News from here and there

India produces world's first Covid-19 DNA vaccine for adolescents and adults

There is an increased interest in DNA vaccines against Covid-19. This is because of technical advances including novel formulations, better delivery mechanisms and gene optimization techniques. On 20 August 2021, the CDSCO (Central Drugs Control Standard Organisation) granted emergency use authorization to Zydus Cadila's ZyCoV-D. This is the world's first DNA vaccine against Covid-19, and also the world's and India's first needle-free Covid-19 vaccine. It will be used in people aged 12 years and above.

The three-dose ZyCoV-D will be administered into the skin using a disposable needle-free injector every 28 days. The injector delivers the vaccine in a narrow stream of fluid. Interim results from a phase 3 clinical trial involving over 28 000 participants showed that the vaccine was 67% effective in preventing symptomatic infections. After the second dose of the vaccine, there were no severe cases or Covid-19-related deaths, and there were no moderate cases after the third dose.

ZyCoV-D contains an engineered plasmid with a promoter sequence and gene for the SARS-CoV-2 spike protein. This plasmid, on entry into the host cell, is transported to the nucleus, where it is used to synthesize a messenger RNA, which is subsequently translated into the viral spike protein in the host cell cytoplasm.

Unlike mRNA vaccines, which need to enter only the host cell cytoplasm, DNA vaccines need to first enter the host cell nuclei. As a result, DNA vaccines could not induce potent immune responses and were approved only in animals till date. ZyCov-D has sidestepped this problem by being deposited under the skin, a location with plenty of immune cells that take up foreign antigens including the vaccine particles, than being injected deep in the muscle tissue.

While late-stage trial results of ZyCoV-D are yet to be published, the company announced that the full analysis will be submitted soon. The first doses of the vaccine are to be administered beginning September 2021, and up to 50 million doses will be produced by early 2022.

Around the globe, other DNA vaccines for Covid-19 are undergoing clinical trials. While many are in early-stage trials, at least two, one by a Japanese company AnGes, and the other by Inovio Pharmaceuticals, are in late-stage trials.

DNA vaccines are safe, stable and reasonably inexpensive. They can be stored at a (higher) temperature range of –2 ºC to 8 ºC. Another important feature of DNA vaccines is that they can encode complex proteins or even several proteins. This makes them promising as anti-cancer vaccines.

Dr Rakesh Aggarwal, Director, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, told this correspondent, 'Zycov-D has brought to fruition the attempts at DNA vaccination that started in 1990s. This path-breaking success has opened the door to the use of DNA for vaccination against other diseases too. Since it is easier to rapidly scale up the production of DNA than of proteins, this technology can, in the long run, help reduce the cost and obviate supply constraints of vaccines—two important issues for the developing world. The vaccine currently needs three doses, which is somewhat of a spoilsport. Trial of a two-dose schedule of this vaccine is already under way and, if successful, should give the vaccine a further boost.'

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New Alzheimer's drug approved by US FDA, sharply divides medical opinion

Aduhelm (Aducanumab), an experimental agent targeting beta amyloid plaques in the brains of patients diagnosed with Alzheimer disease, was granted Fast Track™ approval by the USA in June 2021. The move has been hailed by researchers affiliated with Biogen, the parent company involved in the manufacture and distribution of the drug, as timely and essential. The drug is a first-of-its-kind innovation therapy which causes reduction of amyloid beta plaques in the brain—a pathognomonic feature of Alzheimer disease, which was studied in settings across double-blind, randomized, placebo-controlled dose-ranging trials of over 3450 patients. It is the first new treatment approved since 2003 by USA Food and Drug Administration (FDA) for Alzheimer disease.

Neurologists and family physicians treating patients with Alzheimer disease are, however, unconvinced that the drug will be effective on the essential pathophysiology of Alzheimer disease and have raised doubts on whether clearance of beta amyloid plaques can actually improve the cognitive decline in these patients. Of the two major trials submitted in 2019 whose results were used to request approval by Biogen, one showed no difference in the patients' condition when amyloid was reduced from the blood circulation while the other showed a marginal benefit when highest doses of Aducanumab were administered. These high doses were associated with side-effects such as headache, altered mental status and disorientation, which aggravated the underlying symptoms the patients inherently displayed.

Those skeptical of Aduhelm's performance have pointed out that similar amyloid-clearing agents were discovered in the past, but had no convincing therapeutic benefit outside of experimental trials. The high cost of annual therapy is also being regarded as a deterrent—a year's worth of Biogen's Aduhelm will cost US$ 56 000 to a patient and US$ 29 billion to the US Federal Government if it is covered as part of Medicare for even 25% of the patients receiving Alzheimer's treatment with state support.

Fast Track™, the accelerated approval pathway used to make Aduhelm available for general use, is traditionally reserved for drugs and therapies for serious or life-threatening illness that provide a meaningful therapeutic advantage over existing treatments. With its effectiveness in dispute and its cost being prohibitively expensive, the timeline between research to urgency of granting Aduhelm sanction for public use has raised concerns.

