Clinical Infectious Diseases

MAJOR ARTICLE

The Frequency and Incidence of QT Prolongation with Extended Use of Bedaquiline or Delamanid in a Large, Multi-Country MDR/RR-TB Cohort

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Background: The 2022 WHO guidelines on multi-drug/rifampicin resistant tuberculosis (MDR/RR-TB) recommend six months of bedaquiline (Bdq) in the all-oral 9-month shorter regimen and six months or longer for Bdq and delamanid (Dlm) in the 18-20-month longer regimen. However, lack of evidence on extended treatment using Bdq or Dlm has limited their use to six months. We examine the frequency and incidence of QT prolongation based on duration of Bdq and/or Dlm use in longer regimens.

Methods: We analyzed a prospective cohort of MDR/RR-TB patients from 16 countries who initiated treatment with Bdq and/or Dlm containing regimens from 1 April 2015-30 September 2018. Data were systematically collected using a shared protocol. The outcome of interest was the first clinically relevant prolonged QT interval (grade 3 or above) or a Serious Adverse Event (SAE) involving prolonged QT of any grade.

Results: Among 2,553 patients, 59% received >6 months of Bdq and/or Dlm. Of these, 579 (20.9%) patients experienced a prolonged QT event, the majority (95.5%) being grade 1 or 2. Sixty-four(2.5%) patients experienced the outcome of interest with only 12 (0.5%) having ≥ 1 QT prolonging drugs permanently suspended. The incidence rate of the first prolonged QT event was highest in the first six months of treatment and lower in subsequent six-month periods.

Conclusion: We demonstrate that Bdq and/or Dlm use beyond six months is safe in longer MDR/RR-TB regimens with most clinically relevant QT prolongation events occurring in the first six months. ECG monitoring for early identification of QT prolongating events is possible in programmatic conditions.

Keywords: QT prolongation; Extended use; Bedaquiline; Delamanid; adverse events

INTRODUCTION

The introduction of Bedaquiline (Bdq) and Delamanid (Dlm) has revolutionized the treatment of multi-drug/rifampicin resistant tuberculosis (MDR/RR-TB) by shortening treatment and enabling use of all-oral regimens with fewer tolerability issues(1, 2). The 2022 WHO guidelines on MDR/RR-TB recommend six months of Bdq in the all-oral 9-month shorter regimen and six months or longer for Bdq and Dlm in the 18 to 20-month longer regimen(3). However, safety concerns such as QT prolongation and arrhythmia risks along with drug costs and lack of evidence on efficacy have restricted the extended use of Bdq or Dlm in longer MDR/RR-TB regimens in practice(4, 5).

Initial regulatory approvals for Bdq and Dlm were based on industry-led studies evaluating the use of these drugs for a fixed 6-months within a multi-drug regimen(1, 2, 6). This lack of evidence on the benefits and risks of extended treatment with these drugs has limited their optimal use in longer MDR/RR-TB regimens(4). While WHO recommendations provide reassurance in the safe use of Bdq and Dlm beyond six months, their use in practice is still considered off-label due to historical restrictions. Fear of QT prolongation and potential additive toxicities when Bdq and/or Dlm are used concomitantly with other QT prolonging drugs (such as clofazimine and/or fluoroquinolones) contribute to their suboptimal utilization in MDR/RR-TB regimens(7, 8).

Additionally, insufficient resources and training for ECG monitoring may have led clinicians and TB programs to limit the use of Bdq and Dlm to six months, potentially resulting in suboptimal treatment durations for patients who may benefit from extended therapy. This approach to MDR/RR-TB treatment can be harmful, especially given the risk of acquired resistance to effective second-line TB drugs, comorbidities, extensive lung disease, or delayed treatment response. Inadequate treatment strategies can compromise the regimen and increase the risk of bacteriological reversion(9, 10). This is exacerbated when national TB treatment guidelines restrict the extended use of Bdq or Dlm in MDR/RR-TB regimens. Consequently, Bdq and Dlm are mostly limited to 6-month use, while potentially more toxic second-line drugs are recommended for the entire duration of MDR/RR-TB treatment(3).

