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MAJOR ARTICLE

Reducing initial loss to follow up among people with bacteriologically confirmed tuberculosis: linkedin, a quasi-experimental study in South Africa

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Every person diagnosed with tuberculosis (TB) needs to initiate treatment. The WHO estimated 61% of people who developed TB in 2021 were included in a TB treatment registration system. Initial loss to follow up (ILTFU) is the loss of persons to care between diagnosis and treatment initiation/registration.

LINKEDin, a quasi-experimental study, evaluated the effect of two interventions (*hospital-recording* and an *alert-and-response patient management intervention*) in six sub-districts across three high-TB burden provinces of South Africa. Using integrated electronic reports, we identified all persons diagnosed with TB (Xpert MTB/RIF positive) in hospital and at primary healthcare facilities. We prospectively determined linkage to care at 30 days after TB diagnosis. We calculated the risk of ILTFU during the baseline and intervention periods and the relative risk reduction in ILTFU between these periods.

We found a relative reduction in ILTFU of 42.4% (95%CI:28.5,53.7) in KwaZulu Natal (KZN) and 22.3% (95%CI:13.3,30.4) in the Western Cape (WC) with no significant change in Gauteng. In KZN and the WC, the relative reduction in ILTFU appeared greater in sub-districts where the alert-and-response patient management intervention was implemented; KZN (49.3% (95%CI:32.4,62) vs 32.2% (95%CI:5.4,51.4)); and WC (34.2% (95%CI:20.9,45.3) vs 13.4% (95%CI:0.7,24.4)).

We reported a notable reduction in ILTFU in two provinces using existing routine health service data and applying a simple intervention to trace and recall those not linked to care. TB programs need to consider ILTFU as a priority and develop interventions specific to their context to ensure improved linkage to care.

Key words: Tuberculosis; initial loss to follow up

INTRODUCTION

Tuberculosis (TB) is the leading cause of death from a single infectious disease (1). In the END TB strategy, all member states of the World Health Organization (WHO) committed to a world free of TB, to be achieved through reductions in TB incidence, mortality and the catastrophic costs faced by TB-affected households (2). A pillar of this strategy included integrated, patient-centred care and prevention, with an emphasis on early diagnosis and treatment of all people with TB (2).

After accessing TB tests, every person with TB (PWTB) needs to receive their results, initiate TB treatment, and be recorded in a TB reporting system to enable accurate surveillance and monitoring and evaluation of TB care. Initial loss to follow up (ILTFU) has been defined as the loss of persons to care following their diagnosis of TB, prior to their inclusion in a TB reporting system. People who are ILTFU are at elevated risk of morbidity and mortality, (3, 4) and untreated disease contributes to ongoing transmission of *Mycobacterium tuberculosis* (3, 5). In

2021 39% (4.2 million people) of those who developed TB were not treated and/or not recorded in a TB registration system (1). ILTFU is estimated to be between 4-38% globally, 18% in Africa (6) and 17.1% in South Africa (7).

South Africa is a high TB burden country with an estimated incidence of 304,000 TB cases in 2021, with >120,000 either not diagnosed or not included in routine reporting (1). In South Africa 12% of persons with drug-susceptible TB (7) and 37% of persons with drug-resistant TB (8) are lost between diagnosis and TB registration. Reducing ILTFU in South Africa is a priority to improve TB control. Interventions addressing ILTFU could have a substantial impact on the TB epidemic. These persons have accessed healthcare services, have a laboratory confirmed diagnosis of TB, yet have not been linked to a TB treatment facility for registration and initiation of treatment. Few studies have evaluated interventions addressing ILTFU across diverse settings. The LINKEDin Study evaluated the effect of two interventions to reduce ILTFU at the hospital and primary healthcare facility level in three high-burden provinces in South Africa.

