How safe should donor blood be?

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Chapter 4:

Donor blood screening and moral responsibility: how safe should blood be?

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ABSTRACT

Some screening tests for donor blood that are used by blood services to prevent transfusion-transmission of infectious diseases, offer relatively few health benefits for the resources spent on them. Can good ethical arguments be provided for employing these tests nonetheless?

This paper discusses – and ultimately rejects – three such arguments. According to the "rule of rescue" argument, general standards for cost-effectiveness in health care may be ignored when rescuing identifiable individuals. The argument fails in this context, however, because we cannot identify beforehand who will benefit from additional blood screening tests. On the "imposed risk" argument, general cost-effectiveness standards do not apply when health care interventions *impose* risks on patients. This argument ignores that imposing risks on patients is inevitable in health care and that these risks can be countered only within reasonable limits. Finally, the "manufacturing standard" argument premises that general cost-effectiveness standards do not apply to procedures preventing the contamination of manufactured medical products. We contend that while this argument seems reasonable insofar as commercially manufactured medical products are concerned, publicly funded blood screening tests should respect the standards for general health care.

We conclude that these particular arguments are unpersuasive, and we offer directions to advance the debate.

1. BACKGROUND

Transfusing blood and blood derivatives is an effective treatment of various medical conditions, including major blood loss due to injury and thrombocyte deficiency after chemotherapy. Various risks of blood transfusion, such as haemolysis due to blood type incompatibility, have also been known for decades, but attention shifted radically with the emergence of AIDS in the 1980's [1,2]. The risk of transfusion-transmission of HIV/AIDS, which was initially gauged at 'one in a million' [3], proved to be around 1:100 per blood product transfused [4]. AIDS also proved to be more lethal than previously known infectious risks of transfusion, in particular hepatitis B – thousands of transfusion (and blood derivatives) recipients died of transfusion-transmitted AIDS within a few years [4].

Apart from dominating the general public's perception of transfusion risks, transfusion-transmitted infections (TTIs) have since this crisis become a focal concern in blood system regulation [1,2,4]. Almost all developed countries have installed extensive safety measures against TTIs, including blood testing procedures against HIV, Hepatitis B, Hepatitis C, syphilis and other diseases. Transfusion-transmission of serious infections has hence become rather uncommon (compared, e.g., to non-infectious transfusion accidents and accidents in traffic and sports). In the United States, for example, the residual risk of transmitting serious infections is estimated at 1 per 1,860,883 donations for HIV, 1 per 1,657,722 donations for hepatitis C virus (HCV), and between 1 per 765,000 and 1,006,000 donations for hepatitis B virus (HBV) [5,6]. Nonetheless, there seems to be pressure on blood services to reduce these risks ever further.

2. COST-EFFECTIVENESS OF DONOR BLOOD TESTS

Although the risks may be small, no test is 100% sensitive, so testing can always be improved. Testing may be marginally enhanced, for example, by performing a single test repeatedly or by using screening assays from multiple manufacturers in parallel. Moreover, serological screening, which detects antibodies against infectious agents, can often be complemented by nucleic acid testing (NAT). NAT targets genetic material of infectious microorganisms, which enables the detection of infections prior to seroconversion (i.e. the formation of antibodies). The timeframe in which recent infections are undetectable (the 'window' period) is therefore

shorter for NAT than for serological screening.[1] NAT can be applied to pools of (e.g. 48, 24 or 6) donations, but sensitivity increases if pools contain fewer donations, or if every donation is tested individually.

The added value of additional or improved testing is typically small, however. Donor blood screening in the Netherlands includes a (combined) NAT test for Hepatitis B, hepatitis C, and HIV in pools of 6 donations. The incremental cost-effectiveness ratio (ICER) of NAT, which represents the 'value for money' of applying NAT on top of serological testing, is estimated at €5,199,220 per Quality-adjusted life-year (QALY) [7]. Serological screening for Human T-cell Lymphotrophic Virus (HTLV-I/II), a virus that causes disease in a minority of infected persons, was in the Netherlands even estimated to cost €45,182,666 per QALY.[7] This has improved after switching from testing all donations to testing new donors only, but the cost-effectiveness ratio is still over €2.000.000 per QALY [7]. Similar cost-effectiveness ratios for NAT and HTLV screening have been reported in other western countries [8,9].

