Review Article

HBV genetic diversity and transfusion safety: A Conceptual Analysis and Integrative Model

Abstract

Background : Blood transfusion carry the risk of transmitting blood-borne infections. HBV genetic diversity and transfusion safety are concepts that are increasingly used in public discourse. However, how the concepts are used and how they are defined remains unclear. The objective of this study is to clarify the concepts emanating from the research project entitled : «Genetic diversity of HBV and its effect on the transmission risks in blood transfusion in Gabon».

Methods : Three databases were used in the Quantitative analysis: Pubmed, Medline and Google Scholar. We delimited the search to full articles in the databases. The eligibility criteria were based on published studies in English between january 2012 and decembre 2020, looking at the HBV genetic diversity and the transfusion safety. The Cochrane tool was used to assess the risk of bias. A systematic review was performed on concepts and definitions. Eligible publications were reviewed using concept analysis that led to the extraction of text data for the themes “definition”, “attributes”, “antecedents”, “consequences”, and “related concepts”. The quantitative methods was used to quatify the associations between HBV Genetic diversity and transmission risk examined in the literature.

Results: 2685 records were identified by primary and secondary search, of which 802 were retained after examination of titles and abstracts. 144 (18%) publications were included in the review, 123 dealing with hepatitis B virus, 38 with genetic diversity, 94 with transfusion safety and 94 with transmission risks were all coded. The final concept coding scheme contained 14 items, each with a satisfactory inter-author reliability score (r) (r ranging from 0. 6 and 1), coding hepatitis B virus, genetic diversity, transfusion safety, transmission risks, blood donation-transmission risks, demographic factors-transmission risks, HBsAg-transmission risks, Anti-HBc-transmission risks, viral load-transmission risks, measurement errors-transmission risks, viral load-HBsAg, viral load-Anti-HBc, sequencing-viral load, genotype-transmission risks. In the resulting integrative model, the elements were mapped to different levels of care.

Conclusion : This integrated theory suggests a number of directions to improve the understanding of transfusion safety in the context of HBV genetic diversity, to speak the same language. It provides a basis for creating better measures and interventions in transfusion

medicine.

Keywords: HBV; Genetic diversity ; Transfusion ; Transmission risks

1. INTRODUCTION

Hepatitis B virus (HBV) remains a major public health problem worldwide [1]. Near 400 million people worldwide are exposed or infected with HBV. Less than 1% of HBV-infected people are diagnosed in sub-Saharan Africa and a considerable increase in the number of people dying each year from cirrhosis and hepatocellular carcinoma (HCC) [2-3-4]. Chronic hepatitis B prevalence, as indicated by the presence of circulating HBsAg, ranges between 5% and 25% of the population, including blood donors [5-6]. Outcome of chronic infection or OBI is even not clear and the real place of OBI in the clinical and biological spectrum of HBV infection is not well known. The determinants and markers of disease outcome are not fully understood, but include viral, host and environmental factors. Viral factors include HBV genotype, HBV DNA level and HBeAg status. Abundant evidence has shown that the genetic diversity of HBV plays critical roles in modulating the pathogenesis in HBV infection [7-8-9-10-11-12-13].

Since the introduction of laboratory testing for hepatitis B virus (HBV) surface antigen (HBsAg) testing in the early 70s, the hepatitis B virus transmission risks has steadily declined or extremely low among récipients over the past four decades [14-6]. Despite these few failures, the impact of NAT for HBV reduced the residual risk of transfusion-transmission of this viruse below 1 per million donations in most developed countries where it was introduced [15]. In low-income and middle-income countries such Africa countries, testing or screening for HBV relies almost exclusively on HBsAg because HBV DNA testing is not universally deployed [16-17]. HBV transmission remains the most frequent transfusion transmitted viral infection in african countries [18-19-20-21-22]. The transmission risks of HBV remains associated with extremely low to high viral DNA levels in blood donors with occult HBV infection (OBI) or window period infection that are intermittently or not detectable even by highly sensitive individual donation (ID) NAT [23-24-25-26-27-13].The choice of a best approach therefore depends upon a clear understanding of these methods and concepts used.

This study based on a Conceptual Analysis and Integrative Model, aims to clarify the different concepts of the research project entitled « Genetic diversity of HBV and its effect on the transmission risks in blood transfusion in Gabon ».

