What have been the major contributions of pathology to managing COVID-19?

By Rebecca Sarsam

Since initial reports of a cluster of cases of 'pneumonia of unknown origin' in Wuhan City, China in December 2019[1], massive advances have been made in only 18 months- from the identification and genome sequencing of the causative viral pathogen SARS-CoV-2 in January 2020[2], to the development of effective testing for the virus using PCR tests (January 2020)[3], tests for neutralising antibodies (approved May 2020)[4] and lateral flow tests (confirmed to be sufficiently accurate in November 2020)[5]. In addition, knowledge of the clinical picture of COVID-19 has evolved since its discovery, from fever, dyspnea and invasive lesions of both lungs on chest radiographs[1] to a more systemic condition affecting multiple organ systems such as the heart, kidneys and gastrointestinal tract[6]. Treatments reducing mortality have been trialed and integrated into clinical practice, such as dexamethasone for hospitalised patients[7]. New variants of SARS-CoV-2 have been identified and tracked[8]. And finally and most importantly, a number of effective vaccines against COVID-19 have been created[9-11].

At each stage, the contributions of pathologists such as virologists, histopathologists and immunologists to combating the COVID-19 pandemic have been vital.

Initially, SARS-CoV-2 was isolated by a team of Chinese virologists led by Zhang Yongzhen, from swab samples from the initial outbreak of pneumonia of unknown origin in Wuhan, and the genome of the novel virus was published on virological.org[2]. From the discovery of the similarity of the novel coronavirus to SARS, Zhang was also able to suggest that the virus was spread by respiratory transmission and was likely to be more dangerous than influenza/H5N1 Avian flu and that it was therefore vital to enact public health measures to protect against the new disease[12].

Having access to the genome sequence of SARS-CoV-2 allowed diagnostic PCR tests for COVID-19 to be developed rapidly- from the publication of the genome on January 11th, Malaysian virologists were able to create and optimise a real-time PCR test for COVID-19 by January 21st, with a similar protocol published by the World Health Organisation days later, allowing testing for patients with suspected COVID and isolation and contact tracing of early cases[3,13]. Though COVID tests were scarce during the initial stages of the pandemic and contract tracing systems became overwhelmed, the development of effective PCR testing for COVID-19 by pathologists placed the nation in a far stronger position to respond to the pandemic in later months. The discovery by virologists that SARS-CoV-2 RNA is shed not only in respiratory secretions, but also in the faeces of infected individuals[14] allowed wastewater testing to be in place to provide an 'early warning system' to detect localised COVID outbreaks[15].

Pathology labs carrying out PCR tests were able to acquire massive numbers of genome sequences from SARS-CoV-2 infections, which were used to monitor the development of mutations and analyse whether new variants were more contagious or deadly[16]. The discovery of the highly contagious B117 variant in Kent in late 2020 enabled public health measures to be put in place before case numbers were extremely

high to slow the spread of the virus and prevent hospital systems from becoming overwhelmed[17]. The ability to track variants has also been vital to efforts to prevent the spread of variants from abroad, by allowing detection of variants before they become widespread in the country and may still be contained by contact tracing and isolation measures[8].

During the pandemic, the work of histopathologists has also been incredibly important in understanding the pathogenesis of COVID-19, aiding advances in treatment. For example, post-mortem studies of patients who died from COVID-19 were used to show that immunopathology plays a large role in severe COVID-19, while virally-infected cells were only sporadically present late in the disease course[18]. These findings, in addition to preliminary data from the RECOVERY trial[7], added evidence in favour of the use of immunomodulatory therapies such as low-dose dexamethasone in treatment of severe COVID-19 which many guidelines considered either contraindicated or not recommended early in the pandemic due to the risk of delayed viral clearance[19]. Dexamethasone was shown in the RECOVERY trial to reduce mortality by one third in ventilated COVID-19 patients, and its use to treat COVID-19 has been estimated to have saved one million lives globally[20].

