12th July, 2020

OPERATION PLAN FOR OPTIMAL USE OF XPERT XPRESS SARS COV-2 TESTING FOR COVID-19, NEPAL

VERSION 1 – JULY 2020

NATIONAL TB CONTROL CENTER
In Collaboration with Nationl Public Health Laboratory
Department of Health Services
Ministory of Health and Population, Nepal

Contents

1. INTRODUCTION -Xpert Xpress SARS Cov-2 testing

1.1. Background

The Xpert Xpress SARS-CoV-2 test is a rapid, real-time RT-PCR test intended for the qualitative detection of nucleic acid from the SARS-CoV-2 in either nasopharyngeal swab and/or nasal wash/ aspirate specimens collected from individuals suspected of COVID-19 by their healthcare provider. The Xpert Xpress SARS-CoV-2 test is a molecular in vitro diagnostic test that aids in the detection and diagnosis of SARS-CoV-2 and is based on widely used nucleic acid amplification technology.

The Xpert Xpress SARS-CoV-2 test contains primers and probes and internal controls used in RT- PCR for the in vitro qualitative detection of SARS-CoV-2 RNA in nasopharyngeal swab specimens

Testing of nasopharyngeal swab specimens using the Xpert Xpress SARS-CoV-2 test run on the GeneXpert System is authorized to be used in a laboratory setting with biosafety cabinet-Class II facility.

The test detects SARS-CoV-2 RNA in the specimens. The SARS-CoV-2 RNA is generally detectable in nasopharyngeal swab specimens and/or nasal wash/ aspirate specimens during the acute phase of infection. Positive results are indicative of active infection with SARS-CoV-2; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status.

Testing with the Xpert Xpress SARS-CoV-2 test is intended for use by trained operators who are proficient in performing tests using GeneXpert Dx systems.

The Xpert Xpress SARS COV-2 tests for diagnosis of COVID-19 has high sensitivity and specificity and has been approved on 23rd June 2020 by WHO under Emergency Use Listing[1]

1.2. Specimen Collection, Transport, and Storage

Proper specimen collection, storage, and transport are critical to the performance of this test. Inadequate specimen collection, improper specimen handling, and/or transport may yield a false result. Follow National Public Health Lab guidelines for the swab collection and transport procedure. Nasopharyngeal specimens can be stored at room temperature (15–30 °C) for up to 8 hours and refrigerated (2–8 °C) up to seven days until testing is performed on the GeneXpert System.

1.3. Testing and turnaround time

Samples are processed in the Bio-safety cabinet and tested in currently available Genexpert machines in the country (currently used by TB program for the diagnosis of TB). The test can provide rapid detection of the current pandemic coronavirus SARS-CoV-2 in as soon as 30

[1] https://www.who.int/diagnostics_laboratory/200625_eul_sars_cov2_product_list.pdf

minutes for positive results, and 45 minutes for negative results, with less than a minute of hands-on time to prepare the sample.