2. METHODS

2.1 Study Design

This study is part of a larger research project on the ‘‘Genetic diversity of HBV and its effect

on transmission risks in blood transfusion in Gabon''.This study was the result of a quantitative analysis of several studies that focused on the genetic diversity of HBV and transfusion safety.A systematic literature review was performed on HBV, Genetic diversity, Transfusion and Transmission risk concepts and definitions. Eligible publications were reviewed using concept analysis that led to the extraction of text data for the themes "definition", "attributes", "antecedents", "consequences", and "related concepts". Concept analysis is a formal and rigorous process by which an abstract concept is explored (see figure 1), made transparent, defined, and differentiated from similar concepts to be used in theory formulation and communication about it [28-29]. The quantitative methods was used to quatify the associations between HBV Genetic diversity and transmission risk examined in the literature. All relevant studies reporting data on HBV-genetic diversity and blood safety published in English between January 2012 and December 2020 have been identified for context.

2.2 Research Question and strategy

The first step was to define operationally the concepts, the second step was to empirically derive a list of items which, in the judgment of some people, require a readjustment, The next step was to determine the magnitude of readjustment using the methods of psychophysics. The research question for our concept analysis study is : « Do HBV genetic diversity and transfusion safety researchers share the same concepts to describe the genetic diversity of HBV ? ». This research question clarified all the different articulations of concepts related to the context of the study. Studies on the genetic diversity of HBV and transfusion safety were systematically searched for in the databases, namely PubMed, MEDLINE, Google Scholar and we carried out a manual search in the main transfusion journals. This data search was performed using the following search terms, alone or in combination : « Transfusion safety AND concept OR construct OR definition » .

2.3 Selection Criteria

The preferred reporting elements for systematic reviews and meta-analyses (PRISMA) from the 2020 guidelines were used as a template for the report of this review [30]. Full-text articles including titles and abstracts were included in the review after independent analysis by two individuals from the research team. Any discrepancies in the analysis required a third opinion to discriminate (see figure 2). Papers were analyzed using a list of assessment criteria, which was developed based on criteria used to establish inter-rater reliability in the coding and identification of the use of the key terms and its evolution.

2.4 Quality of the Studies Included

The studies were assessed according to the scoring criteria [31]. For a study associated with a score of 1-3; 4-6; 7-9 was low, medium or high respectively. We only included moderate and high-quality studies.

2.5 Data Abstraction

Data extraction was done independently and information contributing to the conduct of this study. And if there was a difference of opinion between the two people responsible for the extraction, a third person was invited to resolve the ambiguity to reach a consensus. All data from eligible studies were extracted. All data abstractions have been verified by all members of the research team. However, studies for which data were not obtained were simply excluded from our study.

2.6 Review and coding process

Initially, we divided the publications equally between the four authors for the thorough reading process. In order to systemize the reading, we constructed an initial sorting template to capture the scientific approach in the articles. Besides identifying how the two concepts in each article were defined and used, we wanted to identify the HBV genetic diversity and transfusion safety for each article to gain an overview of the addressing the concepts.

2.7 Data analyses

After the initial coding and iterative readings of the 802 publications, the authors collaboratively identified four different types of usage of the concepts. To establish inter-rater reliability in the coding and identification of the use of the key terms, we conducted a statistical analysis as previously described by Shweta [32]. The coding sheet was developed in an iterative process. First, one author (DMB) randomly selected 144 full texts and initially coded the included definitions to develop a preliminary coding sheet. This sheet was then revised by discussion with JF, CM and TN. In a next step, we coded the definitions in the remaining full texts, while continuously extending the coding sheet if new codes emerged during the analysis of new full texts. In each article the given definition of HBV Genetic diversity and transfusion safety was coded independently by two members of the research team (DMB and JF). Discrepancies that emerged from this multiple coding strategy gave valuable insights for refining the coding scheme and were resolved by discussion [29]. Finally we discussed the codes within the research team and grouped them into meaningful clusters [33], i.e. aggregated them into different dimensions of HBV genetic diversity and transfusion safety. In a final analysis step for the development of the model, the method of concept mapping was applied to relate the

inductively developed categories to each other. Furthermore, we mapped the identified dimensions (diagnostic process dimension : Hepatitis B surface Antigen, anti-HBc antibody, Viral load and Sequencing) onto different levels of healthcare described in the literature. Concept mapping allowed visualising the hierarchical and relational nature of the categories across the concept themes [34]. We discussed the model until we found consensus within the team (DMB, JF, CM, TN).

