Impact of GxAlert on the management of rifampicin-resistant tuberculosis patients, Port Moresby, Papua New Guinea

J. K. Banamu,1 E. Lavu,1 K. Johnson,1,2 R. Moke,3 S. S. Majumdar,4 K. C. Takarinda,5 R. J. Commons4,6

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Setting: GxAlert is an automatic electronic notification service that provides immediate Xpert© MTB/RIF testing results. It was implemented for the notification of patients with rifampicin resistant-tuberculosis (RR-TB) at Port Moresby General Hospital, Port Moresby, Papua New Guinea, in May 2015.

Objective: To determine if there were differences in pre-treatment attrition, the time to treatment initiation and patient outcomes in the 12 months pre- and post-introduction of GxAlert for RR-TB patients.

Design: This was a retrospective cohort study.

Results: The median time from Xpert testing to treatment initiation decreased from 35 days [IQR 13–131] prior to GxAlert to 10 days [IQR 3–29] after GxAlert (P = 0.001), with the cumulative proportion of patients initiating treatment within 30 days increasing from 25% (95%CI 17–37) to 54% (95%CI 44–64; P < 0.001) over these periods. However, our analysis of the time to treatment prior to the introduction of GxAlert suggests that a decrease had already occurred prior to implementation. There was no difference in interim clinical outcomes between the periods.

Conclusion: Although a decrease in time to treatment initiation cannot be attributed to GxAlert, there was a significant improvement over the 2-year period, suggesting that considerable improvements have been made in timely RR-TB patient management in Port Moresby.

Multidrug-resistant tuberculosis (MDR-TB, i.e., resistance to rifampicin and isoniazid) is a major threat to TB control and elimination. There were an estimated 558000 new cases of rifampicin-resistant TB (RR-TB) and 460000 new cases of MDR-TB globally in 2017.1 Early diagnosis with rapid testing for resistance and prompt linkage to effective treatment is a key component of the World Health Organization’s (WHO) End TB Strategy.2

New molecular diagnostics are increasingly being rolled out for rapid diagnosis of TB and rifampicin resistance, with the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) the most widely implemented to date.3 Despite evidence that these tests increase diagnostic accuracy and decrease the time to diagnosis, it has not been established whether they improve patient outcomes, such as time to treatment initiation and mortality.4–7 This is due to additional implementation and operational barriers, including delays with testing that affect the patient diagnostic and care cascade. The potential diagnostic delay between a positive test result and treatment initiation should be preventable.3,7 A GxAlert (SystemOne, Boston, MA, USA) is a remote cloud-based data monitoring system and automatic electronic notification service that connects to Xpert instruments to provide a data dashboard for the central laboratory and immediate result notification from Xpert to the treating health care worker via e-mail and/or short message service (SMS).9

RR-TB is a pressing public health crisis in Papua New Guinea (PNG), with an estimated TB incidence of 432 per 100000 population and with a RR-TB incidence of 23/100000 in 2017.1 The Xpert assay was introduced in PNG in 2012 and has now been expanded to 18 of 22 provinces. There is currently no national hospital electronic health information system for laboratory result reporting. The paper-based reporting of results from laboratories to clinicians has the potential to delay the time to appropriate TB treatment initiation in both urban and remote settings. Such delays may also lead to the pre-treatment attrition of diagnosed TB patients, as has been reported in RR-TB patients in several settings, although there are no data from PNG.10–12 To address this barrier, the GxAlert system was piloted at Central Public Health Laboratories (CPLH, Port Moresby, PNG) and Daru General Hospital (Daru, PNG) on the Xpert platform commencing in May 2015.

Although time from specimen testing to clinician notification is reduced, there is minimal evidence of the impact of GxAlert on time to treatment initiation or patient outcomes in a resource-constrained setting.9,13 We undertook this study to determine if there were differences in pre-treatment attrition, time to treatment initiation and interim patient outcomes for RR-TB patients at Port Moresby in two 12-month periods before and after the introduction of GxAlert in May 2015.

