

The biosafety of COVID-19 vaccines

In the Administrative Normative 1721/2020, released on September 18th, the Argentine government established the guidelines for the acquisition of vaccines against coronavirus and the principles to be considered for the direct purchase of vaccine intended to generate immunity in the population¹.

Several candidate vaccines with different platforms are currently in the preclinical or clinical phase. Once approved, these vaccines will be highly demanded globally within a context of limited supply, thus requiring measures to ensure timely access. The authorities declared that health safety, expeditious provision, and efficiency/effectiveness criteria should be prioritized over economic criteria for the selection of providers¹.

What types of vaccines are in advanced stages of development, as of September 2020?²

Viral vector vaccines (in phases II / III). The 4 best known are *Cansino* (Adenovirus type 5 vector expressing S protein), *Astra Seneca* (ChAdOx1 vector expressing S protein), *Gamaleya* (Recombinant vector based on human adenovirus type 5, 26, expressing the S protein), and *J&J – Janssen* (Adenovirus type 26 vector expressing the S protein).

DNA encoding the S protein. There are 4 vaccines in phase I / II.

RNA vaccines. mRNA encapsulated in a lipid nanoparticle system, which encodes the S protein. There are 6 vaccines, of which *Moderna* is in stage III and *Pfizer/BioNTech* is in stage II / III.

Inactivated virus. Two vaccines, *Sinopharm* (Wuham) and *Sinovac Biotech*, in stage III, and three (*Beijing Sinopharm*, *Chinese Acad. Science* and *Bharat Biotech*) in stage I / II.

Protein based vaccines (including recombinant protein, virus-like particle, or synthesized peptide antigens). There are 9 projects, of which two (*Anhui Zhifei Longcom Biopharmaceutical/IMCAS* and *No-vavax*) are in phase II.

On the Oxford-AstraZeneca vaccine³

On September 9, an Oxford University spokesperson stated that the pause applied to phase III trials was necessary to allow the review of safety data by an independent committee, and by national regulators. Following this independent review process and another one by the Medicines and Healthcare products Regulatory Agency (MHRA), trials were resumed in the UK⁴.

Clinical development programs are designed to explore the benefits of vaccines, with the demonstration of efficacy being the primary goal. These trials are generally underpowered to support post-immunization adverse event analyses. The safety data collected there is sufficient to characterize the most common adverse events that occur shortly after vaccination. Only after licensure, when the vaccine is administered to large populations, is it possible to detect rare adverse events that have not been observed in clinical trials⁵.

Post-licensure monitoring of vaccine safety is based on a combination of passive and active surveillance. Pharmacovigilance in passive surveillance comprises notification systems with nationwide

coverage collecting spontaneous reports of adverse effects. Routine safety surveillance is based on a statistical analysis that detects disproportionality between the number of observed and expected adverse events of a vaccine, followed by clinical validation and statistical evaluation. On the other hand, active surveillance systems seek to know all the reports on side effects in a representative sample (sentinel sites)⁵.

An advantage of these systems is that the denominator (size of the population from which the specific adverse events following immunization arose) is known. This process is followed by comparative analyses of the incidence of the events in subpopulations that have not received the vaccine (or in a period of time prior to vaccination for subjects that experienced adverse events after vaccination), using standardized case definitions and health system networks^{5,6}.

Safety surveillance for COVID-19 vaccines

The current infrastructure for the surveillance of vaccine safety will be critical at this stage, for the vaccine (or vaccines) against COVID-19. Inter-individual variation is expected to occur in response to this vaccine, as it happens with other vaccines. As always happens, we can learn from history. Numerous studies failed to demonstrate the association between influenza A (H1N1) 2009 vaccine and the Guillain-Barré syndrome. In one of these studies carried out in 5 European countries (Denmark, France, the Netherlands, Sweden, and the United Kingdom) in 2009-2010, it was concluded that the risk of Guillain-Barré syndrome occurrence did not increase after vaccination, OR 1.0 (95% CI 0.3- 2.7), showing that the effect of vaccination could vary from one case of Guillain-Barré syndrome avoided to 3 excess cases per million vaccinated⁶.