We evaluate the frequency and incidence of QT prolongation based on duration of Bdq and/or Dlm – up to 6 months versus 6 months or longer – within the longer RR/MDR-TB regimens used in the endTB Observational Study(11). Because a subset of patients will require longer MDR/RR-TB regimens, it is crucial to determine if extended use of Bdq and/or Dlm is associated with an increased risk of QT prolongation in longer regimens – a knowledge gap that is essential to guide clinical practice.

METHODS

Study design and patient population

We analyzed data from the endTB Observational Study, a prospective study that enrolled patients with MDR/RR-TB who initiated a multidrug regimen containing Bdq and/or Dlm from 1 April 2015-30 September 2018 in 17 countries. Study design, enrollment and monitoring procedures are described in the study protocol(11). We excluded patients who were not eligible to have completed at least 12 months follow-up by 30 September 2019, and patients from Democratic People's Republic of Korea (DPRK) due to inconsistent monitoring and adverse event (AE) reporting at that site (Figure 1).

Study procedures

Patients initiating a Bdq- and/or Dlm-containing regimen for MDR/RR-TB based on national guidelines and WHO recommendations consented to participate in the endTB Observational Study. All participants received individualized therapy based on clinical history, evaluation, and investigations. The duration of Bdq or Dlm treatment was based on local guidelines, response to treatment (clinical and bacteriological), likely effective drugs in the regimen, AEs, and treatment adherence(12). Sites had additional support, including key monitoring resources such as ECG machines, the *endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs* and access to the global endTB Medical Committee, enabling local clinicians to consult regarding regimen design or modifications when extending Bdq or Dlm use(13).

Data were systematically collected in a customized, electronic medical record system across sites through a shared protocol. All serious adverse events (SAE) including AEs of special interest (AESI) - defined a priori as important events possibly related to Bdq, Dlm, linezolid, injectable drugs, and other commonly used drugs - were reported to a central pharmacovigilance (PV) unit(14). All SAEs, AESIs and other AEs leading to treatment change, or that the attending clinician judged clinically significant, were documented. Clinicians assessed and documented severity, outcome, and causality of all non-serious and SAEs. More details on recording, reporting and management of AEs and study procedures are described elsewhere(15).

QT interval monitoring

Information on medical history, including comorbidities and concomitant non-TB medications, was documented on standardized forms at the start of treatment and during follow-up visits. ECGs were performed at baseline, after 2 weeks and monthly until the end of treatment for each patient. Corrected QT (QTc) interval was recorded and reported using the Fridericia formula (QTcF).

Prolonged QT interval was considered an AESI. QT grading was informed by a standardized scale implemented across endTB sites (Table S1). A QTcF of Grade 3 or Grade 4 was classified as a clinically significant AE. All instances of prolonged QT, regardless of grade, were managed

following the recommendations outlined in the endTB Clinical Guide(13). Furthermore, all SAEs recorded as death and involving a prolonged QT of any grade had an additional narrative explanation of medical treatment and disease condition, including co-morbidities.

Definitions: Exposure and Outcome

The exposure of interest was use of Bdq or Dlm beyond six months. The outcome was classified as the first clinically relevant prolonged QT interval defined as any QT prolongation Grade 3 or above or a reported SAE that involved a prolonged QT of any grade.

Statistical analysis

We used standard descriptive statistics to compare characteristics of patients who did and did not receive extended Bdq or Dlm within longer MDR/RR-TB regimens. We calculated the incidence rate of the outcome of interest for three 6-month intervals from start of treatment, i.e., 0 to 6 months, 6.1 to 12 months and 12.1 to 18 months. The exposure time (in 1000 person-months) for each interval was calculated from start of interval until the earliest of four possible events: the outcome of interest or, for those without an event of interest, the end of interval time, end-of-treatment outcome date or censoring on 30th September 2019. Patients were classified into one of two groups, based on whether either Bdq or Dlm use was extended from entry into the cohort. Since we considered a dichotomous exposure, patients in the >6 months group contributed person-time to this exposure category even after cessation of Bdq or Dlm. For example, an individual who received Bdq for seven months of an 18-month regimen would contribute person time to the >6-month group for the 6.1-to-12-month period and 12.1-to-18-month period.

Ethical considerations

The endTB Observational Study protocol (www.clinicaltrials.gov record number: NCT03259269) was approved by the Médicines Sans Frontières Ethics Review Board (Geneva, Switzerland), the Partners Healthcare Human Research Committee (Boston, MA, USA), Interactive Research & Development Institutional Review Board (Karachi, Pakistan) and the local ethics review boards in all countries where the study was conducted. Written informed consent was obtained prior to participation.

