Received: 23 December 2022 | Revised: 20 February 2023 | Accepted: 25 February 2023

DOI: 10.1111/xen.12797

Xenotransplantation WILEY

REVIEW ARTICLE

Xenotransplantation: A historical–ethical account of viewpoints

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Funding information
Work in DKCC's lab is funded by an NIH U19 grant, Grant/Award Number: 7U19AI090959-14

Abstract

Formal clinical trials of pig-to-human organ transplant—known asxenotransplantation—may begin this decade, with the first trials likely to consist of either adult renal transplants or pediatric cardiac transplant patients. Xenotransplantation as a systematic scientific study only reaches back to the latter half of the 20th century, with episodic xenotransplantation events occurring prior to that. As the science of xenotransplantation has progressed in the 20th and 21st centuries, the public's knowledge of the potential therapy has also increased. With this, there have been shifting ethical stances toward xenotransplantation in key areas, such as religious and public viewpoints towards xenotransplantation, animal rights, and public health concerns. This review provides a historical–ethical account of xenotransplantation and details if or how viewpoints have shifted over time.

KEYWORDS
ethics, history, transplantation, xenotransplantation

1 | INTRODUCTION

The subject of ethics in relation to xenotransplantation (XTx) has been widely explored since the late 20th century. The highly publicized case of Baby Fae in 1984 brought many of the ethical issues regarding XTx to the foreground, whereas prior to this event, one is hard-pressed to find ethical viewpoints discussed in the literature. Today, XTx has come to the foreground of medicine, with several recent experiments of XTx being performed in individuals declared dead by neurologic criteria[1–4] and one case of the emergency use of a transgenic pig heart being transplanted into a living patient who was reportedly not a candidate for an allograft.[4–6] The medical literature now includes many ethical analyses of various XTx issues, and both governmental and nongovernmental committees have published guidelines and opinions on ethical considerations. However, on occasion, viewpoints conflict and may even change over time, as ethical opinions may adjust to reflect changing scientific and social understandings.

The purpose of this review is not to provide a detailed reiteration of what has been covered in the ethics literature previously. Rather, our purpose here is to trace in which directions the ethical conversations have moved over time and to highlight what we believe the literature shows to be the most pressing ethical questions regarding clinical trials of XTx. To do this, our analysis will examine the following ethical considerations regarding XTx clinical trials and if or how these issues and viewpoints have shifted over time: (i) theological perspectives, (ii) the use of animals as sources of organs, (iii) public attitudes toward XTx, and (iv) public health concerns about xenozoonotic disease.

2 | RELIGIOUS VIEWPOINTS

The first known theological viewpoints toward XTx occurred in the late 17th century,[7,8] as recounted:

> The first tissue xenograft was reputedly recorded in 1682, when a Russian nobleman, who had lost part of his scalp and skull in battle, had the defect in his skull successfully repaired by a surgeon with a piece of bone from the skull of a dog.
>
> The Russian church, however, believing that no man could be Christian if he had a dog bone in his head, threatened the nobleman with excommunication. Clearly, a God-fearing man, he chose to have the fragments of dog bone removed, thus presumably saving himself from a fate worse than death.[9]

Not much else is known about this curious story, including the eventual fate of the nobleman. Nonetheless, this early account is indicative of the wariness of some sectors of Christianity toward XTx that would persist.

XTx was essentially dormant until the mid-20th century due to medical limitations. Once experimental treatments began to be carried out, theological viewpoints also began to be published. In particular, the case of Baby Fae would provoke much conversation about the ethical and theological viewpoints toward XTx. In 1984, at Loma Linda University Medical Center, Leonard Bailey transplanted a baboon heart into an infant girl who was born with hypoplastic left heart syndrome and was just days old at the time of surgery. The child would die 20 days later from an acute rejection of the graft.[10] This case would spur significant attention toward XTx in both the academic and lay literature, as well as from both theological and secular viewpoints.

