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Strategy

Revisiting regulatory framework in India for accelerated vaccine development in pandemics with an evidence-based fast-tracking strategy

The COVID-19 global pandemic has led to an unprecedented collaborative effort amongst industry, academia, regulatory bodies and governments with huge financial investments. The only goal is to accelerate the development and deployment of a safe and effective vaccine to control the pandemic. One can refer to the past experience of accelerated development of vaccines such as H1N1/swine flu in 2009, which took 93 days to start the clinical trial after identification of the vaccine candidate, and the similar interval was 167 days for Ebola vaccine in 2014[1]. The vaccine for H1N1 could be deployed while the epidemic was in progress. The Ebola vaccine clinical testing took five years and was approved in 2019 by the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA) long after the outbreak got over. The vaccines for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and Zika viruses are still under clinical testing[1].

For controlling novel pandemics (or for similar epidemics and large outbreaks), it is important to get the approval for vaccine/s while the outbreak is actively spreading in the community. The combined collaborative effort for SARS-CoV-2 has significantly accelerated the vaccine development through discovery phase, lead candidate optimization, preclinical studies and starting of clinical trials within two months of onset of pandemic. More than 25 vaccine candidates are already in different phases of clinical trials in the second half of 2020[2] (Table).

Multiple new vaccine platforms are under development along with the traditional ones. Due to the need of rapid development, DNA and RNA platforms are most suitable followed by recombinant subunit vaccine. The DNA and RNA vaccines can be quickly developed by synthetic process and do not need culture or fermentation[3]. The regulators have experience of approval of DNA vaccines for personalized cancer management, which may help them in the current situation in examining such candidate vaccines. The application of reverse genetics and next-generation sequencing can also reduce the development time in comparison to vaccine development by conventional platform[3]. Application of nanotechnology interventions such as lipid nanoparticle and virus-like particles (VLP) of plant origin as carrier/adjuvant is a unique approach[2] (Table). However, these novel platforms need to prove their safety and efficacy in adequate non-clinical and clinical trials.

Internationally, acceleration of COVID-19 vaccine development is being done by different groups following a matrix with overlapping tracks from discovery phase and translation to approved product through policy and practice. Hanney *et al*[4] have conceptualized and proposed four tracks: (*i*) discovery phase and non-clinical research, (*ii*) clinical trial, data analysis with review of discovery phase research, (*iii*) clinical practice and public policy development, and (*iv*) resource mobilization[4]. The essential requirements for the translation of vaccine candidate from discovery to product are documentation of quality, safety and efficacy. In the emerging regulatory science paradigm, the implementation of evidence-based regulatory practice is becoming more important which helps to evaluate a novel product according to the innovation pathway with more flexibility[5].

According to the draft report published on August 13, 2020 by the WHO, there are 138 vaccine candidates against SARS-CoV-2 developed and 29 are in different phases of clinical trials[2]. Several new types of vaccines are being developed, such as RNA vaccine, which have not been tested in people earlier or have any precedence for regulatory approval. Such new vaccine candidates may need detailed exploration during discovery and

Table. List of vaccine candidates in different phases of clinical trials

Manufacturer/ developer	Type of candidate vaccine	Vaccine platform	Dosing			Clinical trial phase			
			Route of administration	Number of doses	Timing of doses (days)	1	1 and 2	2	3
Sinovac	Inactivated	Inactivated	IM	2	0, 14		+		+
Wuhan Institute of Biological Products/ Sinopharm	Inactivated	Inactivated	IM	2	0, 14 or 0, 21		+		+
Beijing Institute of Biological Products/ Sinopharm	Inactivated	Inactivated	IM	2	0, 14 or 0, 21		+		+
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Inactivated	IM	2	0, 28	+	+		
Bharat Biotech	Inactivated	Inactivated	IM	2	0, 14		+		
University of Oxford/AstraZeneca	ChAdO×1-S	Non-replicating viral vector	IM	1			+	+	+
CanSino Biological Inc./Beijing Institute of Biotechnology	Adenovirus Type 5 Vector	Non-replicating viral vector	IM	1		+		+	
Janssen Pharmaceutical Companies	Ad26COVS1	Non-replicating viral vector	IM	2	0, 56		+		
Gamaleya Research Institute	Adeno-based	Non-replicating viral vector	IM	1		+			
ReiThera/ LEUKOCARE/ Univercells	Replication defective simian adenovirus (GRAd) encoding S	Non-replicating viral vector	IM	1		+			
Institute Pasteur/ Themis/University of Pittsburgh CVR/ Merck Sharp and Dohme	Measles-vector-based	Replicating viral vector	IM	1 or 2	0, 28	+			
Moderna/NIAID	LNP-encapsulated mRNA	RNA	IM	2	0, 28	+		+	+
BioNTech/Fosun Pharma/Pfizer	3 LNP-mRNAs	RNA	IM	2	0, 28		+		+
Arcturus/Duke-NUS	mRNA	RNA	IM	1			+		
Imperial College London	LNP-nCoVsaRNA	RNA	IM	2		+			
Curevac	mRNA	RNA	IM	2	0, 28	+			
PLA Academy of Military Sciences/ Walvax Biotech	mRNA	RNA	IM	2	0, 14 or 0, 28	+			

Contd...

