How safe should donor blood be?

Kramer, K.

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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.

REFERENCES

1. United Nations Environment Programme (UNEP) (1992). *Rio declaration on environment and development*. Available from: http://www.unep.org/documents.multilingual/default.asp?documentid=78&articleid=1163 (last accessed March 2016).
2. Science and Environmental Health Network (SEHN) (1998). Wingspread Statement on the Precautionary Principle. Available from: http://www.sehn.org/wing.html (last accessed March 2016).
3. Commission of the European Communities (CEC) (2000). Communication from the commission on the precautionary principle. Available from: http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52000DC0001 (last accessed March 2016).
4. Stoto MA (2006). The precautionary principle and emerging biologic risks: Lessons from human immunodeficiency virus in blood products. *Seminars in Hematology* 43: S10–2.
5. Epstein, JS, Jaffe HW, Alter HJ, Klein HG (2013). Blood system changes since recognition of transfusion-associated AIDS: Blood System Changes since AIDS. *Transfusion* 53:2365–74.
6. Leveton LB, Sox Jr HC, Stoto MA (eds.) (1995). *HIV and the blood supply: an analysis of crisis decisionmaking*. Washington D.C.: Institute of Medicine National Academy Press..
7. Krever H (1997). *Final report: Commission of inquiry on the blood system in Canada*. Ottawa: Canadian Government Publishing.
8. Feldman EA, Bayer R (eds.) (1999). *Blood feuds: AIDS, blood, and the politics of medical disaster*. Oxford: Oxford University Press.
9. Alter HJ, Purcell RH, Holland PV, *et al.* (1981). Donor transaminase and recipient hepatitis: Impact on blood transfusion services. *Journal of the American Medical Association* 246: 630-634.
10. Turner ML (2006). Transfusion safety with regards to prions: Ethical, legal and societal considerations. *Transfusion Clinique et Biologique* 13:317–9.
11. Wilson K, Wilson M, Hébert PC, *et al.* (2003). The application of the precautionary principle to the blood system: The Canadian blood system's vCJD donor deferral policy. *Transfusion Medicine Reviews* 17: 89–94.
12. Wilson K, Graham I, Ricketts M, *et al.* (2007). Variant Creutzfeldt–Jakob disease and the Canadian blood system after the tainted blood tragedy. *Social Science & Medicine* 64:174–85.
13. Blood Products Advisory Committee (BPAC) (2009). *Transcript of 94th meeting*. Available at: http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/bloodproductsadvisorycommittee/default.htm/ (last accessed March 2016).
14. Vamvakas EC, Kleinman S, Hume H, *et al.* (2006). The development of West Nile virus safety policies by Canadian Blood Services: Guiding principles and a comparison between Canada and the United States. *Transfusion Medicine Reviews* 20:97–109.
15. Leiss W, Tyshenko M, and Krewski D (2008). Men having sex with men donor deferral risk assessment: An analysis using risk management principles. *Transfusion Medicine Reviews* 22:35–57.
16. Vamvakas EC (2011). Relative risk of reducing the lifetime blood donation deferral for men who have had sex with men versus currently tolerated transfusion risks. *Transfusion Medicine Reviews* 25:47–60.

17. Galarneau C (2010). Blood donation, deferral, and discrimination: FDA donor deferral policy for men who have sex with men. *The American Journal of Bioethics* 10: 29–39.
18. Hergon E, Moutel G, Duchange N, *et al.* (2005). Risk management in transfusion after the HIV blood contamination crisis in France: The impact of the precautionary principle. *Transfusion Medicine Reviews* 19:273–80.
19. Wilson K (2011). A Framework for applying the precautionary principle to transfusion safety. *Transfusion Medicine Reviews* 25:177–83.
20. Custer B, Janssen MP (2015). Health economics and outcomes methods in risk-based decision-making for blood safety. *Transfusion* 55:2039–47.
21. Schippers EI (2014). Ministerieel plan bloedvoorziening 2015-2017. Available from http://www.tweedekamer.nl/kamerstukken/detail?id=2014D32795 (last accessed March 2016).
22. Alliance of Blood Operators (ABO) (2015). Risk-based decision-making framework for blood safety. Available from: https://allianceofbloodoperators.org/media/115522/rbdm-framework-2-april-2015-v11-for-website.pdf (last accessed August 2017)
23. Farrugia A (2002). The regulatory pendulum in transfusion medicine. *Transfusion Medicine Reviews* 16: 273-282.
24. Moreno JD (2003). "Creeping precautionism" and the blood supply. *Transfusion* 43:840–842.
25. Alter HJ (2008). Pathogen reduction: A precautionary principle paradigm. *Transfusion Medicine Reviews* 22: 97–102.
26. Pereira A (2008). Risk management. In Barbara JAJ, Regan FAM, Contreras MC (eds.). *Transfusion microbiology*. Cambridge: Cambridge University Press. Pp. 341–61.
27. Dodd RY (2010). Prions and precautions: Be careful for what you ask. *Transfusion* 50:956–8.
28. Vamvakas EC (2011). *Decision making in transfusion medicine*. Bethesda: American Association of Blood Banks.
29. Farrell A-M (2012). *The Politics of Blood: Ethics, Innovation and the Regulation of Risk* (eBook). Cambridge: Cambridge University Press.
30. Menitove JE, Leach Bennett J, Tomasulo P, Katz LM (2014). How safe is safe enough, who decides and how? From a zero-risk paradigm to risk-based decision making. *Transfusion* 54:753–7.
31. Sandin P., Peterson M, Hansson SO, *et al.* (2002). Five charges against the precautionary principle. *Journal of Risk Research* 5: 287–99.
32. Trouwborst A (2006). *Precautionary right and duties of states*. Leiden/Boston: Martinus Nijhof.
33. Ahteensuu M, Sandin P (2012). The precautionary principle. In: Roeser S, Hillerbrand R, Sandin P, Peterson M (eds.). *Handbook of risk theory*. Dordrecht: Springer. Pp. 961–78
34. Hartzell-Nichols L (2013). From "the" precautionary principle to precautionary principles. *Ethics, Policy & Environment* 16: 308–20.
35. Manson NA (2002). Formulating the precautionary principle. *Environmental Ethics* 24:263–74.
36. Sandin P (2004). The precautionary principle and the concept of precaution. *Environmental Values* 13:461–75.

