(e) ISSN Online: 2321-9599

(p) ISSN Print: 2348-6805

ORIGINAL ARTICLE

Strategic framework of safe and effective blood transfusion services

[1]Ritcha Saxena, [2]Melad Ahmed, [3]Jeffrey Messner

[1]Professor, [2]Assistant Professor, Department of Pathology, Seba University, Seba, Libya, North Africa
[3]Specialist, Department of Pathology and Transfusion Medicine, Seba Medical Center, Seba, Libya, North Africa

ABSTRACT:
Blood banking has advanced significantly in the past few centuries and has become a crucial component of healthcare. The life expectancy and quality of life of patients with a variety of acute and chronic illnesses is significantly increased due to transfusion, and it helps save millions of lives. All healthcare facilities that perform transfusions must have timely access to safe blood and blood products and data on best clinical transfusion practices, but in many developing and low-resource nations, there is a significant gap between blood requirement and blood availability. Furthermore, recognition of transfusion-associated complications and related information is not widely available everywhere. Despite their ubiquitous use, transfusion decisions are usually made without the proper training and on the basis of scant, frequently subpar evidence.Appropriate laws, regulations, frameworks, procedures, and structures are a necessity in order guarantee the security, efficacy, accessibility, and prompt availability of blood and blood products. However, there are many circumstances, particularly in less developed nations, when these requirements have hardly been put into practice.It is crucial that pathology and transfusion medicine departments worldwide collaborate to improve training, share best practice experiences, and advance the development of accepted standards in transfusion medicine in order to make high significant impact and lasting changes.This article aims to evaluate the issues and challenges with blood transfusion, and opportunities for improvement of blood banking services in the current climate
Keywords: Blood banking, transfusion, voluntary donor, transfusion-associated infection, nucleic acid amplification

Corresponding author: Ritcha Saxena. Professor, Department of Pathology, Seba University, Seba, Libya, North Africa

This article may be cited as: Saxena R, Ahmed M, Messner J. Strategic framework of safe and effective blood transfusion services. J Adv Med Dent Scie Res 2014;2(4):220-224.

INTRODUCTION

Medicine has made significant progress today. A contemporary blood banking network, however, has not been able to keep up with that advancement.Since the early 1900s, significant progress has been made in our understanding of blood components, blood storage, and blood type. Medical professionals from a variety of specialties, including pathology, hematology, anesthesia, and pediatrics, contribute to the field of blood banking and transfusion services.Blood donation continues to save countless lives following medical emergencies such as trauma, delivery, surgery, transplant, and other conditions.[1-4]Transfusion of allogeneic blood products, especially RBC infusion, is one of the most common interventions in clinical practice. Over the past few years, risk and safety concerns,as they pertain to blood transfusion, have taken centerstage in the industry andtheprimary focus continues to be on making blood transfusion safe.Allogeneic blood transfusions have a long history of being associated with a variety of complications. Improvements in blood banking (such as testing for antibodies and infectious agent markers), have significantly reduced some risks (such as transfusion reactions and the pathogen transmission), while they are unlikely to ever be entirely eradicated.Multiple studies are being conducted on the impact of blood storage age on patient outcomes; the findings of these investigations, if they show that the universally acceptable shelf-life of stored blood is prolonged and should be revised, might fundamentally alter the blood bank paradigm. This is another possible danger to safe and easily accessible transfusions. Furthermore, transfusion-related direct and indirect expenses have shown to be gradually increasing, which is another reason to improve blood banking practices.[5-9]

The spread of infection via blood transfusion risk factor has received the greatest attention.Guidelines for blood safety have been seen as essential since 1981, when the global HIV/AIDS pandemic began, in order to stop the spread of HIV and other transfusion-associatedinfections (TAIs).[10-12]Even though blood transfusion is likely much safer today than it has ever been, it is the role of the blood banking department to restore faith in this process. Blood banking has become a semi-clinical specialty; in contrast with other pre-and para-clinical disciplines, it deals not only with samples but also with living donors and recipients. Many areas require particularconsideration, including blood storage and management, spreading awareness in society and debunking misconceptions about transfusions, outlining the function of blood banks in general hospitals along with the role of physicians in blood donation. [13-15]

