VOLUME 14 NO 2 PP 136–142 FEBRUARY 2009

No decrease in annual risk of tuberculosis infection in endemic area in Cape Town, South Africa

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Summary

OBJECTIVE To estimate the change in annual risk of tuberculosis infection (ARTI) in two neighbouring urban communities of Cape Town, South Africa with an HIV prevalence of approximately 2%, and to compare ARTI with notification rates and treatment outcomes in the tuberculosis (TB) programme.

METHODS In 1998–1999 and 2005, tuberculin skin test surveys were conducted to measure the prevalence of *Mycobacterium tuberculosis* infection and to calculate the ARTI. All 6 to 9-year-old children from all primary schools were included in the survey. Notification rates and treatment outcomes were obtained from the TB register.

RESULTS A total of 2067 children participated in the survey from 1998 to 1999 and a total of 1954 in 2005. Based on a tuberculin skin test cut-off point of 10 mm, the ARTI was 3.7% (3.4–4.0%) in the 1998–1999 survey and 4.1% (3.8–4.5%) in 2005. The notification rate for pulmonary TB increased significantly from 646 per 100 000 in 1998 to 784 per 100 000 in 2002. In Ravensmead, there was no significant change in ARTI [first survey: 3.5% (3.1–3.9%), second survey: 3.2% (2.9–3.6%)], but in Uitsig the ARTI increased significantly from 4.1% (3.6–4.6%) to 5.8% (5.2–6.5%). The difference in ARTI between the two areas was associated with differences in reported case rates and the proportion of previously treated cases.

CONCLUSION Tuberculosis transmission remains very high in these two communities and control measures to date have failed. Additional measures to control TB are needed.

keywords annual risk of infection, tuberculosis, tuberculin, treatment outcome, notification rates, South Africa

Introduction

Tuberculosis (TB) remains an important public health problem (Corbett *et al.* 2003). WHO targets for the Stop-TB strategy are to detect at least 70% of incident cases of smear-positive TB and to cure at least 85% of these patients (Stop TB Partnership & WHO 2006). Mathematical models predict that reaching these targets will lower the transmission of TB, the incidence of TB, and the annual risk of TB infection (ARTI) (Dye *et al.* 1998; Borgdorff *et al.* 2002).

The prevalence of TB infection and the ARTI, which are estimated from repeated tuberculin surveys of children, are considered the best epidemiological indicator to monitor ongoing TB transmission in a community (Arnadottir *et al.* 1996). Changes in the ARTI over time reflect the impact of TB control measures. In Africa, a number of tuberculin surveys have been published in the last 10 years, and ARTIs between 0.3% and 3.1% have been reported (Bosman *et al.* 1998; El Ibiary *et al.* 1999; Odhiambo *et al.* 1999; Salaniponi *et al.* 2004; Trébucq *et al.* 2005; Egwaga *et al.* 2006). For South Africa, ranking 7th among the 22 highest TB burden countries in the world (WHO 2007), no recent national ARTI estimates are available, although a recent TST survey in a small community in Cape Town showed an ARTI of 4.1% (Middelkoop *et al.* 2008). The aim of this study was to assess the trend in ARTI in Ravensmead and Uitsig, two high incidence urban communities in Cape Town with a prevalence of HIV of approximately 2%. We performed two tuberculin skin test (TST) surveys among school children. The first survey was done in 1998–1999 and the second in 2005. Then we compared the ARTI data with the trends in pulmonary TB (PTB) notifications and treatment outcomes over the period 1993–2002.

Methods

Study population

Ravensmead and Uitsig have a total surface area of 3.4 km^2 and had a census population of 34 294 in 1991 and 36 343 in 2001 (Statistical Support and Informatics 2001). The average monthly income per household was R6,750 in Ravensmead and R3,290 in Uitsig in 2001 (1 USD ≈ 7.8 Rand). Employment rates were approximately 51% in Ravensmead and 40% in Uitsig between 1996 and 2001. The infant mortality rate in these communities is 19 per 1000 live births and two primary health care clinics and an adjacent tertiary hospital serve the area. A TB survey in 2002 showed a prevalence of 10 per 1000 for bacteriologically confirmed TB (Den Boon *et al.* 2007). BCG vaccination in the neonatal period has been compulsory since 1972 and the vaccination coverage is estimated at 80–99% (Fourie 1987; Corrigal *et al.* 2008).