METHODS

Study design

We conducted a quasi-experimental study to investigate the effect of 1) a hospital-based recording intervention which linked PWTB to standard hospital management and referral processes and 2) an alert-and-response patient management intervention to reduce ILTFU among individuals routinely diagnosed with TB. We defined ILTFU as all persons diagnosed with TB (Xpert MTB/RIF positive) for whom there was no evidence of linkage to a public TB treatment facility for TB registration and treatment within 30 days of the date of diagnosis.

To measure the effect of these interventions, we calculated the relative reduction in ILTFU between the 3-month baseline period (October 2018 to December 2018) and the intervention period (January 2019 to December 2020). Prospective data was collected for both periods.

Using integrated electronic reports, we identified all persons routinely diagnosed by Xpert MTB/RIF, as per standard of care in South Africa, in hospital and at PHC facilities and prospectively determined ILTFU.

Study setting

The study was implemented in KwaZulu-Natal (KZN), Gauteng (GP) and the Western Cape (WC) provinces, 3 of the highest TB burdened provinces in South Africa (9). Study site selection and implementation was in consultation with provincial and district TB program managers. We identified a district within each province; Ugu in KZN, City of Johannesburg in GP and City of Cape Town in WC (Suppl Table 1: Key differences in setting). Two sub-districts within each district were then selected. We liaised with local TB programme managers, who used their routine TB data; TB burden and estimated ILTFU among PWTB, to help guide selection of facilities for inclusion. Willingness of sub-district and facility mangers to be included in the study was also considered..

In South Africa, TB investigation, diagnosis, and treatment initiation take place at any level of care in the public healthcare system, but TB reporting systems are maintained at designated TB treatment sites. This included primary healthcare (PHC) facilities, where persons with TB receive treatment on an outpatient basis, and specialised TB hospitals, where persons who require hospitalisation for TB are treated. PWTB initiated on TB treatment in general hospitals needed to be linked to a PHC facility for recording, and continuation of their TB treatment.

Unique to the WC, the Department of Health houses a provincial health data centre (PHDC) which harmonises all electronic patient health data from all public sector services in the province, producing a single patient record (10). The PHDC generates disease specific reports, and for TB, collates data from laboratory sources (including smear, culture or Xpert MTB/RIF), pharmacy or clinical records, TB treatment registers or TB-specific elements recorded in electronic data systems at PHC or hospital level (10).

Interventions

Within each district, we implemented a hospital-recording intervention in one sub-district and an alert-and-response patient management intervention in the second sub-district (Table 1).

1. ***Hospital-recording intervention***

Study-appointed data clerks were placed at each hospital and used the routine data system available in the province. In KZN and GP they used '*Xpert Alerts'* (a weekly National Health Laboratory Service (NHLS) line list of all people newly diagnosed using the Xpert MTB/RIF ultra-assay). These are sent from NHLS to health district offices for further distribution to health facilities to improve patient management. In the WC, the clerk used the PHDC (10), to identify all newly diagnosed PWTB.

Lists of newly diagnosed PWTB were shared with hospital staff to confirm whether patients were initiated on treatment in hospital. There were no additional interventions to assist patients to link to a TB treatment facility once discharged from hospital, beyond the routine referral mechanisms already in place.

2. ***Alert-and-response patient management intervention***

Clerks based at the hospitals in Ray Nkonyeni, Region E and Khayelitsha sub-districts, used the 'Xpert alerts" (KZN/GP) and PHDC (WC), to identify all persons routinely diagnosed with TB at the selected PHC facilities in addition to those identified at the hospital. They monitored linkage and registration at TB treatment facilities for all persons identified with TB. In KZN and GP they used the electronic TB treatment register (TIER.Net) to check for a TB treatment start

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date. TIER.Net is an electronic register used to capture patient-level HIV and TB information at facility level and is integrated with the district health information system (DHIS) for reporting various program data from sub-district to the national level (11, 12). In the WC they used the PHDC to check for evidence of linkage to and registration at a TB treatment facility. All patients eligible to link but with no evidence of linkage were followed up by a short message service (SMS), followed by a phone call and then creating a referral for a community-based health worker (CHW) to do a home visit to facilitate linkage. Persons with TB who had no telephonic details were immediately referred to a CHW. In KZN and GP, SMS messaging and telephone calls were done by data clerks using mobile phones. In the WC, the capabilities within the PHDC enabled SMS messaging initially, and later telephone calls to be made directly via the PHDC.