Blood services are at extremely varied stages of development around the world.We have reached an age where resource-rich nationsnow enjoy broad

exemption from TAIs, while also acknowledging that zero risk transfusions is a distant goal.The likelihood of an HIV or HCV infection from a blood donation is extremely low in developed nations, because of the implementation of strict donor deferral criteria, along with more sensitive screening tests like nucleic acid amplification testing (NAT).[16-19]However, people continue to perish in many developing nations owing to a lack of blood and blood products, and many more are at danger of contracting an infection through unregulated blood transfusions.An overall shortage of blood, especially from volunteer donors; few and inconsistent testing facilities; extremely limited availability of blood components; and a shortage of healthcare professionals in the field of blood banking are all factors that contribute to the poor infrastructure of blood transfusion services.[20,21]High prevalence of infectious agents and a lack of motivation to donate result in increased incidence of infections in donated blood, including HIV, HBV, HCV, syphilis, and even other infectious diseases like West Nile virus, malaria, and chagas.[22-23]

To improve the detectable limit of pathogens, novel advances have been made to increase the sensitivity of diagnostic techniques. Modern tests have also been introduced, in addition to boosting the sensitivity of older tests,as pathogens evolve, and newer infections have constantly become risks.[24]Earlier, some pathogens were never considered a concern during transfusions, however, new transfusion-related infections have come to light as a result of changes in human and animal behavior, advances in knowledge and detection methods, and increased awareness.The greatest risk is posed before a specific agent is identified as a potential problem, a screening test for that risk is developed, and the addition of such tests to any laboratory's inventory of screening tests.[25] The potential use of products from donors who may have recently contracted an illness, but in whom current tests cannot detect the presence of the infectious agent also carries a reduced, but still significant risk. Since newly emerging infectious diseases are bound to crop up periodically and consequently put our blood supply at danger, it is the need of the hour to use the lessons learned in the past to proactively address the challenges of the future.

The price of safe, untainted blood is another facet of this issue. Costs must be incurred in order to make safe blood and blood products available.[26,27] However, an insufficient or unsafe blood supply is ultimately considerably more expensive, both financially and in terms of human lives. Therefore, it is essential to consider new approaches that maximize blood safety by minimizing or eliminating major—rather than minor—concerns, or that concurrently addressvarious transfusion-associated risks while having the least negative impact on blood availability and prices. The reactive approach to risks related to infectious disease, with the adoption of each new deferral criterion or screening test procedure in response to the issue of the day, stands in stark contrast to this approach. As new infectious agents are discovered, it will become increasingly difficult to sustain this antiquated strategy due to the cumulative adverse impact on cost and blood supply.

BLOOD SAFETY AND SAFE DONATION

Global research suggests that inadequate donor selection procedures, poor organization and uncoordinated blood transfusion services, as well as inessential clinical use of blood and blood products are all major factors that contribute to unsafe transfusion.[28,29] Severalother challenges include dearth of voluntary blood donors; sluggish implementation of national blood policies and weak blood regulatory systems; poor quality management of screening tests, blood grouping, and compatibility testing; improper clinical utilization of blood; and a lack of adequate funding for blood safety.

For all these reasons, the establishment of appropriate blood banking frameworkmust be a fundamental component of the global health strategy and healthcare infrastructure. It is crucial for blood bank departments all over the world to collaborate to share best practices, advance education and training, and aid in the development of accepted standards in blood bankingso as to create lasting impact and successful reforms.

Various techniques, such as enzyme linked immunosorbent assay (ELISA), have historically been used by blood banks for donor screening. Other tests with higher sensitivity or shorter turnaround times, such as the chemiluminescence (CLIA)/enzyme-linked fluorescence assay (ELFA), nucleic acid testing (NAT) and red cell antibodies screening, has also been implemented by many blood banks internationally, contributing to blood safety. In the future, it is anticipated that methods for processing blood, such as leukoreduction, irradiation, and pathogen inactivation, will play a bigger part in improving blood safety.[30-37]The purpose of treating blood components with pathogen inactivation is that it is again, as a safety measure. In low-resource nations, where donor infection rates are frequently high, donor bases are less stable, and reagents, expertise, and technology for microbiological testing are intermittently available, pathogen inactivation appears to have a major potential influence.[14]

Safe blood saves lives in a variety of situations, not the least of which are emergencies. Blood transfusions and blood products are essential for during gestation, to both the mother and the child; to ensure the survival and quality of life of people with life-threatening illnesses like cancer, immune deficiencies, and hemophilia; as well as for treating traumatic injuries and performing medical and surgical procedures.