Baby Fae died on November 15, 1984, and the Roman Catholic Church weighed in on the case very early. Leading Vatican moral theologian, Father Gino Concetti stated on November 18, 1984, that the Church approved of implanting animal organs into humans under certain conditions but that these conditions had not been met in the case of Baby Fae.[11] Concetti listed the following six reasons by which the transplantation of a xenograft into a human could be justified:

1. The patient needed it
2. No suitable human or artificial organ was available
3. The surgical team was properly qualified
4. The hospital had the right equipment
5. The patient or guardians agreed
6. A "broadly positive outcome" was foreseeable

Interestingly, Father Concetti did not specify which condition(s) had not been met. It seems likely that the primary focus of his objection was directed to condition 6: "that a 'broadly positive outcome' was foreseeable." Systematic clinical trials of animal-to-human organ transplants had not been performed at this point in the history of XTx. Moreover, an understanding of graft rejection and how to control it was relatively modest. Hence, meeting condition 6 seems impossible in this case.

In 1998, the Council of the Evangelical Church in Germany and the German Catholic Bishops' Conference formed a working group and produced a document to aid ethical discernment regarding XTx.[12] This group recommended the need for ongoing ethical dialogue regarding: (i) the moral status of nonhuman animals and humankind's legal and moral responsibility towards them; (ii) the risks posed by the potential spread of xenozoonotic disease and how an individual patient can give informed consent for a potentially global risk; and (iii) the potential for negative psychosocial sequelae from receiving a xenograft. There was one dissenting voice in the working group who argued that the benefits that could be accrued did not justify violating humankind's responsibilities towards protecting animals and their special dignity, concluding that further research into XTx should not be permitted. These ethical concerns have been mirrored within the secular community and continue to be debated with no definitive consensus.

By 2001, the Roman Catholic Church would become highly supportive of XTx research and its potential clinical usage. The Pontifical Academy for Life—a select group of scientists, theologians, and ethicists approved by the Pope who comment upon issues of ethics and moral theology—issued a document that was, on the whole, supportive of XTx. The Academy provided commentary on ethical, social, and anthropological considerations for XTx. While the group forbade the transplant of an animal brain or sexual organs to a human, there was support for extending XTx to humans if proper informed consent is followed and steps are taken to minimize risks to the xenograft recipient and society at large. This document from the Pontifical Academy for Life represents a change of direction for the Church from the time of Baby Fae. While Father Concetti did not provide a systematic argument of *why* the Baby Fae experimental therapy was not justified, the Pontifical Academy provided a methodical process for considering the ethics of XTx and concluded that, as long as certain parameters are kept and risks minimized, then XTx would be permissible.

Currently, from published commentaries from various Christian denominations and traditions, there is nothing in Christian doctrine or Scripture that explicitly rules out XTx. However, there remain several theological questions regarding humankind's responsibility towards nonhuman animals and their use for human benefit. Jewish religious law rules out the consumption of pigs—the primary nonhuman animal organ source used in XTx research—but there is nothing that explicitly rules out their use to save a human life through XTx.[13,14] Similarly, the consumption of pigs is prohibited under Islamic law, but Qotadah and Syarifah have argued that their use for XTx would be permissible should certain conditions be satisfied in light of the Islamic principle of *hifz al-nafs* (protection of life).[15] These conditions are (i) that it must only be performed in an emergency where there is no acceptable alternative, and (ii) the harm from the xenotransplant must be less than the harm from not performing the surgery. Zailani and colleagues have recently argued that, due to Islamic legal maxims, "chimeric organ transplantation using pigs should only be done in emergency situations."[16] However, despite this, there remains no definitive Islamic ethico-legal ruling on XTx and even less is known about Muslim receptibility toward this kind of therapy.[17]

Viewpoints of other religious groups, such as followers of Buddhism and Hinduism remain largely unexplored. In 2003, the Ethics Committee of the International Xenotransplantation Association (IXA) published a report that included brief overviews of the viewpoints

of major world religions toward XTx. The report states that both Buddhists and Hindus would be opposed to XTx.[18] Recent scholarship has posited that there has not been enough research conducted in Asia—the epicenters of Buddhism and Hinduism—to form any firm conclusions based on these religious viewpoints.[19] Regarding Hinduism, one commentator has posited the following:

> [T]here are important religious ideas and stories that could inform Hindu attitudes to xenotransplantation, but the exact direction of the argument can be ambiguous. Therefore, it will be crucial to explore values and views with all persons involved in a xenotransplant in a way that reflects cultural competence and cultural humility.[20]

Therefore, further study of the viewpoints of Buddhists and Hindus toward XTx is needed.

