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REVIEW ARTICLE

TRANSFUSION

A review of attitudes to urgent RhD-positive transfusions in female patients and the risk for hemolytic disease of the fetus and newborn

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1 | INTRODUCTION

At the onset of the resuscitation of a patient with life-threatening bleeding, when their ABO and RhD blood groups are not likely to be known, group O red blood cells (RBCs) or low titer group O whole blood (LTOWB) must be transfused to ensure serological compatibility with the recipient's naturally occurring anti-A and/or -B. The selection of the RhD type of blood products issued early in the resuscitation is not as definitive; the convention has been to use RhD-negative blood products if the recipient's RhD type is unknown or negative, with special emphasis on using RhD-negative products for females of childbearing potential (FCP). Surveys on the issuing practices of RBCs and LTOWB at both pediatric and adult trauma centers show a general preference for issuing RhD-negative products to women and girls.[1,2] Due to supply constraints on RhD-negative LTOWB, some centers use RhD-positive LTOWB as a first-line treatment or in the setting of life-threatening bleeding for FCPs.[3,4]

The risk of transfusing RhD-positive RBCs or LTOWB to a recipient that turns out to be RhD-negative is that they could become D-alloimmunized;[5,6] for males and females who are no longer of childbearing potential, producing this antibody is of minor concern and relates primarily to potential delays in providing RhD-negative transfusions in the future. For FCPs, becoming D-alloimmunized could result in future pregnancies being complicated by hemolytic disease of the fetus and newborn (HDFN) if they go on to become pregnant with

Abbreviations: FCP, female of childbearing potential; HDFN, hemolytic disease of the fetus and newborn; IUT, intrauterine transfusion; LTOWB, low titer group O whole blood; UAB, University of Alabama at Birmingham.

an RhD-antigen positive fetus. While using RhD-negative blood products for patients of unknown RhD type would be the safest, only approximately 10% of total RBC distributions are group O RhD-negative, while 39% are group O Rh-positive.[7] Thus, the relative scarcity of RhD-negative compared to RhD-positive blood products renders them difficult to supply to hospitals where trauma and massively bleeding patients are uncommonly seen or to emergency medical services that provide prehospital transfusions due to the sporadic nature of their use.

Luckily, if an RhD-positive unit is transfused to an injured FCP who turns out to be RhD-negative, having severe complications of anti-D mediated HDFN in a future pregnancy is unlikely if the woman has access to modern antenatal healthcare.[8] Numerous mathematical models have predicted that experiencing severe anti-D mediated HDFN should occur rarely in this situation, with one model predicting a 0.04% risk of fetal death from HDFN and a 0.24% risk of fetal death or other severe outcomes like requiring an intrauterine transfusion or neonatal exchange transfusion;[9] other models predicted that the risk of HDFN of any severity will vary with age and they indicated that the peak lifetime incidence (approximately 6%) would occur if an 18- to 20-year-old RhD-negative FCP was transfused with RhD-positive products during her resuscitation.[10,11] A model simulating the situation whereby RhD-positive LTOWB was exclusively provided for prehospital transfusion in England predicted that there would be one case of fetal demise from anti-D HDFN in this setting every 5.7 years,[12] while the introduction of RhD-positive prehospital LTOWB transfusions in two large areas of Finland would be expected to cause severe HDFN in 6–12 pregnancies over 100 years.[13] Similarly, it was estimated that it would take approximately 250 years for 100 RhD-negative FCPs to receive RhD-positive LTOWB during their resuscitation, resulting in between 3 and 30 D-alloimmunized patients.[14] Hence, the risk of future HDFN from prehospital RhD-positive transfusion is expected to be low.

This article will review the surveys that have assessed the risk tolerances of both medical professionals and lay people vis-à-vis urgent transfusion and its potentially harmful effect on future pregnancies. The community perspective is particularly important since most trauma victims will not be abreast of the risk estimates that are disseminated in academic fora. The values and risk tolerances of potential transfusion recipients should inform medical policy so that community- and patient-centered care can be provided to all trauma patients.