A voluntary donor is someone who gives blood without expecting anything in return, thereby providing safe blood, because they are driven

by compassion, a desire to help others, and a sense of moral obligation or social responsibility. Hence, they are likely to be truthful about their medical history and their eligibility to donate.[38,39] A voluntary donor who donates on a regular basis is thought to be safer than occasional voluntary donors. In contrast, family and replacement donors are likely to be unaware or blithe about health issues that would make them ineligible to donate. Replacement donors may withhold information regarding their health status or lifestyle choices out of a desire to preserve the life of a family member or out of a fear of upsetting their loved ones. Because of this, there is a higher chance that an infection will spread. Hence, they are not actually safe donors, because they are coerced into giving blood.[40-43]Professional or paid donors may occasionally be misidentified as replacements.Typically, paid or commercial donors have the highest rate of transfusion-transmissible illnesses since they frequently indulge in lifestyles that put them at risk for contracting HIV and other blood-borne illnesses that may be transmitted through their blood.[44-46]Researchcontinues to show that paid donors have high likelihood of blood-borne infections than unpaid donor populations. The pattern analysis also indicates that the risk differential between populations of paid and unpaid donors has not decreased over time. The likelihood of blood donations within the window period, when blood-borne viruses may not be detectable, notably in serologic screening tests, is higher among paid donors, according to evidence.[47,48]

The author of a study on blood banking in China highlights a formerly common practice of using paid donors, usually from underdeveloped rural areas, to augment their income. The new blood donation law, however, which forbids all paid whole-blood donations for clinical use and encourages all Chinese residents, who meet the health requirements for blood donation, to give blood voluntarily, transformed the situation in China. It was also noted, however, that several unauthorized collecting facilities continued to display extremely high viral infection rates.[49] In another article from Chile, the authors indicated that a proportion of voluntary, unpaid blood donors has increased, directly leading to decreased frequency of viral indicators in the donor pool.[50]

The incontrovertible evidence identified above indicates a need for novel initiative that focuses on a transition away from paid and replacement donors. There is ample proof that both donor categories pose a higher risk.

HEALTH ECONOMICS

According to recent studies, the benefits of significant and ongoing costs of blood safety should be considered against further expensive clinical trials. Such trials are required to establish a sufficient empirical basis for the use of transfusion and to determine when transfusion is necessary and effective.[51-54]Some studies also reveal that the implementation of NAT does lessen hazards, but those risks were already extremely low before its introduction. Recent analysis also cast shadow on the cost-effectiveness, while another inquires as to whether other safety-improving methods would be more beneficial.[55,56]

Global blood services experience a contradiction. The balance between rich and developing countries would become more equitable if infrastructure investments were made in developing nations. It is crucial that the assistance provided by developed, wealthy nations legitimately acknowledge the competence and capacity of another nation to make investments and bring about long-lasting change.The process of securing new investment to implement such changes and the ensuing recurrent funding to guarantee the changes are sustainable do, in fact, necessitate the highest level of government assistance in any nation.

TRAININGS IN BLOOD BANKING

To ensure that improvements can be made, sustained, and improved, training and learning are required. It is imperative that the World Health Organization collaborate with other blood banking societies like AABB, NACO (National AIDS Control Organization, India), and (recently created group that aim to strengthen the blood transfusion system in Libya), along with others to create detailed strategies for teaching and education. It is recommended that global transfusion societies offer additional grants to help people working in blood banking services in developing nations to receive training in transfusion medicine. Training could involve working with advanced techniques. By doing this, they will have access to the most recent developments in transfusion.

