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HOW SAFE SHOULD DONOR BLOOD BE?

Koen Kramer

How safe should donor blood be?

Koen Kramer

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HOW SAFE SHOULD DONOR BLOOD BE?

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op dinsdag 16 januari 2018, te 10.00 uur

door **Koen Kramer**

geboren te Alkmaar

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Contents

Chapter 1	General Introduction	7
	Part I: Qualitative empirical research	
Chapter 2	An inventory of concerns behind blood safety policies in five western countries *Transfusion 2015, 55:2816-2825*	19
Chapter 3	Arguments for tolerance or intolerance towards risks of blood transfusion: views of stakeholders in the Dutch blood supply *Submitted*	45
	Part II: Ethical analysis	
Chapter 4	Donor blood screening and moral responsibility: how safe should blood be? *Journal of Medical Ethics (Online First: February 11, 2016)*	75
Chapter 5	The precautionary principle and the tolerability of blood transfusion risks *The American Journal of Bioethics 2017, 17:32-43*	91
Chapter 6	Interpreting and Applying the Precautionary Principle *The American Journal of Bioethics 2017, 17:W4-W6*	117
Chapter 7	Are there ethical differences between stopping and not starting blood safety measures? *Vox Sanguinis 2017, 112:417-424*	125
	Part III: Wrapping up	
Chapter 8	Summary	143
Chapter 9	Samenvatting	149
Chapter 10	General Discussion	155
Chapter 11	Addendum (co-authors |publications | portfolio | dankwoord | CV)	165

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:

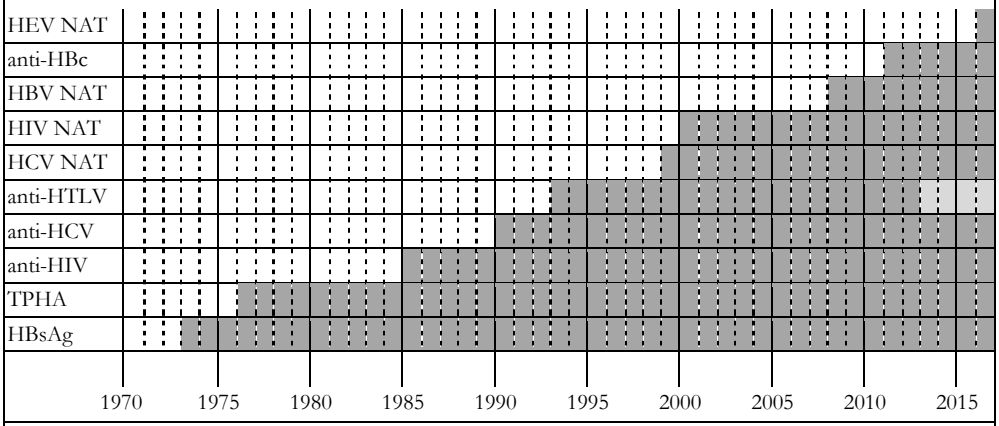
> "Concerning the safety tests that Sanquin [the Dutch blood service] currently applies, my opinion is that the number of safety tests should be reduced, provided that the safety of blood product recipients is not endangered. I will therefore request Sanquin to conduct research into the utility and necessity 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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Part I: Qualitative empirical research

Chapter 2:

An inventory of concerns behind blood safety policies in five western countries

Published as:.

Kramer K, Verweij MF, Zaaijer HL (2015). An inventory of concerns behind blood safety policies in five western countries, *Transfusion* 55:2816–2825.

ABSTRACT

Background: The availability of costly safety measures against transfusion-transmissible infections forces Western countries to confront difficult ethical questions. How to decide about implementing such measures? When are such decisions justified? As a preliminary to addressing these questions, we assessed which concerns shape actual donor blood safety policy-making in 5 Western countries.

Study design and methods: Our qualitative study involved determining which issues had been discussed in advisory committee meetings and capturing these issues in general categories. Appropriate documents were identified in collaboration with local decision-making experts in Canada, Germany, the Netherlands, the United States, and the United Kingdom. The introduction of hepatitis B virus nucleic acid testing and selected measures against variant Creutzfeldt-Jakob disease, West Nile virus, and Q-fever were chosen as cases representing decision-making on safety measures with high costs and low or uncertain added safety.

Results: A broad inventory of concerns was established, including: (1) 9 categories of advantages and disadvantages of candidate safety policies; (2) 6 kinds of difficulties in assessing risks and forecasting the effects of safety policies; (3) 13 decision-making principles; and (4) 6 kinds of practical barriers hampering the translation of candidate policies into decisions.

Conclusion: Blood safety policy-making involves a wide variety of competing concerns, and approaches to reconcile these considerations are themselves contested. Developing a systematic decision-making approach requires ethical reflection on, among others, reasonable costs of safety and the value of transparency in public policy.

INTRODUCTION

Inquiries into the acquired immune deficiency syndrome (AIDS) and hepatitis C crises in blood establishments in the late eighties and early nineties concluded that policy-makers had faced a variety of competing concerns, including political and economic ones, and that institutional arrangements had been insufficient to ensure accountability and avoid conflicts of interests [1-5]. Policy-makers were also criticized for their conservatism: they had allegedly required unreasonably strong evidence that AIDS and hepatitis C did indeed compromise transfusion safety before taking drastic safety measures, the downsides of which they had overemphasized. Policy-making had therefore been ill-suited to deal with dangerous emerging pathogens [1-4,6-8]. Decision-making has changed profoundly since these crises. In many countries, institutional responsibilities have been redistributed and clarified, and stakeholders have embraced a commitment to precautionary thinking and minimizing risks [3,4,9-11]. Various safety measures have accordingly been implemented to reduce the risks posed by the major transfusion-transmissible viruses – human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) – and to contain the impact of newly emerging pathogens [7,11,12].

Still, several authors and decision-makers express unease with contemporary policy-making practice. The high costs of the blood safety apparatus are a cause of growing concern in Western countries [5,13-14], including the Netherlands [15,16]. Safety measures with high incremental cost-effectiveness ratios (ICERs) are particularly controversial. Publicly funded health care interventions are by general standards expected to cost well below €100.000 per quality-adjusted life-year (QALY) gained [17-19], but some blood safety measures are estimated to cost hundreds of thousands to millions of Euros per QALY [20-21]. Safety measures with high costs and uncertain benefits pose related problems. Should we implement expensive safety measures against some emerging pathogen when the magnitude of the risk faced is unknown, or when we are unsure whether this pathogen affects transfusion safety at all [13,14]? The 'precautionary principle' is sometimes thought to settle these cases, but this principle itself is subject of controversy [13,14,22,23]. A recent and broadly supported initiative to reinstate cost-effectiveness considerations in blood safety decision-making is 'risk-based decision-making' (RBDM) [24-26]. Although RBMD is a laudable initiative, some issues require attention: how to reconcile a societal perspective with a responsibility for the well-being of

individual patients [25]; how to weigh cost-effectiveness considerations against other concerns (both in general and in particular situations) [27]; and how to *justify* any of this.

We contend that viewing these issues from a philosophical-ethical perspective can advance the debate and enrich RBDM. This involves evaluating standpoints on what donor blood safety may cost by appealing to main ethical concepts (e.g. harm, right and responsibility), theories (e.g. utilitarianism, contractualism and theories of justice) and principles (e.g. nonmaleficence, the precautionary principle). The underlying idea is that views on reasonable costs of donor blood safety are justifiable insofar as they fit fundamental ethical convictions.

Concern with the safety of donor blood can itself be understood as an ethical issue, for instance by interpreting the imposition of transfusion-transmission risks in terms of harm and responsibility. Moreover, the allocation of limited resources to donor blood safety is ethically significant because it implies forgoing some other morally valuable goal, e.g. offering access to expensive oncological or antiviral treatments. Where the application of safety measures with high ICERs takes away opportunities to implement more cost-effective health policies elsewhere, we could (at least theoretically) have gained more health benefits (QALYs) by investing in the latter rather than the former. Investing in cost-ineffective measures hence seems wrong from a utilitarian perspective, according to which we should maximize the total amount of well-being in the world. Might there be ethical arguments that justify the application of expensive blood safety measures nonetheless [13,28]? Are they for example justified by considerations of justice or special responsibilities towards transfusion recipients [cf. 29,30]?

An obvious starting point for the identification and evaluation of ethical arguments for the application of expensive safety measures is what policy-makers themselves consider important in donor blood safety policy-making. In addition, an inventory of decision-making concerns would be valuable when translating ethical deliberations into concrete guidelines for decision-makers, because realistic guidance must answer to the real-life concerns which decision-makers face. This paper therefore offers an inventory of concerns in actual donor blood safety decision-making, where 'concern' broadly denotes all issues that policy-makers recognize as important. It focuses on policy-making surrounding safety measures that are controversial from a cost-effectiveness perspective (because they are costly and publicly funded and their benefit is either manifestly low or very uncertain at the time of their introduction).

MATERIALS AND METHODS

Selection of countries and decision-making episodes

We studied policy-making in Canada, Germany, the Netherlands, the United Kingdom, and the United States. Key contacts in a sixth country decided not to cooperate. The selection of countries was based on the consideration that our study aims to guide policy-making in a democratic, high-income context. Expecting that many documents would be available in national languages only, our selection of countries also aimed to avoid language barriers.

Table 1 provides details on the policy-making episodes we studied.

Table 1: the decision-making episodes analyzed, and the pathogens involved

Country	*Pathogen*	*Decision-making episode selected*
Canada	HBV	Introduction of MP-NAT (2011)
	WNV	Responses to US WNV outbreak (2002) until introduction of MP-NAT (2003)
Germany	HBV	Introduction of MP-NAT (1997)
	Coxiella burnetii	Responses to Dutch Q-fever outbreak*
The Netherlands	HBV	Introduction of MP-NAT (2008)
	Coxiella burnetii	Recognition as a threat (2008) until introduction of targeted ID-NAT (2010)
The United Kingdom	HBV	Introduction of MP-NAT (2009)
	vCJD	Recognition as a threat (1996) until introduction of leukocyte depletion (1999)
The United States	HBV	Introduction of MP-NAT (2009)
	WNV	Recognition as a threat (2002) until introduction of MP-NAT (2003)

*Although Germany neighbored the Dutch Q-fever outbreak, it apparently took no safety measures besides the usual targeted deferrals. However, the *Arbeitskreis Blut* did update its position statement on Q-fever and blood safety.

HBV=hepatitis B virus; WNV=West Nile virus; vCJD=variant Creutzfeldt-Jakob disease; MP-NAT=minipool nucleic acid testing; ID-NAT=individual donation nucleic acid testing

For each country, we analyzed the introduction of HBV-NAT. The introduction of HBV-NAT is paradigmatic for policy-making on safety measures with high ICERs, as adding HBV-NAT to Hepatitis B surface antigen (HBsAg) testing is estimated to cost hundreds of thousands to millions for each QALY gained [21,31]. We considered this an appropriate case because the introduction of HBV-NAT affects publicly funded blood banks, because it involves a recent safety policy against a well-known pathogen, and because it has spurred

considerable debate. In addition, our study covered the introduction of costly safety measures in the face of substantial uncertainty. It included the implementation of leukocyte depletion in the context of the mid-90's rise of vCJD in the United Kingdom; the implementation of West Nile virus (WNV) RNA testing in the context of the turn of the century outbreak of WNF in the United States of America; and the implementation of *Coxiella burnetii* DNA testing in the context of the recent Q-fever epidemic in the Netherlands (which peaked in 2009). The responses of Canada and Germany to the developments in their respective neighboring countries were also covered.

Exploratory interviews, selection and analysis of documents

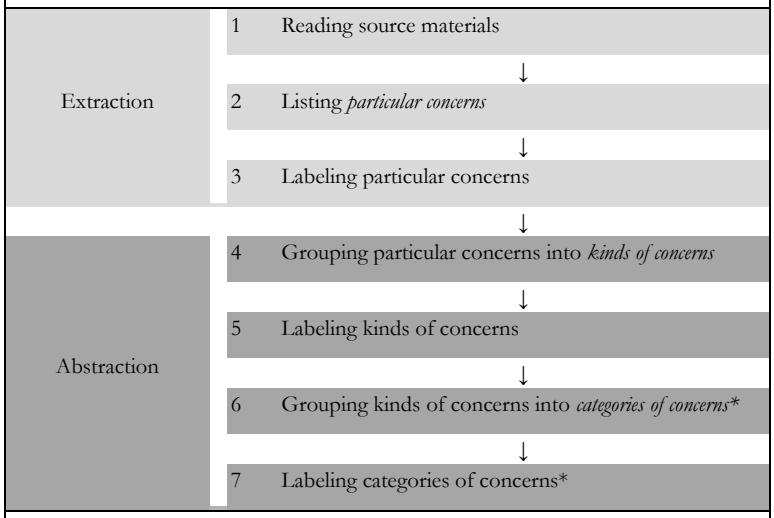
We explored each country's policy-making context via open interviews with key officials from regulatory agencies, blood banks, and advisory committees. These interviews facilitated the selection of appropriate materials for further analysis and provided a meaningful background to interpret those materials against. (Supplementary Table 1 presents the distribution of decision-making responsibilities amongst key blood agencies in the countries studied.) Potential interviewees were identified with help from the European Blood Alliance. Additional interviewees were sought where necessary, often in collaboration with the primary interviewees.

In the course of these exploratory interviews, it became clear that advisory committees often included representatives of blood banks, regulatory agencies, and funding agencies and that the documents of advisory committees were much more widely accessible than those of boards of directors of such agencies. To ensure that our research would remain feasible, we focused on meeting minutes, discussion papers, and position papers from main donor blood safety advisory committees, and included documents from other agencies (operators, regulators or funders) only when they were readily available and when advisory committee documents were insufficiently informative.

Our analysis of these documents was inspired by Grounded Theory [cf. 32]. The point of Grounded Theory is to determine what general concerns drive some social or discursive domain (e.g. contemporary blood safety decision-making) by abstracting these from specific issues being discussed (e.g. the impact of different WNV-NAT pool sizes on the release time of blood products). By being grounded in data, the resulting 'theory' surpasses mere preconceptions on what is at stake in the domain at hand; it is empirically supported, it can suggest specific applications of general concerns, and it can incorporate unexpected concerns.

Our analysis accordingly aimed to establish a broad and empirically informed taxonomy of concerns in blood-safety decision-making (without attempting to assess the relative importance of concerns at the same level of generality) by listing specific concerns and capturing these under general categories. The primary author identified, listed, and labeled specific issues that our source materials discussed as being important. The authors then jointly abstracted broader categories of concerns by grouping issues and capturing them under ever more general headings. The entire procedure is summarized in Figure 1.

Figure 1: Categorizing concerns behind blood safety policies



* To reach categories of concerns that were as general as possible, steps 6 and 7 were sometimes applied iteratively.

RESULTS

Our analysis identified 4 broad classes of concerns, namely: (1) advantages and disadvantages of possible safety policies; (2) uncertainties and theoretical problems affecting the assessment of risks or of the probable effects of safety measures; (3) principles on how to deal with uncertainties or on the relative importance of certain advantages and disadvantages of safety policies; and (4) practical obstacles for translating assessments of candidate policies into actual decisions. They are represented in tables 2 through 5, which jointly constitute our taxonomy of concerns.

First, we unraveled 9 main categories and 30 subcategories of supposed advantages and disadvantages of candidates safety policies. These are presented in table 2.

Table 2: advantages and disadvantages* of donor blood safety policies

(Part A: advantages and disadvantages* of setting a safety policy at all)

Main categories	*Intermediate categories*	*(Kinds of) advantages and disadvantages**
Finding the right extent of regulation and standardization	Harmonizing safety levels	Establishing a single protocol to reduce probability of error and to reduce exposure to liability
	Avoiding overregulation	Not being insensitive to local situations or specifics of cases; not limiting operator freedom or clinical choice; not setting unrealistic requirements for a profession already under heavy requirements
	Avoiding adverse effects of mandating safety measures	Not empowering manufacturers to increase prices of measures made mandatory
Meeting expectations and managing public perception	Showing vigilance	Appearing proactive by starting decision-making before media attention starts, getting credit even for false negatives; being seen to invest in the safety of the blood supply
	Avoiding unfavorable suggestions about safety	Not suggesting that a safety measure is introduced because safety has been inadequate
	Meeting regulators' expectations	Meeting expectations of regulators that action will be taken against some threat
(Part B: advantages and disadvantages* of specific safety policies)		
Promoting safety	Reducing risk magnitude	Having high yield (due to high effectiveness/sensitivity and capacity)
	Ensuring timely implementation	Allowing quick implementation; allowing implementation ahead of peaks in risk
	Avoiding indirect risks	Not stimulating risky donor behavior; not introducing another infectious agent into the blood supply; not having adverse clinical side-effects
Securing supply	Ensuring donor motivation	Increasing donor motivation; not decreasing donor motivation

Table 2: advantages and disadvantages* of donor blood safety policies (continued)

(Part B: advantages and disadvantages* of specific safety policies)

Main categories	*Intermediate categories*	*(Kinds of) advantages and disadvantages**
	Avoiding product loss and donor deferral	Not having high product loss rates due to false-positives or unrepeatable failed tests; not introducing new standards that disqualify donors or stored products
	Avoiding supply deficiencies	Not leading to shortages (in or outside one's own jurisdiction) of common or rare products due to product or donor loss or increased demand for blood products or donations
Gaining structural advantages	Enhancing the overall safety repertoire	Making other interventions superfluous; adding safety against a wider spectrum of threats; providing a useful infrastructure for future interventions
	Advancing the potential for knowledge generation	Generating (or not disallowing the generation of) valuable data for epidemiological or fundamental (e.g. microbiological) research
Securing operational feasibility	Respecting logistical limitations	Not exceeding logistical (staffing, equipment, and information systems) limitations; not depleting operational resources for other (current, planned or unforeseen) future safety measures; not causing delays in turnaround time for end products; not involving a high chance of procedural errors
	Ensuring ease of implementation	Not requiring intricate adaptations of current (technological) systems or practice; not setting new standards that would require strenuous withdrawals of products
	Ensuring availability of (high quality) measures	Requiring only apparel and materials being (commercially) available in sufficient quantities; not running the risk that quality reduces when demand rises
Securing acceptability of costs	Avoiding high or unrecoverable costs	Not involving high cost increases; not requiring expenses that are unacceptable to or cannot be recovered by the operators, hospitals or recipients
	Securing economic advantages	Allowing the operator and the system at large to save costs associated to TTIs or to save on other safety measures; increasing the value of products that enter commercial markets
	Ensuring cost-effectiveness	Offering good value-for-money (either directly or in the predictable future); involving a justifiable use of or impact on public funds

Table 2: advantages and disadvantages* of donor blood safety policies (continued)

(Part B: advantages and disadvantages* of specific safety policies)

Main categories	*Intermediate categories*	*(Kinds of) advantages and disadvantages**
	Ensuring continued availability of funds	Not depleting financial resources for other planned safety measures or in case of future disease outbreaks
Ensuring consistency	Ensuring consistency with other agencies/disciplines	Being consistent with practice or recommendations by other (national, foreign, or international) agencies involved in the blood supply or related disciplines (e.g. vaccine); not contradicting other agencies' policies on politically or scientifically sensitive issues.
	Ensuring consistency across services	Not introducing different levels of safety between geographical regions, operators, or product types (unless good epidemiological reasons are available)
	Ensuring consistency across time	Being consistent with earlier (currently effective) decisions, well-established paradigms, or usual conduct (unless there are good reasons to divert); not setting a precedent that cannot be maintained for future emerging pathogens or outbreaks
Meeting legal requirements, public expectations, and ethical demands	Meeting legal requirements and avoiding liability	Having a legally required hallmark; not exposing operators to liability due to being only partially effective, being inconsistent with common practice, or being introduced untimely
	Managing one's reputation	Meeting public demand or promoting public trust; not involving reputational risk or lack of public acceptance; not being viewed as inadequate due to being only partially effective or comprehensive
	Advancing legitimate interests of others	Advancing public health; benefitting donors; providing (additional) therapeutic benefits to transfusion recipients
	Avoiding harm to others	Not harming the people involved (more than it would benefit them); not decreasing the therapeutic benefit of transfusions; not causing the suffering of individuals
	Respecting moral duties	Respecting the right to life; respecting duties towards recipient that were infected with a TTI in the past
	Meeting informed consent	Not involving risks and benefits that cannot be explained well to patients

* For presentational simplicity, the *avoidance* of a potential *dis*advantage is presented as an *advantage* of a safety policy.

While most advantages and disadvantages were expected effects of safety measures, some characteristics were apparently considered (also) intrinsically important – for example ensuring consistency and meeting ethical demands. Interestingly, we found some advantages and disadvantages of setting a safety policy *at all*. Overregulation, for instance, was deemed an unfavorable aspect of implementing any safety policies and appearing proactive a favorable one. We also found advantages and disadvantages of specific safety measures, which we captured under the general rubrics of promoting safety, securing supply, gaining structural advantages, securing operational feasibility, securing acceptability of costs, ensuring consistency, and meeting legal requirements, public expectations, and (miscellaneous) ethical demands.

By way of an example of conflicting advantages and disadvantages of safety measures, consider the introduction of *Coxiella burnetii* (Cb) NAT in the context of the 2007-2009 Dutch Q-fever outbreaks. Although only one case of transfusion-transmitted Q-fever had been reported world-wide, there was (public) concern with donor blood safety due to the high incidence of Q-fever in the Netherlands. Introducing Cb-NAT would seem a proactive response to this concern, would threaten supply less than geography-based deferrals would, and would secure certain structural advantages (namely the generation of valuable epidemiological data and the founding of a testing infrastructure that could be exploited in case new pathogens emerged). On the other hand, introducing Cb-NAT involved delays in the release of blood product and could lead to wastes; in addition, the introduction of Cb-NAT after three years of Q-fever outbreaks might suggest that safety had been insufficient so far.

At various points, policy-makers appeared uncertain about which advantages and disadvantages a candidate safety policy would have, for instance whether implementing WNV minipool NAT would significantly increase transfusion safety or whether it would induce supply shortages. Table 3 (see next page) presents 2 main categories and 6 subcategories of difficulties in assessing risks or in forecasting the effects of candidate safety policies.

Empirical uncertainties, i.e. gaps in relevant data regarding the specific situation faced, were a recurring topic. Facing new policy-making situations typically meant facing new uncertainties, for example regarding the level of risk before and after implementation of the safety measure under discussion, the impact on supply, and the probability of operational problems occurring. Abstract limitations of the methods and tools with which risks were assessed and characterized were also discussed. These included, for example, limitations of the incidence-window period model and animal experiments in assessing transmission risks, as well

Table 3: Difficulties in assessing risks or the advantages and disadvantages of candidate donor blood safety policies	
Main categories	*(Kinds of) difficulties in assessments*
Empirical uncertainties	Empirical uncertainties where additional research (e.g. epidemiological studies, transmission studies) could remedy data gaps
	Empirical uncertainties where additional research could barely remedy data gaps, due to limitations on the studies that would be required (e.g. the required size of valid epidemiological studies, ethical standards)
Conceptual and theoretical difficulties	Lack of (commonly accepted) concepts and definitions
	Lack of (commonly accepted) parameters or a gold standard for judging the effectiveness (or effective performance) of safety measures
	Inherent limitations of formal risk models (e.g. incidence-window period model)
	Limitations of analogies/comparisons with other infections or epidemiological episodes

as difficulties in drawing analogies between newly emerging pathogens and the past emergence of pathogens such as HIV.

