Early results from COVID-19 vaccine trials and implications for ongoing and future trials of other COVID-19 vaccines

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Key questions in a pivotal (Phase 3) vaccine trial

- Is the vaccine safe?
- Is the vaccine efficacious?

Addressing these questions generally requires a double-blind randomized comparator group who have not been vaccinated (generally given a placebo).

- Do the short-term results (after follow-up of participants for a few months) justify “licensure” or “emergency use listing”?
- Will the characteristics of the vaccine and the results from Phase 3 trials convince public health authorities to deploy the vaccine (and potential recipients to take it up)?

Important secondary endpoints which may, or may not be, addressed in pivotal vaccine trials

- Does the vaccine protect against severe disease and death?
- Are there sub-groups in the population in which the vaccine is more or less efficacious/safe? (e.g. elderly, pregnant, immunocompromised, co-morbidities)
- How does protection change with time since vaccination?
- Can protection be prolonged by booster doses, if necessary?
- Are there rare adverse effects of vaccination, too uncommon to have been detected in Phase 3 trials?
- Are there “late” adverse effects of vaccination? Especially, is there evidence of enhanced disease induced by vaccination (possibly as vaccine-induced antibody levels decline)?
- Does the vaccine protect against asymptomatic infection? (which might indicate potential induction of herd protection)
- Can a correlate of protection be identified?

Some of these issues may be addressed in Phase 3 trials, others through post-deployment studies – some as part of a manufacturer’s risk management plan.

Interim SARS-CoV-2 vaccine trial results (press releases) to December 2020

	Pfizer BIONTECH	moderna	AstraZeneca	THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOG
Platform	mRNA	mRNA	ChAdOx-1	Ad26 >> Ad5
Doses (days)	0, 21	0, 28	0, 28	0, 21
Trial size (approx.)	43,500	30,000	23,000	19,000
Ages included	≥ 12y	≥ 18y	≥ 18y	≥ 18y
Trial sites	US + 5 other countries	US	UK, Brazil	Russia
Randomization (V:C)	1:1	1:1	1:1	3:1
VE from days post D2	7	7	14	7
Vaccine efficacy (V:C)	**95%** (8: 162) (18Nov20)	**94%** (11: 185) (30Nov20)	**70%** (30: 101) [lo-hi dose 90% (3: 30)] [hi-hi dose 62% (27:71)] (23Nov20)	**91%** (8: 31) (23Nov20)
Severe COVID-19 (V:C)	1: 9	0: 30	0: ?	?: ?
Planned follow-up	2y	2y	1y	6mo
Production 2020	50m	20m	-	-
Capacity (doses) 2021	1.3b	0.5-1.0b	3b	1b?
Storage	-70˚C (2-8˚C ≤5d)	-20˚C (6mo) (2-8˚C ≤30d)	(2-8˚C ≤6mo)	Lyophilized (2-8˚C)
Approx. cost (/dose)	$20	$33	$4	$<10

Other ongoing Phase 3 trials of SARS-CoV-2 vaccines

From London School of Hygiene & Tropical Medicine COVID-19 Vaccine Tracker – 30 Nov 20

Vaccine	Platform	N	Age (years)	N doses	Location	Start date
Janssen Ad26.COV2.S	Non-replicating viral vector	60,000	≥18	1	USA, Argentina, Brazil, others	07/09/2020
	Non-replicating viral vector	30,000	≥18	2	USA, Belgium, Colombia, others	15/11/2020
Oxford ChAdOx1-S	Non-replicating viral vector	40,000	≥18	2	USA, Argentina, Chile, others	28/08/2020
Novavax NVX-CoV2373	Protein subunit	30,000	≥18	2	USA, Mexico, Puerto Rico	01/11/2020
	Protein subunit	15,000	18–84	2	UK	28/09/2020
WIBP/BIBP vaccines Sinopharm	Inactivated	45,000	≥18	2	Bahrain, Jordan, Egypt, UAE	16/07/2020
	Inactivated	6,000	18–60	2	Peru	10/09/2020
Cansino Ad5-nCoV	Non-replicating viral vector	40,000	≥18	1	Argentina, Chile, Mexico, others	15/09/2020
Sinovac CoronaVac	Inactivated	13,060	≥18	2	Brazil	21/07/2020
	Inactivated	13,000	18–59	2	Turkey	14/09/2020
Bharat COVAXIN	Inactivated	25,800	≥18	2	India	25/11/2020