Between 1985 and 2017, the possible relationship between several neurological conditions (including transverse myelitis, clinically isolated syndrome, and optic neuritis) and vaccination against 3 viral diseases (hepatitis B, influenza, and HPV) was investigated in the United States through a CDC/FDA Vaccine Adverse Event Reporting System (VAERS). Reporting rates per million of these syndromes were found to be within the expected range for the general population. This surveillance system remains active^{7,8}.

Post-vaccination cases of transverse myelitis have been described, including one in the US following vaccination with nasal influenza A (H1N1) vaccine⁹, and another in Argentina, during the vaccination campaign against influenza A, with monovalent Influenza A (H1N1) vaccine, in 2010¹⁰.

Anti-vaccine campaigns

Conspiracy theories about vaccines abound. Some campaigns claim that the scientific literature on vaccines is influenced by pharmaceutical companies, or that the laws regulating vaccination are contrary to human rights.

Such disinformation and conspiracy campaigns on the risks associated with vaccines have led to a decrease in the number of vaccinations in several countries, including Argentina, and the resulting outbreaks of vaccine-preventable diseases, such as measles, with the consequent number of fatal victims^{11,12}. Public perception of the review of medications and vaccines for COVID-19 has also been enmeshed in politics¹³. The best answer is an effective and widely available COVID-19 vaccine that will also be, by all accounts, the only way out of the current pandemic.

Isabel N. Kantor
isabel.kantor1@gmail.com

1. Ministerio de Salud. Boletín Oficial N° 34.477 - Primera Sección. 18/9/2020. Decisión Administrativa 1721/2020 DECAD-2020-1721-APN-JGM - Adquisición de vacunas para generar inmunidad adquirida contra el COVID-19. En: <https://www.boletinoficial.gob.ar/suplementos/2020091801NS.pdf>; accessed September 2020.
2. Le TT, Cramer JP, Chen R, Mayhew S. Evolution of the COVID-19 vaccine development landscape. *Nat Rev Drug Discov* 2020. doi: 10.1038/d41573-020-00151-8. Online ahead of print.
3. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; 396: 467-78.
4. Cyranovsky D, Mallapaty S. Relief as coronavirus vaccine trials restart - but transparency concerns remain. *Nature* 2020; 585: 331-2.
5. Chandler R. Optimizing safety surveillance for COVID-19 vaccines. *Nat Rev Immunol* 2020; 20: 451-2.
6. Dieleman J, Romio S, Johansen K, et al. Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. *BMJ* 2011; 343: d3908. doi: 10.1136/bmj.d3908.
7. Shah S, Patel J, Rahman A, Fakher M, Souayah N. Development of transverse myelitis after vaccination, a CDC/FDA Vaccine Adverse Event Reporting System (VAERS) study, 1985-2017. (P5.099). *Neurology* 2018; 90 (15 Suppl). Abstract.
8. Fakher Eddin M, Patel J, Rahman A, Souayah N. Development of clinically isolated syndrome after vaccination, a CDC/FDA Vaccine Adverse Event Reporting System (VAERS) study, 1985-2017. (S51.001). *Neurology* 2018; 90 (15 Suppl). Abstract.
9. Akkad W, Salem B, Freeman JW, Huntington MK. Longitudinally extensive transverse myelitis following vaccination with nasal attenuated novel influenza A(H1N1) vaccine. *Arch Neurol* 2010; 67: 1018-20.
10. Arcondo MF, Wachs A, Zylberman M. Mielitis transversa relacionada con vacunación anti-influenza A (H1N1). *Medicina (B Aires)* 2011; 71: 161-4.
11. Luthy IA, Kantor I. Sarampión. *Medicina (B Aires)* 80: 162-8.
12. Phadke VK, Bednarczyk RA, Omer SB. Vaccine refusal and measles outbreaks in the US. *JAMA* 2020. doi: 10.1001/jama.2020.14828. Online ahead of print.
13. Bauchner H, Malani PN, Sharfstein J. Reassuring the public and clinical community about the scientific review and approval of a COVID-19 vaccine. *JAMA* 2020. doi:10.1001/jama.2020.18860. Online ahead of print.