Approaches and policies for COVID-19 mitigation

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When a new infection arrives:
what do we need to do immediately?

Detection and Diagnosis:
accessible, feasible, high throughput,… methods

Controlling the spread:
technical, behavioral, governmental,… interventions

Associated issues:
new normals, information/policy,… ideas

Considering the scientific and technical context, academic organizations must take initiative, innovate and contribute.

Communicating the unknown

Keeping politicians, policymakers, academic peers, media & general public informed

In times of uncertainty, it becomes extremely important for people to have credible sources of information.

Scientists hold an extremely important role during the crisis, and hence it has been more important than ever to be accessible.

Also new information is coming out every few days. So, it is important to have a continued discussion with media, policymakers and public to give them the best suggestions for that time.

Multiple roles in fight against COVID-19

-Training, Testing, Validation center, National repository (virus and patient samples)

- Culturing the virus in lab to enable: Testing/screening of drugs/validation of devices

- Developing diagnostic, protocols, SOPs, Genome dynamics & biology of the virus

CSIR Labs Supporting COVID-19 Testing

Testing of Covid-19 Patient Samples

>5,00,000 Samples
Testing at 13 CSIR labs
Jammu to Jorhat
Chennai to Chandigarh

Supporting State Governments

Testing center at Ladakh

Training of Human Resource for Testing

~200 persons trained Government hospitals, Research institutes Universities Distribution of SOPs

Innovations in Diagnostics for SARS-CoV-2

Desirable Parameters

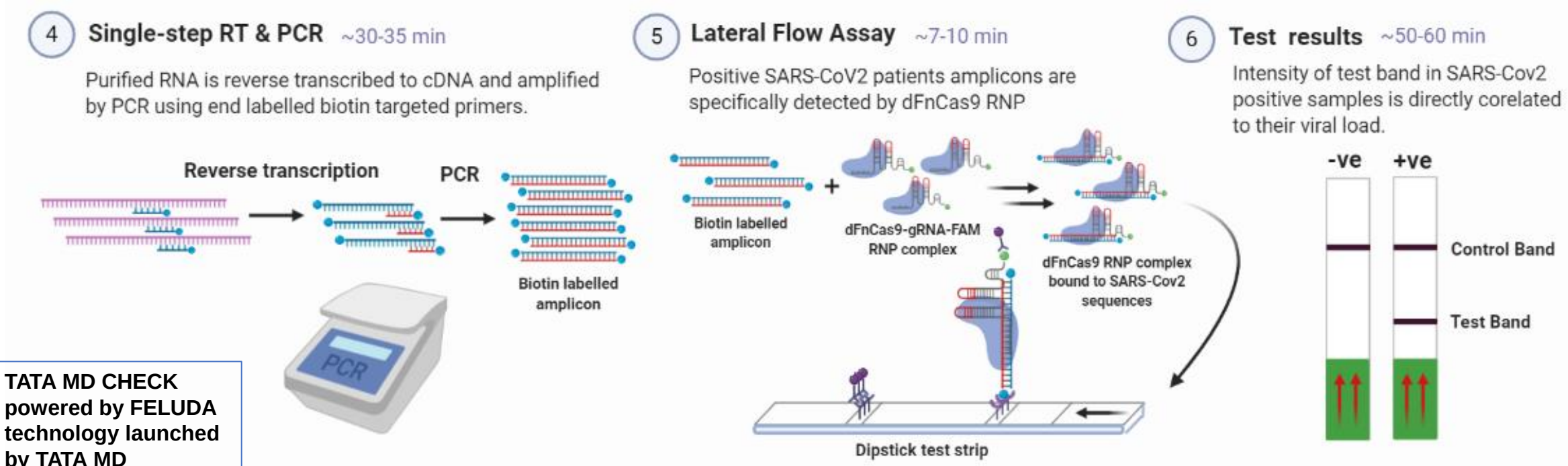
- Point of Care
- High Throughput
- Reliable
- Affordable
- Speed
- Ease

CSIR Possesses Spectrum of Expertise to Address any National Emergency

- **Established sequencing and bioinformatics pipelines**
- **Expertise in diagnostics**
- **Design and engineering expertise for medical devices**
- **Capacity and capability for R&D**

CRISPR Based Diagnostics, FELUDA: How and Why?

