Pathogen Reduction Technology for Blood Products: Surveying Knowledge, Perceptions and Acceptability among Canadian Physicians

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Executive Summary

Pathogen reduction (PR) technology for cellular blood components has been under development for several decades. If the decision is made to implement PR in Canada understanding stakeholder awareness and perceptions of PR, especially physicians who prescribe and administer blood transfusions, will be to essential to facilitating effective implementation.

Two surveys of different physician groups were undertaken, one of specialists from across Canada and one of family medicine physicians in Ontario, to assess: awareness; risk perceptions; information needs; and preferred knowledge transfer formats. Surveys were administered electronically using Survey Monkey and LimeSurvey, results were analyzed descriptively.

Physician awareness of PR for blood was low overall, but was higher among specialists. Physicians were less accepting of risks that could pose harm to recipients (i.e., potential carcinogenic effects of chemicals used in PR, and increased risk of acute non-infectious complications), and were more willing to accept risks affecting supply and demand (i.e., shortened shelf life). The majority of respondents were interested in receiving information about PR, especially regarding risks and benefits of PR and differences between PR and non-PR blood products. Specialists preferred to receive this information via email, and family medicine physicians from a journal article.

If PR of blood products is implemented in Canada, extensive knowledge transfer of information about PR to physicians will be vital. Attention to the different needs and preferences of specialists and family medicine physicians will help to ensure successful knowledge transfer and uptake.

INTRODUCTION

Pathogen reduction (PR) technologies for cellular blood components have been in development for several decades (1), leading to the gradual but steady adoption of PR for plasma and platelet products (2) primarily throughout Europe and Asia (3)(4) over the past 10 years. The three most widely available PR methods for plasma and/or platelets are: Mirasol (TerumoBCT, Lakewood CO), Theraflex (Macopharma, Tourcoing, France), and Intercept (Cerus Corporation, Concord CA)(4). The Cerus system has been approved by the United States (US) Food and Drug Administration (FDA) and has been European Conformity or Conformité Européenne (CE) marked for platelets and plasma in Europe. The Macopharma and TerumoBCT systems have received regulatory approval in Europe and obtained CE mark (5). A phase three international RCT using the TerumoBCT platelet product has been been performed by Sanquinin with participation in the Netherlands, Canada and Norway (6). Research into PR of whole blood and red blood cells has been slow to develop, but is underway (5).

Although PR is being used in routine clinical practice in some parts of the world it has not yet been approved for use in Canada (with the exception of plasma). Canada's participation in a phase three international, randomized controlled trial of PR platelets has inform scientific evidence related to efficacy and safety and may pave the regulatory pathway for its introduction (6). Discussions regarding the potential implementation of PR in Canada have encouraged public consultation (7) as well as consultation with physician stakeholder groups. It has been recommended that, prior to the introduction of PR blood products, an educational program be put in place for blood centres, hospitals, healthcare providers and patients (8).

Minimal consultation has taken place with stakeholders and, until recently, little was known about their knowledge and perceptions of PR for blood (9). A recently published survey of the public in Quebec and Ontario found a general lack knowledge of PR and uncertainty about its place as a blood safety initiative (10). To our knowledge there has not been any research into physicians' knowledge or perceptions of PR in Canada, nor internationally. Yet, given their roles prescribing transfusions and ordering blood products, physicians will need to be informed about PR and the successful implementation of PR will require physician understanding and acceptance of this new innovation in blood safety. To explore and assess physician knowledge and perceptions of PR for cellular blood products, we conducted two surveys. In the event that the decision is made to implement PR in Canada, these survey findings can be used to inform policy decisions about PR and knowledge translation strategies.

MATERIALS AND METHODS

Canada-wide Survey of Specialists

The survey sample was developed using Scott's Directories, online Canadian Medical Directory (11). An email circulation list was collated using database access granted from a trial membership. Physicians with email addresses from the following nine specialties were included: oncology; hematology; anesthesiology; pediatrics, neonatology; intensive and critical care; emergency medicine; obstetrics and gynecology; and surgery. These specialties were selected because they tend to most frequently transfuse blood products. Clinical immunologists were also included in the study to serve as a control group because they infrequently order blood transfusions.

