COVID-19 vaccine candidates and trials

- Types of vaccine candidates
  - prior success (or not)
  - manufacturing issues
- Placebo issues
- Clinical trial design issues due to -
  - end points
  - numbers
  - time windows

DRAFT landscape of COVID-19 candidate vaccines – 3 November 2020

COVID-19 Vaccine developer/manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Administration	Clinical Stage			
						Phase 1	Phase 1/2	Phase 2	Phase 3
Sinovac	Inactivated	Inactivated	2	0,14 days	IM		NCT04383574 NCT04352608 NCT04551547		NCT04456595 669/UN6.KEP/EC/2020 NCT04582344
Wuhan Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM		ChiCTR2000031809 Interim Report		ChiCTR2000034780 ChiCTR2000039000
Beijing Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM		ChiCTR2000032459 Study Report		ChiCTR2000034780 NCT04560881
University of Oxford/AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	2	0,28 days	IM		PACTR202006922165132 2020-001072-15 NCT04568031 Interim Report	2020-001228-32	ISRCTN89951424 NCT04516746 NCT04540393 CTRI/2020/08/027170
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM	ChiCTR2000030906 NCT04568811 Study Report		ChiCTR2000031781 NCT04566770 Study Report	NCT04526990 NCT04540419
Gamaleya Research Institute	Non-Replicating Viral Vector	Adeno-based (rAd26-S+rAd5-S)	2	0,21 days	IM		NCT04436471 NCT04437875 Study Report	NCT04587219	NCT04530396 NCT04564716
Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	Ad26COVS1	2	0,56 days	IM		NCT04436276		NCT04505722
Novavax	Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2	0,21 days	IM		NCT04368988 Study Report	NCT04533399 (phase 2b)	2020-004123-16 NCT04611802
Moderna/NIAID	RNA	LNP-encapsulated mRNA	2	0,28 days	IM	NCT04283461 Interim Report final Report		NCT04405076	NCT04470427
BioNTech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	2	0,28 days	IM	NCT04368728 Study Report	2020-001038-36 ChiCTR2000034825 NCT04537949 NCT04588480 Study Report1 Study Report2		NCT04368728

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Vaccine candidates

- Stages
  - 10 in phase III clinical trials
  - 37 in pre-phase III clinical evaluation
  - 155 in pre-clinical evaluation

- Routes
    - All 10 in phase III trials are intramuscular injections
    - In the 37 in early clinical evaluation
        - 2 intra-dermal (into skin) injections
        - 1 sub-cutaneous (under skin) injections
        - 2 (and maybe one more) oral, NOT injections

- Doses
    - 9 in phase III trials need two doses 2-4 weeks apart
    - 1 in phase III trials is one-dose
    - In the 37 in early clinical evaluation -
        - 1 needs three doses (0, 4, 8 weeks)
        - 7 need one dose
        - 30 need two doses, 2-4 weeks apart

Vaccine candidate platforms

- Infectious virus ('attenuated')
  - None
- Non-infectious virus ('inactivated')
  - 3 of 10 in phase III trials
  - 4 of 37 in early-stage clinical evaluation
- Replicating viral carrier
  - None in phase III trials
  - 4 of 37 in early-stage clinical evaluation
- Non-replicating viral carrier
  - 4 in phase III trials
  - 5 of 37 in early-stage clinical evaluation
- DNA
  - None in phase III trials
  - 5 of 37 in early-stage clinical evaluation
- RNA
  - 2 in phase III trials
  - 4 of 37 in early-stage clinical evaluation
- Protein
  - 1 in phase III trials
  - 15 of 37 in early-stage clinical evaluation

Primary outcome for all trials:

Number of virologically-confirmed symptomatic COVID-19 cases, starting two weeks after second dose of vaccine

Regulatory requirement for 'efficacy':

50% efficacy, and not less than 30% at lower limit with 95% CI

This means that 100 cases occurring in control group versus 50 cases in test group will be enough

This will be achieved so soon that:

- **Placebo effects due to 'non-specific' immune activation will need ruling out (but no placebo info)**
- **Duration of protection will be a huge unknown**
- **Immunological protective correlates might be weak**

Related issues:

In some trials, frequency of adverse reactions is measured only in the seven days following each immunisation

In other trials, a one-year adverse event follow-up is a primary outcome, but these are mostly uncoupled from efficacy test trials

Some trials include elderly, some not (no other co-morbidities are targeted)

Some trials include pre-screening for prior exposure, some not

Some give placebo information, many not
(placebos used, alum/adjuvant, other vaccine, normal saline)

Vaccine nationalism, vaccine capitalism

COVID-19 vaccine trials should seek worthwhile efficacy

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Three issues are crucial in planning COVID-19 vaccine trials: (1) whether to demand not only proof of some vaccine efficacy but also proof of worthwhile efficacy; (2) whether the initial trials of vaccine against placebo should prioritise not only single-vaccine trials but also a multivaccine trial; and (3) whether to assess safety, protection against severe disease, and duration of protection by continuing blinded follow-up of the vaccine and placebo groups after definite evidence of short-term efficacy has emerged, but before an effective vaccine has been deployed locally in the general population.