- In 2019, CSIR-IGIB developed a new highly specific FnCas9. A sickle cell disease test was developed with a patented platform technology (**FELUDA, F**ncas9 **E**ditor **L**inked **U**niform **D**etection **A**ssay)
- For COVID-19 pandemic, it was decided to also create a SARS-CoV2 diagnostic
- After one step reverse transcription PCR, a CRISPR (FnCas9) recognizes specific nucleic acid sequence and produces paper strip band. Because of inbuilt simple PCR and CRISPR – **high sensitivity and specificity comparable to qRT-PCR**
- After sample collection, transport, and RNA extraction (1-3), the steps are:



TATA MD CHECK powered by FELUDA technology launched by TATA MD

Dry Swab-Direct RT-PCR Diagnostic Method

- **RNA Extraction Free and Direct RT-PCR**; **should be used with ICMR approved kit for RTqPCR.**
- No new equipment or reagents needed
- With the current manpower and funds up to **3 times more testing can be done with this method immediately**

INDEPENDENT VALIDATION in comparison to Gold Standard RT-PCR

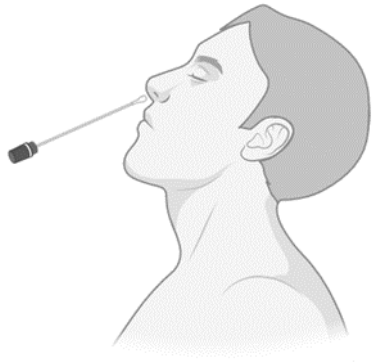
1. CDFD, Hyderabad
2. IISER, Berhampur
3. NEERI, Nagpur
4. IGGMCH, Nagpur
5. MAFSU, Nagpur
6. GenePath, Pune
7. AIIMS, Nagpur
8. GMCH, Nagpur

Globally Accepted Method

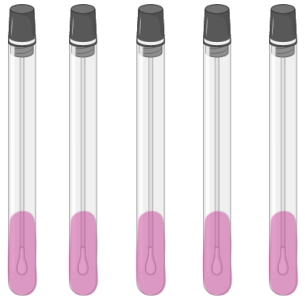
- *Easing diagnosis & pushing the detection limits of SARS-CoV-2; **Biol Methods Protoc**. 2020 Aug 20;5(1):bpaa017*
- *Massive and rapid COVID-19 testing is feasible by extraction-free SARS-CoV-2 RT-PCR; **Nat Commun**. 2020 Sep 23;11(1):4812.*
- *Direct RT-qPCR detection of SARS-CoV-2 RNA from patient naso-pharyngeal swabs without an RNA extraction step; **PLoS Biol**; 2020, Oct 2: 18(10): e3000896*
- *Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing: **N Engl J Med**. 2020 Oct 8;383(15):1492-1494.*

Saliva based diagnostics without RNA isolation step have received FDA approval

Limitations associated with the standard method



Swab collection



Swabs in Viral Transport Media (VTM)

Potentially hazardous
Risk of leakage

Pack and transport to testing centre

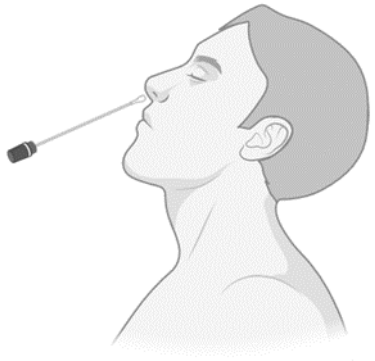
Unpacking and cataloguing

RNA isolation

Expensive
Laborious
Time-consuming

RT-PCR and reporting

Easing the diagnosis using the dry-swab-based method



Swab collection and transport in dry condition

No risk of leakage

↓

Unpacking and cataloguing

↓

No RNA isolation

Elution of RNA using **TE-P buffer**

Add 400 µl TE-P buffer to the dry-swabs and incubate at room temp. for 30’

↓

Heat an aliquot of the buffer extract at 98°C for 6’

