department of Health. Australian Immunisation Handbook, 10th Ed. Section 4.23. Yellow fever. Canberra, Australian Government; 2014, pp 439-40. Available at: www.immunise.health.gov.au (accessed October 2014).
6. Centers for Disease Control and Prevention. Health information for travelers to Sudan. Available at: wwwnc.cdc.gov/travel/destinations/traveler/none/sudan (accessed October 2014).
7. Reithinger R, Mohsen M, Aadil K, Sidiqi M, Erasmus P, Coleman PG. Anthroponotic cutaneous leishmaniasis, Kabul, Afghanistan. Emerg Infect Dis 2003; 9(6):727-9.
8. Australian Government Department of Health. Middle East respiratory syndrome coronavirus (MERS-CoV). Situation update, 25 September 2014. Available at: www.health.gov.au/mers-coronavirus (accessed October 2014).
9. Brennan LB. Australian battle casualties – East Timor to Afghanistan. Australasian Military Medicine Association, Conference Abstracts, 2014. Available at: www.amma.asn.au (accessed October 2014).

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ONCE THE SENSITIVITIES ARE KNOWN: A SYSTEMATIC REVIEW OF ANTIBIOTIC CHOICE IN TYPHOID FEVER

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Abstract

Typhoid fever is primarily a disease of the developing world, which can also be seen in travellers returning to developed countries. Treatment guidelines vary between countries and are complicated by evolving resistance patterns. Currently nalidixic acid-resistant (NaR) and multidrug resistant (MDR) isolates are common. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were adhered to in this review. Data were identified through an electronic search of PubMed/MEDLINE and Scopus databases. Pre-defined inclusion/exclusion criteria determined the final selection of seven open-label, well-powered randomised controlled trials.

Overall, no definite recommendation can be made due to the small number of large, well-powered comparative trials conducted on typhoid. Broadly, the results of this systematic review suggest that quinolones and azithromycin are equally effective in treating fully-sensitive *Salmonella enterica* serotype Typhi, while azithromycin is favoured over quinolones in the presence of nalidixic acid resistance. Quinolones are favoured over oral cephalosporins in all typhoid resistance types. Gatifloxacin is highly efficacious even in a population with high nalidixic acid resistance and chloramphenicol is as effective as either azithromycin or gatifloxacin in patients who do not have MDR typhoid. However, caution is recommended with the use of chloramphenicol, as there should be careful monitoring for evidence of serious toxicity. There is a need for further comparative trials, involving ceftriaxone, ciprofloxacin and azithromycin.

Key words: typhoid, enteric fever, fluoroquinolones, cephalosporins, azithromycin, chloramphenicol, treatment, guidelines, MDR, NaR.

Introduction

Typhoid fever is a tropical infectious disease, transmitted through the faecal-oral route, which is prevalent in the Indian subcontinent, Southeast Asia, South America and Africa.[1,2] It commonly occurs in impoverished, crowded areas with poor sanitation and sewage systems that lead to faecal contamination of food and water supplies.[3,4] The systemic infection is caused by the Gram-negative bacillus *Salmonella enterica* serotype Typhi, and commonly presents with fever, malaise, chills, dull frontal headache, abdominal pain and diarrhoea or constipation. A proportion of patients may present with splenomegaly, relative bradycardia or rose spots – blanching erythematous maculopapular lesions.[4,5] The classic fever pattern is initially low grade, which fluctuates over the first week, but then rises and becomes sustained. Similar symptoms of enteric fever can also be caused by *S. enterica* serotype Paratyphi organisms, but this is a milder illness with a short duration.[1,4] Diagnostic confirmation for typhoid is mainly by blood or bone marrow culture.[4-6] The estimated global burden of typhoid fever in 2010 was 26.9 million cases.[1] It is important to recognise typhoid fever in returning travellers to developed countries since typhoid can have severe complications e.g. intestinal perforation, gastrointestinal bleeding, encephalopathy and even death.[4,5] The estimated case fatality rate is 1%.[1,2] Typhoid needs to be recognised early by clinicians and treated with the most effective antibiotic, which can be selected on the basis of the susceptibility profile.

Background of antibiotic resistance

Treatment for typhoid involves an appropriate choice of antibiotic as well as supportive management, such as adequate hydration, nutrition and use of antipyretics.[6,7] The optimal choice of antibiotic varies between countries and is complicated by the evolving nature of antibiotic resistance. Multidrug-resistant (MDR) typhoid emerged globally in the late 1980s. MDR is defined as resistance against chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (cotrimoxazole), and rates vary around the world. Rates of MDR typhoid in returning travellers to Australia are relatively stable at between 4 and 11%.[8,9] Chloramphenicol-sensitive strains are re-emerging in developing countries.[10-12] Quinolone-resistant typhoid predominantly occurs in Southeast Asia and the Indian subcontinent, and rates of resistance are increasing worldwide, reflecting increased quinolone use.[8] In Egypt, for instance, the first line of treatment against typhoid is quinolones but there has been increasing incidence of resistance and studies have shown this to be related to point mutations in the *gyrA* gene in resistant isolates.[13] Most recent prevalence rates in Nepal indicate 63.4% nalidixic acid resistant (NaR) *S.* Typhi and 90.5% NaR *S.* Paratyphi.[8] Quinolone resistance is confirmed by testing for nalidixic acid resistance of *Salmonella* Typhi isolates or if the quinolone minimum inhibitory concentration (MIC) of the isolate is >0.125 microgram/mL.[7,14]

Rationale for this review

Antibiotic treatment guidelines for typhoid fever vary. For instance, the World Health Organization (WHO) recommends fluoroquinolones for fully-sensitive typhoid, fluroquinolones or cefixime for MDR typhoid, and azithromycin or ceftriaxone for quinolone-resistant typhoid.[6] Second-line drugs recommended by the WHO are chloramphenicol, amoxicillin, or cotrimoxazole for fully-sensitive typhoid, azithromycin for MDR typhoid, and cefixime for quinolone-resistant typhoid. However, the WHO has not updated these guidelines since 2003. The online Australian Therapeutic Guidelines for Antibiotics recommends azithromycin or ceftriaxone as first-line treatment, especially when waiting for antibiotic susceptibilities. Azithromycin is the primary choice of drug for quinolone-resistant typhoid. Ciprofloxacin is recommended for quinolone-sensitive isolates. Ceftriaxone IV is an alternate antibiotic that is recommended either for initial IV treatment, or if there is a delayed clinical response (e.g. fever >7 days).[7] Lastly, UpToDate, a resource that frequently supports clinicians to make evidence-based clinical decisions, recommends ceftriaxone for severe systemic typhoid illnesses and ciprofloxacin as first-line treatment for uncomplicated typhoid, unless patients are from regions with high rates of fluoroquinolone resistance.[15] The only consistency amongst the three guidelines is that quinolone-resistant uncomplicated typhoid can be treated with either azithromycin or ceftriaxone. The rationale for undertaking this review was the age of the WHO guidelines (>10 years), the apparent variability in different guidelines for antibiotic treatment, and the lack of guidelines that take into account known sensitivities. Furthermore, the comparative clinical efficacy of the three most commonly-used classes of antibiotics for typhoid (fluoroquinolones, cephalosporins and macrolides), has not been systematically analysed. Hence, the aim of this review of the available literature is to determine the most clinically-effective antibiotic once the antibiotic sensitivity results become available – a common clinical scenario in countries with the resources to test sensitivity.

Methods

The literature search, selection and data analysis were all conducted by the one author (R.M.). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were adopted to produce a transparent systematic review.[16]

Literature search

Data was identified through a systematic electronic search of PubMed/MEDLINE and Scopus databases for English language articles up to June 2014, without date restriction. Combinations of the following search terms were applied: 'enteric fever', 'typhoid fever', '*Salmonella* Typhi', 'fluoroquinolones', 'ciprofloxacin', 'ofloxacin', 'gatifloxacin', 'cephalosporins', 'ceftriaxone', 'cefixime', 'macrolides', 'azithromycin' and 'chloramphenicol'. The search was limited to 'clinical trials' or 'reviews'. Firstly, relevant titles were identified, and then abstracts were screened according to prior inclusion/exclusion criteria. A secondary search through the reference lists of key review articles was undertaken. Even though the reviews identified in the primary search were not included for the final qualitative analysis, those articles assisted in this secondary search. The full text articles obtained were further assessed for eligibility.

Selection Criteria

Articles selected answered the formulated clinical question, which was based on the PICO principle.[17] The trials had to compare antibiotics from at least two different classes in culture-proven enteric fever patients, and assess the majority of the following clinical outcomes: mean fever clearance time (FCT), clinical failure (CF)/treatment failure (TF) rate, microbiological failure (MF) rate and relapse rate (RR). Detailed specific reasons for excluding articles are highlighted in Figure 1. For instance, only randomised controlled trials (RCTs) were included to ensure there were no sources of selection bias in the trials. Measurement bias in trials was assessed by ensuring that only blood- or bone marrow-culture-confirmed enteric fever studies were included. Other inclusion criteria were: blinded or open-labelled studies (conducted in resource-poor countries, where most typhoid occurs), available resistance data and an 80% minimum power analysis calculation.[18] An adequate power analysis, to determine the minimum sample size required to detect any difference between the treatment arms, was included as a requirement. There were 22 studies with inadequate or no power analysis and hence they were excluded. Clinical trials that assessed the efficacy of single antibiotics or those that compared two antibiotics within the same class were excluded. Other types of articles excluded were reviews, retrospective studies, case reports and articles primarily about irrelevant typhoid related topics. The WHO states that norfloxacin has inadequate oral bioavailability and is no longer recommended for use,[6] whilst pefloxacin and fleroxacin are also no longer used due to their specific toxicities e.g. phototoxicity and central nervous system effects.[19] Six trials involving these three antibiotics were excluded.