The survey contained 21 questions and was programmed using the online survey software, Survey Monkey. The survey covered the following domains: physician awareness and understanding of PR for blood products; physician acceptance of theoretical risks of PR treated products; and, physician knowledge transfer needs and preferences. The survey was pilot tested by three physicians from McMaster University to ensure readability and clarity of

questions. An email invitation to participate, containing a link to the e-survey was sent to 2178 Canadian physicians in all 13 provinces and/or territories in July 2009; two reminder emails were sent prior to the pre-specified deadline for submission (August 31, 2009). Computer software (SAS 9.1.3, SAS Institute, Inc., Cary, NC; and WESVAR, Westat, Rockville, MD) was used to perform a descriptive analysis of the survey response data and subgroup analyses by specialty and province. Some participants did not answer every question; the proportion of 'no answer' responses for each question is reported throughout this manuscript.

Ontario-wide Survey of Physician Leads of Family Health Teams

A second survey containing eight questions was created using LimeSurvey, open source survey software (12). This survey, tailored for family physicians, covered the same domains as the Canada-wide survey: physician awareness of PR; physician acceptance of theoretical risks associated with PR; knowledge transfer needs and preferences; and also included a question about the family physicians' perceived role related to PR. The questions in this survey were similar to those in the Canada-wide survey of specialists but were not identical. The length of the survey was shortened in an attempt to achieve a good response rate. Email invitations containing a link to the survey were sent to a sample of 50 family medicine physicians who were leads of the Ontario Association of Family Health Teams. Respondents completed the surveys between March and April 2011. Descriptive data analysis was performed using LimeSurvey software. Research ethics approvals for both surveys were obtained from the Hamilton Health Sciences/McMaster University Research Ethics Board. The term pathogen inactivation was used in both surveys; however, for this manuscript we have used the term PR as it is now accepted as a more accurate reflection of the capabilities of these technologies.

RESULTS

Survey 1: Canada-wide Survey of Specialists

Of the 2138 surveys distributed, 152 responses were received (7.1%). Data from the three surveys conducted in the pilot were also included in the analysis for a total of 155 responses. Table 1 shows the province and/or territory of practice for the 107 individuals who indicated location of practice; Ontario was the most common practice location, followed by Quebec and Alberta. The specialties of the 111 physicians who answered this question are summarized in Table 2: hematology was the most common specialty followed by anesthesiology. Only two responses were received from clinical immunologists, a specialist group originally intended to serve as a control group. Sixty-nine percent of survey respondents indicated that they order blood products for transfusion, 3.9% did not order products and 27.1% did not provide an answer.

Province/Territory of Current Practice	Number of Responses (%)
No answer	48 (31.0)
Ontario	53 (34.2)
Quebec	16 (10.3)
Alberta	13 (8.4)
British Columbia	9 (5.8)
Nova Scotia	4 (2.6)
Saskatchewan	4 (2.6)
Newfoundland	3 (1.9)
Manitoba	2 (1.3)
New Brunswick	1 (0.6)
Northwest Territories	1 (0.6)
Nunavut	1 (0.6)

Table 1: Province or territory of respondents' current practice

Specialization	Number of Responses (%)
No answer	44 (28.4)
Hematology	33 (21.3)
Anesthesiology	20 (12.9)
Surgery	13 (8.4)
Pediatrics	11 (7.1)
Oncology	11 (7.1)
Obstetrics	9 (5.8)
ICU	8 (5.8)
Emergency	4 (2.6)
Clinical Immunology	2 (1.3)

Table 2: Respondent specialties

Awareness and Understanding

Respondents were divided in their awareness of PR for blood products (Figure 1). Just over 40 percent (63/155) of respondents were aware of PR being used for blood products, 8.4% of respondents were 'somewhat' aware of PR, and 51.0% of physicians surveyed were not aware of PR. Several physicians indicated that they had heard of PR but lacked detailed knowledge of the processes involved. Hematologists reported the greatest awareness of PR.

