CORRESPONDENCE

Need for long term safety studies before recommending viral vector vaccines in kids [version 1; peer review: awaiting peer review]

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Abstract
Vaccines have played a central role in dealing with COVID-19 pandemic. Now regulatory agencies in USA and around the world have begun approving vaccination for kids. Long term safety profile of live attenuated viral vaccines, inactivated viral vaccines and peptide-based vaccines are well studied in children, are safe and can play a central role in controlling the spread of COVID19 in children. But the long-term safety profile of viral vector-based vaccines is not studied. In the present correspondence we highlight the possibility of random insertional mutagenesis and potential side effects, which might be evident after long-term. Regulators must take into consideration the possibility of insertional mutagenesis and conduct long term studies before approving the viral vector vaccines in children, so that the public have trust in the regulatory agencies and are compliant towards vaccinating their children with safe and effective vaccines.

Keywords
Vaccine, Viral Vector Vaccines, COVISHIELD, Astrazeneca, Insertional mutagenesis, Leukemia, Cancer, Carcinogenesis, COVID19

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Introduction
COVID-19 infection which is caused by (SARS)-related coronavirus species 2 or SARS-CoV-2 has caused more than 545,226,550 confirmed cases and 6,334,728 deaths as of 30 June 2022. Vaccines have played a major role in combating the COVID-19 pandemic with a total of 11,986,040,938 vaccine doses have been administered so far globally. Given COVID 19 was a first global pandemic in the digital age, individuals were bombarded with an overabundance of information, some accurate and some not, resulting in a high level of suspicion and decreased compliance for COVID-19 infection testing and vaccines. Hence it is imperative to provide accurate information to the people, in order to allow them to take appropriate decisions to combat the pandemic.

There are four main types of COVID-19 vaccines which are either approved or are in clinical trial. They are broadly classified into: 1) Nucleic acid vaccines (DNA & RNA vaccines), 2) Viral vector vaccines, 3) Protein subunit vaccines and 4) Whole virus vaccines. As of Saturday, June 18, 2022, CDC has recommended that all children six months through five years of age should receive a COVID-19 vaccine. SARS-CoV-2 seroprevalence was 68% (95% CI, 63-72%) among children aged 1-4 years, 77% (95% CI, 75-79%) among children aged 5-11 years, and 74% (95% CI, 73-75%) among adolescents aged 12-17 years as of February 2022. As of 4th July 2022, there were no published clinical trial studies, assessing the safety and efficiency of vaccination in children aged below five years. Since there is a presence of high level of basal SARS-CoV-2 seroprevalence in children and lack of clinical trial studies with sufficient power, in the age group below five years, there are divergent opinions among scientific and medical community regarding the CDC recommendation of vaccinating the kids under five years of age.

On 5th May 2022 FDA restricted the use of the J&J shot because of the threat of rare but serious blood clots, to individuals eighteen years and older who cannot access other vaccines. Moreover, applications for the use of viral vector vaccines in the pediatric population are still in process. Hence it is imperative to assess the long term and short-term safety profile of viral vector vaccines in the population, especially the pediatric population.

The viral vector vaccines uses a viral vector to deliver viral spike protein DNA into the cell like modified chimpanzee DNA adenovirus which is an icosahedral viruses with double-stranded DNA (dsDNA) genome in the case of Astrazeneca COVISHIELD, or adenovirus 26 CoV2 in the Johnson & Johnson Ad.26.COV2.S vaccine. After the viral vector containing the spike protein DNA epitopes is injected into the body, the vector latches to the human cells and releases the DNA fragment corresponding to spike protein epitopes into the cytoplasm. The released DNA migrates to the nucleus of the host cell where it is transcribed into mRNA, which is further translated into COVID-19 Spike protein epitopes, leading to the activation of cytotoxic T‐cells and humoral B-cell responses.