CONCLUSION

Blood banking generally involves donor screening, blood collection, component preparation, and blood testing and is more akin to a pharmaceutical activity. Research and active participation of specialists in patient treatment using cellular therapies and therapeutic apheresis are a part of transfusion medicine. Combining the manufacturing of high-quality cellular and noncellular blood components with the advancement of need-based research and clinical engagement by transfusion medicine experts is a challenge.In order to guarantee quality, effectiveness, and widespread access to blood and blood products, every nation must have well defined structures, methods, and strategies to implement the laws, rules, regulations, and guidelines related to blood banking.Given the rapid technological developments and the increasingly intricate systems and procedures in blood banking, novel measures must be initiated to ensure and increase blood safety. With this article, we aim to promote some of the current initiatives while also providing data on more

effective means of working to ensure that these initiatives are more broad, successful, and long-lasting.

REFERENCES

1. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood. 2008 Oct 1;112(7):2617-26. doi: 10.1182/blood-2008-07-077370.
2. Sharma R. South East Asia faces severe shortage of safe blood. BMJ. 2000 Apr 15;320(7241):1026.
3. Sardana VN. Blood banking services in India. Health Millions. 1996 Nov-Dec;22(6):11-3.
4. Chawla SC, Lal S. Blood safety and rational use of blood. J Indian Med Assoc. 1994 Jan;92(1):22-3.
5. Shander A, Javidroozi M. A reductionistic approach to aged blood. Anesthesiology. 2010;113:1–3.
6. Heddle NM, Cook RJ, Arnold DM, et al. The effect of blood storage duration on in-hospital mortality: a randomized controlled pilot feasibility trial. Transfusion. 2012;52:1203–12.
7. Lacroix J, Hebert P, Fergusson D, et al. The Age of Blood Evaluation (ABLE) randomized controlled trial: study design. Transfus Med Rev. 2011;25:197–205.
8. Steiner ME, Assmann SF, Levy JH, et al. Addressing the question of the effect of RBC storage on clinical outcomes: the Red Cell Storage Duration Study (RECESS) (Section 7) TransfusApher Sci. 2010;43:107–16.
9. Kanavos P, Yfantopoulos J, Vandoros C, Politis C. The economics of blood: gift of life or a commodity? Int J Technol Assess Health Care. 2006 Summer;22(3):338-43. doi: 10.1017/s0266462306051233.
10. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med. 1996 Jun 27;334(26):1685-90. doi: 10.1056/NEJM199606273342601.
11. Fiebig EW, Busch MP. Emerging infections in transfusion medicine. Clin Lab Med. 2004 Sep;24(3):797-823, viii. doi: 10.1016/j.cll.2004.05.009.
12. Nanu A. Blood transfusion services: organization is integral to safety. Natl Med J India. 2001 Jul-Aug;14(4):237-40.
13. Barbara JA. Evolution of microbial safety. Hematol J. 2004;5 Suppl 3:S69-73. doi: 10.1038/sj.thj.6200426.
14. Barbara JA. The Rationale for Pathogen-Inactivation Treatment of Blood Components. Int J Hematol 80, 311–316 (2004). https://doi.org/10.1532/IJH97.04120
15. Glynn SA, Kleinman SH, Schreiber GB, Busch MP, Wright DJ, Smith JW, Nass CC, Williams AE. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. Retrovirus Epidemiology Donor Study (REDS). JAMA. 2000 Jul 12;284(2):229-35. doi: 10.1001/jama.284.2.229.