RESULTS

The analysis resulted in four core components, which together defined all concepts. It was apparent that no theme could be missed in order to understand the concept. After initial coding and iterative reading of the 144 publications, the authors collaborated to identify four different types of use for each concept. Publication 144 resulted in a total of text passages which served as the basis for the qualitative analysis (see Table 1). One hundred and forty-three publications offered their own definitions of the concepts and 61% included at least one approximate citation of a definition. Characteristics of the included full texts are described in Table 2. Approximately 41% of the full texts originated from Africa and 7.6% are from Europe.

To establish inter-rater reliability in coding and identifying the use of key terms, the authors independently coded a subsample of publications (Table 3). The inter-rater reliability score (r) was associated with a score of 0.0-0.4 ; 0.5-0.7 ; 0.8-1.0 was a low, moderate or high level of agreement between authors respectively.

3.1 Hepatitis B virus

Viral hepatitis was first described by Lurman in 1885, who reported the development of jaundice after their vaccination with human derived smallpox vaccine. Blumberg detected Australia Antigen, in 1963 in serum from an Australian aborigine that reacted with an antibody in the serum of an American haemophiliac. The *Hepadnaviridae* family are DNA viruses infecting humans and other primates, rodents and avian hosts targeting the liver. The definition of hepatitis B is a complex exercise, as it depends on subjective and therefore debatable perceptions. There is no single definition recognised by all the players. According to some authors, there are 4 types of chronic viral B infection that can be distinguished according to the level of viral load, HBsAg positivity and transaminases (ASAT, ALAT).

(i) Chronic active hepatitis, characterised by positive HBsAg, elevated transaminases (AST, ALAT) and serum HBV DNA levels $>10^4$ copies/mL, (ii) chronic inactive hepatitis,

characterised by positive HBsAg with normal transaminases and serum HBV DNA levels < 10^4 copies/mL or undetectable, (iii) chronic hepatitis associated with immune tolerance characterised by HBsAg positive with serum HBV DNA >10^4 copies/mL but with normal transaminases and (iv) seropositive OBI (anti-HBV positive) and seronegative OBI (anti-HBV negative), characterised by HBsAg negativity, normal or fluctuating transaminases, extremely low levels of undetectable or intermittently detectable viral DNA (viral load < 10^3 copies/mL or < 200 IU/mL). On the other hand, for our study, chronic viral B infection was differentiated according to HBsAg positivity, so chronic viral B infection was defined as the carriage of anti-HBc antibodies and HBV DNA regardless of HBsAg (hepatitis B surface antigen) status. Related cases show that a blood donor can transmit a blood pathogen to a recipient when transfusing the blood of a former blood donor (HBV-seropositive samples from repeat donors with a prior negative donation within the prior 2 years) or during a blood transfusion from any HBsAg-negative donor (incident cases) [Tables 1, 3].

2.8 Genetic diversity

HBV is a partial double-stranded DNA virus, with a size of 3.2kb, 10 genotypes (A-J), 47 subgenotypes, 4 majors serotypes (adw, adr, ayw, ayr) and 4 reading frames (P, S, C, X). Despite the small size of the genome and the constraints dictated by its genomic organization, HBV shows great variability. The concept is further used in its plural form, according to several authors, genetic diversity is defined according to phenotype and genotypes. Phenotypic diversity is the result of the emergence of variants as a result of selection pressures (antiviral treatments or host immune pressure), these are the processes of selection of viral quasispecies as well as the different nucleotide modifications and their impact on the biology of the HBV infection. Genotypic diversity is the result of the molecular analysis of viral strains and the classification of these into genotypes and subgenotypes. For our study, genetic diversity was defined as a defect in proofreading activity in the HBV reverse transcriptase region of the polymerase or the set of different genotypes, subgenotypes and genotypic mutations in the HBV genome leading to chronic and/or HBsAg-negative forms of HBV infection in healthy individuals. Genetic diversity appears to be associated with outcomes of overt or chronic HBV infection in blood donors or recipients [Tables 1, 3]..