Manufacturer/ developer	Type of candidate vaccine	Vaccine platform	Dosing			Clinical trial phase			
			Route of administration	Number of doses	Timing of doses (days)	1	1 and 2	2	3
Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Adjuvanted recombinant protein (RBD-dimer)	Protein subunit	IM	2 or 3	0, 28 or 0, 28, 56	+		+	
Novavax	Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Protein subunit	IM	2	0, 21		+		
Kentucky Bioprocessing, Inc.	RBD-based	Protein subunit	IM	2	0, 21		+		
Clover Biopharmaceuticals Inc./GSK/Dynavax	Native-like trimeric subunit spike protein vaccine	Protein subunit	IM	2	0, 21	+			
Vaxine Pty Ltd/ Medytox	Recombinant spike protein with Advax™ adjuvant	Protein subunit	IM	1		+			
University of Queensland/CSL/ Seqirus	Molecular clamp stabilized Spike protein with MF59 adjuvant	Protein subunit	IM	2	0, 28	+			
Medigen Vaccine Biologics Corporation/NIAID/ Dynavax	S-2P protein + CpG 1018	Protein subunit	IM	2	0, 28	+			
Inovio Pharmaceuticals/ International Vaccine Institute	DNA plasmid vaccine with electroporation	DNA	ID	2	0, 28		+		
Osaka University/ AnGes/Takara Bio	DNA plasmid vaccine + adjuvant	DNA	IM	2	0, 28		+		
Cadila Healthcare Limited	DNA plasmid vaccine	DNA	ID	3	0, 28, 56		+		
Genexine Consortium	DNA vaccine (GX-19)	DNA	IM	2	0, 28		+		
Medicago Inc.	Plant-derived VLP adjuvanted with GSK or Dynavax	VLP	IM	2	0, 21	+			

PLA, People's Liberation Army; VLP, virus-like particle; GSK, GlaxoSmithKline; IM, intramuscular; ID, intradermal; LNP, lipid nanoparticle; NIAID, National Institute of Allergy and Infectious Diseases; +, ongoing trial

Source: Adapted with permission from Ref. 2

non-clinical phase which can continue during initial phase of clinical trial for new risk identification along with documentation of safety and efficacy. Another challenge is to compare the safety and efficacy among the different vaccines. The WHO has proposed a blue print of Solidarity Trial for vaccines for their prioritization[6].

Regulatory science approaches in India in COVID-19 pandemic context

According to the practice of US FDA and Central Drugs Standard Control Organization (CDSCO) in India, a demonstration of vaccine effectiveness is based on a clinical disease end point (*e.g*. prevention of disease) or, alternatively, an accepted correlate of protection. While the US FDA's regulations provide for expedited pathways and emergency use licensure, CDSCO in India does not currently have an expedited pathway formalized for new products addressing novel pandemics or public health emergencies. The authorizing legislations for responding to public health emergencies vest in the Ministry of Home Affairs through the National Disaster Management Act of 2005[7] and with the Ministry of Health and Family Welfare through the Epidemic Diseases Act of 1897[8]. Emergency response and expedited pathways for regulatory approval do not find specific mention in the Drugs and Cosmetics Act 1940 and Rules 1945, as amended up to 2016[9], but do so in the subsequently released New Drugs and Clinical Trials (NDCT) Rules 2019[10].

It is noted that the US FDA "approval under this pathway is subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate end point to clinical benefit"[11]. Specifically, with the recent amendment, the FDA Safety and Innovation Act (FDASIA) of 2012 "expanded the scope of available end points that can be used to demonstrate that a product qualifies for accelerated approval, but do not affect the quantity and quality of evidence needed to demonstrate substantial evidence of effectiveness or safety"[11]. Furthermore, "in 2002, the FDA amended the biological products regulations to incorporate 21 CFR §601.90, Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible. This rule, referred to as the 'Animal Rule', allows the use of animal efficacy data in lieu of human efficacy data when human challenge studies cannot be conducted ethically, and field efficacy studies are not feasible because of infectious disease epidemiology (in the case of vaccines)"[11]. In these situations it has been suggested that, "certain drug and biological products (*e.g*., vaccines) that are intended to reduce or prevent serious or life-threatening conditions caused by lethal or permanently disabling toxic chemical, biological, radiologic, or nuclear substances may be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals and additional supporting data"[11].

