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How safe should donor blood be?

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Chapter 1:

General Introduction

BACKGROUND

In July 2012, the Dutch Minister of Health, Welfare and Sport sent the parliament a letter about the costs of the blood supply, which concluded:

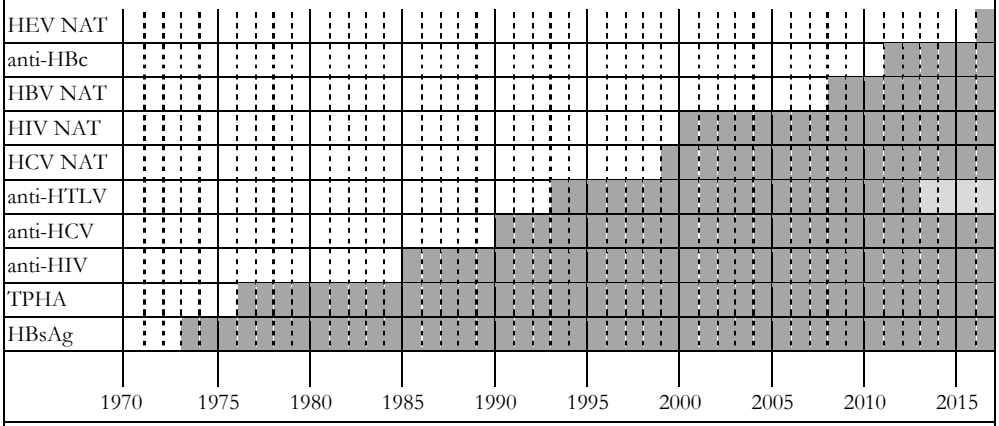
> "Concerning the safety tests that Sanquin [the Dutch blood service] currently applies, my opinion is that the number of safety tests should be reduced, provided that the safety of blood product recipients is not endangered. I will therefore request Sanquin to conduct research into the utility and necessity of the safety measures, and to compare these to similar countries, to consider whether the safety measures that Sanquin currently applies are still effective and contribute to the safety and quality of the blood supply. This viewpoint results from a period of research into the costs of the Dutch blood supply." (Translated from [1])

Although the Minister's letter is officially a response to the 'ConQuaestor' research report [2], her statement is primarily based on an earlier government-commissioned research report [3]. This 'Plexus' report compared the Dutch blood supply to the blood systems of four similar countries, and concluded that the Dutch blood supply involved relatively high costs. A main explanation, according to the Plexus report, can be found in the safety tests applied: Sanquin applies more types of safety tests and more expensive safety tests than blood services in the benchmark countries do.

What safety tests do blood services apply, then? EU law mandates that all European blood services test all blood donations for serological markers of infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) [4]. Because serological testing depends on the formation of antibodies by the donor's immune system (or the formation of sufficient quantities of viral antigens in the donor's blood), serological screening fails to detect early-stage infections in donors. Most developed countries reduce this 'window period' by applying nucleic acid tests (NAT), which can demonstrate recent infections by amplifying and detecting viral genetic material (DNA or RNA). Finally, although HIV, HBV and HCV are historically blood services' main concern, donor blood is also screened for various other infections (e.g. lues/syphilis, human t-cell lymphotropic virus). Blood testing is complemented by other types of safety measures, such as the exclusion of high-risk donors through donor education and predonation questionnaires, and the heat treatment and nano-filtration of plasma-derived products.

There have been significant changes in the countries' testing arrays since the Plexus benchmark. The Plexus report mentioned additional NAT screening as an explanation for higher testing costs in the Netherlands. By now, each of the countries in the benchmark (Belgium, Finland, France, and Ireland) has adopted NAT screening for HIV, HBV, and HCV [5]. Furthermore, the Netherlands have implemented anti-HBc screening and hepatitis E virus (HEV) NAT, but have relaxed testing all donations for anti-HTLV 1/2 into testing new donors only. The historical development of blood screening tests in the Netherlands is depicted in Figure 1.

Figure 1: Screening tests performed on blood donations for labile blood products, the Netherlands, 1970-2017 (adapted with permission from [6])



Legend:
HBsAg: Hepatis B surface antigen testing; TPHA: *Treponema pallidum* haemagglutination testing; anti-HIV: human immunodeficiency virus antibody testing; anti-HCV: hepatitis C virus antibody testing; anti-HTLV: human T-cell lymphotropic virus antibody testing (switched from testing all donors to testing only new donors in 2013); HCV NAT: hepatitis C virus nucleic acid testing; HIV NAT: human immunodeficiency virus nucleic acid testing; HBV NAT: Hepatitis B virus nucleic acid testing; anti-HBc: Hepatitis B core-antigen antibody testing; HEV NAT: Hepatitis E virus nucleic acid testing.