Third, advisory committee members invoked various principles or approaches on how to make reasonable decisions when facing uncertainties or when safety policies had certain mixes of favorable and unfavorable characteristics. These are presented in table 4.

Table 4: Principles or approaches on how to make reasonable decisions when facing uncertainties or on the relative weights of particular advantages and disadvantages of safety policies		
Main categories	*Denominations*	*Subordinate norms and/or description*
Principles on the relative weight of safety	Zero-risk-tolerance principle	Strive for maximum safety; limit transfusion-transmissible infections as much as possible
	Cost-are-unimportant principle	Cost considerations should not affect safety decisions; cost is subsidiary to safety, efficacy, and supply
	Paramountcy-of-safety principle	Assign safety highest but not necessarily overriding priority
	Cost-benefit principle	Implement only safety measures that provide a necessary or important additional safety margin; implement only safety measures that provide a favorable balance of benefits over costs (taking a broad and long-term view on benefits and costs)

Table 4: Principles or approaches on how to make reasonable decisions when facing uncertainties or on the relative weights of particular advantages and disadvantages of safety policies (continued)

Main categories	*Denominations*	*Subordinate norms and/or description*
	Cost-effectiveness principle	Implement safety measures whose cost-effectiveness rates meet general norms or compare to safety measures or life sustaining/promoting interventions already in place
	Progressive-safety-and-feasibility-balancing principle	Implement imperfect but easily implemented safety improvements; gradually scale up safety measures, balancing benefit and feasibility
Other principles on the weights of particular pros and cons of safety policies	Right-and-duties principle	Base decisions on rights of recipients (e.g. the right to life) and duties of decision-makers and operators (e.g. the duty to promote and maintain supply)
Principles for putting risks into perspective	Comparative-risk-priority principle	Assign higher priority to pathogens (and blood products) with higher residual transfusion-transmission risks; assign higher priority to pathogens for which transfusion-transmission is a comparatively frequent mode of transmission
	Adequacy-of-status-quo principle	If epidemiological situations remain unchanged, consider current practice adequate, compared to historical TTI risks; avoid supply-induced demand for epidemiologically unnecessary safety measures; realize that potential threats, few of which materialize, come and go
Principles for dealing with uncertainties (including future contingencies)	Safety-layering principle	Implement several safety measures in tandem, even where one would in normal circumstances suffice, to be safe even in exceptional situations; have contingency or back-up safety measures available
	Precautionary principle	Choose safe over risky assumptions and take doomsday scenarios seriously; take preventative measures even when there is no evidence of danger; make sure that nothing unexpected is going on or that risks are indeed low; make sure that at least one protective barrier is in place against a theoretical risk
	Reversible precautionary principle	Implement reversible precautionary measures, assess their usefulness, reverse if they prove unnecessary
	Evidence-based decision-making principle	Implement safety measures only if there is evidence that there is a significant risk; proceed upon the best data available; make decisions on a purely scientific basis

We discovered 7 principles on the relative weights of particular advantages and disadvantages of safety policies, 6 of which concerned the relative priority of safety; 2 principles for putting risks into perspective; and 4 principles for dealing with uncertainties. Among principles addressing the same issues, some showed considerable overlap (e.g., the *costs-are-unimportant* and *paramountcy-of-safety* principles), while others pointed in opposite directions (compare the *costs-are-unimportant* and *cost-effectiveness* or the *precautionary* and the *evidence-based* principles). We did encounter some frameworks that encompassed multiple decision-making principles, but found no universally applicable decision-making algorithms.

Fourth, we found 2 main categories and 6 subcategories of practical obstacles to policy-making, which are presented in table 5.

Table 5: practical obstacles in decision-making on donor blood safety

Main categories	*(Kinds of) practical obstacles*
Lack of consensus on decision-making principles or criteria	Lack of a decision-making framework for setting priorities
	Lack of consensus on what levels of (epidemiological) risk are acceptable
	Lack of consensus on what costs are acceptable for reducing risks
Unclarity on decision-making responsibilities and procedures	Unclarity concerning respective remits of decision-making actors, including funding decisions
	Unclarity concerning the legal force of a decision-making actor's statements
	Unclarity on which process to follow for the implementation of drastic measures

Practical obstacles complicated the translation of assessments of the pros and cons of candidate safety policies into actual decisions. They included lack of consensus on policy-making principles, unclarity about which procedures to follow, and unclarity about the official powers of decision-making participants.

Finally, it is noteworthy that the introduction of HBV-NAT barely seems to have been an issue for some advisory committees. The limited involvement of these advisory committees may be explained by the fact that the introduction of HBV-NAT in their countries involved switching from duplex (HCV + HIV) to triplex (HCV + HIV + HBV) NAT in the context of a tender procedure. Because tender procedures are confidential, we cannot establish under

which conditions HBV-NAT was introduced. The switch to triplex NAT may hence have been uncontroversial from cost-perspective or may have been practically forced. However, this is contrary to what most advisory committees assumed when discussing the introduction of HBV-NAT. (For which reason HBV-NAT is still an appropriate case for this study.)

DISCUSSION

Several observations deserve attention. First, we found a broad variety of concerns in policy-making, including advantages and disadvantages of safety policies, uncertainties and limitations of theoretical approaches, principles on how to weigh certain pros and cons of candidate safety policies or handle uncertainties, and practical barriers to policy-making. As expected, promoting safety and securing supply were prominent issues. However, it would be oversimplification to single out these two issues as the core concerns of blood safety policy-making. If we are to rethink policy-making realistically and productively, we should be aware that policy-makers confront a multiplicity of concerns. Our inventory of concerns facilitates this awareness; it draws attention to additional issues like the acceptability of costs, consistency, and socio-political and ethical demands. This is not to deny that some concerns may, in general or in particular situations, be considered more important than others or even that certain concerns *should* be considered more important than others. In view of their impact on decisions, however, priorities among concerns deserve *explicit* consideration.

Second, principles or approaches on how to decide between alternative safety policies with different combinations of favorable, unfavorable and unknown characteristics were often contested. There was notable discussion on acceptable levels of risks and acceptable costs of safety measures. We found competing principles that assigned different (qualitative) priorities to safety and costs, and did not encounter risk or cost thresholds that were broadly recognized across or within countries. If blood safety decision-making is to be principle-based, agreement should be reached on which principles are appropriate. This includes assessing the applicability of principles developed in other policy areas (such as the precautionary principle) to blood safety policy-making. Perhaps more importantly, we should reflect on the proper *function* of principles in policy-making. They need not necessarily function as decision rules, analogous to standard operating procedures, from which to derive a standard response in well-defined conditions. Striking a reasonable balance between competing concerns may require sensitivity to the specific context of the decision [cf. 33-35]. Accordingly, decision-makers should perhaps

be allowed sufficient leeway for judgments on what the circumstances require. Principles should then serve primarily to elucidate normative dimensions of candidate decisions rather than to dictate outcomes.

Where policy-making requires a complex balancing of concerns, for example in prioritizing health care interventions for public funding, transparent procedures are considered necessary to secure accountability for fairness and reasonableness [36,37]. Remarkably, though, decision-making within blood banks, regulatory agencies, and funding agencies proved rather inaccessible. Transparency also varied significantly among advisory committees. Some published minutes of all meetings, some released only position papers, others nothing at all. Minutes that were available offered different degrees of detail: some included literal transcriptions of the discussions that took place, others were limited to decisions taken.

On the other hand, limited transparency might serve to shield decision-making from adverse influences. In a very open setting, decision-makers might be disproportionately concerned about reputation or personal liability, especially when decisions are made about sensitive issues and when no universally accepted decision-making rules are available. An important ethical question is whether decision-making needs a degree of confidentiality (and hence opacity) to enable policy-makers to make reasonable but unpopular decisions. (Or even to get 'dirty hands', in the sense of making decisions that have ethically objectionable aspects but are overall best [38,39].)

The limited transparency of actors in the decision-making process affected our research. Keeping the research doable required focusing on materials from advisory committees, which were relatively easy to obtain. Researching decision-making in blood banks, regulatory agencies, and funding agencies proved to be unfeasible. Still, by including advisory committees in which these decision-making actors were all represented, our inquiry did cover many of their concerns. Moreover, advisory committees do – according to our interviewees – have a pivotal role in the decision-making process. They typically mediate between decision-making actors, for instance when a regulatory agency decides that *something* must be done against an emerging pathogen, a blood bank determines which specific measure will be taken, and a funder approves of the budgetary requirements. In such cases, where no single actor seems to qualify as *the* author of *the* decision, advisory committee recommendations are often decisive. Because they are considered authoritative and establish grounds for liability for decision-makers that fail

to heed them, they are indeed nearly always followed. Our inquiry hence did map a crucial and explicit part of the decision-making landscape.

There is no agreement on principles for the prioritization of concerns in blood safety decision-making. In the context of escalating health care expenditures, the variation among principles on the relative weights of safety and costs is particularly interesting: some allow that containing costs may sometimes outweigh promoting safety, but others assign absolute priority to safety. As a follow-up to this study, we will consider the ethical acceptability of high blood safety costs. Giving due attention to the actual concerns and views of policy-makers – as presented in the current paper – should help us offer realistic and well-considered ethical guidance.

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SUPPLEMENTARY TABLES

Supplementary table 1: decision-making actors in Canada, Germany, The Netherlands, The United Kingdom, and The United States

Country	*Blood Bank(s)*	*Regulating agency*	*Funding agency*	*(Selected) advisory committees*
Canada	Canadian Blood Services (CBS) *Héma-Québec* (HQ)	Biologics and Genetic Therapies Department (BGTD) of Health Canada (HC)	Provincial/ Territorial Ministers of Health	National Advisory Committee on Blood and Blood Products (NAC) →Advises CBS National Liaison Committee (NLC) →Advises CBS Expert Advisory Committee on Blood Regulation (EAC) →Advises HC
Germany	*Deutsches Roter Kreuz (DRK)* Hospital-based, academic, municipal, and private commercial blood banks	*Paul Ehrlich Institut (PEI) of the Bundesministerium für Gesundheit (BMG)*	*Bundesminsterium des Gesundheits (BMG)*	*Arbeitskreis Blut (AK Blut)* →Advises operators, *PEI, BMG*
The Netherlands	*Stichting Sanquin Bloedvoorziening*	*Ministerie van Volksgezondheid, Welzijn en Sport (VWS)*	*Ministerie van Volksgezondheid, Welzijn en Sport (VWS)*	*Medische Adviesraad (MAR)* →Advises *Sanquin* *Gezondheidsraad (GR)* →Advises *VWS*

Supplementary table 1: decision-making actors in Canada, Germany, The Netherlands, The United Kingdom, and The United States (continued)

Country	*Blood Bank(s)*	*Regulating agency*	*Funding agency*	*(Selected) advisory committees*
The United Kingdom	National Health Services Blood and Transplant (NHSBT) Welsh Blood Service (WBS) Scottish National Blood Transfusion Service (SNBTS) Northern Ireland Blood Transfusion Service (NIBTS)	Medicines and Healthcare Products Regulatory Agency (MHRA) of the Department of Health (DH)	Department of Health (DH)	Joint United Kingdom Transfusion Services Professional Advisory Committee (JPAC) →Advises operators Standing Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) →Advises DH Advisory Committee on the Microbiological Safety of Blood, Tissues and Organs for Transplantation (MSBTO) →Advised DH (up until 2008) Spongiform Encephalopathy Advisory Committee (SEAC) →Advised DH (up until 2011)
The United States	American Red Cross (ARC) Independent non-profit blood banks organized as America's Blood Centers (ARC) Hospital-based, academic, municipal, and private commercial blood banks	Food and Drugs Administration (FDA) of the Health and Human Services (HHS)	Assistant Secretary of Health (ASH)	Blood Products Advisory Committee (BPAC) →Advises FDA Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) →Advises ASH

Supplementary table 2: selected materials on the introduction of HBV-NAT and of measures against vCJD, WNV, and Q-fever		
Country	*Topic*	*Materials and references*
Canada	Decision-making procedures	EAC – Terms of reference (2005) [Available at http://www.hc-sc.gc.ca/] CBS – Open board meeting guidelines (2006) [Available at http://www.blood.ca/] NLC – Terms of reference (2008) [Available at http://www.blood.ca/]
	Introduction of HBV-NAT	[None obtained]
	Early WNV decision-making	CBS – Board of Director meeting minutes (2002 – 2003) [Available at http://www.blood.ca/] NLC – Meeting minutes (2002 – 2003) [Available at http://www.blood.ca/]
Germany	Decision-making procedures	*Ak Blut – Geschäftsordnung* (2012) [Available at http://www.rki.de/]
	Introduction of HBV-NAT	*Ak Blut – Votum 18 – NNT Voraussetzungen* (1998) [Available at http://www.rki.de/] *Ak Blut – Votum 19 – NNT Voraussetzungen (Ergänzung: Kosten Nutzen Aspekte)* (1999)[Available at http://www.rki.de/] *Ak Blut – Votum 31 – Anti-HBc* (2005) [Available at http://www.rki.de/] *Ak Blut – Stellungnahme HBV* (2000) [Available at http://www.rki.de/]
	Early Q-fever decision-making	*Ak Blut – Stellungnahme Q-fieber* (2005) [Available at http://www.rki.de/] *Ak Blut – Stellungnahme Q-fieber* (2013) [Available at http://www.rki.de/]
The Nether-lands	Decision-making procedures	*MAR – Reglement en werkwijze* (2010)* *MAR – SOP opdoemde infecties* (2010)*
	Introduction of HBV-NAT	*MAR – Advies prioriteitsstelling uitbreiding NAT screening* (1999)* *MAR – Advies additionele HBV Screening* (2007)* *Julius Centrum – Kosten-effectiviteitsanalyse (KEA) van additionele HBV-NAT screening bij de Stichting Sanquin Bloedvoorziening* (2007)*
	Early Q-fever decision-making	*GR – Brief bijeenkomst over Q-koorts in Nederland* (2008) [Available at http://www.gezondheidsraad.nl/] *MAR – Projectplan Q-NAT screening van high-risk donaties* (2010)*

Supplementary table 2: selected materials on the introduction of HBV-NAT and of measures against vCJD, WNV, and Q-fever (continued)

Country	*Topic*	*Materials and references*
The United Kingdom	Decision-making procedures	JPAC – About JPAC [Available at http://www.transfusionguidelines.org.uk/] SaBTO – Code of Practice (2013) [Avaialable at https://www.gov.uk/] NHSBT – Framework to Guide Decision-making on Safety Issues (2010) [Available at http://www.nhsbt.nhs.uk/] JPAC/SACTTI – Position statement emerging infections (2013) [Available at http://www.transfusionguidelines.org.uk/]
	Introduction of HBV-NAT	JPAC – Meeting minutes (2002 – 2008) [Available at http://www.transfusionguidelines.org.uk/] JPAC – Discussion Paper on Policies to Reduce Transfusion Transmitted-hepatitis B (2006) [Available at http://www.transfusionguidelines.org.uk/] JPAC – Discussion paper on policies to reduce transfusion transmitted HBV (2008) [Available at http://www.transfusionguidelines.org.uk/]
	Early vCJD decision-making	MSBTO – Meeting minutes (1995 – 1998)* SEAC – nvCJD and Leucodepletion – Advice to Government (1998)* Det Norske Veritas – Assessment of the Risk of Exposure to vCJD in Blood and Blood products. Final Report for the Spongiform Encephalopathy Advisory Committee and the Department of Health (1999)*
The United States	Decision-making procedures	ACBTSA – Charter (2012) [Available at http://www.hhs.gov/] BPAC – Charter (2014) [Available at http://www.fda.gov/] FDA – Decision Making Process at CBER for Responding to a Threat to the Safety of the Blood Supply (2014)*
	Introduction of HBV-NAT	BPAC – Transcript of 94th meeting (2009) [Available at http://www.fda.gov/]
	Early WNV decision-making	BPAC – Transcript of 74th meeting (2002) [Available at http://www.fda.gov/] BPAC – Transcript of 76th meeting (2003) [Available at http://www.fda.gov/]

*: Not freely available; obtained from our contacts.

Chapter 3:

Arguments for tolerance or intolerance towards risks of blood transfusion: views of stakeholders in the Dutch blood supply

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ABSTRACT

Introduction: The perception of transfusion-transmitted infections (TTIs) is sensitive to various concerns besides the probability of infection. These factors may reflect legitimate ethical considerations. Understanding stakeholders' reasons to consider TTI risks tolerable or intolerable is imperative to advance thinking on reasonable blood safety.

Methods: We held 25 interviews and 2 focus group discussions with policy-makers, hematologists, blood donors, and blood product recipients. Respondents discussed the tolerability of TTI risks by comparing TTIs to other hazards, and by commenting on the costs of blood safety. Arguments for tolerance or intolerance towards TTI risks were identified and categorized by qualitative analysis.

Results: 414 relevant quotes were extracted from the interviews and group discussions. These quotes could be clustered into 7 categories: the clinical impact, probability, and avoidability of infection; cost and health benefits and other consequences of safety measures; non-consequentialist ethical arguments; and stakeholders' interests.

Discussion: Remarkable findings included contrasting views on whether TTI risks are tolerable because the a priori probability of becoming infected is low; and the controversial idea that lower safety standards may be applied for patients with a poor prognosis. On the assumption that resources spent on inefficient blood safety measures could be applied more beneficially elsewhere, several responders expressed tolerance towards TTI risks. Others argued that the value of life cannot be translated into monetary costs, or that saving money on blood safety would not make a difference elsewhere, suggesting that initiatives to increase efficiency in blood safety should be matched by similar initiatives in other domains of health care.

INTRODUCTION

According to health economic research, certain tests to detect transfusion transmissible infections (TTIs) in donated blood rank among the least efficient health care interventions. Incremental cost-effectiveness ratios exceeding €1.000.000 per quality-adjusted life-year (QALY) have been reported, for example for serologic testing on human t-cell lymphotropic virus (HTLV) and nucleic acid testing (NAT) on hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) [1-4]. These costs per QALY reflect how few infections these safety measures prevent, given the presence of further safety measures. For example, if effective donor selection and sensitive serological screening for HBV, HCV, and HIV are in place, adding NAT screening will have limited value for safety. While cost-sensitive decision-making approaches have recently been proposed [5], initiatives to downscale inefficient safety measures have been scarce [6], and blood services continue to introduce safety measures of questionable efficiency (e.g. Zika virus NAT in the United States and hepatitis E NAT in Ireland, the United Kingdom and the Netherlands).

The continuation and introduction of inefficient safety policies presumably reflects a low public tolerance for TTI risks. A number of studies have applied risk perception theory to chart public attitudes towards the risks of blood transfusion (see [7] for an overview). These studies found that blood transfusion was considered more risky than many activities with a comparable or a higher mortality rate. The perception of blood transfusion risks, which focused strongly on TTI risks, was dependent on test subjects' demographic variables, worldviews, and cognitive heuristics. The perception of these risks was also sensitive to the three 'risk dimensions' from psychometric theory: the extent to which risks are dreaded and considered severe; the extent to which they are considered controllable and well-understood; and the extent to which the activity that generates these risks is considered beneficial. Compared to other hazardous activities, blood transfusion was perceived as very beneficial, and its risks as moderately severe and uncontrollable [7-10].

One might conclude that the perception of TTI risks is distorted by irrational biases. For example, whereas Ngo et al. [7, p.120] call a probabilistic approach to risk 'rational', 'systematic', and 'reliable', they call the public's perception of risk 'intuitive' and 'subjective'. On this appraisal, decision-makers face a dilemma: they must either prioritise rationality in their choices but ignore public perception, or take public perception into account even if this implies that some policies are less rational [cf. 11,12].

Public estimates of the probability that hazards will strike, e.g. of the chance of contracting a TTI, may indeed be unreliable. However, risk perception may not (only) concern probability. Risk perception appears sensitive to ethically relevant characteristics of risks, including the extent to which being at risk is voluntary; the distribution of risks and benefits; and the existence of alternatives to hazardous activities [11-14]. Furthermore, risk perception may be based upon emotions but such emotions may well point to valid ethical concerns. Anger might for example be a reasonable response to injustice, and fear to a significant threat to one's well-being [12]. Dismissing public risk perception as subjective and irrational may thus be too hasty: rather than being a distorted appraisal of probability, public risk perception may be responsive to a complex set of ethical issues [12, 14]. This does not mean that public perceptions should be accepted at face value. Analysing views towards risks may yield relevant ethical perspectives, but further reflection may reveal mistaken empirical assumptions or problematic ethical implications [12, 13].

Previous studies considered whether insights from established theories on risk perception, notably Slovic and others' psychometric theory, applied to TTI risks [cf. 7]. Therefore, these studies could not identify influences on TTI risk perception that risk perception theory did not already recognize. Furthermore, these quantitative studies used closed answer formats and did not attempt to understand the reasons behind respondents' answers. In what ways were risks of blood transfusion considered controllable or uncontrollable, for example, and why were they dreaded? On what assumptions and emotions were such perceptions based? This paper offers an overview of arguments for tolerance or intolerance towards TTI risks, based on qualitative empirical research among stakeholders in the Dutch blood supply. It clusters and categorizes these arguments, highlights remarkable and controversial arguments, and offers explanatory stakeholder citations. This reveals whether previous research has overlooked or undertheorized perspectives on the tolerability of TTI risks.

(Note on terminology: we hold that 'tolerating' a risk means having a negative attitude towards a risk but choosing, for certain overriding reasons, not to reduce it. The term risk 'acceptance' may be more applicable when a risks is not regarded negatively at all or cannot be reduced. In what follows, though, we do not distinguish arguments for risk tolerance from arguments for risks acceptance.)

METHODS

Selection of respondents

Aiming for a broadly constituted set of respondents, we planned to interview 5 blood product recipients, 5 donors, 5 haematologists, 5 policy-makers (members of the Dutch Ministery of Health, Welfare and Sport [VWS], members of the Dutch Parliament with blood safety in their portfolios, and members of Sanquin's Board of Directors), and 5 policy-advisors (members of Sanquin's Medical Advisory Board). In addition, we planned to have one focus group discussion with 5 donors and one focus group discussion with 5 blood product recipients. The dynamics between participants in group discussions was expected to yield perspectives that could not be attained in interviews. Recruiting haematologists, policy-makers and policy-advisors for group discussions was judged unfeasible.