Study design and sampling

The two TST surveys were conducted according to the WHO/IUATLD guidelines (Arnadottir *et al.* 1996). The first TST survey was conducted in 1998–1999 and it was repeated using the same method in 2005. Using the exact average calendar time of the survey, and the exact average age of the children, we determined that the 1998–1999 survey gives the average ARTI in 1994 and the 2005 survey represents the average ARTI in 2000.

All primary schools, nine in 1998–1999 and eight in 2005 (one school in Ravensmead closed), were included in the survey and all children (grade 1–7) were asked to have a skin test. The Committee for Human Research, Faculty of Health Sciences, Stellenbosch University, the Department of Health, City of Cape Town and the Department of Education of the Western Cape Province gave permission for the study. Written informed consent was obtained from parents/legal guardians and assent from participants was sought.

Data collection

Sex and the presence of a BCG scar were recorded for each child. In the 1998–1999 survey, the age of the child was recorded while in the 2005 survey we calculated age using the date of birth and the date of the survey. A trained and experienced field worker performed the TST. A quantity of 0.1 ml from a single batch of PPD RT 23 (Statens Serum Institut, Copenhagen, Denmark), at a dose of 2TU was injected intradermally on the ventral aspect of the left forearm. The maximum transverse diameter of the induration was read with a calibrated calliper after 72 h. Parents received a letter that informed them of their child's result and symptomatic children were asked to attend the local health facility where they were screened for active TB and managed accordingly.

Statistical analyses

All 6 to 9-year old children whose BCG scar status and TST induration were recorded were included in the data analysis. Children older than 9 were excluded from the analysis to ensure that no child included in the first survey could be included in the second survey. The frequency distributions of the TST indurations of children with and without BCG-scar were compared using the Mann–Whitney test. Analyses were done on all children irrespective of BCG scar status, but we also did sensitivity analysis excluding children with a BCG scar. Reactions greater than or equal to 10 mm were considered to be attributable to infection with *Mycobacterium tuberculosis*. Besides the cut-off point of 10 mm we also explored the cut-offs of 7, 8, and 9 mm. Prevalence of TB infection and its 95% confidence intervals (95% CI) were adjusted for non-response in each school. The formula $1-(1-\text{prevalence})^{1/\text{mean age}}$ was used to calculate the ARTI (Rieder 1995, 2005; Arnadottir *et al.* 1996). In the 1998–1999 survey we obtained age and not birth date, therefore mean age was calculated after adding 0.5 years to the reported age.

All data were dually entered in a *Microsoft Access* database and the two entries were compared with *Epidata*. The dataset with the least errors was corrected after verification with the original data. Statistical calculations were performed with STATA version 8.0 (StataCorp 2003).

Notification rates and treatment outcomes

Notification rates were calculated from the number of recorded TB cases at a clinic and the population size of the community served by the TB clinic. The number of PTB cases and the treatment outcomes of smear-positive PTB cases were obtained from the provincial TB database for Ravensmead and Uitsig TB clinics. Unfortunately the recorded PTB cases and the treatment outcome of these cases were only available for 1998–2002. We therefore used additional data from our epidemiological research database to study the trend in smear-positive TB notification rates for the period 1993–1998. This epidemiological database was based on the notification data 1993–1996 and on the data from the TB treatment registers form the clinics in Ravensmead and Uitsig. For the calculation of rates we obtained the population size from the 1991, 1996 and 2001 census data for Ravensmead and Uitsig. The population size for the interim years was calculated with the inter-census growth rate.

Cure and completion of treatment were considered as successful treatment outcomes. Unfavourable treatment outcomes included failure, default and transfer. Death was considered separately.

We compared the trend in notification rates and treatment outcomes for the two areas using logistic regression analysis with the population as those exposed, and the TB cases as those with the disease outcome. Area, year and the interaction term area*year were included as independent variables in the model.