There remains a dearth of scholarly theological engagement across all of the major world religions regarding XTx. However, this is beginning to change as recent cases of XTx in both living and brain-dead persons have been reported in the medical and popular lay literature. Individuals with religious beliefs have, on balance, viewed XTx favorably with explicit concerns predicated on religious beliefs being rare.[21,22] Yet, this is based on a very limited number of studies that have explored the role of religious belief and its impact on attitudes toward XTx and so more research is still required.

3 | THE USE OF ANIMALS AS SOURCES OF XENOGRAFTS

The use of animals in medical and scientific research is not a novel issue. Experimental drugs and therapies are often tested on nonhuman animals in preclinical development. However, in some sense, there is a defined end-date to nonhuman animal use—the study is run, results are gathered, and that is the end of nonhuman animal use for the study. Additionally, there is a principle that underlies animal studies called the 3Rs—replace, reduce, refine. Replace animal experiments, when possible, reduce the number of animals needed, and refine methods to reduce the need for animals. Yet, for XTx to be a viable clinical option, animals would need to be bred and then killed on a large scale to meet the demand for organs for the foreseeable future until a less contentious alternative is identified.

If we go back to the early 1960s, we encounter the work of the pioneering surgeon James Hardy. In 1963, Hardy would perform the world's first lung allotransplant at the University of Mississippi in the United States, which received some public support. Hardy was also determined to carry out the first clinical heart transplant. Based on the prior transplantation of chimpanzee kidneys into patients by Reemtsma, in 1964, Hardy acquired some chimpanzees to serve as potential sources of organs in case a deceased human donor did not become available.[8,9] Hardy identified a patient who, reportedly, was already in a state of dying and was a less than ideal candidate for transplantation. Furthermore, the commentaries that exist on this event are not entirely clear if adequate consent was gained by the patient and/or surrogate decisionmaker for the transplant. Regardless, Hardy transplanted a chimpanzee heart into his patient.[9]

From this event, we have at least two serious ethical issues to consider: (i) the ethics of performing a xenotransplant—a very risky experimental procedure—on a patient who was unlikely to benefit due to his already declining state, and (ii) the question of whether adequate consent was obtained. Granted, the concept of informed consent during the 1960s was not as developed as it is today, yet the standard that a patient or their surrogate must agree to the procedure did exist.[23] Today, the informed consent issues involved in XTx are numerous, such as an individual's ability to withdraw from the trial, potential restrictions on reproduction, and possibly the need to quarantine the patient (and possibly his/her close contacts) due to the risk of a xenozoonosis. These issues have been detailed at length elsewhere.[24,25]

> The reception by the public toward Hardy's xenotransplant was not welcoming:
>
> In contrast to the response to the attempted lung allotransplantation, the public and medical professional response to the heart xenotransplantation was adverse and dissuaded Hardy and his colleagues from carrying out any further attempts.[9]

It is not entirely clear in the existing literature what specifically the public and medical community found objectionable. There is some evidence that people have stronger negative reactions and greater moral concern toward the use of primates than to lower-status animals used for food, such as the pig.[26,27] Primates seem to have greater intelligence; emotions that humans can identify with; look more human than other animals; and possess other traits that humans can relate to—this moral concern is likely rooted in our phylogenetic proximity. Many in society would likely have grave concerns about the killing of primates in large numbers to act as organ donors for humans, and there remains continued unease about their use in many scientific endeavors.[28] Nevertheless, there remain concerns about the use of pigs as a source of organs, given their high intelligence, complex mental lives, and capacity for suffering. For instance, Peter Singer has long advocated against speciesism,[29] which he has defined as the "prejudice or attitude of bias in favor of the interests of members of one's own species and against those of members of other species."[30] Further, in recent focus groups, even persons in favor of XTx expressed reservations about the use of pigs.[21,31] While the use of animals as sources of organs for humans may not be morally ideal, it seems likely to continue if it can provide significant benefits to humans.[32]