Blood product recipients were recruited via the Dutch haemophilia society (NVHP), an advocacy group for patients with haematological malignancies (Hematon), and an advocacy group for patients with rare blood disorders (SZB). Donors were approached through donor societies (DVNL and DAR). Blood product recipients and donors were preferably recruited by means of open calls, but when open calls yielded insufficient response, our contacts at patient and donor societies approached candidates personally. Haematologists, policy-advisors, and policy-makers (members of the Dutch Parliament with blood safety in their portfolio, representatives of the Dutch Ministry of Health, and members of Sanquin's Board of Directors) were approached directly. Diversity among respondents was a key consideration in these recruitment efforts.

Potential respondents were informed that the interviews and focus group discussions would be recorded, that their personal data would be stored locally, that all published data would be anonymized, and that they could opt out of the research at any time.

Because few policy-makers external to Sanquin proved willing to partake in our research, we set up a combined category for policy-makers and policy-advisors, which consisted of 1 member of Parliament, 2 members of Sanquin's Board of Directors, and 5 members of Sanquin's Medical Advisory Board. Also, we decided to expand the number of interviews with blood product recipients, as the group discussion included fewer participants than planned, owing to last-minute cancellations. Respondent data is listed in table 1.

Table 1: Data of participants in interviews and focus group discussions

Code	*Age*	*Sex*	*Education*
Blood product recipients, interviews			
R01	70-79	M	Mid-level professional
R02	40-49	M	Mid-level professional
R03	50-59	F	Mid-level professional
R07	50-59	F	High-level professional
R09	50-59	M	Mid-level professional
R10	50-59	M	Mid-level professional
R12	50-59	M	Academic
Blood product recipients, group discussion			
R11	20-29	M	Academic
R13	70-79	M	High-level professional
Blood & plasma donors, interviews			
D01	40-49	M	Academic
D02	60-69	F	Academic
D03	30-39	M	Academic
D04	60-69	M	High-level professional
D08	40-49	F	High-level professional
Blood & plasma donors, group discussion			
D05	50-59	M	High-level professional
D06	60-69	M	Academic
D11	60-69	M	High-level professional
D15	20-29	F	High-level professional
D16	40-49	M	Academic
Haematologists			
H01	40-49	M	Academic
H02	40-49	F	Academic
H03	30-39	F	Academic
H04	50-59	M	Academic
H05	50-59	F	Academic
Policy-makers & policy-advisors			
P01	60-69	M	Academic
P02	60-69	M	Academic
P03	60-69	M	Academic
P04	40-49	M	Academic
P05	70-79	M	Academic
P06	50-59	M	Academic
P07	60-69	M	Academic
P08	60-69	M	Academic

Design and execution of interviews and focus group discussions

Interviews and group discussions were scheduled for an hour. Some interviews took more than an hour to complete, especially interviews with blood product recipients who had intricate medical and personal histories, some of which lasted 2 hours. The interviews were performed by the first author, the focus group discussions were led by a professional moderator. Oral permission was acquired before recording each session.

The interviews and group discussions had four main parts and were semi-structured, meaning that a list of questions was followed in a flexible order and that respondent input that was unrelated to preconceived questions was stimulated. In the first part, which was meant to break the ice, we asked respondents how and why they were involved in the blood supply, and we probed their experiences with the blood supply. Subsequently, respondents were invited to share issues concerning the blood supply, including safety issues, that worried or upset them. In the third part, respondents compared the risk of contracting a serious TTI to a number of other risks, commented on the tolerability of each risk, and offered reasons for their comparative tolerability judgments. We included three hazards to represent extremes in the main risk dimensions of risk perception theory: the risk of having a serious traffic accident represented known, controllable, but not strongly dreaded hazards; the risk of having a nuclear meltdown represented unknown, uncontrollable, and dreaded hazards; the risks of genetically modified foods represented unknown, uncontrollable, and moderately dreaded hazards. We also included a number of hazards that resembled TTI risks in some respects, while differing in others: the risk of having adverse reactions to prescription drugs; the risk of having severe complications during surgery; and the risk of contracting a dangerous infection through food. Finally, respondents commented on the tolerability of TTI risks in relation to some research-supported claims about the costs of the Dutch blood supply, including the claim that blood products are more expensive in the Netherlands than in neighbouring countries [15]; the claim that the Dutch blood services applies more safety tests than most blood services abroad [15]; and the claim that some of these tests have incremental cost-effectiveness ratios of over €1.000.000/QALY [1].

Analysis

The first 12 interviews (3 in each category) were written out verbatim, except for parts that were completely unrelated to the research topic, which were summarized. Fragments that seemed to address relevant issues were listed and coded in a separate file (using Microsoft Excel 2013). We subsequently rejected fragments that did not address reasons for tolerance or intolerance towards TTI risks, or that concerned risks taken by donors, recipients, or haematologists rather than the blood service.

The remaining fragments were open coded, i.e. given initial labels, based on their content. Fragments with related labels were grouped and captured under increasingly general categories.

From the remaining 13 interviews and the focus group discussions, we extracted fragments that seemed to add something new to our initial list of fragments, whether in terms of the topic addressed, in terms of the view expressed about this topic, or in terms of wording. A revised list of fragments and categories was obtained by incorporating these additional fragments and revisiting the passages from our initial analysis.

RESULTS

We extracted 414 relevant passages from 25 interviews and 2 group discussions. We identified clusters of passages in which similar arguments for risk tolerance or intolerance were addressed (whether or not these arguments were considered valid). These clusters were captured under seven headings: 'clinical impact of infection'; 'probability of infection'; 'avoidability of infection'; 'costs and health benefits of safety measures'; 'miscellaneous consequences of safety measures (logistics, supply, and clinical effectiveness)'; 'non-consequentialist ethical arguments'; and 'stakeholder interests'. The arguments involved are summarised in Tables 2 – 8. Below, we follow these headings and discuss remarkable or controversial arguments captured under them.

1. Clinical impact of infection

Arguments that related to the clinical impact of TTIs are presented in table 2.

Table 2: Arguments for tolerance or intolerance toward TTI risks: clinical impact

Argument:	*Tolerance or intolerance:*
The disease is/is not serious	—/+
The disease is/is not lethal	—/+ | x
The disease is/is not curable	+/—
Some patients are especially vulnerable	—
Without the TTI, patients have a good/bad prognosis	—/+
Infection does not imply disease	+ | x

Legend:
/: Separates alternative values of variables
+: Argument for risk tolerance
—: Argument for risk intolerance
X: Argument or variable deemed irrelevant
|: Separates alternative evaluations of arguments

That the seriousness, lethality and curability were considered relevant variables for the tolerability of TTI risks, and that the vulnerability of specific patient groups was offered as an argument for risk intolerance, seems unsurprising. Non-lethality was sometimes denied to be relevant for risk tolerability, which was supported by arguing that even non-lethal TTI could be serious, or by calling attention to especially vulnerable groups of patients, to whom TTIs that are generally non-lethal might prove fatal. Most interesting, there were some respondents who seemed to deny that the special vulnerability of certain patients groups supports intolerance towards TTI risks. Upon closer consideration, however, these respondents argued that having a poor prognosis even without a TTI justified tolerating some TTI risks. In the words of respondent D01:

> "If you lose a lot of blood while giving birth, and need a transfusion because of that, that is something entirely different than if someone needs his third transfusion that week. (…) When you're dealing with a bottomless pit, you could accept some more risk. (…) [Whether someone] needs a blood transfusion just one or two times, but whose life-expectancy is not affected, or whether you're talking about someone whose life expectancy is very limited anyway." (Fragments D01-19 & D01-20)

A further argument in this cluster is that someone who becomes infected need not develop disease symptoms. This argument was offered to support risk tolerance, but its relevance can be contested, as respondent P08 did, by highlighting that the infection could be transmitted further, that carrying the infection affects one's social interactions, and that the infection might develop into disease later in life.

2. Probability of infection

The probability of acquiring a TTI was another unsurprising consideration behind our respondents' views on the tolerability of TTI risks. Still, some interesting arguments were offered (see table 3, next page).

One notable finding is that although the risk (in terms of the possibility of becoming infected) varies per TTI, many respondents considered this risk small in general. As respondent R01, a polytransfusee, said:

> "If you consider how much blood is collected in the Netherlands, and how few people have the bad luck of experiencing an adverse event, that is such a minimal amount, it's negligible." (R01-03)

Table 3: Arguments for tolerance or intolerance toward TTI risks: probability of infection

Argument:	*Tolerance or intolerance:*
The risk of infection is/is not large	−/+
TTI risks are conditional risks	+ | −
Further transmission is not probable	+
Other risks are larger	+
Other non-medical risks are larger	+ | x
Other medical risks are larger	+
Other risks of blood products are larger	+
Different modes of transmission are more probable	+
Many safety measures are already in place against TTIs	+
Some (small) risks must be accepted	+
(Small) risks are part of daily life	+
(Small) risks are part of medicine	+
A line must be drawn somewhere	+
TTI Risks are not distributed evenly	
The at-risk group is/is not a small portion of society	+/−
Certain patient groups run more risk	−

Respondents regularly stated that TTI risks are small and well-managed compared to many day-to-day risks, medical risks, transfusion hazards other than TTIs, and infection risks with other modes of transmission (e.g. eating). They also recognized that some small risk should be tolerated, as risk is ubiquitous and TTI risks cannot be eliminated completely. These views were typically, but not always, offered as arguments for TTI risk tolerance. Some respondents stressed that TTI risks are unevenly distributed. The risk may be small for many patients, but patients who need blood products regularly, like haemophiliacs and polytransfusees, run significantly more risk. This was considered an argument for intolerance towards TTI risks.

Various respondents noted that TTI risks are conditional upon the risk of getting health problems that require blood product therapy, but conflicting conclusions were drawn from this insight. Small risks per blood product translate into even smaller risks for random persons, most of whom never need blood products, which according to some respondents is an argument for risk tolerance. According to others, though, this is an argument for risk intolerance. In the words of respondent R11, who has a rare clotting disorder:

> "The chance of having what I have is one in a million. And the chance that, if I need a transfusion, it is the one transfusion in ten years where something goes wrong, that is just... That is very nasty." (R11-11)

On this view, a small risk is not more tolerable if it is conditional upon another small risk; to the contrary, being stricken by a small conditional risk means one suffers from extreme bad luck, which is a dramatic and undeserved fate. A related view is that risk is especially intolerable when it frustrates attempts to remedy someone's bad luck. As respondents R11 and D11 explain:

> "You see, the reason you receive blood products, something is going on already, something has happened to you, something is wrong that might already be unfair. If you get an infection on top of that, that's like kicking someone when he's down." (R11-10)
> "If you need drugs or an operation, you are in a situation and you are dependent, for instance on medication. If that goes wrong, or you develop nasty adverse reactions, that is just very... Because you already are a victim, actually, you become a double victim." (D11-09)

3. Avoidability of infection

A third cluster of arguments regarded the avoidability of TTI risks.

Table 4: Arguments for tolerance or intolerance toward TTI risks: avoidability of infection

Argument:	*Tolerance or intolerance:*
TTI risks are/are not avoidable	−/+
Recipients can/cannot choose to avoid TTI risks	+/−
Getting a transfusion is/is not a choice	+/−
There are no alternatives for blood products	−
There are no alternative suppliers of blood products	−

Clearly, risks that cannot be avoided must be tolerated (or accepted). However, respondents differed on whether TTI risks are avoidable. Some claimed that TTI risks are typically foreseeable and can be ruled out by taking adequate safety measures. Others argued that TTI risks are unavoidable due to unforeseeable epidemiological developments and technological limitations of safety measures. These claims may hint at different interpretations of the notion of avoidability: if avoiding risk means reducing risk drastically, many TTI risks may be avoidable, but not if avoiding risk means reducing risk to zero.

Another issue was whether individuals (blood product recipients and their clinicians) had options to avoid TTI risks. Various respondents claimed that blood product recipients had no choice but to undergo treatment, although some respondents argued that receiving blood products in the context of elective surgery is avoidable, and one respondent argued that even risks relating to life-saving treatments are avoidable, insofar as such treatments can be refused. Similar arguments were that there are no treatment alternatives for blood products, and that blood product users cannot choose among suppliers, given Sanquin's monopoly in the Netherlands. Lacking choices to avoid TTI risks was considered an argument for risk intolerance.

4. Costs and health benefits of safety measures

A fourth cluster of arguments concerned the costs and (health) benefits of safety measures.

Table 5: Arguments for tolerance or intolerance toward TTI risks: costs and (health) benefits of safety measures

Argument:	*Tolerance or intolerance:*
The absolute costs of safety measures are/are not high	+/− | x
The budget impact of safety measures is/is not high	+/−
Other medical procedures are more expensive	−
Preventing infections saves costs	−
Taking safety measures means the price of blood products will increase	+ | x
The absolute health benefits of safety measures are/are not high	−/+
Health benefits are very valuable	−
The value of health cannot be expressed in monetary terms	−
Safety measures are/are not a beneficial use of resources	−/+
Some safety measures are not cost-effective	+ | x
Resources can/cannot be used to benefit more people	−/+ | x
Resources can be used to save more life-years	+
Other patients have a claim on health care resources too	+
Resources should not go unused	−
Alternative savings are/are not possible	−/+
Costs of safety measures are borne collectively	+ | x

Relating costs to health benefits was a common strategy to put the former into perspective. Some respondents denied the relevance of cost-effectiveness data by arguing that someone's life is extremely valuable or that the value of life cannot be translated into monetary terms. Various respondents would tolerate TTI risks, however, if resources needed to reduce TTI risks could be applied more efficiently elsewhere in the health care system, thus helping more people or saving more life-years. Interestingly, this included recipients of blood products, for example respondents R07 and R12:

> "Of course I want to run as little risk as possible. But I am realistic in understanding that it's not only about me. And that what matters is always how you can help the most people. (…) You can't expect society to spend its money on an individual rather than helping a larger group." (R07-27 & R07-28)

> "If it's indeed like, six million, one life, if we spend that six million in some other way we save ten lives, well, ok, then you have a point. (…) But you have to show that with facts, you have to be transparent about that." (R12-57)

As other respondents expressed, stacking inefficient blood safety measures is difficult to defend if other patients lack adequate care, because those patients have a claim on health care funds too:

> "To be honest, I think that [safety measures costing over one million per QALY] is a little too much, because health care is wildly expensive, and I think everyone has a right to health care, and not just a few people on whom lots of money are spent." (P05-26)

> "What if there's someone who needs a heart transplant, for which you don't have the money, but you would apply these safety measures. That would be very odd. (...) Then you're telling a patient getting a transfusion: you are more valuable." (P04-48)

One respondent deepened this argument by relating other patients' claim on resources to the way health care is funded:

> "It's public money, which means that you want to help as many people as possible, or reduce disease burden to a minimum. (...) We have a social principle that we all pay for it, and that we all want to reap the benefits." (P06-77)

However, various respondents argued that the choice between applying blood safety measures or helping other patients is a false dilemma. One argument was that the budget impact (and thus the opportunity cost) of blood safety measures is negligible in the Netherlands. As respondent P07 stated:

> "If I start calculating and cut costs seriously, I say it's all going well, and we can cut about half our expenses. Then I end up saving around 20 million euros. 20 million in public health care, well, what would you like to use it for? (…) 20 million is nothing in public health care." (P07-28)

Another argument was that freeing health care funds does not require cutting costs on blood safety measures. Other inefficient processes within or outside the blood service should be optimized instead:

> "I would like to visit Sanquin and go through your business process, see if we can make it more efficient. (...) Creativity gets you far. But don't get creative with our safety." (R12-49)

These passages deny that taking blood safety measures excludes supplying other types of health care. Some respondents denied that being able to supply care to more patients is relevant at all, for example:

> "I think that [by saving money on blood safety measures and spending it elsewhere in the health care system, more patients could be helped] is a bit of a platitude, because it applies to a lot of things, right? Like, you know what, let's just leave that patient who costs 150.000 euros a month. Couldn't we do much better things with those 150.000 euros? Actually, couldn't we do much better things, on a global scale, with the 100 billion we spend on health care in the Netherlands? Such questions can be developed indefinitely." (P08-21)

Another way to put the costs of blood safety measures into perspective was to compare them to the costs of other medical procedures. Respondents who chose this framing downplayed the relevance of the costs of blood safety measures:

> "Compared to blood products, there are so much more expensive drugs. A haemophilia patient, for example, costs 150.000 euros a year, you know, and we spend that too. So if it's really necessary, we should do it." (H05-28)

> "If we would all consider how many sports-related injuries there are, and how much costs these injuries entail, I would like to compare that to this figure. (…) You would have to consider carefully why you would do the one thing, but wouldn't do the other." (R10-45)

5. Miscellaneous consequences of safety measures

Besides costs and health benefits, some other consequences of safety measures were considered relevant (see table 6).

Table 6: Arguments for tolerance or intolerance toward TTI risks: miscellaneous consequences of safety measures

Argument:	*Tolerance or intolerance:*
Safety measures do/do not cause logistical problems	−/+
Safety measures do/do not threaten the supply of blood	−/+
Safety measures do/do not threaten clinical effectivity of blood products	−/+
Safety measures do/do not invade donors' privacy	−/+
Safety measures do/do not decrease the market value of plasma	−/+

Logistical problems, supply problems, diminished clinical effectivity of blood products, and invasions on donors' privacy were mentioned as reasons not to take safety measures, and thus as arguments to tolerate some risk.

6. Non-consequentialist ethical arguments

A sixth cluster of arguments comprises non-consequentialist ethical arguments for risk intolerance (confer table 7, next page).

That these arguments are non-consequentialist means that they appeal to other ethical concerns than the (balance of) good and bad effects of decisions. A number of arguments revolved around the ethical premise harm is especially objectionable, from an ethical perspective, if it is caused by human action (compared to harm not prevented by human action). Some respondents argued that taking TTI risks means inflicting harm upon patients who contract a TTI:

> "Risks in traffic are things that if, well, if you're the one stricken by risk, you've done it to yourself. This is a risk that you, as a doctor, inflict on someone through your treatment. It does not strike you

> because you're just unlucky, it strikes you because someone else is actively doing something to you." (H03-12)

> "If I am administered something, uh, like blood, then I feel that I should not contract some kind of disease, which I did not have in me, but which is thus administered, in fact." (D04-44)

Table 7: Arguments for tolerance or intolerance toward TTI risks: Non-consequentialist ethical arguments

Argument:	*Tolerance or intolerance:*
Do no harm	
Taking TTI risks means being causally responsible for harm	−
TTIs are a serious breach of bodily integrity	−
Blood products are traceable sources of harm	− | x
Taking TTI risks is contrary to the aims of giving blood transfusions	−
Someone has been made responsible for avoiding TTIs	− | x
Stopping safety measures is particularly objectionable	
The status quo should be cherished	−
Stopping safety measures feels unsafe	x
Stopping safety measures is an active decision	−
(Potential) patients have acquired a right to the continuation of safety measures	−
Reintroducing safety measures is/is not problematic	− | +

One recipient argued that harms caused by taking TTI risks are especially serious, compared to harms caused by other medical procedures, because administering blood products constitutes an active and serious breach of bodily integrity:

> "You violate a body's integrity, and that calls for extra safeguards. (…) By infusing something, a barrier is crossed that normally remains untouched. Swallowing, eating and drinking, is something we all do. In that sense it goes further than taking a pill." (P01-12 & P01-14)

Blood products were considered easily traceable and well-delineated causes of harm; blood products, whether specific products or blood products in general, are easy to point at as the source of TTIs. Whether respondents accepted this argument was somewhat unclear, but they did offer it as an explanation of risk intolerance:

> "The question is: what is the cause? The cause could be the patient's natural disease progression. Here, [in the case of TTIs], it's quite clear that the cause is not the patient's natural disease progression." (H05-17)

> "It's administered, so it seems easier to pinpoint, like you can say, something was amiss there. That was what went wrong. You've externalized it, so to speak. It's someone else's, who gives it to you, who is therefore also guilty." (P06-41)

Several respondents noted that tolerating risks to patients conflicts with the aim of medicine, which is to improve patients' health. Thus, even if not construed as causing harm, taking TTI risks was considered inconsistent with the rationale of providing blood product therapy in the first place:

> "A serious infection through blood products is something you want to avoid at all times, because you want to help someone by giving blood products, and things go completely in the opposite direction if you do this." (D08-09)

> "It's a medical necessity for you, but it turns against you." (H05-13)

Some other ethical arguments applied specifically to TTI risks that result from discontinuing blood safety measures, which on these arguments are particularly intolerable (compared to TTI risks that persist because safety measures are not introduced). Various respondents indicated that the status quo should be maintained even if current safety measures are inefficient, although the rationale was sometimes unclear. One respondent explained and criticized this standpoint by arguing that maintaining ineffective safety measures just feels safe:

> "Take safety seats for children in the backs of cars, suppose that research would show they do not contribute to safety. Suppose that research would emerge, you would still see safety seats for children. (…) It still feels safe. (…) It feels like a loss." (P04-52)

Two respondents related stopping safety measures to being causally responsible for harm patients suffer:

> "If you really remove tests, then someone has consciously made a decision, and that influences your health. I think that is the point. (…) Something's afflicted upon you." (R11-45)

> "The one is an active decision, the other is passive. In the one case you really do something, you remove that, eh, that test, in the other you leave the situation as it is. Of course you could say that you do something by not introducing that test, and it's a decision not to make a decision. But emotionally, it's different." (D03-51)

The latter respondent also suggested that (potential) recipients of blood products had acquired a right to the continuation of inefficient safety measures:

> "Withdrawing funds from blood safety, if applying it elsewhere benefits more people. (…) Instinctively, I say no. (...) It's a bit like the idea of acquired rights, you see? (…) I think everybody [has acquired this right]. Everyone who could come into contact with the blood supply." (D03-46)

An important factual issue for the tolerability of withdrawing safety measures was whether these safety measures could, if necessary, be reintroduced easily and quickly. Competing views towards this issue were expressed.

7. Stakeholder interests

Arguments in the final cluster referred to the position or interests of specific stakeholders in the blood system (see table 8, next page).

Clearly, arguments in the preceding clusters already related, in some way, to the interests of blood product recipients. The current cluster comprises arguments that fit the previous clusters poorly but do address stakeholders' interests, where not only recipients' interests but all stakeholders' interests are included.

A diversity of arguments addressed the interests of blood product recipients and their families, or the special situation they are in. Respondents argued that recipients of blood products are in a dependent position, because they must entrust their safety to clinicians and have little control over their own safety. In addition, respondents argued that recipients of blood products deserve solidarity because their health is priceless to them and their loved ones, and because everyone could have been or could become a blood product recipient.