METHODS

Study design and participants

We conducted a retrospective cohort study of patients diagnosed with RR-TB using Xpert and treated at Port Moresby General Hospital (PMGH), with a pre-post comparison after the introduction of GxAlert. Study participants were RR-TB patients from PMGH between two periods: 1 May 2014 to 30 April 2015 and 1 June 2015 to 31 May 2016. Patients from May 2015 were...
excluded as this was the implementation period for GxAlert.

**Setting**
Port Moresby, situated in the National Capital District (NCD), is the capital of PNG, and has an estimated population of 364 125. PMGH is a 1000-bed tertiary referral hospital servicing NCD and the adjacent Central Province (population 269 756). The hospital provides TB diagnosis and treatment facilities for adult and paediatric TB, TB-human immunodeficiency virus (HIV) co-infection and RR-TB. RR-TB patients from NCD and Central Province are managed through the PMGH ward or TB clinic, with approximately 100 RR-TB patients treated each year.

**Rifampicin-resistant TB diagnosis in Papua New Guinea**
The CPHL is the country’s national reference laboratory for TB, HIV and malaria. All newly diagnosed RR-TB patient specimens detected using Xpert instruments around the country are sent to the CPHL, which refers specimens to the Queensland Mycobacterial Reference Laboratory (Brisbane, QLD, Australia) for culture and drug susceptibility testing. The CPHL laboratory was also the diagnostic centre for PMGH until February 2018, performing acid-fast bacilli microscopy and Xpert for all PMGH patients with presumed TB. Testing and results were recorded in the laboratory TB register.

Xpert testing was piloted in four provinces in 2012, with expansion to 30 Xpert instruments in 2018. The GxAlert software was introduced in May 2015 as a pilot project in two provinces (NCD and Western Province). In 2016, the GxAlert system was expanded to 16 Xpert instruments and is now operational on 25, with plans to expand to all remaining government sites by the end of 2018.

**Treatment model for rifampicin-resistant TB at Port Moresby General Hospital**
Treatment and care were carried out in accordance with the 2012 PNG National TB Protocol. RR-TB was presumed among patients with treatment failure, patients returning after loss to follow-up (LTFU) and MDR-TB contacts. Presumed RR-TB cases underwent sputum collection at TB clinics (including urban clinics in NCD), outpatient services, the PMGH emergency department and inpatient wards before subsequent Xpert testing. Confirmed RR-TB patients were recorded in the MDR-TB treatment register and commenced on a standardised treatment regimen at the PMGH TB ward. Baseline investigations, patient education and contact screening were conducted. The MDR-TB regimen implemented during the study period included an 8-month intensive phase comprising five drugs (kanamycin, levofloxacin, ethionamide, cycloserine and pyrazinamide) and a 12-month continuation phase (all drugs except kanamycin). Once patients were stable, repatriation to their local health service was organised for ongoing care and treatment supervision. RR-TB patients were reviewed every month at the PMGH TB clinic for adverse event monitoring and follow-up sputum collection.

**Data variables, collection and analysis**
A structured data collection form was used to collect data from the MDR-TB treatment register at the TB clinic at PMGH and the laboratory register at the CPHL. Data were double-entered in EpiData v 3.1 (Epi-Data Association, Odense, Denmark). Collected data were cross-linked with the data extracted from the existing electronic laboratory register. The data were reviewed extensively and validated using Stata v 15 (StataCorp, College Station, TX, USA) before analysis.