Participation is a vaccine trial should be driven by altruism

- Vaccine trials are not conducted for the benefit of those in the trial.
- Participants may benefit from better care, and have a chance of receiving the vaccine, which might be beneficial, ineffective or cause harm.
- Participants should not be disadvantaged compared to those in the same community not included in the trial.
- Nor should they be unduly advantaged.

(However, altruism may not be the prime driver for some participants in vaccine trials)

How long will it be possible to preserve a “placebo” group in ongoing trials?

- New vaccines showing early evidence of efficacy
  - Important issues for the public health assessment of these vaccines, such as duration of protection and longer-term safety issues, are best addressed by maintenance of the placebo group for as long as possible.
- Vaccines which have not yet been in trials for long enough to show short-term-efficacy and safety results, or vaccines that have not yet entered Phase 3 trials
  - Evaluation of efficacy and safety will be potentially compromised without the maintenance, or inclusion, of placebo groups

Statement on continuation of vaccine trials - 28 Nov 20

"Unless maintaining participants in their randomised treatment groups (vaccinated or control) after a vaccine is approved is clearly infeasible, we recommend that clinical trials should proceed as initially planned with a follow-up of at least one year or more from completion of assigned doses."

"We recognise that the feasibility of maintaining the group assignment for at least one year will depend on factors such as the population enrolled into a trial (e.g. in terms of whether they are young and healthy or have reasons to be predisposed to develop severe COVID-19), informed decisions made by clinical trial participants, the availability of COVID-19 vaccine(s), and the characteristics of SARS-CoV-2 epidemics."

"It will be necessary for sponsors, investigators, public health authorities and regulators to assess each situation that may arise."

Covid-19 Vaccine Studies May Suffer as Volunteers Consider Dropping Out

People who believe they got a placebo during testing say they want to leave to get the real shots once they are approved

WSJ 27/11/20

Johnson & Johnson last month sought guidance on the matter from the committee of independent experts advising the FDA on vaccines. J&J expressed concern that clearance of the first vaccine would compromise other companies' ability to recruit volunteers for their own studies, and make it harder to keep volunteers enrolled if they are eligible for the first vaccine.

Situations in which use of a placebo in vaccine trials may be justifiable when there is already an efficacious vaccine

WHO report

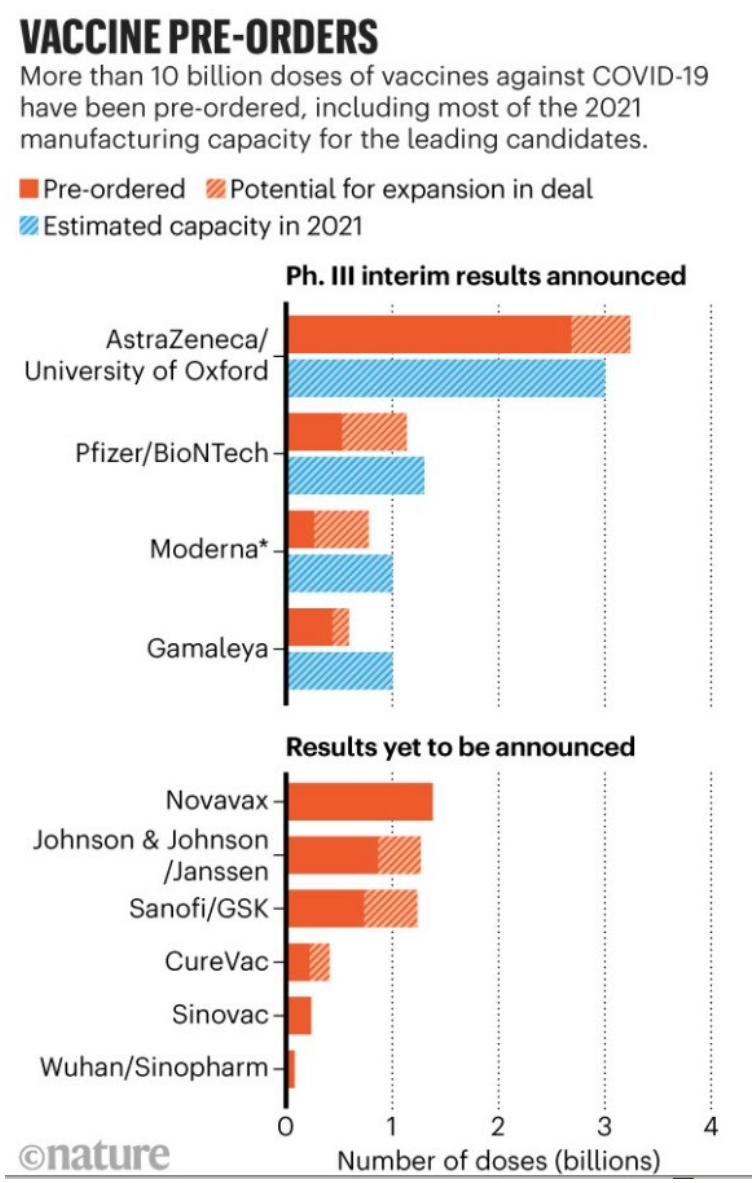
Placebo use in vaccine trials: Recommendations of a WHO expert panel