Since Hardy's experiment and especially since the 1990s, there has been a shift away from the use of nonhuman primates (NHPs) as sources of organs in XTx research to the pig.[33,34] Sachs noted that the rarity of NHPs, such as chimpanzees, makes their use impractical.[35] Furthermore, baboons, which are more readily available, have smaller organs than an adult human. The serious potential risk of xenozoonotic

infection from an NHP was also a concern. Sachs provided four advantages to the use of pigs over NHPs: (i) unlimited availability, (ii) size (similar to human beings), (iii) breeding characteristics, (iv) and physiologic and immunologic similarities to humans.[35] Furthermore, pigs can readily be genetically modified, for example, by using CRISPR–Cas9 genome editing, to help prevent immune rejection.[36]

In addition, our society is already accustomed to using pigs in a purposeful manner for the betterment of humans. Pigs are purpose-bred in industrial farming for food, porcine insulin is administered for the treatment of insulin-requiring diabetes mellitus, and their heart valves have been used to replace diseased human heart valves since the 1960s. A common argument given in support of the use of pigs for XTx is an analogical one—pigs are already used for industrial farming and so, if this is considered morally permissible, then using them for the prima facie more morally acceptable purpose of saving a human life is even more justifiable. This has been the often-unstated ethical assumption behind the use of pigs—and nonhuman animals in general—in XTx research. Yet, this assumption is increasingly being challenged, primarily by arguing that a more serious wrong does not justify a less serious one.[37]

While transitioning from a NHP to a pig as a source of organs may bring about less ethical tension, hesitation about the use of animals as a supply of organs for humans has remained. For example, in recent focus group studies, participants expressed concern about breeding a population of animals specifically for the purpose of transplantation, even though they agreed that pigs were bred for other human purposes (e.g., food).[21] In quantitative studies exploring whether the public are willing to consider a pig organ transplant, the response is generally favorable, especially if the outcome might be similar to that of allotransplantation—which is not yet known.[38] While hesitation exists, there is limited data to clearly evaluate the public's viewpoints on whether the use of pigs as a source of organs for clinical XTx is acceptable or not.[39] Hence, while shifting from NHPs to pigs for XTx was scientifically sound and likely a positive shift in terms of the public's outlook, the lack of clear empirical data on this point leaves room for additional research.

4 | PUBLIC ATTITUDES TOWARDS XENOTRANSPLANTATION

Experimental surgeries on brain-dead persons,[1–3] and the emergency authorization of a clinical pig heart transplant have shown mixed,[4,5] but some encouraging, results,[6] and so the likelihood of moving to formal clinical trials in the near future is increasing. Yet, despite this, caution is warranted due to the potential global health risk posed by xenozoonosis. This caution is reflected in guidance from the World Health Organization (WHO) and the IXA, both of which have identified consideration of ethical issues and public perception of XTx as priorities—primarily because patients often feel excluded from the decisions made by scientists, clinicians, and public policymakers.[40] Furthermore, it is important to have some understanding of the degree of risk that the public and stakeholders are willing to accept before permitting formal clinical trials. Despite the numerous studies that have been conducted and reported with regard to exploring the attitudes of patients, the general public, and health care workers towards XTx, the answer to the question of the public's acceptance of risk remains undetermined.[39]

Given what is at stake, most importantly the risk to public health—as well as the significant potential benefits to individual patients—a high degree of transparency and precaution is necessary, as a failure to do so could impede future research and development. There is a precedent for this kind of failure. A public consultation on XTx in Australia was compromised in 2002 and 2004 because its design and process were biased towards permitting clinical trials of organ XTx. This failure led to a moratorium on clinical trials of XTx until December 2009.[41]