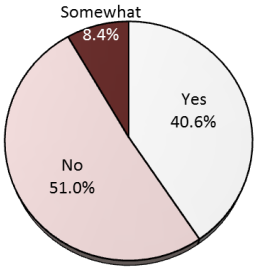


Figure 1: "Are you aware of PR for blood products?"

Understanding of PR for red blood cells (RBCs), platelets, and plasma were assessed, among respondents who were aware, or somewhat aware of PR (Figure 2). Of eligible respondents, 10.5% did not answer these questions. There were 51.3% of respondents who rated their understanding of PR for RBCs as 'very limited', 'poor', or 'neutral' and 38.1% reported their understanding as 'good', 'very good' or 'excellent'. For platelets, the numbers were similar: 48.7% indicated a 'very limited', 'poor' or 'neutral' understanding of PR for platelets, and 40.8% reported their understanding as 'good', 'very good' or 'excellent'. Self-reported levels of understanding of PR for plasma were slightly higher in the group reporting 'good', 'very good' or 'excellent' levels: 48.7%, compared with 40.8% who reported 'neutral', 'poor', 'very limited' understanding. The level of understanding indicated by hematologists was much higher than other specialties for all blood components.

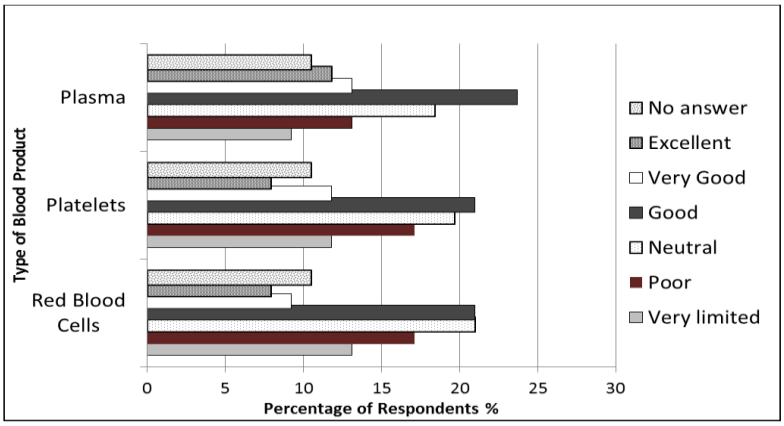


Figure 2: Understanding of PR for cellular blood products

Respondents were asked to indicate their level of agreement with the following statements "*PR is a necessary progression to ensure a safer future blood supply across Canada*", and "*Patients should be informed that they are receiving PR blood".* There were 42.6% of respondents who did not answer the question about safety: the majority of those who did respond indicated that they agreed (20% strongly agreed, 25.2% agreed) that PR is a necessary progression in blood safety. Just over 1% disagreed with the statement and 10.3% reported a 'neutral' opinion. The majority of respondents also agreed or strongly agreed (43.2%) that patients should be informed they are receiving PR blood, compared with 5.8% who disagreed and 12.9% who indicated a 'neutral' response (38% of respondents did not answer this question).

Information Needs and Preferences

Respondents were asked questions designed to understand their information needs and preference around receiving information. The majority of respondents (61.3%) answered yes to the question, "*Do you need additional information to make informed decisions about PR for blood products?"* Eleven percent of respondents did not require additional information about PR, and 27% did not answer this question. The majority of respondents (72%) were interested in receiving information about PR from the blood suppliers (fewer than 1% were not, and 27% did not answer). Respondents were asked to indicate what types of information they wanted to receive. Physicians were most interested in receiving information about the possible risks of PR (59.4%), results of clinical trials comparing PR blood products to non-PR blood products (58.1%), differences between PR and non-PR products (i.e. changes to product viability, shelf-life, efficacy), (57.4%) and the benefits of PR products (56.8%), and were least interested in

receiving information about the techniques of PR (32.9%) and possible changes to current testing on donated blood (32.9%).