2.9 Transfusion safety

Blood-donor screening began in the 1940s with testing for syphilis, followed in the early 1970s by testing for hepatitis B surface antigen (HBsAg). Data from initial HBsAg screening demonstrating higher rates of infection in paid donors led to conversion to an all-volunteer

blood supply in the rich countries and many sub-Saharan Africa countries in the mid and after 1970s. The authors do not agree on a single use for ensuring the safety of labile blood products or blood components against HBV. The protective measure for blood is recruitment, selection of low-risk donors (voluntary unpaid donors) and prevention of TTIs through biological testing of blood products. For our study, blood safety is the combination of serological and molecular testing of all blood donors. The use of this concept is in the field of laboratory transfusion medicine and safer blood product from donor to recipient.The information collected in the literature review was then analysed to identify the attributes of this concept, such as donor selection (donor history questionnaire), diagnostic tools for HBV serological and molecular markers and interpretations, pathogen reduction technology, tracking and tracing of diagnostic information (tracing, backtracking, donor/recipient pair testing). Related cases show that a blood donor can transmit a blood pathogen to a recipient during transfusion if the diagnostic sources of risk are not well measured [Tables 1, 3].

3.4 Transmission risks

Attributes of TTIs that pose greatest risk to blood safety include an asymptomatic infectious phase in the donor and the ability to persist despite processing and storage. According to the literature, the risk of transmission is the central link between the diagnostic test used by blood banking services and its ability to detect blood-borne infections such as hepatitis B virus.
According to several authors, there are 4 forms of transmission risk. According to some authors, the risk of transmission corresponds to the risk of occult infection or immunosilent HBV infections, the risk of the window period, the risk of mutations (vaccine escape, diagnostic escape, antiviral resistance) and risk attributable to unit donations reflecting the contribution of test error (due to the relatively high prevalence of HBV). Risk can be expressed directly or by mathematical models. Transmission risk for our study was defined as a viremic threshold or probability of transmission during occult or overt infection from a particular blood unit. Post-transfusion infection has several dimensions, some factors are involved in the recognition of most transfusion-transmissible infections, these include: many TTIs are asymptomatic and the incubation period may be prolonged [Tables 1, 3].

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3.5 Model development

For the development of the model, we specified the quality of each dimension by dividing the identified dimensions into four different levels of health care including serological screening (hepatitis B surface antigen or HBsAg, hepatitis B core antibody or anti-HBc) and molecular

diagnosis (viral genome quantification or viral load, viral phylogeny or sequencing). None of the dimensions of blood safety identified in the literature focus on the effect of HBV genetic diversity in recipients of blood products. The integrative model of safety of labile blood products or blood components is presented in Figure 3.

1. Discussion

4.1 The importance of the underlying concept of complex systems for transfusion safety, strengths and limitations, practical implications

The objective of this literature review on transfusion safety in the context of HBV genetic diversity was to clarify each concept or facilitate their use and to propose an integrative model based on current patterns and trends in order to effectively address the risks of HBV transmission in our blood banks, especially in resource-limited settings. This study systematically analysed the different definitions of blood safety against the different forms of HBV infection found in the literature, identified 14 distinct elements or concepts of blood safety and proposed an integrative model based on these dimensions. For our study, the model emphasises that the key terms are related to each other. Prevention of the risk of post-transfusion transmission of all forms of HBV infection in blood components is achieved through the different dimensions subdivided into 7 lines of defence or prevention in our study (standard medical screening, post-donation screening, serological testing, viral load, pathogen reduction technology, lookback and sequencing). In addition, only a few publications develop the concepts further, addressing different levels of prevention, focusing mainly on clinical or medical screening of blood donors with safe blood products. One of the strengths of this study is the use of a systematic review method to identify conceptual definitions in the literature. This provided a panoramic view of the spectrum of existing definitions and allowed the development of an integrative model based on a literature dataset of over 80 comprehensive texts. In this way, this work adds to previous studies, which have been limited to the comparison of only a few definitions [35-36-37-38-39-40-41-42] or were less comprehensive [43-44-45].

A limitation of the study is that the identified dimensions or key terms are increasingly used or reflect predominantly Sub-Saharan African and Asian conceptual definitions. Further research should examine whether the dimensions or concepts identified in our study are applicable to other regions of the world. Although these concepts originate from a variety of traditions around the world, they share their paradigm of safe blood component transfusion or care [6-5]. The integrative model proposed in our study is a compass that allows researchers, clinicians and policy makers to speak the same language. It can have an impact on clinical practice if everyone is looking in the same direction regarding the provision of transfusion medicine care of labile blood products or blood components.