https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931821-3

The world needs efficient, speedy, and reliable evaluation of many candidate vaccines against COVID19. There is a danger that political and economic pressures for rapid introduction of a COVID19 vaccine could lead to widespread deployment of a vaccine that is in reality only weakly effective (eg, reducing COVID19 incidence by only 10–20%), perhaps because of a misleadingly promising result from an underpowered trial. Deployment of a weakly effective vaccine could actually worsen the COVID19 pandemic if authorities wrongly assume it causes a substantial reduction in risk, or if vaccinated individuals wrongly believe they are immune, hence reducing implementation of, or compliance with, other COVID19 control measures. Deployment of a marginally effective vaccine could also interfere with the evaluation of other vaccines, as subsequent vaccines would then have to be compared with it rather than with a placebo. For a vaccine superior to the weakly effective vaccine, the increased sample size required could delay recognition of its efficacy. More importantly, if the weak vaccine is compared against an even weaker vaccine, the statistical criteria used to analyse non-inferiority trials could well endorse the even weaker vaccine as being noninferior (so-called biocreep).

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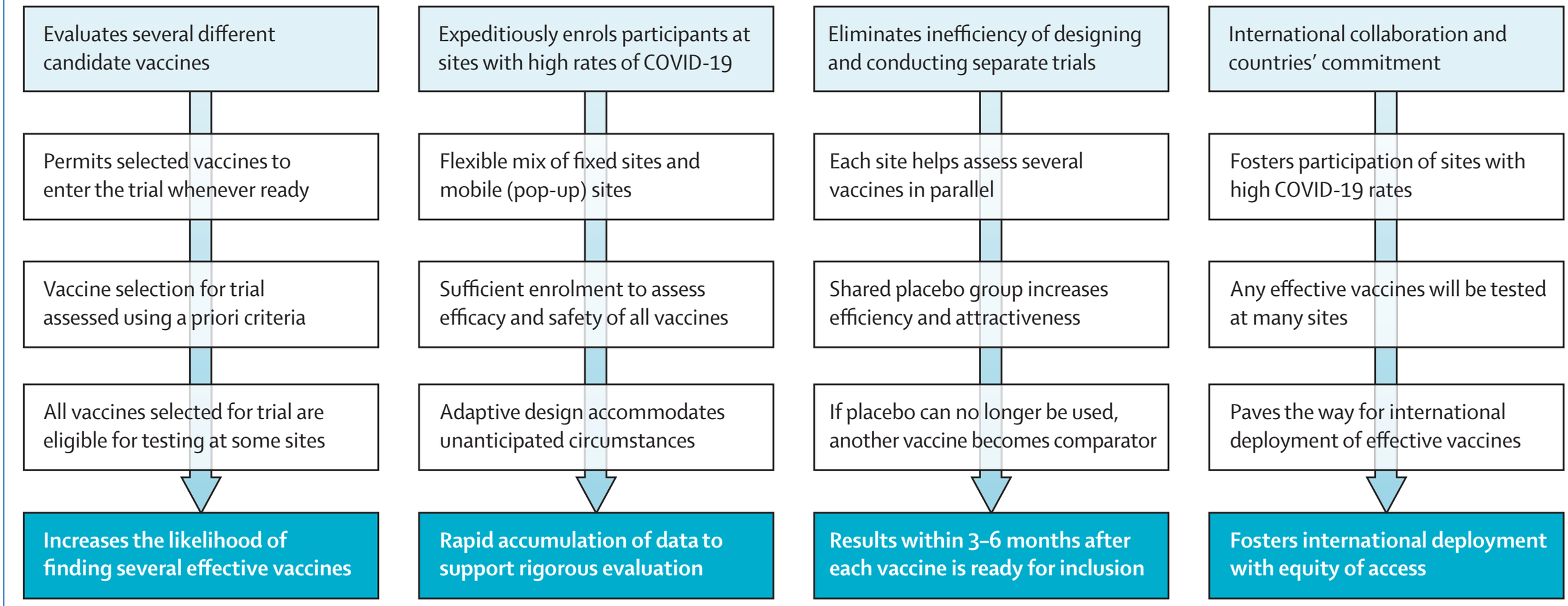

Figure: **Selected design features of the WHO Solidarity Vaccines Trial**

The primary outcome is laboratory-confirmed symptoms >14 days after vaccination is completed. Analyses of each vaccine after about 40, 70, and 100 primary outcomes occur in the placebo group will report success if they show ≤10 versus 40, ≤30 versus 70, or ≤50 versus 100 outcomes. The third analysis is reported regardless of its findings. In all cases placebo-controlled follow-up continues until at least month 12 (or local deployment of an effective vaccine) to assess safety, disease severity, and duration of protection.

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