Data collection

Post intervention, we used the electronic health records to determine ILTFU for the baseline and intervention periods. In KZN and GP, we used matching algorithms to compare individuals with a TB diagnosis against TIER.Net. Linkage to care was confirmed when the PWTB had a TB treatment start date recorded in TIER.Net. Individuals with no TB treatment initiation date or a date >30 days after their date of diagnosis in TIER.Net (TB register) were defined as ILTFU. To account for patient movement between facilities, we searched for PWTB in TIER.Net at district level for the baseline and intervention periods. To validate the matching algorithm output, data clerks in KZN searched TIER.Net for TB treatment start dates for everyone labelled as ILTFU. We were unable to follow this process in GP as permission to access data beyond the subdistrict was not granted beyond the intervention phase. In the WC, linkage to care was confirmed when the PWTB had evidence in the PHDC of accessing a TB treatment facility anywhere in the province for TB treatment within 30 days.

As LINKEDin was embedded within health services, and should reflect the routine TB program, we included data from the period April to June 2020 (COVID-19 lockdown), when study field staff were withdrawn, but routine hospital and PHC activities continued, with restrictions. (Suppl Tables 3-5: analysis excluding the COVID-19 lockdown period).

Statistical analysis

We conducted a before and after analysis comparing ILTFU in the baseline and intervention phases of the study. We calculated the risk of ILTFU in both periods and conducted 1-sided t-tests to assess if there was a reduction between the baseline and intervention period. We calculated the relative risk reduction in ILTFU between the intervention and baseline periods equivalent to 1-relative risk. In the WC, through the PHDC, we had data on all PWTB (confirmed and clinical diagnoses) and conducted an additional analysis for the WC (Suppl Table 2). SAS software, Version 9.4. Copyright © 2002-2012 SAS Institute Inc., Cary, North Carolina, USA was used for data analysis.

Ethics

The study was approved by the Health Research Ethics Committee at Stellenbosch University (N18/07/069), the University of the Witwatersrand (M190128), and the relevant provincial departments of Health. The authors have no conflict of interest to declare.

Patient consent statement

This study does not include factors necessitating patient consent.

RESULTS

During the intervention period there were 1999 PWTB diagnosed in KZN; 5399 in GP; and 9359 in the WC (Table 2) at the selected facilities. The proportion of PWTB diagnosed in hospitals was 37.8% in KZN, 29.2% in GP and 20.7% in the WC while the proportion of ILTFU diagnosed in hospital was 42.1% in KZN, 56.8% in GP, and 46.7% in the WC.

Overall ILTFU between baseline and intervention periods across provinces

Following the interventions, we found a considerable relative reduction in ILTFU of 42.4% (95%CI:28.5,53.7) in KZN and 22.3% (95%CI:13.3,30.4) in WC. In GP there was no change in ILTFU (Table 2). In the WC, an additional analysis not restricted to Xpert confirmed TB, showed a higher proportion of ILTFU but no difference in the relative reduction of ILTFU compared to the primary analysis (Suppl. Table 2).

ILTFU between baseline and intervention periods by sub-districts across provinces

In KZN and WC, the relative reduction in ILTFU appeared greater in sub-districts where the alert-and-response patient management intervention was implemented compared to sub-districts where only the hospital-recording intervention was implemented. The relative reduction in KZN was49.3% (95%CI:32.4,62.0) vs 32.2% (95%CI:5.4,51.4); and in the WC, it was34.2% (95%CI:20.9,45.3) vs 13.4% (95%CI:0.7,24.4). In Gauteng, there was no relative reduction in ILTFU (Table 3).

ILTFU in sub-districts where the alert-and-response patient management intervention was implemented.