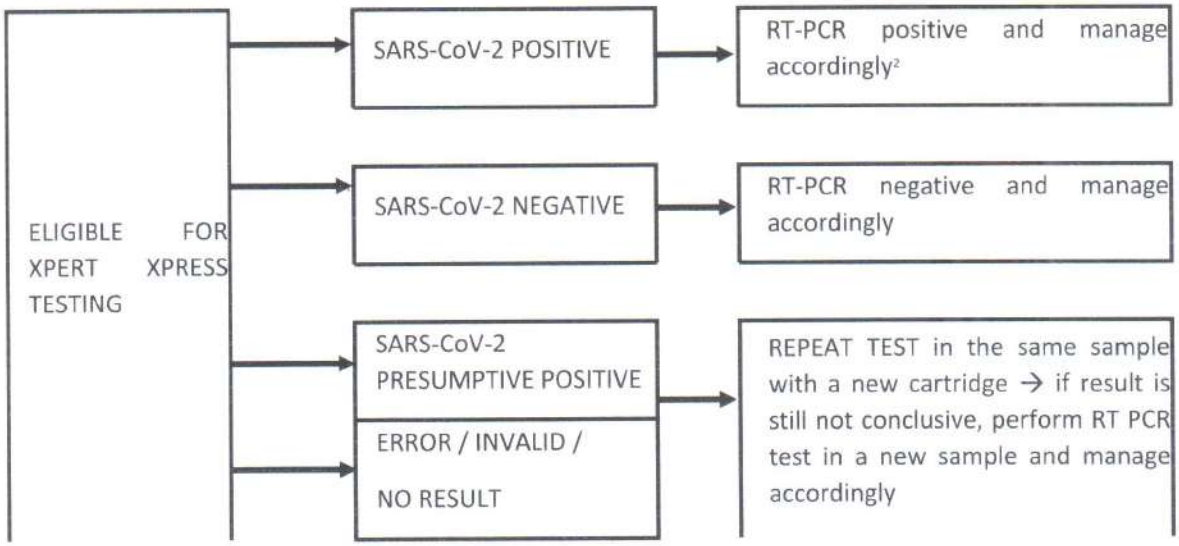
1.4. Interpretation of Results

The results are interpreted automatically by the GeneXpert System and are clearly shown in the **View Results** window. The Xpert Xpress SARS-CoV-2 test provides test results based on the detection of two gene targets according to the algorithms shown in (Table 1) and the details of a diagnostic algorithm for testing and interpretation are given in (Figure 1)

TABLE 1: XPERT XPRESS SARS-COV-2 POSSIBLE RESULTS

Result Text	N2	E	SPC
SARS-CoV-2 POSITIVE	+	+	+/-
SARS-CoV-2 POSITIVE	+	-	+/-
SARS-CoV-2 PRESUMPTIVE POSITIVE	-	+	+/-
SARS-CoV-2 NEGATIVE	-	-	+
NO RESULT – REPEAT TEST	-	-	-

FIGURE 1: TESTING ALGORITHM



² As per Interim pocket book of Clinical Management of COVID-19 in Healthcare Setting, Page no. 4, https://drive.google.com/file/d/1aa4R7r7AgwY83PjDqw_BwlsWk4p6mTkZ/view

2. Eligibility criteria for patients

The eligible population for testing with Xpert Xpress SARS Cov-2 testing is from within the group of eligible for testing with RT-PCR as per the National Testing Guidelines for COVID-19 by MoHP, but those **who need results more urgently**, given the very short turnaround time for this test and given that the tests could be done even for individual samples.

TABLE 2: ELIGIBILITY CRITERIA FOR XPERT XPRESS SARS COV-2 TESTING

Sites	Eligible Population for Xpert Xpress testing	Rationale

At COVID clinics	- Suspected cases of COVID-19 with co-morbidities.
	  ○ Chronic Kidney disease
	  ○ Chronic heart disease
	  ○ Immunosuppressed conditions
	- Tuberculosis patient
	- Diabetics
	- PLHIV
	- Severe Acute Malnourished
	- Undergoing chemotherapy or other immunosuppression therapy
	- Suspected cases 3of COVID-19 with Severe Acute Respiratory Illness (SARI) requiring hospitalization.
	- Suspected cases of COVID-19, whose age is above 60 years
	- Suspected cases of COVID-19 who is pregnant / or in postpartum period
		- To ensure early management and infection prevention and reduce death.
		- Among suspects, with comorbidity, are at higher risk of developing COVID-19 and severe progression of disease including death.

At hospital Emergency	- Any patient COVID 19 suspected with:
	  ○ SARI cases requiring oxygen support and ICU admissions.
	  ○ Presenting for management of snake bite / OP poisoning / Burn Cases and other life threatening conditions
	  ○ Requiring urgent life saving surgery like Severe Head Injuries / Acute intestinal perforation / Emergency C/S for obstructed pregnancy / severe bleeding
		- To ensure early management and infection prevention and reduce death.
		- Snake bites are very common in Nepal and needs management and/ or admission. Ruling out COVID is important for proper management and isolation in such and similar other emergency conditions as well.

