R-fact study: risk factors for alloimmunization after red blood cell transfusions : methodology, risk factors and challenges in transfusion medicine research

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ADDENDUM

SHORT SUMMARY

KORTE SAMENVATTING (DUTCH SUMMARY)

ACKNOWLEDGMENTS (DANKWOORD)

CURRICULUM VITAE

SHORT SUMMARY

A matched case- referent study was designed (presented in **chapter 2**) where a "clinical risk period for alloimmunization" was defined for cases as the period in which transfusion most likely caused the observed primary alloimmunization. Potential transfusion related risk factors and clinical risk factors were studied in this implicating period. We designed a new incident user cohort study in a general transfused patient population in **chapter 3**, and observed that the risk of alloimmunization increases up to 7% up until 40th transfused unit, and the risk was comparable between men and women. We then focused on the transfusion related risk factors for alloimmunization. Next, we studied if the storage time of transfused RBCs was a risk factor of alloimmunization in **chapter 4**; and found that given our study design and population, the storage time of RBCs is not associated with post-transfusion risk of alloimmunization within the clinically relevant storage time ranges of 7-28 days. In **chapter 5**, we examined the association between the transfusion intensity and the risk of clinically relevant RBC alloantibody formation in a previously non-transfused, non-alloimmunized cohort using another incident new user cohort study design; and did not find a difference between the intensively transfused (with intensive transfusions studies separately as ≥5, ≥10 and ≥20 units transfused in 48 hours) and non-intensively transfused patients, and their risk of alloimmunization. In **chapter 6**, we showed that the use of corticosteroids and other immunosuppressants was associated with a lower risk of clinically relevant red cell alloantibodies against donor red blood cells. Finally, using results from ISBT 2012 conference at Cancun, we aimed to delineate the distinction between etiologic and prediction research, issues of confounding accompanying these research aims and how a multivariate model deals with confounding. To this effect we provided educational messages that might serve as a point of reference to deal with these methodological issues in **chapter 7**.

SAMENVATTING (DUTCH SUMMARY)

In **hoofdstuk 2** hebben we een cohort gevolgd van patiënten die voor het eerst een transfusie ontvingen. Het risico op allo-immunisatie liep op tot 7% bij de 40st transfusie en was vergelijkbaar tussen mannen en vrouwen. Om transfusie-gerelateerde risicofactoren voor allo-immunisatie verder te onderzoeken hebben we vervolgens een gematchte case-referent studie opgezet (zoals beschreven in **hoofdstuk 3**). Hierbij werd een "klinische risico periode voor allo-immunisatie" voor cases gedefinieerd als de periode waarin gegeven transfusies het de hoogste waarschijnlijkheid voor het veroorzaken van een primaire allo-immunisatie hadden. Mogelijke transfusie-gerelateerd en klinische risicofactoren werden voor deze risico-periode geanalyseerd. Vervolgens onderzochten we in **hoofdstuk 4** of de bewaarduur van RBC een risicofactor voor allo-immunisatie was. Met onze studie-opzet en binnen deze populatie vonden we geen associatie van klinische relevante bewaarduren van 7-28 dagen met het risico op allo-immunisatie na transfusie. In **hoofdstuk 5** onderzochten we of transfusie intensiteit geassocieerd was met het risico op klinisch relevante RBC allo-antilichamen in niet eerder getransfundeerde en niet eerder ge-allo-immuniseerde patiënten en vonden geen verschil in het allo-immunisatie-risico tussen intensief getransfundeerde (gedefinieerd als ≥5, ≥10 en ≥20 eenheden binnen 48 uur) en niet-intensief getransfundeerde patiënten. In **hoofdstuk 6** laten we zien dat het gebruik van corticosteroïden en andere immuunsuppressiva geassocieerd is met een lager risico op klinisch relevante allo-antilichamen tegen rode bloed cellen van de donor. Tot slot hebben we resultaten van een survey onder bezoekers van de ISBT 2012 in Cancun gebruikt om het onderscheid tussen etiologisch en predictie onderzoek duidelijk te maken en de verschillende rollen van confounding en het gebruik multivariate modellen in beide typen onderzoek te benadrukken. Hiertoe geven we in **hoofdstuk 7** een educatieve uitleg over deze onderwerpen.

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A PhD project is an encapsulation of years of effort and commitment by a harmonious team culminating in a thesis; much like a balanced football team ending an arduous season with the championship trophy. This thesis is no exception and it would be fitting to extend my gratitude to the team, bringing this match to its finale.

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CURRICULUM VITAE

Saurabh Zalpuri was born on the 19th of February, 1982 in Chandigarh, India to Susheel Zalpuri and Padma Zalpuri. In April 2000, at the age of 18 years, he graduated from Bharatiya Vidya Bhavan High School, Chandigarh with biology, chemistry, physics, English and sports education as core subjects. He then enrolled in Moscow Medical Academy I.M. Sechenov in September 2000 and graduated as a medical doctor in June 2006. Following his graduation, he was admitted to Utrecht University, Bio-Medical Sciences Faculty on a Utrecht Excellence Scholarship for a two year prestige master's programme in Clinical Epidemiology. During the master's programme, he completed his practical internship at the Julius Center, Utrecht under the supervision of Dr. Cuno Uiterwaal; an optional internship at Charité, Berlin at the Department of Social Medicine, and finished his master's thesis at the AIDS foundation East-West, Amsterdam. After graduating as a Clinical Epidemiologist in August 2008, he began his PhD project at the department of Clinical Epidemiology, Leiden University Medical Center and the department of Clinical Transfusion, Sanquin Research in Leiden. The results from this PhD project are described and discussed in this thesis. He is currently employed at MSD/ Merck, the Netherlands, as an associate principal epidemiologist.