How can we accelerate randomised trials of COVID-19 vaccines and preventative treatments?

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Introduction: There are over 100 candidate vaccines and treatments being evaluated to prevent infection with SARS-CoV-2. Most randomised clinical trials are statistically powered to demonstrate reductions of SARS-CoV-2 infections of at least 50%. However, these clinical trials show a wide range of inclusion criteria, primary endpoints and sample sizes.

Methods: We reviewed 83 prevention (PrEP – pre-exposure prophylaxis and PEP – post-exposure prophylaxis) and vaccine phase III trials registered on clinicaltrials.gov with 400 or more participants and collected data on primary endpoints, sample sizes and study designs. We also analysed in more detail the protocols for 10 studies, which had data available regarding their estimated attack rates and power calculations. We conducted power calculations to determine the sample size of two-arm trials required to detect a 50% reduction in infection at 80% power and at the $p<0.05$ significance level. We conducted an additional search on PubMed and EMBASE to gather the incidence rates of COVID-19 in available studies that reported both nasopharyngeal swab PCR results and percentage of symptomatic individuals.

Results: Of the 83 trials reviewed, inclusion criteria were either healthcare workers, other at-risk populations or the general population. Primary efficacy endpoints included either any symptomatic infection, moderate/severe symptomatic infection only, PCR positive results or a combination of PCR positivity with symptoms. Study primary endpoints were heterogeneous, for example in their definitions of 'symptomatic infection' as some would include anosmia, headache, fever, cough or breathlessness whilst others did not, and some studies would require two PCR positive tests for case confirmation whilst others did not. Total sample sizes ranged from 440 to 43,998 for two-arm studies. We identified 18 prospective, observational studies of infection without vaccines or treatment in different populations including healthcare workers, nursing home residents and close contacts (Table 1) that reported PCR positive and symptomatic infection. With an endpoint of infection rate of both symptomatic and PCR infections, the median infection rate was 9.3%, (range 0.25% to 57.7%). With an endpoint of all PCR positive test results, the median infection rate was 16.7%, (range 0.38% to 100%). A primary endpoint of all PCR positive infections would provide 60% more infections than only including symptomatic infections. Power calculations for two-arm studies showed that 948 participants would be required to demonstrate reductions in infection from 10% on control to 5% on treatment/vaccine, 1968 participants to demonstrate reductions from 5% to 2.5%, and 12682 participants to demonstrate reductions from 0.8% to 0.4%.

Discussion: Healthy volunteers, healthcare workers and other at-risk populations who are willing and able to participate in PrEP, PEP and vaccine studies are generous and a valuable asset in the urgent search for an effective preventative therapy or vaccine for COVID-19. Given limited available resources, vaccine and prevention trials that recruit high-risk populations and use all PCR positive endpoints could be smaller and conducted more quickly. Clinical trials targeting high-risk populations with a primary endpoint of all PCR positive cases could be conducted with 500 patients per arm, versus over 12,500 patients per arm required for trials in the general population using endpoints of symptomatic infection. This approach using all infections as endpoints has previously been adopted in randomised HIV pre-exposure prophylaxis (PrEP) studies.

Table 1: Summary of Viral PCR Positive and Symptomatic Infection Rates.

Country	Population	Sample Size	Follow-up time	No. symptomatic and viral PCR positive	No. viral PCR positive
US	Patients scheduled for surgery	4751	6 weeks	0.25%	0.38%
UK	HCW	1152	2 weeks	1.6%	2.0%
Egypt	HCW	4040	3 weeks	1.3%	4.2%
US	HCW	546	2 weeks	2.6%	7.3%
South America	Pregnant women at delivery	583	6 weeks	3.6%	6.3%
UK	HCW	11,424	10 weeks	4.3%	5.5%
China	HCW	1407	5 weeks	7.6%	10.3%
Japan	Diamond cruise ship	3711	2 weeks	8.2%	16.7%
US	HCW	14,764	8 weeks	9.3%	12.9%
US	HCW	500	8 weeks	11%	17.8%
UK	HCW	266	4 weeks	11.7%	18.0%
France	HCW	92	5 weeks	14.0%	24.0%
US	Nursing home residents	126	30 days	17.5%	26.1%
Argentina	Cruise ship	217	21 days	19.0%	59.0%
US	Nursing home residents	76	3 weeks	26.3%	30.0%
US	Nursing home residents	76	23 days	31.6%	63.0%
China	Close contacts	78	8 weeks	57.7%	100.00%