In DOTS center, DR TB treatment centers or referral centers and other TB service outlets	- Among TB patients suspected of being Co-infected with SARS Cov-2 infection. - Among TB patients with sudden clinical deterioration while on TB Tx, where other causes have been ruled out. - All newly diagnosed DR TB cases, where sample collection and transportation to Xpert Xpress testing sites are possible.	- Both TB and COVID-19 have similar symptoms. - TB patients are at high risk of being infected by SARS Cov-2, with increased severity of disease. - New DR TB patients mostly managed at DR TB centers and admitted, where diagnosing SARS Cov-2 is also important for proper isolation and management.
To rule out SARS Cov-2 infection among COVID-19 suspects who died	- Among COVID-19 suspects who died, where there is urgent need to rule of SARS Cov-2 infection, but not diagnosed prior.	- Cultural, legal sensitivity and urgency

[3] Suspected COVID Cases – as per the definition of Annex9.1.2andAnnex9.1.1

Note: testing for SARS COV-2 using Xpret Xpress to be done upon written recommendation by on-duty medical doctor.

3. Selection of sites

3.1. Number of Xpert Xpress SARS Cov-2 cartridges allocated per province.

Currently, there are around 75 Genexpert sites in the country. Out of them, 18 sites have access to the use of a bio-safety cabinet or where a bio-safety cabinet is planned for immediate installment.

The principle direction is to provide at-least 1 such testing facilities per province and expand in the future as per the situation. Based on the burden [4] of current COVID-19 and burden of TB in the different provinces, priority setting was done and no. of cartridges per labs per province were estimated.

TABLE 3: XPERT XPRESS SARS COV-2 CARTRIDGES ALLOCATED PER PROVINCE

Province	COVID 19 burden[5]		TB burden[6]	Distribution weights in percent[4]	No. of Xpert Xpress SARS Cov-2 cartridges allocated for each site
	Case notified n (Col %)	Death among COVID-19 positive n (Col %)	DS TB case notified n (Col %)		
Province 1	534 (5%)	0 (0.0%)	4356 (13.6%)	6%	300
Province 2	3500 (30%)	3 (10.7%)	6844 (21.4%)	19%	1100
Bagmati	364 (3%)	5 (17.9%)	7714 (24.1%)	13%	600
Gandaki	834 (7%)	2 (7.1%)	226 (7.1%)	9%	400
Province 5	3300 (28%)	10 (35.7%)	6347 (19.8%)	23%	1100
Karnali	1424 (12%)	4 (14.3%)	1374 (4.3%)	14%	700
Sudur-Paschim	1799 (15%)	4 (14.3%)	3148 (9.8%)	16%	800
Total	11755 (100%)	28 (100%)	32043 (100%)	100%	5000

3.2. Selected sites for Xpert Xpress SARS Cov-2 testing for COVID-19

[4] Burden calculation using – Proportion of COVID cases, Deaths among COVID-19 cases and burden of TB . The details is in Annex 9.1.3

[5] No. of cases reported in cumulative numbers till 3rd July 2020, HEOC situation report.

[6] Total no of all forms of TB cases notified to TB program, NTP annual TB report 2018

Based on the availability of GeneXpert machines, availability of biosafety cabinet, feasibility, and access following sites were selected from each province for testing for Xpert Xpress SARS Cov-2 testing for COVID-19.

THE FUNCTIONING OF XPERT XPRESS TESTING SHOULD NOT INTERRUPT THE REGULAR FUNCTIONING OF TB TESTING, WHICH SHOULD RUN NOT LESS THAN 2 CYCLES PER DAY FOR MTB RIF TESTING

TABLE 4: FOR XPERT XPRESS SARS COV-2 TESTING

Province	Proposed sites for Xpert SARS 2 test	No. of Xpert Xpress SARS Cov-2 cartridges allocated for each site
Province 1	B. P. Koirala Institute of Health Sciences, Dharan	300
Province 2	Narayani Hospital, Birjung	1100
Bagmati	- Sukraraj Tropical and Infectious Disease Hospital, Teku	300
	- TUTH, Maharajung	300
Gandaki	Provincial TB Center, Pokhara	400
Province 5	- Bheri Hospital , Nepaljung	550
	- Lumbini Provincial Hospital, Butwal	550
Karnali	Provincial Hospital, Surkhet	700
Sudur-Paschim	Dadeldhura Hosptial	800
Total	9 sites	5000

4. Logistic management system

The supply of all the logistics required with regards to the functioning of GeneXpert machines e.g.; Xpert Xpress SARS Cov-2 cartridges, will be managed and supplied to the testing sites by DoHS. The catrideges will be sent in 3 cycles as per the allocation.