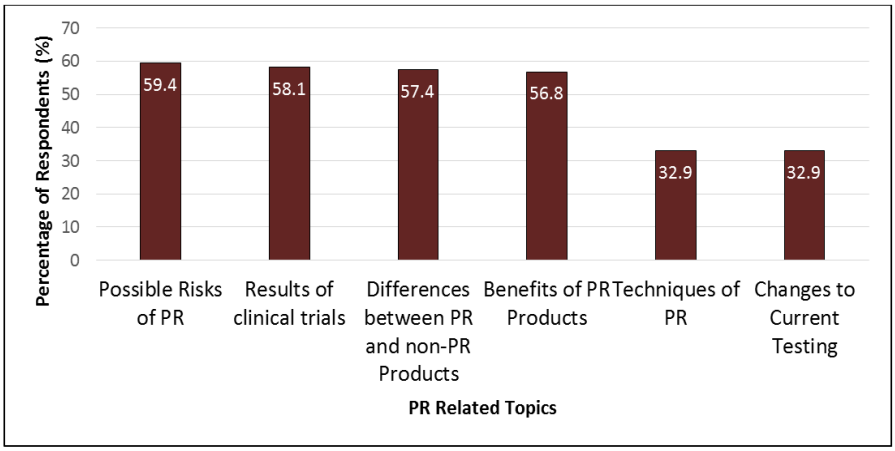
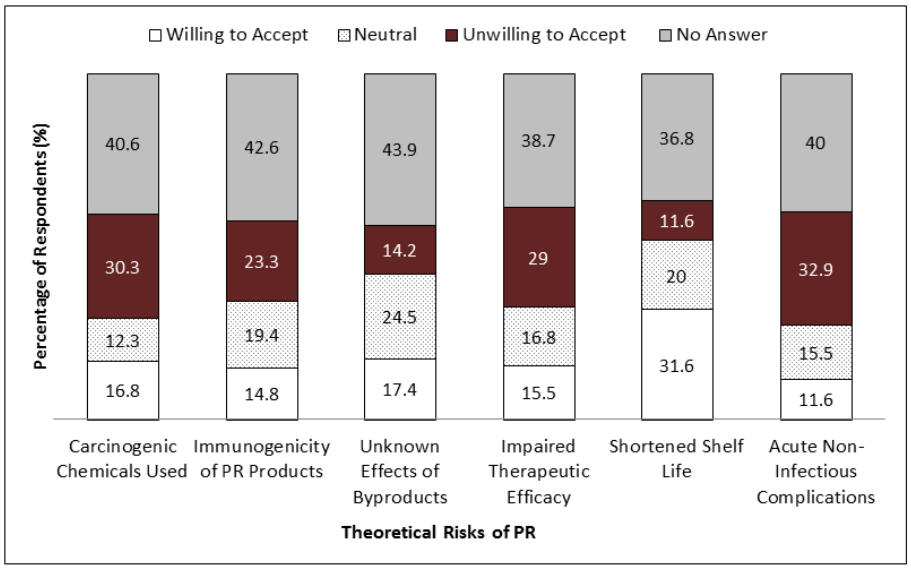


Figure 3: PR related topics that specialists want to receive more information

Respondents were asked to rank the effectiveness of a list of eight different formats for receiving information about PR, using a Likert scale where 1 represented the most effective and 8 the least effective. Email was deemed the most effective method of receiving information about PR followed by short online interactive modules and websites. Word of mouth was perceived to be the least effective method for receiving information about PR.

Risk and Acceptability

Physicians were asked to evaluate the acceptability of a variety of different theoretical risks that could be associated with PR of blood products (Figure 4).



Just over 30% of respondents were unwilling to accept the risk that the chemicals used in PR could have carcinogenic effects, 12% indicated a neutral response and 16.8% were willing to accept this theoretical risk. There were 40.6% who did not answer this question. When asked about their willingness to accept the risk of increased immunogenicity of PR treated products, 14.8% indicated a willingness to accept this risk, 19.4% selected a 'neutral' response and 23.2%

were unwilling to accept this risk. As with the previous question, a significant proportion of respondents (42.6%) did not answer the question. The risk of unknown effects of residual chemicals and byproducts in products treated with PR was acceptable to 17% of physicians, unacceptable to 14% of physicians and 24% indicated a 'neutral' perspective, (43.9% did not respond). The risk of impaired therapeutic efficacy of PR products was acceptable to 15.5% of respondents, whereas 29% were unwilling to accept this risk. Sixteen percent of respondents indicated a neutral response and 39% did not answer this question.