37. Resnik DB (2003). Is the precautionary principle unscientific? *Studies in History and Philosophy of Biological and Biomedical Sciences* 34(2):329–44.
38. Hansson SO (1999). Adjusting scientific practices to the precautionary principle. *Human and Ecological Risk Assessment: An International Journal* 5:909–21.
39. Munthe C (2011). *The price of precaution and the ethics of risk* (eBook). Dordrecht: Springer.
40. Steel D (2015). *Philosophy and the precautionary principle: Science, evidence, and environmental policy*. Cambridge: Cambridge University Press.
41. Forland F, De Carvalho Gomes H, Nokleby H, *et al.* (2012). Applicability of evidence-based practice in public health: risk assessment on Q fever under an ongoing outbreak. *Euro Surveillance* 17:1–6.
42. Hayenhjelm M. and Wolff J (2012). The moral problem of risk impositions: A survey of the literature. *European Journal of Philosophy* 20: E26–51.
43. Von Schomberg R (2012). The precautionary principle: Its use within hard and soft law. *European Journal of Risk Regulation* 2:147–56.
44. Sunstein CR (2005). *Laws of fear: Beyond the precautionary principle*. Cambridge: Cambridge University Press.
45. Federal Drug Administration (FDA) (2015). *Revised recommendations for reducing the risk of human immunodeficiency virus transmission by blood and blood products*. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM446580.pdf (last accessed March 2016).
46. Hansen SF, von Krauss MK, Tickner JA (2008). The precautionary principle and risk-risk tradeoffs. *Journal of Risk Research* 11:423–64.
47. Hansen SF, Tickner JA (2013). The precautionary principle and false alarms - lessons learned. In Gee D, Grandjean P, Hansen SF, *et al.*(eds.). *Late lessons from early warnings: Science, precaution, innovation*. Copenhagen: European Environment Agency.
48. Goklany IM (2001). *The precautionary principle: A critical appraisal of environmental risk assessment*. Washington DC: Cato Institute.
49. AuBuchon JP, Petz LD (2001). Making decisions to improve transfusion safety. In *Policy alternatives in transfusion medicine*, AuBuchon JP, Petz LD, Fink A (eds.). Bethesda: American Association of Blood Banks. Pp. 193–226.
50. Holm S, Harris J (1999). Precautionary principle stifles discovery. *Nature* 400:396.
51. Nollkaemper A (1996).'What you risk reveals what you value', and other dilemmas encountered in the legal assaults on risks. In: Freestone D and Hey E (eds.). *The precautionary principle and international law*. The Hague (etc.): Kluwer Law International. Pp. 73-94.
52. European Environment Agency (EEA) (2001). *Late lessons from early warnings: the precautionary principle, 1896-2000*. Luxembourg: Office for official publications of the European Communities.
53. European Environment Agency (EEA) (2013). *Late lessons from early warnings: Science, precaution, innovation*. Luxembourg: Publications office of the European Union.
54. Wilson K, Atkinson K, Keelan J (2014). Three decades of MSM donor deferral policies: What have we learned? *International Journal of Infectious Diseases* 18:1–3.

55. Feinberg J (1984). *The moral limits of the criminal law volume I: Harm to others*. Oxford: Oxford University Press.
56. Holtug N (2002). The harm principle. *Ethical Theory and Moral Practice* 5:357–89.
57. Ahteensuu M (2007). Rationale for taking precautions: normative choices and commitments in the implementation of the precautionary principle. *Risk & Rationalities* (Conference Proceedings), Queens' College, Cambridge, UK. Available from: http://www.kent.ac.uk/scarr/events/ahteensuu.pdf. (last accessed December 2014).
58. Sandin P (1999). Dimensions of the precautionary principle. *Human and Ecological Risk Assessment: An International Journal* 5:889–907.
59. Hourdequin M (2007). Doing, allowing, and precaution. *Environmental Ethics* 29:339–58.
60. John SD (2011). Risk and precaution. In: Dawson A (ed.). *Public health ethics*. Cambridge: Cambridge University Press. Pp. 67-84.
61. Jensen KK (2002). The moral foundation of the precautionary principle. *Journal of Agricultural and Environmental Ethics* 15:39–55.
62. Tickner JA (2002). The precautionary principle and public health trade-offs: Case study of West Nile virus. *Annals of the American Academy of Political and Social Science* 584:69–79.
63. Saner MA (2002). An ethical analysis of the precautionary principle. *International Journal of Biotechnology* 4:81–95.
64. Cranor CF (2004). Toward understanding aspects of the precautionary principle. *Journal of Medicine and Philosophy* 29:259–79.
65. Custer B, Hoch JS (2009). Cost-effectiveness analysis: What it really means for transfusion medicine decision making. *Transfusion Medicine Reviews* 23:1–12.
66. Borkent-Raven BA, Janssen MP, van der Poel CL, Bonsel GJ, van Hout BA (2012). Cost-effectiveness of additional blood screening tests in the Netherlands. *Transfusion* 52:478–88.
67. Verweij MF, Kramer K (2016). Donor blood screening and moral responsibility: How safe should blood be? *Journal of Medical Ethics*. Published Online First: February 11, 2016.