The expiry of the current stock of catridges are by 16th May 2021.

VTM, PPEs and other required logistics will be supported by DoHS

The other logistical supply to support the functioning of the machines (e.g. uninterrupted power supply and back-up, Air condition, adequate safety, and workspace, etc.) to be the same as before and will be the responsibility of the testing center.

Software to operate Xpert Xpress SARS Cov-2 will be installed in the machines of the identified sites by NTCC.

5. Training and capacity development

Training on detailed procedures required for handling and processing of the samples will be carried out by NTCC virtually at all sites in collaboration with NPHL and also onsite if necessary

6. Monitoring and evaluation and data management

The reports of the test will be sent as per the reports send for RT-PCR, i.e. from testing sites to EDCD and HEOC with a copy to NPHL and NTCC daily. An additional component regarding TB history to be added to the existing reporting template.

7. Quality assurance

The batch of the Xpert Xpress SARS-COV-2 cartridges will be verified at the national level as well as in the testing sites. NTCC and NPHL will jointly conduct the kit verification and quality assurance of Xpert Xpress SARS-COV-2 testing.

7.1. Verification of kits at National level

Either external reference materials (external QC materials) or known positive and negative patient samples can be used for kit verification purposes.

For determining the accuracy of the Xpert® Xpress SARS-CoV-2 test, at least 10 known SARS-CoV-2 positive and 10 SARS-CoV-2 negative patient samples (total 20 samples) was used. The samples which have been previously confirmed by other RT-PCR platforms was used. To determine the precision of the test, triplicates of one strongly positive sample, one moderately positive sample, and one negative sample will be tested i.e. the same sample was tested three times.

Each new batch/ lot of the Xpert Xpress SARS-CoV-2 cartridges arriving in the country in the future will be verified using the confirmed SARS-CoV-2 positive and SARS-CoV-2 negative samples as stated above or using the commercially available standard positive and negative reference materials.

At central level, NTCC and NPHL has jointly conducted the kit verification of Xpert Xpress SARS-COV-2 testing on **9th July 2020 , with agreement rates of 100% and reproducibility of 100% in reference to the RT-PCR.**

7.2. Verification at testing laboratories

Each laboratory designated to perform SARS-CoV-2 testing using the Xpert® Xpress SARS-CoV-2 cartridges will receive one confirmed positive sample and one confirmed negative sample along with the first lot of the cartridges.

The laboratory will test these samples using the provided cartridges and communicate the results back to NPHL and NTCC in the provided format.

After confirmation of successful testing, the designated laboratory will start testing the patient specimens and provide SARS-CoV-2 testing services according to the predetermined criteria.

7.3. External Quality Assessment

Each laboratory designated to perform SARS-CoV-2 testing using the Xpert Xpress SARS-CoV-2 cartridges will participate in the External Quality Assessment (EQA) of SARS-CoV-2 testing organized by the NPHL.

7.4. Internal Quality Control:

Each Xpert cartridge is self- contained test device with internal controls that enable the system to detect specific failure modes within the cartridge. Each cartridge includes a Sample Processing Control (SPC) and Probe Check Control (PCC) for the purpose.

8. Timelines

TABLE 5: TENTATIVE TIMELINES

Date		Activity	Responsibility
Start date	**completed by**		
	Sunday, June 7, 2020	All draft documents ready	NTCC and NPHL
Tuesday, July 7, 2020	Friday, July 10, 2020	Primary Verfication and report	at NTCC (with support from NPHL)
	3rd week of July, 2020	Finalization and endorsement of the interim operation plan	DoHS
3rd week of July, 2020	3rd week of July, 2020	Software installation at testing sites	at selected sites by NTCC (by distance)
3rd week of July, 2020	3rd week of July, 2020	Identification of HR of the selected sites	DoHS
4th week of July, 2020	4th week of July, 2020	Capacity building of the identified HR at the selected sites	NTCC and NPHL (by distance, vritual training)
4th week of July, 2020	4th week of July, 2020	Supply of cartridges at the testing sites	DoHS
		Module replacement at testing sites, where needed	NTCC and NPHL
	4th week of July, 2020	Start of actual testing at all sites	Selected sites

