A strategy for the development of a combination SARS-CoV-2 vaccine containing a DNA vaccine (ZyCoV-D) and an inactivated virus vaccine (Covaxin)

In India, Covaxin and ZyCoV-D have been approved for emergency use. Covaxin contains 6 μg of whole-virion inactivated SARS-CoV-2 antigen (strain: NIV-2020-770), aluminium hydroxide gel (250 μg), imidazoquinolinone, a TLR7/8 agonist (15 μg), 2-phenoxyethanol (2.5 mg) and phosphate buffer saline (0.5 ml). ZyCoV-D is a DNA vaccine consisting of a plasmid encoding the spike protein of SARS-Cov-2 virus and is administered intradermally using a spring-powered jet injector. Both vaccines have shown efficacy of >65% in clinical trials. Covaxin is manufactured in biosafety level-3 high-containment facilities, which poses a serious challenge for scale-up and mass vaccination. Vaccination with ZyCoV-D involves administration of three doses using a powdered jet injector, posing logistical problems. We propose a simple strategy to overcome the drawbacks of both these vaccines.

We had earlier demonstrated that intramuscular injection of plasmid DNA encoding rabies virus surface glycoprotein induces rabies virus neutralizing antibodies in mice and monkeys[1,2]. However, the potency of this plasmid DNA rabies vaccine was lower than that of purified, vero cell-derived inactivated rabies virus vaccine (PVRV), as evident from the low levels of rabies virus neutralizing antibody titres and low levels of protection from intracerebral rabies virus challenge of immunized animals[1,2]. Fivefold dilutions of PVRV (5, 25, 125 and 625-fold) were prepared and the diluted vaccines were administered intramuscularly to mice. Dilution of PVRV led to a decrease in potency with 625-fold diluted vaccine showing very little protection against virus challenge[3]. However, co-inoculation of DNA rabies vaccine and 625-fold diluted PVRV without any adjuvant exhibited potency equivalent to that of undiluted PVRV, paving the way for the development of a combination rabies vaccine. The efficacy of the combination rabies vaccine was demonstrated in animal models[3] and preclinical toxicity studies were carried out in mice as well as monkeys[4–6]. Phase-I human clinical trials were abandoned due to denial of regulatory approvals in India and lack of interest from the industry partner.

We propose that the strategy employed to develop combination rabies vaccine can now be adapted for the development of a potent combination SARS-CoV-2 vaccine by combining ZyCoV-D with diluted preparations of Covaxin. This will obviate the need for the use of powderject injector and is also likely to reduce the number of immunizations (three, at present). The use of diluted preparations will enhance the production capacity of Covaxin in existing facilities obviating the need for further expansion or creation of new manufacturing plants. A patent on the development of a novel DNA vaccine formulation consisting of DNA vaccine and inactivated virus expired recently[7], and hence there is no violation of intellectual property. If successful, India will be the first country to have examined the potency of a novel SARS-CoV-2 vaccine containing an adjuvant-free combination vaccine containing DNA vaccine and inactivated virus vaccine that can be administered by simple intramuscular injection.

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