The adequate availability of blood is at the centre of the multiple challenges facing blood banking services worldwide. This work provides the developers of health policy reports with a comprehensive model of the dimensions of blood safety of blood components or recipients that should be taken into account if a blood donor- or recipient-centred approach to transfusion medicine is to be implemented, including increased accessibility to health services or improved quality of care in routine practice. The proposed model can also be used in transfusion medicine education and other health care settings to design new curricula with a greater emphasis on recipient orientation of labile blood products [46-47-48]. In addition, this proposed integrative scheme, the focus on transfusion medicine in the laboratory provides a basis for the operationalisation of different measures and interventions on recipients of different blood bags in future research. The analysis of the different tests in the transfusion medicine laboratory and their level of safety of labile blood products or blood components leads to two classes of resilience, namely maximum performance of the tests in the laboratory and a low risk blood product. This integrative scheme can be used to identify gaps in the measurement of blood products and possibly develop new assessment tools to fill these gaps and overcome the difficulties associated with measuring donor blood components or blood bags [19-49-50-51-52]. This is a prerequisite for a paradigm shift towards more patient-centred care, as this shift needs to be evaluated and monitored. This can only be done with the help of good measurement tools [53-54-55-56-57-58]. In order to increase the validity of the proposed model, which is based on a comprehensive systematic review, an evaluation of its relevance should be conducted by including different stakeholders (haemovigilance, clinicians, blood donors, recipients, etc). Furthermore, the mere fact that these 14 dimensions emerge from the literature on compound-based care does not automatically imply that they lead to positive outcomes for patients or recipients of these labile blood products. This should certainly be the subject of further research. However, in order to assess the outcomes of certain dimensions of labile blood product-centred care, we need to know which dimensions exist, which was the aim of this study.

4.2 Conclusion

Finally, of the 14 dimensions identified, the genetic diversity of the hepatitis B virus was not associated with the risk of transmission in blood transfusion, i.e. the definitions analysed did not contain information on what the various risks of HBV transmission mean in terms of transfusion policy, diagnostic strategies and health regulations.

Consent to publication

Not Applicable.

Availability of data and materials

Data used for this study is available on request.

Ethics declarations

Ethics approval and consent to participate

Not Applicable.

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Reference

1. World Health Organization. Global hepatitis report 2017. Available 03/04/2019. https://apps.who.int/iris/handle/10665/255016
2. Béguelin, C., Fall, F., Seydi, M., Wandeler, G. The current situation and challenges of screening for and treating hepatitis B in sub-Saharan Africa. Expert Review of Gastroenterology & Hepatology, (2018), 12:6, 537-546. https://doi.org/10.1080/17474124.2018.1474097
3. Seto, W.-K., Ying-Ru Lo, Jean-Michel Pawlotsky, Man-Fung Yuen. Chronic hepatitis B virus infection. The lancet, Vol 392 November 24, 2018. Pages 2313-2324. https://doi.org/10.1016/S0140-6736(18)31865-8
4. Saitta, C. , Pollicino, T. , Raimondo, G. Occult Hepatitis B Virus Infection: An Update.
   Viruses 2022, 14, 1504. https://doi.org/10.3390/v14071504
5. Allain, J.-P., Owusu-Ofori, S., Ye, X., Bisseye, C., El Chaar, M., Li, C. Hepatitis B Virus Chronic Infection in Blood Donors from Asian and African High or Medium Prevalence Areas: Comparison According to Sex. Viruses 2022, 14, 673. https:// doi.org/10.3390/v14040673
6. Roberts, D.J., Field, S., Delaney, M., Bates, I. Problems and approaches for blood transfusion in the developing countries. Hematology/Oncology Clinics, (2016), 30(2),
   477–495. https://doi.org/10.1016/j.hoc.2015.11.011
7. Zehender, G., Ebranati E., Fiaschi, L., Ciccozzi, M., Galli, M. HBV Virus in the Future.
   In: Borini A., Savasi M. (eds) Assisted Reproductive Technologies and Infectious
   Diseases. Springer, (2016), Cham. https://doi.org/10.1007/978-3-319-30112-9_2
8. Zhang, Z.H., Wu, C.C., Chen, X.W., Li, X., Li, J., Lu, M.J. Genetic variation of hepatitis B virus and its significance for pathogenesis. World journal of gastroenterology, (2016a), 22(1), 126–144. https://doi.org/10.3748/wjg.v22.i1.126
9. Zhang, Z., Zhang, L., Dai, Y., Zhang, Y., Li, J., Li, X. Occult hepatitis B virus infection: influence of S protein variants. Virology Journal, (2016b), 13 :10. https://doi.org/10.1186/s12985-