The variables collected from the laboratory register were name, age, sex, sample collection date, sample receipt date in the laboratory and the date of Xpert testing. The variables collected from the MDR-TB register were name, age, sex, risk category for Xpert testing, date of treatment initiation and outcome at 6 months. The date the clinician received the Xpert result was not recorded in either register. Pre-treatment attrition was defined as a patient diagnosed with RR-TB on Xpert, recorded in the laboratory register but not recorded as commencing treatment in the MDR-TB register within 30 days of diagnosis, with additional analyses performed at 60 days and 6 months. Time to treatment initiation was defined as the number of days between sputum collection and treatment initiation. An operational definition was used for interim treatment outcomes at 6 months with an ‘unfavourable’ outcome defined as patient death or patient LTFU at 6 months after treatment initiation.

Analysis was undertaken using EpiData v 3.1 and Stata v 15. Categorical variables were described by frequency (percentage), and continuous variables by median (interquartile range [IQR]). The differences in categorical variables were tested using the χ² test; the differences between skewed continuous variables were tested using the Wilcoxon rank sum test for the periods before and after the introduction of GxAlert. The proportion of patients commencing treatment after Xpert testing was calculated using Kaplan-Meier survival analyses; the two 12-month periods were compared using the log-rank test.

**Ethical approval**
Ethical approval to conduct this study was obtained from PNG Medical Research Advisory Council (Waigani, PNG) and the Alfred Hospital Human Research Ethics Committee (Melbourne, VIC, Australia).

**RESULTS**
Of 172 patients diagnosed with RR-TB and registered in the MDR-TB register at PMGH in the study period, 74 were diagnosed before the introduction of GxAlert and 98 were diagnosed after. The seven patients diagnosed with MDR-TB in May 2015 were excluded. The median age of the patients was 29 years [IQR 22–40]; 94 (55%) were female, and 91 (53%) who underwent testing were RR-TB contacts. The demographic and clinical characteristics of the patients are shown in Table 1; there were no significant differences between the two periods.
Data on the time to treatment initiation were available and assessed in 125 patients: 51 patients before the introduction of GxAlert and 74 after. The median number of days between Xpert testing and treatment initiation decreased from 35 days [IQR 13–131] in the first period to 10 days [IQR 3–29] (P = 0.001) (Table 2). The median number of days between sample collection and Xpert testing, and between sample collection and treatment initiation, also decreased (respectively 4 vs. 7 days, P = 0.002, and 17 vs. 44 days, P = 0.001).

The time between sample collection and treatment initiation was explored in more detail by assessments over 6 month blocks. The median time to treatment initiation in the 6 months immediately prior to GxAlert introduction was 15 days [IQR 7.5–72], which was similar to the time to treatment initiation in the 12-months following GxAlert introduction (17 days, [IQR 8–43]; P = 0.839) (Figure 2).

There was a decrease in pre-treatment attrition following the introduction of GxAlert, with a cumulative 25% (95% confidence interval [CI] 17–37) of patients commencing treatment within 30 days of diagnostic testing in the first period compared to 54% (95%CI 44–64) in the second period (P < 0.001). The cumulative treatment initiation within 60 days of Xpert testing was 39% (95%CI 29–52) in the first period compared to 60% (95%CI 51–71) in the second period (P = 0.003), and within 6 months this was 61% (95%CI 50–72) in the first period and 70% in the second period (95%CI 61–79) (P = 0.025) (Figure 1). The proportion of patients who died or had LTFU at 6 months did not differ between the two periods (15/51, 29% vs. 16/75, 21%; P = 0.301) (Table 2).

**DISCUSSION**

We observed a significant reduction in the time to treatment initiation for RR-TB patients at PMGH 6 months before the implementation of GxAlert. The reduction in time to treatment initiation for RR-TB patients was maintained in the 12 months after

