LETTERS TO THE EDITOR

THE PRECAUTIONARY PRINCIPLE IN BLOOD SAFETY: NOT QUITE THE SAME AS AIMING FOR ZERO RISK

To the Editor:

The recent article by Professor Kumanan Wilson raised important issues concerning the application of the precautionary principle to transfusion safety [1]. The article reviews and criticizes various scenarios in which the precautionary principle has or has not been applied in the blood transfusion setting. It also contains a proposed framework that could be used to decide in a more systematic fashion whether to implement precautions when faced with a specific threat to transfusion safety. We agree with most of the points made by Professor Wilson, which will certainly help to strengthen the case in favor of a more rational and consistent application of the precautionary principle. However, we believe that there are lingering issues with the current precautionary paradigm in transfusion safety, which still need to be resolved. In particular, Professor Wilson states that "the precautionary principle reflects an effort to achieve a zero-risk blood supply" and that "a parallel and closely related policy process is the reduced tolerance for known or minimal risks." We do not entirely agree with this statement, and we would like to offer some specific examples for discussing this important point. We also wish to offer additional comments regarding the uses and misuses of the precautionary principle.

PRECAUTIONS AGAINST VARIANT CJD: A "TEXTBOOK" CASE

The potential threat of variant Creutzfeldt–Jakob disease (vCJD) to transfusion safety, as it raised its head about 15 years ago, fits very well the set of requirements that one would expect to find before invoking the precautionary principle. First, the potential threat was certainly severe: the human form of mad cow disease was a universally fatal condition, with no cure at hand. Second, the evolution of the threat was uncertain, and in fact, most experts were warning that it could progress into a very large epidemic within the United Kingdom and even abroad. Finally, by virtue of the very long incubation period of the disease, the science in this field would take a long time to accumulate data to better understand and quantify the true risk posed to humans, in particular, the risk of transmission by transfusion. Finally, certain biologic characteristics of the agent (in particular the propensity to infect lymphoid tissues) suggested strongly that it could be transmitted by transfusion, a possibility that was later confirmed by experimental and clinical data. Because of this, it seemed quite reasonable to consider the application of possible risk mitigation strategies for transfusion. One of these strategies, in countries not directly affected by the vCJD epidemic, was to limit donations from people who might have been exposed to the agent, that is, who lived in countries where contaminated meat had been made available for human consumption. To maintain the principle of proportionality, different jurisdictions adjusted the intensity of their deferral policies according to the level of donor loss that could be tolerated without creating a blood shortage.

We believe that geographical deferrals applied for the vCJD threat represent an unadulterated application of the precautionary principle. It is also one of the few instances where the same basic precautions were widely applied by the transfusion community across the developed world. This is not to say that these measures were adopted with glowing enthusiasm and unanimity. There were certainly heated debates around this issue, and many experts openly disagreed with the approach that was taken. However, the objections often related to specific misuses of the precautionary principle in a given context. For example, Kirkland [2] criticized this approach by pointing out that the geographical deferrals in New Zealand led to blood product shortage. If this is true (we do not wish to debate whether this was the case or not), then one could argue that the specific measure that was applied in New Zealand failed to meet the proportionality criterion. In most places where deferrals were introduced, however, such measures were well tolerated and well received by the public, including blood donors.

One very important aspect of the vCJD crisis is that the precautions that were taken with blood were never expected to be maximally effective.

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For example, in our own jurisdiction, we estimated that we would prevent approximately 80% of contaminated units from entering the blood supply, if contamination ever occurred on a large scale, while preserving our capacity to supply hospitals adequately. This is still far from the maximal risk reduction that could have been achieved if we had decided to exclude anyone who spent even the shortest length of time in a country at risk for BSE. A "zero risk" paradigm does not allow for this kind of compromise. In fact, if one had held on to the zero-risk approach with the vCJD threat, the choice would have been to invest massively in donor recruitment efforts to rapidly make up for an even more stringent geographical deferral policy. This is all to make the point that geographical exclusions were never meant to aim for zero risk. Instead, it was a compromise between the purely theoretical risks of a full-blown vCJD crisis vs the real risks and costs associated with donor deferrals. In other words, the principle of proportionality itself dictated that our precautions should not aim for zero risk.