In sub-districts where the alert-and-response intervention was implemented, there appeared to be greater relative reductions in ILTFU in the PHC facilities surrounding the hospital compared to in the hospital itself; KZN (56.9% (95%CI:41.1,68.5) vs 3.4% (95%CI:-103.7,54.2)) and WC (52.4% (95%CI:40.9,61.7) reduction vs an increase of 11.6% (95%CI:-61.4,22.9) (Table 4).

ILTFU in sub-districts where only the hospital-recording intervention was implemented.

GJ Crookes hospital, KZN, had a 40.2% (95%CI:12.0,59.4) relative reduction in ILTFU, while no change was seen in hospitals in GP and the WC. In the PHC facilities surrounding Tygerberg Hospital (WC), there was a relative reduction in ILTFU (24.6% (95%CI:9.4,37.3)) (Table 4).

DISCUSSION

LINKEDin was an operational research study, aimed to reduce ILTFU among PWTB in South Africa. With limited data on reducing ILTFU, LINKEDin provides important findings across 3 heterogeneous contexts in South Africa.

We demonstrated successful reductions in ILTFU in KZN (from 24.8% to 14.3%) and WC (from 22.4% to 17.4%). The study was implemented in rural sub-districts of KZN, where PHC facilities are further apart and we hypothesise that PWTB may be more likely to access services within their communities, closest to their homes, where they were known. This may have made these persons easier to track. This, together with the much lower numbers of PWTB, compared to GP and WC, may have made the manual process of tracking individuals easier, and played a role in the reduction in ILTFU observed in KZN. In the WC, the PHDC enabled us to evaluate linkage beyond the district. This is especially important in South Africa, where there is frequent movement of people within and across provinces (13).

We did not show a reduction in ILTFU in GP overall (from 31.7% to 32.8%). This was potentially driven by the increase in ILTFU by 8.8% in Region D (sub-district where we implemented the hospital recording intervention at the Chris Hani Baragwanath Academic hospital (CHBAH), a large tertiary level hospital). The numbers of PWTB in this sub-district were much higher compared to those in Region E (sub-district where the alert-and-response patient management intervention was implemented) and where we did find a relative reduction in ILTFU of 10.3%.The disparity across settings makes it extremely difficult to compare results across provinces. What is important to note is that irrespective of geographical location or access to automation, systematically identifying persons with TB and following them up, using the data and systems available in each setting, can reduce ILTFU.

There was a tendency towards a greater reduction in ILTFU in settings where the alert-and-response intervention was implemented compared to settings where the hospital-recording intervention was implemented. This implies that while there is some benefit to registering persons with TB in hospital, additional patient-centered interventions to follow-up PWTB who fail to link to care soon after their diagnosis or discharge from hospital are vital. Previous studies that addressed patient referral and education (14) and combined patient education and telephonic follow-up (15) showed improved linkages from hospitals. For sustained impact, an emphasis on health system interventions which support the existing services rather than activities that are externally supported are needed.

ILTFU was higher at hospitals (range: 21.2% to 63.9%) compared to PHC facilities (range: 11.5% to 23.8%). This is consistent with earlier work in South Africa which showed that ILTFU was high (between 37% and 50%) among people diagnosed with TB in hospitals (16, 17). Gamalakhe CHC (ILTFU was 11.5%) was used as a proxy for a hospital, but is not comparable to other study hospitals, as the referral process to Gamalakhe CHC is more like a PHC facility referral process.