The US FDA can accelerate the availability of appropriate pharmaceutical products and vaccines by using the mechanism of emergency use authorization (EUA). Under an EUA, it is possible for US FDA to authorize the marketing of an unapproved product or the unapproved use of an approved product when a justifiable health emergency or a potential emergency exists[11]. In response to the COVID-19 pandemic, there has been a growing consensus among regulatory authorities, including from India, to address the urgent need for a safe and effective vaccine. Consequently, the following positions have been communicated following a virtual meeting held under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA): 'Some vaccine constructs for which there is adequate support from the knowledge around the immune response elicited, may be allowed to proceed to First in Human (FIH) trials without first completing animal studies to assess the potential for enhanced disease provided adequate risk mitigation strategies are put in place in these FIH trials. For some vaccines, preclinical data (*e.g*. post-vaccination challenge data from animal models, immunopathology studies in animal models) may be required before advancing to FIH clinical trials. In the event that FIH clinical trials are allowed to proceed in the absence of studies in animals that would address the potential for enhanced disease, such studies are, in general, expected to be conducted in parallel with FIH trials so that these data are available prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials'[12].

Provision for regulatory flexibility in accommodating novel medical countermeasures and interventions in disease management and pandemic control is of utmost importance. India's NDCT Rules, 2019 accommodates "special situations for a new drug where relaxation, abbreviations, omission or deferment of data may be considered"[10], but this does not explicitly include public health emergencies such as novel epidemics and pandemics, nor does it have

the provision for granting EUA. However, given the scale of the COVID-19 pandemic and absence of specific medical countermeasures, the regulators in India appropriately responded to the unmet need and allowed 'restricted emergency use' permission for a few drugs, and also put out a formal notification allowing for manufacture of novel vaccines for COVID-19 and keeping in abeyance rules 81 and 83 of the NDCT Rules, 2019[13].

For the current COVID-19 pandemic situation, as well as for any such future public health emergency situations such as pandemics, epidemics or localized outbreaks, where there is no specific vaccine, drug or diagnostic tools available, early-stage investigational efforts should be enhanced through idea sharing meetings between research sponsor teams and the regulator's office, expanding the scope of 'pre-submission meetings' provided for in the NDCT 2019. In addressing pandemic situations, such meetings should be prioritized, and guidance may be given at the meetings, with records of meeting minutes being put on file for future reference.

This proactive approach may allow for refinement of approaches at the idea stage and prevent wastage of time and resources on the part of the research team as well as at the regulatory end for establishing validity for the candidate in non-clinical (laboratory/*in vitro*/animal) studies. For time optimization in public health emergency/pandemic response situations, several or all of the clinical evaluation, production planning, distribution strategy and safety evaluation steps of the vaccine development continuum could be conducted in parallel, rather than in a sequential manner. In addition, non-clinical studies should be continued even after the candidate vaccine has been approved to be taken into clinical trial phases.

As of the writing of this article (August 18, 2020), India had three candidate vaccines in varying phases of their clinical development. One of those is a collaboration between a university-based research group that has licensed its candidate to a lead commercialization partner along with an Indian counterpart (Oxford/AstraZeneca Serum Institute/ChAdOx1), while the other two are being developed by Indian commercial entities (Bharat Biotech/Inactivated Virus and Zydus Cadilla/DNA). It is possible that there may be more candidates that will need to be assessed and approved for development in India, mirroring the global trend.

Ensuring timely vaccine - A possible approach

Vaccines in pandemic settings serve dual functions of providing individual protection and curtailment of disease transmission in the community. Timing of the availability and use of the vaccine is key to reducing the overall number of infections and related morbidity and mortality. An adaptive model for vaccine development in public health emergency contexts, comprising one concurrent phase and three sequential phases as illustrated in the Figure, could fulfil the requirements

