GENEXPERT TESTING IN KHYBER PAKHTUNKHWA

ANNUAL REPORT -2019

Abstract

The report presents the analysis of data from the Provincial TB Program Khyber Pakhtunkhwa GeneXpert network, collected through GxAlert, and provides insights into the status of the program, instrument utilization, TB burden, quality of testing and disease surveillance. The analysis focuses on 2019 data but also presents analysis on trends over the last three years (2017-2019).

Provincial TB Reference Laboratory-KP

National TB Reference Laboratory

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Preface

Every year the National reference laboratory write a report on laboratory network including GeneXpert performance. Besides comprehensive laboratory annual report, key elements of this report are also embedded in the National annual report. This report presents in-depth analysis of performance of the GeneXpert instrument, collected through GxAlert, and provides insights into the status of the program, instrument utilization, TB burden, quality of testing and disease surveillance. The analysis focuses on 2019 data and trends analysis over the last three years (2017-2019).

For this in-depth analysis, we have only used data uploaded from GeneXpert machines connected to server with the possibility that for some of the machines, data uploaded might have been incomplete due to inactivity and issue with net coverage.

The analysis is arranged in four main sections namely GeneXpert network, module Utilization, Xpert performance for diagnosis of TB and drug resistance and quality of testing. We intended to include fifth section on inventory management but due to incompleteness of data, this section was not included in this report.
For each section data is analyzed for annual national trend followed by stratified provincial performance in 2019 only. However, we do plan to work with provincial team to develop an in-depth report for each province after completion of this report.

Data used for this analysis was accessed on 11th December 2020. The results shown in this report may change as more machines are connected to the GxAlert server in coming months. Readers are also likely to notice some difference in key performance indicator between this report and NRL annual report due to difference in sampling frame.

The report is result of a collaborative effort of SystemOne team and National TB reference laboratory. Preliminary draft was prepared by SystmeOne, which was extensively revised (With the exception of section on Quality) with inputs from National TB reference laboratory and Khyber Pakhtunkhwa TB reference laboratory teams. We are thankful to Ms. Natasha Ghaus (SystemOne), Mr Faisal Masood (Sr. Molecular biologist), Mr. Anwer Sheed (Senior Laboratory Supervisor) and Mr Hassan Rizvi (Coordinator GxAlert support desk) from National and Provincial TB Reference laboratory for their contribution.

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Khyber Pakhtunkhwa GeneXpert Annual Report

The report presents the analysis of data from the, GeneXpert instruments installed in TB laboratory network, Khyber Pakhtunkhwa which were managed by National/Provincial TB Control Program in 2017-2019. The data was collected through GxAlert, and provides insights into the status of the program, instrument utilization, TB burden, quality of testing and disease surveillance. The analysis focuses on 2019 data and also presents analysis of trends over the last three years (2017-2019).

1. GeneXpert Network

1.1 GeneXpert TB testing fleet

Table 1. GeneXpert testing sites and number of total instrument installed in Khyber Pakhtunkhwa.

Year	GeneXpert testing sites	GeneXpert instrument			Total modules*
		Total	Gx-IV	Gx-XVI	
	(n)	(n)	(n)	(n)	(n)
2017	23	23	22	1	104
2018	33	33	28	5	192
2019	37	38	32	6	224

Table 2 provides a breakdown of the GeneXpert TB testing footprint in Khyber Pakhtunkhwa in terms of number of GeneXpert sites and modules **reporting data to GxAlert**, in 2017 and 2019. The numbers of GeneXpert four (IV) and GeneXpert 16 (XVI) module instruments are also shown per year. In 2019, there were 31 sites connected and reporting to GxAlert, including 30 Gx-IV and 5 Gx-XVI module instruments.

Table 2: National GeneXpert TB testing fleet connected to GxAlert 2019

Year	GeneXpert testing sites	GeneXpert instrument			Total modules*
		Total	Gx-IV	Gx-XVI	
	(n)	(n)	(n)	(n)	(n)
2017	21	19	18	5	152
2018	31	36	31	5	204
2019	31	31	30	5	200

*Includes replaced modules

Note: Discrepancy noted between two tables above is due to the fact if a Gx is moved to a different lab, it gets counted twice by GxAlert. Furthermore, GxAlert has no way of knowing if the instrument is a Gx-IV or Gx--XVI, and any attempt to calculate based on instrument serial numbers is complex. Any differences in module count is because again, the data does not show if a module is replaced. So if a Gx-IV instrument has a module replaced, it will be counted as 5 modules on the instrument as Tableau just counts the unique module serial numbers appearing in the dataset.

The breakdown of the GeneXpert TB testing fleet per District for the year 2019 is shown in Table 2. Peshawar had the highest number of GeneXpert testing sites and modules reporting to GxAlert in 2019 with two Gx-IV and three Gx-XVI instruments. Mardan and Swat also each had one Gx-XVI instrument.

Table 3: District breakdown of GeneXpert TB testing fleet, 2019

Sr. No.	District	GeneXpert Testing sites	GeneXpert instrument			Total modules*
			Total	Gx-IV	Gx-XVI	
		(n)	(n)	(n)	(n)	(n)
	Khyber Pakhtunkhwa	**31**	**35**	**30**	**5**	**200**
1	Abbottabad	3	2	2	0	8
2	Bannu	2	2	2	0	8
3	Battagram	1	1	1	0	4
4	Buner	1	1	1	0	4
5	Charsadda	1	1	1	0	4
6	Chitral	1	1	1	0	4
7	DI Khan	2	4	4	0	16
8	Hangu	1	1	1	0	4
9	Haripur	1	2	2	0	8
10	Karak	1	1	1	0	4
11	Kohat	1	1	1	0	4
12	Lakki Marwat	1	1	1	0	4
13	Lower Dir	1	1	1	0	4
14	Malakand	1	1	1	0	4
15	Mansehra	1	1	1	0	4
16	Mardan	3	4	3	1	28
17	Peshawar	5	5	2	3	56
18	Shangla	1	1	1	0	4
19	Swabi	1	2	2	0	8
20	Swat	1	1	0	1	16
21	Upper Dir	1	1	1	0	4

1.2 Type of Xpert Assay used and transition to Xpert MTB/RIF Ultra

Xpert MTB/RIF ultra after the recommendation of WHO was introduced for the first time in last quarter of 2017. The number of Xpert testing sites switched to the Xpert MTB/RIF Ultra assay, has steadily increased, from one site in 2017 to 4 sites (12.9%) in 2019 (Table 4). Simultaneously test performed on Ultra assay has increased. In 2019 of 33,568 tests reported to GxAlert, 7% (n=2,377) were tested on Ultra assay (Table 4).

Table 4: GeneXpert testing site/tests performed stratified by Xpert assay type

	Testing sites by Xpert assay type used				Test numbers by Xpert assay type used			
Year	All Xpert testing sites	Xpert MTB/RIF sites	Xpert MTB/RIF Ultra sites	Xpert MTB/RIF Ultra sites	Total tests (n)	Xpert MTB/RIF tests	Xpert MTB/RIF Ultra tests	Xpert MTB/RIF Ultra tests
	(n)	(n)	(n)	(%)	(n)	(n)	(n)	(%)
2017	21	21	0	0	12,117	12,117	0	0
2018	31	31	0	0	27,360	27,360	0	0
2019	31	31	4	12.9	33,568	31,191	2,377	7.0

In figure-1 below are shown GeneXpert testing and transition to Xpert ultra over three years

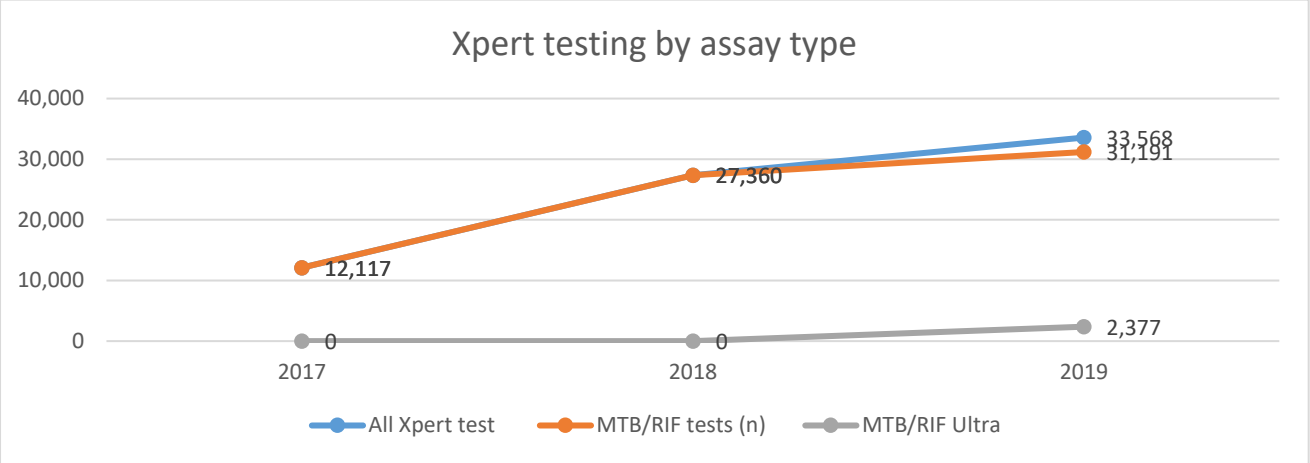


Figure 1: Test numbers reported by assay type, per year 2017 - 2019

The number of sites performing Xpert MTB/RIF and MTB/RIF Ultra testing and test numbers per assay in 2019 per District for 2019, are shown in Table 5. Mardan and Peshawar were the only Districts performing Ultra testing in 2019. Peshawar, which had 60% of its sites performing Ultra testing, reported significantly more TB results compared to other districts in 2019. The lowest test numbers reported in 2019 were by Kohat and Swabi District.

Table 5: GeneXpert testing site and TB Tests performed by Assay Type in 2019

Sr. No.	District	Testing sites by Assay type used				Test numbers by assay type used			
		Xpert testing sites	Xpert MTB/RIF sites	Xpert MTB/RIF Ultra sites		Total Test	Xpert MTB/RIF tests	Xpert MTB/RIF Ultra-Test	
		(n)	(n)	(n)	(%)	(n)	(n)	(n)	(%)
	Khyber Pakhtunkhwa	31	31	4	93.3	33,568	31,191	2,377	21.0
1	Abbottabad	3	3	0	0	1,583	1,583	0	0
2	Bannu	2	2	0	0	1,421	1,421	0	0
3	Battagram	1	1	0	0	361	361	0	0
4	Buner	1	1	0	0	485	485	0	0
5	Charsadda	1	1	0	0	372	372	0	0
6	Chitral	1	1	0	0	420	420	0	0
7	DI Khan	2	2	0	0	2,428	2,428	0	0
8	Hangu	1	1	0	0	255	255	0	0
9	Haripur	1	1	0	0	1,969	1,969	0	0
10	Karak	1	1	0	0	474	474	0	0
11	Kohat	1	1	0	0	212	212	0	0
12	Lakki Marwat	1	1	0	0	405	405	0	0
13	Lower Dir	1	1	0	0	687	687	0	0
14	Malakand	1	1	0	0	382	382	0	0
15	Mansehra	1	1	0	0	532	532	0	0
16	Mardan	3	3	1	33.3	3,161	2,916	245	8.0
17	Peshawar	5	5	3	60.0	15,834	13,702	2,132	13.0
18	Shangla	1	1	0	0	620	620	0	0
19	Swabi	1	1	0	0	265	265	0	0
20	Swat	1	1	0	0	1,251	1,251	0	0
21	Upper Dir	1	1	0	0	451	451	0	0

In 2019, transition to ultra-expanded from no sites in 2018 to 04 sites by end of 2019. As all Xpert sites used both the assays during this period, therefore number of total sites is same as those which used MTB/RIF assay shown in Table-5.

