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

Hannah Wentzel[1], Jacob Levi[2], Anna Garratt[3], Shahini Shah[4], Francois Venter[5], Andrew Hill[6]

[1]School of Public Health Imperial College London, [2]Department of Intensive Care University College London Hospital, [3]Cardiff and Vale University Health Board Cardiff, [4]Faculty of Medicine Imperial College London, [5]Ezintsha Faculty of Health Sciences, [6]Department of Translational Medicine Liverpool University.

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.

In preliminary results, some vaccines have shown efficacy against COVID-19. Pfizer and BioNtech's vaccine has shown up to 95% efficacy[1] against COVID-19 in 43,998 volunteers whilst Moderna's vaccine shows 94.5%[2] in 30,000 volunteers. Future vaccine and prevention trials will need to be conducted as non-inferiority trials, and so the sample sizes required will be even larger.

Methodology

We reviewed 83 prevention (PrEP – pre-exposure prophylaxis and PEP – post-exposure prophylaxis) and vaccine phase III trial protocols that were 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 of these studies, which had data available regarding their estimated attack rates and power calculations. 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. We conducted sample size calculations to determine the sample size of two-arm trials required to determine non-inferiority compared to the 95% efficacy rate of the Pfizer vaccine at 80% power and at the $p<0.05$ significance level. The non-inferiority limit was set at 90% efficacy.

Results

Of the 83 vaccine and prevention clinical 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 (Table 2).

We identified 26 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 7.9%, (range 0% to 71%). With an endpoint of all PCR positive test results, the median infection rate was 9.3%, (range 0.38% to 75%). The ratio of symptomatic infection to all infection tests was 1:1.5.

At the current infection rate in the Pfizer vaccine trial control arm, sample size calculations for two-arm non-inferiority studies showed that 83 246 participants would be required to demonstrate non-inferiority. This assumes a 95% reduction in infection from 0.75% to 0.038% with the Pfizer or Moderna vaccine.

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 (both symptomatic and asymptomatic positive cases) could be conducted at feasible sample sizes to determine non-inferiority compared to current vaccine candidates.

References

1. Pfizer. Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints | Pfizer [Internet]. [cited 2020 Nov 18]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine
2. Moderna. Moderna's COVID-19 Vaccine Cadidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study [Internet]. [cited Nov 19]. Available from:https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy

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	Author
Germany	German nationals repatriated from Hubei province	126	2 weeks	0.0%	1.6%	Hoehl et al
China	Supermarket cluster	8000	2 weeks	0.2%	0.3%	Tian et al
US	Patients scheduled for surgery	4751	6 weeks	0.3%	0.4%	Singer et al
Greece	Repatriats	783	2 weeks	0.6%	5.1%	Lytras et al
China	Close contacts	4950	2 weeks	1.1%	1.3%	Luo et al
Japan	Japanese nationals repatriated from Wuhan	566	2 weeks	1.4%	2.0%	Arima et al
UK	HCW	1152	2 weeks	1.6%	2.0%	Brown et al
Egypt	HCW	4040	3 weeks	1.3%	4.2%	Mostafa et al
China	In-flight transmission	325	2 weeks	2.5%	3.1%	Yang et al
US	HCW	546	2 weeks	2.6%	7.3%	Barrett et al
South America	Pregnant women at delivery	583	6 weeks	3.6%	6.3%	Diaz-corvillon et al
UK	HCW	11,424	10 weeks	4.3%	5.5%	Eyre et al
China	HCW	1407	5 weeks	7.6%	10.3%	Zhao et al
Dubai	Asymptomatic cancer patients	85	4 weeks	8.2%	8.2%	Al-Shamsi et al
Japan	Diamond cruise ship	3711	2 weeks	8.2%	16.7%	Mizumoto et al
US	HCW	14,764	8 weeks	9.3%	12.9%	Nagler et al
US	HCW	500	8 weeks	10.5%	17.8%	Venugopal et al
UK	HCW	266	4 weeks	11.7%	18.0%	Khalil et al
France	HCW	92	5 weeks	14.0%	24.0%	Sacco et al
US	Nursing home residents	126	30 days	17.5%	26.1%	Patel et al
Argentina	Cruise ship	217	21 days	19.0%	59.0%	Ing et al
UK	4 nursing home residences	313	3 weeks	23.0%	40.0%	Graham et al
USA	Nursing home residents	76	3 weeks	26.3%	30.0%	Kimball et al
US	Nursing home residents	76	23 days	31.6%	63.0%	Arons et al
Wuhan	Close contacts of case	78	2 months	57.7%	100.0%	Yang et al
US	Nursing home residents	76	3 weeks	71.0%	75.0%	Mellisa et al

