How safe should donor blood be?

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Chapter 2:

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

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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

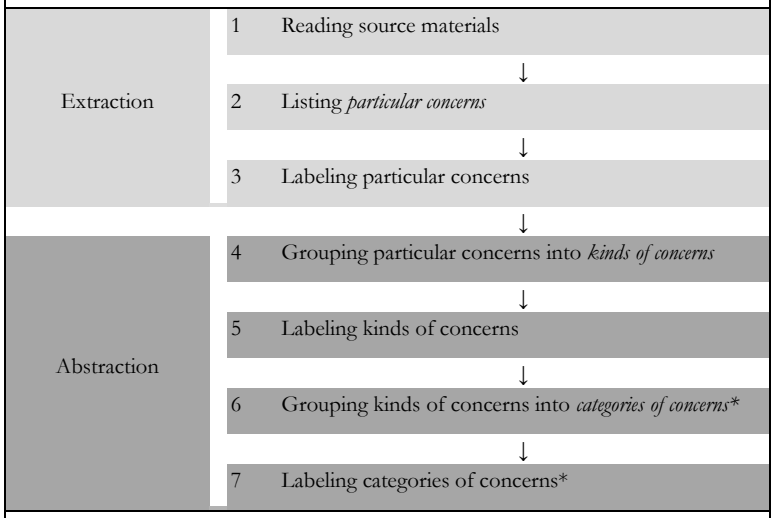
We explored each country's policy-making context via open interviews with key officials from regulatory agencies, blood banks, and advisory committees. These interviews facilitated the selection of appropriate materials for further analysis and provided a meaningful background to interpret those materials 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.