### TABLE 1
Demographic and clinical characteristics of patients diagnosed with rifampicin-resistant TB using Xpert at the Central Public Health Laboratory, Port Moresby, Papua New Guinea, before and after GxAlert implementation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n = 172)</th>
<th>Pre-GxAlert implementation May 2014–April 2015 (n = 74)</th>
<th>Post-GxAlert implementation June 2015–May 2016 (n = 98)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median [IQR]</td>
<td>29 [22–40]</td>
<td>30 [23–44]</td>
<td>28 [21–38]</td>
<td>0.149</td>
</tr>
<tr>
<td>&lt;15</td>
<td>16 (9.3)</td>
<td>8 (10.8)</td>
<td>8 (8.2)</td>
<td>0.501</td>
</tr>
<tr>
<td>15–45</td>
<td>113 (65.7)</td>
<td>45 (60.8)</td>
<td>68 (69.4)</td>
<td></td>
</tr>
<tr>
<td>≥45</td>
<td>43 (25.0)</td>
<td>21 (28.4)</td>
<td>22 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>94 (54.6)</td>
<td>33 (44.6)</td>
<td>61 (62.2)</td>
<td>0.070</td>
</tr>
<tr>
<td>Male</td>
<td>74 (43.0)</td>
<td>39 (52.7)</td>
<td>35 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Not recorded</td>
<td>4 (2.3)</td>
<td>2 (2.7)</td>
<td>2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Risk category for Xpert testing</td>
<td></td>
<td></td>
<td></td>
<td>0.437</td>
</tr>
<tr>
<td>DR-TB contact</td>
<td>91 (52.9)</td>
<td>36 (48.6)</td>
<td>55 (56.1)</td>
<td></td>
</tr>
<tr>
<td>Early failure</td>
<td>21 (12.2)</td>
<td>11 (14.9)</td>
<td>10 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Age &lt;14 years</td>
<td>18 (10.5)</td>
<td>6 (8.1)</td>
<td>12 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Not recorded</td>
<td>42 (24.4)</td>
<td>21 (28.4)</td>
<td>21 (21.4)</td>
<td></td>
</tr>
</tbody>
</table>

TB = tuberculosis; IQR = interquartile range; DR-TB = drug-resistant TB.

### TABLE 2
Comparison of interim outcomes of patients diagnosed with rifampicin-resistant TB using Xpert® at the Central Public Health Laboratory, Port Moresby, Papua New Guinea, before and after GxAlert implementation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-GxAlert implementation May 2014–April 2015 (n = 74)</th>
<th>Post-GxAlert implementation June 2015–May 2016 (n = 98)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on DR-TB treatment</td>
<td>74 (100)</td>
<td>98 (100)</td>
<td></td>
</tr>
<tr>
<td>Interim patient outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR-TB patients initiated on treatment</td>
<td>51 (68.9)</td>
<td>75 (76.5)</td>
<td></td>
</tr>
<tr>
<td>Cumulative treatment initiation at 6 months, % (95%CI)</td>
<td>61 (50–72)</td>
<td>70 (61–79)</td>
<td>0.025</td>
</tr>
<tr>
<td>Death or LTFU at 6 months</td>
<td>15 (29.4)</td>
<td>16 (21.3)</td>
<td>0.301</td>
</tr>
<tr>
<td>Time taken, days, median [IQR]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample collection to treatment initiation</td>
<td>44 [20–144]</td>
<td>17 [8–43]</td>
<td>0.001</td>
</tr>
<tr>
<td>Sample collection to Xpert testing</td>
<td>7 [3–13]</td>
<td>4 [1.5–7]</td>
<td>0.002</td>
</tr>
<tr>
<td>Xpert testing to treatment initiation</td>
<td>35 [13–131]</td>
<td>10 [3–29]</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Data available for 51 patients.
† Data available for 71 patients.
‡ Data available for 88 patients.
§ Data available for 74 patients.

TB = tuberculosis; DR-TB = drug-resistant TB; CI = confidence interval; LTFU = loss to follow-up; IQR = interquartile range.
GxAlert implementation. We also found high rates of pre-treatment attrition and unfavourable outcomes in RR-TB patients, with no differences in the interim clinical outcomes between these two periods. The majority of the RR-TB patients diagnosed with Xpert were RR-TB contacts.