RESULTS

2,553 MDR/RR-TB patients were included in this analysis (Figure 1). Among these, 1,123 (44%) received >6 months of Bdq and/or Dlm: 627 (56%) on Bdq (median [IQR] treatment duration: 5.3 months [4.67 - 9.4]), 311 (28%) on Dlm-containing regimens (median [IQR] treatment duration: 5.8 months [4.4 - 9.1]), and 185 (17%) on both Bdq and Dlm (median [IQR] treatment duration: 11.3 months [5.8 - 16.3]). 1,697 (66%) of patients received 3 or more QT prolonging TB drugs (Bdq, Dlm, clofazimine [Cfz], moxifloxacin [Mfx] or levofloxacin [Lfx]) during treatment. In five

of the 16 countries, the majority (>60%) of patients received >6 months of Bdq and/or Dlm (Supplementary Table S3).

Baseline characteristics of patients with ≤6 months (non-extended) and > 6 months (extended) of Bdq or Dlm treatment were generally similar, with a few notable differences (Table 1). Patients who received extended treatment with Bdq and/or Dlm had a higher proportion of resistance to fluoroquinolones (FQ), a positive sputum culture, and low BMI at baseline. Supplementary Table S2 provides a comparison of the regimen composition at baseline and at start of 6-month period based by extended or non-extended use.

579 of 2553 patients (22.7%) had documented prolonged QT events, with the majority (79.5%) experiencing grade 1 and a further 15% experiencing grade 2. Overall, 64 (2.5%) patients reported an outcome of interest, i.e., a clinically relevant prolonged QT interval (grade 3 or 4) or a reported SAE involving a prolonged QT of any grade. 51 of 64 patients experienced the outcome of interest in the first 6 months, with 41 (80%) of these occurring in the group that did not have Bdq or Dlm extended. Among these 64 patients, 12 individuals had one or more QT prolonging drug permanently suspended: Cfz was stopped in 9 patients, Bdq in 5, Mfx in 1, Lfx in 2, and Dlm in 1.

In two instances of sudden death, QTcF >500 msec was previously documented. The first patient was a 24-year-old male with fluctuating blood glucose levels who, suspected of having an undiagnosed heart condition, died in his second month of treatment with a recorded QTcF of 536 msec. The second patient was a 50-year-old diabetic male with probable ischemic heart disease and on multiple TB and non-TB QT prolonging drugs. Previous QTcF readings >500 msec were resolved before his death, which occurred after more than six months of treatment(16).

Figure 2 shows the incidence rate of first prolonged QT event of interest in each time period, with rates stratified based on whether patients received >6 months of Bdq and/or Dlm for the second and third time periods. The highest incidence rate of prolonged QT occurred in the first 0-6 months, with little difference in incidence rates in the following time periods with extended use of Bdq and/or Dlm. Notably, the fewest events of interest occurred in the 12.1-to-18-month time period. Further, the mean number of ECGs performed per person per time period was comparable between the two groups (Table 2).

DISCUSSION

Our findings indicate that the incidence of the first clinically relevant prolonged QT event decreased after the initial six months of treatment. We observed a comparable rate between the two groups after six months: those who received >6 months treatment with Bdq and/or Dlm and those who did not. Notably, the highest incidence of the first clinically relevant prolonged QT event or a SAE associated with a documented prolonged QT was observed during the first six

months, providing reassurance for the safe extended use of Bdq and/or Dlm in MDR/RR-TB regimens under programmatic conditions.

Previous studies have reported low rates of prolonged QT in Bdq or Dlm containing MDR/RR-TB regimens. However, these studies were limited to retrospective or programmatic cohorts that restricted use of Bdq or Dlm to 6 months or reported safety events in a specific setting(17-20). In contrast, our study builds on emerging evidence evaluating extended use of Bdq or Dlm in smaller studies (21, 22). It is a large multi-country, prospective cohort of MDR/RR-TB patients on longer regimens, representing a heterogeneous group including individuals with highly resistant forms of TB, extensive disease, previous exposure to second-line TB drugs, and those affected by diabetes, HIV, or hepatitis C. Additionally, the use of standardized data collection tools and a robust PV system facilitated a more comprehensive analysis to assess the effect of extended use of Bdq and/or Dlm on QT prolongation across diverse settings and patient demographics.

