The future of research into rotavirus vaccine

Benefits of vaccine may outweigh risks for children in developing countries

The future of a potentially lifesaving vaccine for developing countries has been imperiled by its recent withdrawal from the United States market. In August 1998, tetravalent rhesus rotavirus vaccine was licensed for routine vaccination in the United States on the basis of randomised controlled trials there and in Finland. The trials showed that the vaccine had an efficacy of 49-68% in preventing rotavirus diarrhoea overall and, importantly, 69-91% efficacy in preventing severe disease.[1–4]

In July 1999 the US Centers for Disease Control and Prevention reported a clustering of cases of intussusception in the weeks after vaccination with tetravalent rhesus rotavirus vaccine, representing an additional risk of 1 in 10 000 for this complication.[5] On the basis of this finding they recommended "postponing administration of tetravalent rhesus rotavirus vaccine to children," and in October 1999 the manufacturer voluntarily withdrew the product from the United States market. This leaves researchers with a moral quandary: should randomised controlled trials of tetravalent rhesus rotavirus vaccine proceed in developing countries?

Firstly, it may be thought that other vaccines in development (for example, human-bovine rotavirus vaccine) may not cause intussusception. This is pure speculation. About one million children have been vaccinated with tetravalent rhesus rotavirus vaccine. Other vaccines in development have two or three orders of magnitude less experience in humans, numbers far too small to rule out a complication in the order of 1 in 10 000. Indeed, we cannot rule out the possibility that rotavirus itself causes intussusception in children who are predisposed to this problem; thus, vaccination with any live oral agent may be a triggering event.[6] Secondly, the public health community generally believes that one must do no harm.

Assuming a worst case scenario of a 25% fatality rate from intussusception in developing countries, widespread use of tetravalent rhesus rotavirus vaccine could cause 2000-3000 deaths a year. For some, the prospect of causing this many deaths—or perhaps even any deaths—is morally untenable. The context of developing countries differs starkly from North America. Despite efforts to prevent death with programmes of oral rehydration therapy, about three million children die of diarrhoea annually.[7] Of these deaths, approximately 600 000 to 800 000 are caused by rotavirus diarrhoea. Tetravalent rhesus rotavirus vaccine may prevent 80% of these deaths. If the next vaccine in development takes three to five years to get to the stage where tetravalent rhesus rotavirus vaccine is now, the choice to wait must be weighed against the cost of waiting: 1.4 to 3.2 million preventable deaths. Some have falsely assumed that inaction is a morally neutral state. But if one is culpable for vaccine related deaths, then one is also culpable for deaths caused by withholding the vaccine.

Is there a moral difference between a treatment that may cause a sick child to die and a vaccine that may cause a healthy child to die? Because public health doctors treat unhealthy populations rather than unhealthy patients the risk of death or serious disability must be lower with vaccines than with clinical treatments. The risks of tetravalent rhesus rotavirus vaccine seem comparable to the risks associated with measles, mumps, and rubella vaccine.[8] The moral yardstick for the public health physician is ultimately the same as for clinicians: do the benefits of vaccination exceed the risks? In a developing country in which a child's risk of death from rotavirus diarrhea is 1 in 200 or greater the answer may well be yes.

Thirdly, as a result of the controversy over randomised controlled trials on the prevention of perinatal transmission of HIV in Africa and Thailand, there is sensitivity surrounding such trials in developing countries.[9–11] Some critics of the HIV trials believe that there should be a universal standard of care for a disease that is independent of the care that is available locally.[9 10] Others argue more convincingly that this would lead to randomised controlled trials that are less responsive to the health needs of developing countries.[11]

To make the standard of care in the United States the universal standard of care would only be unjust and would perpetuate the unjust distribution of healthcare resources globally. Tetravalent rhesus rotavirus vaccine was withdrawn from the market in the United States because the possibility of a 1 in 10 000 risk of intussusception seemed unduly high in comparison to only 20 deaths annually from rotavirus diarrhoea.[12] It is imperialistic to transfer this standard of care to a country in which 1 in 200 children die of rotavirus infection, and thereby to deny even further study of the tetravalent rhesus rotavirus vaccine.