Studies have shown that plasmid DNA or linear dsDNA as in the case of a (linearized) plasmid or PCR products undergo homologous recombination or may integrate randomly at any nicked sites in the genome. DNA integration can occur at any phase of cell cycle but is favored during S phase of the cell cycle because the genomic DNA is more accessible during replication. Moreover retroviral, lentiviral, and adeno-associated virus (AAV) vectors have been shown to cause random integration of therapeutic gene in the target cell genome. This is exemplified by random integration of transgenes in transgenic animals. Hence there is a theoretical possibility of rare events of random integration of viral vector DNA or spike protein DNA into the DNA of human cells.

There are reports of Human adenovirus type 12 (Ad12) inducing primitive neuroectodermal neoplasia’s in virus-inoculated newborn Syrian hamsters T637 cell lines, secondary to the random integration of Ad12 DNA into T637 genome. The integration of foreign DNA into the host DNA can disrupt the genes in the host chromosome, giving rise to mutations with a probability of 1/100 th per random integrating event. On an average adenoviral vaccine contains 5 × 10⁹ viral particles per dose of vaccine, and adenovirus vectors have been shown to integrate at an efficiency of 10⁻³ to 10⁻⁵ integration per cell. Given a single dose of vaccine contains 10⁹ viral particles, and repetitive booster doses are being used, as well as the fact that millions of people are being vaccinated with viral vector vaccine, the probability of random integration into the genome occurring and knocking out tumor suppressor gene or activating oncogene is significant.

When lentiviral vector was used to shuttle the IL2 gene into Severe combined immunodeficiency (SCID) infants, four of the nine infants developed leukemia between three and six years after the treatment, with the first case being clinically evident after 3.5 years of therapy. In these infants the leukemic process was attributed to LMO-2 proto-oncogene up-regulation secondary to integration of the wild type IL2RG gene along with the vector into the genome. In addition when adeno-associated viral vectors were used to target hemophilia A gene in nine dogs, researchers discovered 1,741 distinct AAV integration occurrences in genomic DNA of five dogs. Similarly, the viral vector-based vaccines may integrate into our genome at frequencies not known to us and effects of which might be evident many years after vaccination.
On the other hand, Stephen et al. showed that when the replication-deficient adenovirus vectors carrying different transgenes were injected intravenously into mice, they integrated into mouse hepatocytes at a very low frequencies comparable to that of spontaneous mutations in mammalian cells. Since the rate of random integration also depends on the concentration of heterologous DNA and the amount of virion-packaged adenovirus vector and viral vector vaccines contain far less virions than that used in gene therapy, Stephen et al. concluded that the chance of viral vector vaccine induced insertional mutagenesis is very low. However, heterologous DNA integration occurs at an increased rate in dividing cells, which are predominantly in S-phase and hence integration also depends on the percentage of the cells which are actively dividing and are in S-phase. But Stephen et al. measured DNA integration in normal mammalian liver wherein the majority of hepatocytes are quiescent and very few cells are in S-phase or are actively dividing. Hence the low rate of integration of replication-deficient adenovirus vectors in hepatocytes may be secondary to low percentage of hepatocytes being in S-phase. Moreover, the viral vector induced insertional mutagenesis and consequent neoplasia’s were evident in rapidly dividing hematopoietic lineages in kids. A more appropriate model to measure the integration rate of replication-deficient adenovirus vectors would be rapidly dividing cells like hematopoietic cells and gastrointestinal epithelial cells, instead of mice hepatocytes. In-addition, the fact that millions of people have received the viral vector vaccines, increases the probability of integration with an increased number of subjects. Moreover, since children are growing and have greater percentage of cells which are dividing than adults, the probability of integrational mutagenesis occurring in children should be higher than the adults.

While the jury is still out regarding the occurrence of the viral vector vaccine associated random insertional mutagenesis, extreme care should be exercised while recommending viral vector vaccine in children and infants, especially when alternative safer vaccines like mRNA vaccines and inactivated viral vaccines are available. Given the first case of leukemia was evident after three and a half years of gene therapy (from three and half years to six years post gene therapy four out of nine infants developed leukemia), it’s important to conduct long term safety studies for viral vector vaccines before recommending these viral vector vaccines in children.

Data availability

No data.

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