Monthly medical update – Issue 5

4 December 2020

By Nicola Oliver and Dan Ryan for

COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.

Given the pace of change with 'all things COVID', it can be hard – even for those who follow all the updates – to know what the overall state of play is regarding medical developments in particular, as opposed to just the most recent news. In this new type of Bulletin, we provide a summary of what we believe the current medical position to be. We will aim for these summaries to be accurate as at the date of publication, but they will of course date rapidly, so we plan to issue an updated summary each month.

Vaccines

As at 30 November 2020, the following potential vaccines were in clinical trials[1][2]:

Stage	Phase 1	Phase 1/2	Phase 2	Phase 3
Vaccine Candidates	32	23	11	13

Three more candidates have reached phase 3 since our last update. These include two inactivated vaccines being developed by Bharat Biotech in Canada and Medicago in India, and a protein sub-unit vaccine being developed by Anhui Zhifei Longcom Biopharmaceutical in China.

There are 163 candidate vaccines in preclinical evaluation which is a significant drop from last month (over 200), and it may be that the success of the three recently announced phase 3 trials has had an impact. Regulatory bodies have conducted rolling evaluation of the trial results hence they are able to provide much faster responses to authorisation applications than normal.

Phase 3 results

Moderna

The Moderna vaccine is an mRNA vaccine: fragment codes for a part of the virus instruct the host cell to make copies of this fragment of genetic material, thus provoking an immune response in the host which prepares you for the next time you encounter the virus. The vaccine is called mRNA-1273. Moderna have announced that interim analysis of its phase III trial showed it was 94.5% effective.

The company plans to file a request for emergency use authorization (EUA) for its vaccine with the U.S. Food and Drug Administration (FDA), and has submitted an application to the European Medicines Agency (EMA) for conditional marketing authorisation. The UK Government has reportedly secured five million doses.

Pfizer/BioNTech

The Pfizer/BioNTech vaccine is also an mRNA vaccine, and the phase 3 results report up to 95% protection against COVID-19. This vaccine has now been approved for use in the UK (the first country to approve it), and the government has reportedly ordered 40 million doses, enough for 20 million people, and plans to start administration next week. The Joint Committee on Vaccination and Immunisation (JCVI) have issued updated priority groups for the vaccine, as detailed in the JCVI segment below.

---

[1] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
[2] https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

This vaccine has more complex storage requirements than the Moderna vaccine: it must be kept at around -70C and also has to be mixed with another liquid before it can be administered. The Moderna vaccine has been shown to last for up to 30 days in household fridges, at room temperature for up to 12 hours, and remains stable at -20C (i.e. most household or medical freezers) for up to six months.

AstraZeneca/Oxford

The AstraZeneca vaccine is a viral vector vaccine which use a different virus that has been weakened in order to deliver the genetic code for the SARS-CoV-2 virus to the host. This vaccine puts the code for the spike protein into the genetic information of a completely different virus that is harmless to humans. The viral vector in the Oxford vaccine is derived from a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees.

This vaccine does not have complex storage requirements and can be shipped like most standard vaccines in cool boxes.

The Oxford trial found with two doses its vaccine was 62% effective, but when people were given a half dose followed by a full dose at least a month later its efficacy rose to 90%. It is not clear, however, if the dosing schedules were deliberate or inadvertent. Clarification is awaited from both the University of Oxford and AstraZeneca.

Vaccines and infectiousness

While most of the attention for all of the vaccines has been on the ability to prevent symptomatic infections and severe COVID-19, the press release from the Astrazeneca/Oxford trial provided an early indication that the vaccine could reduce virus transmission through reducing asymptomatic infections. This was possible to state because the Astrazeneca/Oxford trial has been swabbing participants on a weekly basis, regardless of symptoms.

JCVI

The Joint Committee on Vaccination and Immunisation (JCVI) advises that the first priorities for any COVID-19 vaccination programme should be the prevention of COVID-19 mortality and the protection of health and social care staff and systems (link). JCVI have advised that the Pfizer vaccine be used in the first phase of the programme. The priority list is:

1. residents in a care home for older adults and their carers
2. all those 80 years of age and over and frontline health and social care workers
3. all those 75 years of age and over
4. all those 70 years of age and over and clinically extremely vulnerable individuals
5. all those 65 years of age and over
6. all individuals aged 16 years to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality
7. all those 60 years of age and over
8. all those 55 years of age and over
9. all those 50 years of age and over

The focus for the second phase of vaccination could be on further preventing hospitalisation. Vaccination of those at increased risk of exposure to SARS-CoV-2 due to their occupation could also be a priority in the next phase. This could include:

1. first responders
2. the military
3. those involved in the justice system
4. teachers
5. transport workers
6. public servants essential to the pandemic response

Treatment

At the start of the pandemic when the mechanism by which the SARS-CoV-2 virus entered cells was still being investigated, a number of early studies had suggested that ACE inhibitors and angiotensin receptor blockers, used in the treatment of hypertension, may have increased the risk of infection and the likelihood of survival for infected patients. However, these studies were thought to be insufficiently powerful and clinical guidance was to continue these treatments once prescribed. A succession of studies have further investigated the risks, and supported the continued guidance.

A recent pre-print study provides the most comprehensive meta-analysis of the use of these treatments involving 69,000 COVID-19 patients and 3 million controls , and concludes that there is no increased risk of either severe COVID-19 or mortality for those taking ACE inhibitors or ARBs.