Dr Roop Gursahani, Consultant Neurologist and Epileptologist, P.D. Hinduja National Hospital, Mumbai, in an email to this correspondent, told the *Natl Med J India,* 'Aducanumab is the triumph of hope over experience/common sense. Hope from the patient organizations, wanting at least something to (/anything that can) slow down the ravages of Alzheimer. Hope from big pharma, that there are some returns from the multiple billions of dollars spent on dementia research. And hope matters…'

MAHARRA HUSSAIN, *Dubai, United Arab Emirates*

Government plans to open new medical colleges in India

Globally, India produces the most numbers of medical professionals every year. But owing to the rising population and poor doctor–patient ratio of 1:1800 (as against the WHO recommendation of 1:1000), the Central Government wishes to increase the number of medical colleges all over the country. The government aims to achieve the desired doctor–patient ratio by 2024.

The Central Government announced in 2014 a plan to set up 157 new medical colleges by upgrading existing district hospitals. The Ministry of Health and Family Welfare sponsored a scheme for the 'Establishment of new medical colleges attached with existing district or referral hospitals'. As per these plans, 58, 24 and 75 new colleges were to be set up in three phases.

Fifty-eight districts in 20 states and Union Territories were approved for these new medical colleges. Each medical college costs ₹189 crore. The Central Government paid ₹7541 crore for their construction. Of the 58 colleges in the first phase, 48 have started. This has added over 5000 undergraduate seats. The remaining ones are at different stages of development.

The second phase was launched in 2018 and involved the construction of 24 new medical colleges in eight states. The total cost of establishment of one medical college is ₹250 crore; the Central Government is reported to have released ₹3150 crore.

The third phase of the scheme began in 2019 with a proposal to build 75 new medical colleges in 18 states. The Central Government has released ₹4111 crore. In this phase, 15, 14 and 11 medical colleges were approved in Rajasthan, Uttar Pradesh and Tamil Nadu, respectively. About 700 seats have been increased in Uttar Pradesh for the 2021–22 academic session.

According to the parliamentary committee on health and family welfare, in the third phase, medical colleges are approved in few backward districts ('aspirational districts') and isolated, underserved areas. Construction of the colleges approved in 2019 are in various stages of completion. The Central Government's think-tank, NITI Aayog, is also developing draft guidelines for a 'viability gap funding' to attach these medical colleges to existing district hospitals in the public–private partnership mode.

In the past 6 years, as per government data, the MBBS seats in the country have increased by 56% from 54 348 seats in 2014 to 84 649 seats in 2020. Similarly, postgraduate seats have increased by 80% from 30 191 in 2014 to 54 275 seats in 2020. During the same period, 179 new medical colleges have been established. Now there are 558 medical colleges in the country of which 289 are government-run and 269 in the private sector. Admission to all of these colleges is through the single entrance test for MBBS in the country, the National Eligibility cum Entrance Test (NEET).

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Beyond visual line of sight (BVLOS) medical drone: An idea whose time has come!

India's first legal/official beyond visual line of sight (BVLOS) medical drone delivery experiment was started on 21 June 2021 in Gauribidanur taluk (near Bengaluru) by a consortium of firms led by Bengaluru-based Throttle Aerospace Systems (TAS). The trials are scheduled to run for a duration of 30–45 days, flying the drones for about 125 hours during the trial period; the guidelines of the Directorate General of Civil Aviation (DGCA), mandate that the drones are to be flown for at least 100 hours during the trial period.

Though approvals from the DGCA and the Central Government were obtained in March 2020, there were delays in securing permissions from other agencies due to the Covid-19 pandemic and the experiment could eventually take off much later. Two variants of the MedCOPTER drone were tested; these were assisted by an on-demand delivery software called RANDINT. While the smaller variant has the capacity to deliver a payload of up to 1 kg and has a range of 15 km, the other variant accompanying it can carry up to 2 kg and can travel up to 12 km. The service is designed to be user-generated and demand-based. However, in the experiment, the crew will pack the medicine and place it in the drone which will then go and drop it off in the place specified by the software. The organization *Narayana Health* will provide medicines to be used for transport during trials. Unmanned traffic management (UTM) system is being provided by Involi-Swiss, which specializes in air traffic awareness systems for professional drone applications; Honeywell Aerospace is the safety expert.

Dr Y. Sathyanarayana Raju, Professor of Medicine, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, in an email to this correspondent, told the *Natl Med J India* that 'The logistics of access to remote rural areas or hilly terrains, or even across busy metropolitan cities such as Bengaluru especially for fast-track delivery of life-saving medicines has always been a nightmare. Use of BVLOS medical drone for delivering medicines is an out-of-the-box idea whose time has come.'

Interestingly, 'Medicine from the Sky' an initiative of the Telangana government to test the feasibility of delivering medicines and vaccines to remote locations by drones was launched on 11 September 2021 at Vikarabad near Hyderabad, Telangana. This initiative involves the Emerging Technologies Wing of the ITE&C (Information Technology, Electronics and Communications) Department, in partnership with the World Economic Forum, NITI Aayog and HealthNet Global (Apollo Hospitals).

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