2 GeneXpert test volumes and utilization rate

2.1 GeneXpert Update

Khyber Pakhtunkhwa GeneXpert TB Control program has shown exponential growth over the last few years in terms of results being reported. A total of 33,568 TB results were reported to GxAlert in 2019, equating to an overall average of 133 tests reported per day of 2019 and an average of 161 tests reported per module in 2019 (Table 6).

Table 6 GeneXpert TB testing trends

Year	Total results	Total modules	Avg. tests/ day	Avg. tests/ module
	(n)	(n)	(n)	(n)
2017	12,117	152	48	80
2018	27,360	204	109	134
2019	33,568	200	133	168

Disaggregated by District (Table 7), we see that the most capacitated region, namely Peshawar, reported an average of 63 tests per day of 2019 and an average of 255 tests per module in 2019. This was followed by Mardan with an average of 13 tests per day of 2019 and an average of 113 tests per module.

Table7: GeneXpert TB testing trends by District in 2019

Sr. No.	Province /Regions	Total results	Total modules	Avg tests/ day	Avg tests/ module
		(n)	(n)	(n)	(n)
Khyber Pakhtunkhwa		33,568	200	133	168
1	Abbottabad	1,583	8	6	198
2	Bannu	1,421	8	6	178
3	Battagram	361	4	1	90
4	Buner	485	4	2	121
5	Charsadda	372	4	1	93
6	Chitral	420	4	2	105
7	DI Khan	2,428	16	10	152
8	Hangu	255	4	1	64
9	Haripur	1,969	8	8	246
10	Karak	474	4	2	119
11	Kohat	212	4	1	53
12	Lakki Marwat	405	4	2	101
13	Lower Dir	687	4	3	172
14	Malakand	382	4	2	96
15	Mansehra	532	4	2	133
16	Mardan	3,161	28	13	113
17	Peshawar	15,834	56	63	283
18	Shangla	620	4	2	155
19	Swabi	265	8	1	33
20	Swat	1,251	16	5	78
21	Upper Dir	451	4	2	113

2.2 Instrument Utilization rates

The assessment of instrument utilization rates is a useful metric for determining improvements in program efficiency as it can be used to identify sites that require additional testing capacity versus those that are over-capacitated.

2.2.1. Annual and quarterly utilization rates

To calculate yearly utilization, the number of tests performed per instrument (numerator) is divided by the estimated optimal number of tests that could be performed in a year (denominator). This is based on the assumption that each Gx module is capable of running an optimal of 3 tests per day, with 252 working days in a year. The calculation takes into account the number of modules that are reporting.

Thus, yearly utilization = number of results reported in [year] / (number of modules reporting in [year] x 3 tests x 252 days) x100.

Using this as the benchmark, yearly utilization rates were calculated nationally and per Province for 2019 and then colour-coded according to the following utilization categories for ease of understanding:

Table 8: colour coding scheme Guide for utilization rate

1-20%	21-30%	31-50%	51-75%	>75%
red	orange	yellow	light green	dark green

2.2.1.1 Provincial annual utilization rate

Looking at the general trend in data, Khyber Pakhtunkhwa has been achieving low overall annual utilization rates since 2017 but it shows steady improvement (Figure 2). Low utilization indicates that GeneXpert instruments have not been fully absorbed into the health system and have not yet reached full testing capacity.

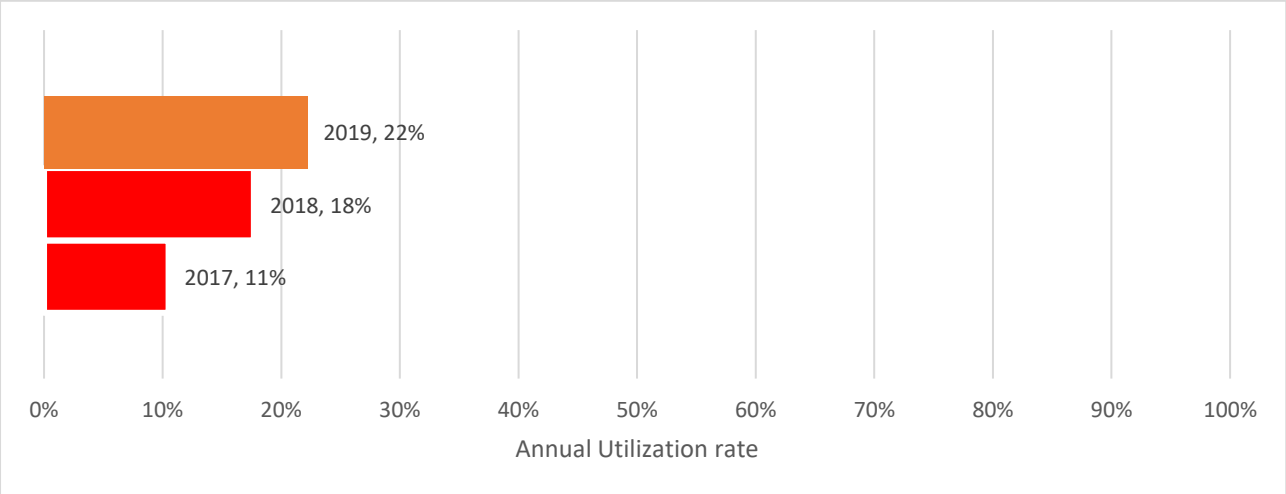


Figure 2: Trends in the annual utilization rates 2017 - 2019

2.2.1.2 *Provincial Annual Utilization rates*

Figure 3 shows the yearly utilization rates per District for 2019. Peshawar, Haripur and Abbottabad were the only districts with utilizations above 25% in 2019. Hangu, Chitral, Kohat and Swabi were all below 10%.

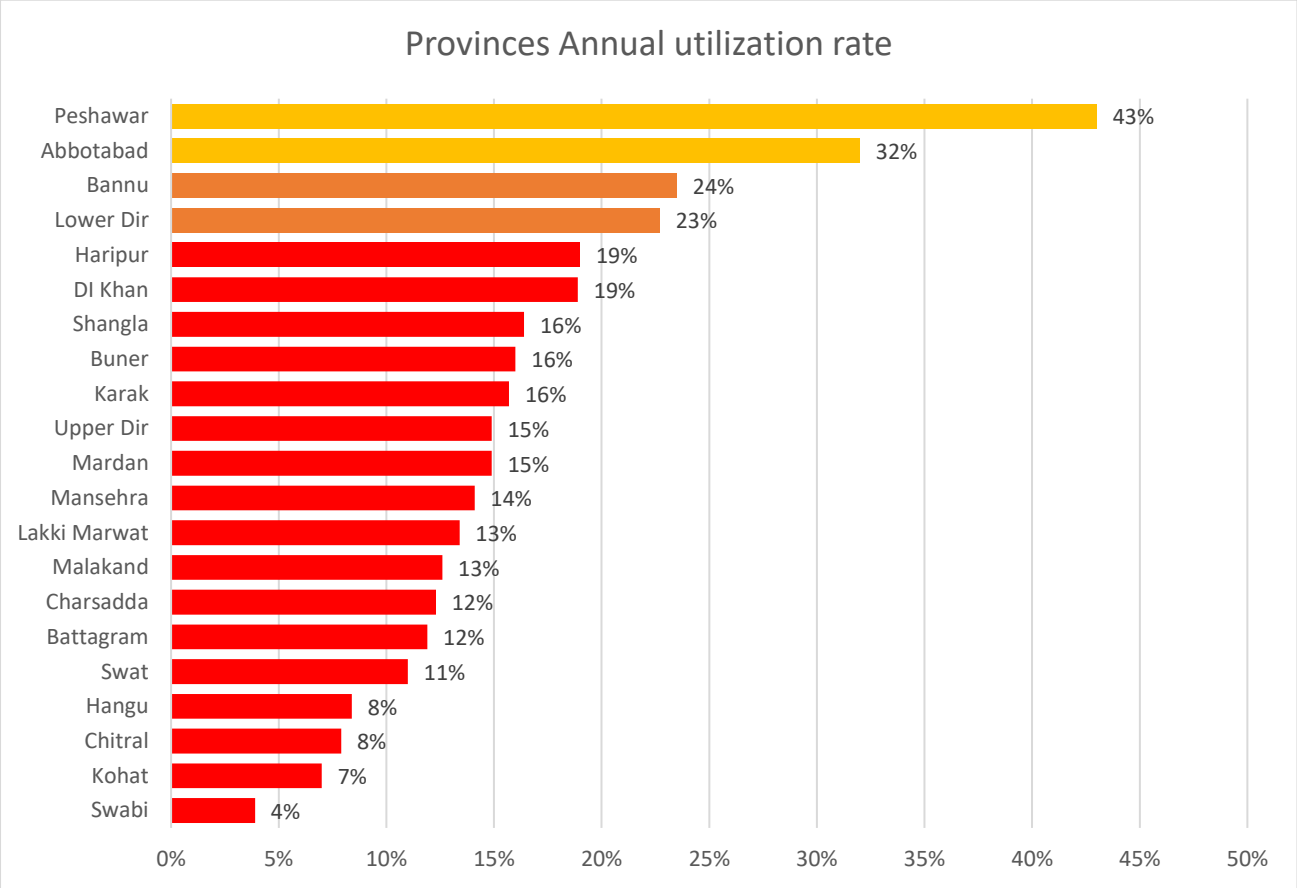


Figure 3 Annual utilization rates (%) per District for 2019. Each bar represents utilization as a percentage and colors represent what category of utilization the District falls into.
Key: Utilization 1-20% (red); 21-30% (orange); 31-50% (yellow); 51-75% (light green); 76% and above (dark green)

2.2.2 Quarterly utilization rates

A more accurate estimation of instrument utilization is to look at quarterly utilization rates. This calculation counts the number of modules reporting per quarter and assumes that each module can test 3 specimens per day, 21 days in a working month and 3 months in a quarter.

Thus, quarterly utilization = number of results reported [Quarter] / (number of modules reporting [quarter] x 3 tests x 21days x 3months) x100.

Table 9: Trends in Provincial Quarterly utilization rates (%), 2017 – 2019

	Quartwise utilization in 2019			
	Q-1	Q-2	Q-3	Q-4
2017	14.6	15.4	20.0	14.6
2018	21.4	18.8	19.1	22.4
2019	27.2	23.7	23.2	20.3

1-20% (red); 21-30%(orange); 31-50% (yellow); 51-75%(light green); 76% and above (dark green).