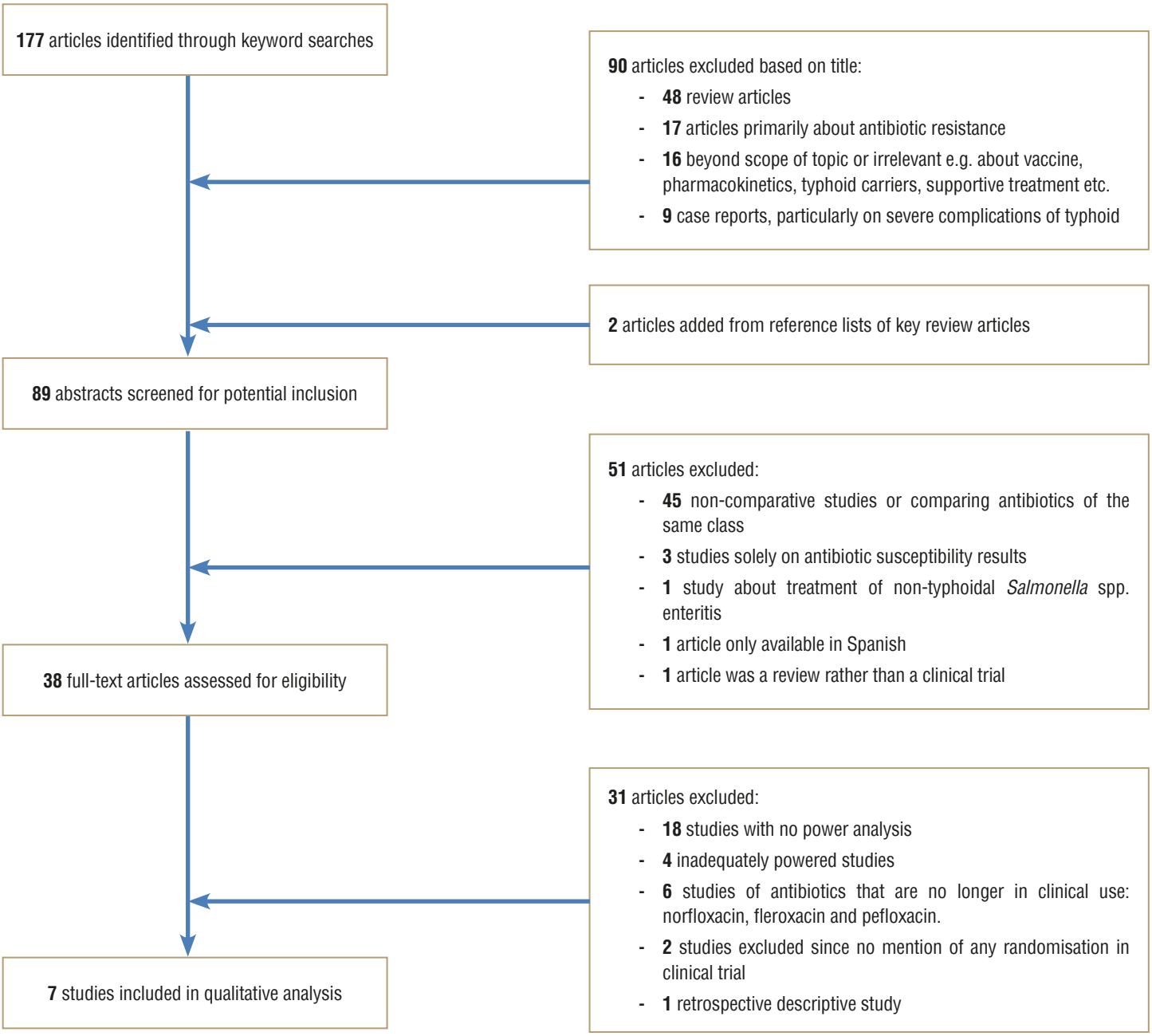

Figure 1. Search and selection strategy flow diagram

Data analysis

Seven well-powered studies were included for final detailed analysis. Each study was analysed by tabulating the following data: sample size, participant demographic, location of study, percentage MDR or NaR, follow-up duration, and the statistical significance (P<0.05) of CF, MF, RR and mean FCT for comparative antibiotics in each study. This summarised analysis is provided in Table 1. Methodological quality of the trials was assessed to ensure there was an adequate method of randomisation and allocation concealment. For continuous outcomes (e.g. FCT), arithmetic means and confidence intervals were extracted.

Results

The two treatment arms in each study were comparable in terms of demographic and baseline characteristics.[20-26] One study included both blood culture-positive as well as clinically-diagnosed participants.[25] It was decided to include this study since the main clinical outcomes being assessed in this review were reported separately for culture-positive patients and all patients.[25] One study added tetracycline resistance to their definition of MDR.[24] FCT was defined as the time in days since the start of treatment until body temperature ≤37.5°C, which persisted for 48 hours. One study, however, defined it as <38°C, while another stated a temperature ≤37.5°C maintained for at least 24 hours.[24,26] MF was defined as having a positive blood culture after treatment was completed. CF was defined as persistent fever and symptoms or possibly even the development of complications, often requiring a rescue treatment. TF encompassed CF as well as relapse cases.[21,25] Relapse was defined as the recurrence of signs and symptoms of typhoid fever with a positive blood culture within a month. The definition of relapse in two studies did not specify if these were blood culture confirmed.[21,22] There was an adequate length of follow-up in all included studies with a good percentage of participants returning in the majority of trials.

Table 1. Summary of data extracted from trials included in the systematic review

Trial ID, Setting	Comparative treatment arms (N)*	Mean age (inclusion criteria)	% MDR strains (N)*	% NaR strains (N)*	Mean FCT in days [95% CI, range]	CF/TF (%) [95% CI, range]	MF (%)	Relapse rate (RR)	Length of follow-up, compliance
Parry 2007,[20] Vietnam, hospital inpatients.	1. Ofloxacin (63) 2. Azithromycin (62)	1. 8.8 years 2. 10.5 years	88% (110/125)	93% 116/125	1. 8.2 days [7.2-9.2] 2. 5.8 days [5.1-6.5] P<0.001	CF 1. 23/63 (36.5%) 2. 11/62 (17.7%) P=0.053 (NS)‡ Note: all 23 who failed in group 1 were NaR.	Both groups =2 (3.2%) P>0.05 (NS)	Both groups = zero P>0.05 (NS)	6 months, 114/125 (91.2%) returned for follow-up.
Chinh 2000,[21] Vietnam, hospital inpatients.	1. Ofloxacin (44) 2. Azithromycin (44)	1. 24.7 years 2. 26.6 years (only of adults >15 years).	78% (68/87) 1. 35/44 2. 33/44	52.3% (46/87) 1. 21/44 2. 25/44	1. 5.6 days (0.5-11) 2. 5.4 days (2.5- 8.5) P=0.19 (NS) NaR patients: 1. 7.25 (2.5-11) 2. 5.6 (3-7.75 days) P=0.004	TF 1. 6/44 (13.6%) 2. 2/44 (4.5%) P=0.27 (NS) NaR patients: 1. 4/21 (19%) 2. 1/25 (4%) P=0.16 (NS]	1. 2/44 (4.5%) 2. 1/44 (2.3%) P=1.00 (NS) NaR patients: 1) 1/21 (4.8%) 2) 0 P=0.46 (NS)	1. 2 (4.5%) 2. Zero P>0.05 (NS)	6 weeks, 38/91 (42%) returned for follow-up.
Dolecek 2008,[22] Vietnam, inpatients at 3 hospitals.	1. Gatifloxacin (145) 2. Azithromycin (140)	NM† but majority children <15 years (73%), rest adults (<41 years).	58% (153/263)	96% 254/263	1. 4.4 days (3.9 - 4.9) 2. 4.4 days (3.7 - 4.7) P=0.98 (NS)	CF 1. 6/145 (4.3%) 2. 6/140 (4.2%) P=1.0 (NS)	1. 2/145 (1.4%) 2. 3/140 (2.2%) P=0.68 (NS)	1. 4/137 (2.9%) 2. 0/127 P=0.05 (NS)	6 months, 275/287 (96%) returned at 1 month follow-up.
Pandit 2007,[23] Nepal, outpatients.	1. Gatifloxacin (88) 2. Cefixime (70)	17 years (35.5% were children <14 years, otherwise range of 2-65 years).	Zero (however 1 isolate resistant to chloram-phenicol only).	83%	1. 3.8 days (3.5 - 4.75) 2. 5.75 days (4.4 - 6.8) P<0.0001	CF 1. 1/88 (1%) 2. 19/70 (27%) P<0.001	NM†	1. 2/87 (3.4%) 2. 6/51 (12.4%) P=0.0199	6 months (seen at 1, 3 & 6 months), 138/158 (87%) returned for follow-up.
Phuong 1999,[24] Vietnam, hospital inpatients.	1. Ofloxacin (38) 2. Cefixime (44)	6.9 years (only children <15 years).	85% (70/82)	Zero	1. 4.4 days (4 - 5.2) 2. 8.5 days (4.2 - 9) P<0.0001	CF 1. 1/38(3%) 2. 8/44 (18%) P value NM†	1. 0/38 (0%) 2. 2/44 (4.5%) (NS)	1) 0/38 (0%) 2) 1/44 (2.3%) (NS)	1 month, 40/82 (49%) returned for follow-up.
Arjyal 2011,[25] Nepal, Outpatients.	1. Gatifloxacin (177) 2. Chloramphenicol (175)	16 years (range of ages 8 - 22).	2/352 (0.57%), both of which were in the gati-floxacin group.	71.3% 251/352	1. 3·90 days (3·58–4·27) 2. 3·95 days (3·68–4·68) P=0·59 (NS) NaR patients: Significantly slower FCT for gatifloxacin P=0·002	TF 1. 12/177 (6.8%) 2. 14/175 (8%) P=0·70 (NS)	1. 2/177 (1%) 2. 0/175 (0%) P=0.24 (NS)	At 2 months: 1. 3/177 (1.7%) 2. 5/175 (2.9%) P=0·35 (NS)	6 months (seen at 1, 3 & 6 months), 302/352 (86%) returned at 1 month follow-up.
Butler 1999,[26] India, inpatients at 4 hospitals.	1. Azithromycin (42) 2. Chloramphenicol (35)	1. 26.3 years 2. 28.5 years (all adults aged ≥ 18 years).	10/77 (13%)	NM† (all suscep-tible to cipro-floxacin by MIC).	1. 4.1 days +/-2.4 (SD) 2. 4.3 days +/- 3.1 (SD) (NS)	CF 1. 5/42 (11.9%) 2. 5/35 (14.3%) (NS)	On day 8: 1. 0% 2. 6% P=0.12 (NS)	Zero overall	35 days (seen at days 21 and 35), 100% returned for follow-up.

* N = number of participants in each study

† NM= Not mentioned

‡ NS= Non-significant difference

Fluoroquinolones versus azithromycin

Three included studies (Table 1) compared fluoroquinolones and azithromycin, all of which had significant proportions of MDR and NaR *S.* Typhi.[20-22] One study showed that ofloxacin had a significantly longer mean FCT than azithromycin (P<0.001).[20] A second study comparing the same drugs did not reveal any significant difference (P=0.19); however, when specifically assessing NaR patients, a statistically-significant difference in mean FCT was detected (P=0.004). The FCT in nalidixic acid-sensitive (NaS) typhoid in this study was 4.3 days compared to 7.25 days in NaR strains.[21] The first study included a much higher percentage of NaR strains (93%), whilst in the second study only 52.3% of strains were NaR. Evidently, in NaR-infected patients, ofloxacin treatment results in a longer FCT. There were no significant differences between CF/TF, MF or RR in either study, despite accounting for NaR in the second one.[20,21] It was noted in the first study that all participants who failed in the ofloxacin treatment arm were NaR.[20] The third study compared a newer fluoroquinolone, gatifloxacin, against azithromycin.[22] No significant difference was detected between the two treatment groups for FCT, CF, MF and RR. Hence, the efficacy of gatifloxacin is equivalent to azithromycin, and both are useful in regions with high rates of MDR and NaR. Self-limiting gastrointestinal side effects occurred in the three studies.