↓

Direct RT-PCR and reporting

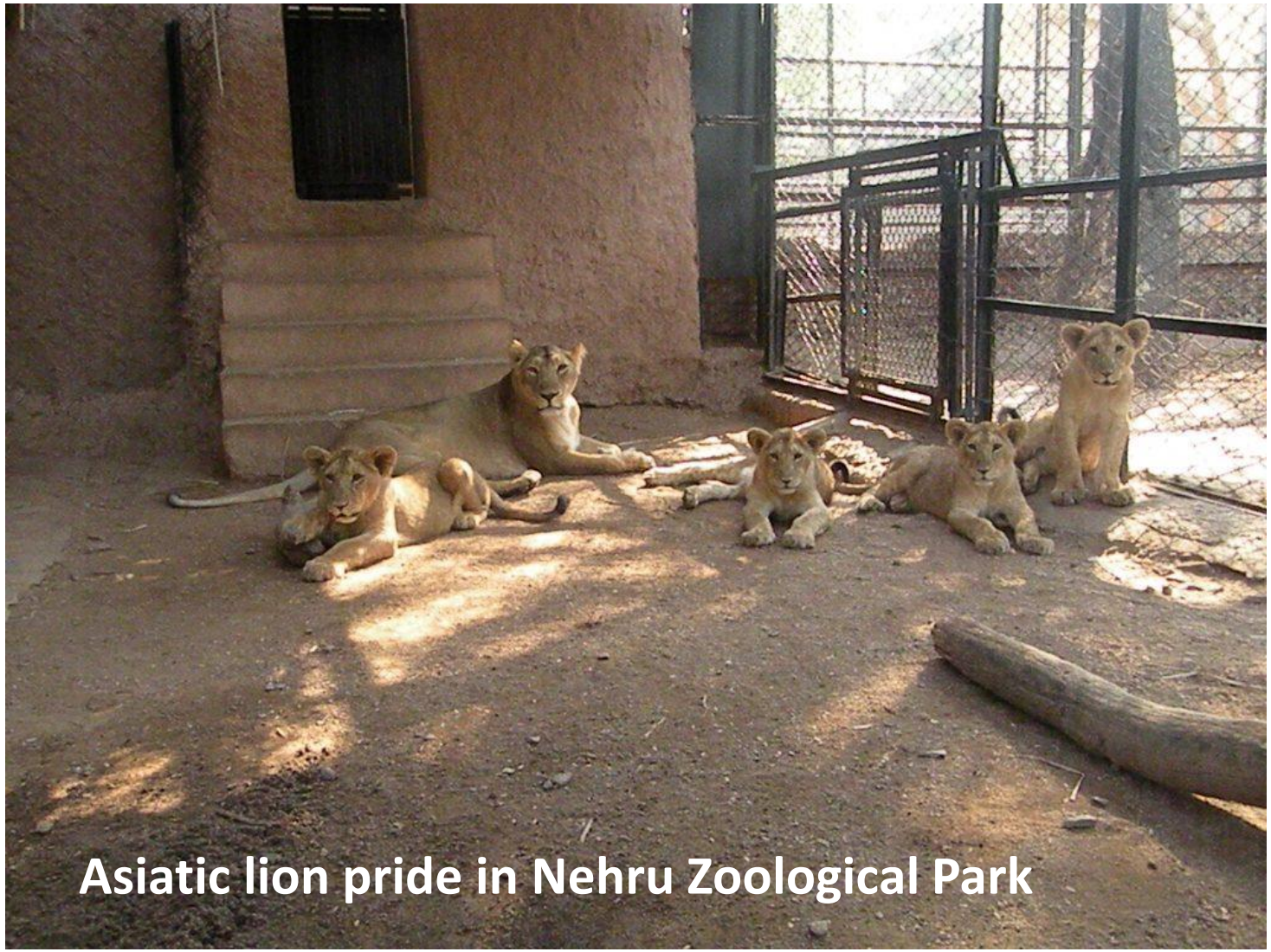
Advantages of the dry-swab-based method

- ✓ **No VTM** (increased biosafety)
- ✓ **No RNA isolation step** (less laborious)

- ✓ **50% reduction in time consumption**
- ✓ **50% reduction in manpower requirement**
- ✓ **40% reduction in cost incurred**

- ✓ **With existing resources, the capacity of testing could be increased 3-fold**

SARS CoV-2 testing in zoo and wild samles



Asiatic lion pride in Nehru Zoological Park

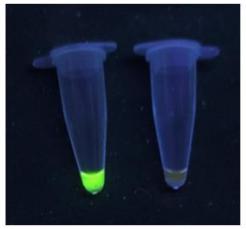
CZA approached CSIR-CCMB

sample collection, testing

Hyderabad Zoo is the coordinating conservation breeding of Asiatic lions in the country

RT-LAMP PCR based SARS-CoV-2 Detection

- **Rs. 100 – Rs. 200 per test**
- **Low set-up cost**
- **No sophisticated instrumentation required (Rs 30,000 vs 10-25 Lakhs)**