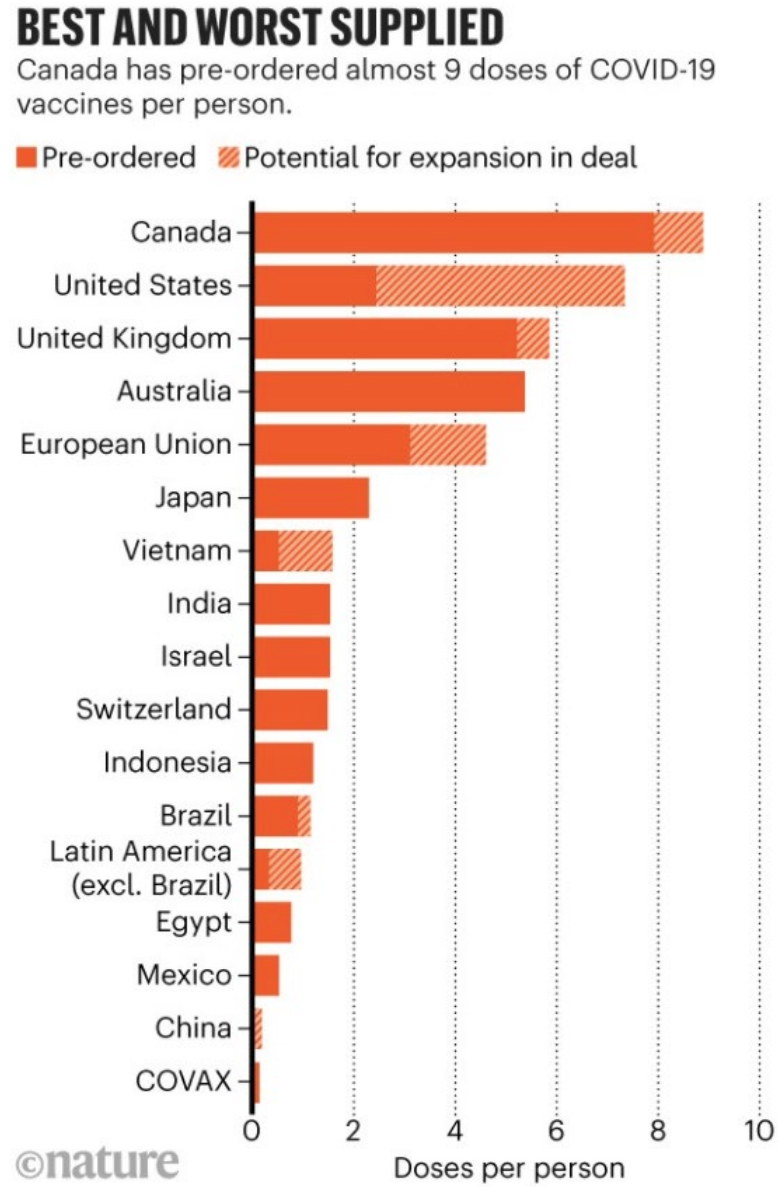
Annette Rid[a,*], Abha Saxena[b], Abdhullah H. Baqui[c], Anant Bhan[d], Julie Bines[e], Marie-Charlotte Bouesseau[f], Arthur Caplan[g], James Colgrove[h], Ames Dhai[i], Rita Gomez-Diaz[j], Shane K. Green[k], Gagandeep Kang[l], Rosanna Lagos[m], Patricia Loh[n], Alex John London[o], Kim Mulholland[p], Pieter Neels[q], Punee Pitisuttithum[r], Samba Cor Sarr[s], Michael Selgelid[t], Mark Sheehan[u], Peter G. Smith[v]

