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ORIGINAL ARTICLE

The burden of presumed tuberculosis in hospitalized children in a resource-limited setting in Papua New Guinea: a prospective observational study

Villa Watch[a], Jimmy Aipit[a], Tina Kote-Yarong[a], Allanie Rero[a], John W. Bolnga[b], Elvin Lufele[c] and Moses Laman[a,c,*]

[a]Modilon General Hospital, Department of Paediatrics, Madang Province; [b]Modilon General Hospital, Department of Obstetrics and Gynaecology, Madang Province; [c]Papua New Guinea Institute of Medical Research, Madang Province, Papua New Guinea

*Corresponding author: Present address: Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province 511, Papua New Guinea. Tel: +675 4222909; Fax: +675 4223289; E-mail: drmlaman@yahoo.com

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Background: In Papua New Guinea, TB is considered to be a major public health problem, but little is known about the prevalence and prognosis of presumed TB in children.

Methods: As part of a prospective hospital-based surveillance on the northern coast of mainland Papua New Guinea, the authors investigated the admission prevalence and case fatality rate associated with presumed TB over a 6-year period (2011–2016). All children admitted who were diagnosed with TB were followed-up until discharge or death.

Results: Of 8992 paediatric admissions, 734 patients (8.2%) were diagnosed with presumed TB and there were 825 deaths, with TB accounting for 102 (12.4%). Extrapulmonary TB was the final diagnosis in 384 admissions {prevalence 4.3% [384/8992 (95% CI 3.9–4.7)]} with a case fatality rate of 21.4% [82/384 (95% CI 17.4–25.9)]. TB meningitis, disseminated TB and pericardial TB had high case fatality rates of 29.0% (53/183), 28.9% (11/38) and 25% (4/16), respectively. Severe malnutrition was more common in patients with pulmonary compared with extrapulmonary TB (25.4% vs 15.6%; p<0.01).

Conclusions: Improved community-based case detection strategies, routine BCG vaccinations and other effective forms of TB control need revitalization and sustainability to reduce the high case fatality rates associated with childhood TB in Papua New Guinea.

Keywords: Children, Extrapulmonary tuberculosis, Papua New Guinea, Tuberculosis

Background

TB is endemic in many resource-limited countries, with devastating rates of long-term morbidity and mortality.[1] Of the estimated 10.4 million new cases reported in 2015, India, Indonesia, China, Nigeria, Pakistan and South Africa accounted for 60% of the burden.[1,2] However, when considering the incidence of TB per 100 000 population, Papua New Guinea, despite being a small country with a population of 7.5 million, is amongst the 30 countries with the highest burden in the world.[1] WHO estimates suggest a TB incidence rate of 432 cases per 100 000 population, while in some areas of the country, incidence rates of nearly 1300 cases per 100 000 have been reported.[1,3]

However, even though TB is currently considered a major public health problem in Papua New Guinea,[4–6] there is a lack of clinical data from hospital-based studies that can estimate TB-related morbidity and case fatality rates of various forms of TB, particularly in children in this setting where diagnostic modalities for TB are limited. Of 22 799 paediatric admissions in 14 hospitals throughout Papua New Guinea in 2016, presumed TB accounted for 12% (201/1679) of deaths, with the majority of these TB-related deaths being attributed to extrapulmonary TB.[7]

In order to document the prevalence and case fatality rates associated with the various forms of extrapulmonary TB, we analysed data collected at Modilon Hospital on the north coast of Papua New Guinea as part of an ongoing hospital-based surveillance of severe childhood infections in children over a 6-year period.

Method

Study site and setting

This study was conducted in the paediatric wards of Modilon Hospital, the main provincial hospital in Madang Province of Papua New Guinea. Modilon hospital attends to an average of 3000 deliveries per year[8] with an in-hospital neonatal mortality rate of 15% (370/2426),[9] and an overall child mortality rate of 9.6%.[10] The high burden of childhood mortality in this setting is often a result of the weak health care system contributing to multiple pre- and in-hospital factors, as well as delayed presentations.[8] Presumed TB is a common comorbidity in this setting, particularly in children with malnutrition.[11] Although rates of HIV remain <1%, the burden of HIV is higher in vulnerable children, including those who are neglected, abused and/or malnourished.[12]

Study design

Data analysed in the present study were collected as part of a prospective surveillance of severe childhood infections at Modilon Hospital over a 6-year period between 2011 and 2016. The surveillance reporting system was established as part of the Papua New Guinea Paediatric Society monitoring of paediatric disease burden, morbidity and mortality,[13] while the diagnostic laboratory support was provided as part of ongoing paediatric research programmes led by the Papua New Guinea Institute of Medical Research in collaboration with the paediatric and obstetric divisions of Modilon Hospital.