Of all the risk questions, the risk of shortened shelf-life of products was the most acceptable risk: 31% of respondents were willing to accept that PR impaired the viability of treated products. Eleven percent of respondents were unwilling to accept this risk, 20% selected a 'neutral' response to this question and almost 37% of respondents did not answer this question. Of all the theoretical risks presented, the increased risk of non-infectious acute complications of transfusion (i.e., fever, hemolysis, anaphylaxis, transfusion-related acute lung injury) was least acceptable to respondents – only 11% of the physicians who answered this question were willing to accept this risk compared with over 32% who were not. Fifteen percent indicated a neutral response for this question and 40% did not answer.

Survey 2: Ontario-wide Survey of Physician Leads of Family Health Teams

Awareness and Understanding

There were 45/50 surveys returned, for a response rate of 90%. Respondents were provided with a brief statement describing PR and were then asked if they were aware of this technology being used for blood products. The overwhelming majority of respondents (93%, 42/45) had no awareness of PR for blood products (Figure 5); only one respondent indicated an awareness of PR, and 2 out of 45 (4.4%) of respondents did not answer this question.

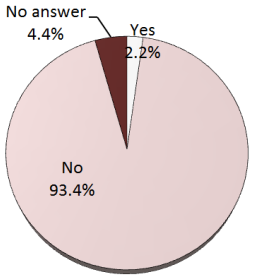


Figure 5: "Are you aware of PR for blood products?"

Information Needs and Preferences

Almost 49% of family medicine physicians (22/45) indicated that they would like to receive information about PR. Respondents who indicated they would like information about PR were prompted to complete a follow-up question where they were asked to 'choose all that apply' from a list of PR related topics. Among family medicine physicians interested in receiving information the topics of greatest interest were: the possible risks (91%); the benefits of PR (86%); the differences between PR treated products and current products (82%); and the risks of transfusion transmitted infection with PR products (77%). The techniques of PR were of least interest to respondents, with only 45% of respondents expressing an interest.

Respondents who expressed an interest in receiving more information were asked to indicate their preferences for various formats for receiving information from a list of nine options (Figure 6). The preferred formats for receiving information were a journal article in *Canadian Family Physician* (77%) and a journal article in the *Canadian Medical Association Journal* (13/22, 59%). An email briefing from InfoPOEMs (Canadian Medical Association) and an email from the Ontario College of Family Physicians were the next most popular formats (45% for both).