Table 2: Current registered vaccine and prevention trials

Trial ID Link, Location Type of study, Sponsor	Treatment arms Groups: (n)	Total Sample Size (n)	Population (Group, age)	Primary Endpoint
https://ClinicalTrials.gov/show/NCT04368728 **USA** **Vaccine** **Pfizer, BioNTech SE**	Group 1: 21,999 (BNT162b1, Vaccine) Group 2: 21,999 (Placebo)	43,998	Healthy Volunteers 16 – 85 (aim is >40% participants are +55 years)	Rt-PCR positive + Symptoms
https://ClinicalTrials.gov/show/NCT04470427 **Vaccine** **ModernaTX, NIAID, USA**	Group 1: 15,000 mRNA-1273 Vaccine Group 2: 15,000 Placebo	30,000	Healthy Volunteers 18+	Rt-PCR positive + Symptoms
https://ClinicalTrials.gov/show/NCT04516746 **Vaccine** **AstraZeneca, USA**	Group 1: 20,000 AZD1222 Vaccine Group 2: 10,000 Placebo	30,000	Healthy Volunteers 18+	Rt-PCR positive + Symptoms
https://ClinicalTrials.gov/show/NCT04341441 **PrEP** **Henry Ford Health System, USA**	Group 1: 1000 HCQ (daily) Group 2: 1000 HCQ (weekly) Group 3: 1000 Placebo Group 4: Healthcare workers on HCQ for other diseases (non-randomised comparator group)	3,000	Healthy Volunteers 18 – 75 + HCW or first responders in group 4	Rt-PCR positive + Symptoms
https://ClinicalTrials.gov/show/NCT04483635 **PrEP** **Canadian Institutes of Health Research, Canada**	Group 1: 1,212 Vit D PrEP Group 2: 1,212 Placebo	2,414	Healthcare Workers 18 - 69	Rt-PCR Positive
https://ClinicalTrials.gov/show/NCT04534803 **Vaccine** **Harvard Medical School , USA**	Group 1: 1,050 BCG Vaccine Group 2: 1,050 Placebo	2,100	Elderly nursing home residents >70 years old	Severe symptoms only
https://ClinicalTrials.gov/show/NCT04400019 **PrEP** **University of Malaga, Spain**	Group 1: HCQ Group 2: Placebo	1,930	Healthcare workers (880 participants) and nursing home residents (1050) 18+	Rt-PCR Positive Only
https://ClinicalTrials.gov/show/NCT04542330 **Vaccine,** **Bandim Health Project, Denmark**	Group 1: 950 BCG Vaccine Group 2: 950 Placebo	1,900	Healthy Volunteers >65 years old - 110	Mild or Severe Symptoms
https://ClinicalTrials.gov/show/NCT04328467 **PrEP** **University of Minnesota, USA** **Published:** https://pubmed.ncbi.nlm.nih.gov/33068425/	Group 1: 500 HCQ PrEP Group 2: 500 2x HCQ PrEP Group 3: 500 Placebo	1,500	Healthcare Workers 18+	Rt-PCR positive + Symptoms
https://ClinicalTrials.gov/show/NCT04336748 **Austria, PrEP, Medical University of Vienna**	Group 1: 220 HCQ PrEP Group 2: 220 Placebo	440	Healthcare Workers	Rt-PCR positive Only

Presented at RespiDART & Emerging Viruses Conference | 17 December 2020

Corresponding Author: Hannah Wentzel
School of Public Health, Imperial College London
hbw19@ic.ac.uk