Using this calculation, Khyber Pakhtunkhwa Province achieved an average quarterly utilization rate of 27.2% in Q1, 23.7% in Q2, 23.2% in Q3 and 20.3% in Q4 of 2019 (Table 10). This was slightly higher than previous years.

When disaggregated by District for 2019 (Table 8), we again see how Peshawar consistently achieved the highest utilization rates across quarters compared to other districts, followed by Haripur.

Table 10: Trends in Quarterly utilization rates (%) per District for 2019

	Quartwise utilization in 2019			
District	Q-1	Q-2	Q-3	Q-4
Abbottabad	32.0	22.2	29.1	21.4
Bannu	20.5	26.1	25.3	22.0
Battagram	18.7	21.3	4.2	13.5
Buner	20.1	16.5	15.3	12.2
Charsadda	11.2	13.6	12.3	12.0
Chitral	13.5	12.2	16.1	13.8
DI Khan	18.2	22.4	32.2	26.8
Hangu	12.4	5.0	8.7	7.5
Haripur	38.4	35.1	29.0	27.6
Karak	22.2	15.5	16.0	9.0
Kohat	26.1	2.0	0	0
Lakki Marwat	14.0	13.4	13.1	13.1
Lower Dir	19.8	30.2	25.1	15.7
Malakand	12.4	15.5	12.4	10.2
Mansehra	24.3	16.8	16.3	13.0
Mardan	16.1	13.5	15.3	16.5
Peshawar	46.1	39.0	33.6	28.9
Shangla	19.6	11.0	25.8	20.8
Swabi	3.7	0.5	18.8	16.2
Swat	14.6	10.1	10.6	8.7
Upper Dir	14.2	14.8	16.0	14.7

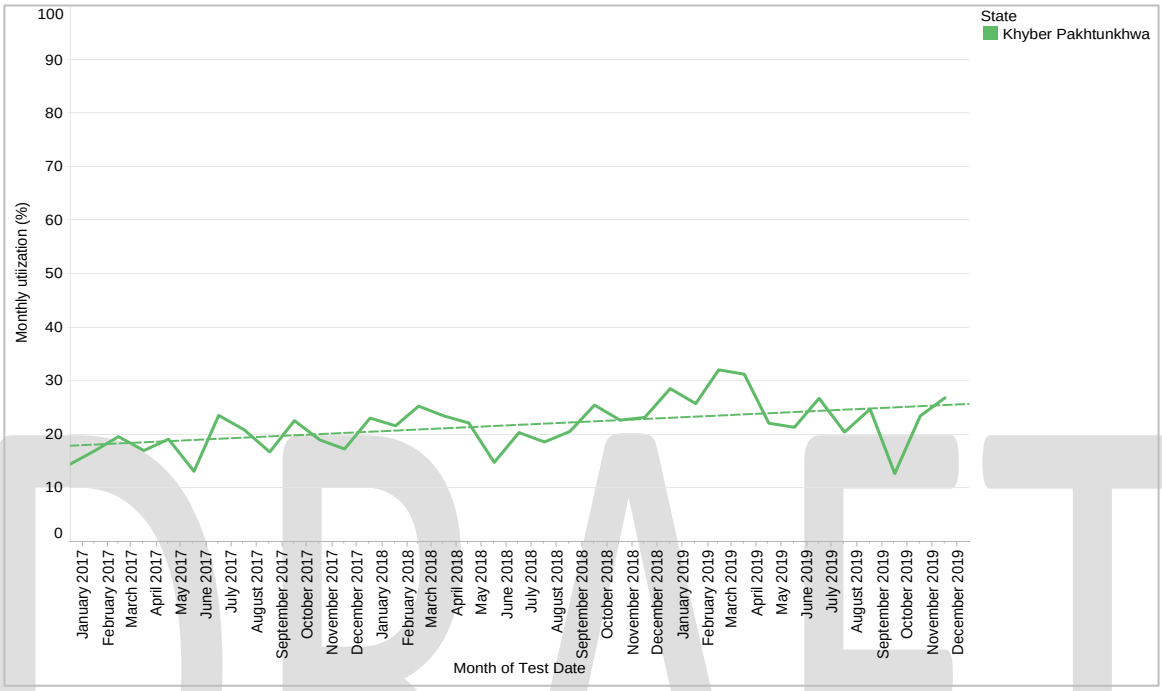
1-20% (red); 21-30%(orange); 31-50% (yellow); 51-75%(light green); 76% and above (dark green).

Swabi, achieved utilizations below 5% in Q1 and Q2 of 2019. Kohat appears to have stopped testing in Q3 of 2019, which would explain their overall low yearly utilization rate.

2.2.3 Trends in Monthly utilization

In general, different patterns of instrument utilization across a country; declining, stagnant or increasing (ideal scenario). If utilization rates are disaggregated down to month, Khyber Pakhtunkhwa shows a generally low, but slightly increasing trend in instrument utilization, month-on-month from 2017 onwards (Figure 4).

Figure 4 Trends in monthly utilization rates (%), 2017 – 2019



3 Xpert Performance: Diagnosis of TB and Rifampicin Resistant TB

3.1 Valid Results by Assay type

The breakdown of test numbers by Xpert result category and assay type for 2019 is shown in Table 11. Although Ultra testing volumes are still picking up in the country, overall, we see lower rates of errors, no results and invalids for the Ultra assay as well as lower rates of TB positives detected compared to Xpert MTB/RIF assay.

Table 11: Clinically valid, invalid results and error by assay type - 2019

Results	All Xpert		Xpert TB/RIF assay		MTB/RIF Ultra assay	
	Test (n)	(%)	Test(n)	(%)	Test(n)	(%)
Positive	7,655	22.8%	7,270	23.3%	385	16.2%
Trace	73	0.2%			73	3.1%
Negative	23,014	68.6%	21,185	67.9%	1,829	76.9%
Error	2,187	6.5%	2,115	6.8%	72	3.0%
Invalid	273	0.8%	264	0.8%	9	0.4%
No Result	366	1.1%	357	1.1%	9	0.4%
Total	33,568	100.0%	31,191	100.0%	2,377	100.0%

3.2 MTB positivity rates

The breakdown of result categories for all clinically valid results (i.e. MTB positives, trace and negatives) is shown in Figure 5. The rates of MTB positives being reported has been decreasing year-on-year. In 2019, the Khyber Pakhtunkhwa TB Control program reported 7,656 MTB positive results (24.9%) and 73 Trace results (0.23%) out of the total 30,742 clinical valid results reported.

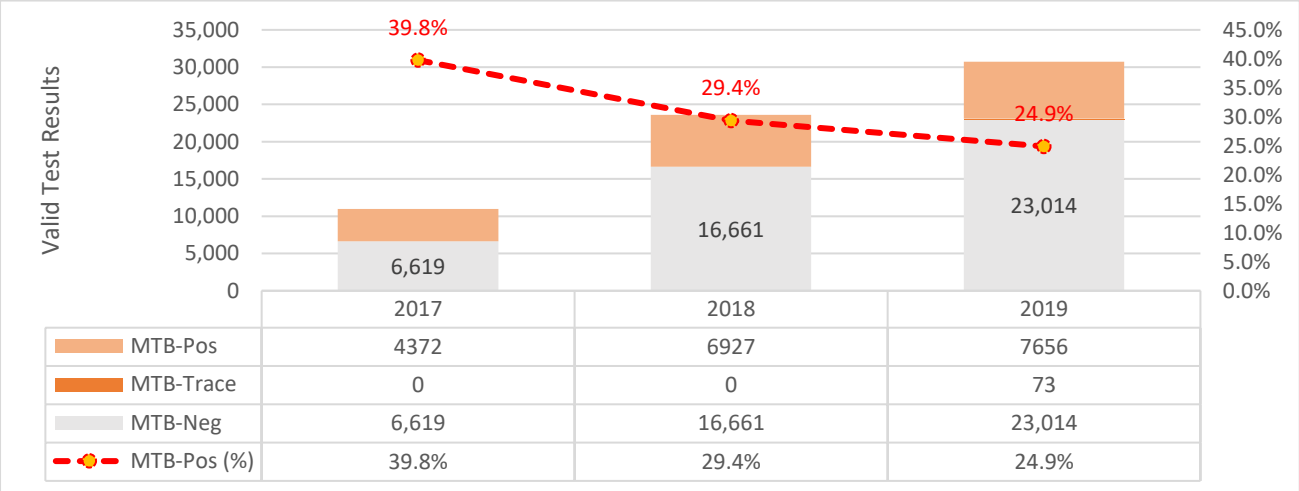


Figure 5: MTB positivity trend among all clinically valid results reported between 2017 and 2019

Table 12: Comparison of MTB positivity rate among all clinically valid results 2017 and 2019

	Valid Results	MTB-Neg	MTB-Trace	MTB-Pos	MTB-Pos
Districts	**(n)**	**(n)**	**(n)**	**(n)**	**(%)**
Khyber Pakhtunkhwa	28,455	20,562	458	7,270	25.6%
Abbottabad	1,420	957		454	32.0
Bannu	1,314	762		541	41.2
Battagram	284	194		88	31.0
Buner	469	374		95	20.3
Charsadda	355	209		144	40.6
Chitral	284	235		48	16.9
DI Khan	2,200	1,126		1,065	48.4
Hangu	227	182		44	19.4
Haripur	1,864	1,545		317	17.0
Karak	423	348		73	17.3
Kohat	178	111		66	37.1
Lakki Marwat	352	188		159	45.2
Lower Dir	659	453		205	31.1
Malakand	319	235		80	25.1
Mansehra	468	307		159	34.0
Mardan	2,706	2,109	24	562	21.7
Peshawar	12,689	9,531	434	2,641	24.2
Shangla	513	393		115	22.4
Swabi	225	157		68	30.2
Swat	1,121	851		257	22.9
Upper Dir	385	295		89	23.1