Definitions of tuberculosis

A diagnosis of pulmonary TB or extrapulmonary TB was based on medical history, chest X-ray findings and a Papua New Guinea paediatric TB score of ≥7.[14] For pulmonary TB, sputum microscopy was the main diagnostic method used, particularly in older children who were able to provide specimens. Nevertheless, smear-negative patients with a presumed diagnosis of pulmonary TB were not excluded due to the poor sensitivity of sputum microscopy. Extrapulmonary TB was mainly a clinical diagnosis, but in a small number of children with TB lymphadenopathy, this was confirmed by fine needle aspiration and Ziehl–Neelsen staining. In patients suspected of having TB meningitis, a medical history suggestive of TB and the use of the Papua New Guinea TB scoring system,[14] a lymphocytic cerebrospinal fluid leucocyte count of ≥10 cells/μL and/or an elevated protein was used as a criteria for Ziehl–Neelsen staining (Figure 1) as well as the exclusion of cryptococcal meningitis[15] and acute bacterial meningitis[16] before a clinical diagnosis of TB meningitis was made. In this setting, TB culture facilities are unavailable and GeneXpert diagnosis of TB was not performed as part of the present study. However, where appropriate, samples were stored with plans for molecular analysis to be conducted retrospectively.

Clinical management of patients

All children were admitted to the paediatric wards and managed according to the Papua New Guinea National Paediatric Standard Treatment Guidelines.[14] Prior to 2015, patients classified as Category I were new cases who failed to complete treatment previously, but are currently not severely ill, based on the WHO severity criteria.[17] These patients received a combination therapy of isoniazid, rifampicin, pyrazinamide and ethambutol administered daily according to weight bands for 2 months during the intensive phase, as well as isoniazid and rifampicin daily for 4 months during the continuation phase.

Category II patients were: those 1. who completed treatment, but had a relapse and 2. those who defaulted from treatment and became severely ill.[14]

These patients received a combination therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) daily for 3 months during the intensive phase, administered according to weight bands, and isoniazid, rifampicin and ethambutol daily for 5 months during the continuation phase. The continuation phase was extended to 7 months for patients with severe forms of TB, such as TB meningitis. Patients suspected of having drug-resistant TB were admitted to an isolation ward and received 2 months of streptomycin i.m. injection in hospital, in addition to Category II treatment.[14] The treatment for multidrug-resistant TB in Papua New Guinea involves fluoroquinolones (levofloxacin or moxifloxacin), aminoglycoside (kanamycin or amikacin), cycloserine, ethionamide and pyrazinamide. Newer agents, such as bedaquiline, and delamanid were unavailable in 2011, but became available after 2013.

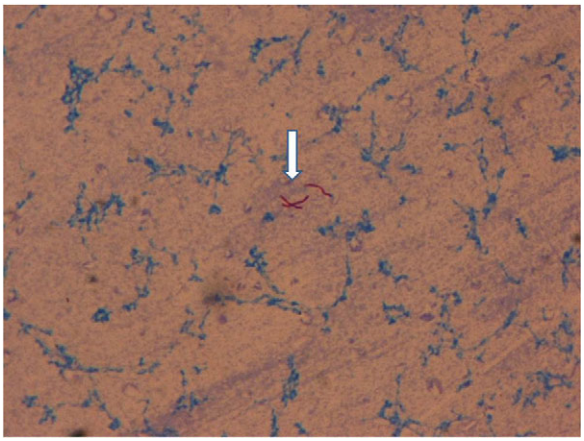

Figure 1. Ziehl–Neelsen staining of acid-fast bacilli (×1000 magnification), isolated from the cerebrospinal fluid of a child who died with TB meningitis at Modilon Hospital, Madang Province, Papua New Guinea.

Statistical analysis

Data were analysed using the STATA analysis program (Version 11.0, Texas, Stata Corp Inc.). Two-way comparisons of proportions were made by Fisher's exact test, while comparisons of three or more independent samples were made by the Kruskal–Wallis test. Proportions with 95% CIs with continuity correction were used to determine prevalence. A two-tailed significance level of $p<0.05$ was used throughout.

Results

Between January 2011 and December 2016, there were 8992 paediatric admissions to Modilon Hospital, with presumed TB being the final diagnosis in 734 patients (8.2%). Extrapulmonary TB accounted for 384 admissions (52.3%), while pulmonary TB accounted for 350 (47.7%). Over the 6-year period, there were a total of 825 deaths (9.2%), with TB accounting for 102 [extrapulmonary TB 82 (9.9%) and pulmonary TB 20 (2.4%)].