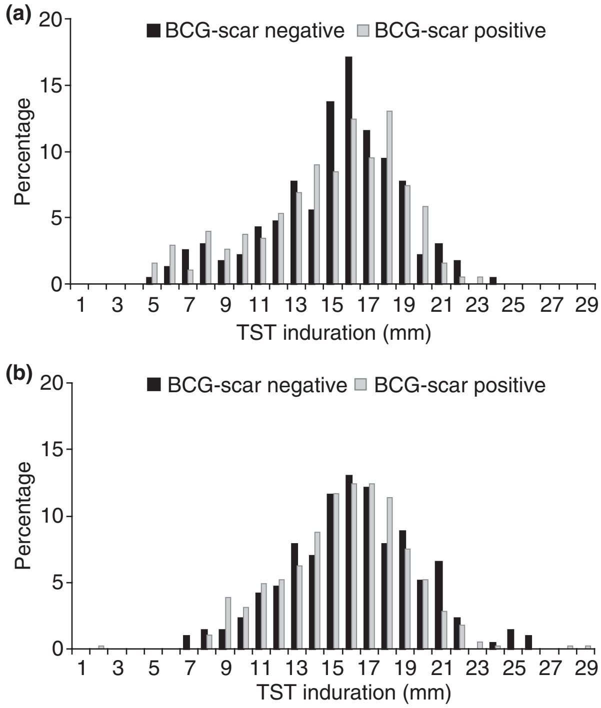

Figure 1 (a) Frequency distribution of tuberculin skin test indurations in the 1998–1999 survey. (b) Frequency distribution of tuberculin skin test indurations in 2005.

Results

TST survey 1998–1999

In the first TST survey 5779 children were registered as primary school attendees; 2566 being between 6 and 9 years old. Children without parental consent, not present on both days of the TST survey and those with missing data were excluded. Of the 6 to 9-year old children 2067 (81%) were included in the analyses. Seven to nine year old children were more often included (82%) than six year old children (75%) (OR: 1.51, 95% CI: 1.21–1.89). Boys (80%) and girls (81%) had an equal participation rate (OR: 1.06, 95% CI: 0.87–1.29). The participation rate in Uitsig (89%) was higher than in Ravensmead (76%) (OR = 2.63, 95% CI: 2.08–3.32). 65% of children had a BCG scar. The distributions of TST indurations of children with and without BCG scars were not significantly different (Figure 1a) (Z = 0.501, P = 0.616). In this survey, 958 (72%) of children with a BCG scar and 491 (68%) of children without a BCG scar had no measurable skin test reaction (OR = 1.21, 95% CI: 0.99–1.47).

TST survey 2005

In the second TST survey, 4759 children were registered as primary school attendees of whom 2460 were between 6 and 9 years old. Children without parental consent, not PTB resent on both days of the TST survey and those with missing data were excluded. Of those 1954 (79%) were included in the survey. Seven to nine year old children were more often included (81%) than 6-year-old children (72%) (OR: 1.68, 95% CI: 1.34–2.10). Boys (81%) had a higher participation rate than girls (78%) (OR: 1.22, 95% CI: 1.01–1.49). The participation rate was 82% in Uitsig and 78% in Ravensmead (OR = 1.34, 95% CI: 1.10–1.65). The proportion of children with a BCG scar was 68% and there were no significant differences between the distribution of TST indurations of children with and without a BCG scar (Figure 1b) (Z = 1.439, P = 0.150). In this survey, 944 (71%) of children with a BCG scar and 409 (66%) of children without a BGC scar had no measurable skin test reaction (OR = 1.29, 95% CI: 1.05–1.58).

Prevalence of infection and ARTI

The prevalence of *M. tuberculosis* infection was 26.2% (95% CI: 24.3–28.1%) in 1998–1999, corresponding to an ARTI of 3.7 (95% CI: 3.4–4.0%). In 2005, the prevalence of infection was 28.9% (95% CI: 27.0–30.9%), corresponding to an ARTI of 4.1% (95% CI: 3.8–4.5%) (Table 1). For Ravensmead the ARTI was calculated to be 3.5% (95% CI: 3.1–3.9%) in 1998–1999 and 3.2% (95% CI: 2.9–3.6%) in 2005; a difference that was not

Table 1 Prevalence of *Mycobacterium tuberculosis* infection (TST ≥10 mm) and annual risk of tuberculosis infection (ARTI) in Ravensmead and Uitsig