Reducing ILTU in hospitals is extremely challenging and LINKEDin could not fully address this challenge, irrespective of the size or level of hospital. ILTFU is specifically higher at tertiary level hospitals where the number of people diagnosed with TB is considerably higher than at district level hospitals. At CHBAH and Tygerberg hospitals, there were 1167 and 1132 people diagnosed with TB respectively during the intervention period compared to 345 at GJ Crookes. ILTFU at CHBAH and Tygerberg was 63.9% and 45% respectively during the intervention period compared to 21.2% at GJ Crookes. Previous studies have observed a similar phenomenon, whereby ILTFU was more likely at high volume facilities (18) and in high burden settings (19). Previous data from Chris Hani Baragwaneth in 2001, reported that only half of the TB patients referred to PHC facilities attended services within 2 weeks (16) and, following an intervention between 2003-2005, that >90% attended the PHC facility with the help of research staff (14). Our findings differed as we only implemented the hospital-recording intervention at some hospitals and encountered additional complexities within the alert-and-response intervention. Studies in hospitals have attributed high workload, staff shortages and inadequate skills resulting in insufficient information and health education for persons with TB and their caregivers (20) as well as a fragmented hospital information system without linkages (21) resulting in less than optimal linkage to care.

People diagnosed in hospital are often sicker, diagnosed late and therefore more likely to die before they link to a PHC facility (6). They may also not have accessed a PHC facility previously and be unfamiliar with access to community-level care, thereby delaying linkage. Interventions to promote earlier diagnosis in primary healthcare are needed. An additional exacerbating factor is that a proportion of PWTB are discharged prior to their positive TB test result being known with no systematic process at hospital level for recall. Improved communication from hospital staff with an emphasis on navigating the organisational barriers in the health system is required to support better linkage for these patients (22, 23). Future work that differentiates the point of diagnosis within hospital (outpatient vs in-patient), and offers tailored engagement as reported in a recent cohort from China (24) to PWTB and/or their caregivers during or prior to discharge is key. The South African Department of Health has (post the LINKEDin study) launched the National Health Hotline which aims to improve contact with persons who tested positive, trace or unsuccessful for TB Xpert, through communication of test results and improving linkage to care for access to treatment at a health facility. Having correct patient contact details is vital for the success of any intervention that promotes linkage (25), irrespective of setting, level of care or patient volume.

Practical recommendations

The challenge of ILTFU can be addressed using setting-specific programmatic data to systematically identify and follow up persons diagnosed with TB. This should be done using existing personnel and be embedded within the existing health system interventions. It is important that interventions to reduce ILTFU should be part of the routine monitoring and evaluation of TB programmes (26). We recommend updating patient contact details at every health visit to ensure that patients who require additional support with linkage can be easily traced (22).

Interventions to address ILTFU should be prioritised for hospital-diagnosed patients. We recommend person-centred communication between healthcare provider and the patient prior to discharge, that includes practical advice on where and how to access a PHC facility for treatment and offers the PWTB an opportunity to ask questions and better understand their disease (27).

A major strength of our study was the implementation of interventions in diverse geographical and healthcare settings, embedded within the routine TB program. The use of existing resources within this operational research study, demonstrates the feasibility of implementing the interventions. Despite varying reductions in ILTFU, we reported a notable reduction in ILTFU in two settings between the baseline and intervention periods.

A before-and-after study is vulnerable to temporal and other changes beyond the intervention and we cannot attribute the successes solely to our interventions. The variation in sample sizes is a limitation for comparability across the settings. This, combined with the small changes in ILTFU in some settings resulted in significant statistical uncertainty around some of the relative reduction estimates.

A limitation in our definition was that persons with TB who linked after 30 days from diagnosis were categorized as ILTFU, irrespective of where they were diagnosed. This may have overestimated ILTFU. Further analysis is planned to address the time to linkage.

In Gauteng we could not search for patients reported as ILTFU in baseline or intervention periods in other sub-districts, as had been done in the other provinces. This has likely resulted in an over-estimation of ILTFU and an under-estimation of relative reductions in ILTFU in Gauteng.

We experienced severe limitations during the COVID-19 pandemic. For a quarter of 2020, no study staff were in place and all study activities were suspended. Routine clinic activities continued, with many resources redirected away from TB toward COVID-19 services. We conducted an analysis excluding the period when there were no study staff in the field and saw no significant difference in the primary analysis. (Suppl. Tables 3-5). Finally, we could not determine the wider impact of these interventions towards reducing community transmission; this presents an opportunity for further research e.g., modelling.