Eventually, vCJD was shown to be transmissible by transfusion, a fact that could be seen to vindicate the precautions that were taken. However, in view of the progression of the human epidemic over the last 15 years, the overall vCJD threat to transfusion now appears to be extremely small. In fact, there is no indication that geographical deferrals ever prevented a single case of transfusion-transmitted vCJD. There are not even data showing that deferrals were able to avoid taking blood from someone who later came down with the disease. The evidence is accumulating to the effect that vCJD is not posing a significant risk to transfusion, at least not in countries spared by the BSE contamination, yet we continue to apply the same precautions that were introduced more than 10 years ago. This goes against another tenet of the precautionary principle, which states that a precaution should be "subject to review" [3]. It might be argued that the theoretical risk has now become very real, given the 4 cases of documented transmission and that we are now in a more "traditional" risk reduction mode. However, this risk reduction strategy now appears to be out of proportion with the extremely small risk that vCJD poses in most countries around the world. In other words, we are still very much committed to the same, nonreversible precautions, when in fact the accumulating data would allow us to revisit and reduce the intensity of our risk mitigation strategies. What keeps us from doing this? This is where the zero-risk paradigm unfortunately kicks in. There is no way to demonstrate with absolute certainty that a reduction in the scope and/or stringency of travel deferrals would lead to zero increase in risk. Therefore, reducing the intensity of our measures might be seen as making the blood less safe, even if the risk increment is so minuscule that it cannot be estimated.

PRECAUTIONS AGAINST XMRV (XENOTROPIC MURINE LEUKEMIA VIRUS-RELATED VIRUS): LESS OF A TEXTBOOK CASE

In November 2009, a case-control study published in Science reported the possible link between a recently discovered murine retrovirus, XMRV (xenotropic murine leukemia virus-related virus), and chronic fatigue syndrome (CFS) [4]. The study also found that a substantial proportion of healthy controls were possibly infected with the virus. These findings almost immediately triggered a lot of discussion and debate in the transfusion community as to whether some precautions should be put in place to reduce the possible risk of transmitting this retrovirus through transfusion. One such readily applicable measure could be to defer donors who report a previous diagnosis of CFS. The Food and Drug Administration Blood Product Advisory Committee, in fact, made the recommendation that transfusion agencies should systematically screen for CFS through the donor qualification questionnaire [5].

In view of the precautionary principle, how does the CFS situation compare with vCJD? Chronic fatigue syndrome is certainly a debilitating condition, but it is not a rapidly progressive and universally fatal neurodegenerative disease. In addition, there is no indication that we are facing an impending CFS epidemic, contrary to what was feared for the human form of mad cow disease. Chronic fatigue syndrome has been with us for a long time, and the incidence appears to be low and stable. Finally, screening donors for CFS by asking questions at the time of donation would likely be impractical and inefficient.

Possibly, the most important difference between CFS and vCJD is the fact that science has been able to progress much more rapidly regarding the potential threat posed by the XMRV agent. Since the first publication linking XMRV with CFS,

multiple studies have been conducted to address this hypothesis, and less than 2 years later, there is a substantial body of scientific data regarding this question. We do not wish to debate this particular issue, but it seems fair to say that the consensus is now that XMRV has no role in the pathogenesis of CFS [6].

Even if we put aside the more recent scientific developments around this issue, we do not believe that the XMRV situation ever justified the adoption of precautions similar to those applied for vCJD. In fact, in jurisdictions where specific actions were taken, the scope of these actions has been very modest. At most, donors are indefinitely deferred if they self-report a current or past diagnosis of CFS, and to our knowledge, no one has implemented a systematic screening question for current or past diagnosis of CFS. In our own jurisdiction, we were already deferring donors who had active CFS, and we believed that this was a sufficient level of precaution, even after the initial study linking CFS with XMRV. (Interestingly, the deferral of donors with active CFS was applied mainly for the sake of protecting the donor, not the recipient.)

SHOULD PRECAUTIONS BE REGULATED?