Table 8: Arguments for tolerance or intolerance toward TTI risks: interests/position of stakeholders

Argument:	*Tolerance or intolerance:*
Recipients' interests/position	
Recipients deserve solidarity	
Recipients' health is priceless to them (and to their loved ones)	−
Everyone could have been and may become a recipient	−
TTIs affect recipients' families	−
Families of infected recipients do/do not get adequate support	+/−
Recipients are in a dependent position	
Recipients must entrust their health to physicians	−
Recipients have limited influence on their safety	−
Recipients have more serious health-related worries	+
Blood products do/do not benefit the recipient significantly	+|− / −
Recipients should accept (some) bad luck	+ | x
Donors' interests/position	
Donors' blood should be used beneficially	
Donors' altruism should be supported or rewarded	−
Products for which donors have made an effort should not be spilled	−
Donors do not always take their responsibility for safety	−
Safety measures should not prevent donors from donating	
Donors want to donate	x
Donors have a right to donate	x
Rejecting donors is discrimination	x
Haematologists' interests/position	
Haematologists must trust in the safety of blood products	−
Haematologists have a special relation with recipients	
Haematologists are personally involved with recipients	−
Haematologists have a relationship of trust with recipients	−
Haematologists are (or feel) responsible for recipients	−

Table 8: Arguments for tolerance or intolerance toward TTI risks: interests/position of stakeholders (continued)

Argument:	*Tolerance or intolerance:*
Policy-makers' interests/position	
Policy-makers are empathetic with recipients	—
Policy-makers do not want to be responsible for TTIs	—
Policy-makers fear reputational damage	x
Policy-makers do not bear the costs of safety	x
Policy-makers are liable for TTIs	— | x
Policy-makers should be follow procedures and be consistent	
Tolerating TTI risks is/is not consistent with expressed values	+/—
Tolerating TTI risks is/is not consistent with democratic procedures	+/—
Tolerating TTI risks is/is not consistent with safety policies abroad	+/—
Society's interest/perspective	
Public acceptance of TTI risks is low	
The public expects blood to be safe	— | x
The public fears TTIs	— | x
Blood is special to the public	x
Safety policies affect public perception of blood safety	— | +

Another argument for risk intolerance, offered by recipients, was that TTIs affect victims' families. This argument was made by several recipients who had been infected by TTIs in the past, who expressed worrying for their loved ones rather than for themselves:

> "My first response [when I learned I had HIV] was: shit, how about my wife? (…) And how about my parents? I wasn't thinking about myself at all. Not at that point." (R09-02)

> "I have never really been afraid of what happens to me. I have never been afraid of death or whatever. Yes, I've feared for my relatives more, right. As I said, when the doctor told me, you are indeed infected, the first thing I thought was, oh great, how about her?" (R12-12)

One recipient explained that financial and practical problems for his family were intolerable to him:

> "If a father has a family, and that father has contracted something, then you can say, we couldn't help it. But still, such a family has a huge problem, if that father gets seriously ill at some point, or dies. (…) You're in fact saying, I'm exaggerating: if something happens, it's your problem. Then I think that as a recipient you're entitled to say: but then I want you to put maximum effort into keeping it safe." (R10-33 & R10-34)

Upon further questioning, this respondent stated that if families were offered more security against such problems, he would be more tolerant towards TTI risks:

> "You would have to consider carefully how much trouble this causes in the family, and how one can help out there. (…) OK if you do something on this side, but then do something on the other side as well. If you do this [remove safety measures], then take responsibility for problems you might cause." (R10-39 & R10-44)

Blood product recipients explained the limited concern for their own safety by appealing to their medical histories and prospects:

> "Maybe that's also something, as a haemophilia patient you've gone through so many things early in life, I think your coping mechanism works differently than for someone else who learns a shocking fact about his health." (R12-12)

> "If I would have no problems, would be completely healthy, and would have to imagine: I will get a blood transfusion, and I know it might not be tested for this or for that – wait, I won't accept that. While from my current perspective I'm saying, it means nothing. What I have is much more serious, and it won't get worse because of that." (R13-20)

Several respondents noted that blood products are very beneficial, or indeed life-saving, to recipients. Some saw this as an argument for the tolerability of TTI risks, others saw it as an argument for their intolerability. The latter view, expressed most clearly by respondent H05, seems surprising:

> "You might die if you do not get these drugs, that operation or that blood product, so your life might depend on it. (…) And you might also die because of adverse reactions, serious complications during surgery, or an infection. That makes it very dramatic, and that's why something needs to be done." (H05-16)

Contracting a TTI was also considered dramatic in another sense, namely that because the risk is small, contracting a TTI means being extremely unlucky. One recipient suggested that he would accept being stricken by bad luck:

> "If that happens, than maybe it's my time. Then I've just been unlucky." (R01-02)

This view was opposed by another recipient, who appealed to the personal tragedy of becoming a victim of risk:

> "Some risk you can always, right, you can live with that, but if you happen to be that one person who suffers from it, then you feel totally shit." (R11-37)

A few arguments related to donors' and haematologists' interests. Some respondents discussed and rejected the argument that certain TTI risks should be tolerated because donors have a right to donate, or because rejecting donors from high-risk groups is discrimination. One respondent suggested that donors' altruistic motives and the effort required for donating are reasons for risk intolerance:

> "The donor gets no remuneration, does it voluntarily, so you must ensure that the product he supplies is used optimally, and does not pose risks to the recipient. (…) To reward his altruism, so to speak." (H03-06)

> "You don't want to waste blood. Not because it costs money, but because someone made time to donate blood, and accordingly loses half a point or a full point of Hb." (H03-07)

On this respondent's view, these arguments apply not just to the use of blood by clinicians, but also to safety decisions at blood services.

Arguments relating to haematologists' interests centred on haematologists' relation with blood product recipients. Haematologists stressed that they feel responsible for their patients' safety, with whom they have a fiduciary relationship, and with whom they are personally and emotionally involved. Policy-makers were taken to have an interest in not being responsible for TTIs, and some respondents seemed to consider this a legitimate reason for risk intolerance:

> "You don't want anyone getting sick from an infected blood product or something like that. Think of HIV or things like that, you wouldn't want to have that on your conscience, would you? (P01-05)"

> "One patient with AIDS a year, although it's very subjective, I can't explain it to him. Like: I could have prevented it, but we thought that was too expensive." (H04-34)

These arguments seem to relate primarily to policy-makers empathy with recipients. Respondents also mentioned motives to avoid responsibility that they considered inappropriate: policy-makers' fear for reputational damage, their fear for liability, and the fact that policy-makers do not pay safety measures out of their own pockets. Some further arguments revolved around the idea that policy-makers (being in a political position) should follow procedures and be consistent. On this idea, policy-makers' tolerance or intolerance towards TTI risks must square with the values they express:

> "If you say (...) we place high value on safety, then you should not take measures that are only or mostly intended to improve efficiency. Then you should say: no, we're opting for safety. If it can be done more effectively, fine, but then you must say: we place high value on effectivity." (H04-46)

Also, risk tolerance or intolerance must be democratically legitimate. Any change in direction therefore requires political legitimation:

> "We have collectively decided to apply those safety tests, based on an attitude, one which we discuss each time, and that is evaluated by external parties. If that's the outcome, then that's a given. Of course you can say: perhaps these committees should apply different safety criteria, but that's something they must decide on." (P03-23)

Finally, certain arguments addressed the interests and concerns of the general public. The general public was stated to fear TTIs, to expect that blood products are safe, and to attach a special meaning to blood. Respondents usually, but not always, seemed to reject these public views as reasons for risk intolerance. The influence of risk tolerant or intolerant safety policies on the public perception of blood transfusion was considered important. A lack of trust in the safety of blood products was considered problematic, for example for public health:

> "If someone becomes infected with HIV, then that causes an enormous amount of problems for Sanquin's reputation and for the trust in blood products. People will no longer want to use them. So then the very treatment of all sorts of diseases is endangered." (H05-36)

Public trust was mentioned by some respondents as an argument for risk intolerance, but also, by one respondent, as a possible reason for risk tolerance. Safety measures might in this respondent's view have an adverse effect on public trust:

> "If a blood bank has to do this often, tell donors: we do not want to draw your blood, because you've visited this or that place, then people will become more and more aware of the kind of disease problems they have, and so will become more afraid, will think of blood as something scary. (...) If I put locks on my door, it means something's wrong outside. So if I start implementing security systems, it means that I don't, uh, that what I supply can't be good." (P02-25)

DISCUSSION

The aim of this study was to identify and understand the spectrum of arguments regarding the tolerability or intolerability of TTI risks, providing perspectives that deserve closer consideration in research and policy-making. Because the study design was strictly qualitative, the views expressed by our respondents cannot be generalized: no conclusions can be drawn about what recipients, donors, haematologists and policy-makers think in general. Our research was limited to stakeholders in the Dutch blood supply. In a way, all citizens qualify as stakeholders: everyone may become a patient someday, and the blood supply is funded collectively. Because the public's risk perception has been addressed in previous research and because we were interested in *informed* views on TTI risks, the current study included only stakeholders with first-hand experience with the blood supply.

While the number of new arguments declined steeply as we analysed more interviews, we cannot claim to have reached saturation. Now and then, new arguments arose, some of which were expressed by only one or two respondents. In spite of the high number of arguments we have found, it is conceivable that additional arguments for the tolerability or intolerability of TTI risks can be retrieved by further research.

We found some undertheorized arguments for tolerance or intolerance towards TTI risks. We had expected to find more appeals to what is 'special' about blood (e.g. its symbolic significance) and blood donation (e.g. its social function and the distribution of responsibility between donors and the blood service). Although blood and blood donation were framed in diverse ways, this framing rarely connected to the tolerability of TTI risks. Still, some

interesting new perspectives were opened. Whether these perspectives are valid and persuasive deserves further reflection.

An important insight is that recipients may not be primarily concerned about their own health. Some recipients said that they were accustomed to facing health risks and that blood products brought them much good, but said they did fear the (medical and practical) impact of TTIs on their families. Understanding such perspectives is necessary to engage stakeholders in constructive deliberation about TTI risks and to develop safety policies they can accept.

A remarkable argument for risk intolerance was that because TTI risks are small, contracting a TTI is a dramatic and undeserved fate. A related argument was that TTIs frustrate attempts to remedy patients' bad luck, whose bad luck thus strikes in two steps. One may perhaps support these arguments by appealing to luck egalitarianism: the idea that justice requires neutralizing the effects of bad luck on peoples' lives [16]. Building on this idea, one could argue that tolerating TTI risks *reinforces* some patients' bad luck and is therefore unjust. But perhaps we should acknowledge the sense of tragedy behind these arguments without granting it ethical weight. Allocating scarce health care resources is inherently tragic: if providing care to some patients means that others must forego care, every allocation decision will have losers. At least on a societal level, some bad luck must be accepted, as neutralizing everyone's bad luck is beyond our means.

Respondents offered some non-consequentialist ethical arguments for risk intolerance. Some respondents argued that taking TTI risks means causing harm or defended the view that terminating safety measures is more objectionable than not introducing them. These views have been discussed and criticized elsewhere [6, 17]. Respondents also argued that taking TTI risks is contrary to the aims of providing blood transfusions, that blood products are traceable or recognizable sources of harm, and that TTIs are a serious breach of bodily integrity. An important question in evaluating these arguments (which is beyond the aims of this paper) concerns their scope. Taking health risks is always contrary to the aims of medicine but is inevitable in many medical interventions – this does not only apply to administering blood products. In addition, other iatrogenic harms may also involve violations of bodily integrity and have traceable sources (e.g. surgical errors). Thus, these arguments might not support stronger intolerance towards TTI risks than towards other iatrogenic risks.

A remarkable argument for risk tolerance applied to patients with a poor prognosis. The respondent who expressed this view argued that patients with bad prospects might not live long enough for a TTI to develop into disease, for which reason the TTI would have little

impact. The rationale behind this view, which is similar to triaging in emergency settings, is that scarce resources should not be 'wasted' on patients with bad prospects if that excludes helping patients with better prospects. It might then be reasonable to allow somewhat higher TTI risks in the context of high-risk surgery or when treating severe haematological malignancies than, for example, in the context of haemophilia treatment or blood loss after delivery. But even if this sort of risk stratification is ethically acceptable, which would be an issue for further research, the question remains whether having different safety policies for different groups of recipients is logistically feasible.

On the assumption that resources spent on inefficient blood safety measures could be applied more beneficially, to help more people or save more life-years, various respondents expressed tolerance for TTI risks. Respondents also offered reasons to doubt that assumption, though: the amount of resources spent on blood safety measures might be too small to make a difference somewhere else, and alternative ways to save and reroute money might be available. Initiatives to contain the costs of blood safety measures should address these doubts. Perhaps it should be conceded that saving costs on blood safety measures will be neither sufficient nor necessary to reap substantial benefits elsewhere. Still, one might argue that taking responsibility for efficiency is important because inefficient forms of health care *collectively* disallow achieving better health outcomes. But then initiatives to increase efficiency in blood safety should be matched by similar initiatives in other domains of health care.

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Part II: Ethical analysis

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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Chapter 5:

The precautionary principle and the tolerability of blood transfusion risks

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ABSTRACT

Tolerance for blood transfusion risks is very low, as evidenced by the implementation of expensive blood tests and the rejection of gay men as blood donors. Is this low risk tolerance supported by the precautionary principle, as defenders of such policies claim?

We discuss three constraints on applying (any version of) the precautionary principle and show that respecting these implies tolerating certain risks. *Consistency* means that the precautionary principle cannot prescribe precautions that it must simultaneously forbid taking, considering the harms they might cause. *Avoiding counterproductivity* requires rejecting precautions that cause more harm than they prevent. *Proportionality* forbids taking precautions that are more harmful than adequate alternatives.

When applying these constraints, we argue, attention should not be restricted to harms that are human-caused or that affect human health or the environment. Tolerating transfusion risks can be justified if available precautions have serious side-effects, such as high social or economic costs.

1. THE PRECAUTIONARY PRINCIPLE IN CONTEMPORARY BLOOD SAFETY DECISION-MAKING

After its introduction in environmental policy-making in the nineteen eighties, the precautionary principle has become increasingly influential in public health issues, including the safety of donor blood. The principle's proper interpretation and application have been debated extensively, however, which has led to the development of alternative definitions. Whereas the 'Rio' definition states that '[w]here there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation' [1], for example, the 'Wingspread' definition states that '[w]hen an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically' [2]. Various institutions have consolidated their own interpretation of the principle in official guidelines [3].

The precautionary principle caught the attention of donor blood safety policy-makers after the AIDS and hepatitis C crises of the nineteen eighties and nineties [4,5]. Originally labelled 'non-A-non-B' hepatitis, hepatitis C had been a known risk of blood transfusion and blood product infusion since the mid 1970's. Following developments in hepatitis B testing in the early 1970's, it had gradually become recognized that 80-90% of all transfusion-transmitted hepatitis cases involved an unknown causative agent. However, acute hepatitis C infections typically involved only mild symptoms, and the serious effects of chronic infection remained unrecognized for several more years [6]. Hepatitis C was hence considered an acceptable side-effect of blood transfusion and plasma product use, which meant that ensuring product availability at reasonable costs superseded safety concerns [6-8]. While the seriousness of chronic hepatitis C gained recognition, however, securing supply and containing costs remained dominant concerns. For example, the implementation of surrogate testing (by screening for the presence of antibodies to the hepatitis B core antigen or of heightened alanine aminotransferase levels) was delayed because of its costs and because false-positive test results would result in donor losses [7,9]. A similar stance was taken when AIDS emerged. In contrast to hepatitis C, AIDS was considered severe, but decision-makers underestimated the possibility and frequency of AIDS-transmission through blood products. Arguing that transfusion-transmissibility was 'unproven' or that the risk was 'one in a million', they held that only firm evidence that AIDS threatened transfusion recipients could justify disrupting

standard practice [6-8]. But even when cases of AIDS in hemophiliacs and transfusion recipients accumulated, decision-makers remained reluctant to introduce safety measures (such as universal exclusion of high-risk groups such as gay men, anti-HBc surrogate testing, and heat treatment of plasma products) that might offend donors, threaten product availability or add costs.

When decision-makers finally agreed that thorough safety measures were necessary, thousands of transfusion and plasma product recipients had already been infected worldwide. Various inquiries following the AIDS and Hepatitis C crises concluded that blood services (and regulators) had responded negligently. Not only had decision-makers failed to take adequate action when the risks of AIDS and hepatitis C had become undeniable – they had also taken insufficient precautions at earlier stages [6-8].

Blood safety policy-making has subsequently embraced the precautionary principle. The principle has for example been invoked to justify leukocyte depletion and donor deferral policies against variant Creutzfeld-Jakob Disease in the United Kingdom and Canada [10-12], hepatitis B virus Nucleic Acid Testing (NAT) in the United States [13], and various safety measures against West Nile Virus in Northern America [14]. The precautionary principle has also been invoked to reject or criticize initiatives to change the lifetime deferral of male donors who have had sex with other men (MSM) into a temporary (e.g. 1-year or 5-year) deferral.

The application of the precautionary principle to blood safety is nevertheless controversial. A main charge against the precautionary principle is that it is unrealistically intolerant of risks and therefore requires unreasonable sacrifices in the name of safety. In the interpretation of several countries (including the U.S. and Canada), the precautionary principle only allowed relaxing MSM-deferrals if proof could be offered that risk would not increase *at all* [15-17]. As a result, MSM-deferrals have been relaxed only recently and, according to gay-rights activist groups, half-heartedly. The principle is also taken to sanction very high safety expenditures [18-20]. Growing concern over the high costs of blood safety [e.g. 21] is hence matched by increasing unease with the precautionary principle. Recent decision-making frameworks – notably those proposed by Wilson [19] and by the Alliance of Blood Operators [22] – recognize both safety and cost-containment as legitimate concerns but leave important issues unaddressed. Containing costs requires discontinuing or not introducing safety measures that are considered unreasonably expensive. But forgoing safety measures that would add some safety, no matter how marginally, means tolerating some risk. Can tolerating risks be squared

with the precautionary principle at all? And if so, is cost-containment a morally sound reason to tolerate transfusion risks?

In this paper we argue that some risk tolerance is legitimate when applying the precautionary principle to blood safety, sometimes even to contain costs. After distinguishing various versions or interpretations of the precautionary principle (§2), we offer a number of constraints (or meta-principles) that any version, interpretation, or application of the precautionary principle should observe (§3). These constraints forbid taking (or prescribing) safety measures that are (i) sufficiently hazardous to be forbidden by the precautionary principle itself; (ii) more harmful than the hazards they avert; or (iii) more harmful than alternative adequate safety measures. While satisfying these constraints clearly requires tolerating some risks, what type of risks they cover crucially depends on the interpretation of 'harm', which is therefore discussed next (§4). Finally, we consider whether safety measures can be harmful in virtue of having high *opportunity costs* (§5). We conclude that applying the precautionary principle requires considering what will be sacrificed in the name of (blood) safety.

2. VERSIONS OF THE PRECAUTIONARY PRINCIPLE

We have already noted that the precautionary principle is defined in various ways – and as table 1 shows, we have only seen the tip of the iceberg. This is an immediate and obvious difficulty in answering whether 'the' precautionary principle sanctions high blood safety expenditures. In this section we probe the differences between formulations (definitions, versions, interpretations, applications) of the precautionary principle and discuss what the lack of a common definition means for how the principle applies to blood safety issues.

Table 1: Definitions and accounts of the precautionary principle in literature on transfusion safety policy* (ordered chronologically)

Definition	*References*
"Where there is uncertainty as to the existence or extent of risks to human health ... institutions may take protective measures without having to wait until the reality and seriousness of those risks becomes fully apparent."	[23, p.277]
"[W]here there are threats of serious or irreversible damage to the environment, lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to prevent environmental degradation."	[11 p.90] [24 p.840]

Table 1: Definitions and accounts of the precautionary principle in literature on transfusion safety policy* (ordered chronologically) (continued)

Definition	*References*
"[C]omplete evidence of risk does not have to exist to institute measures to protect individuals and society from that risk."	[11 p.90] [12 p.181]
"[E]ven in the absence of scientific certainty, (...) measures need to be taken to face potential serious risks."	[18, p.273]
"Preventive action should be taken when there is evidence that a potentially disease-causing agent is or may be blood borne, even when there is no evidence that recipients have been affected. If harm can occur, it should be assumed that it will occur. If there are no measures that will entirely prevent the harm, measures that may only partially prevent transmission should be taken."	[10, p.318]
"The balancing of the risks and benefits of taking action should be dependent not only on the likelihood of the risk materializing but also on the severity of the effect if the risk does materialize, the number of persons who could be affected, and on the ease of implementing protective or preventative measures. The more severe the potential effect, the lower the threshold should be for taking action. (...) If there are no measures that will entirely prevent the harm, measures that may only partially prevent transmission should be taken."	[14, p.106]
"[F]or situations of scientific uncertainty, the possibility of risk should be taken into account in the absence of proof to the contrary(...) [and] measures need to be taken to face potential serious risks."	[25, p.97]
"If there is concern about a possible or potential risk, even if it is yet unproven, then precautionary interventions are implemented."	[26, p.352]
"[A]ctions that might harm the environment should not be undertaken unless the proponents of those actions [can] establish that they [are] harmless."	[27, p.956]
"[W]hen a purported risk presents a threat of "serious or irreversible damage", complete evidence of risk does not have to exist to justify the institution of measures to protect individuals and society from that risk."	[28, p.11]
"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context, the proponent of an activity, rather than the public, should bear the burden of proof."	[19, p.179]
"[P]roactive action [should] be taken to prevent or minimise threats to human health or the environment, notwithstanding the absence of full scientific certainty about the nature and scope of such threats."	[29, ch.7]
"[I]f there is a risk, no matter how small, the (blood) operators should seek to mitigate that risk (...) in the absence of evidence, precautionary steps should be taken."	[30, p.754]
***** For overviews of definitions in other areas, in particular environmental policy debates, see e.g. [31] and [32]	

A primary distinction can be made between versions or interpretations of the precautionary principle as (i) a 'rule of choice', (ii) a 'procedural requirement' or (iii) an 'epistemic principle' [33,cf. 34]. The difference between these interpretations is whether the precautionary principle is taken to prescribe certain (i) *actions*, (ii) *decision-making procedures* or (iii) *beliefs* (or belief-like attitudes). Differences and overlaps between 'rule of choice' versions can then be mapped by means of a structural account of the precautionary principle [33,35,36]. On this account, versions of the precautionary principle arise from varying elements in a common structure. The first slot in this structure is a harm condition, which refers to some kind of adverse event, for example to 'catastrophic risks', to 'serious or irreversible damage', to 'very costly and/or irreversible consequences', or merely to 'harm'. The second slot, the knowledge condition, specifies an extent of plausibility that this adverse event will come to pass. It may require that the harm is '(theoretically) possible', 'suspected', or 'not proven not to occur'. The third element concerns the precautions that should be taken if the harm and knowledge condition are met. It may either specify which qualities precautions should have (e.g. being 'cost-effective' or having 'little risk of causing harm') or identify particular precautions (e.g. 'banning' or 'developing alternatives for' hazardous activities). Finally, the fourth slot concerns the force with which precautions are prescribed: taking them may be mandatory, recommended, or merely permitted.