Given these changes, it is unlikely that the benchmark's conclusion still holds – that the Dutch screening programme is relatively expensive because it is relatively extensive. Nevertheless, reasons to be critical about costly safety measures remain, both in the Netherlands and internationally. In 2013, NAT screening in the countries of the Plexus benchmark intercepted one HIV-positive, one HCV-positive, and eight HBV-positive donations that were missed by serologic screening, on a total of approximately 4.5 million donations [5]. Comparable ratios

are listed for other years and other countries. In combination with its high cost, the implication is that HIV/HBV/HCV NAT screening offers little 'value for money'. Health economists have calculated that NAT screening costs over €5,000,000 per quality-adjusted life-year (QALY) saved in the Netherlands [7], over $4,000,000/QALY in the United States [8], and more than $2,000,000/QALY in Sweden [9]. Such high costs per QALY are not limited to HIV/HBV/HCV NAT screening. For example, the Dutch policy of screening new donors for anti-HTLV 1/2 has been calculated to cost over €2,000,000/QALY [7]; screening all donors for anti-HTLV 1/2 costs the United Kingdom between £310,000 and £1,700,000/QALY [10]; and testing for *babesia microti*, a parasite transmitted by ticks, costs the United States at least $2.000.000/QALY [11]. As new threats to the blood supply emerge, the introduction of costly safety measures continues (e.g. Zika screening in the United States [12]). Some of these safety measures may prove effective and efficient, others may not. (For ease of exposition, we will use 'cost-effectiveness' and 'efficiency' interchangeably and will loosely call safety measures with high incremental cost-effectiveness ratios 'inefficient'.)

Why should we care about the costs of blood safety? On a utilitarian perspective, healthcare should be as beneficial as possible: healthcare resources should be applied where they save the most QALYs. Sensitive to the general idea that efficiency saves life-years, several countries have developed cost-effectiveness thresholds to guide the allocation of healthcare funds. In the Netherlands, for example, €80,000/QALY has been suggested as a limit for covering life-saving treatments by basic health insurance [13], while in the UK medical treatments are expected to cost under £20,000–£30,000/QALY [14]. The large discrepancy between these thresholds and some cost-effectiveness ratios in blood safety suggests that inefficient blood safety measures actually cost QALYs. Because resources are limited, funding blood safety measures implies that these funds cannot be used for other purposes (e.g. to develop or distribute orphan drugs). Assuming that alternative investments would have had larger benefits in terms of QALYs gained, funding inefficient blood safety measures means missing an opportunity to save QALYs. This utilitarian argument applies only to safety measures with a small impact on safety at a relatively high cost. Some blood safety measures are efficient in most contexts (e.g. serological screening for HIV [15]). In addition, safety measures that are inefficient in some countries may be efficient in countries with high infection rates among prospective donors (e.g. HIV/HBV/HCV NAT if it were applied in developing countries). Such arguments are outside of this dissertation's scope: we focus at inefficient blood safety measures in western contexts.

The utilitarian argument can be questioned in various ways. It can be doubted that funding blood safety measures excludes any alternative investments in health care. Blood safety measures consume only a small share of the total health care budget, and that budget is typically flexible. One may also question whether blood safety measures are as inefficient as cost-effectiveness studies have concluded, and one may criticize normative assumptions behind such studies, for example assumptions in quantifying health and quality of life. Addressing these issues must engage with (the methodology of) health economics, which is outside of this dissertation's scope. Instead, this dissertation discusses counterarguments of a different type: ethical arguments that might override the utilitarian argument even if it is correct. In other words, it considers whether there are good ethical reasons to apply inefficient blood safety measures even if more lives or QALYs would be saved by directing the required funds elsewhere.

RESEARCH GOALS

This thesis considers whether applying inefficient blood safety measures (i.e. blood safety measures with very high cost-effectiveness ratios) is ethically acceptable. This question is approached from two complementary angles.