	1998–1999				2005			
	Analyzed *n*	Average age years	Prevalence of infection % (95% CI)	ARTI % (95% CI)	Analyzed *n*	Average age years	Prevalence of infection % (95% CI)	ARTI % (95% CI)
Total area	2067	8.08	26.2 (24.3–28.1)	3.7 (3.4–4.0)	1954	8.07	28.9 (27.0–30.9)	4.1 (3.8–4.5)
Ravensmead	1237	8.05	24.8 (22.4–27.2)	3.5 (3.1–3.9)	1197	8.06	23.3 (20.9–25.7)	3.2 (2.9–3.6)
Uitsig	830	8.13	28.6 (25.6–31.7)	4.1 (3.6–4.6)	757	8.08	38.4 (35.0–41.9)	5.8 (5.2–6.5)

statistically significant. The ARTI in Uitsig increased significantly from 4.1% (95% CI: 3.6–4.6%) to 5.8% (95% CI: 5.2–6.5%). In 2005, the ARTI in Uitsig was significantly higher than in Ravensmead. Using cut-off points of 7, 8 and 9 mm increased the estimates for the prevalence of infection and the ARTI when compared with 10 mm but it did not change the trend over time or the differences between the two areas (data not shown).

We repeated our analysis including only children without a BCG scar. ARTI estimates obtained in these analyses were slightly higher than the ARTI estimates reported for all children irrespective of BCG scar status but the trend over time or the difference between the two areas did not change (data not shown).

Notification rates and treatment outcomes

Both Ravensmead and Uitsig had high and increasing PTB notification rates (Figure 2). In Ravensmead the notification rate for total TB increased from 596 to 686 per 100 000 between 1998 and 2002. In Uitsig it increased from 750 to 987 per 100 000 over the same period. The PTB notification rate in Uitsig was higher than in Ravensmead ($P < 0.001$). Over the period 1998–2002 Ravensmead had a significantly higher proportion of new PTB cases, and thus a lower proportion of previously treated PTB cases than Uitsig ($P = 0.008$) (Figure 3).

The notification rates of smear-positive TB were available from 1993 to 2002. The notification rates for the first period (1993–1998) show a similar trend as for the second period (1998–2002) (Figure 4). The smear positive notification rates increased significantly between 1993 and 2002 in both Ravensmead and Uitsig ($P < 0.001$). The notification rates were higher in Uitsig compared to Ravensmead both for smear-positive TB ($P < 0.001$) as for new smear-positive TB ($P < 0.001$). There was no significant difference in the proportion of new cases among smear positive cases between the two areas ($P = 0.627$) or over time ($P = 0.083$).

Treatment success rates were similar in Ravensmead and Uitsig ($P = 0.788$) and increased during the period 1998–2003 ($P = 0.055$) (Figure 5). This was the case for new as well as previously treated smear positive cases (data not shown). Unfavourable outcomes decreased in both areas, but only became below 15% in 2003. Unfavourable treatment outcomes were more often seen among previously treated cases. The death rate was approximately 3%, and remained the same (data not shown).

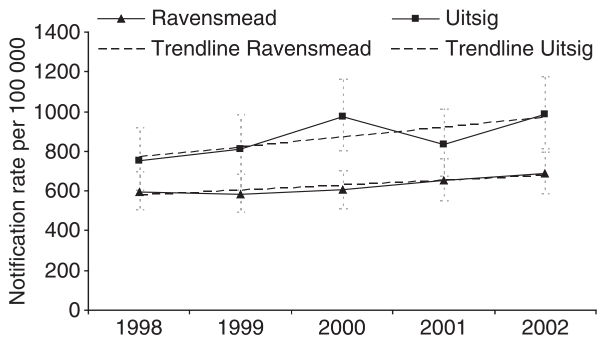

Figure 2 Pulmonary tuberculosis notification rates for Ravensmead and Uitsig.

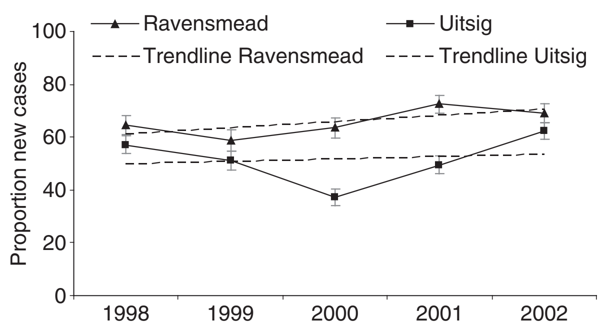

Figure 3 Proportion new pulmonary tuberculosis cases among total PTB cases.