In early November, aspirin was added to the list of treatments that will be evaluated in the RECOVERY trial that has so far recruited over 16,000 patients. Aspirin has a constellation of beneficial actions that may help COVID-19 patients including lowering fever, pain relief reducing inflammation and preventing blood clots, but is contraindicated for those already at a high risk of bleeding. The trial will investigate the benefits of aspirin 150mg daily in addition to standard-of-care. Low molecular weight heparin, another blood thinner, is already recommended for prophylactic use in preventing venous thrombo-embolism.

This extends the list of treatments that are currently being investigated in the RECOVERY trial to the following, after the successful demonstration of the benefits of dexamethasone in adult patients:

- Low dose dexamethasone (for children)
- Colchicine
- Tocilizumab
- Convalescent plasma (first person in November to be both donor and recipient)
- REGN-COV2
- Aspirin

Antibodies

In addition to the REACT-2 study in England, other countries have been carrying out regular surveys of seroprevalence in the population. The CDC is working with a range of government, academic and commercial partners in the USA. One output has been the Nationwide Commercial Laboratory Seroprevalence Study. The study is repeated every 2 weeks, and the most recent results relate to the beginning of October. At that time, seropositivity ranged from 0.4% of the population in Alaska to 15.1% in New Jersey, with the highest rates seen in younger age groups (22.3% for 0-17 yrs vs 9.5% for 65+ yrs).

Testing

A pilot study of community mass testing in Liverpool during the partial England lockdown in November has been credited in reducing case rates down by 75% , although it is difficult to extract the effect that the lockdown will have had on people mixing. The UK Government announced on 30 November that community testing would be available over a 6-week period on application for all local authorities entering or returning Tier 3 on 2 December. However, the Community Testing Program has raised doubts as to whether this service could be rolled out to a population of 23 million people, and stated that different local authorities are at very different levels of preparedness.

The intention is to use lateral flow assay tests that do not require a lab on nasal swabs, and results are displayed within 15 to 30 minutes. The goal is rapid detection at the expense of sensitivity. According to evaluation by

Porton Down, 70% of all PCR-positive tests would be detected whilst over 99% of all PCR-negative tests would be reported as negative. In Liverpool, at present, current PCR testing capacity is 580,000.

Interim results have also been released from round 7 of the ongoing REACT-1 study (tests over the period 13 November to 24 November). These indicated a weighted prevalence of positive cases of 0.96%, leading to a national estimate of R_t of 0.71. Sub-regional analyses suggested significant declines in the North West and North East with increasing rates in the East Midlands and West Midlands. Further analysis indicated a strong socio-economic gradient, and relatively higher levels of positivity in the largest households.

The following table illustrates the prevalence of positive swabs from all of the rounds so far in the REACT-1 study.

Table 1. Unweighted and weighted prevalence of swab-positivity across seven rounds of REACT-1.

Round	Tested swabs	Positive swabs	Unweighted prevalence (95% CI)	Weighted prevalence (95% CI)	First sample	Last sample
1	120,620	159	0.13% (0.11%, 0.15%)	0.16% (0.13%, 0.19%)	1/5/2020	1/6/2020
2	159,199	123	0.077% (0.065%, 0.092%)	0.088% (0.068%, 0.11%)	19/6/2020	7/7/2020
3	162,821	54	0.033% (0.025%, 0.043%)	0.040% (0.027%, 0.053%)	24/7/2020	11/8/2020
4	154,325	137	0.089% (0.075%, 0.11%)	0.13% (0.096%, 0.15%)	20/8/2020	8/9/2020
5	174,949	824	0.47% (0.44%, 0.50%)	0.60% (0.55%, 0.71%)	18/9/2020	5/10/2020
6	160,175	1732	1.08% (1.03%, 1.13%)	1.30% (1.21%, 1.39%)	16/10/2020	2/11/2020
6a	85,965	863	1.00% (0.94%, 1.07%)	1.28% (1.16%, 1.42%)	16/10/2020	25/10/2020
6b	74,210	869	1.17% (1.10%, 1.25%)	1.32% (1.20%, 1.45%)	26/10/2020*	2/11/2020
7a	105,123	821	0.78%(0.73%, 0.84%)	0.96% (0.87%, 1.05%)	13/11/2020**	24/11/2020**

*Includes small number of samples from prior period

**Small number of samples collected on 13 - 15 Nov and 24 Nov

Round 7a is updated with data on 25 Nov, not complete.

Long COVID

Long COVID describes persistent and debilitating symptoms following infection with SARS-CoV-2 which includes chronic joint and muscle pain, insomnia, reduced exercise tolerance, shortness of breath, mental health issues and headaches.

Predictors of long COVID risk were identified in this study which reported that increasing age, females sex, and requiring initial hospital assessment were all significant predictors. In addition, in those aged over 70 years, fever, loss of smell and comorbidities were most predicative of long COVID.

Qualitative analysis reports that persisting symptoms seem to fall into three categories:

- people who were initially hospitalised with acute respiratory distress syndrome (ARDS) and now have long-term respiratory symptoms dominated by breathlessness
- people who were not hospitalised initially but who now have a multisystem disease with evidence of cardiac, respiratory, or neurological end-organ damage manifesting in a variety of ways
- people who have persisting symptoms, often but not always dominated by fatigue, with no evidence of organ damage

4 December 2020