The journey from discovery of a new virus to development of numerous effective vaccines in less than a year has been a historical first, made possible by the essential contributions of immunologists to the vaccine effort. Vaccinology research at Oxford's Jenner Institute developing a vaccine against MERS (also a coronavirus) had shown that use of a viral vector platform using chimpanzee adenoviruses was effective in inducing a strong immune response. By repurposing this technology for COVID-19 vaccine development, scientists were able to cut down on the time required to prepare for clinical trials, allowing the vaccine to reach approval faster[21]. Messenger RNA vaccines had also been in progress before the pandemic began, against influenza (BioNTech)[22] and various forms of cancer (Moderna)[23]. Scientists at these companies started vaccine development in January 2020 using the genome sequence published by Zhang's team, leading to clinical trials beginning in April 2020[24,25]. The creation of antibody tests for the SARS-CoV-2 spike protein allowed immunogenicity of the new vaccines to be researched[26]. Development of the vaccine candidates so early after the novel virus was discovered allowed manufacturing to start early during the pandemic, increasing the supply of doses available in late 2020 and early 2021.

In conclusion, a historically unparalleled response to the novel disease has been achieved over the last year and a half. As cases and deaths dwindle in many countries including the United Kingdom, it has clear that the contributions of pathology to this process have been critical. From discovering the causative virus, to developing and interpreting testing, to researching the pathogenesis of the disease in order to suggest treatment, and most recently to the development of multiple highly effective vaccines: without pathology, the chasm between this viral pandemic and recovery could not be bridged.

References:

[1]World Health Organisation. *Pneumonia of unknown origin- China.* Available from: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/ (accessed 14/05/2021)

[2]Edward Holmes. *Novel 2019 Coronavirus Genome.* Available from: https://virological.org/t/novel-2019-coronavirus-genome/319 (accessed 14/05/2021)

[3]Director General of Health, Malaysia. *Laboratory readiness for detecting the 2019 novel coronavirus (2019-nCOV) infection in Malaysia.* Available from: https://kpkesihatan.com/2020/02/13/laboratory-readiness-for-detecting-the-2019-novel-coronavirus-2019-ncov-infection-in-malaysia/ (accessed 14/05/2021)

[4]US Food and Drug Administration. *EUA Authorized Serology Test Performance.* Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance (accessed 14/05/2021)

[5]Department of Health and Social Care. *Oxford University and PHE confirm high sensitivity of lateral flow tests.* Available from: https://www.gov.uk/government/news/oxford-university-and-phe-confirm-high-sensitivity-of-lateral-flow-tests (accessed 14/05/2021)

[6]Vishwajit Deshmukh, Rohini Motwani, Ashutosh Kumar, Chiman Kumari & Khursheed Raza. Histopathological observations in COVID-19: a systematic review. *Journal of Clinical Pathology.* 2020. 74(2): 76-83. Available from: https://jcp.bmj.com/content/74/2/76.info (accessed 14/05/2021)

[7]The RECOVERY Collaborative Group. Dexamethasone in hospitalised patients with COVID-19. *New England Journal of Medicine.* 2021. 384: 693-704. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2021436 (accessed 14/05/2021)

[8]Public Health England. *Confirmed cases of COVID-19 variants identified in UK.* Available from: https://www.gov.uk/government/news/confirmed-cases-of-covid-19-variants-identified-in-uk (accessed 14/05/2021)

[9]Merryn Voysey, Sue Ann Costa Clemens, Shabir A Madhi, Lily Y Weckx, Pedro M Folegatti, Parvinder K Aley et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa and the UK. *The Lancet.* 2021. 397(10269): 99-111. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext (accessed 14/05/2021)

[10]Fernando P. Pollack, Stephen J. Thomas, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart et al. Safety and efficacy of the BNT162b2 mRNA COVID vaccine. *New England Journal of Medicine.* 2020. 383: 2603-2615. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2034577 (accessed 14/05/2021)

[11]Lindsey R. Baden, Hana M. El-Sahly, Brandon Essink, Karen Kotloff, Sharon Frey, Rick Novak et al. Efficacy and safety of mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine.* 2021. 384: 403-416. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2035389 (accessed 14/05/2021)

[12]Charlie Campbell/Shanghai. *Exclusive: The Chinese scientist who sequenced the first COVID-19 genome speaks out about the controversies surrounding his work.* Available from: https://time.com/5882918/zhang-yongzhen-interview-china-coronavirus-genome/ (accessed 14/05/2021)