Fluoroquinolones versus cephalosporins

Two studies (Table 1) compared fluoroquinolones with cephalosporins. The first compared gatifloxacin against cefixime, in a sample group with no MDR typhoid but in which 83% of isolates were NaR.[23] *In vitro* studies showed no resistance to cefixime. Gatifloxacin proved to have a shorter mean FCT (P<0.0001), a lower CF rate (P<0 .001), as well as a lower RR (P=0.0199) compared to cefixime. Clearly, gatifloxacin has a greater efficacy than cefixime. The ability of gatifloxacin to be highly efficacious even in a population with high rates of NaR infections is promising. *In vitro* microbiological analysis also shows that gatifloxacin has a lower MIC compared to other traditionally-used fluoroquinolones.[22] The second study compared ofloxacin against cefixime in a population with no NaR but 85% MDR typhoid.[24] Ofloxacin had a significantly shorter mean FCT (P<0.0001); however, MF rates and RR were not significantly different between the two treatment arms. The statistical significance of the CF rates was not specified; however, the difference seemed quite large: 3% for ofloxacin and 18% for cefixime. There were no NaR strains of *S.* Typhi in the study; hence the higher cure rates for ofloxacin must be cautiously interpreted, since there are high rates of NaR worldwide. Regardless, ofloxacin is more effective than cefixime since it has a faster FCT. Adverse effects reported in both studies were limited to mild gastrointestinal effects. The first trial had one death in the cefixime group, and the second trial had one death in the ofloxacin group. Overall, both studies highlight the greater efficacy of fluoroquinolones over oral cephalosporins.

Azithromycin versus cephalosporins

There were no adequately powered studies comparing azithromycin against cephalosporins.

Chloramphenicol studies

One adequately-powered study (Table 1) compared chloramphenicol against fluoroquinolones. The study involved a population with 71.3% NaR infections, but 0.57% MDR, and the fluoroquinolone used was gatifloxacin.[25] There was no significant difference in FCT, TF, MF or RR. The chloramphenicol culture-positive group had a higher rate of adverse events, but the statistical significance of this was not explicit. Within the chloramphenicol study group, 25% of the participants developed at least one adverse effect due to the medication, compared to 16.9% of the gatifloxacin group. The adverse effects of chloramphenicol, from most to least common, included vomiting, nausea, diarrhoea, abdominal pain, dizziness, anorexia, oral candidiasis and leukopenia. The most common side effects of gatifloxacin were hyperglycaemia, abdominal pain, vomiting, and diarrhoea.[25] In all patients (including ones only clinically diagnosed) within the chloramphenicol group, 3 developed leukopenia and discontinued use of the drug. During days 2-7 of the trial, there was a significantly higher proportion of grade 2 hyperglycaemia (non-fasting blood glucose level of 161-250 mg/dL) in the gatifloxacin treatment arm, which included only clinically-diagnosed cases (P=0.04). However, there was no significant difference in rates of hyper/hypoglycaemia after day 8 between the antibiotics. The efficacy of gatifloxacin in terms of FCT, TF, MF and RR was shown to be clinically equivalent to chloramphenicol in a population with low MDR.

There were no adequately-powered studies comparing chloramphenicol against cephalosporins. There was only one trial (Table 1) comparing chloramphenicol with azithromycin in the entire literature search and it had a power of 80%.[26] The study had 13% MDR typhoid, but no MDR patient was in the chloramphenicol group. There was no significant difference in FCT, TF, MF or RR. Hence, azithromycin was proved to be equivalent in clinical effectiveness to chloramphenicol. No severe adverse events occurred, including no reported leukopenia in the chloramphenicol-treated patients, since any patient who had slight leukopenia at the pre-treatment stage was excluded from the trial.

Discussion

Recent studies on typhoid treatment have had larger sample sizes with 80% power analysis, which provide results that are applicable to the general population. However, there is a lack of evidence comparing the three main classes of antibiotics currently being used worldwide: fluoroquinolones, cephalosporins and macrolides. There is a need for adequately-powered studies comparing azithromycin against cephalosporins e.g. ceftriaxone. There were only two trials in total within the literature search that reported such a comparison and both were inadequately powered.[27,28] Both studies had small sample sizes and reported no significant difference between ceftriaxone and azithromycin in terms of FCT, clinical cure and microbiological cure. There is a need for large, well-powered studies that specifically test the comparative efficacy of ciprofloxacin and ceftriaxone. One inadequately-powered study comparing azithromycin to ciprofloxacin discovered no significant difference in any clinical outcomes.[29] A small study comparing ofloxacin with ceftriaxone determined that ofloxacin is more clinically effective than ceftriaxone, since there was a statistically significant difference in CF and mean FCT.[30] The lack of large, well-powered studies with ceftriaxone probably relates to the cost of this antibiotic.[3,21] All RCTs have been conducted in resource-poor typhoid-endemic countries, and therefore large studies with ceftriaxone have not been feasible. Investigations of less-expensive alternatives, such as gatifloxacin, have been undertaken instead.

This systematic review concludes that older fluoroquinolones such as ofloxacin, compared to azithromycin, have a slower FCT in NaR typhoid.[20,21] However, there is no statistically significant difference between ofloxacin and azithromycin in fully-sensitive typhoid fever patients. On the other hand, newer fluoroquinolones, such as gatifloxacin, have proven to be clinically equivalent to azithromycin, even in regions of MDR and NaR.[22] Fluoroquinolones are more efficacious than oral cephalosporins (e.g. cefixime).[23,24] Chloramphenicol, azithromycin and gatifloxacin are clinically equivalent in terms of FCT, TF, MF and RR. However, the adverse events profile of chloramphenicol is significantly worse than azithromycin or gatifloxacin.[25] Evidently there is potential risk for serious toxicity such as leukopenia, as well as the rare potentially fatal drug reaction of haematopoietic depression.[31,32] Historically, chloramphenicol was the first antibiotic used to treat typhoid fever, but was not considered ideal due to its adverse reaction profile and the development of resistance.[31] Hence, other antibiotic options were pursued. This is important since chloramphenicol-sensitive strains are now re-emerging in developing countries.[10-12] Hence, reintroducing the use of chloramphenicol in the treatment of typhoid fever in developing countries should be done with caution and careful monitoring for adverse events and serious toxicity. A controlled double-blind RCT highlights the fact that bone marrow suppression was more likely to occur in chronically-ill patients with coinciding liver or renal disease.[32] The study also supports the fact that haematopoietic suppression is associated with higher plasma levels and

increased length of exposure to chloramphenicol.[32] The primary approach to reducing the risk of chloramphenicol toxicity is by opting for an alternative antibiotic treatment, if available, especially in patients with liver or renal impairment. Otherwise, discontinue chloramphenicol immediately if there are signs of serious toxicity and alter the choice of antibiotic.

The recommended and commonly-used antibiotics for typhoid fever in various developing countries are highly influenced by the cost of the drugs. Overall, the order from most to least expensive is third-generation cephalosporins (especially IV ceftriaxone), azithromycin, fluoroquinolones and chloramphenicol.[3,21,22] Due to its relative cheapness, and its proven efficacy in studies, continued use of chloramphenicol in developing countries is warranted for chloramphenicol-susceptible typhoid cases, but with caution regarding early signs of toxicity. Furthermore, gatifloxacin has great potential in the treatment of typhoid fever, since it costs a third of the price of azithromycin in Vietnam, and in contrast to other fluroquinolones, it is effective in treating NaR typhoid.[22]

Significantly-increased risk of hypo- or hyperglycaemia after administration of gatifloxacin in older patients was reported recently,[33] following which, gatifloxacin was removed from the US market.[32] Only one of the three studies in this review reported a significantly greater proportion of gatifloxacin-treated patients experiencing grade 2 hyperglycaemia.[25] In this study the hyperglycaemia resolved upon completion of treatment and did not return during follow-up. The other two studies did not specifically look for dysglycaemia.[22,23] A majority of the participants for the two studies were children or teenagers, and hence dysglycaemia may have been an unlikely adverse event.[22,23] It is recommended to use gatifloxacin cautiously, particularly in patients who have a known difficulty achieving glycaemic control.[34] As evidence for dysglycaemia was specific for patients ≥66 years,[33] the use of gatifloxacin in typhoid patients who are usually young and otherwise healthy does not seem to be contraindicated, especially in light of its benefit against NaR typhoid.

There are certain public health measures that need to be encouraged worldwide to reduce further development of antibiotic resistance in typhoid. A major concern is the ease of accessibility to antibiotics in developing countries.[35] One of the main public health measures to combat this is to monitor the appropriate distribution and prescription of antibiotics. Many developed countries have implemented antimicrobial stewardship programs in hospitals and the community. These programs aim to monitor and regulate antibiotic prescribing, educate health professionals in the appropriate prescribing of antibiotics, and support them in their practice.[36] Such programs, as recommended by various organisations worldwide such as the Centers for Disease Control and Prevention (CDC) and the Australian Commission on Safety and Quality in Health Care,[37,38] should be implemented in developing countries as well.

A limitation of this review is that one author conducted the final selection of articles. For optimal research results, data should be searched, selected and analysed independently by at least 2 authors simultaneously, to reduce the chance of human error. We attempted to reduce the risk of any selection bias as the co-author supervised the literature search, reviewed the literature and advised on inclusion/exclusion criteria. A limitation at the outcome level was the unavoidable use of open-label trials, which places the studies at risk of performance and detection biases. Other limitations for comparative analysis were different dosages of drugs used, varying age restrictions applied, and some variations in definitions for the clinical outcomes being assessed.

Conclusions

Overall, no definite recommendation for the most efficacious antibiotic treatment for typhoid fever can be made. There is a need for further comparative trials, especially involving ceftriaxone, ciprofloxacin and azithromycin. However, such large RCTs are difficult to perform, due to the high cost of ceftriaxone in particular and the lack of resources in typhoid-endemic developing countries. Broadly this systematic review suggests that quinolones and azithromycin are equally effective in treating fully-susceptible *S.* Typhi, while azithromycin is favoured over quinolones in the presence of nalidixic acid resistance. Quinolones are favoured over oral cephalosporins (e.g. cefixime) in resistant and fully-susceptible typhoid strains. Gatifloxacin is highly efficacious even in populations with high rates of nalidixic acid-resistant infection. Chloramphenicol is clinically as effective as both azithromycin and gatifloxacin in patients without MDR strains, but chloramphenicol has the potential risk of serious toxicity. Treatment of typhoid fever is a significant public health problem that needs to be addressed. It is essential to obtain antibiotic susceptibilities to guide treatment. There are already reports of increasing MICs for azithromycin and there have even been case reports of enteric fever resistant to ceftriaxone and azithromycin.[8,39-41] The ease of accessibility to antibiotics in developing countries is the primary cause of this rapidly-evolving pattern of resistance. Clinicians must be aware of potentially emerging resistance to antibiotics for typhoid, and public health measures must be put in place in developing countries worldwide to ensure the rational use of antibiotics.

Conflicts of interest

None declared.

Author's contributions

All authors significantly contributed to conception and design of this review. RM searched the literature, selected articles, analysed data extracted from included studies, and drafted the manuscript. JM supervised the literature search, reviewed the literature, advised on inclusion/exclusion criteria, and critically edited the drafted manuscript. All authors approved the final manuscript.

