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RESPONSES AND DIALOGUE

Xenotransplantation Can Be Safe—A Reply

A response to: L Syd M Johnson, "Existing Ethical Tensions in Xenotransplantation" (CQ31(3))

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In this very comprehensive publication highlighting all aspects of xenotransplantation, L Syd M Johnson also addresses viral safety.[1] Unfortunately, her statements are too pessimistic, and, as a virologist who has been active in the field of viral safety of xenotransplantation for decades, I noticed that she does not consider the chances and advantages of this life-saving technology.

The transmission of potentially zoonotic (*zoonotic* means inducing a disease in the infected host) porcine viruses is one of the hurdles xenotransplantation has to overcome. The other hurdles are the immunological rejection, especially the hyperacute rejection (HAR), and the physiological incompatibility. The fact that during the worldwide first transplantation of a pig heart into a human patient, a porcine virus was transmitted,[2] underlines the importance of viral safety. Despite the virus transmission, the patient lived two months with the pig heart, which was a great success.

L Syd M Johnson writes in the abstract of her publication that "Individual consent to transplant is in tension with public health threats that include zoonotic diseases." However, this is only partially correct. Research in the field shows that the risk is very low, especially what concerns the public threat, and this must be underlined.

Fears of this kind were fueled by the knowledge that the human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2) were transmitted from non-human primates and that COVID-19 is the result of the transmission of a bat-derived coronavirus. When these viruses broke into the human population, no one knew what they were, there were no detection methods, no antiviral drugs, or even vaccines. In the case of xenotransplantation, the situation is absolutely different. In the last several years, sensitive methods have been generated to detect numerous porcine viruses and elimination programs have been developed to eradicate these viruses by antiviral drugs, vaccines, early weaning, colostrum deprivation, or embryo transfer. Theoretically, all known viruses with the exception of the porcine endogenous retroviruses (PERVs) can be eliminated by these methods. The risk of transmission of unknown pathogens is relatively low since humans have lived together with pigs for ten thousand years and only the hepatitis E virus had been transmitted to humans either by undercooked meat or contact.

The transmission of a porcine virus, the porcine cytomegalovirus/porcine roseolovirus (PCMV/PRV), to the patient in Baltimore, which obviously contributed to the death of the patient, was only possible because unsuitable methods had been used for the detection of the virus in the donor pig. Using the appropriate methods, this can be easily prevented.

I do not agree with the sentence, "The same risks exist and are magnified with xenotransplantation." As we all know, viruses such as human herpesviruses, for example, the human cytomegalovirus, the human herpes simplex virus, the Epstein–Barr virus and other viruses such as HIV-1, hepatitis B, and hepatitis C viruses as well as rabies virus, had been transmitted during transplantation of human organs into human recipients. In xenotransplantation, the animals will be screened for viruses several times before transplantation, and therefore xenotransplantation will be eventually safer compared with allotransplantation. The cited "Guidance to industry" by the FDA from 1999 is a worst-case scenario

based on the knowledge of 1999, and is outdated nowadays. In all clinical trials of xenotransplantation (more than 200 recipients)[3] only in one patient, in the Baltimore patient, the transmission of a porcine virus was observed, and all other patients did not receive a porcine virus.

The author writes "that it will be necessary for xenotransplantation organ recipients to submit to extended, potentially lifelong surveillance for zoonotic diseases." The author forgets that the xenotransplant recipients as well as the allotransplant (human organ) recipients should submit to lifelong treatment with immunosuppressive drugs and surveillance concerning the rejection of their organ. In parallel, infection and possible diseases can be detected. A withdrawal from treatment with immunosuppressive drugs is also deadly for an allotransplant recipient, therefore neither an allotransplant nor a xenotransplant recipient can withdraw, and the ethical consequences are identical.

The cited report of the UK-based Nuffield Council from 1996 is even more outdated on the basis of the recent results concerning virus safety. There is no need to screen close contacts for virus infection, if the organ recipient is not infected.

The considerations of the author are based mainly on documents written at the beginning of the development of xenotransplantation when aspects of virus safety were not well studied, and therefore the authors of the 1996/1999 documents discussed the worst case. Meanwhile, we have methods on how to detect these viruses and how to eliminate them.[4,5] Even in the case of PERVs, which can be eliminated by only CRISPR/Cas from the pig genome, there is, at the moment, no evidence of transmission in the first clinical trials. Meanwhile, we have sensitive detection methods and strategies on how to prevent PERV transmission, for example, by RNA interference, antiviral drugs, vaccines, and CRISPR/Cas.

In summary, based on recent achievements in research on porcine viruses, the transmission of these viruses to xenotransplant recipients is extremely low when the correct methods for detection and elimination—that are available—are applied. Xenotransplantation is safe if it is done properly.

Conflicts of Interest. The author declares none.

Notes

1. Johnson LSM. Existing ethical tensions in xenotransplantation. *Cambridge Quarterly of Healthcare Ethics* 2022;**31**(3):355–67.
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