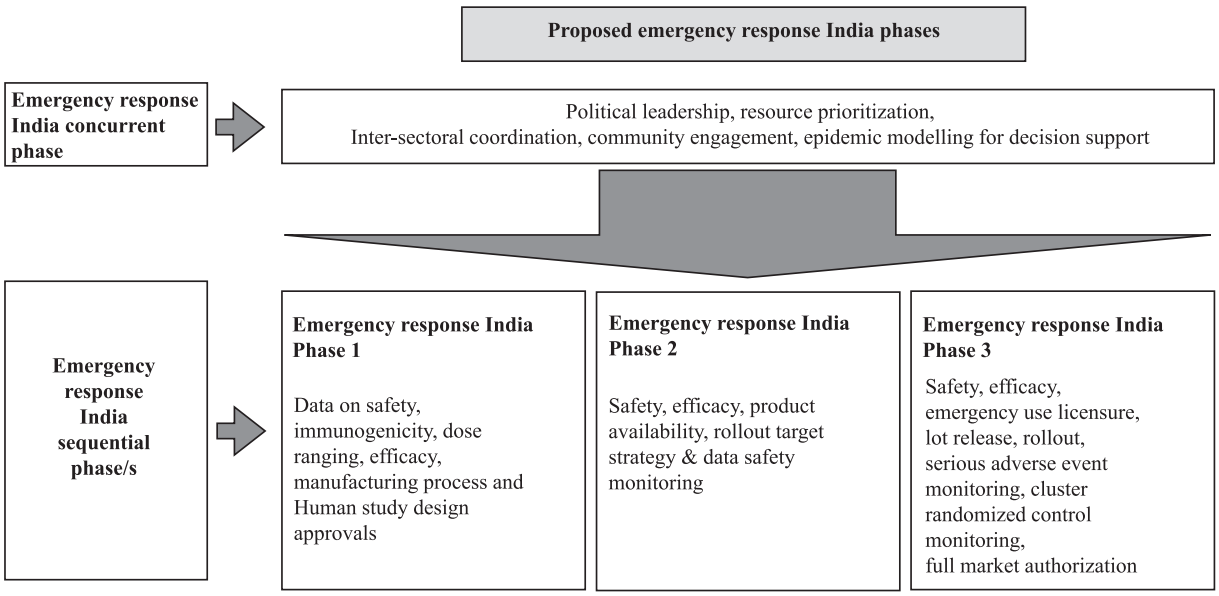

Figure. Adaptive model for vaccine development in public health emergency contexts.

for demonstration of safety and efficacy and enable shortening of the overall vaccine development timeline.

Proposed emergency response India cross-cutting phase

In confronting novel pathogens, there are no prior experiences or data points to rely on. Early responses and strategies to contain novel pathogen outbreaks are predicated on simulation and modelling of the transmission and outcomes of the infection in its early days. Epidemic models are directional tools, factoring in available and potential interventions, and need to be repeatedly assessed and reoriented in the light of emerging data following every intervention applied. Epidemic models inform decision-making at the political level, as well as the research and regulator communities to the need for new tools such as vaccines to address the emergent situation. Assumptions forming part of the model, especially the use of vaccines, need to be continuously evaluated as these get developed and rolled out, for adaptations and reference by the research, policymaking, clinical and regulatory stakeholders. Political leadership is critical to shaping national and global emergency responses, especially to enable the development of new tools and strategies to address novel pathogens and pandemic situations. Early, informed and decisive political support for the development of new tools including vaccines requires active information sharing amongst, and coordinated communication from, the apex medical research agencies, health administrators and regulatory authorities on the nature of the emergency. This also unlocks financial, human and administrative resources needed to bring into active development of new vaccines, diagnostics and therapeutics as part of the overall emergency response. In addition, inter-sectoral coordination as well as community engagement which is critical to the success of the overall emergency response also gets mobilized. Strategic and mass communications, community-level information sharing and confidence building also ensure that misinformation and adverse attitudes to vaccine rollout when it happens, are mitigated in advance and enable better post-marketing follow up of possible vaccine-related adverse reactions.

This concurrent phase could start at the earliest possible time following recognition of a public health emergency and continue till the required set of new tools are fully in use and the emergency situation has abated, and would have as its outcomes the following: disease dynamics modelling, political leadership, resource allocation, inter-sectoral coordination, and community engagement for a new vaccine addressing the emergency situation.

Proposed emergency response India Phase 1

This proposed phase would comprise the set of efforts incorporating regular non-clinical/pre-clinical phase and Phase 1 clinical studies of the vaccine development cycle, identifying the immunogen, establishing safety, immunogenicity, dose ranging and early efficacy indicators for the vaccine candidates, while, in parallel, ensuring that the manufacturing process and designing of the next phase of human studies are thought through with the perspective of time savings. The outcomes from this phase would be to establish the mechanisms of action through non-clinical/animal model studies, as well as safety of the candidate vaccine in humans. In parallel, the manufacturing process for the candidate vaccine as well as the next steps for clinical trials could be designed with appropriate engagement and authorizations from regulatory authorities. No candidate vaccine should be allowed to proceed to the next phase of clinical trials without demonstrating a clear safety profile. With new platform technologies becoming more prominent, non-clinical studies should be encouraged to continue even after the candidate vaccine moves on to the next phase of trials. The expected outcomes from this phase would be data on safety, immunogenicity, dose ranging, efficacy, manufacturing process and human study design approvals.