16. Velati C, Romanò L, Fomiatti L, Baruffi L, Zanetti AR; SIMTI Research Group. Impact of nucleic acid testing for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus on the safety of blood supply in Italy: a 6-year survey. Transfusion. 2008 Oct;48(10):2205-13. doi: 10.1111/j.1537-2995.2008.01813.x.
17. Roth WK, Weber M, Seifried E. Feasibility and efficacy of routine PCR screening of blood donations for hepatitis C virus, hepatitis B virus, and HIV-1 in a blood-bank setting. Lancet. 1999 Jan 30;353(9150):359-63. doi: 10.1016/S0140-6736(98)06318-1.
18. Vermeulen M, Lelie N, Sykes W, Crookes R, Swanevelder J, Gaggia L, Le Roux M, Kuun E, Gulube S, Reddy R. Impact of individual-donation nucleic acid testing on risk of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission by blood transfusion in South Africa. Transfusion. 2009 Jun;49(6):1115-25. doi: 10.1111/j.1537-2995.2009.02110.x.
19. Allain JP. Genomic screening for blood-borne viruses in transfusion settings. Clin Lab Haematol. 2000 Feb;22(1):1-10. doi: 10.1046/j.1365-2257.2000.00265.x.
20. Choudhury N. Transfusion Medicine in the year 2025: Facts or Fantasy? Asian J Transfus Sci. 2008 Jan;2(1):1-2. doi: 10.4103/0973-6247.39501.
21. Ramani KV, Mavalankar DV, Govil D. Study of blood-transfusion services in Maharashtra and Gujarat States, India. J Health PopulNutr. 2009;27:259–70
22. Jones KE, Levy MA, et al. Global trends in emerging infectious diseases. Nature. 2008;451:990–994. doi: 10.1038/nature06536
23. Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, Dodd RY. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009 Aug;49 Suppl 2:1S-29S. doi: 10.1111/j.1537-2995.2009.02279.x.
24. Pang T, Peeling RW. Diagnostic tests for infectious diseases in the developing world: two sides of the coin. Trans R Soc Trop Med Hyg. 2007 Sep;101(9):856-7. doi: 10.1016/j.trstmh.2007.04.014. Epub 2007 Jun 1.
25. Bihl F, Castelli D, Marincola F, Dodd RY, Brander C. Transfusion-transmitted infections. J Transl Med. 2007 Jun 6;5:25. doi: 10.1186/1479-5876-5-25.
26. AuBuchon JP, Birkmeyer JD, Busch MP. Cost-effectiveness of expanded human immunodeficiency virus-testing protocols for donated blood. Transfusion. 1997 Jan;37(1):45-51. doi: 10.1046/j.1537-2995.1997.37197176950.x.
27. Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR. Estimating the cost of blood: past, present, and future directions. Best Pract Res Clin Anaesthesiol. 2007 Jun;21(2):271-89. doi: 10.1016/j.bpa.2007.01.002.
28. Strauss RG. Blood donations, safety, and incentives. Transfusion. 2001 Feb;41(2):165-7. doi: 10.1046/j.1537-2995.2001.41020165.x.
29. Sanchez AM, Ameti DI, Schreiber GB, Thomson RA, Lo A, Bethel J, Williams AE; Retrovirus Epidemiology Donor Study. The potential impact of incentives on future blood donation behavior. Transfusion. 2001 Feb;41(2):172-8. doi: 10.1046/j.1537-2995.2001.41020172.x.
30. Chatterjee K, Coshic P, Borgohain M, Premchand, Thapliyal RM, Chakroborty S, et al. Individual donor nucleic acid testing for blood safety against HIV-1 and hepatitis B and C viruses in a tertiary care hospital. Natl Med J India. 2012;25:207–9.
31. Schmidt M, Geilenkeuser WJ, Sireis W, Seifried E, Hourfar K. Emerging Pathogens-How Safe is Blood? Transfus Med Hemother. 2014;41:10–7.
32. Shyamala V. Factors in enhancing blood safety by nucleic acid technology testing for human immunodeficiency virus, hepatitis C virus and hepatitis B virus. Asian J Transfus Sci. 2014;8:13–8.