A majority of patients received more than one QT prolonging anti-TB drug including Cfz, Mfx or Lfx, Bdq and/or Dlm. QT prolongation generally resolved quickly when QT prolonging drugs were suspended. The review of safety monitoring data from this cohort provides evidence of other non-TB drug-related risk factors that may have contributed to QT prolongation(15).

In the two instances of sudden deaths where QTcF was documented as >500 ms prior to death, it is important to recognize other contributing factors. No autopsies were performed. Given the absence of a definite cause of death, both instances were conservatively deemed possibly related to QT prolonging drugs. The first patient received multiple pro-arrhythmic drugs, including a beta-blocker. Polypharmacy and the use of beta-blockers (sometimes prescribed without a clear cardiac indication) may pose a particular risk for patients on QT prolonging anti-TB drugs. The second patient had an underlying cardiac condition, received non-TB QT prolonging drugs, and had electrolyte disturbances, all potentially contributing factors. The endTB safety surveillance system and observed fatal and serious adverse events have been previously described(14, 16).

Although our findings suggest a low frequency and incidence of QT prolongation in patients receiving >6 months of Bdq and/or Dlm-based regimens compared to those receiving ≤6 months, there is still a risk involved. Clinicians should weigh the risk of QT prolongation against discontinuing an effective regimen or introducing more toxic drugs. As treatment guidelines for MDR/RR-TB evolve to include shorter and longer all-oral Bdq-based regimens, stopping an effective drug during treatment may weaken the regimen and lead to resistance to newer drugs, such as Bdq(23). Therefore, an upfront effective regimen with appropriate monitoring and management of concomitant non-TB QT prolonging drugs can prevent antimicrobial resistance and improve outcomes(24).

We did not examine the optimal frequency of ECG monitoring. However, the number of ECGs performed between the group receiving ≤6 months of Bdq and/or Dlm and those receiving >6 months in MDR/RR-TB regimens was comparable(14). Clinicians received support through

clinical guidance, resources such as ECG machines, training to monitor and manage AEs, and access to consult the endTB medical committee. Therefore, the systematic ECG reporting may have led to early identification of patients at risk of a QT prolonging event. However, our findings reassure clinicians that while frequent monitoring, as in the endTB cohort, may not necessarily be required to use Bdq and/or Dlm beyond 6 months in effective MDR/RR-TB regimens, it underscores the importance of routine monitoring, access to laboratory investigations and capacity building of local clinicians to improve overall care quality. These findings also provide valuable lessons for the uptake of future drugs developed for TB and other diseases (25).

Our study had limitations. The decision to extend Bdq and/or Dlm was not randomized. The duration of treatment with Bdq or Dlm was heterogeneous. Specifically, in the >6 months group, the person-time for all periods was not uniformly exposed for the entire duration of treatment. Therefore, our analysis was akin to an intention-to-treat analysis, where exposure was defined at six months, preventing examining a dose-response effect of extended Bdq and/or Dlm use on clinically relevant prolonged QT events.

CONCLUSION:

The extended use of Bdq and/or Dlm in MDR/RR-TB treatment beyond six months shows minimal to no increase in cardiac toxicity related to QT prolongation, offering reassurance on safety to patients, clinicians, and TB programs. ECG monitoring and the early identification of clinically relevant QT prolongating events are feasible under programmatic conditions. Adequate resources providing a comprehensive safety monitoring strategy, along with trainings to empower clinicians with knowledge around best practices that guide appropriate and effective regimen design and duration, are crucial to identify and manage safety concerns as new molecules and regimens become available for the treatment of MDR/RR-TB. Future analysis and studies should identify the minimal ECG monitoring criteria to ascertain which patients require less or more monitoring particularly in the later stages of MDR/RR-TB therapy.

NOTES

Author Contributions: U.K, P.Y.K, M.F, M.R, H.H, C.D.M, C.H, K.S, M.B, and F.V conceived and designed the study. S.A, S.I, M.K, F.A.P, C.Y.I.S, C.L.T, E.H.F, J.F, J.B, L.N.Q.V, A.B, A.K.I, M.R.S, P.N, Y.A, N.M, N.A.S, S.C.V, R.F, Y.Y.N, S.S, and S.M contributed to data collection. P.Y.K analyzed the data. U.K wrote the manuscript. U.K, M.F.F, M.R, C.D.M, C.H, H.H and P.Y.K critically reviewed the manuscript. All authors agreed with the study's results and conclusions.