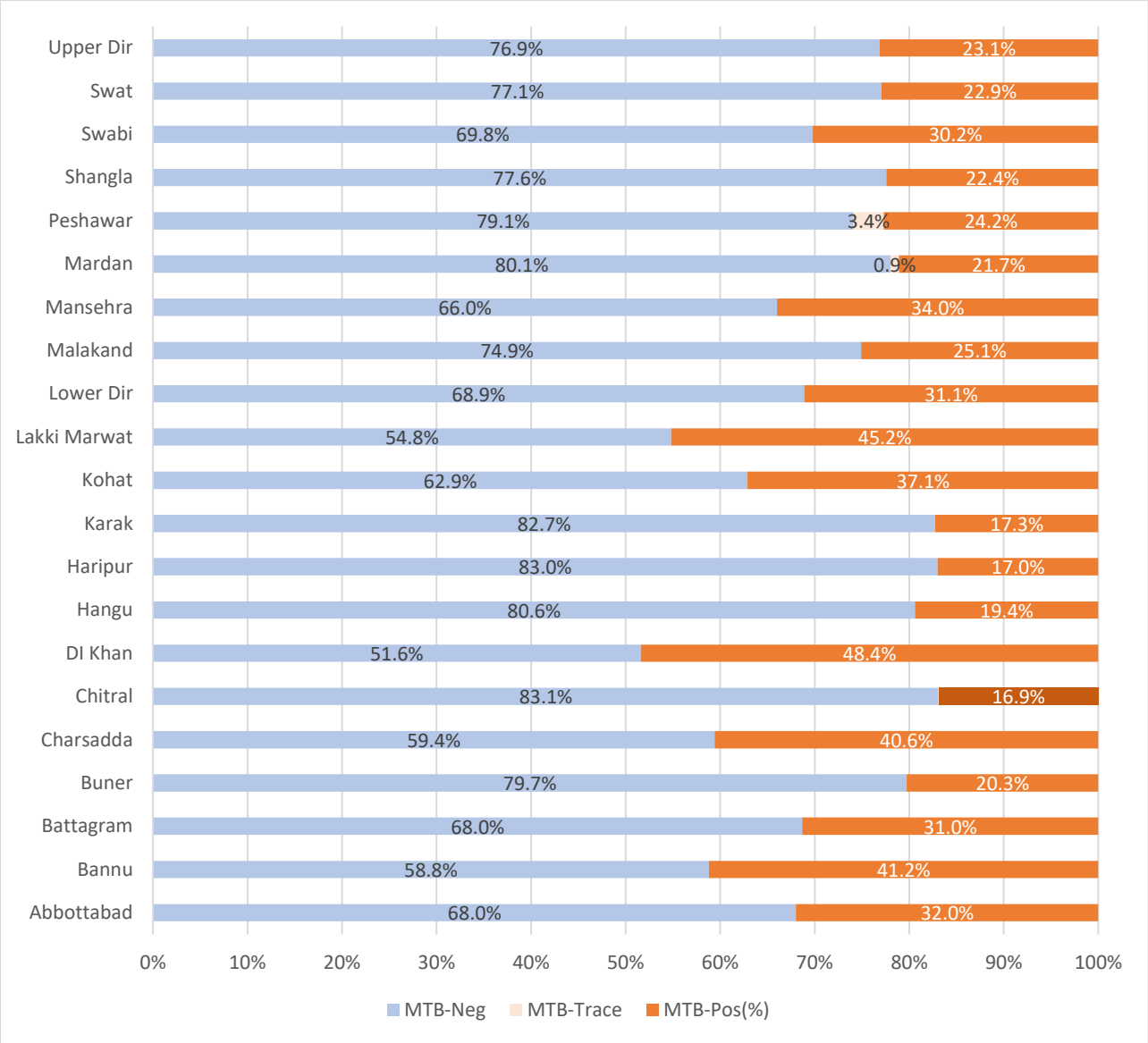


Figure 6 MTB positivity rate among all clinically interpretable results, by District for 2019

3.3 MTB positivity Rates by Assay type

When stratified down by assay type, the Xpert MTB/RIF assay reported TB positivity of 25.5% in 2019 and with Ultra assay, 20.7% were reported MTB positive and 3.2% Trace positive in 2019 (Table 13).

Table 13 Trends in TB positivity in absolute numbers and percentages by assay type

Year	GeneXpert TB/RIF assay			GeneXpert MTB/RIF Ultra assay				
	Total results	MTB Positive	MTB positivity[1]	Total results	MTB Positive	Trace positive	MTB positivity[2]	Trace positivity[3]
	(n)	(n)	(%)	(n)	(n)	(n)	(%)	(%)
2017	10,991	4,372	39.8					
2018	23,588	6,927	29.4					
2019	28,455	7,270	25.5	2,287	385	73	16.8	3.2

1. Xpert MTB/RIF MTB positivity = Total MTB detected/ (MTB detected + MTB not detected) x 100
2. Xpert Ultra MTB positivity = Total Ultra MTB detected/ (Ultra MTB detected + MTB Trace detected + MTB not detected) x 100
3. Xpert Ultra Trace positivity = Total Trace detected/ (Ultra MTB detected + MTB Trace detected + MTB not detected) x 100

Thus, taking both MTB positives and Trace positives into account for the Ultra assay, this equates to a total MTB positivity rate of 20% for Ultra, compared to 25.5% reported by the Xpert MTB/RIF (Figure 7).

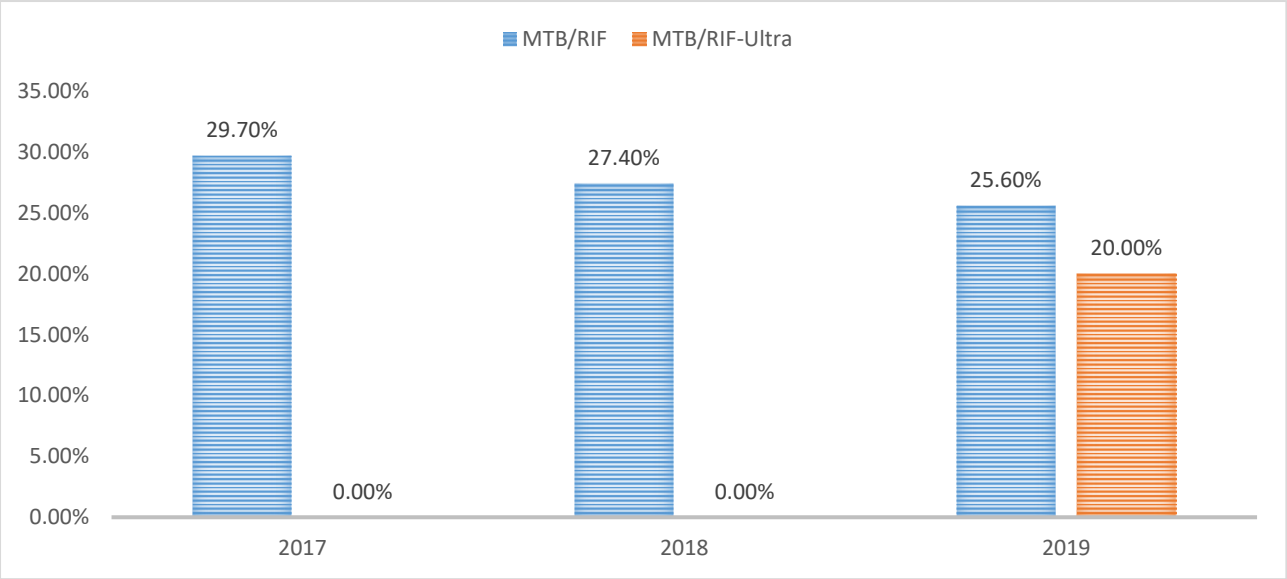


Figure 7: MTB positivity rates (%) by assay type

TB positivity rates by assay type for 2019 are shown in Table 14. Mardan reported a 20.8 TB positivity with the Xpert MTB/RIF assay but only 9% positivity with Ultra and 1.3% Trace rate. Peshawar reported similar TB positivity rates between the two assays with a 3.4% Trace rate reported by Ultra.

Table 14 TB positivity rates in absolute numbers and percentages, per assay type and by District, 2019

	GeneXpert TB/RIF Assay			GeneXpert MTB/RIF Ultra Assay				
	Total results	MTB Positive	MTB positivity	Total results	MTB positive incl. Trace	Trace positive	MTB positivity incl. Trace	Trace positivity
	(n)	(n)	(%)	(n)	(n)	(n)	(%)	(%)
Khyber Pakhtunkhwa	28,455	7,270	26.0	2,287	458	73	17	3.2
Abbottabad	1,420	454	32.0					
Bannu	1,314	541	41.2					
Battagram	284	88	31.0					
Buner	469	95	20.3					
Charsadda	355	144	40.6					
Chitral	284	48	16.9					
DI Khan	2,200	1,065	48.4					
Hangu	227	44	19.4					
Haripur	1,864	317	17.0					
Karak	423	73	17.3					
Kohat	178	66	37.1					
Lakki Marwat	352	159	45.2					
Lower Dir	659	205	31.1					
Malakand	319	80	25.1					
Mansehra	468	159	34.0					
Mardan	2,706	562	20.8	233	24	3	9.0	1.3
Peshawar	12,689	2,641	20.8	2,054	434	70	17.7	3.4
Shangla	513	115	22.4					
Swabi	225	68	30.2					
Swat	1,121	257	22.9					
Upper Dir	385	89	23.1					

3.3.1 MTB positives by semi-quantitative results in 2017-2019

All MTB positive results were disaggregated by semi-quantitative result category (high, medium, low and very low) for each assay type, for the years 2017 - 2019 (Table 15), and by District for 2019 (Table 16). Overall, the majority of TB positive results were reported in the medium result category for the MTB/RIF assay and in the low result category for the Ultra assay in 2019.

Table 15 Trends in MTB positive semi-quantitative results by assay type, 2017 - 2019

Year		Xpert MTB/RIF: MTB+results					Xpert MTB/RIF Ultra: MTB+results					
		All	High	Med	Low	Very low	All	High	Med	Low	Very low	Trace
2017	n	4,372	1,122	1,849	990	411						
	%	100.0	25.7	42.3	22.6	9.4						
2018	n	6,927	1,571	2,559	1,812	985						
	%	100.0	22.7	36.9	26.2	14.2						
2019	n	7,270	1,582	2,734	1,788	1,166	458	128	63	150	44	73
	%	100.0	21.8	37.6	24.6	16.0	100.0	27.9	13.8	32.8	9.6	15.9

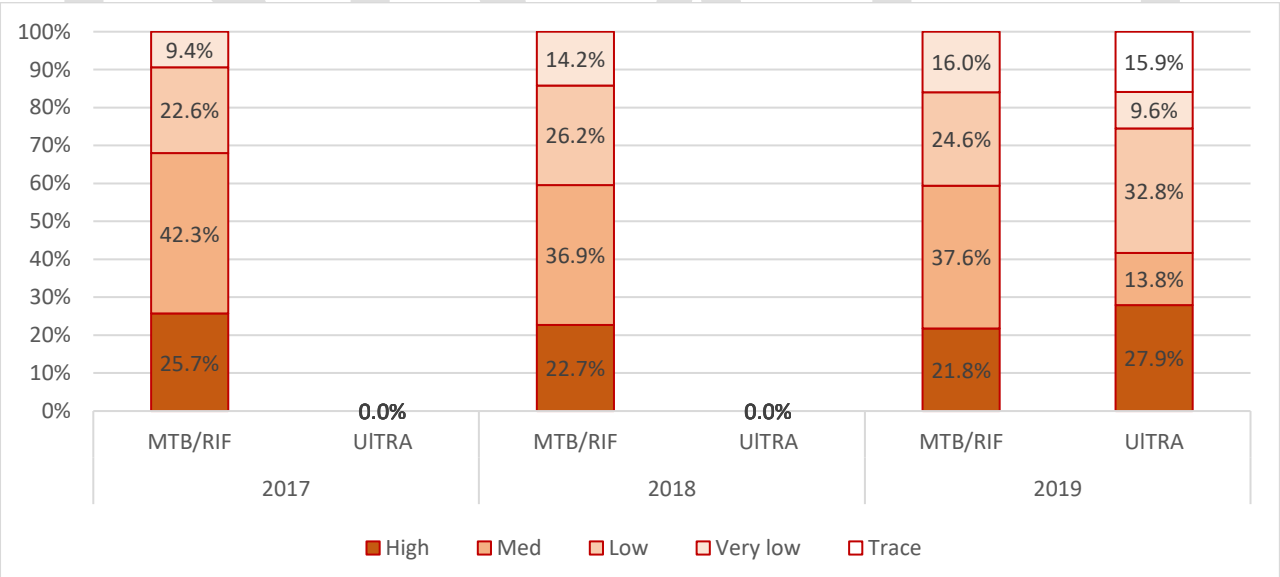


Figure 8: Trends in MTB positive semi-quantitative results by assay type, 2017 - 2019