The knowledge condition is typically conceived as a minimal amount of plausibility that harm will occur. Interpretations also differ, however, on what extent of *uncertainty* must remain to apply the precautionary principle. Some scholars call only the management of *theoretical* risks (where the possibility of harm occurring has not been proven) 'precautionary', which suggest that managing *proven* risks requires a different approach. Others hold that while the precautionary principle does apply to proven risks if these are *unquantifiable*, risk-cost-benefit analysis is preferable when facing *quantifiable* risks [e.g. 37]. Yet others have defended applying the precautionary principle even to quantifiable risks [38-40].[1]

Blood safety policy-makers and scholars have invoked the precautionary principle to justify precautions against all these types (theoretical, proven but unquantifiable, and

[1] The principle has for example been interpreted as a 'maximin' decision-making strategy (i.e. choosing the option where the minimal outcome value is highest) [38-40]. Another strategy is to weight negative outcome values and probability estimates unequally when quantifying risks: precaution then requires assigning more weight to relatively serious outcomes than to relatively probable ones [39].

quantifiable) of risks.[2] It has been applied (i) when facing infections which had not been shown to transmit through transfusion, as with variant Creutzfeld Jakob Disease [10,11]; (ii) when the probability of exposure to infections that were known to be transfusion-transmissible was highly uncertain, as with West Nile virus 14]; and (iii) when the frequency of transfusion-transmission would, by all plausible estimates, be very low, as with Hepatitis B breakthrough infections and Q-fever [13,41].

A number of competing conclusions could be (and have been) drawn from the observation that interpretations of the principle differ. Some have argued that the principle is simply too ill-defined to be of use to policy-making and that it should therefore be discarded [cf. 31]. Others have attempted to establish the superiority of one of the principle's definitions or interpretations. We think that it is preferable and realistic, however, to allow varying formulations across different contexts. First, different versions of the precautionary principle may fit different decision-making styles. In particular, decision-makers may prefer more general or more specific interpretations of the precautionary principle: whereas general versions are intuitively plausible and relatively flexible, more specific interpretations provide more concrete guidance [cf. 34]. Second, we cannot expect that a single version will have ethically acceptable implications in strongly diverging domains. Simply importing a version of the precautionary principle from environmental policy-making into blood safety policy-making is dubious, for example, because the hazards involved differ [24]. This may mean that blood safety policy-making should adopt a customized version of the precautionary principle [11]. Third, countries may want to set their "own level of protection, (...) depending on [their] economic situation and socio-political priorities" [43, p.148,cf. 3]. What amount of protection is reasonable against transfusion-transmissible infections, for example, may depend on cultural values and on the amount of resources available for donor blood safety and other important societal goals (cf. *infra* §5). It would be unrealistic, for instance, to require the same level of precaution in the blood systems of high and low income countries. Fourth, it may be sensible to allow (or combine) different versions of the precautionary principle even within one context, depending

[2] It must be conceded that these types of risk, while neatly separable in theory, are difficult to disentangle in practice. Rarely are all possible outcomes and their probabilities accurately known, as 'pure' quantifiable risk would require; the probabilities of some possible outcomes are typically uncertain, and ignorance of some possible outcomes is usual as well [42]. Furthermore, because proof is often neither conclusive nor entirely absent, there is also a grey area between 'proven' and 'theoretical' risks. By classifying risks, therefore, one typically simplifies the decision-making situation [42].

on the magnitude of the risks faced in particular cases. This would enable meeting more serious hazards with stricter precautions and less serious hazards with milder ones [19, 40].

Allowing multiple versions or interpretations of the precautionary principle does not mean that every version should be accepted. In the following section we outline three constraints or 'meta-principles' that should be observed in precautionary policy-making. §4 and §5 discuss the scope of these constraints and explore their implications for the question whether (or to what extent) precautionary decision-making should be sensitive to the costs of safety.

3. CONSTRAINTS ON THE PRECAUTIONARY PRINCIPLE: CONSISTENCY, AVOIDANCE OF COUNTERPRODUCTIVITY, AND PROPORTIONALITY

This section presents three general constraints on versions (interpretations, applications) of the precautionary principle. First, *consistency* requires that (any version of) the precautionary principle does not simultaneously prescribe safety measures and, considering the potential harms involved in those measures themselves, advise against them. Second, *avoidance of counterproductivity* requires that recommended safety measures are no more harmful than the hazards they avert. Finally, *proportionality* requires that precautions are no more harmful than alternative adequate precautions.

Some preliminary qualifications are in order. First, these constraints are not intended as complete guidance on defining or applying the precautionary principle. The constraints are important because they point at reasonable *limits* of precaution and thus affect the question when risks should be tolerated. Second, we acknowledge that these constraints have appeared, in some form or other, in guidelines or commentaries on the precautionary principle (e.g. [3,40]. The current paper explicitly defines the constraints with 'harm' as a central notion. This helps answering when (transfusion) risks should be tolerated even on the precautionary principle, namely when taking precautions against those risks would according to our constraints be unjustifiably harmful.

The present section shows that these constraints must be respected to avoid powerful and commonly raised objections against the precautionary principle. There has been little question that these objections are serious *if* they apply; debates have focused on *whether* they apply. Lacking a universally accepted account of the precautionary principle, however, the question must be whether particular versions (definitions, interpretations, applications) of the

precautionary principle can avoid them. These objections thus set constraints on how to interpret the precautionary principle: only interpretations of the principle that avoid these objections are defensible [cf. 39,40].

A first objection is that the precautionary principle is *inconsistent* (or *incoherent*), in that it simultaneously prescribes and forbids certain safety measures. This applies if the precautionary principle undermines its own prescriptions because the very safety measures it prescribes involve unacceptable hazards [40]. The precautionary principle then offers contradictory recommendations, e.g. to *ban and not ban* the use of asbestos in car brakes. Because contradictory recommendations fail to help (or even paralyze) decision-making, inconsistency is not just a logical but also a practical flaw [32,35,40].

Because we can always envisage some scenario in which precautions lead to serious harm, inconsistency is allegedly inescapable when applying the precautionary principle [cf. 44]. For example, if the precautionary principle required avoiding *any* risk to transfusion recipients, then it would oppose *maintaining* lifetime MSM-deferrals just as much as relaxing them: maintaining indefinite deferrals may erode prospective donors' willingness to disclose MSM-behavior and thus involves risk too [cf. 35]. Applying the precautionary principle to very implausible or improbable hazards thus leads to inconsistent recommendations. The same conclusion follows if it is taken to cover very small harms [32,39]. For example, a vaccination is always somewhat uncomfortable, so if the precautionary principle required avoiding even mild discomforts, it could not consistently recommend providing vaccines as a precaution against some emerging disease.

A common response is to limit the principle's scope to sufficiently credible and serious hazards, as specified in knowledge and harm conditions [31,32,40]. The principle might for example require 'reasonable grounds for concern' or 'some scientific evidence' that 'significant' or 'serious' harm is impending (cf. §2). Precautionary measures can then be recommended consistently if the hazards they introduce are not credible or serious enough to 'trigger' the principle.

Even accounts of the precautionary principle with relatively strict knowledge and harm conditions may not always evade inconsistency, however [32,40]. Cases have been offered where meeting serious and credible hazards seemed to require equally hazardous precautions. While such 'risk-risk trade-offs' are no exception when facing environmental risks [e.g. 45,46], the introduction of alternative hazards may be especially common when addressing public

health risks. Spraying DDT to combat malaria, for instance, involves public health hazards because DDT might be toxic or carcinogenic [47]. Similarly, it has been suggested that precautions against credible and serious infectious transfusion hazards posed credible and serious threats to transfusion recipients: chemicals employed in some pathogen inactivation procedures might be carcinogenic, for example, and donor deferral policies against vCJD could cause serious supply shortages [19,28,48]. Candidate precautions against AIDS and hepatitis C were in the 1980s also rejected with reference to the risk-risk trade-offs they involved, in particular the risk that supplies of donor blood would prove insufficient. The conclusion would be that the precautionary principle often fails to offer consistent recommendations, especially when facing threats to public health.

As Daniel Steel points out, though, whether applying the precautionary principle leads to inconsistent prescriptions depends not only on (i) the version of the precautionary principle that is applied but also on (ii) which particular precaution is considered and on (iii) the context and characteristics of the hazard faced [40]. Versions of the precautionary principle that yield inconsistent results systematically, because they have very permissive harm and knowledge conditions, should be rejected. But inconsistency can also result from considering only inappropriately hazardous precautions even though less hazardous alternatives are available [40,44,46]. When arriving at inconsistent recommendations, therefore, decisional paralysis can be avoided by attempting to identify precautions that *can* be recommended consistently. If donor blood is dangerously short in supply, for example, partially effective precautions that do not threaten product availability can be considered [6]. Allowing autologous donations for elective surgery and stimulating (mild to moderate) hemophiliacs to return to cryoprecipitate[3] may have been consistent risk-management options when facing AIDS [8]. Finally, exceptional circumstances may preclude offering consistent recommendations. Even when applying a version of the precautionary principle that generally yields consistent prescriptions, no consistent recommendation may in the circumstances be derivable because every possible decision (including doing nothing) involves credible and serious risks. This might not be a decisive problem for the precautionary principle. There simply might not *be* a reasonable response when addressing certain risks implies introducing equally serious and credible hazards. Some (qualitative) difference between risks can usually be identified, however, and a

[3] Cryoprecipitate had been the preferred blood plasma derivative to stop bleedings in people with clotting disorders until factor VIII was mass-produced. Because the production of cryoprecipitate required pooling of fewer donations, it was less likely to transmit AIDS than factor VIII concentrate.

version of the precautionary principle that cannot handle *every* uncertain situation can still have practical value [cf .40,49].

The preceding discussion has clear implications for what risks should be tolerated even on the precautionary principle. To avoid systematic inconsistency, first, the precautionary principle can only apply to hazards that meet certain minimal conditions of plausibility and seriousness. Thus, taking precautions against implausible or mild hazards cannot be justified by appeal to the precautionary principle. Second, relatively serious and credible risks may have to be tolerated if effective precautions would themselves pose equally serious and credible risks – some level of risk must remain even if certain partially effective precautions *can* be taken consistently.

A different type of objection against the precautionary principle is that following it has harmful consequences. It has been charged to cause harm, for example, by stifling innovation [37,50], by deadlocking the economy [cf. 32], and by requiring safety measures that are so expensive that they reduce overall wellbeing [31,51]. Whereas inconsistency is a logical and pragmatic problem (because the prescription to take and not take some precaution is contradictory and fails to guide decision-making) these are *moral* charges referring to undesirable consequences of applying the precautionary principle. Their most general and forceful point is arguably that the precautionary principle is *counterproductive*, i.e. that following it is more harmful than not following it (and adopting some other decision-making approach instead).

But is this really a new objection? How can following the precautionary principle create more harm than it prevents, if consistency already forbids taking precautions that are unacceptably likely to be unacceptably harmful? One obvious possibility is that decision-makers fail to recognize inconsistency because they simply overlook some side-effects of the precautions they implement. Another possibility is that decision-makers explicitly interpret the precautionary principle as dismissing the relevance of certain types of harm. If the principle is taken to cover harms to the environment but not harms to the economy, for example, shutting down the economy and blocking innovation may be a consistent way to stop environmental degradation. Also, if the precautionary principle is interpreted as applying to *infectious* risks of blood transfusion only, it is not inconsistent to implement pathogen inactivation procedures that severely compromise the clinical effectiveness of blood products.

These cases can indeed be addressed by reconsidering the role of consistency in precautionary decision-making. The precautionary principle's susceptibility to inconsistency,

while previously identified as a problem, can be exploited to halt the rash introduction of inconsistent precautions and to force decision-makers to consider less hazardous alternatives [40]. Candidate precautions should be explicitly checked for consistency by applying the precautionary principle to its own recommendations; precautions that fail this check are likely to cause more harm than they prevent and should not be implemented. Such a check is particularly potent if the precautionary principle is taken to cover various types of harm [cf. 31,39,*infra* §4]. Moreover, available knowledge should where possible be exploited to identify bandwidths of credible outcomes or to characterize risks qualitatively [40]. If we can be confident that some emerging pathogen will affect 0 to 100 immuno-deficient transfusion recipients (or that it poses an 'improbable and small-scale' risk) and that a donor deferral policy will leave 50 to 150 patients without direly needed emergency care (or that it poses a 'credible and serious' risk), for instance, we can conclude that introducing the deferral would be inconsistent.

Still, even precautions that pass a serious consistency check may prove counterproductive. The precautionary principle allegedly has worse consequences than traditional decision-making approaches, in particular cost-benefit analysis, because it rejects *risk neutrality* [cf. 38]. Risk neutrality means treating chances with equal expected outcomes as equally acceptable, regardless of any differences in the probabilities and outcome values that determine their expected outcomes [38,39]. Taking a 1% chance of losing €1000 would for example be equivalent to taking a 100% chance of losing €10. The precautionary principle, on the other hand, is on a common interpretation *risk averse*: it treats losses as more significant than gains and focuses on the prevention of relatively large rather than relatively probable losses [38,39]. Metaphorically speaking, it would advise against taking a 50/50 chance of either winning or losing €100 and would prefer a 100% chance of losing €10 over a 1% chance of losing €1000 [38,39]. In accordance with its stress on avoiding strongly negative outcomes, it would sometimes even require actions with inferior expected outcome values – introducing moderately harmful safety measures against relatively improbable risks, for example, and banning innovations that promise to improve the lives of many people but also pose credible threats (e.g. experimental drugs). If so, following the precautionary principle rather than some risk-neutral decision-making approach will probably be counterproductive in the long run.

The charge that following the precautionary principle is counterproductive has been countered by empirical arguments – by enumerating cases where precautionary action could have avoided catastrophes [40,52,53]; by downplaying the number or impact of cases where

precautionary measures were taken unnecessarily [40,45,46]; and by pointing out advantageous side-effects of precautionary measures, such as impulses to innovation and the economy [32]. While the question whether specific versions of the precautionary principle are counterproductive may only be answerable in the long run, some guidance for particular precautionary policies can be offered.

One obvious strategy is to introduce precautions provisionally whilst monitoring their effects [cf. 3]. Because precautions are typically introduced in uncertain times, they may prove to be unnecessary, ineffective, or unexpectedly harmful. Provisional precautions that prove counterproductive over time can be withdrawn, adapted or replaced. [4]

A second strategy to avoid counterproductivity (but that is also relevant as a criterion for choosing between overall beneficial precautions) is to take *proportional* precautions. This requirement has two complementary faces. First, one should select the least harmful from among adequate or effective precautions – we should refrain from shooting a fly with a cannonball, to invoke a common expression, when a fly swatter would do just as well [40]. The idea of 'adequacy' is of course conceptually challenging. Alternative safety measures will rarely reduce risks to an exactly equal degree, and safety measures that reduce risk more effectively do not necessarily dominate less effective safety strategies, because they may have more objectionable side-effects. For example, testing blood donations for the presence of viral RNA or DNA is most effective when performed on all individual donations, but this testing strategy will typically require wasting more false positive donations than testing selectively (based on donors' risk profiles) or testing pooled donations. This difficulty can be addressed by requiring that precautions are proportional in a second sense: the more serious and credible the hazards faced, the more effective must precautions be in order to be 'adequate' [32,43].

Determining when risks are reduced adequately clearly requires judgment on when risks are tolerable. This may involve comparing the residual risk to an explicit threshold-level for tolerable risks, although this threshold should be sensitive to the specifics of the hazard and the decision-making context [43]. In any case, since proportionality supports selecting the least

[4] Note that withdrawing precautions that have proven counterproductive may be severely complicated by the decision-making context. Removing blood safety precautions may expose decision-makers to liability, may be forbidden by regulations they are under, or may be politically sensitive (see e.g. [54] with regard to MSM-deferrals). Especially if these same pressures encourage precautionary action whenever new infections arise, the continuing expansion of the blood safety arsenal is an understandable consequence.

harmful precaution that reduces risks to some tolerable level, it forbids extreme risk-intolerance. This shows that the precautionary principle does not forbid temporary MSM-deferrals simply because they involve some risk; it might be argued that temporary deferrals reduce risk to a tolerable level while indefinite deferrals have more harmful side-effects. Thus, discussion on when risks are tolerable cannot be silenced by invoking the precautionary principle.

The current paper does not aim to determine which versions of the precautionary principle meet the above constraints when applied to blood safety issues. That would require a careful and largely empirical account of the hazards, uncertainties, and candidate precautions faced. The paper's aim is more abstract: to trace some general criteria for applying the precautionary principle to blood safety that relate to risk tolerance. These criteria can then be used as heuristics when (re)interpreting or applying the precautionary principle. As we have formulated them, however, the constraints offered include 'harm' as a central concept, which must therefore be clarified.

4. THE NOTION OF HARM AND THE SCOPE OF THE PRECAUTIONARY PRINCIPLE

The notion of 'harm' not only figures in the precautionary principle itself, but is also central to aforementioned constraints on that principle's application. Consistency requires that (a version of) the precautionary principle does not prescribe precautions that it simultaneously forbids taking, considering the harms they might cause. Avoidance of counterproductivity means that safety measures should not cause more harm than they prevent. Finally, proportionality advises against taking safety measures that do more harm than alternative adequate safety measures, even if they avert more harm than they cause. How 'harm' is interpreted is hence crucial for the application of (the precautionary principle and) our constraints. If being deferred from blood donation can be said to harm MSM, then maintaining lifetime MSM-deferrals may be disproportionate, counterproductive, or even inconsistent. Similarly, our constraints may forbid implementing expensive blood safety measures if such measures can be considered harmful *qua* being costly (see §5). The current section therefore discusses the scope of this notion. By rejecting proposals to equate 'harm' with (i) *wrongful* damage, (ii) *human-caused*

damage or (iii) damage to *the environment or human health*, we end up with a broad non-normative concept.

It is common to distinguish between a normative (or moralized) and a non-normative sense of 'harm'. The non-normative sense is often spelled out as 'loss of welfare' or 'setback of interests' [55-56], but 'damage', 'injury' and 'negative change' are also non-normative substitutes for 'harm' [32]. 'Harm' in the normative sense signifies, in addition, that this damage is caused by wrongful acts or omissions [55-56]. Understanding 'harm' in a normative sense may be appropriate in such contexts as criminal law [55-56]. Should we also understand 'harm' normatively when applying the precautionary principle, thus limiting it to damages that qualify as wrongful, or should we understand it in a broader non-normative sense?

We do not know any definitions or accounts of the precautionary principle that incorporate an explicitly normative notion of 'harm'. The principle's scope is sometimes limited to *human-caused* damages however [57,58], and justifying this restriction in a deontological spirit yields a tacitly normative notion of harm. The precautionary principle is on a deontological construal an extension of our duty to limit the negative effects of our own (individual and collective) actions; it expresses that this duty also applies when our actions merely *risk* causing damage [59,60]. Performing hazardous activities without taking adequate precautions violates this duty and any damages that ensue are hence wrongful, but there is no comparable wrong in failing to address hazards that do not derive from our (individual or collective) agency. Precautions that address anthropogenic hazards are therefore easier to justify than precautions that address non-anthropogenic hazards – especially if the precautions concerned are coercive [cf. 61]. Justifying the precautionary principle along these lines suggests that any 'harms' it prescribes us to prevent must be anthropogenic, in which case its notion of 'harm' would be tacitly normative.

There are good reasons for applying the precautionary principle more broadly, however, and thus for accepting a wider interpretation of its notion of 'harm'. First, even if the prevention of (primarily) anthropogenic harms is considered especially important, it does not follow that non-anthropogenic harms should be ignored altogether. There might be a stricter responsibility to prevent the spread of a dangerous contagious disease that has been laboratory-bred rather than naturally arisen, for example, but it is perfectly reasonable to consider precautionary measures in the latter case as well. Even though non-coercive

precautions will be easier to justify from a non-consequentialist perspective than coercive alternatives, preventing non-anthropogenic damages is at least *prima facie* right.

Secondly, a strict distinction between anthropogenic and non-anthropogenic damages is difficult to maintain in practice and in principle [32,59]. Given the complexity of natural processes and the ubiquity of human influences, most phenomena should strictly speaking be classified as 'mixed' – various phenomena associated with global warming, for example, depend not only on greenhouse gas emissions but also on environmental feedback mechanisms [32]. A similar point can be made for transfusion-transmissible infections. When a transfusion recipient is infected with HIV and develops AIDS, should we say that the blood bank (or the donor, or the physician who provided the transfusion) *caused* his disease or that the virus did and that the blood service merely failed to prevent the infection? We can apparently identify the blood service's failure to screen out the infectious donation as *the* cause only by presupposing that the blood service should reasonably have prevented the infection ([Self-identifying reference]). Classifying such harms as either 'caused' or 'not prevented' is thus hardly morally neutral [cf. 55].

Finally, the actual application of the precautionary principle employs a wider interpretation of 'harm'. Legal documents and international treaties often use 'harm' interchangeably with 'injury', 'damage' or 'adverse effect' and do not restrict its use to damages resulting from human agency [32]. Moreover, the precautionary principle has been invoked to justify precautions against hazards that seemed primarily natural rather than anthropogenic, for example the spread of West Nile virus by mosquitos [62]. Where the precautionary principle is applied to (primarily) non-anthropogenic damages, such damages must also qualify as 'harms' when applying our constraints.

We thus suggest that the precautionary principle's notion of 'harm' should cover non-anthropogenic and non-wrongful damages. Whether some damage, injury or adverse effect is within the principle's scope should depend on its seriousness and not on its causal background or moral character. There is no conceptual ground to exclude 'natural' hazards that have far-reaching negative consequences from the scope of the precautionary principle. Judging how serious harms are is morally sensitive, of course, and anthropogenic harms may be particularly serious from a moral perspective. But if a broad non-normative interpretation of 'harm' is adopted, the relative seriousness of various (potential) harms can be negotiated *within* the process of applying the precautionary principle.

Moreover, restricting attention to environmental or human health damages is unfounded too, given that value judgments are indispensable when applying the precautionary principle [cf. 57,63,64]. Applying the precautionary principle only makes sense if we consider certain things worth protecting, and the potential side-effects of precautionary measures must be considered less serious (or much less plausible) than damages to those valuable things. Damages to the environment or human health are often particularly serious because they involve a non-compensable loss of intrinsic value, but it does not follow that even small-scale or mild effects on the environment or human health are necessarily more serious than other harms. While lifetime deferrals do not threaten MSMs' physical health, for example, they may harm MSM in some other sense (e.g. psychologically), in which case our constraints apply. The respective harms to transfusion recipients and MSM should be balanced with reference to a broader account of what makes one more serious than another, which must include a discussion on how exclusion from blood donation affects MSMs' wellbeing or legitimate interests. One might still conclude such harms involved are small compared to the risk of contracting a transfusion-transmissible infection, but at least MSM's legitimate concerns will be taken into account.