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Disclaimer: All authors report that the endTB consortium coordinated donations of delamanid from Otsuka Pharmaceuticals to be used for treatment of some patients included in the endTB observational study and donations of bedaquiline from Janssens to be used for treatment of some patients included in the endTB observational study.

Data availability statement: Some of the data included in this analysis are managed in countries governed by the European Union General Data Protection Regulation (GDPR). The data contain sensitive and potentially identifying information and cannot be sufficiently anonymized to meet GDPR standards and retain their utility. Pseudo-anonymized data will soon be available upon request through the endTB Data Sharing Initiative (eDSI), hosted by Médecins Sans Frontières (MSF). Requests can be directed to endTB.ClinicalTrial@paris.msf.org, subject to the execution of a data-sharing agreement or mechanisms that ensure compliance with GDPR principles.

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Potential Conflicts of Interest: M. F. declares support through a NIH-funded grant. P.Y.K declares participation on a DSMB board for an NIH R01 study. All remaining authors: no reported conflicts of interest.

FIGURE LEGENDS

Figure 1: Study Flowchart.

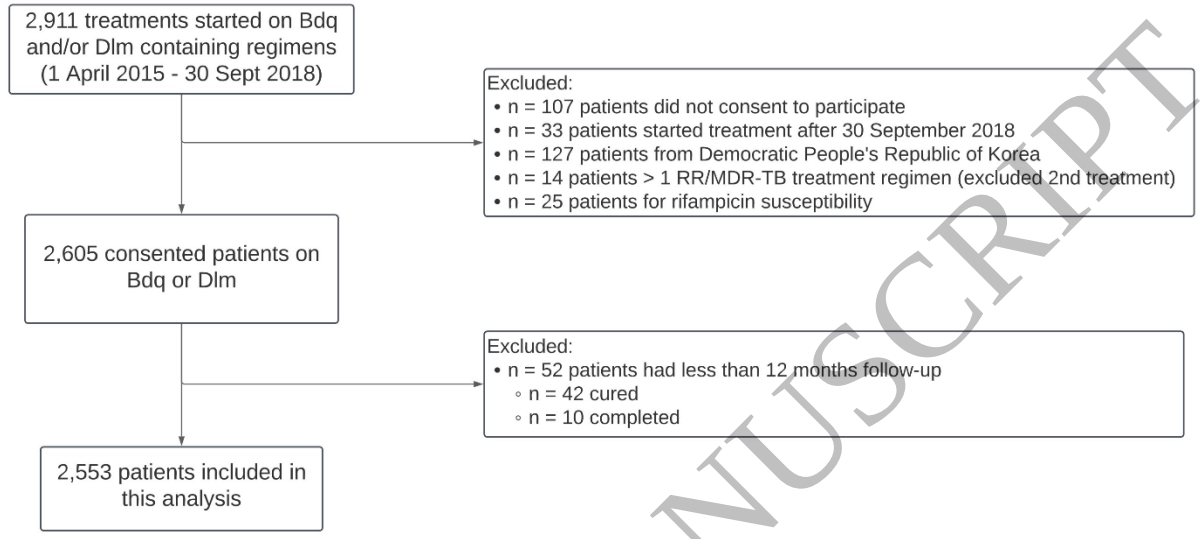

Figure 2: Incidence Rate of First Prolonged QT Event of Interest by Follow-Up Time During MDR/RR-TB Treatment.