Table 16: MTB positive semi-quantitative results by assay type per District, 2019

		Xpert MTB/RIF: MTB+results					Xpert MTB/RIF Ultra: MTB+results					
		All	High	Med	Low	V.low	All	High	Med	Low	V.low	Trace
Khyber Pakhtunkhwa (Total)	n	7,270	1,582	2,734	1,788	1,166	458	128	63	150	44	73
	%	100	21.8	37.6	24.6	16	100	27.9	13.8	32.8	9.6	15.9
Abbottabad	n	454	108	172	108	66						
	%	100	23.8	37.9	23.8	14.5						
Bannu	n	541	112	250	117	62						
	%	100	20.7	46.2	21.6	11.5						
Battagram	n	88	18	29	27	14						
	%	100	20.5	33	30.7	15.9						
Buner	n	95	34	41	8	12						
	%	100	35.8	43.2	8.4	12.6						
Charsadda	n	144	51	61	21	11						
	%	100	35.4	42.4	14.6	7.6						
Chitral	n	48	7	21	11	9						
	%	100	14.6	43.8	22.9	18.8						
DI Khan	n	1,065	245	449	259	112						
	%	100	23	42.2	24.3	10.5						
Hangu	n	44	8	9	16	11						
	%	100	18.2	20.5	36.4	25						
Haripur	n	317	99	114	71	33						
	%	100	31.2	36	22.4	10.4						
Karak	n	73	9	28	19	17						
	%	100	12.3	38.4	26	23.3						
Kohat	n	66	12	23	19	12						
	%	100	18.2	34.8	28.8	18.2						
Lakki Marwat	n	159	38	64	32	25						
	%	100	23.9	40.3	20.1	15.7						
Lower Dir	n	205	29	92	60	24						
	%	100	14.1	44.9	29.3	11.7						
Malakand	n	80	23	35	12	10						
	%	100	28.8	43.8	15	12.5						
Mansehra	n	159	30	71	42	16						
	%	100	18.9	44.7	26.4	10.1						
Mardan	n	562	108	226	136	92	24	4	3	9	5	3
	%	100	19.2	40.2	24.2	16.4	100	16.7	12.5	37.5	20.8	12.5
Peshawar	n	2,641	541	898	680	522	434	124	60	141	39	70
	%	100	20.5	34	25.7	19.8	100	28.6	13.8	32.5	9	16.1
Shangla	n	115	10	17	42	46						
	%	100	8.7	14.8	36.5	40						
Swabi	n	68	30	22	11	5						
	%	100	44.1	32.4	16.2	7.4						
Swat	n	257	58	87	60	52						
	%	100	22.6	33.9	23.3	20.2						
Upper Dir	n	89	12	25	37	15						
	%	100	13.5	28.1	41.6	16.9						

3.4 Rif resistance rates

There were 332 Rifampicin resistant results reported in 2019 in Khyber Pakhtunkhwa (4.3%), with 239 Rifampicin indeterminate results (3.3%) (Figure 9). A declining trend is seen in the proportion of Rifampicin resistant results being reported between 2017 and 2019

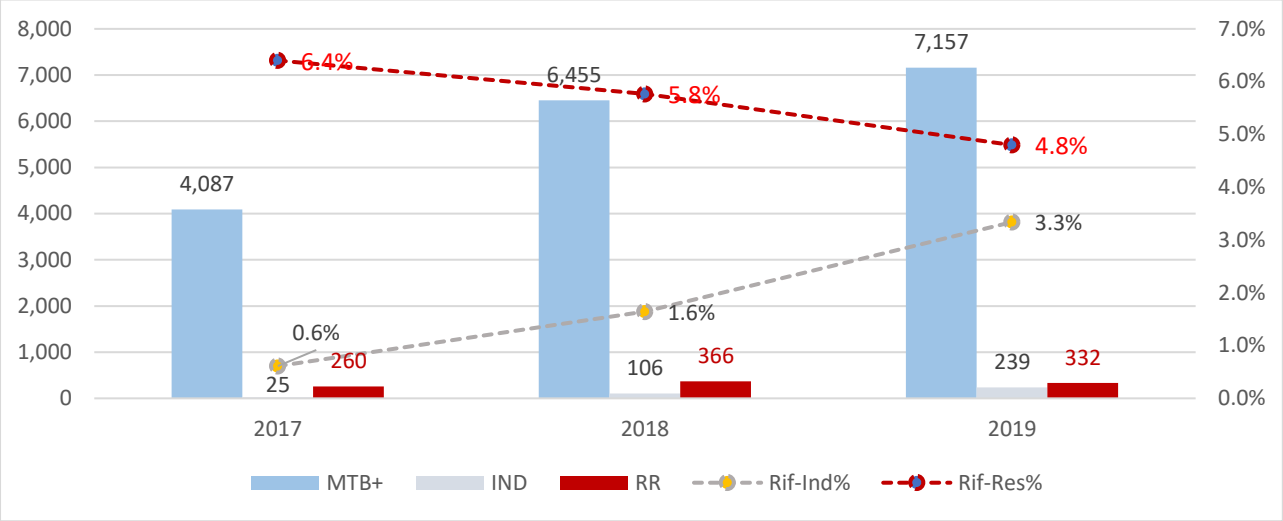


Figure 9 Provincial average Xpert Rif resistance rates (%) for 2017-2019

Table 17: Proportion of Rifampicin resistant among MTB positive by province in 2019

	MTB +	MTB+/Rif-Neg		MTB+/Rif-IND		MTB+/Rif-Res		
	(n)	(n)	(%)	(n)	(%)	(n)	(%) Inc-IND	% Exc-IND
Khyber Pakhtunkhwa	7,270	6,793	93.4	165	2.27	312	4.3	4.4
Abbottabad	454	434	95.6	9	2.0	11	2.4	2.5
Bannu	541	517	95.6	11	2.0	13	2.4	2.5
Battagram	88	80	90.9	2	2.3	6	6.8	7.0
Buner	95	94	98.9		0.0	1	1.1	1.1
Charsadda	144	135	93.8	2	1.4	7	4.9	4.9
Chitral	48	44	91.7	1	2.1	3	6.3	6.4
DI Khan	1,065	1010	94.8	9	0.8	46	4.3	4.4
Hangu	44	40	90.9	1	2.3	3	6.8	7.0
Haripur	317	306	96.5	2	0.6	9	2.8	2.9
Karak	73	64	87.7	2	2.7	7	9.6	9.9
Kohat	66	64	97.0	1	1.5	1	1.5	1.5
Lakki Marwat	159	152	95.6	5	3.1	2	1.3	1.3
Lower Dir	205	198	96.6	1	0.5	6	2.9	2.9
Malakand	80	75	93.8	4	5.0	1	1.3	1.3
Mansehra	159	153	96.2	2	1.3	4	2.5	2.5
Mardan	562	528	94.0	11	2.0	23	4.1	4.2
Peshawar	2,641	2428	91.9	83	3.1	130	4.9	5.1
Shangla	115	108	93.9	5	4.3	2	1.7	1.8
Swabi	68	48	70.6		0.0	20	29.4	29.4
Swat	257	230	89.5	13	5.1	14	5.4	5.7
Upper Dir	89	85	95.5	1	1.1	3	3.4	3.4

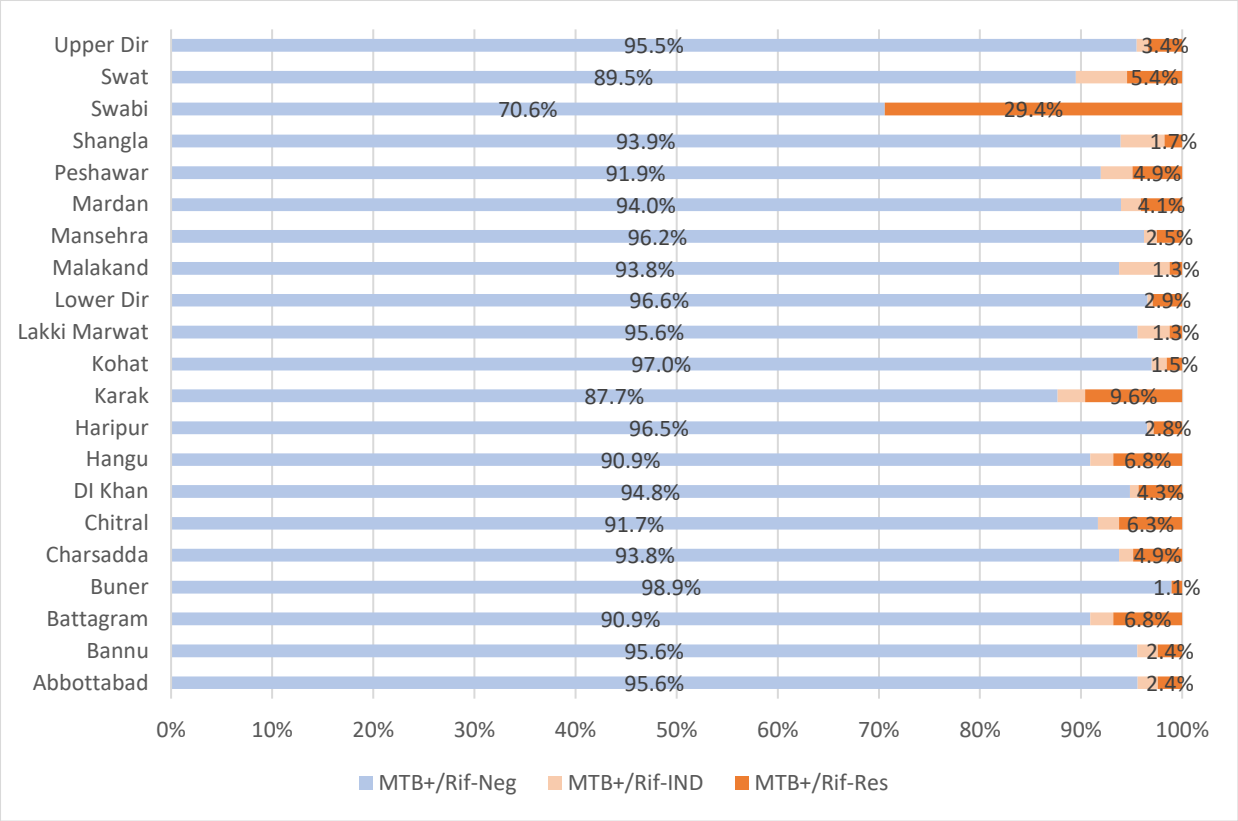


Figure 10: Proportion of Rifampicin resistant among MTB positive by province in 2019

Figure 11: shows trends in Rifampicin resistance reporting per District over the last three years. Swabi reported a major jump in reported Rif resistance rates from previous years; from 5.6% and 5.2% in 2017 and 2018 respectively, to 29.4% in 2019. Karak also showed in increase in reported Rif resistance rates from 2018 rates.