5. COSTS AS HARMS

We have argued (§3) that avoiding inconsistency, counterproductivity, and disproportionality requires tolerating certain risks. How does this affect the question whether the precautionary principle sanctions escalating blood safety expenses? The current section argues that precautions can be considered harmful – and thus inconsistent, counterproductive or disproportionate – in virtue of having high *opportunity costs*. The point is not that expensive precautions are necessarily unjustifiable. Rather, construing costly precautions as (*pro tanto*) harmful allows integrating cost considerations into a precautionary framework: when checking whether particular precautions meet our constraints, the question must be raised how harmful those precautions are on account of their opportunity costs.

Donor blood safety measures are in most western countries funded collectively, for example by taxation schemes or health insurance. Because resources are necessarily limited, however, allocating more resources to one service (e.g. blood safety measures) means that less resources are available for other services (e.g. cancer research or collectively funded orphan drugs).

Choosing which services to make available and which not to fund is therefore inevitable. The notion of 'opportunity costs' applies when choosing to expend resources on one intervention or programme means forgoing the opportunity to fund and reap the benefits of alternative interventions [20,65]. It refers to the benefits thus forgone, which can be non-monetary and can include (e.g.) lives or QALYs lost [20,65]. Thus, while opportunity costs are generally a *function of* monetary costs – because the monetary costs of an intervention determine which benefits of alternative interventions have to be forgone due to a lack of financial resources – they need not *be* costs in the monetary sense.

Interventions can arguably be harmful in a non-normative sense *qua* having high opportunity costs.[5] This is clearest if the intervention which must be forgone would have prevented mortality or significant morbidity. If alternative interventions would have secured more lives or health benefits than the interventions actually implemented, then the wellbeing or interests of more people suffer setbacks, or those setbacks are more serious, than need have been the case. Interventions with high opportunity costs may even be considered (*pro tanto*) harmful if they are overall beneficial. Implementing one intervention often means that we are no longer in a position to reap the benefits of some other intervention, potentially with other beneficiaries. The inherent tragedy of allocating scarce health care resources is that almost every decision sets back the interests or wellbeing of some people.

The opportunity costs of implementing some precaution may often be difficult to determine. First, the financial impact of the precaution itself may be unclear, for example if price developments of precautionary measures are difficult to forecast. Second, it may be unclear how the ability to address other harms will be affected, in particular because precautionary measures may be funded from flexible rather than fixed budgets. Blood services may for example forward the costs of additional precautions to hospitals, insurance companies, or funding authorities (such as a ministry of health). In such a scheme, implementing expensive blood safety measures barely affects blood services' ability to fund other activities – the financial effects instead spread through the wider health care system, where their impact is more difficult to pinpoint but is real nonetheless [cf. 65]. Finally, a meaningful comparison of alternative interventions may be impossible if their respective costs and benefits are very uncertain. If it is entirely unclear whether some serious infection is transfusion-transmissible and how many patients would be at risk, for example, precautions against transfusion-

5 Some allocations of public health care funds may even be wrongful and thus harmful in a normative sense. We will not pursue this thought, however.

transmission of that infection are difficult to compare against alternative interventions against serious health risks.

Uncertainty is rarely this absolute, however [cf. *infra* §2 & §3]. It may be possible to judge that the resources required to address one hazard could be used to address more serious risks or harms instead. One important conclusion is that the precautionary principle does not justify blood safety measures with very unfavorable cost-effectiveness ratios – which sometimes exceed €1.000.000 per quality-adjusted life-year saved [e.g. 66]. While cost-effectiveness calculations do involve some uncertainty, the cost-effectiveness ratios of some blood safety measures are unfavorable on all plausible estimates, which means that allocating health care funds differently would most likely prevent more harm. Unless transfusion-transmitted infections can be considered especially serious from an ethical point of view [cf. 67], such blood safety measures cannot be recommended consistently and will probably prove counterproductive. Another conclusion is that relatively expensive precautions can be considered disproportionate when cheaper adequate alternatives are available. In the Netherlands, for example, testing donor blood against exotic infections such as West-Nile virus, Chikungunya and Chagas is currently considered disproportionate because the universal 4-week deferral of donors who travelled outside Europe adequately reduces risks at lower costs (and with an acceptable impact on supply).

Such examples cannot conceal that our constraints leave various issues open to interpretation: how serious the hazards addressed by alternative interventions are, for example, and when precautions can be considered adequate. Normative views will affect how such issues are decided, so applying our constraints requires normative argumentation no less than applying the precautionary principle itself does. Still, our constraints, the broad analysis of 'harm' and the notion of opportunity costs offer useful resources for normative discussions on precaution and its price.

CONCLUSION

The precautionary principle does not support zero tolerance for transfusion risks: blood safety precautions that are inconsistent, counterproductive, or disproportionate in view of their side-effects should be forgone. Nor can the precautionary principle be invoked to dismiss considerations like the interests of MSM and the costs of safety. The precautionary principle only supports focusing on the prevention of transfusion-transmissible infections, whilst

downplaying the relevance of other types of harm, on the presupposition that transfusion-transmissible infections are somehow especially serious. This presupposition cannot be taken for granted without misapplying the precautionary principle. Rather, the importance of blood safety should be debated frankly and critically.

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Chapter 6:

Interpreting and Applying the Precautionary Principle

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Kramer K, Zaaijer HL & Verweij MF (2017). Interpreting and Applying the Precautionary Principle: A Response to Open Peer Commentaries on "The Precautionary Principle and the Tolerability of Blood Transfusion Risks, *The American Journal of Bioethics*, 17(4), W4-W6

In our paper "The Precautionary Principle and the Tolerability of Blood Transfusion Risks" we have criticized the idea that the precautionary principle would justify extremely risk averse (or 'zero-risk') blood safety policies [1].[1] Such appeals to the precautionary principle ignore the social and economic harms caused by safety policies, or indeed set these aside as irrelevant. While we acknowledged the importance of precaution in blood safety policy-making, we argued that precaution does not imply extreme risk intolerance. Precautions should be consistent, non-counterproductive and proportional, which requires tolerating certain risks. In what follows, we respond to Open Peer Commentaries on our paper and discuss how these contribute to the interpretation of the precautionary principle and its application to blood safety issues.

A main motivation to write our article was the recognition that being committed to the precautionary principle can have (overall) undesirable consequences. Maheshwari and Savić [2] distinguish three ways that following the precautionary principle can be counterproductive in this 'broad' sense: (1) when the precautionary principle prescribes precautions with undesirable consequences; (2) when inconsistent recommendations lead to decisional paralysis and decisional paralysis has undesirable consequences; (3) when being committed to the precautionary principle leads to brushing aside other ethical principles and duties. Maheshwari's distinctions fit well with our account. The constraints we call 'avoiding counterproductivity' and 'consistency' address the first and second routes to counterproductivity in the broad sense. Furthermore, our account of harm suggests how ethical concerns can be accommodated when applying the precautionary principle, and is thus relevant for avoiding the third route. We argued for applying an inclusive, non-normative notion of harm, but we also stressed that the weighting or balancing of harms should be informed by ethical considerations. Taking precautions makes sense only if the harms prevented are considered more serious than the harms caused by taking precautions. Thus, the precautionary principle cannot replace judging how serious harms are; to the contrary, such judgments are a precondition for applying the precautionary principle. Here it should be recognized that the seriousness of harm may depend on moral features besides the size of impact. Our account does not pretend to offer guidance on which ethical considerations affect

[1] We thank our commentators for their insightful analyses of our target article, and we are grateful to AJOB for providing the opportunity to engage in a constructive discussion on this topic.

the seriousness of harms. We believe that this is context-dependent and should therefore be fleshed out for particular domains of application.

Petrini [3] raises two questions that relate to expanding the application of the precautionary principle from environmental hazards to health hazards. First, should the criteria applied for the protection of human health be the same as those applied for the protection of the environment? Petrini argues that the precautionary principle cannot apply across such disparate domains as marine protection and blood transfusion. These domains differ so vastly that only highly abstract principles could apply universally. Second, is it appropriate to speak of a precautionary 'principle'? A proper 'principle' is absolute and without exceptions, but flexibility is crucial when setting precautionary policies. Saunders's [4] commentary differs from Petrini's in interesting respects. Saunders asserts that versions of the precautionary principle do have a common core: if there is evidence of danger, authorities are not obliged to wait for full proof of harm before they may act. This interpretation of the precautionary principle is supposedly valid across the diverse contexts in which it is applied.

We agree with Saunders that there may be accounts of precaution that apply across very diverse contexts, but we share Petrini's concern that only a very general principle or concept of precaution would qualify. This raises a problem, as general accounts of precaution may be too vague to be action-guiding. Saunders acknowledges that his core principle "neither prescribes nor forbids anything", as it addresses when authorities *may* act and not when they *must* act. Yet decision-makers must also judge when taking precautions is reasonable or ethically desirable. Capturing the essence of precaution in creeds like 'it is better to be safe than sorry' and 'look before you leap' faces a similar problem. Although such proverbs may be valid in diverse contexts, their vagueness precludes an effective application to particular cases. Do they require taking every possible precaution against every conceivable risk? Do they allow limiting attention to relatively serious and probable risks?

In our view, it is more important to insist on the precautionary principle's potential to guide action than on its generality. Moreover, the application of the precautionary principle should be sensitive to domain-specific ethical concerns, including the distribution of risks and ethically relevant features of at-risk populations. (We reject the idea that principles should be absolute or without exception, which excludes sensitivity to context and to the plurality of values at stake.) It thus makes sense to develop versions of the precautionary principle for application in limited domains, such as public health or even the subdomain of blood safety. The suggestion in our article is that action-guiding versions of the precautionary principle can

be developed by specifying a knowledge condition, a harm condition, and a recommended precaution, where acceptable specifications must avoid inconsistency, counterproductivity, and disproportionality.

Wilson and Atkinson [5] agree with our assumption that an account of precaution for blood safety should be action-guiding. The core of their 'calibrated' approach is that if there are "more than minimal harms associated with the introduction of precautionary measures", then "the degree of a precautionary measure needs to balance the competing risks". Wilson and Atkinson's advice on how to balance risks is primarily procedural: they suggest taking both public acceptance and expert assessments into account and propose adjusting policies when relevant evidence emerges. As a source of inspiration for which factors to consider in this balancing act, Wilson and Atkinson refer to the Alliance of Blood Operators' [6] framework.

Arguably, some form of 'weighting' or 'balancing' competing values is inevitable, but what this means in practice often remains obscure. In our view, consistency, avoiding counterproductivity, and proportionality help to clarify what it means to 'balance' risks. These constraints explicate that precautionary policies should not introduce risks that are unacceptable according to the version of the precautionary principle which motivated precautionary action, that bring more harm than the risks averted would, or that could be avoided by taking alternative adequate precautions. Arguably, the concept of risk averseness explains what it means to balance risks in a precautionary fashion. On this concept, avoiding relatively serious risks is more important than avoiding relatively plausible ones (see section three of our target article). But it does not follow that the plausibility of harm should be ignored: as long as seriousness gets most weight, risk averseness is perfectly compatible with giving plausibility some weight too. (See [7] for interesting proposals on how to flesh out this idea.) That said, we repeat that our account does not address what factors determine the seriousness of harms, which must in our view be context-sensitive. We have discussed some ethically relevant features of blood transfusion risks elsewhere [8], but much work in the ethics of blood safety remains to be done.

Stabell [9] observes that an action-guiding account of precaution must define the notion of uncertainty and the related notion of plausibility. Stabell is correct that following the decision-theoretic interpretation of uncertainty – knowing the possible outcomes of alternative decisions but lacking knowledge about their probabilities – leads to inconsistency. If the mere possibility of harm were sufficient to trigger precautionary action, then almost no precaution could be taken consistently. But we disagree with Stabell that this problem surfaces when

opportunity costs are taken into consideration: it is nearly always possible that precautions cause harm, even apart from their opportunity costs. With this more general argument, our article (section three) reached the same conclusion Stabell does: the precautionary principle cannot apply to harms that are merely 'possible', but only to sufficiently plausible harms. (Also, we argued that the precautionary principle applies only to relatively serious harms, which means that precautions with plausible but mild opportunity costs can be taken consistently.) We agree that the notion of plausibility requires further clarification, for which Stabell proposes interesting directions. We suggest specifying what makes harms plausible in particular domains of application. For example, factors can be identified that increase the plausibility that some emerging disease is infectious and will strike blood product recipients, including the discovery that the causative micro-organism is blood-borne and that donors can be asymptomatically infected. A general account of plausibility may help to clarify when transfusion hazards are plausible, but should be connected to insights that hematology, microbiology, and related disciplines produce and that decision-makers use almost routinely.

Our article illustrated how our approach can be applied to real-life policy-making by discussing the deferral of men who have had sex with men (MSM) as blood donors. This issue is also frequently engaged in the Open Peer Commentaries. Timmermann [10] and Wilson and Atkinson [5] recognize that donor deferral policies can be harmful to health if their being perceived as discriminatory leads to blood shortages. This insight is not new, but our approach allows casting it in a different light: deferral policies that are sufficiently likely to lead to harmful blood shortages may be inconsistent, counterproductive, or disproportionate, in which case the precautionary principle cannot be invoked to support them. This shows that restricting attention to particular types of harm (e.g. transfusion-transmissible infections) at the expense of others (e.g. the availability of blood products in emergencies) misapplies the precautionary principle. Accordingly, the precautionary principle cannot be invoked to brush aside concerns about MSM deferrals, but rather requires frank discussion on how harmful these deferrals are. Without engaging this discussion, our article makes room for critical reflection on MSM deferrals within a precautionary decision-making approach.

Timmermann [10], Vernillo [11], and DeCoster [12] follow this line of thought and broaden the perspective on the harms involved in deferring MSM. Timmermann calls attention to the consequences of eroding MSM's trust in the healthcare system and of setting barriers to the inclusion of MSM in society. DeCoster discusses how MSM deferrals shape the perception (and self-perception) of LGBTQ community members as unclean, dangerous or otherwise

disvalued. We concur with the legitimacy of these authors' perspectives on this issue. What needs to be discussed is what harms are attributable to MSM deferral policies, how serious those harms are, and how this compares to the hazards avoided by such policies. Rather than misusing the precautionary principle to avoid discussing such issues, policy-makers should explicate how their policies balance different harms. Taking any precaution presumes that the harms introduced are less serious than the hazards plausibly averted, and that less harmful adequate precautions were unavailable. Accountability requires explicating and defending this presumption, for example in public education campaigns, as Timmermann proposes.

Interestingly, none of the commentaries challenges our article's main thesis, namely that opportunity costs can be a legitimate reason to tolerate blood transfusion risks. Yet this idea is controversial in decision-making practice [13]. For example, concern about opportunity costs seems absent in the recent FDA decision to screen all donations for Zika virus [14]. Less expensive safety measures were available, such as screening only in areas where mosquito-to-human transmission occurs or testing blood products for at-risk patients only. On our account, one might judge that the current policy is disproportionate because these alternatives would have been adequate. We acknowledge that such judgements are difficult and controversial. More reflection and public deliberation is needed on when to tolerate transfusion risks, and we hope our work encourages such discussion.

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Chapter 7

Are there ethical differences between stopping and not starting blood safety measures?

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ABSTRACT

Concern with the costs of blood safety is growing, which raises the question whether safety measures that reduce risk only marginally should be discontinued. Withdrawing such safety measures would allow reallocating resources to more efficient health care interventions, but it might raise moral objections.

This paper evaluates two ethical arguments why discontinuing blood safety measures would be more objectionable than not implementing them. The first argument is that whereas withdrawing protective measures *causes* harm to patients, not starting protective measures 'merely' *omits to prevent* harm. The second argument is that patients who benefit from protective measures are *historically entitled* to the continuation of those protective measures.

Both arguments are unconvincing. There is only a weak causal connection between removing blood safety measures and harms that transfusion recipients suffer. Moreover, patients are not entitled to the continuation of protective measures that prove very inefficient, unless applying these protective measures rectifies past injustice towards them. Unless stronger ethical objections can be found, blood system operators and regulators should be more willing to withdraw inefficient safety measures.

1. INTRODUCTION

Blood services apply donor selection criteria, blood screening tests, and pathogen reduction processes to protect transfusion recipients against transfusion-transmissible infections. Because no safety measure is 100% effective, stacking safety measures is important for blood safety. Still, some safety measures add little safety (for example because other safety measures already minimize the risks they address) and thus offer little 'value for money'. For example, some blood screening tests are estimated to cost over $1.000.000 per quality-adjusted life-year (QALY) gained; in the Netherlands and the United States this applies to serological testing for human T-cell lymphotropic virus (HTLV), and to nucleic acid testing (NAT) added to serological testing for HIV, hepatitis C and hepatitis B [1-3]. Such tests are controversial because of their high *opportunity costs*: these tests draw resources away from more efficient medical interventions and thus preclude better public health outcomes elsewhere (especially if low cost-effectiveness is matched by high budget impact) [4, 5].

Since the HIV and hepatitis C crises of the 1980s and '90s, efforts to minimize transfusion risks have shown little concern for costs, which has often been defended by appeal to the precautionary principle [6]. In recent years however, concern for the opportunity costs of blood safety measures has increased, culminating in policy-making frameworks in which health economic assessment is a standard step (notably the Alliance of Blood Operators' 'risk-based decision-making' framework) [7, 8]. These frameworks acknowledge the validity of cost concerns in deciding whether to *implement* safety measures. But an important question remains unaddressed: is cost-containment also a valid reason to *discontinue* safety measures?

In practice, blood services are reluctant to discontinue or downscale safety measures with low value for safety but high social or economic costs. For example, while the yield and cost-effectiveness of HIV, hepatitis C, and hepatitis B NAT screening is low in many countries, there seem to be no initiatives to downscale NAT screening. Neither has the questionable relevance of syphilis for contemporary transfusion practice led to relaxed syphilis testing policies [9, 10], or have precautionary deferral policies for donors with Chronic Fatigue Syndrome been recalled after preliminary evidence of transfusion-transmissibility was discredited [11]. Even when safety measures *are* downscaled, the decision-making process and its outcome often portray a very low tolerance for transfusion risks. For example, the permanent rejection of MSM donors has been changed only recently in the Netherlands, the United States and Canada, after sustained public pressure, into temporary deferral that many

still consider unreasonably strict. Likewise, the Netherlands have since July 2013 stopped testing every donation for anti-HTLV, which costed over €40.000.000/QALY gained, but the new policy to test first-time donors still costs over €2.000.000/QALY gained [1, 3].

Discontinuing or downscaling blood safety measures seems even more controversial than not introducing them. For example, U.S. policy-makers opposed relaxing MSM policies if safety would *decrease*, no matter how marginally, but felt no urgency to *increase* safety by switching to 100% supply of single-unit platelets [12]. The asymmetry between stopping and not starting safety measures is stated explicitly in the decision-making rule that "any changes to existing policies (…) must result in an improved or equivalent level of safety by comparison of what now exists" [13: 46, 14]. Taken literally, this rule forbids relaxing safety measures that offer *some* safety, no matter how small, but does not prescribe implementing measures that would improve safety.

Discontinuing safety measures involves particularly challenging issues, including concerns about reputation, liability and compliance with national or international regulations [14, 15]. In addition, decisions to downscale safety measures may evoke stronger negative emotions than decisions not to improve safety, given the general psychological difference between losing and not winning [16]. But how should we evaluate the reluctance to withdraw or relax inefficient safety measures from an *ethical* perspective? Of course, ethical analysis cannot solve all the difficulties surrounding the discontinuation of inefficient blood safety measures. If reputational, legal, and political barriers to withdrawing safety measures persist, no change in policies can be expected. But agreement that there are no ethical differences between stopping and not starting safety measures could be a first step towards more reasonable blood safety policies: it would press us to re-evaluate our legal and regulatory frameworks and to develop communication strategies that minimize political and reputational damage. So far, ethicists and policy-makers have neglected this issue.

The ethical principle of utility, which advocates maximizing well-being in society, arguably supports withdrawing inefficient safety measures. Withdrawing inefficient safety measures allows reallocating funds to more efficient health care interventions, thus securing more health benefits (QALYs) with the same budget [17]. Some arguments against discontinuing inefficient blood safety measures apply equally against not starting them. For example, one might argue that devoting many resources to transfusion recipients is a demand of distributive justice. Theories on distributive justice address what would be an equitable distribution of (health care) resources – for example, 'prioritarianism' requires that the worst-off receive the largest shares.

But these theories are silent on *how* everyone should come to have his fair share [18]. Accordingly, stopping a blood safety measure is as just or unjust as not starting it: the end-result is in both cases that resources are not allocated to blood safety but are directed elsewhere. This paper focuses on arguments why discontinuing safety measures would be *more* objectionable than not introducing them.

Can such arguments be offered? Although the decision-making rule that forbids increasing risk but does not prescribe reducing risk is allegedly "supported (…) by important ethical considerations" [13: 53], a clear statement and defence of those considerations seems to be lacking. In the parallel debate on withdrawing and withholding life-sustaining therapies in intensive care units, relevant ethical concerns have been articulated more clearly. This paper applies two main arguments from this debate to blood safety decisions. The first argument is that whereas withdrawing a protective measure *causes* harm to patients, not starting a protective measure 'merely' *omits to prevent* harm to them. Because the duty not to cause harm (or the principle of non-maleficence) overrides the duty to prevent harm (or the principle of beneficence), withdrawing protective measures from patients to prevent harm to others would be unacceptable, even if more harm would be prevented than caused. We argue, however, that blood services have only limited causal responsibility for harm patients suffer owing to the withdrawal of blood safety measures. According to the second argument, patients benefiting from protective measures are *historically entitled* to the continuation of those measures. We conclude that transfusion recipients are only entitled to the continuation of inefficient blood safety measures if these transfusion recipients were wronged by historical allocation decisions, and if applying inefficient safety measures can be said to rectify this injustice. Unless stronger support can be offered for the supposed asymmetry between stopping and not starting blood safety measures, the decision-rule that "any changes to existing policies (…) must result in an improved or equivalent level of safety" [13: 46, 14] should be reconsidered.

2. FIRST ARGUMENT: "WITHDRAWING SAFETY MEASURES CAUSES HARM, NOT STARTING ALLOWS HARM TO OCCUR"

The first argument is that withdrawing life-sustaining therapies kills (i.e. *causes* the death of) patients and is therefore inherently objectionable, whereas withholding such therapies 'merely' lets patients die [19]. Obviously, withdrawing blood safety measures differs from withdrawing life-sustaining therapies in various respects – for example, transfusion recipients have a

different health status than patients on life-sustaining therapies, they each have only a small chance of suffering harm when protective measures are lifted, and yet they lack reasons to consent with lifting such measures. Nevertheless, the argument that stopping life-sustaining therapy causes the patient's death and is therefore inherently objectionable can be extrapolated to withdrawing blood safety measures: one might argue that withdrawing donor blood safety measures *causes* harm to transfusion recipients, or at least *imposes risks* on them. This would make withdrawing safety measures more objectionable than not implementing them, which would merely *fail to prevent* harm to transfusion recipients by leaving them *exposed* to risks. The argument assumes that transfusion risks will increase (for some patients) when a safety measure is withdrawn, so it does not apply when safety measures add no safety whatsoever. But even if this assumption applies and if one accepts that causing harm is more objectionable than not preventing harm, it remains to be shown that withdrawing a blood safety measure causes and not just fails to prevent harm. Can a criterion be offered on when harm is caused rather than not prevented, and does withdrawing blood safety measures meet this criterion?