Ethical randomised controlled trials must begin with an honest null hypothesis.[13] Though the recent success of a randomised controlled trial of tetravalent rhesus rotavirus vaccine in Venezuela provides grounds for optimism, randomised controlled trials in other developing countries are needed because of various factors such as serotypical variance in rotavirus and the fact that the disease has an earlier onset and lacks the seasonality seen in developed countries.[14 15] We don't know whether tetravalent rhesus rotavirus vaccine will be as effective in developing countries, but starting with an honest null hypothesis makes it ethical to proceed.

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CW's work is supported by a Medical Research Council of Canada Scholar Award and Operating Grant as well as a Dalhousie University Clinical Research Scholar Award.

The author is grateful to Drs Françoise Baylis, Anthony Belardo, Robert Crouch, Carolyn Ells, Scott Halperin, and Nuala Kenny for their comments on earlier versions of this commentary.

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A fair way of donating hearts for transplantation

Survival rates improve only in patients with the worst heart failure

In the early years after the introduction of heart transplantation the supply of donor hearts increased yearly as greater numbers of transplant centres came into existence and more patients with end stage heart disease were listed as transplant candidates. This parallel expansion of both donor and recipient numbers ceased around 1990, and since then the number of cardiac donors has plateaued at about 3500 a year worldwide while the number of patients listed to receive a heart transplant increases annually.[1 2] This increase in the number of patients waiting for a heart transplant has occurred despite major improvements in medical treatment for heart failure that have been introduced during this time.

This probably reflects the fact that most of the advances in the treatment of heart failure have been essentially palliative. It may also reflect a belief in the medical community that heart transplantation improves the chances of survival for patients who reach an advanced stage of heart failure and do not have contraindications to transplantation. As has been the case with most forms of surgical treatment, this second belief has never been tested or proved in a clinical trial. Even so, this belief in the transplant community shares the same hallowed status as the belief in the use of antibiotics for pneumonia in the infectious disease community, which seems equally unlikely to be the subject of a clinical trial.

The plateau in the number of cardiac donors available has led to the cardiac donor becoming a scarce medical and societal resource, which in turn leads to the need to pursue strict principles of distributive justice in allocating donor organs. Some guidelines for principles of distributive justice for scarce medical resources have been delineated, but they need to be applied in the practical medical context of knowing which subsets of patients are most likely to benefit from the scarce resource.[3]

The article by Deng et al in this issue of the journal helps to address this issue (page 540).[4] The authors analysed the survival benefit from heart transplantation in all patients listed for heart transplantation at all centres in Germany for a one year period and subdivided them into groups at low, medium, and high risk of death from their heart failure. They used a previously validated risk score for heart failure (which also works well prognostically in their patients) and showed that transplantation improved survival only in the patients at highest risk of death from heart failure. The authors did not analyse the impact of transplantation on quality of life or the cost of medical care for their patients. Whether the results are generalisable to other countries is, of course, unknown—it may be reasonable to establish similar registries of advanced heart failure in other countries or even internationally.

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These data certainly lend validity to the idea of organ allocation systems (the scheme used in the United States was recently introduced in Britain) that give priority for organ donation to the sickest patients. Whether these should be the only patients to be listed, given that relative costs and quality of life are unknown, is a matter of speculation.

Deng at al's findings could raise the issue of pursuing a randomised trial of heart transplantation versus medical treatment for heart failure, a proposal that is attractive on theoretical grounds but highly unlikely ever to be undertaken. The logistics and ethics of such randomisation (the impossibility of "blinding" or "placebos" in design, the difficulty of assuring clinical "equipoise" in physicians caring for truly sick patients) would be overwhelming. Instead, the findings will probably be an impetus to continue development of schemes for organ allocation that give donor hearts to those most likely to derive survival benefit from them and will help to define the characteristics of that subset. In addition, they may intensify the pursuit of alternatives to transplantation including chronic mechanical circulatory support devices.

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