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References

1. Buckle GC, Walker CL, Black RE. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. J Glob Health 2012; 2(1): 40-48.
2. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004; 82(5): 346-53.
3. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis 2010; 50(2): 241-6.
4. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th Ed. Philadelphia: Churchill Livingstone/Elsevier; 2010. pp. 2642-2646.
5. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. Lancet Infect Dis 2005; 5(10): 623-8.
6. World Health Organization. The Diagnosis, Treatment, and Prevention of Typhoid Fever. Geneva: WHO; 2003.
7. Therapeutic Guidelines Antibiotics, v. 14. Typhoid and Paratyphoid Fevers (Enteric Fevers). Melbourne: Therapeutic Guidelines Limited; 2014. Available from: http://online.tg.org.au.elibrary.jcu.edu.au/ip/desktop/index.htm (accessed April 1, 2014).
8. Karki S, Shakya P, Cheng AC, Dumre SP, Leder K. Trends of etiology and drug resistance in enteric fever in the last two decades in Nepal: a systematic review and meta-analysis. Clin Infect Dis 2013; 57(10): e167.
9. Commons RJ, McBryde E, Valcanis M, Powling J, Street A, Hogg G. Twenty-six years of enteric fever in Australia: an epidemiological analysis of antibiotic resistance. Med J Aust 2012; 196(5): 332-6.
10. Arjyal A, Pandit A. Treatment of enteric fever. J Infect Dev Ctries 2008; 2(6): 426-30.
11. Yashavanth R, Vidyalakshmi K. The re-emergence of chloramphenicol sensitivity among enteric fever pathogens in Mangalore. J Clin Diagn Res 2010; 4(5): 3016-108.
12. Kumar A, Pandit V, Shetty S, Rao CR, Pattanshetty S, Samarasinghe CM. Study of clinical profile and antibiotic sensitivity pattern in culture-positive typhoid fever cases. Indian J Community Med 2012; 37(4): 256-8.
13. Saleh FO, Ahmed HA, Khairy RM, Abdelwahab SF. Increased quinolone resistance among typhoid *Salmonella* isolated from Egyptian patients. J Infect Dev Ctries 2014; 8(05): 661-5.
14. Parry CM, Vinh H, Chinh NT, Wain J, Campbell JI, Hien TT, *et al*. The influence of reduced susceptibility to fluoroquinolones in *Salmonella enterica* serovar Typhi on the clinical response to ofloxacin therapy. PLoS Negl Trop Dis 2011; 5(6): e1163.
15. Hohmann EL. UpToDate: Treatment and prevention of typhoid fever. Updated 2014. Available from: http://www.uptodate.com/contents/treatment-and-prevention-of-typhoid-fever?source=search_result&search=Typhoid+treatment&selectedTitle=1~64 (accessed September 5, 2014).
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Int Med 2009; 151(4): 264-9.
17. Bragge P. Asking good clinical research questions and choosing the right study design. Injury 2010; 41: S3-S6.
18. Suresh K, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci 2012; 5(1): 7.
19. Stahlmann R. Clinical toxicological aspects of fluoroquinolones. Toxicol Lett 2002; 127(1): 269-77.
20. Parry CM, Ho VA, Phuong le T, Bay PV, Lanh MN, Tung le T, *et al*. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. Antimicrob Agents Chemother 2007; 51(3): 819-25.

21. Chinh NT, Parry CM, Ly NT, Ha HD, Thong MX, Diep TS, *et al.* A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. Antimicrob Agents Chemother 2000; 44(7): 1855-9.
22. Dolecek C, Luong BH, Nguyen TB, Nguyen TAH, Pham ND, Mai NL, *et al.* A multicenter randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. PloS One 2008; 3(5): e2188.
23. Pandit A, Dolecek C, Farrar JJ, Basnyat B, Arjyal A, Day JN, *et al.* An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. PloS One 2007; 2(6): e542.
24. Phuong CXT, Kneen R, Anh NT, Luat TD, White NJ, Parry CM. A comparative study of ofloxacin and cefixime for treatment of typhoid fever in children. Pediatr Infect Dis J 1999; 18(3): 245-8.
25. Arjyal A, Lama S, Shrestha K, Khatri NS, Shrestha U, Campbell JI, *et al.* Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomised, controlled trial. Lancet Infect Dis 2011; 11(6): 445-54.
26. Butler T, Sridhar CB, Daga MK, Pathak K, Pandit RB, Khakhria R, *et al.* Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999; 44(2): 243-50.
27. Frenck JRW, Mansour A, Nakhla I, Sultan Y, Putnam S, Wierzba T, *et al.* Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. Clin Infect Dis 2004; 38(7): 951-7.
28. Frenck RW, Nakhla I, Sultan Y, Bassily SB, Girgis YF, David J, *et al.* Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. Clin Infect Dis 2000; 31(5): 1134-8.
29. Girgis NI, Butler T, Frenck RW, Sultan Y, Brown FM, Tribble D, *et al.* Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. Antimicrob Agents Chemother 1999; 43(6): 1441-4.
30. Smith MD, Duong NM, Hoa NT, Wain J, Ha HD, Diep TS, *et al.* Comparison of ofloxacin and ceftriaxone for short-course treatment of enteric fever. Antimicrob Agents Chemother 1994; 38(8): 1716-20.
31. Butler T, Rumans L, Arnold K. Response of typhoid fever caused by chloramphenicol-susceptible and chloramphenicol-resistant strains of *Salmonell*a Typhi to treatment with trimethoprim-sulfamethoxazole. Rev Infect Dis 1982; 4(2): 551-61.
32. Gussoff BD, Lee SL. Chloramphenicol-induced hematopoietic depression: a controlled comparison with tetracycline. Am J Med Sci 1966; 251(1): 8-15.
33. Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, *et al.* Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006; 354(13): 1352-61.
34. Ge TF, Law PY, Wong HY, Ho YY. Gatifloxacin affects GLUT1 gene expression and disturbs glucose homeostasis in vitro. Eur J Pharmacol 2007; 573(1-3): 70-4.
35. Harris DJ. Initiatives to improve appropriate antibiotic prescribing in primary care. J Antimicrob Chemother 2013; 68(11): 2424-7.
36. MacDougall C, Polk R. Antibiotic Stewardship Programs In Health Care Systems. Clin Microbiol Rev 2005; 18(4): 638-56.
37. Duguid M, Cruickshank M. Antimicrobial Stewardship in Australian Hospitals. Australian Commission on Safety and Quality in Healthcare; 2011.
38. Dodds Ashley ES, Kaye KS, DePestel DD, Hermsen ED. Antimicrobial stewardship: philosophy versus practice. Clin Infect Dis 2014; 59(S3): S112-21.
39. Hassing RJ, Goessens WHF, van Pelt W, Mevius DJ, Stricker BH, Molhoek N, *et al. Salmonella* subtypes with increased MICs for azithromycin in travelers returned to the Netherlands. Emerg Infect Dis 2014; 20(4):705-8.
40. Kulkarni K, Singh M, Kumar R. Is drug-resistant *Salmonella* Typhi an emerging threat? BMJ Case Rep 2009; 2009:bcr04.2009.1783.doi:10.1136/bcr.04.2009.1783.
41. Saha SK, Talukder SY, Islam M, Saha S. A highly ceftriaxone-resistant *Salmonella* Typhi in Bangladesh. Pediatr Infect Dis J 1999; 18(4): 387.

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AN UNUSUAL CASE OF Q FEVER

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Abstract

A previously-well, 44-year-old Australian-born male presented to a Melbourne metropolitan hospital with a systemic inflammatory process comprising respiratory and hepatic dysfunction. He was managed initially for presumed acute cholecystitis, with minimal effect. Improvement was seen only after empiric treatment for a zoonotic infection. Diagnosis of acute Q fever was confirmed serologically. This case illustrates a rarely-seen combination of Q fever pneumonia and cholecystitis. A review follows this case report, highlighting the dearth of contemporary literature that categorises the clinical spectrum of disease seen in the Australian population.

Keywords: Q fever, *Coxiella burnetii*, pneumonia, acalculous cholecystitis, zoonosis

Introduction

Coxiella burnetii is the causative organism for Q fever, a zoonotic infection present in the majority of populated regions of the world.[1] The reservoir for this organism includes livestock, wildlife, birds, and reptiles. Humans are incidental hosts, acquiring the pathogen primarily through inhalation of infected aerosols from livestock. It is hence unsurprising those at highest risk of contracting Q fever have some form of ongoing exposure to infected livestock or their products.[2] This report details a middle-aged man, with minimal work-related risk factors, who likely acquired Q fever infection from a brief camping trip to rural Victoria.

Case report

A 44-year-old male first presented to his general practitioner (day 0) with a three-day history of malaise, fevers, rigors, nausea, vomiting, and generalised myalgia. Notably, he was afebrile but had abdominal discomfort. An abdominal ultrasound was performed and was unremarkable. No specific intervention was implemented at that stage. The next day (day 1), he presented to the emergency department. His core temperature measured 37.7 °C, and he had abdominal tenderness on examination. His full blood count (FBC) was normal other than lymphopenia of 0.5 x 10^9/L (normal range: 1-3 x 10^9/L). Liver function tests were mildly deranged, with alanine aminotransferase (ALT) of 52 IU/L (normal range: 5-40 IU/L), and gamma-glutamyl transferase (GGT) of 76 IU/L (normal range: 10-71 IU/L). His alkaline phosphatase (ALP) was normal at 81 IU/L (normal range: 30-120 IU/L). Abdominal X-ray showed non-specific prominent small bowel loops. As his abdominal discomfort was out of proportion to his X-ray findings, a computed tomography (CT) scan of his abdomen was done, which revealed faecal loading but was otherwise normal. He was managed with aperients, anti-emetics, and intravenous fluids. After spending 8 hours in the emergency department, he was discharged with the diagnosis of constipation and an unspecified viral illness.

At home, he continued to deteriorate over the following 72 hours, and was unable to go to work. He re-presented to the emergency department for the second time (day 4), with similar symptoms of fever, uncontrolled rigors, nausea, vomiting, and generalised pain, most prominent in his abdomen. A productive cough had begun to develop. On examination, he appeared clinically unwell, tachycardic, and was febrile (38.3 °C) with generalised abdominal tenderness. His cardiovascular and respiratory examinations were unremarkable. On investigation, liver function tests were more deranged than previously noted. He had a marked elevation of his bilirubin: a conjugated hyperbilirubinaemia, up to 3 times the upper limit of normal at 66 µm/L. GGT was 415 IU/L, ALP was 277 IU/L, and ALT was 188 IU/L. FBC showed a white cell count (WCC) of 4.5 x10^9/L, a neutrophil count of 2.9 x10^9/L, and a low platelet count of 65 x10^9/L. His lymphopenia persisted. C-reactive protein (CRP) was 281 mg/L (Table 1).