The annual case fatality rate attributed to extrapulmonary TB ranged from 10.2% to 29.3% (Table 1). Extrapulmonary TB had an overall admission prevalence rate of 4.3% [384/8992 (95% CI 3.9–4.7)] and a case fatality rate of 21.4% [82/384 (95% CI 17.4–25.9)]. Over the 6-year period, the burden of extrapulmonary TB was highest in 2015 with 7.2% (Table 1).

Tuberculosis meningitis (183), TB lymphadenopathy (48), miliary TB (46), disseminated TB (38) and TB of the bone/joint (23) were the five most common forms of extrapulmonary TB in children admitted (Table 2). Deaths due to TB meningitis (29.0%; 53/183), TB of the bone/joint (6.3%; 2/32), TB abdomen (14.3%; 3/21), miliary TB (15.2%; 7/46), pericardial TB (25.0%; 4/16) and disseminated TB (28.9%; 11/38) resulted in higher case fatality rates relative to pulmonary TB (5.7%; 20/350).

Severe malnutrition was more common in patients with pulmonary TB compared with all other forms of extrapulmonary TB combined (25.4% vs 15.6%; Fisher's exact test p<0.01; Table 2). Anaemia was also prevalent in children with all other forms of TB, but more common (≥50%) in those with pericardial and disseminated TB (Table 2). Children with TB abdomen were older [median age 108 (72–144) months] than those with other forms of TB, while a significant number of children with miliary TB were younger [median age 8 (4–72) months; Table 2]. There was no difference in rates of HIV between the various forms of TB (Kruskal–Wallis test p=0.30). Other characteristics, such as adoption status and readmission rates according to each form of TB, are shown in Table 2.

Discussion

This study highlights the substantial burden of TB in hospitalized children in Madang Province of Papua New Guinea with an overall admission prevalence of 8.2% and a case fatality rate of 12.4% over a 6-year period. Severe forms of TB such as TB meningitis, disseminated TB, pericardial TB, miliary TB and TB abdomen accounted for over 76% of deaths attributed to TB (Table 2). The high burden of pulmonary and extrapulmonary TB in this setting is consistent with findings from other hospitals in Papua New Guinea[18] and may be a reflection of the high rates of reservoirs in the adult population. This emphasizes the need to improve contact screening through active community-based case finding, as well as the urgent need to strengthen, implement and improve the coverage of vaccination programmes with a particular focus on the availability and accessibility of BCG vaccinations as part of the TB control programme in Papua New Guinea.

Although BCG vaccination does not prevent the transmission of TB, this intervention alone is the most cost-effective and can prevent severe forms of childhood TB and[19–21] leprosy,[22] offer varying levels of protection[19] and possibly reduces childhood mortality due to other causes,[23] because of its effect in promoting a T-helper1 response in children.[21,24] However, in our setting the benefits of BCG vaccine are almost non-existent because of the very low rates of BCG vaccination coverage. For instance, in recent years, the immunization coverage rate for Papua New Guinea showed a consecutive decline in BCG vaccinations over the past 3 years (2013, 88%; 2014, 81%; 2015, 65%),[25] and it has been reported to be as low as 35% for Madang Province in 2016 (unpublished). This was compounded by a 3-month BCG vaccine stock-out countrywide, exacerbated by the global shortage in BCG vaccine production.[26]

In addition to the poor BCG vaccination coverage, the high prevalence of malnutrition in Papua New Guinea makes children more susceptible.[11] Furthermore, challenges of obtaining appropriate specimens to enable diagnosis particularly in young children, lack of sensitive diagnostic tools[27] as well as the challenges of implementing isoniazid preventative therapy for exposed children through weak health care systems[14] make TB difficult to contain. This is often compounded by the unavailability of anti-tuberculosis drugs, mainly because of supply and procurement bottlenecks, lack of health facility admission capacity to directly observe and treat patients adequately over a longer period of time, as well as the lack of appropriate treatment supervision and follow-up in communities, further contributing to the development of TB drug resistance in Papua New Guinea.[6,28]

Our study had limitations. The unavailability of TB confirmatory diagnostic facilities made it difficult for us to confirm all presumed cases of TB in our setting. Additionally, it was not possible for us to differentiate non-tuberculosis mycobacteria from *Mycobacterium tuberculosis*. However, non-tuberculous mycobacteria accounted for only 2.2% in a previous study in this setting.[29] Additionally, the difficulties of obtaining samples from children and the suboptimal sensitivity of GeneXpert in diagnosing TB in children cannot be relied upon to establish a diagnosis of TB in our setting.[27] Furthermore, other important variables such as history or evidence of BCG vaccination scarring in all hospitalized children could not be documented due to limited personnel and the surveillance nature of this study.