LINKEDin was embedded within routine health services and aimed to reduce ILTFU in three diverse settings in South Africa. The findings provide important lessons in each setting. By identifying all persons newly diagnosed with TB using existing routine health service data and applying a consistent intervention to trace and recall those not linked to care following diagnosis, we demonstrated an overall reduction in ILTFU of 49% in KZN and 34% in WC. TB programs must consider ILTFU as a priority and develop interventions specific to their settings. The use of operational research to test ILTFU interventions would address the contextual complexity in different settings. Unless there is a shift to include all persons diagnosed with TB in the routine reporting of TB, the TB treatment cohort will continue to exclude ILTFU.

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Conflict of interest

No conflict of interest.

Author contributions

MO, SM, PN, AvD, ACH designed the study. MO, SM, AvD, FMM developed the implementation plan for the study. MO, SM, AvD, RD, LC, JC, AB oversaw data collection, extraction, and validation. All authors provided critical input for the interpretation of data and contextualization of results.

SM and MO produced the first draft of the manuscript. All authors reviewed the manuscript and provided critical input. All authors have reviewed the final version of the manuscript and approve of its content and submission for publication.

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Table 1: Health facilities per intervention type by district and sub-district included in the LINKEDin study.

District	Sub-district Name	Intervention type	Hospital	PHC TB treatment facilities
Ugu (KZN)	Umdoni	Hospital-recording	GJ Crookes (District hospital, ~ 300 beds)	N/A
	Ray Nkonyeni	Alert-and-response patient management	Gamalakhe[a] (CHC)	10 surrounding PHC facilities
City of Johannesburg (GP)	Region D	Hospital-recording	Chris Hani Baragwanath (Tertiary hospital, ~ 3200 beds)	N/A
	Region E	Alert-and-response patient management	Edenvale (District hospital, ~ 230 beds)	9 surrounding PHC facilities
City of Cape Town (WC)	Tygerberg	Hospital-recording	Tygerberg (Tertiary hospital - 1899 beds)	N/A
	Khayelitsha	Alert-and-response patient management	Khayelitsha (District hospital, ~ 230 beds)	13 surrounding PHC facilities

a. Gamalakhe is a large community health centre (CHC) but used as a proxy for a hospital in this study at the request of the KZN Department of Health as 10 surrounding PHC facilities refer to it.

Table 2: Relative reduction in ILTFU between baseline and intervention periods per province

	Oct-Dec 2018		Jan 2019-Dec 2020		Relative Reduction ILTFU (95%CI)
	Newly diagnosed PWTB	ILTFU % (95% CI)	Newly diagnosed PWTB	ILTFU % (95%CI)	
KwaZulu-Natal	327	81 24.8% (20.1,29.4)	1999	285 14.3% (12.7,15.8)	42.4% (28.5,53.7)
Gauteng	921	292 31.7% (28.7,34.7)	5399	1772 32.8% (31.6,34.1)	-3.5% (-14.7,6.5)
Western Cape	1323	296 22.4% (20.1,24.6)	9359	1627 17.4% (16.6,18.2)	22.3% (13.3,30.4)

CI: Confidence interval

ILTFU: Initial loss to follow up

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Table 3: Relative reduction in ILTFU between baseline and intervention periods by sub-districts across provinces