Color reaction confirming presence of Viral RNA

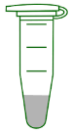
CSIR-IIIM

Reliance Industries Limited

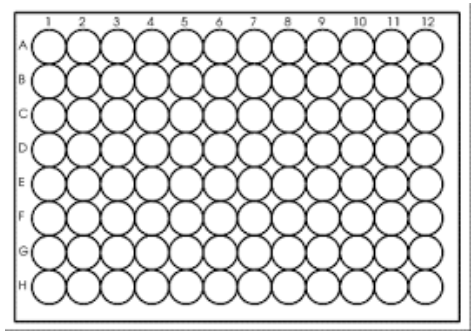
Date	Development
16.06 20	Request to ICMR for validation of **Two Step RT-LAMP Kit-V1.0**
17.06.20	Directives from ICMR to submit kit at NIV, Pune
26.06.20	Submission of kit to NIV, Pune
26.06.20	Kit returned to RIL personnel from NIV, Pune
27.06.20	Letter to ICMR for directives on submission on RT-LAMP kit-V1.0
16.06.20-15.07.20	Development & optimization of one-step RT-LAMP protocol
16.07.20-25.07.20	Validation of 1-step RT-LAMP protocol on 100 patient samples
27.07.20	2nd Reminder to ICMR for directives on submission of 2-Step RT-LAMP kit-V1.0
27.07.20	Submission of request to ICMR for validation of **One Step RT-LAMP Kit-V2.0**
6.09.20	Two step RT-LAMP kit rejected by ICMR without evaluation
6.09.20	Communication for submission of One-Step Kit to NIV
9.09.20	1 step RT-LAMP kit submitted to NIV. Subsequent telephonic conversation regarding inability to follow protocol submitted with kit for quantifying RNA before RT-LAMP
24.09.20	1 step RT-LAMP kit tested by ICMR-NIV; visual detection a challenge

NGS based COVID19 Diagnostics - Strategy

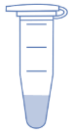
Sample Collection



RNA Isolation (3 hours)



RT-PCR with sample specific barcode (1 hour)



Pooled cDNA Amplification (1.5 – 2 hours)

Ship to central Sequencing facility (4 to 8 hours)

Preparation of NGS Library (6 to 8 hours)

High throughput Sequencing (18 to 25 hours)

Bioinformatic Analysis (1 hour)

Share results

Proof of Concept

- **Trial with ~1000 samples; depth 1500 reads/sample (LAMP-PCR based)**
- ✓ **Concordance: 85%**
- ✓ **Specificity: 98%**
- **Screening large number of people in one go: ready to go**

Current costing:

₹100/sample for sample size of 5000

₹25/sample for sample size of 50,000

(NGS cost, add PCR/RNA isolation costs)

- **Improvements: Extra LAMP-PCR primers to improve concordance significantly; 2 weeks**
- **Next Version→ Dry swab LAMP PCR: 1hr to go for pooling/NGS; total cost, ₹100/sample**
- **Key Factors: Scale and Logistics**