The high ICERs of additional tests contrast sharply with the standards for cost-effectiveness that are (implicitly or explicitly) used to assess public health care interventions. The United Kingdom's NICE committee normally does not consider medical treatments costing over £20,000 - £30,000 per QALY cost-effective [10]. In the Netherlands, vaccinations are expected not to cost more than €20,000 per QALY [11], while the Council for Public Health and Health Care (RVZ) suggested a limit of €80,000 per QALY for life-saving medical treatments that are covered in basic health insurance [12]. Thus, while transfusion is presumably considered a cost-effective intervention (i.e. has an ICER below such standards), some donor blood screening procedures clearly are not.[2]

Economic considerations have thus had a minor role in decision-making on donor blood screening [13,cf. 14]. This to some extent understandable –economic evaluations of public health interventions are not without problems [15,16]; there are good reasons not to set an explicit 'price on life'; and society has since the HIV crisis simply proven to be willing to spend many resources on blood safety [2]. But the tide seems to be changing. The application of blood safety tests with high ICERs (and high opportunity costs) is criticized increasingly, as is the 'zero-risk' or 'maximal safety' decision-making paradigm that motivated their

1 A window period remains because NAT cannot detect low concentrations of genetic material. NAT may also fail when antibodies repress but do not completely clear the virus.

2 One might argue that the cost-effectiveness of individual tests is irrelevant, if testing is on the whole cost-effective. When deciding on additional testing, however, added safety and budgetary impact are surely ethically relevant.

implementation [1,13,17]. Moreover, decision-making frameworks have recently been developed that aspire to reconcile safety concerns and cost-considerations [18,19].

Possible arguments for excepting blood safety tests from general cost-effectiveness standards are rarely discussed systematically, however. This is a lacuna, because it cannot be excluded *a priori* that there are good reasons to perform even economically inefficient tests. We present three such arguments. On the "rule of rescue" argument, general cost-effectiveness standards should not apply when rescuing identifiable individuals. The "imposed risk" argument holds that such standards may be ignored when health care interventions themselves threaten to harm patients. According to the "manufacturing standard" argument, finally, measures that prevent contamination of manufactured medical products are required even if they are highly expensive. In this paper we show that these arguments are unconvincing. First however, some preliminary remarks are in order.

3. WHY THIS IS A MORAL ISSUE

How far one should go in preventing TTIs is not just a matter of economic concern. This issue has at least two moral dimensions.

First, omitting some expensive tests makes resources available to do more good elsewhere. Other things being equal, it is better to save more lives or relieve more health needs than less. This principle – combined with the reasonable assumption that resources are finite – sets moral limits to accepting inefficient interventions in public health and clinical medicine. We will therefore presuppose that some criterion for cost-effectiveness, in terms of costs per QALY gained, should be accepted. Deviating from this standard is then *prima facie* objectionable and must be supported by convincing ethical arguments. Any threshold will be somewhat arbitrary and controversial, but let us set the limit (for the sake of argument) at €100,000/QALY. (Recall that actual standards for the assessment of health care interventions range to €80,000/QALY.)

Secondly, blood safety raises issues about moral responsibility. Blood services might have special obligations to prevent TTIs, for example because of their causal role in the occurrence of TTIs, which may affect what precautions are necessary and reasonable. The arguments explored in the following sections proceed from this general thought.

Other perspectives, in particular political and legal ones, are clearly relevant as well. Since the HIV crisis of the 1980ies, blood safety is a sensitive and heavily politicised topic [1]. Preventing public outrage, blame, reputational damage, and liability may hence require showing a low tolerance of TTI risks, which means that performing blood safety measures with unfavourable ICERs might not be irrational [1,cf. 19]. This cannot be disregarded when reviewing screening policies or decision-making guidelines. But whether or not accepting high costs for blood safety is politically and legally prudent – or even 'rational' – further judgment is required on whether such an allocation of resources is ethical. An ethical viewpoint might help to criticize or counterbalance societal, political, and legal concerns and thus has clear merit.