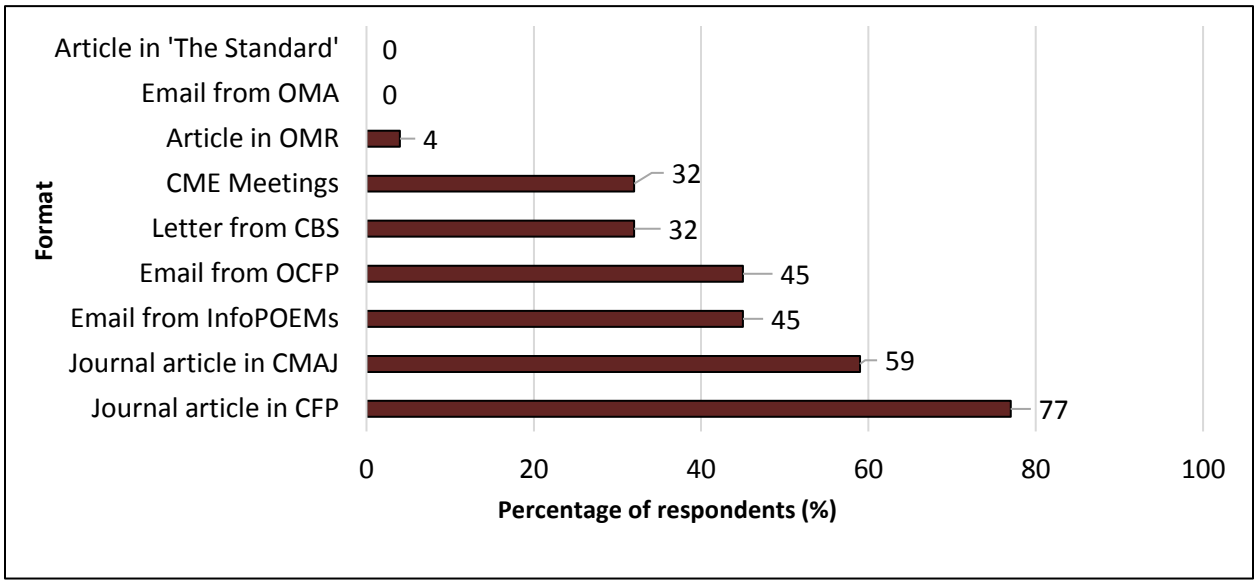


Figure 6 - Abbreviations	
OMA = Ontario Medical Association	OCFP = Ontario College of Family Practice
OMR = Ontario Medical Review	InfoPOEMs = Info Patient Oriented Evidence that Matters
CME = Continuing Medical Education	CMAJ = Canadian Medical Association Journal
CBS = Canadian Blood Services	CFP = Canadian Family Practice

Figure 6: Family medicine physicians' preferred formats for receiving information about PR

Thirty two percent of respondents indicated a preference for the following formats: a letter from the blood supplier - Canadian Blood Services, and Continuing Medical Education meetings. Only 4% of respondents selected 'journal article in OMR' and no one selected 'email from OMA' or an article in The Standard'

Perceived Role

The survey asked respondents whether family medicine physicians should play a role providing education about PR to individuals who require transfusion. Respondents were divided on this issue: 42% believed family medicine physicians should play a role educating individuals who require a transfusion about PR, whereas, 44% did not think this was a family physicians' role. Respondents who indicated physicians should not play an educational role were asked to respond to the open-ended question 'who should?' Sixty-five percent (13/20) of respondents who answered this question indicated that the individual who orders or administers the blood product should educate the patient about PR. Other answers to this open-ended question included: the blood bank, hematologist/internist, nurse specialist, and transfusion medicine specialist. Three individuals commented that they didn't know who should be responsible for patient education about PR, i.e.: "no idea'", "beyond our scope", and "don't know enough to say".

Sub-analysis indicated that 68% of physicians who believed family physicians should play an educational role with patients and 45% of respondents who did *not* think family physicians should have an educational role were interested in receiving information about PR.

Risk Acceptability

Physicians were asked to indicate their willingness to accept three different risks associated with PR using a five-point Likert scale (yes, willing to accept; somewhat willing to accept;

neutral; somewhat unwilling to accept; and no, unwilling to accept) (Figure 7). Just under 50% of respondents were 'willing' or 'somewhat willing' to accept a 20% lower therapeutic efficacy of PR blood products, 24% indicated a neutral response, 13% were 'somewhat unwilling', no one was unwilling and 13% did not answer this question. When asked about the acceptability of the theoretical risk that patients may become immunized to the chemicals used in PR, 31% of respondents were 'willing' or 'somewhat willing' to accept this risk and the same proportion were 'somewhat unwilling' to accept this risk. Almost 25% indicated neutral and 13% did not answer this question. Of the three risks, the risk that chemicals used in PR may be carcinogenic was least acceptable to respondents; just one individual (2.2%) was willing to accept this risk. Just over 26.7% were 'somewhat willing', but 40% of respondents were 'somewhat unwilling' or 'unwilling' to accept the risk that chemicals used in PR may be carcinogenic. Thirteen percent of respondents did not answer this question.