Table 1. Selected laboratory results

Investigation* (normal range)	29/1/2014 (day 0)	1/2/2014 (day 4)	3/2/2014 (day 6)	5/2/2014 (day 8)	7/2/2014 (day 10)
WCC (4-10) x10^9/L	5.4	4.5	5.6	10.5	13.5
Neutrophils (2-7) x10^9/L	4.7	2.9	4.4	5.8	8.9
Lymphocytes (1-3) x10^9/L	0.5	0.5	0.6	4.0	3.8
CRP (<5) mg/L	-	281	289	191	84
Platelets (150-410) x10^9/L	155	65	51	51	86
Bilirubin (<22) µm/L	7	66	96	197	337
ALT (5-40) IU/L	52	188	203	157	155
GGT (10-71) IU/L	76	415	388	438	773
ALP (30-120) IU/L	81	277	258	305	547

*WCC: white cell count, CRP: C-reactive protein, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase

A chest X-ray was normal. A liver ultrasound elicited tenderness in the right upper quadrant on ultrasound device probing, and showed a thickened gallbladder wall of 6 mm (normal ≤4 mm), but no choledolithiasis. The common bile duct was not dilated. The working diagnosis at that time was that of acalculous cholecystitis. Intravenous (IV) ampicillin, ceftriaxone, and metronidazole were commenced and a laparoscopic cholecystectomy was performed the following day (day 5), due to concerns of an evolving necrotising cholecystitis. The surgically-removed gallbladder appeared oedematous with grossly normal surrounding hepatic architecture. An intraoperative cholangiogram did not reveal a biliary tree filling defect. Gallbladder histopathology subsequently reported changes of chronic cholecystitis.

Further history revealed that fourteen days prior to onset of clinical symptoms, the patient took a brief three-day camping trip with his family to Woodside Beach, a coastal town in the Gippsland region of rural southeastern Victoria, Australia. He denied any water activities. The rest of his family remained well during and after his illness. The patient was an industrial air-conditioner technician by profession, working at numerous sites around metropolitan Melbourne. This included a research facility known to house livestock, including sheep. His last exposure there was 10 days prior to first onset of clinical symptoms (day -13). His work there involved, as usual, entrance into the air ventilation systems. His past medical history was unremarkable. He drank minimal alcohol and occasionally smoked marijuana. He lived with his family, comprising his spouse and two young children aged 5 and 7, in a standard housing property. He did not own pets, and aside from his recent travel to rural Victoria, reported no other travel.

Despite removal of his gallbladder (day 5), the patient deteriorated clinically and biochemically. Over the next four days, he became progressively more dyspnoeic and hypoxic with type 1 respiratory failure, necessitating supplemental high-flow oxygen to maintain adequate oxygenation. On chest X-ray imaging, airspaces initially clear on re-presentation (day 4) now showed progression with multilobular consolidation, in particular over the lower lung zones bilaterally (Fig. 1).

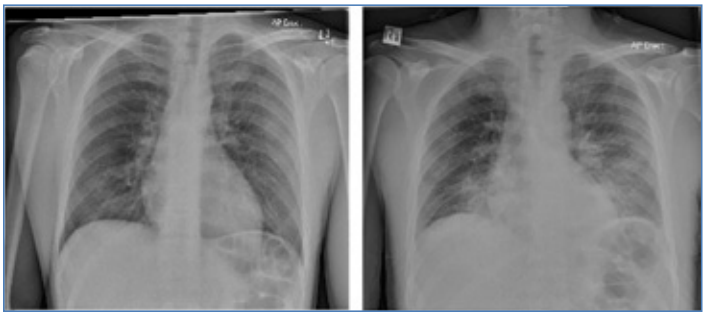

Figure 1. Interval chest X-ray change from day 4 (L) to day 8 (R)

Daily spiking fevers above 38.5 °C were noted. In all, his fevers persisted for almost two weeks (days 0 to 12). Liver function tests continued to worsen, with a predominantly cholestatic picture. A more than four-fold rise in his ALT and ALP, and a ten-fold rise in his GGT were observed (Table 1). Ongoing sepsis, atypical pneumonia, ascending cholangitis, pulmonary emboli, and antibiotic-related acute hepatitis were all considered. IV piperacillin/tazobactam was commenced to replace ceftriaxone, ampicillin, and metronidazole. CT pulmonary angiogram did not reveal pulmonary emboli and magnetic resonance cholangiopancreatography (MRCP) showed no biliary tree abnormalities to account for a diagnosis of ascending cholangitis. Four sets of blood cultures were taken; all had no growth after 5 days of incubation. Hepatitis A, B, and C, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) serologies were all negative. His CRP level improved following his cholecystectomy but in all other ways, he appeared to be worsening.

On day 10, the Infectious Diseases Unit was first consulted. Azithromycin was commenced for possible atypical pneumonia, in particular to cover for *Legionella pneumophila*. Because of concerns of a drug reaction, antibiotics were changed from piperacillin/tazobactam to meropenem. The history of recent rural and occupational exposure led to concerns of a systemic zoonotic infective process, including Q fever, rickettsial disease, and leptospirosis, hence doxycycline was added. Serological tests for rickettsial subspecies, *Coxiella burnetii*, leptospirosis, and atypical pneumonia agents were ordered.

The patient defervesced 48 hours (on day 12) after commencement of doxycycline and azithromycin and showed parallel improvement clinically and biochemically. His myalgias, rigors, and cough abated. Bilirubin and liver enzymes improved. On day 16, he had a bilirubin level of 72 µm/L, ALT of 106 IU/L, GGT of 429 IU/L, and ALP of 468 IU/L. Urinary *Legionella* serogroup 1 antigen, urinary *Streptococcus pneumoniae* antigen, sputum *Legionella* spp. and *Chlamydia pneumoniae* PCR were all negative. Transthoracic echocardiogram (TTE) was not consistent with infective endocarditis.

Initial serological testing by enzyme-linked immunosorbent assay (ELISA), taken at day 10 of hospital presentation showed positive Q fever phase 2 IgM and IgG. The following day, meropenem and azithromycin were ceased. Doxycyline 100 mg BD was continued on discharge. He completed a total of 14 days of doxycycline. A rise in phase 2 IgM titre was demonstrated on convalescence 14 days (day 24) after the initial assay, confirming the diagnosis of acute Q fever. On retrospective analysis, the immunofluorescence (IF) assay method during his acute illness revealed negative *Coxiella burnetii* phase 2 IgM and IgG results (day 10), with titres <25. On convalescent serology performed two weeks later (day 24), there was IFA seroconversion of both his phase 2 IgG, phase 2 IgM (titres >3 200), and phase 1 IgM (Fig. 2). Again, this was consistent with acute Q fever infection. Follow-up IFA at his 6-month outpatient clinic visit revealed a persistent rise in phase 1 IgG and IgA, titres 12 800 and 6 400 respectively. Despite normalisation of his LFTs and FBC, he reported ongoing lethargy. Three-monthly Q fever serology testing continued.

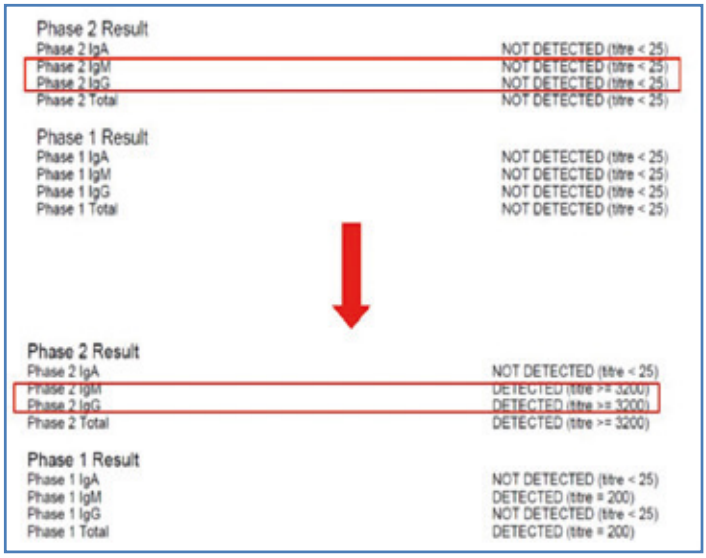

Figure 2. Q fever initial (top) and convalescent serology indicating seroconversion, by IFA test (with permission of Australian Rickettsial Reference Laboratory)

In light of his substantial abdominal discomfort, deranged liver enzymes, and abnormal abdominal ultrasound, Q fever acalculous cholecystitis was considered. Three paraffin block shavings of the gallbladder were were positive for *Coxiella burnetii* by polymerase chain reaction (PCR), which involved amplification of two separate coding regions of the *C. burnetii* genome (*com 1* and *htpAB* genes). We believe our case to be the second reported in the literature of positive *C. burnetii* PCR from the gallbladder.

Discussion

Q fever remains a largely unrecognised disease unless the treating clinician has a high index of suspicion. This is in part due to the myriad number of clinical manifestations that can arise. Q fever was first described by Edward Derrick, an Australian pathologist, in 1937.[3] This followed a two-year period in which he investigated nine Queensland men with unspecified febrile illnesses, drawn together by the fact that they all worked in abattoirs. MacFarlane Burnet and Herald Cox independently isolated the causative organism, resulting in the name given to this pathogen – *Coxiella burnetii. C. burnetii* is a pleomorphic, obligate intracellular, small Gram-negative organism. Similar to other Gram-negative pathogens, it possesses an outer lipopolysaccharide cell membrane.[1] In its natural state it exists in two forms - large and small cell variants. The small cell variant, though having minimal metabolic activity, possesses a spore-like structure which resists desiccation, heat, acid and ultraviolet rays, enabling it to survive freely in the environment for weeks.[4] Humans are incidental hosts, with fauna being environmental reservoirs. These are not limited to livestock, arthropods, birds, and reptiles. Livestock remain the largest source of human infection. The majority of human infection are believed to arise from inhalation of the aerosolised infected bodily fluids of livestock.[1] Other means of transmission are less common, but still well recognised, such as via ingestion of unpasteurised milk, blood transfusion, sexual transmission, and vertical transplacental transmission.[5, 6] The survivability of this organism in the natural environment and the ease at which it can infiltrate its large potential reservoir has led to spread to all regions of the world, with the exception of New Zealand and French Polynesia. The reported incubation period of Q fever varies from 12 to 37 days. A shorter incubation period is postulated to arise from higher inoculation doses.[7]

It is suspected that there may be regional differences in the clinical manifestation of acute Q fever, yet the reason for this variation remains elusive. Theories include regional clinician reporting bias, and sub-strain variation in virulence, host factors, and route of inoculation.[1, 2] There is a dearth of recent data about the clinical manifestations of this disease in Australia. Table 2 summarises the clinical spectrum of disease within Australia, and globally.[2, 8-14]

Table 2. Clinical spectrum of acute Q fever illness

Condition	World rates (%)	Australian rates (%)
Asymptomatic	50-60%	50-60%
Febrile illness	85-100%	82%
Pneumonia	10-35%	7-20%
Hepatitis (abnormal LFTs)	25-80%	5-85%
Hepatomegaly	10-25%	20- 50%
Splenomegaly	5-17%	15-30%
Acalculous cholecystitis	<20 cases reported worldwide	1 reported case
Neurological manifestations	0.2-1.3%	-
Cardiac (pericarditis/ myocarditis)	0.5-1%	1%
GI - diarrhoea	5-20%	7%
Arthralgia	10-60%	20%
Rash	5-20%	7%

The last substantial Q fever case series in Australia was published in 1982.[11] Pneumonia, as defined by chest X-ray changes, was seen in 5% (6 of 111 patients). Despite derangement of liver enzymes being remarkably common in that case series (85%), marked hyperbilirubinaemia was exceedingly rare (only one patient had a serum bilirubin >60 µmol/L). This is consistent with the reported clinical manifestations of Q fever in contemporaneous Australian papers. Two distinct large case reports showed that 4 of 72 (5%) and 10 of 273 (4%) had manifestations of this disease on chest X-ray.[12, 13] Clinical jaundice was only seen in 3 of 72 (4%) and 3 of 273 (1%) respectively.