We will ignore methodological limitations of cost-effectiveness analysis. We acknowledge that CEA is inapplicable (or unreliable) when significant uncertainty persists – for example when it is entirely unclear whether an infection is transfusion-transmissible or how frequently donors are infected. It also faces various conceptual or theoretical limitations, which for example relate to quantifying extremely small risks, to expressing diverse health states in a single unit (such as the QALY), and to deciding which economic and (public) health effects should be included. We can ignore such issues for some tests, however, such as combined HIV/HBV/HCV NAT and serological HTLV testing in the Netherlands. These tests involve well-researched infections and there is ample experience with their (lack of) added value for blood safety. The *onus probandi* is therefore clearly on the person who contends that these tests, the ICERs of which exceed general cost-effectiveness thresholds more than tenfold, *are* sufficiently cost-effective.

4. THE "RULE OF RESCUE" ARGUMENT

Arguments in defence of medical interventions that are not considered cost-effective often invoke the 'rule of rescue' [21]. This is the principle that if we can save the lives of identifiable persons, this might justify even extreme costs. Few societies are willing to set financial limits for rescue operations if a child has fallen down a well, for example, or if miners are trapped underground after an explosion. Investing the same amount of money in measures that prevent such emergencies will often be much more cost-effective, but – so the argument goes – this should not be considered a reason for abandoning rescue attempts now. The implicit assumption is that saving identifiable persons in need should not be considered on a par with saving "statistical lives" through preventive measures. Although we think it can be justified to

accept higher costs for certain rescue operations [22], the relevance and validity of the argument in the context of health care is debatable [21].

Commitment to the rule of rescue has been alleged to explain the disregard of costs in donor blood safety [23]. It cannot apply to donor blood screening, however, precisely because no identifiable individuals will experience the health benefits. The persons who need safe blood may be identifiable, but those who would benefit if we applied additional measures to prevent TTIs are not. To the contrary – following the rule of rescue in public health care would suggest allocating more resources to address the immediate needs of identifiable patients (e.g. those who require life-saving treatment with very expensive drugs), instead of investing in further preventive measures against TTIs.

5. THE "IMPOSED RISK" ARGUMENT

Another possible argument for accepting blood safety tests with high ICERs is that transfusion *imposes* infectious risks on patients and that blood services therefore have a strict responsibility to protect those patients – a responsibility that goes beyond the normal scope of public health care.

Generally speaking, public health care aims to prevent and cure disease whatever its nature and cause, motivated by concerns of beneficence, justice, or solidarity.[3] Given the omnipresence of (risk of) disease, health protection is necessarily limited, and cost-effectiveness standards are one way of setting boundaries. What distinguishes transfusion-transmitted infections from most other medical conditions, though, is that they are in a way caused by the intervention itself. Blood services might be considered to *impose* TTI risks on patients and hence to be causally (and morally) responsible when TTIs occur. Precautions against TTI should then be viewed differently from precautions that society takes against other (say, 'natural') health risks, in which case cost-effectiveness standards that are accepted within regular health care need not apply to precautions against TTIs. This does not imply that all possible precautions are necessary, only that precautions costing more than €100,000/QALY might still be morally reasonable or even required.

The argument presupposes that *imposing* risks on others is more objectionable, morally speaking, than allowing that people are *exposed* to risks that do not originate in one's agency.

3 Some might argue that diseases that are partly caused by individual 'lifestyle' choices should be treated differently, but that does not affect the argument at stake.

This presupposition can in turn be defended by noting its analogy to the intuitive moral distinction between *causing* harm to others and ('merely') *allowing* them to get hurt. Harming others is often considered more straightforwardly wrong than not preventing people from getting injured, and duties of non-maleficence are therefore deemed stronger than duties of beneficence. The conceptual and moral cogency of the distinction is hotly debated among philosophers [24], but we will grant it for the sake of argument. Even then, however, it does not follow that employing blood safety tests with ICERs exceeding general cost-effectiveness standards is justified – or so we argue in the remainder of this section.