016-0464-z

10. Zhang, K., Liu, Y., Chen, R., Li, Q., Xu, Z., Si, L., Cheng, Y., Yang, Y., Chen, J., Xu, D., Lin, S. Antigenicity reduction contributes mostly to poor detectability of HBsAg by hepatitis B virus (HBV) S-gene mutants isolated from individuals with occult HBV infection. Journal of medical virology Volume 90, Issue2, February 2018, Pages 263-
270. https://doi.org/10.1002/jmv.24936

11. Zhu, H.L., Li, X., Li, J., Zhang, Z.H. Genetic variation of occult hepatitis B virus infection. World journal of gastroenterology, (2016), 22(13), 3531-3546. https://doi.org/10.3748/wjg.v22.i13.3531
12. Wu, C.C., Chen, Y.S., Cao, L., Chen, X.W., Lu, M.J. Hepatitis B virus infection: defective surface antigen expression and pathogenesis. World J Gastroenterol; (2018), 24(31): 3488- 3499. https://doi.org/10.3748/wjg.v24.i31.3488
13. Raimondo, G., Locarnini, S., Pollicino, T., Levrero, M., Zoulim, F., Lok, A.S., Allain, J.-P., Berg, T., Bertoletti, A., Brunetto, M.R. (2019). Update of the statements on biology and clinical impact of occult hepatitis B virus infection. Journal of hepatology, 71(2), 397–408. https://doi.org/10.1016/j.jhep.2019.03.034
14. Chevalier, Michelle S., et al. "Progress Toward Strengthening National Blood Transfusion Services — 14 Countries, 2011–2014." *Morbidity and Mortality Weekly Report*, vol. 65, no. 5, 2016, pp. 115–19. *JSTOR*, https://www.jstor.org/stable/24857905. Accessed 10 Aug. 2022.
15. Busch MP, Bloch EM, Kleinman S. Prevention of transfusion-transmitted infections. Blood [Internet]. American Society of Hematology. 2019; 133(17):1854–64. DOI: 10.1182/blood-2018-11-833996
16. Allain JP, Opare-Sem O. Screening and diagnosis of HBV in low-income and middle-income countries. Nature Reviews Gastroenterology & Hepatology [Internet]. Springer Science and Business Media LLC. 2016;13(11):643–53. DOI: 10.1038/nrgastro.2016.138
17. Pruett, C.R., Vermeulen, M., Zacharias, P., Ingram, C., Tayou Tagny, C., Bloch, E.M. The Use of Rapid Diagnostic Tests for Transfusion Infectious Screening in Africa: A Literature Review. Transfus Med Rev (2014), http://dx.doi.org/10.1016/j.tmrv.2014.09.003
18. Barro, L., Drew, V.J., Poda, G.G., Tagny, C.T., El-Ekiaby, M., Owusu-Ofori, S., Burnouf, T. Blood transfusion in sub-Saharan Africa: understanding the missing gap and responding to present and future challenges. International Society of Blood

Transfusion (2018). DOI: 10.1111/vox.12705

19. Candotti D, Tagny-Tayou C, Laperche S. Challenges in transfusion-transmitted infection screening in Sub-Saharan Africa. Transfusion Clinique et Biologique [Internet]. Elsevier BV; 2021;28(2):163–70. DOI: 10.1016/j.tracli.2021.01.007
20. Custer, B., Zou, S., Glynn, S., Makani, J., Tayou Tagny, C., EI Ekiaby, M., Sabino, E.C., Choudhury, N., Teo, D., Nelson, K., Peprah, E., Price, L., Engelgau, M.

Addressing Gaps in International Blood Availability and Transfusion Safety in Low and Middle Income Countries (LMIC): A NHLBI Workshop. Transfusion. 2018 May ; 58(5): 1307–1317. doi:10.1111/trf.14598.