One of the first surveys on attitudes toward transfusion and future pregnancy risks was conducted among directors of the transfusion medicine and trauma services at some of the largest pediatric specialty hospitals in the United States. Perhaps reflective of the strict conventional teaching about not exposing FCPs to RhD-positive blood products if her RhD type is unknown, this survey found that 6/30 (20%) of the transfusion directors and 12/32 (37.5%) of the trauma directors would be willing to expose girls to RhD-positive LTOWB if RhD-negative LTOWB was not available in the context of a clinical trial comparing LTOWB to conventional components in injured children.[15] Interestingly, a large proportion, 12/30 (40%) of the transfusion directors and 14/32 (43.8%) of the trauma directors, were "not sure" if they would use RhD-positive LTOWB for girls. When the same question was asked about exposing RhD-type unknown boys to RhD-positive LTOWB, 24/30 (80%) of the transfusion directors and 23/32 (71.9%) of the trauma directors indicated that they would use RhD-positive LTOWB in this population. A limitation of this survey was that it only solicited the opinions of those working at large centers that treat the most severely injured patients; given that life-threatening bleeding also happens in pediatric patients at other hospitals, it would be informative to survey those who set the transfusion policies at other pediatric hospitals. Given that this study was published in 2021, which coincided with the publication of some of the models that predicted a low risk of HDFN following the transfusion of RhD-positive blood products to RhD-negative FCPs, it would be interesting to repeat this part of the survey to see if these attitudes toward RhD-positive exposure have changed in light of the low risk of HDFN in the trauma setting.

As the aforementioned survey was designed to assess the professional practice at academic centers, participants were not asked about their personal preferences should they or a loved one require an urgent transfusion. To this end, the members of the University of Alabama at Birmingham's (UAB) Department of Surgery and Faculty of Nursing were emailed with a link to an electronic survey designed to probe their personal opinions about transfusion and future pregnancy risk.[16] Self-identified female respondents were asked questions about their risk tolerance for transfusion and the risk for future pregnancy; self-identified males were asked to respond to the same questions on behalf of a theoretical female partner. The response rate was 90/282 (32%), and of the respondents, 51% were female and 49% were male. The vast majority of respondents, 97% of the males and 89% of the females, indicated that they would accept a lifesaving transfusion when the question did not indicate that there was any risk to future pregnancies (phrased as "I would accept a blood transfusion, IF I needed it to save my life"). The positive response rates were similarly very high (87% males and 89% females) when asked if they would accept

a lifesaving transfusion with an unspecified risk to a future pregnancy (phrased as "I would accept a transfusion if I needed it to save my life but it could harm my future pregnancy"). The proportion of positive responses remained high (≥84% of both males and females) when the risks of harm to future pregnancies were quantified at 1:100 and 1:1000. Interestingly, when the responses of females were analyzed separately, there was not a statistically significant difference in the likelihood of accepting lifesaving transfusions between the FCPs and the women who were outside of childbearing age (defined in this study as >50 or <15 years old) regardless of whether a risk of HDFN in future pregnancies was specified or when a certain risk was specified. One limitation of this analysis was that there were only seven respondents who were outside of childbearing age. Another limitation of this survey was that the benefit of transfusion was not numerically specified as, for example, a potential mortality risk reduction percentage. Perhaps the respondents viewed receipt of a transfusion in this setting as all-or-none, that is, they might have considered declining the transfusion to be a harbinger of certain mortality whereas accepting the transfusion might have been interpreted as guaranteed survival.

All of the respondents in the UAB study were in the medical field and perhaps had participated in, or had knowledge of, trauma resuscitations where blood was transfused. Thus, these respondents might have been biased toward accepting a transfusion having seen it being used and understanding that HDFN is a complex but highly treatable disease particularly when women have access to maternal–fetal medicine providers with expertise in managing HDFN. To reduce the potential for a posteriori medical knowledge influencing the highly positive transfusion acceptance rate, a study of the general population was performed. Using the Facebook and Instagram social media platforms, a survey was designed to ascertain the attitudes of FCPs and women who were beyond childbearing years in the United States toward urgent transfusions and the risk of future pregnancies.[17] This survey was open to responses from October 2021 to January 2022, and in that time, the survey advertisement was viewed over 16 million times with 2256/2873 (79%) of the women who began the survey fully completing it; 2049/2256 (91%) of those who completed the survey were women. Overall, about 80% of the respondents were FCPs with a median age of 40 (range 22–48) years. Slightly more than half, 55%, of the respondents had children and compared with women who were not of childbearing age, the FCPs were significantly less likely to work in healthcare, had suffered a serious injury, and already had children.