1. Developing a locally affordable vaccine (e.g. Rotavac in India)
2. Evaluating the local safety and efficacy of an existing vaccine (e.g. Rotarix and Rotateq in Africa)
3. Testing a new vaccine when an existing vaccine is not yet in local use (e.g. Rotasil in Niger) – likely to be relevant for COVID-19 vaccines
4. Determining the local burden of disease (e.g. vaccine-probe studies – Hib)

Options for further evaluation of SARS-CoV-2 vaccines

1. Continue blinded follow-up of participants in existing trials until they become eligible for vaccination in national programme and wish to receive a vaccine nationally available.
    - Will depend upon what commitment was given by Sponsor at entry to the trial.
2. Conduct placebo-controlled trials of new vaccines, including only individuals not (yet) eligible for vaccination in national programme.
    - In many populations vaccine supply will be insufficient to vaccinate more than 20% of population by end 2021 (COVAX).
    - Will have to bridge efficacy results (immunologically) from trial to population groups not in trial.
    - Safety studies (uncontrolled?) may be needed in excluded population groups.
3. Conduct head-to-head efficacy studies of new vaccine against existing efficacious vaccine
    - Unlikely to be feasible because of large study size required and may not be easy to recruit volunteers.
4. Evaluate new vaccine based on an established immunological correlate of protection
    - First have to identify such a correlate and then be reasonably sure it can be used across different vaccines, including those using different platforms.
5. Compare efficacies of new and existing vaccines in human challenge studies
    - Can only conduct in individuals at very low risk of serious disease from challenge
    - Difficult to bridge from efficacy in this group to those at higher risk of severe disease





COVAX has secured an estimated 700 million vaccine doses so far and wants to provide 2 billion by the end of 2021, with the aim of providing coverage to at least 20% of the population of participating countries

https://www.nature.com/articles/d41586-020-03370-6?utm_source=Nature+Briefing&utm_campaign=cb475c9587-briefing-dy-20201201&utm_medium=email&utm_term=0_c9dfd39373-cb475c9587-45884934

Thank you

WHO Prioritisation of COVID-19 Vaccine allocation

Strategy: Initial focus on direct reduction of morbidity and mortality and maintenance of most critical essential services; also, reciprocity. Expand to reduction in transmission to further reduce disruption of social and economic functions.

Stage I (1-10%)

Stage Ia (initial launch)

- Health workers at **high to very high risk** of acquiring and transmitting infection

Stage Ib

- Older adults defined by age-based risk specific to country/region

Stage II (11-20%)

- Older adults not covered in Stage I

- Individuals with comorbidities or health states determined to be at **significantly higher risk** of severe disease or death

- Sociodemographic groups at **significantly higher risk** of severe disease or death

- Health workers engaged in immunization delivery

- High priority teachers and school staff

Stage III (21-50%)

- Remaining teachers and school staff

- Other essential workers outside health and education sectors

- Pregnant Women

- Health workers at **low to moderate risk** of acquiring and transmitting infection

- Personnel needed for vaccine production and other high-risk laboratory staff

- Social/employment groups at **elevated risk** of acquiring and transmitting infection because they are unable to effectively physically distance