Syngene

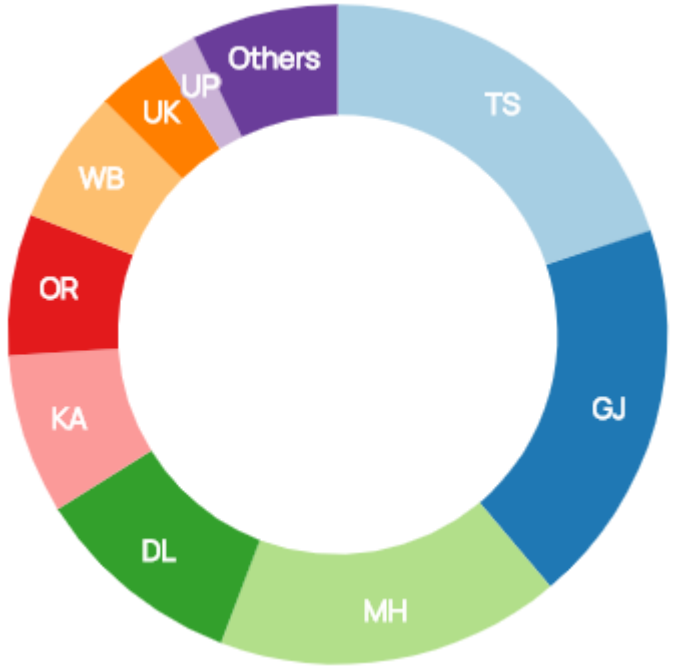
A Biocon company

Genome dynamics of the virus

GEAR-19

Genome Evolution Analysis Resource for COVID-19

BIC, CSIR-CCMB

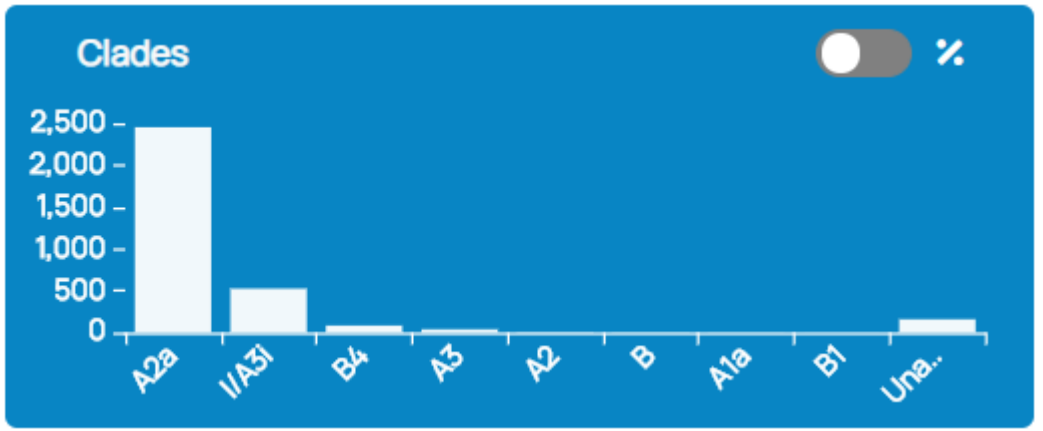


Genomes Sequenced
3280

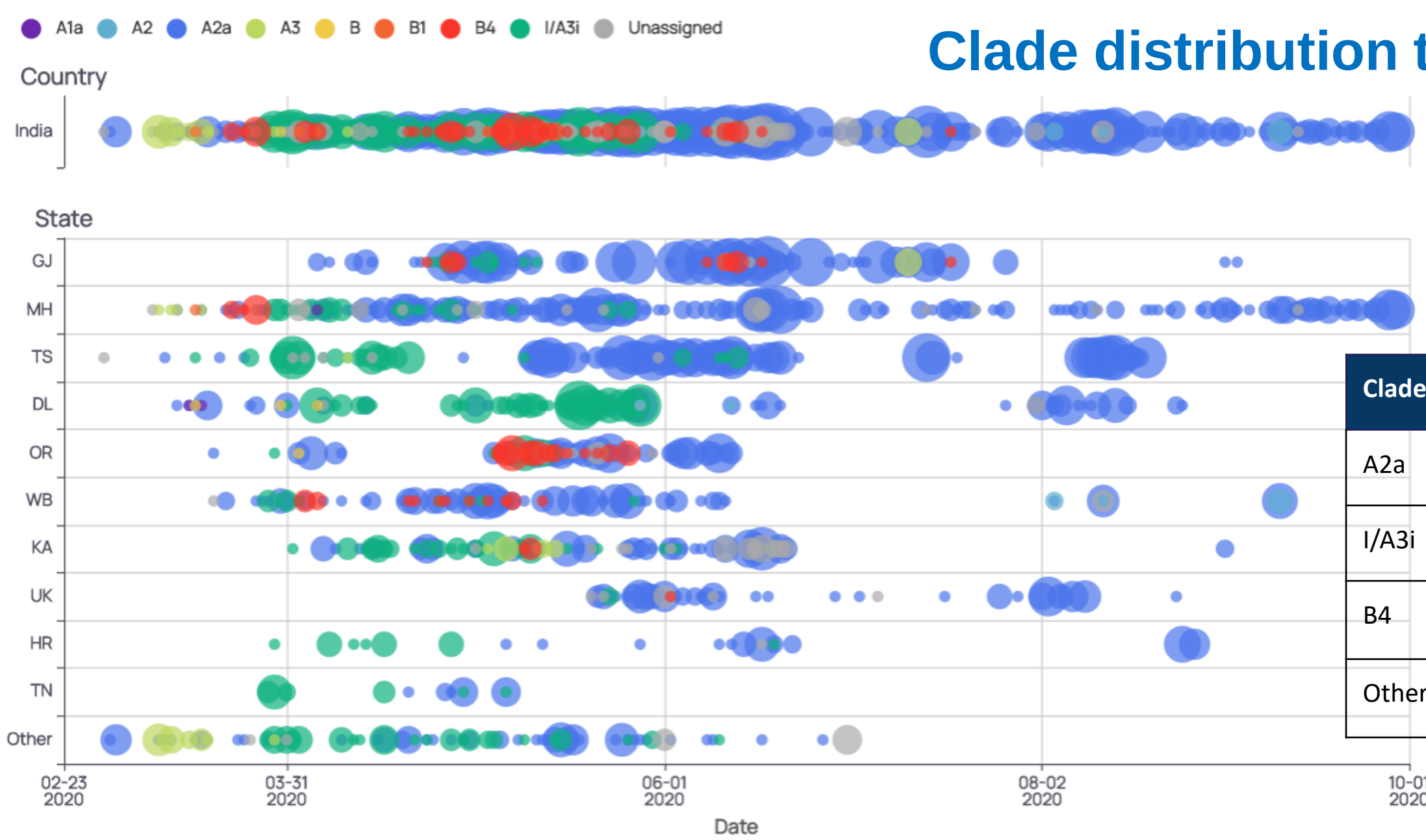
Variants Catalogued
4616

Contributing Labs
35

States Covered
19



Clade distribution timeline



Clade	Prevalence
A2a	74.51%
I/A3i	16.07%
B4	2.73%
Others	6.6%

A3i clade was prevalent till June but is now non-existent. A2a is the current prevalent clade