[13]World Health Organisation. *Diagnostic detection of 2019-nCoV by real-time PCR.* Available from: https://www.who.int/docs/default-source/coronaviruse/protocol-v2-1.pdf?sfvrsn=a9ef618c_2 (accessed 14/05/2021)

[14]Yifei Chen, Liangjun Chen, Qiaoling Deng, Guqin Zhang, Kaisong Wu, Lan Ni et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. *Journal of Medical Virology.* 2020. 92(7): 833-840. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25825 (accessed 14/05/2021)

[15]Department for Environment, Health and Rural Affairs, Environmental Agency, Department of Health and Social Care, The Rt Honourable George Eustice MP, The Rt Honourable Matt Hancock, MP. *Sewage signals early warning of coronavirus outbreaks.* Available from: https://www.gov.uk/government/news/sewage-signals-early-warning-of-coronavirus-outbreaks (accessed 14/05/2021)

[16]The Royal College of Pathologists. *COVID-19 testing: a national strategy.* Available from: https://www.rcpath.org/uploads/assets/2e8d8771-f85a-408a-b5c8e68969cd21d5/5293a4bb-cd96-42ff-8de231d47e637aab/RCPath-COVID-19-testing-a-national-strategy.pdf (accessed 14/05/2021)

[17]James Gallagher. *New Coronavirus variant: What do we know?* Available from: https://www.bbc.co.uk/news/health-55388846 (accessed 14/05/2021)

[18]Bernadette Schurink, Eva Roos, Teodora Radonic, Ellis Barbe, Catherine SC Bouman, Hans H de Boer, Godelieve J de Bree et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe.* 2020. 1(7): e290-299. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7518879/ (accessed 14/05/2021)

[19]Andrew Dagens, Louise Sigfrid, Erhui Cai, Sam Lipworth, Vincent Cheng, Eli Harris et al. Scope, quality and inclusivity of clinical guidelines produced early in the COVID-19 pandemic: rapid review. *The British Medical Journal.* 2020. 369: m1936. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7249097/ (accessed 14/05/2021)

[20]NHS England. *COVID-19 treatment developed in the NHS saves a million lives.* Available from: https://www.england.nhs.uk/2021/03/covid-treatment-developed-in-the-nhs-saves-a-million-lives/ (accessed 14/05/2021)

[21]University of Oxford. *Oxford team to begin novel coronavirus vaccine research.* Available from: https://www.ox.ac.uk/news/2020-02-07-oxford-team-begin-novel-coronavirus-vaccine-research (accessed 14/05/2021)

[22]BioNTech. *BioNTech signs collaboration agreement with Pfizer to develop mRNA based vaccines for prevention of influenza.* Available from: https://biontechse.gcs-web.com/news-releases/news-release-details/biontech-signs-collaboration-agreement-pfizer-develop-mrna-based (accessed 14/05/2021)

[23]Andrew Pollack. *AstraZeneca makes a bet on an untested technique.* Available from: https://www.nytimes.com/2013/03/21/business/astrazeneca-to-pay-240-million-to-moderna-therapeutics.html (accessed 14/05/2021)

[24]Pfizer. *BioNTech and Pfizer announce completion of dosing for first cohort of COVID-19 vaccine candidates in Germany.* Available from: https://investors.pfizer.com/investor-news/press-release-details/2020/BioNTech-and-Pfizer-announce-completion-of-dosing-for-first-cohort-of-Phase-1-2-trial-of-COVID-19-vaccine-candidates-in-Germany/default.aspx (accessed 14/05/21)

[25]National Institutes of Health. *NIH clinical trial of investigational vaccine for COVID-19 begins.* Available from: https://www.nih.gov/news-events/news-releases/nih-clinical-trial-investigational-vaccine-covid-19-begins (accessed 14/05/2021)

[26]Roche. *Roche launches new quantitative antibody test to measure SARS-CoV-2 antibodies to support the development of vaccines.* Available from: https://www.roche.com/media/releases/med-cor-2020-09-18b.htm (accessed 14/05/2021)