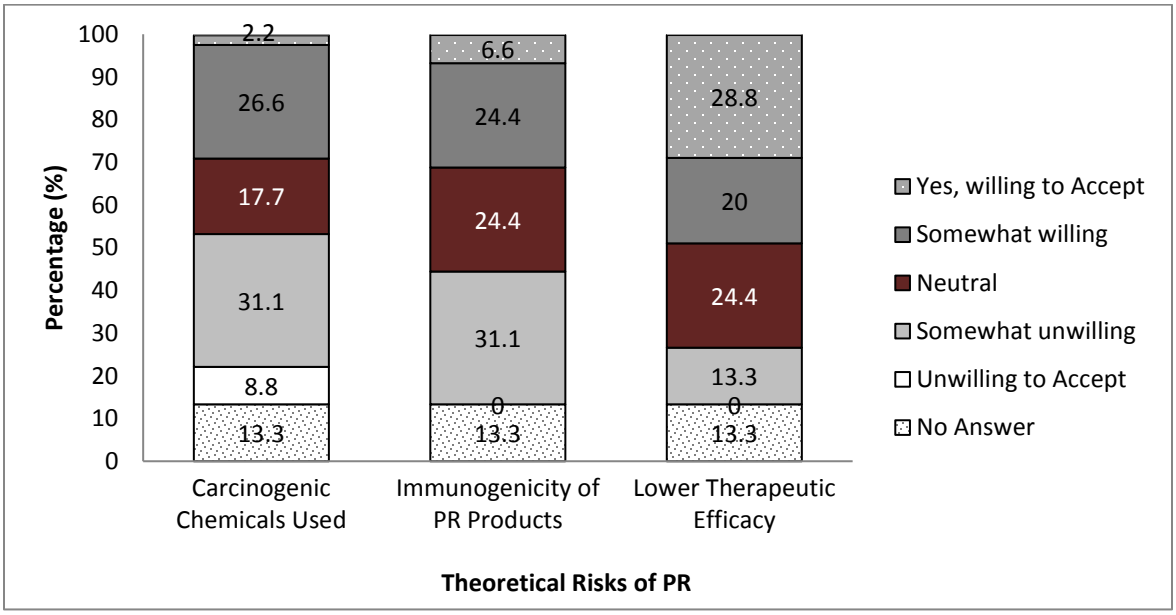


Figure 7: Acceptability of risks to family physicians in Ontario

DISCUSSION

This is the first study that we are aware of to examine physician knowledge, perceptions and awareness of PR for cellular blood products. We surveyed two different physician populations in Canada, (family medicine physicians from Ontario and specialists from across the country) and found both similarities and differences in the opinions, knowledge levels and needs of these two groups, these are summarized in Table 3. Findings from both surveys clearly indicate a dearth of knowledge of PR among Canadian physicians. Awareness of PR was higher in the survey of specialists. However, this should be interpreted cautiously as this sample was skewed by a large proportion of hematologists who would be expected to have greater knowledge of PR. Knowledge of PR among specialists without hematological expertise is lower.

Physicians need and desire information about PR and our findings suggest that if the decision is made to implement PR for blood in Canada, considerable effort should be made to educate both family physicians and specialists about PR; albeit with some consideration for the different roles, information needs, and preferences of these two groups. Physicians were most interested in being informed of the risks and benefits of PR and the differences between PR and non-treated blood products. Physicians were significantly less interested in receiving information about the

techniques of PR or information about how PR might change current testing on donated blood, perhaps perceiving these as blood supplier, not physician level issues.

	SURVEY 1: CANADA-WIDE SURVEY (Specialists)	SURVEY 2: ONTARIO-WIDE SURVEY (Family Physicians)
POPULATION	Physician specialists from across Canada representing a range of specialties (n=155).	Family medicine physicians from across Ontario (leads of Family Health Teams) (n=45).
AWARENESS	Divided in awareness of PR for blood; almost 50% indicated some awareness.	Extremely low awareness of PR, only 1 respondent (2.2%).
RISK ACCEPTABILITY	Least acceptable to specialists were the theoretical risks of acute non-infectious complications (32.9 %) and the risk of carcinogenic effects of chemicals used (30.3%). Most willing to accept the risk of shortened shelf life (31.6%).	Least acceptable to family physicians were the theoretical risks that chemicals added could have a carcinogenic effect (8.8% were unwilling and 31.1% somewhat unwilling) and the risk of immunogenicity of PR treated blood products (31.1%). Most willing to accept risk of lower therapeutic efficacy (28.8%).
KNOWLEDGE NEEDS	Want information about the risks of PR treated blood products and results from clinical trials. Specialists were also interested in the differences between PR and non-PR products and the benefits of PR products. Format – email was the preferred method of receiving information. Seventy-two percent were interested in receiving information about PR from the blood supplier.	Want information about the risks and benefits of PR and the differences between PR and non-PR blood products. Format – journal article from CMAJ or Canadian Family Physician