Multiple Surveillance Strategies

Sero-Surveillance
CSIR Cohort

IGIB
INSTITUTE OF GENOMICS & INTEGRATIVE BIOLOGY
Genomics Knowledge Partner

Serology testing of participating CSIR employees

Most CSIR labs are participating

Analysis going on

AIR

CCMB

CSIR-IMTECH

Air borne transmission of virus is being tested

Sewage
with Pollution Control Board

CCMB

NEERI
ISO 9001:2008

CSIR-IMTECH

Zoonotic

CCMB

COVID-19 Surveillance using Sewage/Wastewater

CCMB
IICT
NEERI

Sample collection from Nacharam STP

SARS-CoV-2 Surveillance Using Sewage Samples

SARS-CoV-2 infected persons

↓

Release viral RNA in faeces

↓

Mix in sewage & reaches Sewage Treatment Plants (STPs)

↓

Sewage samples from the STPs are tested for viral RNA using RT-PCR

- Multiple cities (10) are being monitored on a. weekly basis for past three months

Sewage-based surveillance is an effective approach to study the infection dynamics, which helps in the efficient management virus spread

CCMB COVID Surveillance- Air Sampling

Several studies have shown that SARS-CoV-2 is mainly transmitted by person to person contact

Airborne transmission has been previously reported for SARS-CoV-1 and MERS-CoV

Air sampler

To assess the presence of SARS-CoV-2 in air, air samples from hospitals in Hyderabad are analysed

- COVID Wards
- COVID ICUs
- PPE Undressing Rooms
- OP Corridors
- Nurse Stations
- Non-COVID Wards
- Mortuary
- General Wards

Broad conclusions so far

- If COVID ward / hospital setting where COVID patients are around virus in the air even up to 20 feet, depending on other conditions.
- In closed room living apartment conditions, if COVID positive individual(s) are present, plenty of virus in the air (dining hall, bed room, toilets….).
- If person is talking on phone, virus is in the air.
- If person is wearing mask, virus is not detectable.
- Lot depends on viral load and activity of infected individual.
- Outdoor air is largely free of virus.

New & Repurposed Drugs and Vaccines

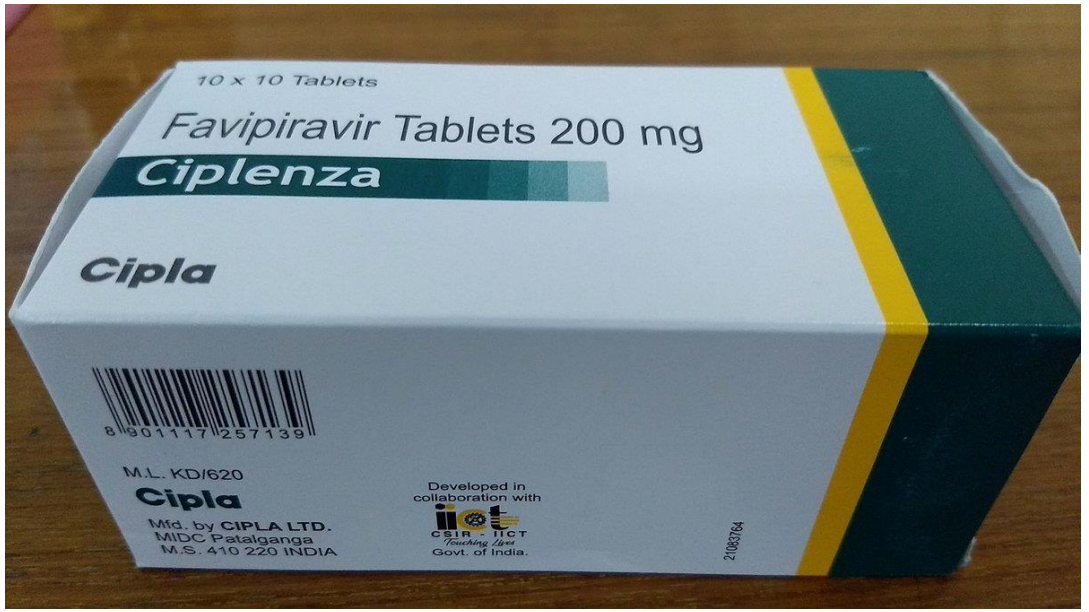
Cost Effective Process Technology of Favipiravir

- Repurposed generic drug
- Cost effective process of API with locally available chemicals developed by CSIR
- Provided API and Key starting materials to Cipla

Cipla

CSIR - IICT
Touching Lives

CSIR has played a pivotal role in launch of Ciplenza by Cipla which has triggered market competition leading to lower pricing of drug