21. Mremi A, Yahaya JJ, Nyindo M, Mollel E, et al. Transfusion-transmitted infections and associated risk factors at the Northern zone blood transfusion center in Tanzania : A study of blood donors between 2017 and 2019. PLOS ONE. 2021;16(3):e0249061. DOI: 10.1371/JOURNAL.PONE.0249061
22. Weimer, A., Tagny, C.T., Tapko, J.B., Gouws, C., Tobian, A.A.R., Ness, P.M., Bloch, E.M. Blood transfusion safety in sub-Saharan Africa: a literature review of changes and challenges in the 21st century. TRANSFUSION Volume 59, January 2019. doi:10.1111/trf.14949
23. Candotti D, Laperche S. Hepatitis B virus blood screening: need for reappraisal of blood safety measures? Frontiers in Medicine [Internet]. Frontiers Media SA. 2018;5. DOI: 10.3389/fmed.2018.00029
24. Farooq, A., Waheed, U., Zaheer, H.A., Aldakheel, F., Alduraywish, S., Arshad, M. Detection of HBsAg mutants in the blood donor population of Pakistan. PloS one, (2017), 12(11), e0188066. https://doi.org/10.1371/journal.pone.0188066
25. Makvandi, M. Update on occult hepatitis B virus infection. World journal of gastroenterology, (2016), 22(39), 8720–8734. https://doi.org/10.3748/wjg.v22.i39.8720
26. Seo DH, Whang DH, Song EY, Han KS. Occult hepatitis B virus infection and blood transfusion. *World J Hepatol* 2015; 7(3): 600-606 [PMID: 25848484 DOI: 10.4254/wjh.v7.i3.600]
27. Tseng, T.-C., Liu, C.-J. Occult Hepatitis B Infection. In: Kao, JH. (eds) Hepatitis B Virus and Liver Disease. Springer,(2021) Singapore. https://doi.org/10.1007/978-981-16-3615-8_17
28. Walker, L. O., & Avant, K. C. (2011). Strategies for theory construction in nursing (5th ed.). Boston, MA: Prentice Hall.
29. Wilson, J. , Mandich, A., Magalhães, L. Concept Mapping: A Dynamic, Individualized and Qualitative Method for Eliciting Meaning. Qualitative Health Research 2016, Vol. 26(8) 1151–1161. DOI: 10.1177/1049732315616623

30. Page MJ, McKenzie J, Bossuyt P, Boutron I, Hoffmann T, mulrow cindy d, et al. Updating guidance for reporting systematic reviews: Development of the PRISMA 2020 statement. Center for Open Science ; 2020. DOI: 10.31222/osf.io/jb4dx
31. Tetzlaff J, Page M, Moher D. PNS154 the prisma 2020 statement : development of and key changes in an updated guideline for reporting systematic reviews and meta-analyses. value in health [internet]. Elsevier bv. 2020;23:S312-S313. DOI :org/10.1016/j.jval.2020.04.1154
32. Shweta, Bajpai, R.C., Chaturvedi, H.K. Evaluation of inter-Rater Agreement and Inter-Rater Reliability for observational Data : An owerview of concepts and methods. Journal of the Indian Academy of Applied Psychology (2015), Vol.41, No.3, 20-27.
33. Lindgren, B.-T., Graneheim, U.H. Abstraction and interpretation during the qualitative content analysis process. International Journal of Nursing Studies, vol. 108, August 2020, 103632.https://doi.org/10.1016/j.ijnurstu.2020.103632
34. Singh, H., Sitting, D.F. Advancing the science of measurement of diagnostic errors in healthcare : the Safer Dx framework. BMJ Qual Saf. 2015 ; 24 (2) :103-10. http://dx.doi.org/10.1136/bmjqs-2014-003675
35. Bulent Cakal, Bilger Cavus, Alp Atasoy, Damla Altunok, Mehves Poda, Mesut Bulakci, Mine Gulluoglu, Mehmet Demirci, Leyla Turker Sener, Aslı Berru Arslan, Muzaffer Arikan, Filiz Akyuz, Comparison of S gene mutations in patients with occult and chronic hepatitis B virus infection,Virus Research, Volume 318, 2022,198855, ISSN 0168-1702, https://doi.org/10.1016/j.virusres.2022.198855.
36. Huang, Y.-S., Tseng, S.-Y., Chen, W.-W., Chang, T.-T., Peng, C.-Y., Lo, G.-H., Hsu, C.-W., Hu, C.-T., Huang, Y.-H. Clinical characteristics and outcomes of drug-induced liver injury in Taiwan: With emphasis on the impact of chronic hepatitis B infection. Journal of the Chinese Medical Association: March 2022 - Volume 85 - Issue 3 - p 286-294. doi: 10.1097/JCMA.0000000000000648
37. Steele, W.R., Dodd, R.Y., Notari, E.P., Haynes, J., Anderson, S.A., Williams, A.E., Reik, R., Kessler, D., Custer5, B., Stramer, S.L. HIV, HCV, and HBV incidence and residual risk in US blood donors before and after implementation of the 12-month deferral policy for men who have sex with men. Transfusion. 2021;61:839–850. https://doi.org/10. 1111/trf.16250
38. Sahmoud, S., Ashry, E.M., El Kalioby, M., Kamel, N. Knowledge Improvement of Blood Transfusion Safety Among Pediatricians: Post Educational Intervention.