Figure 11 National Rifampicin resistance rates (%) for 2019 per District

District	2017	2018	2019
Abbottabad	4.64	4.18	2.42
Bannu	2.22	3.29	2.40
Battagram	3.85	4.17	6.82
Buner		8.33	1.05
Charsadda		0.65	4.86
Chitral	11.11	1.61	6.25
DI Khan	5.72	4.82	4.32
Hangu		2.17	6.82
Haripur	3.19	2.11	2.84
Karak	9.30	4.85	9.59
Kohat	11.82	7.97	1.52
Lakki Marwat		3.13	1.26
Lower Dir	3.59	1.78	2.93
Malakand	2.53	1.61	1.25
Mansehra	3.45	3.43	2.52
Mardan	4.64	6.99	3.95
Peshawar	8.16	6.63	4.99
Shangla		1.36	1.74
Swabi	5.56	5.17	29.41
Swat	7.83	7.87	5.45
Upper Dir		28.57	3.37

0-2% (green); 2-4%(light green); 4-6% (Yellow); 6-10%(Orange); 10% and above (Red).

3.4.1 Rifampicin resistance by Xpert Assay type

Rifampicin resistance rates were disaggregated by assay type; the Xpert MTB/RIF assay reported a 4.3% Rifampicin resistance rate and Ultra reported a 5.2% Rifampicin resistance rate in 2019 (table 18)

Table 18 Trends in Rifampicin resistance rates by assay type, 2017-2019

Year	Xpert TB/RIF assay					Xpert MTB/RIF Ultra assay					
	MTB +ve	Rif Indeter-minate		Rif Resistant[1]		MTB+ inc. Trace +	Rif Indeter-minate (n)			Rif Resistant[2]	
							Trace	Other	All		
	(n)	(n)	(%)	(n)	(%)	(n)	(n)	(n)	(%)	(n)	(%)
2017	4,372	25	0.6	260	5.9						
2018	6,927	106	1.6	366	5.3						
2019	7,270	165	2.3	312	4.3	458	73	1	1.6	20	5.2

1.MTB/RIF Rifampicin resistance = MTB detected, Rifampicin resistance detected / (all MTB detected) x 100
2.Ultra Rifampicin resistance = Ultra MTB detected, Rifampicin resistance detected / (all Ultra MTB detected) x 100

Taking only MTB positive results into account (excluding trace for Ultra), Rifampicin resistance rates are shown by assay type. Overall, the Ultra assay consistently detected higher Rif rates compared with MTB/RIF assay, as expected due to increased sensitivity (Table 19).

Table19: Comparison of Rifampicin resistance by assay type between District

Year	Xpert TB/RIF assay					Xpert MTB/RIF Ultra assay					
	MTB +ve	Rif Indeter-minate		Rif Resistant[1]		MTB+ inc. Trace +	Rif Indeter-minate (n)			Rif Resistant[2]	
							Trace	Other	All		
	(n)	(n)	(%)	(n)	(%)	(n)	(n)	(n)	(%)	(n)	(%)
Khyber Pakhtunkhwa	6816	156	2.3	301	4.4	458	1	73	15.94	20	5.5
Abbottabad	454	9	2.0	11	2.4						
Bannu	541	11	2.0	13	2.4						
Battagram	88	2	2.3	6	6.8						
Buner	95		0.0	1	1.1						
Charsadda	144	2	1.4	7	4.9						
Chitral	48	1	2.1	3	6.3						
DI Khan	1,065	9	0.9	46	4.3						
Hangu	44	1	2.3	3	6.8						
Haripur	317	2	0.6	9	2.8						
Karak	73	2	2.7	7	9.6						
Kohat	66	1	1.5	1	1.5						
Lakki Marwat	159	5	3.1	2	1.3						
Lower Dir	205	1	0.5	6	2.9						
Malakand	80	4	5.0	1	1.3						
Mansehra	159	2	1.3	4	2.5						
Mardan	562	11	2.0	23	4.1	24	3		12.5		
Peshawar	2,641	83	3.1	130	4.9	434	70	1	16.1	20	5.5
Shangla	115	5	4.4	2	1.7						
Swabi	68		0.0	20	29.4						
Swat	257	13	5.1	14	5.4						
Upper Dir	89	1	1.1	3	3.4						

3.4.2 Rifampicin resistance by MTB semi-quantitative results

Trends in Rifampicin resistance rates per semi-quantitative result category are shown in Table 17 and disaggregated per Province for 2019 in Table 18. Overall in 2019, the majority of Rif resistant results were reported in the very low category for Xpert MTB/RIF and high category for Ultra assay.

A trend of declining proportion of RR is seen among high, medium to low MTB+ve, but an increase in proportion of RR is seen again in very low MTB Positive. The reason for this pattern is not clear and need further investigation and exclude possibility of false RR among VL-MTB.

Table 20 Trends in Rifampicin resistance by MTB semi-quantitative results, by assay type

Year			Xpert TB/RIF assay: MTB+ve results				Xpert TB/RIF Ultra assay: MTB+ve results			
			High	Medium	Low	V.low	High	Medium	Low	V.Low
2017	MTB +ve	(n)	1,122	1,849	990	411				
	Rifampicn	(n)	88	119	29	24				
	Resistant	(%)	7.8	6.4	2.9	5.8				
2018	MTB +ve	(n)	1,571	2,559	1,812	985				
	Rifampicn	(n)	101	123	74	68				
	Resistant	(%)	6.4	4.8	4.1	6.9				
2019	MTB +ve	(n)	1,582	2,734	1,788	1,166	128	63	150	44
	Rifampicn	(n)	94	95	49	74	11	6	3	
	Resistant	(%)	5.9	3.5	2.7	6.3	8.6	9.5	2	

Looking at stratified provincial data, similar pattern is seen across all provinces with spike in proportion of RR among VL-MTB positive with Xpert MTB/RIF assay.

Table 21: Rifampicin resistance by semi-quantitative result by assay type, per District 2019

District		Xpert TB/RIF assay: MTB positive semi-quantitative results				Xpert TB/RIF Ultra assay: MTB positive semi-quantitative results			
		High	Medium	Low	V.low	High	Medium	Low	V.Low
Abbottabad	RR/MTB-Det (n)	2/108	5/172	1/108	3/66				
	RR (%)	1.9	2.9	0.9	4.5				
Bannu	RR/MTB-Det (n)	4/112	3/250	2/117	4/62				
	RR (%)	3.6	1.2	1.7	6.5				
Battagram	RR/MTB-Det (n)	1/18	3/29	0/27	2/14				
	RR (%)	5.6	10.3		14.3				
Buner	RR/MTB-Det (n)	0/34	1/41	0/8	0/12				
	RR (%)		2.4						
Charsadda	RR/MTB-Det (n)	2/51	2/61	1/21	2/11				
	RR (%)	3.9	3.3	4.8	18.2				
Chitral	RR/MTB-Det (n)	0/7	1/21	2/11	0/9				
	RR (%)		4.8	18.2					
DI Khan	RR/MTB-Det (n)	16/245	13/449	6/259	11/112				
	RR (%)	6.5	2.9	2.3	9.8				
Hangu	RR/MTB-Det (n)	1/8	1/9	1/16	0/11				
	RR (%)	12.5	11.1	6.3					
Haripur	RR/MTB-Det (n)	5/99	2/114	1/71	1/33				
	RR (%)	5.1	1.8	1.4	3				
Karak	RR/MTB-Det (n)	0/9	4/28	1/19	2/17				
	RR (%)		14.3	5.3	11.8				
Kohat	RR/MTB-Det (n)	1/12	0/23	0/19	0/12				
	RR (%)	8.3							
Lakki Marwat	RR/MTB-Det (n)	0/38	2/64	0/32	0/25				
	RR (%)		3.1						
Lower Dir	RR/MTB-Det (n)	0/29	4/92	2/60	0/24				
	RR (%)		4.3	3.3					
Malakand	RR/MTB-Det (n)	0/23	0/35	0/12	1/10				
	RR (%)				10.0				
Mansehra	RR/MTB-Det (n)	0/30	1/71	2/42	1/16				
	RR (%)		1.4	4.8	6.3				
Mardan	RR/MTB-Det (n)	4/108	7/226	6/136	6/92	0/4	0/3	0/9	0/5
	RR (%)	3.7	3.1	4.4	6.5				
Peshawar	RR/MTB-Det (n)	35/541	39/898	20/680	36/522	11/124	6/60	3/141	0/39
	RR (%)	6.5	4.3	2.9	6.9	8.9	10.0	2.1	
Shangla	RR/MTB-Det (n)	1/10	0/17	0/42	1/46				
	RR (%)	10.0			2.2				
Swabi	RR/MTB-Det (n)	12/30	4/22	4/11	0/5				
	RR (%)	40.0	18.2	36.4					
Swat	RR/MTB-Det (n)	10/58	1/87	0/60	3/52				
	RR (%)	17.2	1.0		5.8				
Upper Dir	RR/MTB-Det (n)	0/12	2/25	0/37	1/15				
	RR (%)		8.0		6.7				

3.4.3 Probe mutation Surveillance

Monitoring probe mutations using the GeneXpert is still largely research-based but can provide important information on circulating strains in the country and if followed longitudinally, can provide some indication if/when the predominant strain changes.

Dropout mutations: Dropout mutations refer to those probes that do not bind at all.

Table 22 details trends (absolute numbers and percentages) of drop out mutations for probes A-E for Rifampicin resistant results from the Xpert MTB/RIF assay. We see that the Probe E has remained the most frequently occurring dropout mutation over the years in Khyber Pakhtunkhwa, accounting for over 65% of mutations seen and relates to mutations in 531 and 533 codons, which are the most frequently occurring RIF mutations worldwide. Of the 312 Rifampicin resistant specimens reported in 2019, there were 259 dropout mutations in total (Table 22), probe E accounted for 68.7% of mutations, followed by probes D, B, A, and C.

Table 22 Trends in probe dropouts in Rifampicin resistant cases tested by MTB/RIF assay, 2017 -2019

Year	Rifampicin resistant results (n)		Probe A	Probe B	Probe C	Probe D	Probe E	Total
2017	260	n	11	29	4	29	174	247
		%	4.5	11.7	1.6	11.7	70.4	100
2018	366	n	21	34	3	49	224	331
		%	6.3	10.3	0.9	14.8	67.7	100
2019	312	n	21	20	5	35	178	259
		%	8.1	7.7	1.9	13.5	68.7	100

This trend seems to be consistent across provinces, with Probe E being the most frequently occurring mutation (Table 23).