		(Oct-Dec 2018)		Jan 2019-Dec 2020		Relative Reduction ILTFU (95%CI)	p-value 1-sided t-test*
		Newly diagnosed persons with TB	ILTFU % (95% CI)	Newly diagnosed persons with TB	ILTFU % (95%CI)		
KwaZulu Natal	Umdoni (Hospital-recording)	131	33 25.2% (17.8,32.6)	790	135 17.1% (14.5,19.7)	32.2% (5.4, 51.4)	0.0131
	Ray Nkonyeni (Alert and Response)	196	48 24.5% (18.5,30.5)	1209	150 12.4% (10.5,14.3)	49.3% (32.4, 62)	<.0001
Gauteng	Region D (Hospital-recording)	713	208 29.2% (25.8,32.5)	4099	1301 31.7% (30.3,33.2)	-8.8% (-23.0, 3.8)	0.9170
	Region E (Alert and Response)	208	84 40.4% (33.7,47.1)	1300	471 36.2% (33.6,38.8)	10.3% (-7.4, 25.1)	0.1288
Western Cape	Tygerberg (Hospital-recording)	761	185 24.3% (21.3,27.4)	5095	1073 21.1% (19.9,22.2)	13.4% (0.7, 24.4)	0.0251
	Khayelitsha (Alert and Response)	562	111 19.8% (16.5,23.0)	4264	554 13% (12.0,14.0)	34.2% (20.9, 45.3)	<.0001

*1-sided t-test: based on the null hypothesis that the percentage ILTFU was not reduced from baseline to intervention

CI: Confidence interval

ILTFU: Initial loss to follow up

Table 4: Relative reduction in ILTFU between baseline and intervention periods by place of diagnosis for sub-districts by intervention type

		Oct-Dec 2018		Jan 2019-Dec 2020		Relative Reduction ILTFU (95%CI)	p-value 1-sided t-test*
		Newly diagnosed PWTB	ILTFU % (95% CI)	Newly diagnosed PWTB	ILTFU % (95%CI)		
Sub-districts implementing the hospital-recording intervention (no intervention in surrounding facilities)							
Umdoni (KwaZulu-Natal)	GJ Crookes Hosp	65	23 35.4% (23.8, 47)	345	73 21.2% (16.8,25.5)	40.2% (12, 59.4)	0.0141
	Surrounding PHC facilities	66	10 15.2% (6.5, 23.8)	445	62 13.9% (10.7,17.2)	8% (-70.2, 50.3)	0.3989
Region D (Gauteng)	CH Baragwanath Hosp	169	94 55.6% (48.1, 63.1)	1167	746 63.9% (61.2,66.7)	-14.9% (-32.4, 0.2)	0.9784
	Surrounding PHC facilities	544	114 21.0% (17.5, 24.4)	2932	555 18.9% (17.5,20.3)	9.7% (-7.5, 2.1)	0.1420
Tygerberg (Western Cape)	Tygerberg Hospital	173	74 42.8% (35.4, 50.1)	1132	509 45% (42.1,47.9)	-5.1% (-26.4, 12.5)	0.7053
	Surrounding PHC facilities	588	111 18.9% (15.7, 22)	3963	564 14.2% (13.1,15.3)	24.6% (9.4, 37.3)	0.0015
Sub-districts implementing the alert-and-response patient management intervention							
Ray Nkonyeni (KwaZulu-Natal)	Gamalakhe CHC	59	7 11.9% (3.6, 20.1)	410	47 11.5% (8.4, 14.5)	3.4% (-103.7, 54.2)	0.4648
	Surrounding PHC facilities	137	41 29.9% (22.3, 37.6)	799	103 12.9% (10.6,15.2)	56.9% (41.1, 68.5)	<.0001
Region E (Gauteng)	Edenvale Hospital	59	43 72.9% (61.5, 84.2)	409	259 63.3% (58.7, 68)	13.1% (-3.2, 26.9)	0.0668

	Surrounding PHC facilities	149	41 27.5% (20.3, 34.7)	891	212 23.8% (21.0, 26.6)	13.5% (-15.1, 35)	0.1728
Khayelitsha (Western Cape)	Khayelitsha Hospital	79	22 27.8% (18.0, 37.7)	808	251 31.1% (27.9, 34.3)	-11.6% (-61.4, 22.9)	0.7261
	Surrounding PHC facilities	483	89 18.4% (15.0, 21.9)	3456	303 8.8% (7.8, 9.7)	52.4% (40.9, 61.7)	<.0001

*1-sided t-test: based on the null hypothesis that the percentage ILTFU was not reduced from baseline to intervention

CI: Confidence interval, ILTFU: Initial loss to follow up