Relevant criteria have been proposed in the debate on whether withdrawing life-sustaining therapies kills patients. These criteria are typically based on a counterfactual account of causation: an action causes an event (e.g. someone suffering harm) if that event would not have happened had that action not been performed. Accordingly, causing harm (death or other) by withdrawing some protection requires that the victim would not have suffered that harm had the protection not been withdrawn. Still, additional conditions can be set on how the agent contributes to the fact that the victim suffers harm. A first criterion ('C1', for short) only requires that withdrawing the protection involved acting [20, 21]:

(C1) An agent causes harm to a victim by withdrawing a protection if:
1 The agent withdraws a protection by acting
2 AND the victim suffers harm
3 AND the victim would not have suffered that harm had the agent not withdrawn the protection

The condition that the agent *acts* to withdraw a protection may seem trivial, but it is not. Some protections can be withdrawn by omission (i.e. deliberate inaction) rather than action, in which case C1 implies that the agent does not cause harm to the victim. For example, artificial nutrition can be withdrawn by omitting to replace a depleted dose [22, 23]. Many blood safety measures can in principle be withdrawn similarly. They are typically applied anew for fresh donations: donor eligibility questionnaires must be answered at each visit and most blood tests

are repeated for each donation. These safety measures can thus be discontinued by not applying them to subsequent donations. The high level of automatization in blood services may complicate disrupting safety measures by omission, in particular if safety measures are applied universally rather than selectively. In analogy to stopping artificial nutrition by omission, one option may be to stop restocking testing reagents. One might even stop the replenishment of reagents by omission, namely by not renewing supply contracts when these expire. Of course, such strategies to avoid causal responsibility for harm to transfusion recipients are impractical, and they make sense only insofar as the current argument is taken seriously.

Even if actions are required to withdraw blood safety measures, identifying those actions as *the* cause, rather than just *a* cause, of harm is not straightforward. While one might argue that withdrawing life-sustaining therapy directly effects death [20], withdrawing blood safety measures causes harm only in combination with many other actions: an infected donor must go to a blood service; the blood service must collect his blood; and a physician must administer this blood. Why pick out the withdrawal of safety measures as *the* cause of harm? Doing so assumes that there is something special about withdrawing safety measures, compared to the other necessary causal factors, for example that withdrawing safety is especially problematic from an ethical perspective. But then the claim that withdrawing safety measures causes harm is based on the claim that withdrawing safety measures is ethically unacceptable, rather than the other way around [17].

Anyhow, ethicists agree that C1 does not distinguish between causing and allowing harm in a way that settles any moral issues [20-24]. Whether or not an agent acted to withdraw a protection is insufficient to settle his moral responsibility for the harm victims suffer as a result. In some cases, actively withdrawing a protection may be no worse than omitting to prevent harm. If we want to distinguish impermissibly causing harm from permissibly allowing harm, the agent's causal role in the occurrence of harm should be considered from a broader perspective.

The ethicists McMahan, Foot and McGee argue that it matters whether the agent who withdraws a protection also *provided* that protection [22-24]. If he (or she) did, his withdrawal of the protection merely negates his earlier actions: the net effect of first providing and then withdrawing a protection is equal to not providing it at all. The victim would already have suffered harm had the agent not provided the protection, so it is false that the harm would not have occurred if not for the agent's actions. Viewed from this perspective, a doctor who first

provides and later removes artificial respiration does not cause death but allows the patient's underlying condition to resume its lethal trajectory [22-24]. By lifting a blockade to an ongoing threat (that would already have killed the victim if not for the doctor's actions), the doctor stops preventing death and lets the patient 'die at a delay'. Moreover, as McMahan argues, "if the action is undone by a different person occupying the same role, we regard individual identity as irrelevant" [22: 264, 23]. When an agent withdraws a protection, on this view, it does not matter whether the agent himself had provided the protection or whether his professional predecessor did. But if the agent is neither identical to nor has the professional capacities of the person who provided the protection, which applies for example when someone sneaks into a hospital to remove his enemy's artificial respirator, the agent does cause the victim's death [22, 23].

From an ethical perspective, it may thus matter that blood safety measures are withdrawn by the (official successors of) institutions that decided on their introduction. After withdrawing safety measures, blood system operators and regulators have 'merely' undone their previous actions, for which reason withdrawing blood safety measures can be considered equivalent to never having implemented them at all. This parallels the case of doctors initiating and removing life-sustaining therapies.

One might object here that whereas withdrawing life-sustaining therapies means letting patients die of their underlying conditions, withdrawing blood safety measures means that patients suffer harm caused by the blood service's own actions. After all, these patients would not have been infected had the blood service not supplied infectious donor blood. This objection refers to a second criterion on when withdrawing a safety measure can be taken to cause harm:

(C2) An agent causes harm to a victim by withdrawing a protection if:

1 The agent withdraws a protection by acting

2 AND the victim suffers harm

3 AND the victim would not have suffered that harm had the agent not withdrawn the protection

4. AND the victim would not have suffered that harm had the agents' actions not initiated the threat to the victim.

We have discussed the question whether blood services cause threats to transfusion recipients elsewhere [17]. But while this issue is relevant for the moral acceptability of withdrawing blood safety measures, it is irrelevant for the question whether withdrawing blood safety measures is

more objectionable than not implementing them. If the agent's actions initiated the threat to the victim, then the agent causes harm whether he provides and subsequently removes a protection or omits to provide a protection in the first place. In either case, the victim would not have suffered harm if not for the agent's actions.

A final suggestion, again following the ethicist Jeff McMahan [22], builds on the idea that *reinitiating* threats one has averted can be said to kill victims. McMahan offers a case where a mechanic first seals a pipe leaking lethal gasses and then returns to remove the seal. Even though the victims would already be dead if not for the mechanic's previous actions, it seems difficult to deny that he kills the victims. He does not merely allow but causes the victims' deaths, as he actively reinitiates a threat to their lives. Generalizing from this example, a third criterion stipulates that:

(C3) An agent causes harm to a victim by withdrawing a protection if:
1 The agent withdraws a protection by acting
2 AND the victim suffers harm
3 AND the victim would not have suffered that harm had the agent not withdrawn the protection
4 AND the protection withdrawn was provided by the agent (or his professional predecessor)
5 AND the agent reinitiates the threat to the victim by withdrawing the protection

In a sense, removing safety measures always 'reinitiates' threats, as victims get exposed to threats they were previously shielded from. Presumably, this is psychologically more challenging than not gaining protection from risks one was never protected against. McMahan's example is particular, however, in that the protection removed was 'complete and self-sustaining': no contribution (physical or otherwise) was required to keep it operating [22]. After the seal was installed, the pipe was functioning normally and independently, so removing the seal renewed a threat that had been effectively eliminated. By contrast, life-sustaining therapies do not eliminate the patient's health problems, but merely block their progression into death. Because life-sustaining therapies cannot eliminate the threat to the patient's life in a complete and self-sustaining way, removing such therapies does not reinitiate those threats but ('merely') stops to hold them at bay [22-24].

Removing blood safety measures seems more akin to removing life-sustaining therapies than to removing seals from gas pipes. Blood safety measures must be applied anew for each fresh donation, which each present a new threat to blood product recipients. Although threats found in individual donations are eradicated (and cannot be reinitiated because those donations

are destroyed), preventing the transfusion-transmission of infections through further donations requires the perpetual application of safety measures, which takes effort and consumes resources. Blood safety measures are not 'complete and self-sustaining' and can therefore be withdrawn by ceasing contributions to their continuation (which may or may not require acting). Doing so means no longer shielding blood product recipients during new exposures to hazards, but because blood safety measures do not eliminate threats in a complete and self-sustaining way, there is no question of reinitiating threats. (At least not in the sense that removing seals from gas pipes reinitiates threats.) On the argument under consideration, this limits blood services' causal responsibility for harm that patients may suffer following the withdrawal of safety measures.

To conclude, we have found no strong reasons why withdrawing blood safety measures should be considered *causing* rather than *allowing* harm. Withdrawing blood safety measures need not require acting, and if actions are required, these effect harm only in combination with various other actions. Furthermore, the persons who withdraw blood safety measures merely negate their own actions or those of their professional predecessors. Finally, withdrawing blood safety measures does not reinitiate threats that had been effectively eliminated, but rather stops repetitively shielding blood product recipients during new exposures to hazards. These factors limit blood services' *causal* responsibility for harms that ensue from withdrawing blood safety measures. Thus, even if we assume that there is something particularly objectionable about causing harm, it does not follow that withdrawing safety measures is ethically unacceptable.

3. SECOND ARGUMENT: HISTORICAL ENTITLEMENT TO CONTINUED TREATMENT

Some argue that undergoing treatment entitles patients to continued treatment. The ethicists Sulmasy and Sugarman offer a thought experiment where identical twins, Prima and Secunda, both need artificial respiration [25]. Because only one respirator is available and no medically or morally relevant difference between the twins is found, the doctors toss a coin. Now if Prima wins the toss and artificial respiration is initiated, this fact entitles Prima to continue receiving artificial respiration instead of her sister. Sulmasy and Sugarman support this claim with reference to philosopher Robert Nozick's entitlement theory [18]. According to this theory, someone is entitled to something he holds if the historical processes through which he

acquired it were just – which includes the ways in which the thing was first appropriated by anyone (*justice in acquisition*), the ways in which it was transferred between persons (*justice in transfer*), and the ways in which injustices with regard to its appropriation or transfer were rectified (*justice in rectification*).

Sulmasy and Sugarman fail to show that withdrawing and withholding therapy are inherently different. Withholding care that someone is entitled to through a just procedure is as illegitimate as withdrawing it [26, 27]. For example, if tossing a coin was just, winning the toss already entitled Prima to receive respiration instead of her sister. What is interesting, though, is the suggestion that past allocation procedures can entitle patients to the continuation of care. Could transfusion recipients claim to be entitled to the continuation of inefficient blood safety measures because these were introduced after just procedures?

What a transfer of holdings entitles the recipient to arguably depends on the (explicit or implicit) presuppositions of the transfer [18]. For example, whereas selling an item confers ownership (and thus certain rights) on the recipient, lending it does not. This explains whether it is legitimate to reclaim or redistribute the item without the beneficiary's consent. To evaluate the argument that transfusion recipients are entitled to continue 'holding' the resources that were allocated to blood safety measures, we thus have to consider the presuppositions under which these resources were 'transferred'. If the presupposition was that blood safety measures would be continued even if they would prove inefficient, transfusion recipients have a strong claim against their withdrawal.

Allocation procedures usually seem to presuppose that reallocating resources is legitimate if the original allocation proves ineffective or very inefficient. For example, there is no legitimate expectation that physicians will continue futile treatments or treatments that deplete scarce resources (such as blood products) for a single patient's benefit [19, 28]. Even though physicians take up a special obligation towards patients they start treating, which may exclude reallocating treatments to prospective patients for whom treatment would be somewhat more beneficial, it does not follow that their patients may expect the unlimited continuation of ineffective or inefficient care. Arguably, this is because continuing very inefficient treatments could make treatment inaccessible for patients with reasonable prospects of benefitting, which would conflict with physicians' obligations towards society at large [19, 29]. Deciding that resources should be reallocated to benefit other patients may be problematic at the bedside, but on a higher policy level (such as hospital or a ministry of health) such decisions are inevitable [30, 31].

There may be different expectations for blood safety. Since the AIDS and hepatitis C crises in the 1980s and 1990s, some blood services have found themselves forced to regain public trust by implementing safety measures aimed at 'maximum safety'. Their rhetoric frequently suggested that costs are unimportant and, one might argue, have raised the expectation that all safety measures will be continued irrespective of costs. Even so, it does not follow that this expectation is legitimate, and hence that blood recipients are entitled to continuation of these safety measures. To the contrary, given that health care funds are public resources, on which every citizen who needs health care has some claim, the number of people benefitted is always relevant (albeit not necessarily decisive). Because interventions may prove beneficial to fewer citizens than expected, the allocation of health care funds cannot reasonably exclude the possibility of reallocation.

Thus far, we have considered whether blood product recipients are entitled to the continuation of inefficient blood safety measures in virtue of *justice in transfer*, but the argument may be stronger if *justice in rectification* is considered. According to judicial inquiries in the 1990s, blood system operators and regulators should have allocated more resources to blood safety when AIDS and hepatitis C emerged [32, 33]. There may be an ethical 'duty of reparation' [34] towards victims of (avoidable) transfusion-transmitted HIV and hepatitis C, for example by giving them priority access to curative treatments and compensating their financial losses. It seems difficult, however, to justify the continued application of inefficient safety measures by referring to a duty of reparation. Blood safety measures do not remove or alleviate the suffering of patients suffering from transfusion-transmissible infections, but primarily benefit patients who have *not* been harmed. (At most, they reduce the risk that surviving victims of transfusion-transmitted HIV and hepatitis C contract dangerous co-infections when they need additional blood products.)

Perhaps maintaining inefficient safety measures rectifies injustice in a different sense: perhaps today's low tolerance for transfusion risks is just because it offsets having tolerated too much risk during the 1980s and 1990s. Viewed from a resource perspective, transfusion recipients could claim to be entitled to see many resources allocated to blood safety because too few resources were devoted to their safety earlier. Accordingly, they could claim that it was legitimate to expect the continuation of safety measures even if these would prove inefficient.

Even if justice in rectification is taken into account, there must be a limit to continuing inefficient safety measures. Devoting many resources to blood safety only rectifies injustice if any blood product recipients who were wronged (but not necessarily harmed) during the 1980s

and 1990s remain. Blood product recipients that were not themselves wronged by historical allocation decisions cannot claim to be entitled to rectification. Moreover, as Nozick argues, rectifying an injustice by redistributing holdings is itself unjust if the person whose holdings are redistributed ends up with less than he is entitled to [18]. In our case, rectification takes place by allocating collective health care resources to interventions that benefit a particular group of people, namely transfusion recipients. If injustice towards them has been sufficiently rectified, transfusion recipients are no longer entitled to the resources consumed by inefficient blood safety measures; other people may be entitled to benefit from those resources. To what extent historical allocation decisions have wronged transfusion recipients and to what extent these wrongs have been rectified should be assessed country by country. In many cases, rectifying injustice will require offering additional medical and financial support to (the families of) victims of transfusion-transmitted HIV and hepatitis C, rather than maintaining safety measures that barely benefit them.

In conclusion, there is some force in the argument that past injustice entitles blood product recipients to the continuation of blood safety measures that fail to meet general cost-effectiveness standards. But it does not follow that such safety measures should be continued indefinitely. While the rhetoric of the 'paramountcy of safety' has suggested that blood safety measures need not be cost-effective, it is difficult to see how it can be legitimate to expect the indefinite continuation of very inefficient blood safety measures. Past injustice must be considered rectified at some point, depending on the specifics of the past injustice and on the rectification that has taken place.

4. CONCLUSION AND DISCUSSION

We evaluated, and ultimately rejected, two arguments for the claim that discontinuing (inefficient) blood safety measures is more objectionable than not introducing them. The argument that withdrawing blood safety measures causes rather than allows harm to patients was found unconvincing. The argument that transfusion recipients are historically entitled to the continuation of blood safety measures seemed stronger, but only insofar as this historical entitlement derives from past injustice that has not yet been sufficiently rectified. We conclude that unless stronger arguments can be found, the supposed asymmetry between stopping and not starting blood safety measures is ill-supported.

Stopping safety measures may sometimes even be less objectionable than deciding not to start them [29, 31]. Safety measures may become redundant when other safety measures are introduced (e.g. HBsAg screening after the introduction of screening for HBV-DNA and HBcore antibodies), or become less important because effective cures against transfusion-transmissible infections are developed (e.g. penicilin against syphilis, modern antivirals which rapidly cure chronic hepatitis C). In addition, precautions against poorly understood hazards may prove unnecessary or ineffective (e.g. deferral of donors with Chronic Fatigue Syndrome). When deciding whether to implement precautions, it is often uncertain whether taking precautions is necessary to avoid harm and, if so, which precautions will be effective. But if there is evidence that precautions could be necessary and effective, deciding not to implement them seems harder to justify than deciding to withdraw safety measures that have proven to add little safety. (Although there are also some constraints to observe when implementing precautions, see [6].)

Applying safety measures for a limited period can close (some) knowledge gaps concerning these safety measures' necessity and effectiveness. Transfusion recipients are then protected on a precautionary basis, but the intention should be to continue only safety measures that prove effective and reasonably efficient. (Leukocyte depletion might fit this description: once implemented as an expensive precaution against the possibility that variant Creutzfeldt-Jakob disease [vCJD] would transmit through blood transfusion, evidence that vCJD is transfusion-transmissible has strengthened and additional advantages of leukocyte depletion have emerged.) By announcing periodic review in advance, decision-makers can counter expectations that safety measures will be continued even if they prove inefficient.

This promising approach is unavailable when obstacles to withdrawing safety measures persist. Paradoxically, this may have negative consequences for both the efficiency and the safety of the blood supply: being unable to withdraw safety measures may raise the threshold for decision-makers to implement them at all [19, 31]. For example, developing pathogen reduction technologies for labile blood products seems unappealing if downscaling current safety measures is out of the question. Being prepared to withdraw safety measures that prove inefficient allows applying the precautionary principle more flexibly and paves the way for a more cost-effective blood supply.

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Chapter 8:

Summary

Blood services apply various safety measures to prevent the transmission of infections through blood transfusion, some of which have very high cost-effectiveness ratios (over €1.000.000 per quality-adjusted life-year saved). This dissertation considers whether it is ethically acceptable to apply such inefficient safety measures. From a utilitarian perspective, these safety measures should be forgone: they consume resources that could probably be used more beneficially elsewhere in the healthcare system, thus saving more (quality-adjusted) life-years. Are there good ethical arguments to apply inefficient blood safety measures nonetheless?

Part I presents qualitative empirical research that aimed to identify such arguments. Our analysis of policy documents, on which we report in chapter 2, reveals that a broad set of concerns shaped decision-making on expensive blood safety measures. Policy-makers did not only balance safety versus costs, but also considered supply, operational feasibility, consistency, and legal, political, and ethical issues. Policy-makers invoked principles on how to prioritize safety versus costs, but these principles differed widely: some principles declared safety paramount and declared costs unimportant, others allowed trade-offs between costs and safety. Cost considerations were thus balanced against safety concerns in diverse ways, and were weighed against various other concerns.

Chapter 3 presents possible arguments for assigning a higher or lower priority to safety, 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. Various respondents concurred with the ethical premise of the utilitarian perspective: they would limit expenditures on blood safety measures if doing so would allow helping more people elsewhere in the healthcare system. Some respondents doubted economic assumptions behind the utilitarian argument: given the small budget impact of blood safety measures and the possibility to cut other budgets, funding inefficient blood safety measures would not exclude funding more efficient healthcare interventions. We also found arguments that might override the utilitarian argument. Some of these arguments suggest directions for future research (see the Discussion of this dissertation).

Part II evaluates ethical arguments why blood safety measures should be applied even if they are inefficient (and more lives or QALYs could be saved by not applying them). Chapter 4 draws three arguments from ethical literature: 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 healthcare 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. While these arguments may be sensible in general, they prove unconvincing when applied to blood safety. The 'rule of rescue' argument fails because inefficient blood safety measures do not save individuals who are identifiable in advance; persons who need blood products may be identifiable, but persons who will get infected are not. The 'risk imposition' argument is unpersuasive because the claim that blood services impose risks on patients (and do not merely leave patients *exposed* to risk) presupposes that they should have taken stricter safety measures, which begs the question. Finally, the 'manufacturing standard argument' applies poorly to publicly funded institutions: while forgoing safety measures in private pharmaceutical firms has no public benefit, cutting budgets in blood services allows funding other public goods.

Chapter 5 addresses the precautionary principle. While the precautionary principle is often invoked to defend strict blood safety policies, we observe that its definition and its role in policy-making are contested. We identify three constraints which any version of the precautionary principle should heed: *consistency* forbids prescribing 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. Chapter 5 then argues that blood safety measures can be inconsistent, counterproductive, or disproportional in virtue of their (opportunity) costs. Acceptable versions of the precautionary principle must thus tolerate some risks, potentially even to save costs.

Chapter 6 discusses a number of published commentaries on our account of the precautionary principle. 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, evaluates arguments for the view that discontinuing inefficient blood safety measures is more objectionable than not introducing them. We reject the argument that stopping safety measures *causes* harm and not starting safety measures *omits to prevent* harm. We apply three criteria for when removing a protection causes harm, none of

which clearly support the view that withdrawing blood safety measures means causing harm. It may be possible to withdraw blood safety measures without acting, and if actions are required, these are insufficient for harm to occur. Furthermore, persons who withdraw blood safety measures merely undo their own actions (or those of their professional predecessors). Finally, withdrawing blood safety measures does not reinitiate threats that had been eliminated, but omits to shield transfusion recipients from new exposures to danger. The argument that transfusion recipients are historically entitled to the continuation of blood safety measures seems stronger, but only insofar as continuing these safety measures rectifies past injustice towards transfusion recipients.

In sum, there seem to be no persuasive arguments that override the utilitarian argument, that is, no good reasons to fund inefficient blood safety measures if funding other health care interventions saves more lives (or QALYs).

Chapter 9:

Samenvatting

Bloedbanken passen allerlei veiligheidsmaatregelen toe om te voorkomen dat bloedtransfusies infectieziekten overdragen, waarvan sommige een hoge kosteneffectiviteitsratio hebben (meer dan €1.000.000 per goed levensjaar dat ermee gewonnen wordt). Deze dissertatie beschouwt of het uitvoeren van zulke inefficiënte bloedveiligheidsmaatregelen ethisch aanvaardbaar is. Vanuit utilistisch perspectief zouden zulke veiligheidsmaatregelen achterwege gelaten moeten worden: ze kosten publiek geld dat elders in de gezondheidszorg nuttiger besteed zou kunnen worden, waardoor waarschijnlijk meer levens (of goede levensjaren) gered zouden kunnen worden. Zijn er desondanks goede ethische argumenten om inefficiënte bloedveiligheidsmaatregelen uit te voeren?