CSIR-Mylan Partnership for Clinical Trials

- **CSIR and Mylan Laboratories Limited are in partnership to address unmet patient needs amidst the evolving COVID-19 pandemic.**
- **Under the partnership, CSIR-IICT and Mylan will collaborate to identify potential therapies for COVID-19.**
- **A series of clinical trials will be conducted towards new and innovative solutions to manage COVID-19 pandemic in India as part of this collaboration.**
- **Application for phase III of Combination clinical trials examined by DCGI and asked to do Phase II Clinical trial; application of Sofosbuvir+Daclatasvir (SOF/DCV) submitted**

CSIR - IICT
Touching Lives

Mylan

Clinical Trials of Repurposed Drugs for COVID-19

Drug	Mode of Action	Industry Partner	Current Status
Umifenovir	**Prevents entry of virus into human cells and also boosts immune system.**	MEDIZEST Agrawal GROUP	• **Phase III trial initiated** • RMLIMS, Era's Lucknow Medical College & Hospital & KGMU
(1) Favipiravir + Colchicine; **(2) Umifenovir + Colchicine** **(3) Nafamostat + 5-ALA**	**Antivirals (viral-entry and replication inhibitors)** **Host-directed therapies (HDTs)**	LAXAI Enriching life through innovation	• Application submitted to DCGI for regulatory clinical phase III trials at Medanta Medicity • Total of 300 patients in 4 different groups • 75 patients in each arm • Treatment for 17 -21 days including screening and treatment.
(1) Favipiravir + Bromohexine **(2) Niclosamide**	**Prevents viral entry Mucolytic drug** **Anti-viral and host directed response modifier**	Cipla Caring for life; LAXAI Enriching life through innovation	• PI driven Clinical Trial • Ethics Approval Received • Cipla shall provide Favipiravir for clinical trial
(1) Sofosbuvir+Daclatasvir (SOF/DCV) **(2) Sofosbuvir+Daclatasvir (SOF/DCV)+Nitazoxanide** **(3) Favipiravir+Bromohexine**	**Used to treat HCV** **SOF Inhibits the NS5B & DCV inhibits the NS5A of HCV** **Nitazoxanide is a broad spectrum anti parasitic and anti viral**	Mylan	• Application submitted to DCGI • The trials will be conducted in adult patients with mild to moderate Covid-19 at risk of complications.

Mycobacterium w (Sepsivac) : Phase II Clinical Trial on Covid19 Patients

- Mycobacterium w (Mw) : TLR2 and NOD2 agonist; antagonist of over expressed endosomal TLR (TLR3,4,7,8,9)
  : Corrects immune dysregulation and establishes immune homeostasis
  : Reduced mortality by 55% compared to control arm in gram negative sepsis. NNT*=9
- *Gram negative bacteria and SARS –COV-2; both intracellular organisms*
- *Immune dysregulation is responsible for morbidity and mortality in both*

Approved for Gram Negative Sepsis

- Double blind placebo controlled clinical trial in critically ill COVID-19# (**CRSC20004)**
  - **40** patients requiring supplemental oxygen enrolled at PGIMER (Chandigarh) & AIIMS (Delhi, Bhopal & Raipur)
    - *Study met primary end-points without any safety concerns*
- ***Approval Received for Phase 3 to enroll 300 critically ill COVID-19 patients***
- *Sites* PGIMER (Chandigarh) & AIIMS (Delhi, Bhopal, Raipur, Patna$), *BHU-Varanasi$, JJ Hospitals- Mumbai$*

Outcome	**Mw group**	**Placebo group**	Remark
Discharged from hospital by Day 21	18 /21 (85.71%)	11/19 (57.89%)	***P=0.049***
Mortality/ on ventilator	2/7 (28.57%)	4/5 (80.00%)	NNT=2

* Number needed to treat to prevent one death
\# Originally designed study to enroll 350 patients with DSMB, CDSCO restricted the study to 40
$ Additional sites

Ongoing Clinical Trials for COVID-19

Sepsivac

- Trials at PGI Chandigarh; AIIMS Delhi, and AIIMS, Bhopal.
- Approval for Phase-III trials in place: one on 600 patients, another on 500 patients.
- **Phase II trial on critically ill Covid-19 patients completed sucessfully**
- **DCGI has given approval for Phase III trials**

CADILA PHARMACEUTICALS LIMITED
The Care Continues...