Table 1. Admission prevalence and case fatality rates (CFR) of extrapulmonary TB (EPTB), according to year. Data are numbers (%) and [95% confidence interval]

Year	Total admissions	EPTB admissions	EPTB deaths (CFR)	EPTB admission prevalence [95% CI]
2011	1356	49	5 (10.2)	3.6 [2.7–4.8]
2012	1548	41	12 (29.3)	2.6 [1.9–3.6]
2013	1301	64	18 (28.1)	4.9 [3.8–6.3]
2014	1954	73	10 (13.7)	3.7 [3.0–4.7]
2015	1196	86	20 (23.3)	7.2 [5.8–8.8]
2016	1637	71	17 (23.9)	4.3 [3.4–5.5]
Overall	8992	384	82 (21.4)	4.3 [3.9–4.7]

Conclusions

The high case fatality rates associated with TB highlights the urgent need to control TB in Papua New Guinea. Many of the

Table 2. Characteristics of children admitted to Modilon Hospital between 2011 and 2016, according to the type of TB. Data are numbers (%) and median [interquartile range]

Factors	Type of TB								Total (overall)	p-values*
	Pulmonary	Meningitis	Lymphadenopathy	Bone/joint	Abdomen	Miliary	Pericardial	Disseminated		
Number of admissions	350	183	48	32	21	46	16	38	734	
Female sex	156 (44.6)[a]	72 (39.3)	15 (31.3)	13 (40.6)	9 (42.9)	31 (67.4)	8 (50)	15 (39.5)	319	0.03
Age in months	24 [9–72][c]	60 [24–96]	66 [18–126]	60 [24–96]	108 [72–144]	8 [4–72]	96 [72–132]	84 [36–144]	60 [24–96]	<0.001
Adopted child	3 (0.9)[a]	2 (1.1)	0 (0)	1 (3.1)	0 (0)	0 (0)	1 (6.3)	0 (0)	7	0.15
Associated comorbidities										
Moderate malnutrition	106 (30.3)[a]	59 (32.2)	10 (20.8)	10 (31.3)	5 (23.8)	14 (30.4)	2 (12.5)	9 (23.7)	215	0.66
Severe malnutrition	89 (25.4)[b]	23 (12.6)	7 (14.6)	5 (15.6)	1 (4.8)	13 (28.3)	3 (18.8)	8 (21.1)	149	0.02
HIV	22 (6.3)[b]	4 (2.2)	1 (2.1)	0 (0)	1 (4.8)	1 (2.2)	0 (0)	1 (2.6)	30	0.30
Anaemia	126 (36)[a]	45 (24.6)	10 (20.8)	8 (25)	8 (38.1)	18 (39.1)	8 (50)	20 (52.6)	243	<0.01
Readmission	52 (14.9)[a]	36 (19.7)	3 (6.3)	7 (21.9)	2 (9.5)	2 (4.3)	0 (0)	5 (13.2)	107	0.05
Case fatality rate	20 (5.7)[c]	53 (29)	2 (4.2)	2 (6.3)	3 (14.3)	7 (15.2)	4 (25)	11 (28.9)	102	<0.001

*Kruskal–Wallis test between the different types of TB.
[a]Mann–Whitney p-value >0.05 between pulmonary and all extra pulmonary TB combined.
[b]Mann–Whitney p-value <0.05 between pulmonary and all extrapulmonary TB combined.
[c]Mann–Whitney p-value <0.001 between pulmonary and all extrapulmonary TB combined.

challenges related to the uncontrolled spread of TB in this setting are intertwined with the weak health care systems in Papua New Guinea. In order to reduce the alarming rates of mortality and morbidity due to TB, greater efforts will be needed to strengthen health care systems in Papua New Guinea, and other similar resource-limited settings, particularly utilizing a community-based case detection approach,[30] followed by sustainable and better quality reforms concerning the way TB is currently managed. There is a great need for collaborative efforts between adult TB programmes, childhood TB programmes, HIV programmes, malnutrition programmes and other maternal and child health platforms, in order to effectively combat and reduce TB in Papua New Guinea.

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Conflict of interest: None declared.

Ethical approval: This study was approved by the Modilon Hospital Ethics Committee [MHEC 1601] and the management of Modilon Hospital, while the mortality surveillance conducted as part of the Papua New Guinea Institute of Medical Research surveillance programme received ethical approval from the Papua New Guinea Ministry of Health [MRAC 10.08].

Availability of data and materials: The authors have permission to publish these data. In order to have access to these data, please request permission from the Modilon Hospital Ethics Committee and Chief Paediatrician at Modilon Hospital—Dr Jimmy Aipit via email: jimmy.aipit@gmail.com.

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