Table 3: Comparison of main results from both surveys

The preferred formats for receiving information about PR differed slightly between physician groups. Specialists considered email to be the most effective format for receiving information about PR, followed by short online interactive modules and websites; and family medicine physicians preferred to receive information about PR from a journal article in *Canadian Family Physician* or the *Canadian Medical Association Journal*. But these formats are not mutually exclusive and a multi-pronged approach using an email that contains a link or copy of a journal article, a website or an interactive module could also be effective. Providing physicians with a compendium of options for learning about PR may be the best strategy for encouraging the uptake of relevant information according to individual needs and contexts.

For implementation of PR of blood products to succeed, it must be acceptable to physicians. The possibilities that PR blood products could cause acute non-infectious complications, provoke an immune response, or engender carcinogenic risk were least acceptable to respondents who were more willing to tolerate risks that could potentially impact the supply of blood and blood products (such as lower therapeutic efficacy and shortened shelf life) compared to risks that could cause harm to patients. At the time this study was initiated there was evidence that therapeutic efficacy as measured by post transfusion platelet response could be lower for the three PR methods for platelets; although recent evidence does not suggest any

major concerns related to increased risk of bleeding (4) (13). Our finding, that physicians are least accepting of risks that could potentially pose harm to recipients suggests the technique with the best safety profile will be most acceptable to physicians.

Family medicine physicians were divided over whether or not it is their role to inform patients requiring transfusion about PR. Some believed this should be done by the person prescribing, ordering or administering the transfusion as part of the informed consent process. However, in situations like scheduled surgeries where it is the physicians' responsibility to give patients adequate time and information to consider blood transfusion options and alternatives, this could be the family physician (14). Regardless of whether physicians' roles are formalized through the informed consent process, they will require knowledge and awareness of PR to stay current in their practice.

Both surveys provide valuable insight into physicians' knowledge and perceptions of PR for blood products, which have been lacking until now. However these findings need to be considered alongside the following limitations. These surveys were conducted in 2009 and 2011, since then there have been advances in the development and awareness of PR, thus this report cannot be assumed to reflect current knowledge and awareness among Canadian physicians. A recent article on PR has tried to reach a broader audience than just Transfusion Medicine specialists which may have increased physician awareness (15) The questions on the two surveys were not identical, in part because they were intended to serve different audiences, but also because they were conducted at different points in time.

Despite including representation from all specialties, the Canada-wide survey had a very low response rate, and a large number of questions yielded 'no answer' from some respondents. The geographic representation of respondents was fairly close to the national distribution (16) however, Ontario was significantly over-represented, Alberta was slightly over-represented, and Quebec and BC were somewhat under-represented. The Ontario survey of family practice physicians was administered to leads of the Family Health Teams. Given their leadership positions, these individuals may be more knowledgeable about PR for blood, thus awareness of PR for the family physician population may be overestimated for the family physician population. These limitations call into question the generalizability of findings to the physician population across the entire nation.

Unintentionally, survey questions focused disproportionately on potential risks associated with PR and to a lesser extent benefits. Risk perceptions and risk tolerance are informed by perceptions of both risks and benefits (17), a more balanced approach to ascertaining perceptions may have yielded different results.

To ensure the successful implementation of PR for blood components in Canada physicians' need to be informed and engaged. These surveys provide the first evidence of insight into physicians' awareness of PR, risk tolerance, preferences and knowledge needs, which can be used to help inform knowledge transfer strategies so that Canadian physicians are adequately equipped to fulfill their clinical roles.

ACKNOWLEDGMENTS
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