In the overall cohort of 2049 female respondents, 96% reported that they would likely accept a lifesaving transfusion when mention was not made of any risk for future fetal harm (Figure 1). When a nonspecific risk of future fetal harm was included in the question, 58% of the respondents indicated that they would likely accept a transfusion. When the risk of future pregnancies from the transfusion was quantified at 1:100 (qualified in the

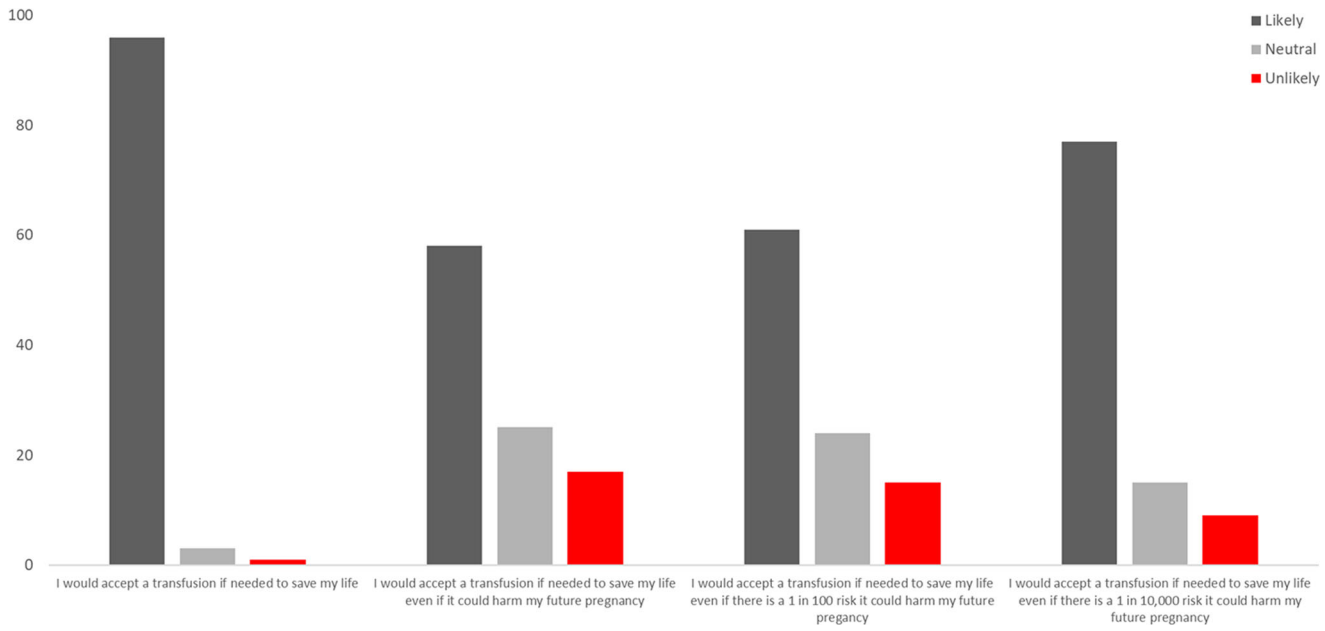

FIGURE 1 Responses from participants who identified as female in a survey distributed on social media. The y-axis represents the percentage of females who responded in the affirmative.[17] Reprinted with the kind permission of Wolters Kluwer Health, Inc. [Color figure can be viewed at wileyonlinelibrary.com]