Of those that contract acute Q fever, only 60% are symptomatic. Globally, there are variable rates of Q fever pneumonia, but it still more common elsewhere than in Australia (5% of cases). As more contemporary data from Australia is elucidated, this difference might indeed be negligible. Q fever pneumonia is the predominant clinical presentation in Nova Scotia in Canada, Switzerland, and in the Basque region of Spain.[2] The other major clinical presentation is acute hepatitis, seen more commonly in California (USA), Ontario (Canada), and Andalusia (Spain). Q fever hepatic changes on biopsy typically show multiple granulomas with the characteristic central 'doughnut hole' and a surrounding fibrin ring.[15] Though not established, variation within a country's regional areas point towards differences in infection route (inhalation from work practices, in comparison to ingestion of contaminated food products, such as unpasteurised milk). A large retrospective analysis of almost 1 400 patients with acute Q fever looked at host factors and their association with clinical manifestations.[2] Patients with hepatitis had a tendency to be younger, with more systemic symptoms such as headaches and myalgias, and be less immunocompromised. Those with pulmonary involvement were older and had concomitant medical reasons for immunosuppression. A non-specific rash is uncommon, observed in less than 20%, and can help in differentiation of this condition from vector-borne rickettsial disease. Acute cardiac issues manifest in the form of myocarditis and pericarditis, which are seen rarely (<1%). The spectrum of neurological involvement varies considerably, from a non-specific headache to seizures and encephalitis. It is well established that adult males have a greater propensity to manifest symptomatic disease.[1]

Q fever acalculous cholecystitis is an underappreciated entity that was first recognised and reported in the literature in 2003.[16] This seminal case series looked at seven patients with serologically-proven acute Q fever. All seven had deranged liver function tests, ultrasonographic evidence of a dilated gallbladder wall, and absence of gallstones. Five of these seven patients had a cholecystectomy during the acute illness setting. It is notable that none had histological changes consistent with acute cholecystitis. A subsequent case report from Australia described Q fever cholecystitis.[14] Not only was there histopathological evidence of acute cholecystitis, but specific PCR testing (*com1* and *htpAB* genes) of these inflamed specimens was positive for *C. burnetii*. This is believed to be the first and only report thus far in the literature that has correlated acute changes of cholecystitis with PCR-confirmed *C. burnetii* sequences. Reported cases of Q fever-associated acalculous cholecystitis are likely a gross underestimation of cases seen, as clinicians may alternatively attribute the presence of acalculous cholecystitis to an acute systemic inflammatory process.

By conservative estimate, up to 5% of acute Q fever, despite treatment, progresses to a chronic state. Endocarditis forms the majority of chronic Q fever, accounting for two-thirds of all cases.[1] Pre-existing cardiac valve disease is a major risk factor in the development of Q fever endocarditis. One large study cited 88% of those with proven endocarditis had pre-existing valvular abnormalities.[2] Vegetations are usually small or absent, so diagnosis is often delayed.[17] Vascular infections are less common than chronic Q fever endocarditis, which in itself is a rare entity. When present, Q fever-associated vascular infections can be catastrophic. As with endocarditis, there are often predisposing factors, such as a known large vessel aneurysm, or a previous vascular graft. A recent study proposes the utility of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT as a means to pinpoint infected vasculature.[18] Q fever chronic osteomyelitis and pulmonary fibrosis are rarely observed. Hepatitis in isolation, without concomitant endocarditis, is also an uncommon feature of chronic disease. Q fever chronic fatigue syndrome is well recognised, the pathophysiology less well so. Immune dysregulation has been put forward as a possible explanation for this condition.[19, 20] One should always remain vigilant in the exclusion of other chronic complications of Q fever, which may present in a protean manner with non-specific symptoms akin to that of Q fever chronic fatigue syndrome.

High risk occupational groups include those with animal exposure such as abattoir workers, farmhands, veterinarians, and certain medical laboratory personnel.[2] Plumbers and similar tradesmen are at unspecified risk. A large case study identified transmission via an infected air-conditioning ventilation system.[21] In summary, a single boarding school in Israel was shown to have an acute Q fever outbreak, in which 108 of 164 cases were confirmed serologically as acute Q fever. Several swabs on filters and inlets of the air-conditioning units were positive on PCR testing for *C. burnetii*, highly suggestive of it as a mode for facilitation and transmission of disease. The Israeli outbreak provides a different perspective to the traditional, better-known means of disease acquisition.

Various serological tests are available to the clinician for acute Q fever testing. Commonly utilised are the immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), and the complement fixation (CF) assay.[8] Immunofluorescence assay is still regarded as the standard reference method for serological diagnosis and follow up, reflected in algorithms for serological follow-up in chronic Q fever.[9,22] Serological diagnosis rather than culture isolation of this organism is sought given its extreme infectivity, confining culture methods to biosafety level 3 laboratories and above. *Coxiella burnetii* exists in two antigenic phases.[23] In its natural state, *C. burnetii* is considered virulent, in the phase 1 state. The avirulent phase 2 variant is derived from passages of *C. burnetii* culture in egg yolk sacs through several generations.[8] On immunofluorescence assay, IgM phase 2 antibodies appear first, 10-17 days after the onset of acute illness.[24] This is followed by IgG antibodies to phase 2. Persistent phase 1 antibodies, with a compatible clinical picture, can be a useful measure of Q fever chronicity. IgG phase 1 antibodies can take up to 6-8 weeks before there is a noticeable increase in titre.[23] Both phase 1 and 2 antibodies can persist, with half-time decay rates measured by years rather than months.[25] PCR testing for Q fever utilises a combination of 2 separate coding regions of the *C. burnetii* genome. The *com1* gene is a 27-kDa outer membrane protein that is related to pathogenesis and protective immunity.[26] The *htpAB* gene is flanked by a repetitive DNA element IS*1111a*, which functions as a transposase.[27] Studies show that on serum, a PCR-positive result for *C. burnetii* drops drastically after the second week of the illness, in conjunction with the rise in phase 2 antibodies.[28]

The recommended antimicrobial agent for treatment of acute Q fever is doxycycline, at a dose of 100 mg twice daily for 14 days.[17] Resistance to doxycycline has not been documented.[29] Macrolides show promise as an

alternative treatment choice in those intolerant of the tetracyclines.[30] In pregnant women, treatment is warranted to reduce foetal complications. As doxycycline and macrolides are undesirable during pregnancy, high-dose cotrimoxazole is a viable option, although often not curative. Definitive treatment is undertaken in the postpartum period.[31] There is a school of thought which emphasises treatment only if symptomatic.[32] Others however, advocate treatment acutely irrespective of symptoms, with the overarching concern of progression to chronic disease, a difficult to treat condition at best.[17, 22] Endocarditis, being the most common manifestation of chronic Q fever, necessitates both surgical and medical considerations. Surgical management, in conjunction with medical therapy, has a role in those with substantial valvular damage or heart failure.[22] Suggested duration of drug treatment varies, from lifelong treatment to a minimum of 18 months of dual antimicrobial agents - doxycycline and hydroxychloroquine.[33] Chloroquine facilitates the bactericidal activity of doxycycline. Despite guidelines assessing fall in phase 1 antibody titres to aid in the decision-making process in chronic Q fever endocarditis therapy, there is no single test that can definitively prove complete cure.[32]

There is no consensus on serological follow-up of treated acute Q fever. Landais *et al.* advocate IFA serological testing at 3 months and 6 months after acute illness.[34] Phase 1 IgG titres greater than 800 serve as a trigger for trans-oesophageal echocardiogram (TOE) and PCR testing on serum, irrespective of the presence or absence of clinical symptoms. Limonard *et al.* argue that in the recovery period following acute disease, an IgG titre >800 on IFA is not uncommon.[9] It was observed that none of their subset of patients with IgG titres >800 developed a clinical picture consistent with chronic Q fever endocarditis. Given the ever-pressing considerations of resource allocation, he raises the impracticality and cost of screening echocardiograms in the absence of a clinical compatible illness. A modified flow diagram is shown (Fig. 3).

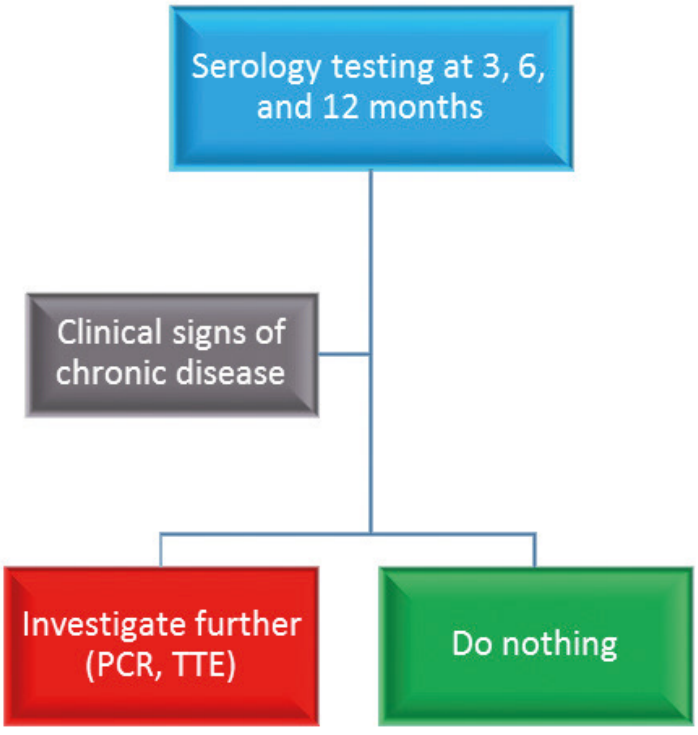

Figure 3. Algorithm for serological follow up in Q fever (modified from Limonard *et al.*[9])

Conclusion

Q fever can give rise to a protean clinical illness. Our patient became critically ill with multi-organ involvement. We report a very rare case of presumed Q fever cholecystitis and coexisting pneumonia, and only the second report of positive PCR in gallbladder tissue. One must recognise that the positive PCR in this case may in fact represent the systemic nature of the disease. Furthermore, it is clear that there exists a gap in knowledge of the clinical spectrum of disease in contemporary Australia. This warrants further investigation. Last, serological follow up remains a perturbing issue with no clear consensus guidelines on a national or global level.