Part I presents qualitative empirical research that identifies potential reasons not to tolerate infection risks of blood transfusion. Chapter 2 presents a broad analysis of blood safety decision-making. Based on an analysis of policy documents from five Western countries, it offers an inventory of considerations behind decisions to adopt expensive blood safety measures, including advantages and disadvantages of candidate safety policies; difficulties in assessing risks and forecasting the effects of safety policies; decision-making principles; and practical barriers in reaching safety decisions. Chapter 3 zooms in on possible reasons to tolerate or not to tolerate infection risks of blood products, based on interviews and focus group discussions with stakeholders in the Dutch blood supply. Stakeholders' arguments appealed to the clinical impact, the probability, or the avoidability of getting infected, to the health benefits, the costs, or miscellaneous consequences of safety measures, to non-consequentialist ethical concerns, or to the interests of stakeholders. More specific arguments are presented in overview and illustrated by citations. Chapter 3 finally reflects on some unexpected and controversial stakeholder perspectives.

Part II evaluates a number of ethical arguments why even inefficient blood safety measures should be applied. Chapter 4 draws three arguments from ethical literature and applies these to blood safety: the 'rule of rescue' argument, according to which saving identifiable individuals justifies applying inefficient safety measures; the 'risk imposition' argument, according to which safety measures against risks imposed by health care interventions should be exempt from general cost-effectiveness criteria; and the 'manufacturing standard' argument, according to which cost-effectiveness standards should not apply to procedures preventing the contamination of manufactured medical products. Although these arguments seem sensible in general, they are unconvincing when applied to blood safety, as chapter 4 argues. Chapter 5 discusses the official motivation of various cost-insensitive blood safety measures: the precautionary principle. The chapter distinguishes different versions or interpretations of the precautionary principle and proposes constraints that any interpretation must meet. *Consistency* forbids taking safety measures that the precautionary principle itself deems intolerably risky; *avoiding counterproductivity* forbids taking safety measures that do more harm than they avert; and *proportionality* forbids prescribing precautions that are more harmful than alternative adequate precautions. We argue that meeting these constraints implies tolerating some risks – sometimes even to save resources, provided that these resources are needed to address more serious harms or risks. Chapter 6 goes deeper into the interpretation of the precautionary principle and its application to blood safety issues. In doing so, it responds to a number of published commentaries on the account of the precautionary principle presented in chapter 5. Some of these commentaries challenge our interpretation of the precautionary principle, others apply our account to the question whether men-who-have-sex-with-men should be deferred as blood donors. However, none of the commentaries challenge the thesis that when the (opportunity) costs of precautions are high, it may be legitimate to tolerate blood transfusion risks. The final chapter, chapter 7, concerns the idea that terminating inefficient blood safety measures is more problematic, from an ethical point of view, than deciding not to implement such safety measures. Our analysis draws on literature regarding the difference between withdrawing and withholding life-sustaining treatments; we extend two main arguments from this literature to blood safety. The first argument is that removing protections causes harm, while not starting them merely fails to prevent harm, the second is that patients are historically entitled to the continuation of medical interventions they benefit from. However, neither of these arguments seems to be persuasive: the claim that stopping blood safety measures causes harm is hard to defend, and

patients cannot be entitled to the continuation of protections that prove inefficient, unless continuing these protections can be said to rectify historical injustice.

This work is in part exploratory. As far as we are aware, there have been few attempts to relate the question whether inefficient blood safety measures should be applied to ethical theory, and to draw relevant considerations from policy-making documents and stakeholder research. The qualitative empirical research presented in part I charts stakeholders' ideas on what matters in blood safety, which enables ethical reflection on those ideas. Not all of the perspectives generated in part I are treated in part II. The research presented in chapter 3, which was completed after our ethical chapters, primarily served to check whether our ethical analyses had missed crucial perspectives. Chapter 3 also analyses some interesting views that surfaced, although this analysis is tentative and suggests directions for future research. Part II applies ethical theory to blood safety. Much of the work consists in making ethical principles applicable to blood safety: to specify, by means of conceptual and normative analysis, how they should be interpreted in this particular context. We provide an in-depth analysis of some ethical principles, but the application of some of these principles to blood safety is novel and thus, to an extent, exploratory. Nevertheless, our failure to find a clear ethical foundation for inefficient blood safety measures poses an important challenge: to either find stronger arguments or set more cost-effective safety policies. The General Discussion of this thesis offers further methodological reflections, as well as recommendations for policy-making and for future research.

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