survey question as "about the same risk as receiving an audit from the Internal Revenue Service") and at 1:10,000 (qualified in the survey question as "about the same risk as getting struck by lightning during your lifetime"), the percentage who responded as likely to accept the transfusion increased to 61% and 77%, respectively. Note that in both situations where a specific risk to a future fetus from transfusion during trauma resuscitation was presented, the acceptance rate of the transfusion was higher than when the risk was not specified. This indicates that presenting a quantifiable risk is important in obtaining a realistic sense of the respondent's true wishes because as the specific risk of future fetal harm decreased, the likelihood of accepting a transfusion increased. Perhaps the respondents could relate to the specific HDFN risks when presented with a commonplace example rather than having to guess at what rate future fetal harm might occur and were therefore more likely to be able to better grasp the risks and benefits of the transfusion and its potential consequences. Further support of the notion that providing specific rates leads to more informed replies come from analyzing the rates at which women in this survey responded that they were *unlikely* to accept an urgent transfusion;[17] when the risk to future fetuses was not specified, 17% responded that they were unlikely to accept a transfusion. However, the percent of respondents who were unlikely to accept a transfusion decreased to 15% and 9% when the risks to future pregnancies were specified to be 1:100 and 1:10,000, respectively. Thus, when presented with a quantifiable risk to a future fetus, the majority of women in the general public were likely to accept an urgent transfusion, which would support using RhD-positive blood products in an emergent trauma resuscitation if RhD-negative products are not available.

A similar finding of increased acceptance of RhD-positive transfusions as the risk/benefit ratio shifted toward a lower frequency of HDFN outcomes was observed in a different study performed in St Louis, Missouri.[18] In this study, where participants were drawn from the database of a university affiliated research enhancement core, 309 responses out of a total of 4896 emailed survey invitations (6.3%) from females ≥18 years old who did not object to receiving transfusions could be analyzed. The participants were presented with various risks of mortality from traumatic hemorrhage along with different degrees of mortality risk reduction conferred by transfusion along with a static range of HDFN frequencies as follows: "...if you suffered a traumatic injury and had a X% chance of bleeding to death, would you want to receive blood if receiving blood would lower your chance of death to Y% but increase the risk of complications with a future or current pregnancy by 0.3%–4.0%?" Overall, ≥90% of the participants indicated that they would likely accept a transfusion in an emergency when the absolute mortality risk reduction in the scenarios was ≥4% (Figure 2), the stated upper bound for the rate of HDFN. Overall, the rate of accepting an urgent transfusion