This is one of the first studies to assess the impact of an electronic results notification tool for Xpert on the time to treatment initiation and patient outcomes. One of the strengths of the study is the use of the national reference laboratory register and database, which ensured inclusion of all patients diagnosed with RR-TB using Xpert over the study period. A limitation of the study was the lack of a record of the date that clinicians received notification of the Xpert result. This prevented an assessment of the effect of GxAlert on the component of the diagnostic cascade that it automate and bypasses. Furthermore, the study findings are not generalisable to the whole country. In a centralised model of care, it is likely that GxAlert would be most effective in reducing the time to treatment initiation in geographically distant regions where Xpert is not available on site. As the data collection was retrospective, some data on patient outcomes were missing. In addition, GxAlert was implemented at the same time as other interventions, making the attribution of benefits to specific interventions difficult. Subgroup analysis of TB-HIV patients would have provided an additional assessment of programmatic care and changes; however, HIV status was not recorded in the study.

Although the median time to treatment initiation decreased by over two thirds between the 12-month period before the introduction of GxAlert and the 12-month period after its introduction, this decrease had already occurred prior to its introduction, and the time to treatment initiation in the 6-month period immediately before GxAlert implementation was similar to the subsequent period. This improvement likely relates to programmatic changes: the National Department of Health established an emergency response taskforce for MDR-TB in August 2014 that included a focus on NCD. This resulted in an increased focus on programme quality, with a monthly review of MDR-TB indicators, training and support to health workers, and the implementation of community-based care programme with health care workers for patient retrieval and support.16

Our study findings indicated a 29% absolute decrease in the proportion of patients who did not start treatment within 30 days of diagnosis (pre-treatment attrition) in the period after the introduction of GxAlert. This is consistent with previous studies that have identified similar decreases with Xpert implementation,5 although the impact of GxAlert in addition to Xpert had not been previously reported. However, we found that almost one third of patients still had not been initiated on treatment by 6 months, which needs to be addressed by the programme.

The median time to treatment initiation of 10 days in the current study is better than many studies of Xpert point-of-care im-

![FIGURE 1](image1.png)

**FIGURE 1** Survival analysis for time to treatment initiation from Xpert testing within 180 days for rifampicin-resistant TB patients at Port Moresby General Hospital (Port Moresby, Papua New Guinea) pre- and post-implementation of GxAlert.

![FIGURE 2](image2.png)

**FIGURE 2** Time between sputum collection and treatment initiation for rifampicin-resistant TB patients at Port Moresby General Hospital (Port Moresby, Papua New Guinea) pre- and post-implementation of GxAlert. IQR = interquartile range.
A systematic review of time to treatment initiation following genotypic drug susceptibility testing identified 14 studies with a mean time to treatment of 38 days (range 9–94). Although the time to treatment initiation in the current study is a considerable way from the goal of same-day treatment initiation, the decrease over the study period highlights improvements in RR-TB management at PMGH.

While earlier initiation of effective TB treatment should theoretically improve clinical outcomes by reducing disease severity, as well as interrupting transmission, this has not been reported in studies assessing the implementation of Xpert. The lack of impact on patient outcomes may be related to patients being initiated on effective early empirical TB treatment irrespective of the Xpert result. Similarly, study findings do not suggest any improvement in 6-month interim outcomes at PMGH. There is an urgent need to close the gaps in TB diagnostic and care cascades to reduce attrition between the different stages, treat patients early and prevent ongoing transmission. This is especially true in high RR-TB burden settings such as PNG, where there are additional barriers to access and use of health services. Our study findings highlight the need for further research into the high rates of pre-treatment attrition and suboptimal patient outcomes in PMGH.

As DR-TB diagnosis and treatment are further decentralised through the implementation of testing closer to the point-of-care, electronic solutions such as GxAlert are likely to be key to providing high-quality care and remote monitoring. It is vital that both the primary diagnostic tools and technological supports undergo appropriate research to ensure that they are beneficial to the patients and the systems they target. Operational research has the potential to play a significant role in this process.