Deel I presenteert kwalitatief empirisch onderzoek dat dergelijke argumenten beoogt te ontdekken. Onze analyse van beleidsdocumenten, waarvan hoofdstuk 2 verslag doet, laat zien dat beleid betreffende dure bloedveiligheidsmaatregelen op een brede verzameling aan overwegingen wordt gebaseerd. Beleidsmakers wogen niet alleen veiligheid en kosten tegen elkaar af, maar beschouwden ook de beschikbaarheid van donorbloed, de operationele implicaties en de consistentie van veiligheidsmaatregelen, en juridische, politieke en ethische kwesties. Beleidsmakers beriepen zich op principes over hoe veiligheid en kosten onderling geprioriteerd moeten worden, maar deze principes verschilden sterk: sommige principes stelden veiligheid strikt boven kosten, andere stonden toe dat veiligheid en kosten tegen elkaar werden afgewogen. Kostenoverwegingen werden dus op verschillende manieren tegen veiligheid afgewogen, en werden met verscheidene andere overwegingen geconfronteerd.

Hoofdstuk 3 biedt mogelijke argumenten om veiligheid van bloedproducten een hogere of lagere prioriteit te geven, gebaseerd op interviews en groepsdiscussies met belanghebbenden in de Nederlandse bloedvoorziening. Geopperde argumenten beriepen zich op de klinische relevantie, de waarschijnlijkheid, en de vermijdbaarheid van de overdracht van infecties middels bloedtransfusie, op de gezondheidsbaten, de kosten, en verscheidene andere gevolgen van het nemen van veiligheidsmaatregelen, op niet-consequentialistische ethische overwegingen, en op de belangen van betrokkenen. Verscheidene belanghebbenden stemden in met het utilistische uitgangspunt: ze zouden uitgaven aan bloedveiligheidsmaatregelen beperken als daardoor elders in de gezondheidszorg meer mensen geholpen zouden kunnen worden. Sommige respondenten betwijfelden echter de economische aannames achter het utilistische argument: gegeven de beperkte absolute kosten van bloedveiligheidsmaatregelen en gegeven de mogelijkheid om andere besparingen door te voeren, zou het uitvoeren van inefficiënte bloedveiligheidsmaatregelen niet uitsluiten dat efficiëntere zorgvoorzieningen ook

verstrekt worden. We vonden ook argumenten die het utilistische perspectief zouden overtreffen, waarvan enkele richting kunnen geven aan toekomstig onderzoek.

Deel II evalueert ethische argumenten waarom zelfs inefficiënte bloedveiligheids-maatregelen uitgevoerd zouden moeten worden (zelfs als meer levens of goede levensjaren gewonnen zouden kunnen worden door ze achterwege te laten). Hoofdstuk 4 put drie argumenten uit ethische literatuur: het 'argument van de reddingsoperatie-norm', volgens welke het redden van identificeerbare personen het toepassen van inefficiënte maatregelen rechtvaardigt; het 'argument van risico-oplegging', volgens welke efficiëntie-eisen niet moeten gelden voor veiligheidsmaatregelen tegen risico's die door medisch ingrijpen worden veroorzaakt; en het 'argument van de productie-standaard', volgens welke efficiëntie-eisen niet moeten gelden voor maatregelen tegen verontreinigingen in medische fabricaten. Hoewel deze argumenten algemeen gesproken redelijk zijn, is hun toepassing op bloedveiligheid niet overtuigend. Het 'argument van de reddingsoperatie-norm' faalt omdat inefficiënte bloedveiligheidsmaatregelen geen personen redden die op voorhand te identificeren zijn: personen die bloedproducten nodig hebben zijn misschien identificeerbaar, maar de personen die daardoor een infectie zullen oplopen niet. Het 'argument van risico-oplegging' is problematisch omdat de bewering dat bloedbanken ontvangers van bloedproducten risico's opleggen (en niet slechts verzuimen risico's weg te nemen) aanneemt wat het zou moeten bewijzen, namelijk dat bloedbanken onvoldoende veiligheidsmaatregelen nemen. Het 'argument van de productie-standaard' gaat niet goed op voor publiek gefinancierde instellingen: waar het achterwege laten van veiligheidsmaatregelen in de private farmaceutische industrie geen publiek belang dient, maken kostenbesparingen in bloedbanken financieringen in andere publieke goederen mogelijk.

Hoofdstuk 5 betreft het voorzorgsbeginsel. Hoewel het voorzorgsbeginsel vaak wordt aangehaald om strikte bloedveiligheidsmaatregelen te verdedigen, blijkt het voorzorgsbeginsel een omstreden status in beleid en een omstreden definitie te hebben. We identificeren drie randvoorwaarden waaraan iedere versie of toepassing van het beginsel moet voldoen: *consistentie* verbiedt het nemen van maatregelen die volgens het beginsel zelf onaanvaardbaar risicovol zijn; *contraproductiviteit voorkomen* verbiedt het nemen van maatregelen die meer schade doen dan ze voorkomen; en *proportionaliteit* verbiedt het nemen van voorzorgsmaatregelen die meer schade doen dan andere adequate maatregelen zouden doen. Hoofdstuk 5 betoogt vervolgens dat bloedveiligheidsmaatregelen inconsistent, contraproductief, of buitenproportioneel kunnen zijn op basis van hun (opportuniteits)kosten. Bij een aanvaardbaar begrip van het

voorzorgsbeginsel moet enkele risico's worden getolereerd, in potentie zelfs om kosten te besparen.

Hoofdstuk 6 bespreekt een aantal gepubliceerde commentaren op onze beschouwing van het voorzorgsbeginsel. Sommige van deze commentaren betreffen onze interpretatie van het beginsel, andere passen onze beschouwing toe op de vraag of mannen-die-seks-hebben-met-mannen (MSM) als bloeddonoren geweerd moeten worden. Echter, geen van de commentaren weerlegt onze centrale stelling: hoge (opportuniteits)kosten van voorzorgsmaatregelen kunnen een legitieme reden zijn om risico's van bloedproducten te tolereren.

Het laatste hoofdstuk, hoofdstuk 7, evalueert twee argumenten voor het idee dat het beëindigen van inefficiënte bloedveiligheidsmaatregelen bezwaarlijker is dan het niet starten ervan. We verwerpen het argument dat het beëindigen van bloedveiligheidsmaatregelen schade *veroorzaakt* terwijl het niet starten ervan schade *verzuimt te voorkomen*. We passen drie criteria toe voor wanneer het verwijderen van bescherming schade veroorzaakt, maar aan geen van deze criteria wordt bij het verwijderen van bloedveiligheidsmaatregelen evident voldaan. Het beëindigen van bloedveiligheidsmaatregelen hoeft geen handelen te vereisen, en als er handelingen nodig zijn, zijn dit slechts enkele van alle handelingen waaruit schade voortvloeit. Verder maken de personen die bloedveiligheidsmaatregelen beëindigen slechts hun eerdere handelingen (of die van hun voorgangers) ongedaan. Tot slot betekent het stoppen van bloedveiligheidsmaatregelen niet dat gevaren die geëlimineerd waren opnieuw ontketend worden, maar verzuimt men te interveniëren wanneer patiënten opnieuw aan gevaar worden blootgesteld. Het argument dat ontvangers van bloedproducten een historisch recht hebben verworven op de voortzetting van inefficiënte veiligheidsmaatregelen lijkt sterker, maar alleen voor zover het continueren van deze veiligheidsmaatregelen een onrechtvaardigheid uit het verleden rechttrekt.

Samenvattend lijken er geen overtuigende argumenten te zijn die het utilistische argument overtroeven, dat wil zeggen, geen goede redenen om inefficiënte bloedveiligheidsmaatregelen te financieren als er met alternatieve financieringen in de gezondheidszorg meer levens (of goede levensjaren) gered kunnen worden.

Chapter 10:

General Discussion

Since the emergence of AIDS and hepatitis C in the 1980s and 1990s, blood services have implemented numerous safety measures against the transmission of infectious diseases through blood transfusion and blood products. Cost-effectiveness analyses have concluded that some safety measures cost over €1.000.000 per quality-adjusted life-year (QALY) saved, while live-saving medical interventions are usually expected to cost well under €100.000 per QALY. Yet the occasional introduction of cost-ineffective (or 'inefficient', for ease of exposition) safety measures continues, and the termination or relaxation of inefficient safety measures is rare.

From a utilitarian perspective, applying blood safety measures with very high cost-effectiveness ratios seems unethical. Such inefficient blood safety measures consume funds that could probably be used more beneficially elsewhere in health care. If so, more QALYs could be saved by forgoing inefficient blood safety measures than by applying them. This dissertation did not evaluate the utilitarian argument as such, which would have required extensive economic analyses that were beyond our expertise. Instead, this dissertation sought to identify and evaluate ethical arguments that would override the utilitarian argument, i.e. reasons to apply inefficient blood safety measures even if directing funds elsewhere would save more QALYs. Compelling arguments were not found, from which we (tentatively) conclude that blood safety policies should be more efficient.

In what follows, we offer recommendations for policy-making, reflect on the strengths and limitations of our research methodology, and propose directions for future research.

RECOMMENDATIONS FOR BLOOD SAFETY POLICY-MAKING

Our analysis has some implications for blood safety policy-making. We recommend as follows:

- Policy-makers should explicitly address the cost-effectiveness and the opportunity costs of blood safety measures. Other stakeholders, including recipients of blood products, seem sensitive to the utilitarian argument that blood safety measures should not be applied if more lives or QALYs could be saved by funding different healthcare interventions. It may not be true that funding inefficient (i.e. not cost-effective) blood safety measures by itself excludes funding more efficient healthcare interventions. Policy-makers should then consider whether there is a collective responsibility for efficiency in healthcare and consider what this entails for blood safety. (See chapter 3.)
- Policy-makers should use precautionary arguments with care: they should avoid introducing inconsistent, counterproductive, or disproportionate precautions. They

should hence consider to what extent precautions may themselves be harmful, where 'harm' should be interpreted broadly. This excludes extreme risk intolerance, but may allow moderately risk-averse policies. (See chapters 5 and 6.)

- Policy-makers should be more prepared to withdraw safety measures that have proven to be very inefficient. (See chapter 7.)
- Policy-makers should explicitly counter any expectations that inefficient safety measures will be continued. They should make clear that the efficiency of safety measures will be evaluated and that inefficient safety measures may be terminated. Policy-makers may even introduce safety measures for a fixed term, and announce that this term will only be extended if the safety measures prove to be sufficiently cost-effective. This means safety measures can be ended (relatively) passively, while prolonging them requires an active decision. (See chapter 7.)
- Policy-makers should engage stakeholders in deliberation about reasonable blood safety, including the framing of policy-making problems. Our qualitative research revealed that some recipients of blood products were more concerned about the well-being of their families than about their own health. Discussing such concerns may open up different policy options, e.g. ensuring practical and financial assistance for victims of transfusion-transmissible infections rather than taking inefficient safety measures. (See chapter 3.)

METHODOLOGICAL REFLECTIONS

The two parts of this dissertation followed distinct but complementary methodologies. Part I used qualitative empirical research methods to chart policy-making issues and stakeholder views regarding inefficient blood safety measures. Chapter 2 sketched a broad background for the ethical analyses in part II. Connecting to actual policy decision-making served to identify concerns that might be ethically relevant and may, conversely, help to translate ethical insights into practice. To be sure, some policy-making concerns fell outside of our ethical scope (e.g. legal and political issues). Chapter 2 thus revealed limitations of our perspective and identified perspectives with which it might clash. The second empirical study, presented in chapter 3, was in fact completed later than our ethical chapters were. In this way, it served to establish whether our ethical analyses addressed the most pressing arguments against efficiency in blood safety, or whether we had overlooked prominent perspectives. Our respondents formulated some of the arguments we had derived from ethical literature, including the 'imposed risk'

argument (chapter 4) and arguments for the view that stopping blood safety measures is particularly objectionable (chapter 7). Chapter 3 also analysed some arguments part II did not address, although this analysis was tentative and primarily served to explore conceptual resources by which stakeholder arguments may be related to ethical theory.

Our analyses in part I were (primarily) 'bottom up': we first identified relevant passages in our materials, which we then gave initial labels, clustered according to content, and captured under increasingly general categories. This resulted in comprehensive taxonomies of policy-making issues and stakeholder views. The analysis was also (largely) 'pre-theoretical': by bracketing preconceived ideas on what matters in blood safety, we strived to be open to new perspectives in our materials. It is well-recognized, however, that interpretation cannot avoid all preconceptions. According to philosophical hermeneutics, interpreting texts (or other meaning-bearers) requires interpreting their constituent parts, which in turn requires a conception of the text as a whole. Having some preconceptions regarding the object of interpretation is thus necessary for interpretation to get off the ground. In our case, knowledge of ethical concepts and theories may have affected our interpretation of policy-making concerns and stakeholder views. To remain receptive to perspectives that are poorly captured in ethical theory, our initial analysis of policy-documents and stakeholder utterances tried to stay clear of ethical terminology (that did not occur in our materials). Integrating views on blood safety with ethical theory, where applicable, was considered legitimate in the later stages of our analyses. We therefore allowed ethical labels for general categories of policy-making concerns and stakeholder views, provided that these labels unified the categories better than non-ethical labels did. We ensured transparency by showing which particular policy-making concerns and stakeholder utterances were clustered under which general headings. Our analysis may not have been completely 'bottom up' and 'pre-theoretical', as it did connect some data to ethical theory, but it avoided squeezing all data into pre-existing theoretical frameworks.

Part II applied ethical principles to blood safety. The main question was whether these could override the utilitarian argument: whether they provided reasons to fund inefficient blood safety measures even if funding different health care interventions would save more lives (or QALYs). The ethical principles we applied have been invoked to override efficiency considerations, whether in blood safety policy-making (e.g. the precautionary principle) or in other domains (e.g. the rule of rescue). Typically, our strategy was not to question general principles, which would have required abstract ethical theorizing, but to consider how well they applied to blood safety. Applying ethical principles does not consist in checking whether

certain conditions apply (or 'ticking boxes'), but requires interpretation [e.g. 1,2]. For example, the ethical principle of non-maleficence forbids causing harm to someone, but does this include performing medical procedures with adverse side-effects? Does it forbid taking small chances that someone will be harmed? Such questions are not answered by the principles themselves: there is a conceptual gap between general ethical principles and particular moral issues. Bridging this gap means adding something to ethical theory: the principles receive a more specific interpretation, which is sensitive to the context of application [2]. Part II of this dissertation built various conceptual bridges between ethical theory and blood safety issues, for example between causing harm and withdrawing blood safety measures (chapter 7) and between harm and the costs of safety measures (chapter 5). Making ethical principles applicable to specific issues requires not just conceptual analysis, but also normative analysis: plausible interpretations of ethical principles must have acceptable ethical implications. Our ethical analyses built on this idea in two interlocking ways. First, we evaluated interpretations of ethical principles that might support inefficient blood safety policies by considering their implications. This led us to reject some interpretations of principles. We dismissed the interpretation of the precautionary principle as a call for 'zero risk', for example, because the precautionary principle would on this interpretation require stopping many beneficial activities (or even daily life). Second, we considered whether plausible interpretations of ethical principles supported inefficient blood safety policies. This was our argumentative strategy when we applied the rule of rescue and the norm not to impose risks on others (chapter 4): we argued that if these ethical rules are interpreted plausibly, they do not support ignoring cost-effectiveness thresholds in blood safety. These two argumentative strategies came together, for example, in our discussion of the precautionary principle. We rejected extremely risk intolerant interpretations of the precautionary principle by appeal to their implications, set constraints for plausible interpretations of the precautionary principle, and argued that these constraints excluded ignoring the costs of blood safety measures.

In sum, our analysis combined 'bottom up' and 'top down' research strategies: part I worked up from views on specific blood safety issues to more general ethical views, and part II set out to bridge the gap from the other side. Following reflective equilibrium theory, different levels of theorizing support each other insofar as they 'cohere' or 'fit' as a whole [2-4]. Views on specific moral issues can be supported or undercut by ethical principles, but the converse also holds: ethical principles gain or lose credibility insofar as they fit well-informed moral views. As explained, an intermediate level of theorizing may be required to connect the more

abstract and the more concrete levels. This intermediate level of theorizing involves the specification of ethical principles (which are thus both general and flexible): to show how these can be plausibly interpreted in (a range of) specific contexts [2]. The coherence between these different parts justifies the whole, which in turn justifies each part [2-4].

The question whether applying inefficient blood safety measures is ethical thus requires a comprehensive treatment. The conclusion will not follow deductively from indubitable premises, but must cohere with a plurality of ethical considerations and perspectives. Which conclusion fits best is in the end a matter of judgment [cf. 5,6]. This judgment is always provisional: it should be open to revision, for example when new considerations surface.

In that regard, it is important to consider the dialectical context in which this thesis was written. Policy-makers and scholars have expressed unease with the escalating costs of blood safety and with the decision-making principles that motivated safety policies (e.g. the precautionary principle). They have performed health economic evaluations of blood safety measures, have formulated utilitarian considerations to heed efficiency [e.g. 7], and have developed more cost-sensitive decision-making approaches [8, 9]. But as far as we know, this dissertation constitutes the first comprehensive attempt to identify arguments for allowing inefficient blood safety measures and to evaluate such arguments from an ethical perspective. The conclusions of our work, and the recommendations we made, should therefore not be received as final or decisive. Yet we do think our work alters the dialectical situation. For example, chapter 5 criticized unreflective appeals to the precautionary principle, and chapter 7 problematized the view that terminating blood safety measures is more objectionable than not starting them. Our arguments arguably change the burden of proof: a stronger justification is demanded for the implementation and continuation of inefficient blood safety measures. Unless better reasons to apply inefficient blood safety measures are spelled out, current blood safety policies seem to lack an ethical foundation. Future research may take up this challenge by addressing issues that were set aside in this dissertation.

DIRECTIONS FOR FUTURE RESEARCH

There have been few attempts to integrate ethical theory and thinking about blood safety, and we could treat only a selection of all relevant issues and perspectives in detail. Ethical approaches that we ignored may apply to blood safety, and some stakeholder views or policy-making concerns deserve a more thorough ethical analysis.

Possibly relevant ethical approaches are theories of justice (e.g. prioritarianism) as applied to health care, rights-based and contract-based approaches, and care ethics. We will not explore these approaches here, but only note that ethical theory still has various resources that can be applied to blood safety. We hope other scholars will continue this work.

There are also more specific issues that require further theorizing. In chapters 2 and 3, we found that being consistent was an important concern for policy-makers. Safety policies were expected to be consistent among each other, to be consistent across time, and to be consistent across geographical regions. Even if we focus at applying a single safety measure at a single time, the question remains what it means to be consistent and why this is important. Perhaps consistency means applying a safety measure in exactly the same manner across different regions, product types, and patient groups. For example, nucleic acid testing on Zika-virus might follow the same parameters for all donations across the country. Being consistent in this way has operational advantages and may be considered just, as all transfusion recipients are treated equally. However, an undifferentiated application of safety measures will not even out differences in the risks patients face (which may derive from factors like geographical location and medical condition). Moreover, safety measures that are efficient (or cost-effective) in high-risk contexts may be inefficient when extended to low-risk contexts. Can consistency be conceptualized differently, in a way that harmonizes operational concerns, justice, and efficiency?

Another important issue is trust. Chapter 3 presented some arguments for risk intolerance that appealed to trust: it was considered important that blood product recipients, physicians, and the general public maintain trust in the safety of blood products. What this trust amounts to requires further attention. Trusting that blood products will never transmit infections seems unrealistic; this expectation cannot be met and should not be fostered. Trusting that blood services will ensure 'maximum' safety by taking every possible safety measure also seems unrealistic. Strictly speaking, there may not be a maximum to safety, or an end to the safety measures that could be applied: further donor screening questions, blood tests, and pathogen inactivation procedures may be developed, safety procedures can be repeated for enhanced effectivity, larger volumes of blood can be tested, etcetera. In addition, blood services may be trusted to use public resources responsibly, which excludes taking unreasonably inefficient safety measures. Future research should consider what blood services are actually trusted to do, and what they can reasonably be trusted to do. Such inquiries should recognize that trust may be indeterminate or open-ended. Trusting someone does not involve prescribing what he

ought to do in every conceivable situation, which is impossible. The person (or institution) trusted must use his 'power of discretion': he must interpret new situations and judge how he should discharge his responsibilities [8]. Thus, further research should not only address which safety decisions blood services are expected to take, but also which decisions are left to their discretion.

Finally, some economic assumptions behind the utilitarian argument against funding inefficient blood safety measures require scrutiny. Some stakeholders in the Dutch blood supply argued that applying inefficient blood safety measures does not exclude funding more efficient health care interventions, given the low budget impact of blood safety measures and given the possibility to cut other costs within blood services. The utilitarian argument could be defended by showing that not taking inefficient blood safety measures is necessary and sufficient to reap more substantial health benefits. Perhaps, though, it suffices to show that inefficient health care interventions collectively have suboptimal outcomes, and to establish a collective responsibility for efficiency in health care.

CONCLUSIONS

We found no strong arguments to fund inefficient blood safety measures if funding alternative health care interventions saves more lives (or QALYs). It does not follow that only safety measures costing under €100.000 per QALY, or some other suggested threshold, should be introduced or continued. Safety decisions must balance a variety of concerns and there may be ethical considerations we have not addressed. However, it seems reasonable to demand a clearer justification for applying extremely inefficient safety measures, like those costing over €1.000.000 per QALY. Unless such a justification is forthcoming, public money should be spent more efficiently.

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Chapter 11:

Addendum

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Kramer K, Zaaijer HL, Verweij MF (2017). The Precautionary Principle and the Tolerability of Blood Transfusion Risks. *The American Journal of Bioethics* 17:32-43.

Kramer K, Zaaijer HL, Verweij MF (2017). Interpreting and Applying the Precautionary Principle: A Response to Open Peer Commentaries on "The Precautionary Principle and the Tolerability of Blood Transfusion Risks. *The American Journal of Bioethics* 17:W4-W6.

Kramer K, Verweij MF, Zaaijer HL (2017). Are there ethical differences between stopping and not starting blood safety measures? *Vox Sanguinis* 112:417–424.

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'Philosophy of Risk'	Dutch Research School of Philosophy (OZSW)	2015
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Biannual conference	International Association of Bioethics (IAB)	2016
Annual conference	Dutch Research School of Philosophy (OZSW)	2016
	Oral presentations	
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'How Safe Should Donor Blood Be?'	Research colloquium, department of Research, Sanquin Blood Supply Foundation	2015
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CURRICULUM VITAE

Koen Kramer was born on the 24th of August in 1984. At the age of four, he moved from his place of birth, Alkmaar, to the nearby village of Limmen, where he would spend the rest of his childhood. After graduating for his VWO, he studied Communication and Information Sciences (bachelor) and Philosophy (bachelor *cum laude* and master *cum laude*) at VU University in Amsterdam. Just after completing his studies in August 2010, he was hired as a replacement teacher of philosophy at a secondary school, OSG West-Friesland in Hoorn, where he worked until mid 2012. Subsequently, he taught seminars in practical and theoretical philosophy at the University of Amsterdam, where he had been involved in ethics education for Dentistry students since September 2011. He started his PhD thesis at Sanquin Blood Supply Foundation and Wageningen University and Research in September 2013.

Koen currently lives in Amersfoort with his wife Kirsten, who is an occupational therapist, and his infant daughter, Lotte.