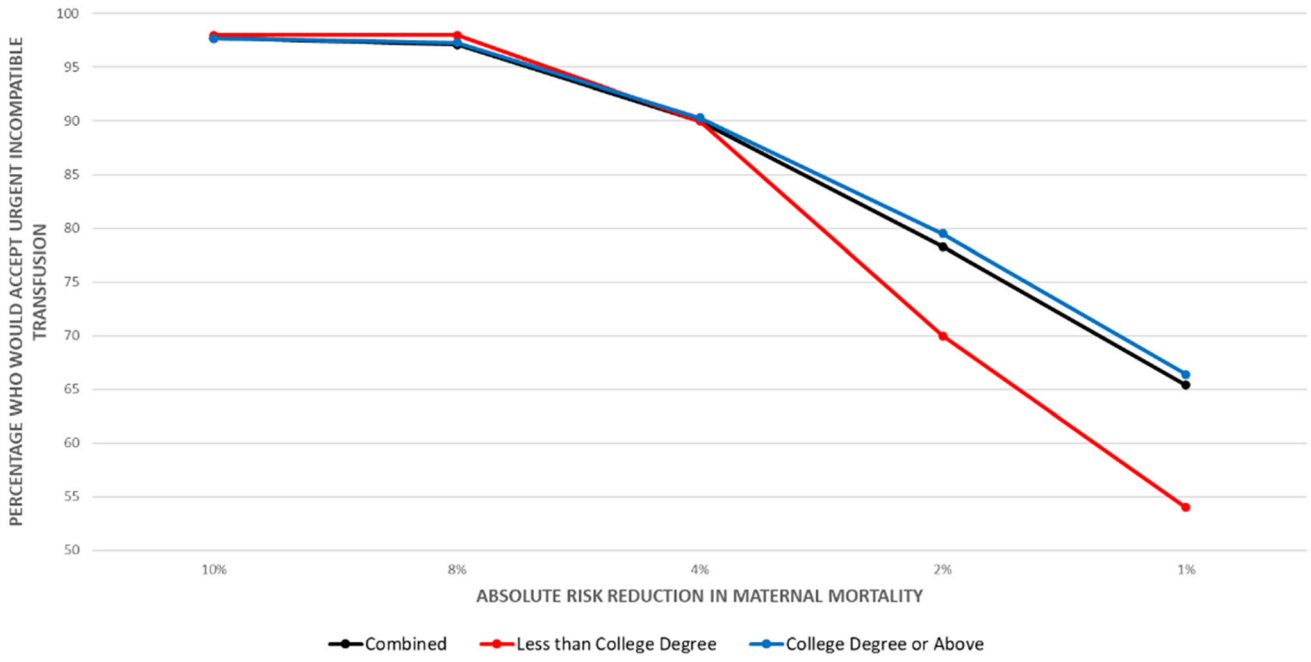

FIGURE 2 The percentage of women who would accept an urgent RhD-positive transfusion stratified by the absolute risk reduction in mortality. In this survey, the risk of HDFN was presented as 0.3%–4%.[18] Reprinted with the kind permission of John Wiley and Sons. [Color figure can be viewed at wileyonlinelibrary.com]

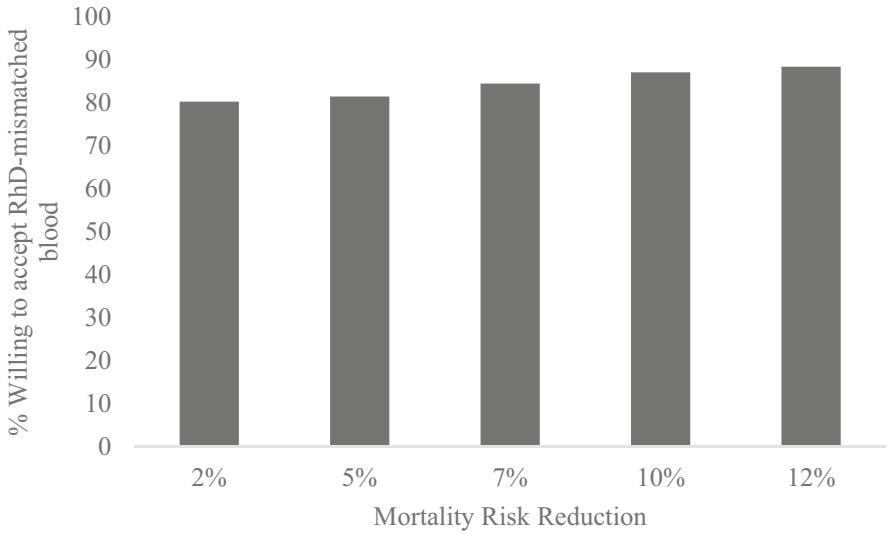

FIGURE 3 The mortality risk reduction that parents would require to consent to administering an urgent RhD-positive transfusion for an RhD-negative female child with the risk of future HDFN presented as ≤6%.[19] Reprinted with the kind permission of John Wiley and Sons.

decreased when the mortality risk reduction was below 4% but was still greater than the approximately 65% acceptance rate even when the mortality risk reduction was only 1%. Taken together, these data suggest that women place a high value on their own survival and are willing to accept the risk of HDFN if it means increasing the probability of saving their lives.