Let's start with the idea that there is a strict responsibility not to impose risks because imposing risks on others is tantamount to harming them. There is agreement in the ethics of risk that imposing a risk at harm does not necessarily constitute a harm itself. Moreover, there cannot be a strict responsibility not to impose small risks on others, because almost any daily activity carries some risk at severe, even lethal, harm to others. Driving a car creates some risk for pedestrians, for example, and risking to infect other people with potentially dangerous diseases (such as influenza) is inevitable in daily life. Thus, if every action that *might* cause serious harm should be banned, life as we know it should halt [25]. Even if actions that will definitely cause some harm to others are categorically wrong, therefore, actions that involve small risks of causing that harm need not be – such actions may be acceptable and are in fact accepted. Moreover, in this specific context, the infection risks are connected to medical treatment (blood transfusion) and befall the same person who enjoys the treatment's benefits.[4] Virtually any medical therapy involves some risk for the patient – yet these risks are normally considered justified if they are outweighed by the expected benefits of the intervention and if the patient consents to the (risks of the) treatment. When administering blood or blood components is necessary to avoid mortality or significant morbidity, the intervention can be well justified even if it brings a risk of infection. Concluding that these risks are morally unacceptable, even if they are in a sense imposed upon patients, is therefore unfounded.

The response is not yet fully on target. Physicians are obviously expected to take some precautions (e.g. washing hands before invasive procedures) and omitting such precautions cannot be justified by appeal to the expected benefits of the medical treatment they offer – imagine a surgeon foregoing hand washing because the risks of infection are small compared

[4] For reasons of space, we will ignore any hazards that the blood transfusion poses to the patient's social environment, in particular his sexual partners.

to the life-saving surgery she is about to do. Yet such precautions will only be required within certain limits of reasonableness, and it can be well justified to stick to basic hygiene (gloves, sterilisation of tools, hand washing) if additional hygienic measures would leave the surgeon significantly less time for patient care. One can similarly argue that blood banks that already have extensive (and effective) safety measures in place have fulfilled their responsibilities within limits of reasonableness and can be justified in forgoing tests that would reduce these risks even further, in particular if these additional tests have significant opportunity costs. After all, the added value of further blood safety tests (e.g. NAT) is often limited *because* prior safety measures (e.g. donor selection and serological testing) are already very effective at reducing TTI risks.

The argument that blood banks have special responsibilities to minimize the risks they impose on patients is also debatable in a different way. Can we indeed say that the blood bank *imposes* TTI risks on transfusion recipients? In case infections occur, the infection originated in a donor and was not detected by the blood services' testing lab. If the infection would have been detected by a test which the blood bank had decided not to apply, the blood service arguably *allowed* the transmission of the infection from the donor to the recipient, rather than *imposed* risks on the latter. Hence, if we accept the moral distinction between allowing harm to occur and imposing risks of harm, we may still conclude that deciding not to implement a specific blood screening test falls in the former category.

Again this response is a bit too fast. Agents can bear moral responsibility for harmful effects even if the harm does not *originate* in their agency. Think again of the surgeon who refrains from hygienic measures and thereby puts her patient at risk. If infection occurs, it seems inappropriate for the surgeon to dismiss her responsibility by explaining that the harm originates in the contaminated tools, in the microbes that dwell on the tools, or in the patient whose surgery led to contamination of the tools. Instead of focusing on the origin of a risk, we should reflect on the causal role an agent plays, among other causal factors, in the occurrence of harm. Following Feinberg, we may say that the agent's causal role is strong if he had the opportunity, the ability, and the knowledge to prevent harm, and if it was reasonable to expect the agent to prevent it [26]. Whether the agent could be expected to prevent the harm in turn depends on his personal and professional commitments and his moral responsibilities – which, as we have seen, involve limits of reasonableness [26]. The surgeon in our example can be

ascribed a strong causal role when an infection occurs because we reasonably expect surgeons to wash their hands and use sterilized tools.