Acknowledgements

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References

1. Maurin M, Raoult D. Q fever. Clin Microbiol Rev 1999; 12: 518-53.
2. Raoult D, Tissot-Dupont H, Foucault C, Gouvernet J, Fournier PE, Bernit E, *et al.* Q fever 1985-1998. Clinical and epidemiological features of 1, 383 infections. Medicine (Baltimore)2000; 79: 109-23.
3. Derrick EH. 'Q' fever, new fever entity: clinical features, diagnosis and laboratory investigation. Med J Aust 1937; 2: 281-99.
4. Heinzen RA, Hackstadt T, Samuel JE. Developmental biology of *Coxiella burnetii.* Trends Microbiol 1999; 7: 149-54.
5. Fishbein DP, Raoult D. A cluster of *Coxiella burnetii* infections associated with exposure to vaccinated goats and their unpasteurized dairy products. Am J Trop Med Hyg 1992; 47: 35-40.
6. Stein A, Raoult D. Q fever during pregnancy: a public health problem in southern France. Clin Infect Dis 1998; 27:592-6.
7. Derrick EH. The course of infection with *Coxiella burnetii.* Med J Aust 1973; 1: 1051-7.
8. Fournier PE, Marrie TJ, Raoult D. Diagnosis of Q fever. J Clin Microbiol 1998; 36: 1823-34.
9. Limonard GJM, Nabuurs-Franssen MH, Weers-Pothoff G, Wijkmans C, Besselink R, Horrevorts AM, *et al.* One-year follow-up of patients of the ongoing Dutch Q fever outbreak: clinical, serological and echocardiographic findings. Infection 2010; 38: 471-7.
10. Gale M, Ketheesan N, Kennedy RL, Govan B, Norton R. Q fever cases at a north Queensland centre during 1994-2006. Intern Med J 2007; 37: 644-6.
11. Spelman DW. Q fever – a study of 111 consecutive cases. Med J Aust 1982; 13: 547-8, 551, 553.
12. Powell O. 'Q' fever: clinical features in 72 cases. Australas Ann Med 1960; 9: 214-23.
13. Derrick EH. The course of infection with *Coxiella burnetii.* Med J Aust 1973; 1: 1051-7.
14. Figtree M, Miyakis S, Stenos J, Graves S, Botham S, Ferson M, *et al.* Q fever cholecystitis in an unvaccinated butcher diagnosed by gallbladder polymerase chain reaction. Vector Borne Zoonotic Dis 2010; 10(4): 421-3.
15. Pellegrin M, Delsol G, Auvergnet JC, Familiades J, Faure H, Guiu M, *et al.* Granulomatous hepatitis in Q fever. Hum Pathol 1980; 11: 51-7.
16. Rolain JM, Lepidi H, Harlé JR, Allegre T, Dorval ED, Khayat Z, *et al.* Acute acalculous cholecystitis associated with Q fever: report of seven cases and review of the literature. Eur J Clin Microbiol Infect Dis 2003; 22: 222-7.
17. Parker NR, Barralet JH, Bell AM. Q fever. Lancet 2006; 367: 679-88.
18. Barten DG, Delsing CE, Keijmel SP, Sprong T, Timmermans J, Oyen WJ, *et al.* Localising chronic Q fever: a challenging query. BMC Infect Dis 2013; 13: 413.
19. Helbig KJ, Heatley SL, Harris RJ, Mullighan CG, Bardy PG, Marmion BP. Variation in immune response genes and chronic Q fever. Concepts: preliminary test with post-Q fever fatigue syndrome. Genes Immun 2003; 4: 82-5.
20. Marmion BP, Sukocheva O, Storm PA, Lockhart M, Turra M, Kok T, *et al.* Q fever: persistence of antigenic non-viable cell residues of *Coxiella burnetii* in the host—implications for post Q fever infection fatigue syndrome and other chronic sequelae. QJM 2009; 102: 673–84.
21. Amitai Z, Bromberg M, Bernstein M, Raveh D, Keysary A, David D, *et al.* A large Q fever outbreak in an urban school in central Israel. Clin Infect Dis 2010; 50: 1433-8.
22. Hartzell JD, Wood-Morris RN, Martinez LJ, Trotta RF. Q fever: epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008; 83: 574-9.
23. Marmion BP. Q fever: your questions answered. Parkville, NSW: MediMedia Communications; 1999.
24. Van der Hoek W, Versteeg B, Meekelenkamp JCE, Renders NHM, Leenders ACA, Weers-Pothoff I, *et al.* Follow-up of 686 patients with acute Q fever and detection of chronic infection. Clin Infect Dis 2011; 52: 1431-6.
25. Teunis PFM, Schimmer B, Notermans DW, Leenders ACA, Wever PC, Kretzschmar MEE, *et al.* Time-course of antibody responses against *Coxiella burnetii* following acute Q fever. Epidemiol Infect 2013; 141: 62-73.
26. Zhang GQ, To H, Yamaguchi T, Fukushi H, Hirai K. Differentiation of *Coxiella burnetii* by sequence analysis of the gene *(com1)* encoding a 27-kDa outer membrane protein. Microbiol Immunol 1997; 41: 871-7.
27. Hoover TA, Vodkin MH, Williams JC. A *Coxiella burnetii* repeated DNA element resembling a bacterial insertion sequence. J Bacteriol 1992; 174: 5540-48.
28. Boden K, Wagner-Wiening C, Seidel T, Baier M, Bischof W, Straube E, *et al.* Diagnosis of acute Q fever with emphasis on enzyme-linked immunosorbent assay and nested polymerase chain reaction regarding the time of serum collection. Diagn Microbiol Infect Dis 2010; 68: 110-16.
29. Honarmand H. Q fever: an old but still a poorly understood disease. Interdiscip Perspect Infect Dis 2012; 2012: 131192. Doi: 10.1155/2012/131932.
30. Gikas A, Kofteridis DP, Manios A, Pediaditis J, Tselentis Y. Newer macrolides as empiric treatment for acute Q fever infection. Antimicrob Agents Chemother 2001; 45: 3644-6.
31. Carcopino X, Raoult D, Bretelle F, Boubli L, Stein A. Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy. Clin Infect Dis 2007; 45: 548-55.
32. Tissot-Dupont H, Raoult D. Q fever. Infect Dis Clin North Am 2008; 22: 505-14.
33. Raoult D, Houpikian P, Tissot-Dupont H, Riss JM, Arditi-Djiane J, Brouqui P. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch Intern Med 1999; 159: 167-73.
34. Landais C, Fenollar F, Thuny F, Raoult D. From acute Q fever to endocarditis: serological follow-up strategy. Clin Infect Dis 2007; 44: 1337-40.

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DELAYED DIAGNOSIS OF WHIPPLE'S DISEASE

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Abstract

Whipple's disease is a rare, chronic infection caused by *Tropheryma whipplei*. The disease classically involves the musculoskeletal and gastrointestinal systems, but can also affect the neurological and cardiac systems. *T. whipplei* is an aerobic Gram-positive actinomycete that has been isolated from human tissue, namely duodenal biopsy specimens, oral swabs, and from environmental specimens. However, its pathogenesis is not completely understood. Diagnosis involves a combination of clinical findings, histopathological examination with periodic acid-Schiff staining for visualisation of positive-stained *T. whipplei* within foamy macrophages, and molecular techniques. We present a case of Whipple's disease that was diagnosed 15 years after the onset of symptoms. This case highlights the difficulty in diagnosis of a rare disease with insidious onset. The use of special histopathological stains and correlation with clinical findings is emphasised.

Key words: Whipple's disease, *T. whipplei*, histopathology, clinical pathology

Introduction

Whipple's disease is a rare, chronic, multisystem infectious disease with a reported incidence estimated to be <1 in 10^6.[1] The causative organism, *Tropheryma whipplei*, is an anaerobic Gram-positive intracellular actinomycete. Its pathophysiology and aetiology remain unknown.[2] *T. whipplei* has been detected in human faeces, saliva, subgingival plaques and duodenal biopsy specimens from both affected and non-affected individuals.[2-5] Disease may be associated with impaired phagocytic and interleukin pathways, autoimmune predisposition or genetic causes linked to HLA-B27 status.[6-7] It commonly manifests as arthritis, followed years later by diarrhoea, weight loss and abdominal pain.[8-9] We present a diagnostically challenging case 15 years after the onset of symptoms, with clinicopathological correlation.

Case report

A 72-year-old man presented with ongoing epigastric pain, nausea, low-grade fevers, and associated weight loss of 6 kg over three months. No cardiac or neurological symptoms were identified. He was a non-smoker, non-drinker, and was on esomeprazole for dyspepsia. He had a 15-year history of intermittent fevers and medium/large joint arthritis, diagnosed as tumour necrosis factor receptor-associated periodic syndrome, and treated with methotrexate and prednisolone. The patient had microcytic anaemia, and was referred to a gastroenterologist. The initial endoscopy investigation for the anaemia revealed a jejunal arteriovenous malformation and Barrett's oesophagus. As a result he was followed up with annual gastroscopy for the last nine years.

On two occasions prior to the current presentation, the patient was investigated for increasing fatigue, anaemia and features of malabsorption, including weight loss, hypoalbuminaemia, peripheral oedema and diarrhoea. Upper GI endoscopy and colonoscopy were normal but histopathology of the duodenal biopsies showed foamy macrophages, and active colitis. Special histochemistry tests were not performed. The findings were attributed to recovery from an infective process, and his symptoms, which were attributed to methotrexate therapy, appeared to improve with adjustment of his treatment.