*Table 23 Drop out probe mutations by District for the Xpert MTB/RIF assay in 2019**

Year	MTB+	Rif resistant (n)		Probe A	Probe B	Probe C	Probe D	Probe E	Total
Khyber Pakhtunkhwa	6816	312	n	21	20	5	35	178	259
			%	6.7	6.4	1.6	11.2	57.0	83.0
Abbottabad	454	11	n	3	2	1	3	2	11
			%	27.3	18.2	9.1	27.3	18.2	100
Bannu	541	13	n		1		2	7	10
			%		10.0		20.0	70.0	100
Battagram	88	6	n		2			3	5
			%		40.0			60.0	100
Buner	95	1	n					1	1
			%					100	100
Charsadda	144	7	n		1		2	3	6
			%		16.7		33.3	50.0	100
Chitral	48	3	n					100	100
			%						
DI Khan	1,065	46	n	1	1	2	4	29	37
			%	2.7	2.7	5.4	10.8	78.4	100
Hangu	44	3	n	2	1			1	4
			%	50.0	25.0			25.0	100
Haripur	317	9	n		2			5	7
			%		28.6			71.4	100
Karak	73	7	n				3	3	6
			%				50.0	50.0	100
Kohat	66	1	n		1				1
			%		100				100
Lakki Marwat	159	2	n					2	2
			%					100	100
Lower Dir	205	6	n					1	1
			%					100	100
Malakand	80	1	n						0
			%						
Mansehra	159	4	n				1	1	2
			%				50.0	50.0	100
Mardan	562	23	n		2		6	11	19
			%		10.5		31.6	57.9	100
Peshawar	2,641	130	n	14	6	2	7	81	110
			%	12.7	5.5	1.8	6.4	73.6	100
Shangla	115	2	n				1		1
			%				100		100
Swabi	68	20	n		1		3	16	20
			%		5.0		15.0	80.0	100
Swat	257	14	n	1			1	10	12
			%	8.3			8.3	83.3	100
Upper Dir	89	3	n				2	1	3
			%				66.7	33.3	100

*Ultra results are not included

4 Quality

4.1 Invalid rates

Invalid results are due to internal control failures which may be caused by the presence of inhibitors in the specimen, which subsequently prevent PCR (e.g. pus, blood, food particles, tobacco). According to global benchmarks, the maximum allowable invalid rate is <2% but according to GLI standards, invalid rates should be below 1%.

Khyber Pakhtunkhwa invalid rates have averaged 2.3% over the last three years (2017-2019) but are highly variable and spiked in 2018 Q1 (Figure 12). In 2019, invalid rates were reported at 0.8% (n=273/33,568), well below the recommended allowable threshold.

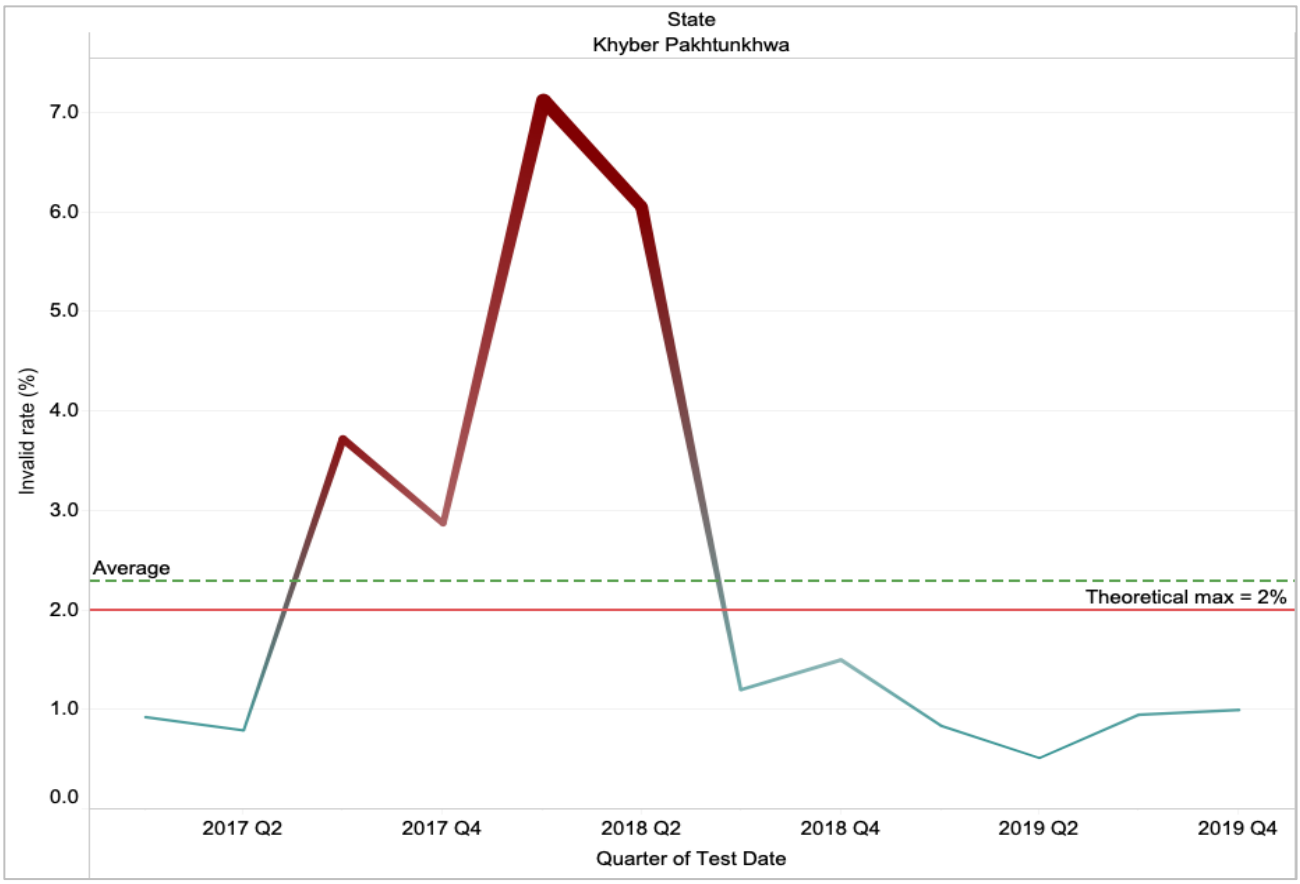


Figure 12 Khyber Pakhtunkhwa invalid rate reporting from 2017 – 2019 in relation to the global benchmark of <2%

4.2 'No result' rates

'No results' are due to the GeneXpert not being able to complete testing or testing is interrupted either due to the test being manually stopped or due to power failure in the case of a PC. According to global benchmarks and GLI standards, the maximum allowable 'no result' rate is <1%. 'No results' increase program costs due to wasted cartridges and the need for repeat testing (delaying diagnosis).

Khyber Pakhtunkhwa reported an average 'no result' rate of 0.8% over the last three years assessed (Figure 13), well below the allowable average. In 2019 the average 'no result' rate stood at 1.1% (n=366/33,568), slightly above the recommended threshold.

To lower 'no result' rates, sites in Khyber Pakhtunkhwa should be prioritized for battery/UPS backup installations to ensure they do not lose tests due to power failure. If UPS's are already in place, these need to be serviced and/or batteries replaced.

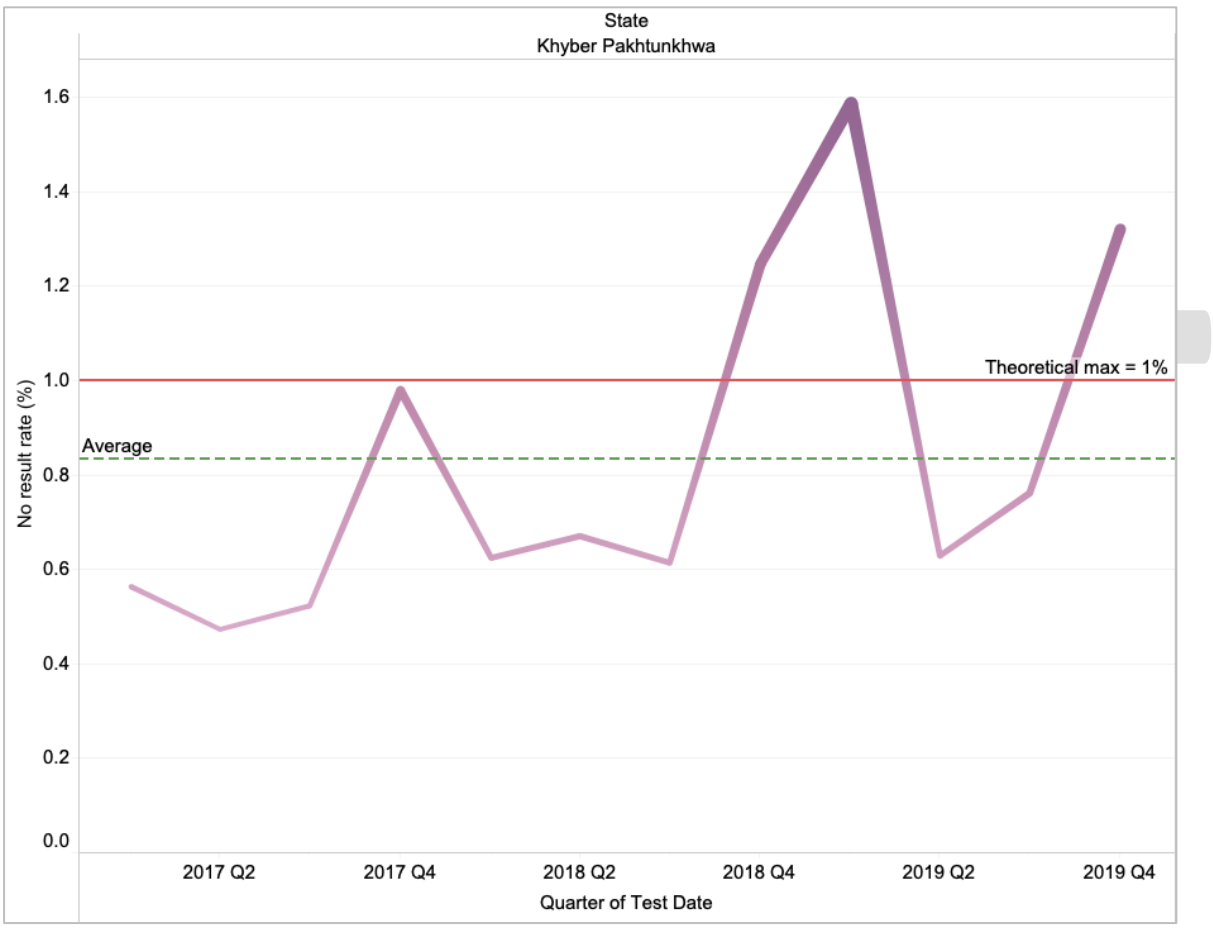


Figure 13 Khyber Pakhtunkhwa 'no result' rate reporting from 2017 – 2019 in relation to the global benchmark of <1%

4.3 Error rates

The WHO-recommended upper allowable benchmark for error reporting is 5% (GLI considers <3% acceptable). Khyber Pakhtunkhwa error rate has averaged 7.2% over the last three years, 2017-2019 (Figure 14). Of the total 33,568 Xpert results reported in 2019, 2,187 error results were reported, giving an overall error rate of 6.5%; the Ultra error rate was 3.0% (72/2,377) and MTB/RIF error rate was 6.8% (2,115/31,191). The cost of error reporting in 2019 was $21,826.