Here we enter a circular line of reflection. We started with the idea that if an agent has a strong causal role in the occurrence of risk, this may imply special moral responsibilities for taking precautions. Conversely, however, a judgment about that causal role presupposes a judgment about the scope of her responsibilities.[5] But this undermines the whole argument so far: attributing a strong causal role to blood services when TTIs occur already *assumes* (rather than *establishes*) that they should have taken stricter precautions. Identifying a blood service's omission to implement safety measures with high ICERs as *a* or even *the* cause of TTIs thus presupposes what is at issue: namely that taking safety measures with high ICERs is reasonable.

6. THE "MANUFACTURING STANDARD" ARGUMENT

One might contend that the previous discussion drew too heavily on the analogy between deciding on the implementation of donor blood screening tests and weighing the risks and benefits of medical interventions. Like surgeons taking precautions against adverse effects of operations, we argued, blood services should observe limits of reasonableness when implementing measures against TTIs, where common cost-effectiveness standards may help to define those limits. But standards for the provision of clinical care may be poorly applicable to blood safety: given that blood services *manufacture medical products* rather than *provide clinical care*, they should adhere to the standards for manufactured medical drugs instead. Now pharmaceutical companies are expected to take extensive measures against contamination of their products. Many medical drugs have adverse side-effects, of course, but these are often linked to the working mechanism or nature of the drug itself. Infectious risks of transfusion are special in that they can be reduced – at least in some cases – by additional steps in the manufacturing process. TTIs in blood products are then like *avoidable* contamination of drugs, against which pharmaceutical industry is expected to take rigorous measures. It indeed seems morally inappropriate for pharmaceutical companies to forgo precautions simply because their ICERs exceed cost-effectiveness standards for public health care.

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5 Feinberg states: "Often then we must know whether the nonrescuer had a duty… to act before we can know whether he caused harm by not acting…, rather than the other way around [26, p. 172]."

Whether this line of argument is persuasive depends on *why* it would be inappropriate for producers of pharmaceutical products to forego safety measures that have high ICERs. Why should there be different cost-effectiveness standards for public health care and for precautions to be taken by pharmaceutical companies to enhance drug safety?

A plausible answer is that the opportunity costs are different. In private pharmaceutical industry, saving money on safety measures might simply be a form of cost-reduction which secures higher profits or 'shareholder value'. Given that blood services are (typically) public institutions aiming it public health, however, resources not spent on donor blood safety will ideally be reallocated to initiatives that secure other public goods (e.g. the provision of orphan drugs). This suggests that the safety measures they apply should respect the cost-effectiveness standards as used in public health care rather than the safety standards of the medical industry.

7. CONCLUSIONS AND LIMITATIONS OF THE ANALYSIS

We have discussed three arguments that might justify applying donor blood screening tests with ICERs exceeding general standards for cost-effectiveness in public health care. The "rule of rescue" argument, the "imposed risk" argument, and the "manufacturing standard" argument were all unpersuasive.

Performing blood tests with high ICERs therefore seems unethical unless more compelling arguments can be offered. Biomedical ethics and decision-making on blood safety are possible sources of inspiration here, but some limitations of our analysis also suggest lines of inquiry.

First, we have assumed that there should be a limit to cost-effectiveness for public health care in general, which includes such diverse interventions as life-saving surgery, care for elderly persons, vaccination of new-borns, and precautions for preventing infections. It might be revealing, however, to survey the willingness to accept interventions with high ICERs in various domains and to correlate this to ethical dimensions of the health issues addressed (such as the social determinants of disease).

Secondly, health has been considered the core value to be promoted and protected. Yet other moral values, that are harder to capture in cost-effectiveness analyses, are involved as well. How trust in the blood supply influences patients, physicians and donors is difficult to quantify, for example, as is the intrinsic value of trust. Taking such values into account might support accepting more demanding precautions.

Finally, we have ignored the cultural and emotional significance people attach to blood and blood-related risks. There might be something 'irrational' in the general public's perception of blood risks, but in a pluralistic and democratic society it cannot be ignored completely. What weight the public's perception should be granted deserves further consideration.

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