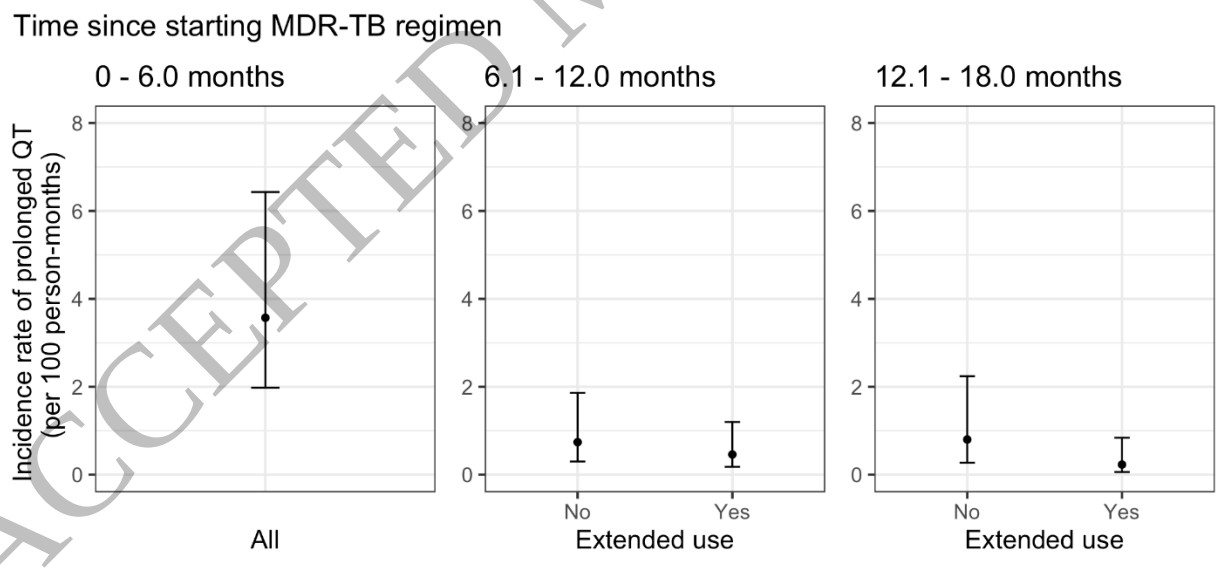

Table 1: Baseline Characteristics in the Cohort Stratified by Non-Extended (≤6 Months) or Extended (>6 Months) Use of Bdq and/or Dlm in MDR/RR-TB Regimens.

	Non-Extended use of Bdq and/or Dlm (N= 1,430) n (%)	**Extended use of Bdq and/or Dlm (N=1, 123) n (%)**
Male	920 (64)	710 (63)
Age, median [IQR]	36 (27 – 48)	35 (26 – 45)
QTcF intervals median (IQR)	400 (379 – 417)	392 (373 – 413)
Diabetes	239 (17)	143 (13)
HIV-positive	232 (16)	130 (12)
Hepatitis C positive antibody	154 (11)	120 (11)
Previous TB treatment		
First-line TB drugs	229 (16)	169 (15)
Second-line TB drugs	986 (69)	827 (74)
Bilateral lung disease	813 (66)	695 (69)
Culture positive	741 (58)	662 (67)
MDR/RR-TB with Fluroroquinolone resistance	683 (48)	660 (59)
BMI < 18 kg/m^2	507 (36)	516 (47)

At least 4 likely effective drugs in baseline regimen[a]	1136 (80)	910 (81)

Abbreviation: BMI, Body Mass Index; Bdq, Bedaquiline; Dlm, Delamanid; IQR, interquartile range; MDR, multidrug-resistant; RR, rifampicin-resistant, TB resistant to rifampicin and isoniazid.

[a]Likely effective drugs were either drugs for which all reported testing (genotypic or phenotypic) showed drug susceptibility (for those drugs with reliable testing, i.e., fluoroquinolones, amikacin, kanamycin and capreomycin) or drugs with no resistance reported and that the patient had not previously received for more than 1 month.

Table 2: Incidence Rate of Clinically Relevant QT Prolongation and ECGs performed, by Extended use of Bdq or Dlm and Follow-Up Period.

Time since start of MDR/RR-TB regimen (months)	Extended use of Bdq or Dlm	Person-months	No. of first clinically relevant QT prolongation	Incidence rate per 1000 person-months (95% CI)*	N	No. of ECG per person per period, median [IQR]
0.0 - 6	-	14, 299	51	3.56 (1.98 – 6.43)	2,553	7 [7 – 8]
6.1 - 12	No	6749	5	0.74 (0.30 – 1.86)	1177	5 [4 – 6]
	Yes	6489	3	0.46 (0.18 – 1.20)	1123	6 [5 – 6]
12.1 - 18	No	5000	4	0.80 (0.27 – 2.36)	1097	5 [4 – 6]
	Yes	4408	1	0.23 (0.06 – 0.84)	1039	6[5 – 6]

*Variance adjusted for clustering by site