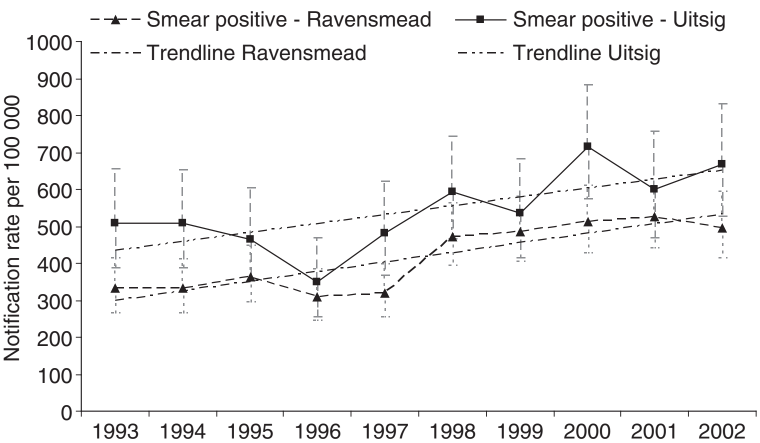

Figure 4 Notification rates for new and total smear positive pulmonary tuberculosis 1993–2002.

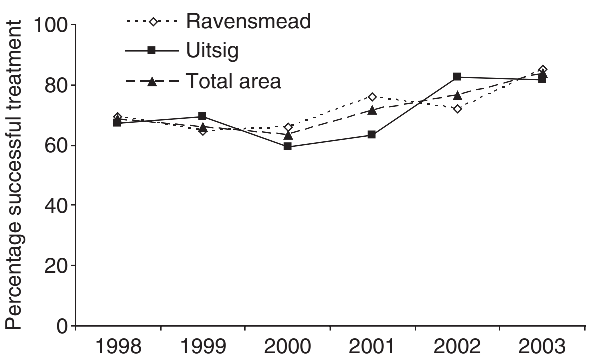

Figure 5 Percentage successful treatment among all smear positive pulmonary tuberculosis cases.

Discussion

In this study, we show that the TB transmission rate remains high in Ravensmead and Uitsig. An ARTI of more than 3.5% is one of the highest reported in the world in the last 10 years (Tupasi *et al.* 2000; Dubuis *et al.* 2004; Trébucq *et al.* 2005; Egwaga *et al.* 2006; Gopi *et al.* 2006). Obviously the TB epidemic is not under control. This is also reflected in the high and rising notification rates. Uitsig had the highest notification rates, which corresponded with a higher ARTI in this area. The increasing notification rates could be partly or in total due to increased case detection. Although information about this is lacking, we think that case detection might have improved between 1993 and 2002, especially after the Stop TB Strategy (then known as the DOTS Strategy) was introduced in 1996–1997. However, we do not think that better case detection can explain the total increase in notification rates.

Approximately 60% of all PTB cases were new TB cases. This means that as much as 40% of PTB cases had been treated for TB before. In Uitsig the proportion of previously treated PTB patients was higher than in Ravensmead over all 5 years studied. These previously treated cases might be at least partially responsible for the ongoing and increasing transmission in Uitsig. A possible explanation for this high proportion of previously treated patients is low cure rates in the past. If patients are not cured they have a higher risk to relapse or to develop drug resistance. Unfavourable treatment outcomes were falling in Ravensmead and Uitsig, but were below 15% only in the last year that we studied. A continuation of this trend is necessary to have a significant effect on transmission (Maher *et al.* 2005). Alternatively, the high proportion of previously treated patients could be due to the high transmission and re-infection rate in the area (Verver *et al.* 2004).

Rising HIV prevalence could partly explain the increase in the ARTI (Odhiambo *et al.* 1999). In some settings however, although TB notification rates increase due to HIV, the prevalence of TB and the ARTI are less affected by HIV (Corbett *et al.* 2004; Egwaga *et al.* 2006).
A possible explanation for this is that HIV-infected persons with TB may be infectious for a shorter period because fast progression to disease leads to death or early case detection and treatment. The shorter duration of infectiousness reduces the prevalence of undetected cases as well as the rate of transmission. Alternatively, the effect of an increasing HIV prevalence is not yet reflected in the ARTI estimate because the ARTI is a measure in the past – an average estimate centred on a point at half the age of the children tested.