9. ANNEX

9.1.1. DEFINITION OF CONTACT:

Definition of "Contacts" are as per the definition in As per Interim pocket book of Clinical Management of COVID-19 in Healthcare Setting, Page no. 3, https://drive.google.com/file/d/1aa4R7r7AgwY83PjDqw_BwlsWk4p6mTkZ/view and is subject to change if the above mentioned guidelines changes.

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;

OR

2. Direct physical contact with a probable or confirmed case;

OR

3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment;

OR

4. Other situations as indicated by local risk assessments. Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

9.1.2. DEFINITION OF SUSPECTED COVID CASES:

Definition of "Contacts" are as per the definition in As per Interim pocket book of Clinical Management of COVID-19 in Healthcare Setting, Page no. 2, https://drive.google.com/file/d/1aa4R7r7AgwY83PjDqw_BwlsWk4p6mTkZ/view and is subject to change if the above mentioned guidelines changes.

The criteria for treating someone as a suspected case is subject to change depending on the dynamics of the epidemic an d prevalence of cases inside and outside the country. Adapted from the most recent World Health Organization (WHO) criteria, with modifications, case definitions for COVID-19 for clinical purposes at hospitals will be as follows:

SUSPECTED CASE

A. A patient with fever or sign/symptoms of respiratory distress (cough or shortness of breath), AND a history of travel to or residence or close contact with a traveler from a location reporting community transmission of COVID-19 disease during 14 days prior to symptom onset;

   OR

B. A patient with fever or sign/symptoms of respiratory distress (cough or shortness of breath), AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; (see definition of contact below)

   OR

C. A patient requiring hospitalization for Severe Acute Respiratory Illness (SARI)

   OR

D. A healthcare worker who provides direct care to patients and has developed fever OR cough OR shortness of breath

   OR

E. A patient with fever or sign/symptoms of respiratory distress (cough or shortness of breath) without alternative explanation/diagnosis to the person's symptoms/signs? (such as congestive heart failure exacerbation, scrub typhus, malaria, Urinary Tract Infection, etc)

9.1.3. Weightage calculation for distribution of Xpert Xpress SARS Cov-2 cartirdges

Province	Total Population (CBS 2011)	Pop %	COVID 19 situation				TB situation		
			Case	%	Death	%	DS TB	%	DR TB
Province 1	4535000	17%	674	4%	0	0.0	4356	13.6	62
Province 2	5404000	20%	3996	26%	4	14.3	6844	21.4	60
Bagmati	5529000	21%	507	3%	5	17.9	7714	24.1	89
Gandaki	2404000	9%	1118	7%	3	10.7	2260	7.1	36
Province 5	4449272	17%	3891	25%	10	35.7	6347	19.8	95
Karnali	1570000	6%	1539	10%	4	14.3	1374	4.3	0
Sudur Paschim	2553000	10%	3535	23%	6	21.4	3148	9.8	50
Total	26444272		15260		32		32043		392

Criteria for priority		
Burden of COVID 19 in terms of cases reported	50%	Highest burden recieves 7 where are least will receive 1
Number of death reported with COVID-19	40%	
Burden of TB notification	10%	

Province	Burden of COVID 19 in terms of cases reported	Number of death reported with COVID-19	Burden of TB notification	Total	%	Cartridge #	Absolute #
Province 1	2	1	4	1.8	0.1	321	300
Province 2	7	3.5	6	5.5	0.2	982	1000
Bagmati	1	5	7	3.2	0.1	571	700
Gandaki	3	2	2	2.5	0.1	446	400
Province 5	6	7	5	6.3	0.2	1125	1100
Karnali	4	3.5	1	3.5	0.1	625	600
Sudur Paschim	5	6	3	5.2	0.2	929	900
				28		5000	5000