Most of the studies conducted over the last 30 years have found that the general public, patients awaiting transplantation, students, and health care professionals have viewed XTx favorably. Nevertheless, several studies have identified an overall unfavorable view towards XTx,[42–45] but these findings have tended to be the exception. The trajectory over the last 15 years has, on balance, been towards a more favorable view.[38,46–57] Nevertheless, the different questions posed, the variations in the levels of knowledge of the participants, and the information they were given prior to the study, make it difficult and imprudent to draw any definitive conclusions. The more recent favorable views could be explained by an increased awareness of XTx research during this period, combined with less awareness of previous clinical failures, or it may merely reflect a pro-innovation bias (i.e., that something new is superior). Until more rigorous research is conducted, on a much larger scale, it is difficult to reliably determine the general public's attitudes toward XTx.

Importantly, there are some reasons to be skeptical of the positive attitude towards XTx identified in many studies because when participants are provided with more information, support often drops significantly. For example, in a study of 327 animal technicians, researchers, and university students, support for the use of pigs for XTx fell from 49 to 30% when participants were told that it would require the use of genetically engineered pigs.[58] In general, when participants are told that XTx may not be as successful as human organ transplantation, support drops.[38,45,47,48,59]

This raises some serious methodological and ethical questions. It is unlikely, at least in the early years of XTx, that an organ xenograft will be as efficacious as an allograft. In that case, research that only asks for the attitudes of participants when the risks and results of XTx are comparable to allotransplantation should be viewed with a degree of skepticism. This is because XTx will not be presented to patients this way when they are asked to participate in a clinical trial, the very trials that are required to assess the efficacy and safety of XTx.

5 | THE POTENTIAL RISK OF A XENOZOONOSIS

For many decades, there have been concerns about the potential risks that XTx poses to global public health.[34] These have primarily focused on the possibility of a xenozoonosis—an infectious disease

transmitted from the animal to a human recipient and then to the community following XTx. In a worst-case scenario, a xenozoonosis could have the potential to cause an epidemic or even a pandemic. From the mid-1990s onwards, this concern increased when the US Food and Drug Administration (FDA) temporarily suspended a plan for a clinical trial of XTx to determine whether or not baboon bone marrow could boost the immune systems of patients with AIDS.[60–65] The risk of an infectious disease developing was the basis for the FDA to introduce a *de facto* ban on XTx from NHPs to humans, as the risk was deemed higher than from more phylogenetically distant animals, such as pigs.[66]

In 1995, the Nuffield Council on Bioethics in the United Kingdom established a Working Party, which published a report in 1996, "*Animal-to-Human Transplants: The Ethics of Xenotransplantation*."[67] This report addressed the perceived ethical, safety, economic, and public health issues that XTx presented. While the report concluded that the use of genetically engineered pigs for XTx was ethically permissible, it recognized that several concerns remained, such as the risk of a xenozoonotic infection. It was concluded that formal clinical trials would not be ethically permissible until this risk had been adequately addressed.

Concerns over the risk of a xenozoonosis were heightened following the COVID-19 pandemic, and these concerns are not unfounded. Zoonotic disease is common, and it has been estimated that three of every four new or emerging diseases in humans originate in non-human animals.[68] Moreover, there is no shortage of well-known zoonotic diseases that have cumulatively contributed to significant and widespread human suffering—just 13 zoonotic diseases are responsible for 2.2 million human deaths and 2.4 billion cases of illness each year.[69]

In January 2022, a heart from a genetically engineered pig with 10 individual gene edits was transplanted into a 57-year-old man with nonischemic cardiomyopathy who was not a candidate for heart allotransplantation. The xenograft functioned well for more than 40 days, but unfortunately, the patient died on day 60.[6] The cause of the failure was likely graft rejection,[4] but because the recipient of the xenograft tested positive for porcine cytomegalovirus, it has been suggested that this may have contributed to his death. It supports the contention that a xenozoonosis is more than just theoretically possible. Importantly, due to the need for immunosuppressive therapy, a xenograft recipient may present the "ideal" environment for the adaptation of a virus in a new host.

