Monthly medical update – Issue 3

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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 September 2020, the following potential vaccines were in clinical trials[1]:

Stage	Phase 1	Phase 1/2	Phase 2	Phase 3
Vaccine Candidates	23	20	6	10

The number of vaccine trials in phase 1, phase 1-2 and phase 2 have almost doubled since our last update. There are an additional 2 in phase 3, the more advanced stage. In phase 3 trials, researchers test the efficacy of the vaccine, while monitoring for adverse reactions in hundreds to thousands of volunteers.

In addition, there are 151 preclinical trials in progress for vaccines to tackle SARS-CoV-2, a small increase of 10 since our last update. These increases are indicative of the race to develop a vaccine and secure approval at a pace not previously witnessed.

Following a pause for all of the global trials of the vaccine being investigated by the University of Oxford, it has been announced that these have now resumed. The pause was to allow the review of safety data by an independent safety review committee and national regulators. Phase 3 trials have been launched in the UK, Brazil, South Africa and the US.

The team at Oxford has also expressed interest in conducting 'challenge studies' on humans, meaning they would deliberately infect low-risk volunteers with the virus, either alongside phase 3 trials or after they are complete.

Johnson and Johnson have recently announced the launch of its large-scale, multi-country Phase 3 trial (ENSEMBLE) for its COVID-19 vaccine candidate, JNJ-78436735. This will be a randomized, double-blind, placebo-controlled clinical trial (ie the best possible) designed to evaluate the safety and efficacy of a single vaccine dose versus placebo in up to 60,000 adults 18 years old and older. The trial aims to cover Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and the United States.

Finally, it has been reported that 90% of Sinovac Biotech Ltd employees and their families have taken the coronavirus vaccine in phase 3 developed by the Chinese firm under the country's emergency use program; the candidate vaccine was offered to approximately 2,000 to 3,000 employees and their families on a voluntary basis.

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

Treatment

The RECOVERY trial aims to compare a range of different treatments that have been recommended to the Chief Medical Officer, Dr Chris Whitty, by an expert panel. The trial, open to all hospitalised patients with confirmed COVID-19 in the UK, has so far recruited 13,000 patients and involves the addition of one of the following treatments to usual care:

- Low-dose Dexamethasone (now only recruiting children)
- Azithromycin (a commonly used antibiotic)
- Tocilizumab (an anti-inflammatory treatment given by injection)
- Convalescent plasma (collected from donors who have recovered from COVID-19 and contains antibodies against the SARS-CoV-2 virus)
- REGN-COV2 (a combination of monoclonal antibodies directed against coronavirus).

REGN-COV2, produced by Regeneron, is the first therapy to be tested in the RECOVERY trial that was specifically designed for COVID-19. It was announced on 14 September that REGN-COV2 was being studied in Phase 3 trials on both the treatment of COVID-19 and on the prevention of COVID-19 in household contacts of infected individuals.

Analysis of seven trials, including results from the RECOVERY trial, on the use of one of three corticosteroids dexamethasone, hydrocortisone and methylprednisolone concluded that 28 day survival increased to 68% compared with 60% without treatment.

Testing

The issue of the accuracy of testing for COVID-19 has recently garnered a great deal of media attention; this issue will be covered in an upcoming bulletin. Here we note two points of recent interest:

- A rapid antigen test has been approved for use in Europe. Becton Dickinson, the manufacturer, said it is on track to produce about 8 million each month by October across its global markets, and 12 million monthly by March 2021. The test can return results in 15 minutes and will likely be used initially by emergency departments, general practitioners and paediatricians.
- Other rapid, point-of-care tests (POC) include this kit from Roche who plan to launch imminently and it will be used by health professionals and will also return a result in 15 minutes. And similarly, lumiradx have announced both FDA and European approval for their rapid POC test.

None of these POC tests are 100% accurate, but they are a significant step towards improved control of the pandemic.

Antibodies

The REACT-2 programme in England is a series of 5 studies that are assessing the accuracy of antibody tests, their ease of use at home and the prevalence of antibodies in the community. The most recent results on the last study (involving 109,076 participants) were released on 13 August and indicated that the prevalence of antibodies in June/July was 6%, with those aged 65 to74 having the lowest prevalence of 3%.

Detectable levels of antibodies were found in more than 16% of care home workers and 12% of healthcare professionals with patient-facing roles. Positive results in Black, Asian and other non-white ethnic groups were found in 17%, 12% and 12% of cases respectively, three times as high as white individuals. The study is currently being repeated with an increased cohort of 200,000 participants.

The main antibody tests currently used in the UK are the Abbott SARS-CoV-2 assay which detects IgG antibodies and the Roche Elecsys assay which detects IgM and IgG antibodies. These tests are chemiluminescence immunoassays (CLIA) that are carried out in a laboratory, whilst point of care tests such as the UK-Rapid Test Consortium "AbC-19TM Rapid Test" will be increasingly available. However, none of these looks at IgA

antibodies which are found in secretions such as saliva, tears and mucus, and which would represent a first line of defence against subsequent infection.

A Cochrane review of 57 publications indicated the patterns of sensitivity of tests for different classes of antibodies over time such that broadly 30% of those with COVID-19 detected 1 week after symptoms, 70% after 2 weeks and 90% after 3 weeks. Whilst the authors did not find convincing differences in accuracy between the different types of test, it is interesting that IgA antibody tests had the highest sensitivity from day 8 onwards. Further, if the true rate of COVID-19 was 5%, the authors predicted that at 3 weeks after symptoms, 21% of positive tests would be false-positives and 0.4% of negative tests would be false negatives.

Table 1 | Sensitivity and specificity by time since symptom onset[6]

	Sensitivity					Specificity
	Days 1-7	Days 8-14	Days 15-21	Days 22-35	Days >35	All time points
IgG*	29.7% (22.1-38.6)	66.5% (57.9-74.2)	88.2% (83.5-91.8)	80.3% (72.4-86.4)	86.7% (79.6-91.7)	99.1% (98.3-99.6)
IgM	23.2% (14.9-34.2)	58.4% (45.5-70.3)	75.4% (64.3-83.8)	68.1% (55.0-78.9)	53.9% (38.4-68.6)	98.7% (97.4-99.3)
IgA	28.4% (0.9-94.3)	78.1% (9.5-99.2)	98.7% (39.0-100)	98.7% (91.9-99.8)	100% (85.2-100)	
IgG or IgM*	30.1% (21.4-40.7)	72.2% (63.5-79.5)	91.4% (87.0-94.4)	96.0% (90.6-98.3)	77.7% (66.0-86.2)	98.7% (97.2-99.4)

Long COVID

We recently covered the emerging condition described as long COVID. Persistent and on-going symptoms of COVID-19 are being reported widely by patients of all ages and spectrum of disease severity, and includes chronic pain and fatigue, respiratory problems, and mental health issues. This condition could present us with a significant future burden of morbidity.

This pre-print study sought to analyse who might be most at risk of developing long COVID by focussing on the prevalence of chronic fatigue. Hospitalisation was not seen as a risk factor; however, females and those with a pre-existing diagnosis of depression or anxiety were at higher risk.

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