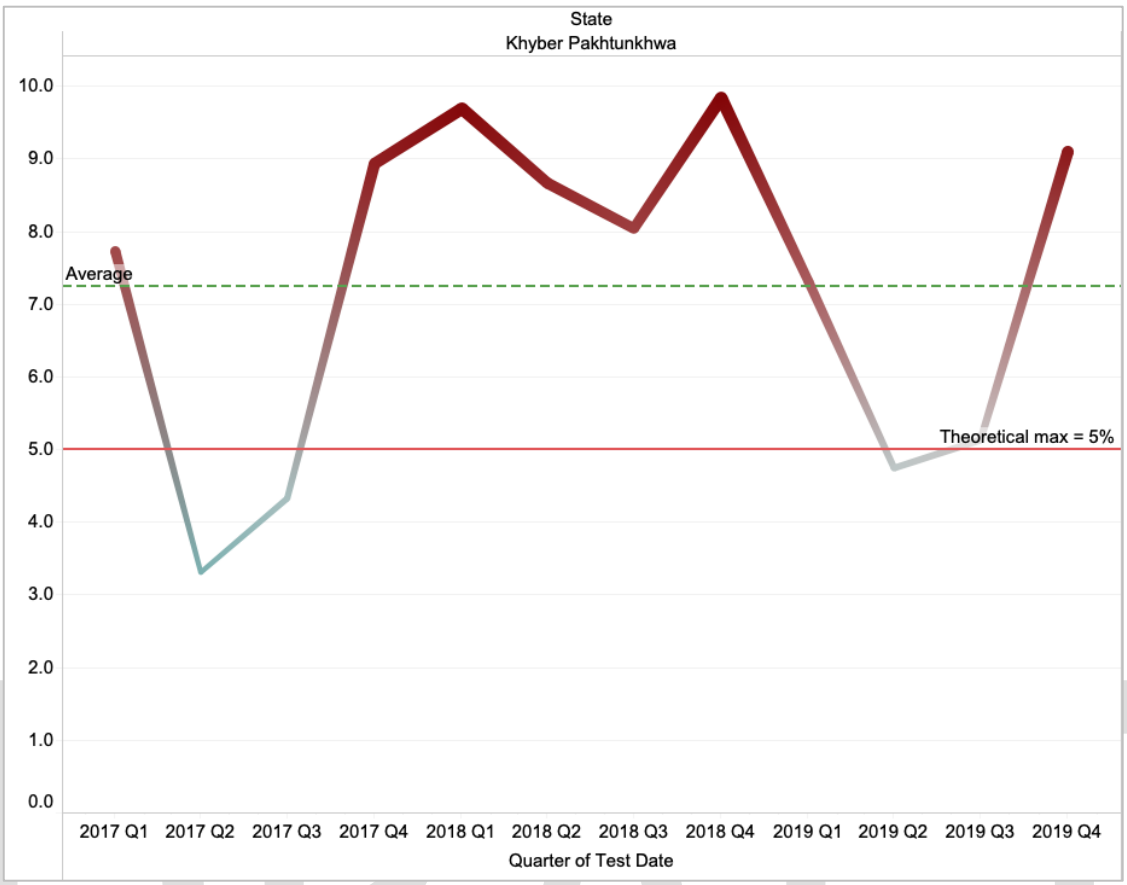


Figure 14 Khyber Pakhtunkhwa error rates from 2017 – 2019 in relation to the global benchmark of <5%

4.3.1 Error code categorization

The Cepheid GeneXpert provides an error code with every error result reported. In the Khyber Pakhtunkhwa Province, the majority of error codes in 2019 were 5007 (42.4%; Post-run analysis error/Probe check failed), followed by 'Null' (23.3%) meaning no error code was available from the GeneXpert and thus could not be analyzed (Figure 15).

Generally speaking, error codes and corresponding Cepheid descriptions are very difficult for laboratory staff to understand and are therefore difficult to formulate corrective actions against. In an attempt to improve the understanding of what error codes mean, SystemOne have categorized them according to their suspected potential sources (this is not an official Cepheid categorization but is based on Cepheid's troubleshooting guidelines, published literature and GLI guidelines).

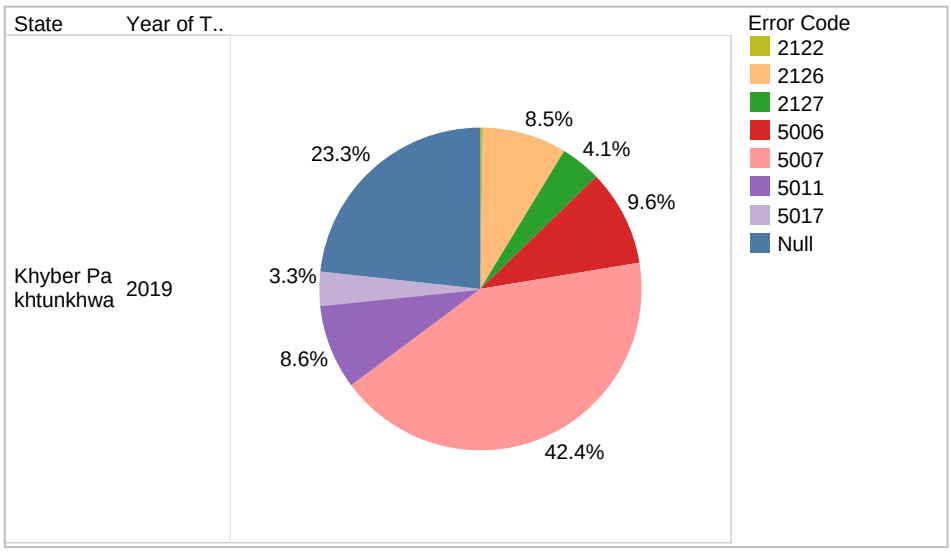


Figure 15 Proportion of Error codes reported in 2019

Using these error code categorizations, we see that error 5007 generally falls into the category of a user-related error. In 2019, user errors (including 5006 errors) accounted for 52.1% of all errors seen (Figure 16) and are caused by either incorrect specimen volume added to the cartridge or incorrect specimen processing (specimen not liquefied, particles present, air bubbles introduced). These types of errors are generally indicative of the need for retraining or refresher training of laboratory staff on correct Xpert specimen processing and testing.

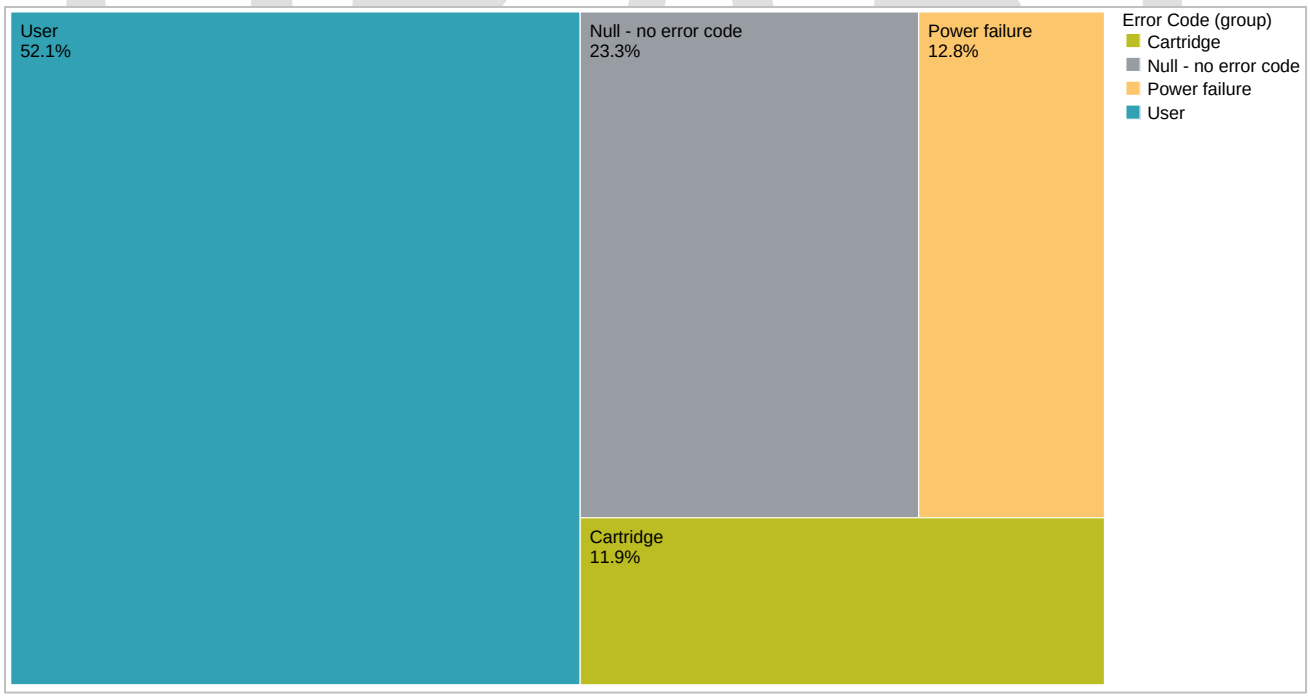


Figure 16 Error code categorization indicates that the majority of errors were user-related in 2019

However, these 5006/5007 errors could also indicate the need for refresher training of clinical staff on how to collect appropriate sputum specimens as the samples being sent to the labs for testing may not be of good quality or of appropriate volume but are being tested anyway. Lab SOP's should be in place for rejection of the inadequate volume and low-quality specimens.

Error codes 2126 are considered power-related and accounted for 12.8% of errors reported (includes error 2122, 2127). They typically occur due to power failure and are caused by problems with the main power. These errors are generally easy to rectify, and sites should be checked to ensure the Ethernet cable is plugged in properly between the PC and GeneXpert, or the communication cable is plugged in properly or that if a UPS is available, these should be serviced, upgraded or repaired.

Cartridge-related errors (mostly 5011, 5017) accounted for 11.9% of errors in Khyber Pakhtunkhwa province and are usually indicative of cartridge quality issues (loss of tube pressure because the cartridge is not air-tight or cartridge valve is not working, or due to inappropriate storage or transport of cartridges. If these errors occur consistently on the same module, they may indicate module failure and thus should be monitored.