Another informative study conducted at four large US pediatric hospitals assessed lay adults' opinions on the benefits of urgent transfusion versus the subsequent risk of HDFN *for their children*.[19] Adult parents or guardians of female patients were solicited to participate in a survey either during the emergency department visit at one of these hospitals or in-person while waiting for a medical or surgical outpatient clinic visit. The participants were asked a series of questions including whether their female child had been previously transfused. Then, they were asked to read some text that described the potential benefits of urgent transfusion and the subsequent risk of HDFN. After reading the text, they were probed about their tolerance of risk associated with emergency transfusion of RhD-positive blood products to an injured female child. Overall, there were 378/621 (61%) parents who agreed to participate in the survey and their median (IQR) age was 38 years (32–43). Most of the respondents were White (64%), female (78%), and 90% indicated that their child had not been previously transfused. When the risk of HDFN following the transfusion of RhD-positive products was presented as ≤6%, at least 80% of respondents indicated that they were likely to consent to an urgent transfusion despite the risk of HDFN. The likelihood of accepting an urgent RhD-positive transfusion for their female child significantly increased as the absolute mortality risk reduction of the transfusion increased from the minimum presented value of 2% (i.e., a 24% risk of mortality reduced to 22% risk following RhD-positive transfusion) up to the maximum presented mortality risk reduction value of 12% (Figure 3). Interestingly, of the 11 parents who reported having a religious prohibition from receiving transfusions, 8/11 (73%) indicated that they would accept an RhD-positive transfusion on behalf of their female child in an emergency. Thus, most parents indicated that they would be willing to accept the future risk of HDFN for their female child even if the mortality risk reduction was fairly small. Furthermore, even when the mortality risk reduction benefit of RhD-positive transfusion for their female child was lower (i.e., 2%–5%) than the stated risk of future HDFN (≤6%), these parents placed more importance on their child's survival than on potential future pregnancy consequences from the transfusion.

A survey featuring a population of women with unique insight into this issue was recently published. The Allo Hope Foundation is a nonprofit organization that advocates for and counsels women who are RBC alloimmunized about their risk for HDFN and how to find the best care for this disease in their area. All of their members have been impacted by RBC alloimmunization in pregnancy and some have experienced pregnancies affected by HDFN firsthand, therefore obtaining their opinion on emergent transfusion and its subsequent RBC alloimmunization and HDFN risks provides a unique opportunity to learn from those who have lived experience with the consequences of HDFN. To that end, members of the foundation who had previously consented to be contacted for research purposes were emailed a link to the survey, and the link was also posted on a members-only page on the foundation's website.[20] Women who lived in the United States were alloimmunized to an RBC antigen that has been implicated in