Since the 1990s, there remain three main perspectives on clinical trials and the risks a xenozoonosis poses. (i) The pandemic risk associated with xenozoonosis is serious enough to warrant never moving to formal clinical trials.[70] (ii) The risk that xenozoonosis poses to public health is serious enough that clinical trials should not proceed until there has been a sufficiently informed public debate to establish whether or not they wish to accept the risks and permit clinical trials, and under what conditions.[71] (iii) The absolute pandemic risk posed by XTx is low enough that clinical trials should be permitted providing sufficient public health surveillance and lifelong monitoring are adopted.[72] Arguably given any global risk, however small, caution is obviously warranted and the conditions outlined in the second and third perspectives seem prima facie reasonable, and yet remain unmet. Despite the growing number of studies conducted, as well as some global media attention,[73] it would be difficult to consider on this basis alone that there has been a sufficiently informed public debate regarding the risks of formal clinical trials. Moreover, despite agreement that some degree of health surveillance and monitoring is justified, there is no agreement to what degree, and what a participant can be reasonably and realistically expected to commit to. How stringent and realistic post-transplant surveillance should be and what is legally and ethically permissible, therefore, remains highly contested. For example, is life-long monitoring necessary? Is monitoring of the social and sexual contacts of the recipient required? If so, for how long? Considerable investment would be required to adequately monitor xenograft recipients and any bystanders that could be at more immediate risk. Coherent plans for how to account for this have not been offered. Ultimately, the benefit of XTx is for a small subset of individuals needing an organ transplant, whilst the costs and harms associated with XTx are potentially global. Exercising due precaution and taking steps to mitigate the potential for harm are necessary next steps and on balance, the trajectory seems to be that the public health risk has been deemed to be low enough that formal clinical trials can be considered sufficiently safe and therefore permissible. Ultimately, the infection risk that XTx poses remains unknown until formal clinical trials begin.

6 | CONCLUSIONS

Since the first recorded xenograft in the 17th century, some viewpoints toward XTx have shifted. From what is currently known, viewpoints of three of the major religions are largely receptive toward the prospect of XTx, which presents a marked shift. Furthermore, as the prospect of XTx has progressed, more robust theological viewpoints have been offered, such as the guidance provided by the Catholic Church's Pontifical Academy for Life. Yet it is clear that more research is needed in this area for a truly comprehensive view.

The use of animals as a source of organs has, since the 1990s, shifted from the NHP to the pig. It is likely that the public is more receptive toward the use of pigs as a source of xenografts than NHPs. However, the undefined risk of xenozoonotic infection still exists, which presents not only a scientific challenge but also an ethical conundrum of whether and how clinical trials should proceed. This ethical point has been quelled to some degree with the genetic engineering processes now employed in source pigs. Some risk to the patient persists, as seen in the recent 2022 clinical pig heart transplant, and perhaps there remains a plausible but albeit small risk at the population level. Last, although public attitudes toward XTx have been studied for decades, more data points are needed to ensure a better understanding.

Many of the ethical issues involved in XTx have been discussed for decades in one form or another. As the science of XTx has advanced, some progress has been made in resolving certain areas of ethical conflict. However, some ethical issues have endured and persisted today.

ACKNOWLEDGMENTS

D.J.H. would like to thank the National Institute for Allergy and Infectious Disease where he initially presented an abbreviated version of this paper. Work on xenotransplantation in DKCC's laboratory is supported in part by NIH NIAID U19 Grant AI090959.

CONFLICT OF INTEREST STATEMENT

D.J.H. is a consultant to a working group on xenotransplantation at the New York University Division of Medical Ethics. D.K.C.C. is a consultant to eGenesis Bio of Cambridge, MA, but the opinions expressed in this article are those of the authors and do not necessarily reflect those of eGenesis.

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How to cite this article: Rodger D, Hurst DJ, Cooper DKC. Xenotransplantation: A historical–ethical account of viewpoints. *Xenotransplantation*. 2023;e12797. https://doi.org/10.1111/xen.12797