CONCLUSION

While the time to treatment initiation improved for patients with RR-TB at PMGH and pre-treatment attrition decreased, our study findings do not suggest that GxAlert was directly associated with this decrease or that it led to improved interim patient outcomes. However, the continued programmatic strengthening of the TB diagnostic cascade, including the use of rapid diagnostics and integrated remote monitoring software, allows many barriers to timely TB treatment to be bypassed and will likely improve outcomes for patients with TB and RR-TB in PNG in the longer term.

References


Contexte : GxAlert est un service de notification électronique automatique qui fournit des résultats immédiats du test Xpert® MTB/ RIF. Il a été mis en œuvre pour la notification des patients atteints de tuberculose (TB) résistante à la rifampicine (RR-TB) à l’hôpital général de Port Moresby, Papouasie Nouvelle Guinée en mai 2015.

Objectif : Déterminer s’il y a eu des différences en termes d’attrition avant le traitement, de délai de mise en route du traitement et de résultats pour les patients au cours des 12 mois précédant et suivant l’introduction de GxAlert chez les patients RR-TB.

Schema : Ceci est une étude rétrospective de cohorte.

Résultats : Le délai médian entre le test Xpert et la mise en route du traitement a diminué de 35 jours [IQR 13–131] avant GxAlert à 10 jours [IQR 3–29] après GxAlert (P = 0.001), avec une proportion cumulée de mise en route du traitement dans les 30 jours augmentant de 25% (IC 95% 17–37) à 54% (IC 95% 44–64 ; P < 0,001) pendant ces deux périodes. L’analyse du délai de traitement avant l’introduction de GxAlert a cependant identifié une réduction déjà survenue avant sa mise en œuvre. Il n’y a pas eu de différence dans les résultats cliniques entre les deux périodes.

Conclusion : Bien qu’une réduction du délai de mise en route du traitement ne puisse pas être attribuée à GxAlert, il y a eu une amélioration significative au cours de la période de 2 ans, ce qui suggère que des améliorations considérables avaient déjà été réalisées dans la prise en charge prompte des patients RR-TB à Port Moresby.

Marco de Referencia: El GxAlert es un servicio electrónico de notificación automática que ofrece resultados inmediatos después de realizar la prueba Xpert® MTB/RIF. El servicio se introdujo en mayo del 2015 con el fin de notificar los pacientes con tuberculosis (TB) resistente a rifampicina (RR-TB) en el Hospital General Port Moresby, en Papúa Nueva Guinea.

Objetivo: Determinar si existían diferencias en el abandono antes de iniciar el tratamiento, el lapso transcurrido hasta el inicio del tratamiento y los desenlaces clínicos en pacientes con RR-TB en los 12 meses anteriores y posteriores a la introducción del servicio GxAlert.

Método: Fue este un estudio retrospectivo de cohortes.

Resultados: La mediana del lapso transcurrido entre la prueba Xpert y el inicio del tratamiento disminuyó de 35 días [IQR 13–131] antes de utilizar el GxAlert a 10 días [IQR 3–29] después de su introducción (P = 0,001) y la proporción acumulada de quienes iniciaban tratamiento en los primeros 30 días aumentó de 25% (IC 95% 17–37) a 54% (IC 95% 44–64 ; P < 0,001) en estos períodos. Sin embargo, el análisis del lapso hasta iniciar el tratamiento antes de la introducción del servicio GxAlert revelaba ya una disminución antes de comenzar a utilizarlo. No se observó ninguna diferencia de los desenlaces clínicos intermedios entre los períodos.

Conclusión: Aunque el acortamiento del lapso hasta la iniciación del tratamiento no se puede atribuir al servicio GxAlert, ocurrió un progreso considerable durante este período de 2 años, lo cual pone de manifiesto los avances notables logrados en el tratamiento oportuno de los pacientes con RR-TB en Port Moresby.