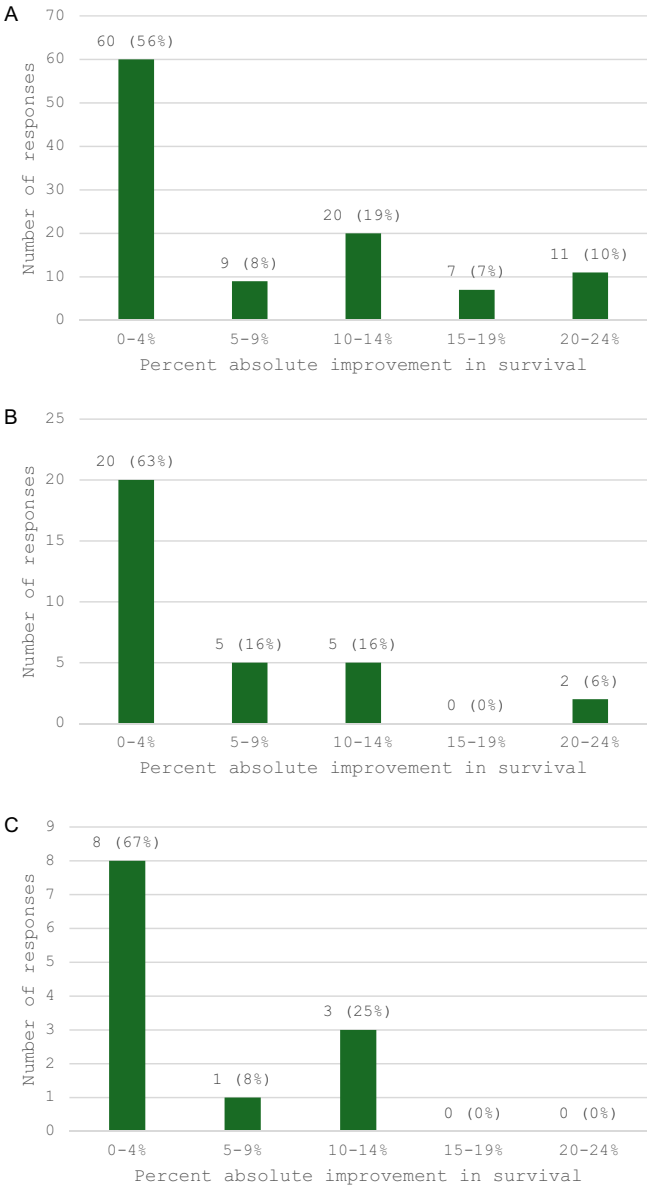

FIGURE 4 The percentage of women who would accept an urgent RhD-positive transfusion for an RhD-negative female child stratified by the absolute risk reduction in mortality. (A) All respondents, (B) respondents with a history of severe HDFN, and (C) respondents with a history of fetal/neonatal loss to HDFN.[20] Reprinted with the kind permission of John Wiley and Sons. [Color figure can be viewed at wileyonlinelibrary.com]

causing HDFN and who had experienced pregnancy after becoming alloimmunized were eligible to participate. The survey posed a scenario whereby an injured RhD-negative female child would be offered RhD-positive LTOWB if RhD-negative LTOWB was not available, and a baseline hemorrhagic mortality rate of 24% was assumed. Respondents were asked to indicate what their absolute mortality risk reduction would be in order to give consent for the RhD-positive transfusion to be administered to their female child. The email response rate to the survey was 78/126 (62%), and an additional 29 responses from members who completed the survey using the website link were also included for a total of 107 analyzable responses. The average (SD) age of survey participants was 34 (4) years, 30% had a history of severe HDFN [history of fetal or neonatal death due to HDFN or HDFN treatment complications (i.e., complications from Intrauterine transfusion (IUT)), fetal or neonatal hydrops, or receipt of an IUT], and 11% had a history of fetal/neonatal loss. Overall, the median absolute mortality risk reduction required to consent to an RhD-positive LTOWB transfusion for an RhD-negative female child was 4% (IQR 1%–14%; Figure 4). Interestingly, among women with a history of severe HDFN ($n = 32$), the median (IQR) absolute mortality risk reduction was 1% (1%–9%), while among those with a history of fetal loss to HDFN ($n = 12$), the median (IQR) was 2% (1%–10%); the former rate was significantly below the median of those without a history of severe HDFN. This fascinating look into the transfusion preferences of women who have experienced a pregnancy impacted by, or who were at risk of, HDFN revealed some of the lowest required mortality risk reductions in order to tolerate an RhD-positive transfusion. This finding confirms the previous trends that women in general prefer lifesaving interventions at the risk of future pregnancy complications.

In summary, these five surveys show that the respondents valued improving their chances of survival in trauma by accepting an urgent transfusion over the risk that transfusion might pose to future pregnancies. This finding was consistent when respondents were asked to reply with what they would like for themselves in this situation, as well as when asked to reply on behalf of a female child. These findings should not be taken to mean that complacency toward trying to provide RhD-negative products is acceptable by the public. Indeed, every effort should be made to provide RhD-negative products to FCPs of unknown RhD-type should they require urgent transfusions. However, if only RhD-positive products are available, these surveys have clearly demonstrated the public's willingness to accept lifesaving interventions.

CONFLICT OF INTEREST STATEMENT

John B. Holcomb is on the board of directors of Decisio Health, CCJ Medical Devices, QinFlow, Hemostatics, and Zibrio. He receives research grant support from the DoD, DARPA, NIH, and CSL focused on hemorrhage control and resuscitation. He consults with WFIRM, Aspen Medical, and is the coinventor of the Junctional Emergency Tourniquet Tool and thus receives royalties from UT Health. Sarah Horvath is funded by the National Center for Advancing Translational Sciences, Grant 2KL2TR002015-05A1 and 5KL2TR002015-06. She is a

Nexplanon trainer for Organon. Philip C. Spinella consults for Hemanext, Cerus, is on the scientific advisory board for Haima and Octapharma and is a cofounder and chief medical officer for Kalocyte. The other authors do not have any conflicts of interest to disclose.

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