33. Chandrashekar S. Half a decade of mini-pool nucleic acid testing: Cost-effective way for improving blood safety in India. Asian J Transfus Sci. 2014;8:35–8.
34. Sniecinski I, O'Donnell MR, Nowicki B, Hill LR. Prevention of refractoriness and HLA-alloimmunization using filtered blood products. Blood. 1988;71:1402–7.
35. Przepiorka D, LeParc GF, Stovall MA, Werch J, Lichtiger B. Use of irradiated blood components: Practice parameter. Am J Clin Pathol. 1996;106:6–11.
36. Lozano M, Cid J. Pathogen inactivation: Coming of age. CurrOpinHematol. 2013;20:540–5.
37. Alvarez M, Chueca N, Guillot V, Bernal Mdel C, García F. Improving clinical laboratory efficiency: Introduction of Systems for the Diagnosis and Monitoring of HIV Infection. Open Virol J. 2012;6:135–43.
38. WHO Blood Safety Indicators, 2007. Geneva: World Health Organization; 2009.
39. Improving blood availability and transfusion safety in the Americas; CD48/11 48th Directing Council; Washington DC: Pan American Health Organization/WHO Regional Office for the Americas; 2008
40. Sultan F, Mehmood T, Mahmood MT. Infectious pathogens in volunteer and replacement blood donors in Pakistan: a ten-year experience. International Journal of Infectious Diseases. 2007;11(5):407–412.
41. Matee MIN, Magesa PM, Lyamuya EF. Seroprevalence of human immunodeficiency virus, hepatitis B and C viruses and syphilis infections among blood donors at the Muhimbili National Hospital in Dar Es Salaam, Tanzania. BMC Public Health. 2006;6:21. [PMC free article] [PubMed]
42. Sharma RR, et al. Prevalence of markers of transfusion transmissible diseases in voluntary and replacement donors. National Medical Journal of India. 2004;17:19–21.
43. La Fleur CG, et al. Safety of donated blood in Guyana; International Conference on AIDS; 2004. abstract no. MoPeB3340
44. Beal R, van Aken WG. Gift or good? A contemporary examination of the voluntary and commercial aspects of blood donation. Vox Sanguinis. 1992;63:1–5.
45. Ekadashi R, Langer S. Seroprevalence of human immunodeficiency virus and syphilis in blood donors of Delhi. Indian Journal of Medical Microbiology. 2009;27:167–168.
46. Likatavicius G, Downs AM, Hamers FF. Worrying levels of HIV prevalence in blood donations in eastern Europe; International Conference on AIDS; 2004. abstract no. MoPeC3574.
47. van der Poel CL, Seifried E, Schaasberg WP. Paying for blood donations: still a risk? Vox Sang. 2002 Nov;83(4):285-93. doi: 10.1046/j.1423-0410.2002.00239.x.
48. Kalibatas V. Payment for whole blood donations in Lithuania: the risk for infectious disease markers. Vox Sang. 2008 Apr;94(3):209-15. doi: 10.1111/j.1423-0410.2007.01015.x.
49. Shan H, Wang JX, Ren FR, Zhang YZ, Zhao HY, Gao GJ, Ji Y, Ness PM. Blood banking in China. Lancet. 2002 Nov 30;360(9347):1770-5. doi: 10.1016/S0140-6736(02)11669-2.
50. Martinez C. Standardization and quality improvement of two international blood services in England and Chile. Presented at AABB meeting 2004, Baltimore (MD)
51. Fraser B. Latin America's urbanisation is boosting obesity. Lancet. 2005 Jun 11-17;365(9476):1995-6. doi: 10.1016/S0140-6736(05)66679-2.
52. Pillonel J, Laperche S; EtablissementFrançais du sang. Trends in risk of transfusion-transmitted viral infections (HIV, HCV, HBV) in France between 1992 and 2003 and impact of nucleic acid testing (NAT). Euro Surveill. 2005 Feb;10(2):5-8. doi: 10.2807/esm.10.02.00519-en.
53. Soldan K, Davison K, Dow B. Estimates of the frequency of HBV, HCV, and HIV infectious donations entering the blood supply in the United Kingdom, 1996 to 2003. Euro Surveill. 2005 Feb;10(2):17-9.
54. McClelland B, Contreras M. Appropriateness and safety of blood transfusion. BMJ. 2005 Jan 15;330(7483):104-5. doi: 10.1136/bmj.330.7483.104.
55. Offergeld R, Faensen D, Ritter S, Hamouda O. Human immunodeficiency virus, hepatitis C and hepatitis B infections among blood donors in Germany 2000-2002: risk of virus transmission and the impact of nucleic acid amplification testing. Euro Surveill. 2005 Feb;10(2):13-14. doi: 10.2807/esm.10.02.00522-en.
56. Alvarez do Barrio M, González Díez R, Hernández Sánchez JM, Oyonarte Gómez S. Residual risk of transfusion-transmitted viral infections in Spain, 1997-2002, and impact of nucleic acid testing. Euro Surveill. 2005 Feb;10(2):11-12. doi: 10.2807/esm.10.02.00521-en. PMID: 29183492.