Because of the proportionality criterion, acceptable levels of precautions usually cannot be uniform between or even within jurisdictions. The vCJD travel deferral is again a good case in point. Deferral periods had to take into account the travel habits of blood donors, which can vary substantially, even within a given country. In Canada for example, one regulatory requirement is to defer donors who spent 3 months or more in the United Kingdom between 1980 and 1996. However, Héma-Québec implemented a 1-month travel deferral period for Québec donors, simply because it was possible to have a more stringent policy with an impact on donor loss that remained tolerable and comparable with the 3-month policy elsewhere in Canada. (Quebeckers do not travel as much to the United Kingdom compared with other Canadians.) Because of these types of differences between jurisdictions, a sound application of the proportionality criterion should allow what would otherwise appear as inconsistent precautions. This is also very different from a zero-risk approach, which does not easily tolerate such discrepancies. It is therefore not possible to define a single "best precaution," even within a single country. The best that can be achieved is to define a minimal set of requirements, which would not necessarily be applicable everywhere. If only for this reason, we would argue that precautions should not be strictly regulated but rather recommended in principle and adapted to the local context and modified according to evolving data. The choice of a given level of precaution is also at least partly subjective, as it can be influenced by societal considerations (the "dread factor," the pressure of advocacy groups, etc). Encasing precautions within regulations also has the pernicious effect of rendering them almost immutable. Even when and if science evolves to a point where the risk is shown to recede, agencies are notoriously slow to make regulations less stringent. For all these reasons, we believe that regulators should apply utmost parsimony when considering precautions for theoretical, unsubstantiated risks. Regulated precautions may also have the pernicious effect of curbing the quest for more definitive scientific data. For example, following the regulator's decision to implement precautions against simian foamy virus in Canada, no additional studies have been conducted to evaluate the true risk that this agent poses to blood transfusion, possibly because the implementation of a precautionary measure sends the message that the "case is closed" [7].

SUGGESTIONS FOR SOME GUIDING PRINCIPLES

Based on these considerations and as a complement to Professor Kumanan's article, here are some additional suggestions for a more judicious application of the precautionary principle in transfusion medicine:

1. The threat should be of significant severity, by virtue of the condition itself, its epidemic potential, or otherwise. Not all threats should necessarily give rise to specific precautions.
2. The precautionary principle should not trump science, whenever evidence can be obtained within a reasonable timeframe.
3. We should tolerate variable forms and degrees of precautions in face of a given threat. The precautions that can be taken will vary depending on the particular situation in a given country or jurisdiction.
4. Precautions should be reassessed periodically and adjusted according to the actualized level of threat. This goes both ways: when the threat appears to increase significantly, precautions

should be cranked up, but if the threat appears to recede, lesser precautions (or even the removal of precautions) can be considered also.
5. As much as possible, the regulatory and normative approach to precautions should be kept to a minimum. Ideally, regulations should target confirmed, well-characterized, real risks. Because of the variability of precautions that need to remain "proportional" to the threat, imposing a one-size-fits-all rule makes little sense.
6. Disentangle zero risk from precautions. A precaution is an imperfect measure that, almost by definition, will never achieve near-to-zero risk, unless the threat is not real or much smaller than anticipated.
7. Recognize and accept the limitations of the precautions that are taken, including the fact that they are at least partly influenced by subjective factors.

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RESPONSE TO THE LETTER-TO-THE-EDITOR BY GERMAIN ET AL

To the Editor:

I would like to thank the authors for their interest in my article and their valuable insights [1]. I had envisioned my article as a starting point based on my observations concerning the blood system's experience with using the precautionary principle and addressing risks to blood safety [2]. Ideally, the framework I proposed in my article would be vetted by individuals who are directly involved in the decisions pertaining to transfusion safety. In that respect, the comments by Germain and colleagues are particularly welcome.

I am in agreement with much of the content of their response: specifically, the question of whether precaution should mean zero risk. This dilemma of what precaution actually means is at the heart of the dilemma that challenges users of the precautionary principle both in the environmental and public health areas, such as blood safety. The absence of a clear definition permits a wide variation of interpretations, one of which is that precaution means zero risk. Implementation in blood safety in many instances has been consistent with a strong interpretation of the principle and has lent itself to the assumption that precaution in blood safety means zero risk.

I also agree with the authors' assessment of the application of precaution to potential transfusion transmission of vCJD and XMRV, and their analyses are similar to what the framework I proposed would have concluded. For example, the application of the precautionary framework would have concluded that an intermediate form of precaution should have been applied to the potential transfusion transmission risk of vCJD—as was instituted in Canada and praised by the authors of the letter. Application of the framework I proposed to the risk of XMRV would have recommended a more evidence-based approach, waiting for higher-quality evidence. Doing so would likely have resulted in no policy being introduced until better evidence was available—which was also the conclusions of the authors of the letter.

With respect to the authors' specific recommendations, I will comment on each individually. Many of the components are incorporated into the framework (see Fig. 1).

(1) The threat should be of significant severity by virtue of the condition itself, its epidemic