Proposed emergency response India Phase 2

This proposed India Phase 2 set of efforts would incorporate the regular safety, immunogenicity and efficacy studies as well a limited efficacy and safety trial among a small number of volunteers with appropriate controls. This telescoped design will enable an earlier submission of safety and efficacy data, allowing for potential regulatory approval for an EUA for the candidate vaccine.

Given the context of public health emergency and the need for novel vaccines, this would be a particularly busy phase for the regulatory administration, not only towards early EUA issuance for the candidate vaccine but also towards regulatory approvals for the manufacture at scale for early rollout. In parallel, robust data systems and a data safety monitoring board will need to be put in place so that post-administration

follow up data are clearly tracked and safety issues flagged up early.

Reputed contract research organizations may be actively engaged in designing the post-emergency authorization rollout plan including cluster randomization of control populations. Depending on the nature of the distribution of cases, the formulated vaccine rollout plan will follow one or more of the following approaches while ensuring that appropriate testing is done to screen out those with antibodies to COVID-19: (*i*) Geospatial approach; (*ii*) Age-wise population segmentation approach; and (*iii*) Risk profile prioritization approach.

This proposed India Phase 2 outcomes would include safety and efficacy data, ready product availability, a fleshed-out rollout target strategy and mechanisms for data safety monitoring.

Proposed emergency response India Phase 3

This proposed India Phase 3 set of efforts would incorporate vaccine rollout post-EUA issuance by the regulator. This provision currently does not exist within the CDSCO India framework, but recent restricted emergency use approvals granted by the regulator in the context of COVID-19 responses point towards a need for such an authorization. Use of emergency use authorized candidate vaccines will be subject to regulatory oversight, rigorous safety and adverse event monitoring and also to revoking of approval on the basis of serious adverse effects.

The rollout will be conducted as per the regulator-approved plan envisaged in India Phase 2. This phase will telescope the conventional Phases 3 and 4, with clustered randomization of control populations built into the rollout design, instead of having a separate control arm. From those receiving the emergency use authorized vaccine, defined end point measures of neutralizing antibody titres will be monitored among selected individuals, as also among those in the cluster control groups to continuously provide efficacy data.

This rollout design, with short efficacy data feedback loop along with safety reporting to the regulator and adverse event following immunization monitoring by statutory bodies set up at appropriate jurisdictional levels in India, will generate real-world evidence for the vaccine, its safety and efficacy, and set up the pathway for full market authorization by the regulator earlier than the conventional approach, while addressing the emergency need for affording protection to at-risk populations, averting morbidity and related mortality, and containing the pandemic. The outcomes from this proposed India Phase 3 would include safety, efficacy, emergency use licensure, lot release, rollout, serious adverse event monitoring, cluster randomized control monitoring and eventually full market authorization.

Conclusion

Even with full authorization in place, it would be useful to keep track of the performance of the initial modelling of the epidemic and the expected effects of the introduction of a vaccine in addressing incidence of new infections, morbidity and mortality reductions, both among those given the new vaccine as well as among the non-immunized groups and containment of the pandemic. Regulators may, on the basis of such follow up, incorporate the use of adaptive models to the decision-making toolkit for further modifications to the regulatory pathways in emergency situations where new tools need to be developed in a timely manner.

In the event that there are multiple vaccines emerging with EUAs, the choice of vaccine recommended to be rolled out would rest on the outcomes of an iterative evaluation undertaken by the public health authority, in consultation with the regulator, of relative safety and tolerability of the vaccine, duration of protection, the logistical ease for its administration and finally the costs of the vaccine. Regulatory authorities would need to anticipate a scenario where the possibility of different vaccines administered to the same person might arise due to the deployment of multiple vaccines with multiple dosing schedules across the country.

While the focus has been on the regulatory science innovations in developing new vaccines during pandemic or public health emergencies, it must be noted that existing vaccines authorized for other indications may be used by clinical and academic researchers for their protective non-specific immunity effects on different age groups or patient categories. Such repurposing studies will need to be documented as fresh clinical trials, with design, conduct and outcomes subject to conventional regulatory oversight. Should such research yield correlates of protection specific

to the emergent pathogen, an accelerated pathway to emergency authorization of such vaccines should also be offered and subsequent rollout strategy would mirror the India Phases 2-3 as outlined above.

***Conflicts of Interest*:** None.

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