Laboratory investigations showed hypoalbuminaemia, microcytic anaemia and mildly elevated inflammatory markers. A repeat capsular endoscopy six months later revealed prominent whitish nodules in the duodenum with mucosal oedema throughout the small intestine (Fig. 1). A diagnosis of Whipple's disease was made on histopathology (Fig. 2-5), and confirmed positive for *T. whipplei* by polymerase chain reaction (PCR). Figure 6 illustrates the typical ultrastructure.[10]

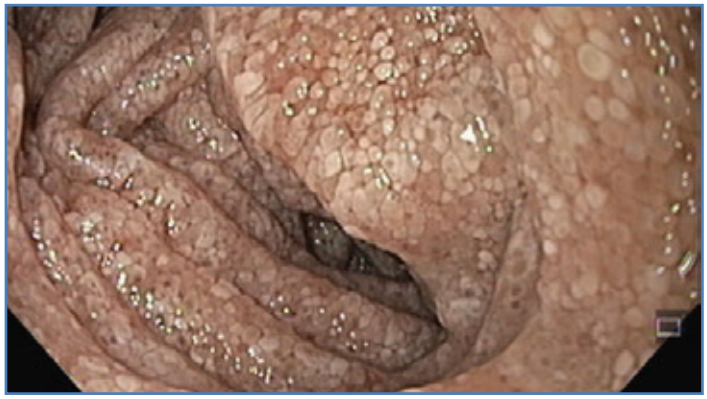

Figure 1. Endoscopic view of proximal duodenum

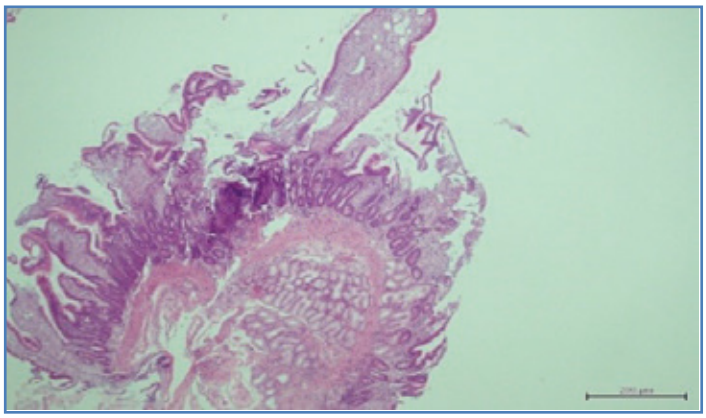

Figure 2. Duodenal mucosa with enlarged and distended villi (H&E, x 100)

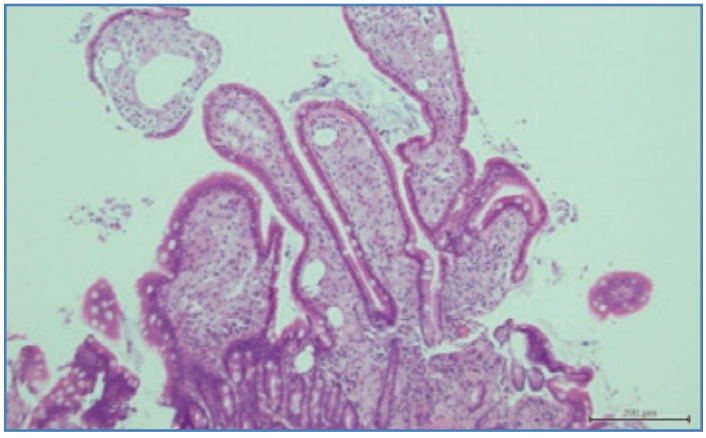

Figure 3. Villi with expansion of the lamina propria by foamy macrophages, which also focally extends to the submucosa (H&E, x 200)

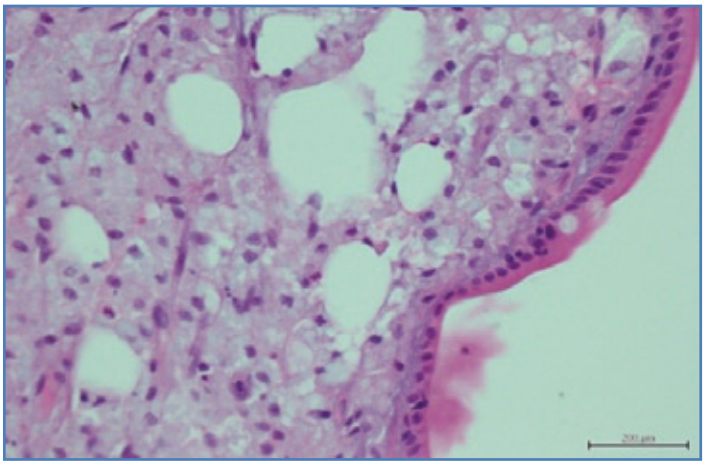

Figure 4. Lipid vacuoles and foamy macrophages (H&E, x 400)

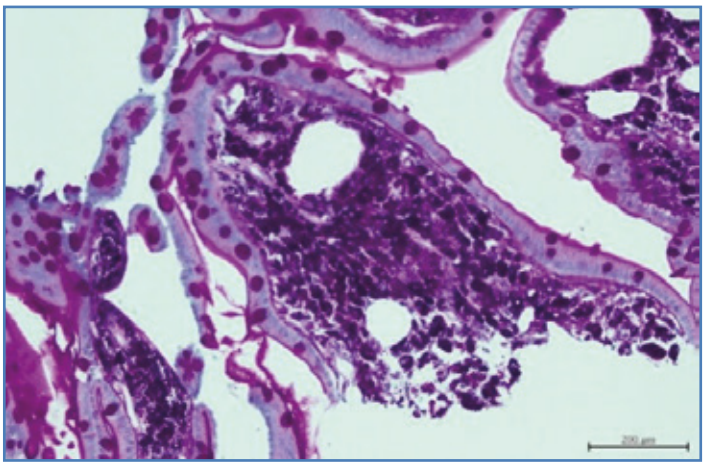

Figure 5. Foamy macrophages packed with bacilli, showing strong PAS-positivity. (PAS, x 400)

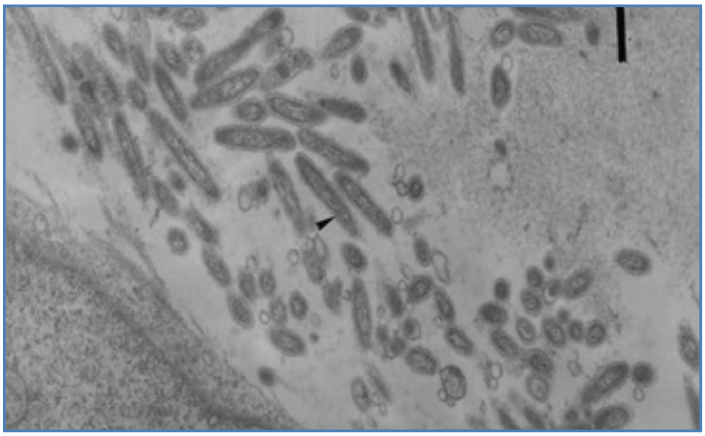

Figure 6. Transmission electron micrograph of *T. whipplei* bacteria (arrowhead; bar = 500 nm). From ref. 10, with permission

Treatment

The patient commenced intravenous ceftriaxone, with improvement of symptoms after one week of treatment. Thereafter, he was given cotrimoxazole orally, with a plan to continue oral antibiotic therapy for one year.

Discussion

This case illustrates the insidious onset of a rare disease and the diagnostic challenge to both the clinician and pathologist. The clinical differential diagnosis of Whipple's disease is wide and includes malabsorptive and infiltrative diseases, such as coeliac disease, tuberculosis, *Mycobacterium avium* infection of the small bowel, histoplasmosis, non-steroidal anti-inflammatory drug-induced injury to the small intestine, non-Hodgkin lymphoma and amyloidosis.[16] Endoscopic investigation with biopsy should be performed if symptoms of malabsorption, seronegative arthritis, lymphadenopathy and low-grade fever are present. The differential diagnosis on histopathological examination includes infective and non-infective causes. Special histochemistry using Gram, Ziehl-Neelsen (ZN), Grocott's methenamine silver, and PAS may help to identify infective causes.[7,11] In this case, the identification of *T. whipplei* was made with routine H&E and PAS stains, with ZN to exclude *Mycobacterium avium* infection. Subsequent specific PCR for *T. whipplei* was also performed.

Weight loss with diarrhoea is the most common gastrointestinal symptom in classic Whipple's disease.[9] Occasional abdominal pain, hepatosplenomegaly and ascites are also documented.[1] Joint involvement occurs in 65%-90% of patients and may occur without gastrointestinal symptoms.[13] Neurological complications have also been reported.[8-9] *T. whipplei* has also been associated with culture-negative endocarditis.[1,14] Approximately 15% of patients do not have classic signs and symptoms.[9,15]

Without appropriate treatment the prognosis is poor, and the disease is potentially fatal, with a 40% risk of disease relapse if treatment is ceased prematurely.[12] The recommended treatment is intravenous ceftriaxone or penicillin G for two to four weeks, followed by oral cotrimoxazole for one to two years.[11] Because cotrimoxazole crosses the blood-brain barrier in the case of neurological involvement, it is the oral antibiotic of choice. A one-year regimen of doxycycline and hydroxychloroquine, followed by lifelong treatment with doxycycline, has also been suggested, due to resistance of some strains to sulphonamides.[12] Tetracycline, previously used as a first-line treatment, is no longer used, due to the high frequency of disease recurrence.[1]

Conclusion

Whipple's disease, a rare but significant condition, has a variety of clinical manifestations and should be considered in any patient with joint and/or gastrointestinal symptoms. Endoscopy and biopsy of an infected region is critical to allow for appropriate histopathology and molecular diagnosis. Clinical correlation is essential due to the ubiquitous nature of the causative organism. Treatment with appropriate antibiotics for a sufficient length of time is necessary for a favourable clinical outcome.

References

1. Fenollar F, Puechal X, Raoult D. Whipple's disease. N Eng J Med 2007; 356: 55-66.
2. Marth T, Raoult D. Whipple's disease. Lancet 2003; 361: 239-46.
3. Street S, Donoghue HD, Neild GH. *Tropheryma whippelii* DNA in saliva of healthy people. Lancet 1999; 354: 1178-9.
4. Amsler L, Bauernfeind P, Nigg C, Maibach RC, Steffen R, Altwegg M. Prevalence of *Tropheryma whipplei* DNA in patients with various gastrointestinal diseases. Infection 2003; 31: 81-5.
5. Ehrbar HU, Bauerfeind P, Dutly F, Altwegg M. PCR-positive tests for *Tropheryma whippelii* in patients without Whipple's disease. Lancet 1999; 353: 2214.
6. Moos V, Kunkel D, Marth T, Feurle GE, La Scola B, Ignatius R, *et al.* Reduced peripheral and mucosal *Tropheryma whipplei*-specific Th1 response in patients with Whipple's disease. J Immunol 2006; 177: 2015-22.
7. Sagaert X, Tousseyn T, De Hertogh G, Geboes K. Macrophage-related diseases of the gut: a pathologist's perspective. Virchows Arch 2012; 460: 555-67.
8. Dutly F, Altwegg M. Whipple's disease and '*Tropheryma whippelii*'. Clin Microbiol Rev 2001; 14: 561-83.
9. Durand DV, Lecomte C, Cathebras P, Rousset H, Godeau P. Whipple disease. Clinical review of 52 cases. Medicine (Baltimore) 1997; 76: 170-84.
10. Fenollar F, Raoult D. Whipple's disease. Clin Diagn Lab Immunol 2001; 8: 1-8.
11. Bures J, Kopacova M, Douda T. Whipple's disease: our own experience and review of the literature. Gastroenterol Res Pract 2013; 2013: 1-10.
12. Lagler J, Fenollar F, Raoult D. Whipple's disease: surprised by the surprise. Lancet 2014; 384: 1184-5.
13. Puechal X. Whipple disease and arthritis. Curr Opin Rheumatol 2001; 13: 74-9.
14. Richardson DC, Burrows LL, Korithoski B, Salit IE, Butany J, David TE. *Tropheryma whippelii* as a cause of afebrile culture-negative endocarditis: the evolving spectrum of Whipple's disease. J Infect 2003; 47: 170-73.
15. Misbah S, Mapstone N. Whipple's disease revisited. J Clin Pathol 2000; 53: 750-55.

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