Because an accurate measure of the HIV prevalence in the study area is lacking, we can only estimate this using other data available: In the district where Ravensmead and Uitsig are located the prevalence of HIV infection among mothers attending antenatal clinics has been reported to increase from 7.9% in 2001 to 15.1% in 2004 (Shaikh *et al.* 2006). However, we think the prevalence of HIV is lower in the communities we studied: Voluntary counselling and testing (VCT) of registered adult (≥15 years) TB patients during 2002 and 2003 showed a HIV seroprevalence among TB patients of 7.9% at Ravensmead clinic and 10.9% at Uitsig clinic (Personal communication Caldwell). However, the prevalence of HIV in the general population is likely to be lower than in TB patients (Corbett *et al.* 2003; WHO 2007). We therefore estimate that the prevalence of HIV among adults in the study area is approximately 2%, which corresponds with the reported estimate of 1.9% for the Western Cape Province in the population older than 2 years (Shisana *et al.* 2005). Death rates due to TB do not suggest an increase in HIV since the death rates have not increased between 1998 and 2002. The prevalence of HIV in these communities and the Western Cape Province in general is lower than the national prevalence of 10.8% in South Africa (Shisana *et al.* 2005) and can therefore not be generalized to the whole country. However, our findings of high TB transmission rates in these communities raise concerns about the ARTI in areas that are more affected by HIV.

Our study has several limitations. The interpretation of tuberculin survey data has some methodological difficulties that influence sensitivity and specificity of the test. These include small TST indurations following BCG vaccination (Farhat *et al.* 2006), misclassification of vaccination status (not all vaccinated children develop a typical scar) (Fjallbrant *et al.* 2008, Fine *et al.* 1989), loss of TST sensitivity due to HIV infection, and the influence of environmental mycobacteria on TST induration (Rieder 1995, 2005). In our setting however, there are little environmental mycobacteria which resulted in very few children with TST indurations between 7 and 10 mm. The prevalence of TB infection varied therefore little by the chosen cut-off points. The prevalence of infection and the ARTI were also very similar among BCG-vaccinated and non-vaccinated children and therefore we think that our trend estimates are fairly robust. We expect that very few 6 to 9-year old children in this community are infected with HIV, which is therefore unlikely to have influenced our estimates of prevalence of infection and ARTI.

Another limitation is that we had to obtain the smear positive notification rates for the period 1993–2002 from two sources. However, since both sources of information are based on the data in the treatment registers from the clinics, we expect they are comparable. By doing a school survey we only included the children that attended school which could have introduced a bias. Children from less poor families may go to school outside the study area, while children from poorer families may not attend school at all. But school attendance rates are high and we think they were unlikely to differ between the two surveys.

Although there seem to be associations between the ARTI, the high notification rates, the estimated HIV prevalence, and a high proportion of previously treated PTB cases, the ecological nature of this comparison warrants careful interpretation. In addition, our ARTI data represent the epidemiological situation of on average 4–5 years before the surveys and because of that notification and outcome trends may not correspond completely with the ARTI trends.

Conclusion

This study shows that there is an ongoing high transmission rate of *M. tuberculosis* to children in these high burden communities. TB control measures to date have failed to control TB and an intensified effort is needed to decrease the transmission of *M. tuberculosis* and to lower TB incidence in Ravensmead and Uitsig. Improving health services and the diagnostic process, active or intensified case finding, and active tracing of defaulters could all contribute to control of TB. Although treatment outcomes have been improving, a continuation of this trend is necessary to reach the 85% cure rate target and stop transmission. A follow up TST survey in 2011 will enable us to measure changing trends in the ARTI and to reassess the impact of the program.

Acknowledgements

We thank Dr. Bernard Fourie from the South African Medical Research Council for his assistance with the first TST survey, and Dr. Ivan Toms, Director of Health of the City of Cape Town, and the Department of Education Western Cape province for permission to work in the communities. Judy Caldwell is kindly acknowledged for providing us with the notification and treatment outcome data of the clinics in Ravensmead and Uitsig. We are grateful to Katherine Lawrence for the data management and Nico Nagelkerke for advice on the statistical analysis. We thank the field team for collecting the data and the teachers and children of the primary schools in Ravensmead and Uitsig for their participation.

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