ACQH

- DCGI approval for clinical trials.
- First-ever approval in India in phytopharmaceutical route
- Clinical trials being done by Sun Pharma in collaboration with ICGEB & CSIR-IIIM Jammu.
- Clinical trials on at 12 centers; in 210 patients
- **Trial to be completed soon**

SUN PHARMA

CSIR-IIIM

ICGEB

Plasma Therapy

- The trial involves CSIR-IICB, Calcutta Medical College and Iinfectious Disease Hospital, Belegata, Kolkata
- Dedicated 'Epidemic Immune Monitoring Lab' has been prepared for this program.
- Clinical trial has been approved by DCGI
- **To be completed soon**

IICB Translational Research Unit of Excellence

CSIR-Indian Institute of Chemical Biology

Medical College and Hospital, Kolkata

Infectious Diseases & Beliaghata General Hospital (I.D. & B.G. Hospital)

Vaccine and immunotherapeutic Development

- Agreement has been signed between CSIR and Aurobindo Pharma, for development of several novel COVID-19 vaccines.
- CSIR-CCMB Hyderabad, CSIR-IMTECH, Chandigarh and CSIR-IICB, Kolkata are developing vaccine candidates using different technology platforms.
- **Aurobindo Pharma** will undertake clinical development and commercialization of the vaccines.

CSIR-CCMB CSIR-IMTECH AUROBINDO

Industry collaboration under CSIR NMITLI program to produce **COVID-19 vaccine** using inactivated virus

Bharat Biotech International, Hyderabad

CSIR-CCMB BHARAT BIOTECH

Partnered with industry to use inactivated virus for **antibody production** in horses for **therapeutic purpose**

VNS Bioproducts Ltd., Hyderabad

CSIR-CCMB VINS BIOPRODUCTS LIMITED VINS RESEARCH WINS LIFE

Clinical Trials of AYUSH Drugs

Clinical trials jointly by CSIR & Ministry of AYUSH

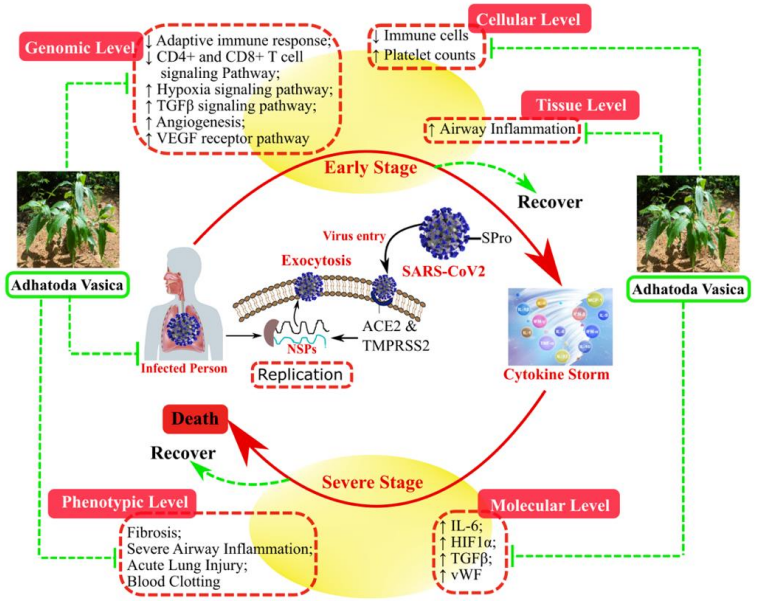
The four studies include:

- 1 Prophylactic trial: *Withania somnifera* (Ashwagandha)
- 3 Therapeutic trials in mild to moderate patients
  - ✓ *Tinospora cordifolia* (Guduchi) + *Piper longum* (Pippali)
  - ✓ *Glycyrrhiza glabra* (Yashtimadhu)
  - ✓ Polyherbal AYUSH drug (AYUSH-64**)**
- These multi-location trials following modern medicine protocols are in progress in hospitals around the country; expected to be completed by March 2021

A prospective clinical study to assess role of Vasa Ghana (*Adhatoda Vasica*), Guduchi Ghana (*Tinospora Cordifolia*) and Vasa-Guduchi Ghana in therapeutic management of symptoms in Covid19 positive cases: a randomized, open label three armed study

IGIB Institute of Genomics & Integrative Biology
Genomics Knowledge Partner

Adhatoda Vasica: a potential ayurvedic intervention against COVID-19 associated impaired immune response and hypoxia-inflammation



Pre-Print: https://www.researchsquare.com/article/rs-92502/v1

Drug Discovery Initiatives

Drug Discovery HACKATHON (DDH2020)

MHRD, AICTE and CSIR with Guidance of Principal Scientific Advisor

CSIR may take forward the drug hits/drug targets of DDH2020 for experimental validation and further Drug Discovery

1st Round Open

In Silico	Target Based Assays	Testing on Viral Cultures
• CSIR-CLRI • Screening underway	• CSIR-CDRI • CSIR-IICB • Spike-ACE 2 Interaction • PLPro • MPro	• CSIR-CCMB • CSIR-IMTECH • Screening ongoing

Major Industry Partners

and more.....

Thank you