Transfusion Medicine Reviews 35 (2021) 135–139. https://doi.org/10.1016/j.tmrv.2021.03.002

39. Beykaso, G., Mulu, A., Giday, M., Berhe, N., Selamu, M., Hailu, D., Teklehaymanot, T. Occult Hepatitis B Virus Infection and Its Risks of Cryptic Transmission in Southern Ethiopia. Infection and Drug Resistance 2022:15 619–630. https://doi.org/10.2147/IDR.S344668
40. Harvala, H., Reynolds, C., Gibney, Z., Derrick, J., Ijaz, S., Davison, K.L., Brailsford, S. Hepatitis B infections among blood donors in England between 2009 and 2018: Is an occult hepatitis B infection a risk for blood safety? Transfusion, (2021), 61(8), 2402-2413. https://doi.org/10.1111/trf.16543
41. Grubyte S, Urboniene J, Nedzinskiene L, Jelinskaite A, Zagminas K, Ambrozaitis A, et al. Prevalence, incidence and residual risk of transfusion transmitted viruses (HBV, HCV and HIV infections) in Lithuanian blood donors from 2004 to 2018: The incidence/window-period model study. Chemin I, editor. PLOS ONE [Internet]. Public Library of Science (PLoS). 2021;16(2):e0246704. DOI: 10.1371/journal.pone.0246704
42. Wahome, P.K., Kiende, P., Nakazea, R.J., Mwakidedela Mwasowa, N., Waweru NyamuI, G. Occult hepatitis B virus infections and risk factors among school-going adolescent voluntary blood donors in Kwale County Kenya, January 2020–June 2021: Cross sectional study. PLoS ONE 17(7): e0263473. https://doi.org/10.1371/journal.pone.0263473
43. Wongjarupong N, Oli S, Sanou M, Djigma F, Kiba Koumare A, Yonli AT, et al. Distribution and Incidence of blood-borne infection among blood donors from regional transfusion centers in burkina faso: A comprehensive study. The American Journal of Tropical Medicine and Hygiene [Internet]. American Society of Tropical Medicine and Hygiene. 2021;104(4):1577–81. DOI: 10.4269/ajtmh.20-0601
44. Guo, Y., Lan, Y., Jing, Y., Cai, B., Gong, H., Zhang, Y., Duan, Y. The Investigation of HBV Pre-S/S Gene Mutations in Occult HBV Infected Blood Donors with anti-HBs Positive. Canadian Journal of Infectious Diseases and Medical Microbiology Volume 2022, 8 pages. https://doi.org/10.1155/2022/1874435
45. El Ekiaby, M., Tanaka, J., van Drimmelen, H., Allain, J.-P., Lelie, N. Infectivity of hepatitis B virus (HBV) surface antigen (HBsAg) positive plasma with undetectable HBV-DNA: Can HBsAg screening be discontinued in Egyptian blood donors? Journal of viral hepatitis (2022). Volume29, Issue , Pages 330-339. https://doi.org/10.1111/jvh.13666

46. World Health Organization. GLOBAL STATUS REPORT ON BLOOD SAFETY AND AVAILABILITY 2021. Available 31.07.2022. http://apps.who.int/bookorders.
47. Zhou, K., Terrault, N.A. Gaps in Viral Hepatitis Awareness in the United States in a Population-based Study.Clinical Gastroenterology and Hepatology Volume 18, Issue 1, January 2020, Pages 188-195.e4. https://doi.org/10.1016/j.cgh.2019.05.047
48. Drews, S.J., Dodd, R.Y. Transfusion-Transmitted Infections. Practical Transfusion Medicine, (2022), (1) pages 153-167 . https://doi.org/10.1002/9781119665885.ch17
49. Ogbenna, A.A., Akinsete, A.M., Kalejaiye, O.O., Matthew, O.K., Sharma, D., Andrews, J., Kassim, A.A. Reduction in seroprevalence of viral transfusion-transmitted infections in southwest Nigeria in children with sickle cell disease using an enhanced screening strategy.British Journal of Hemaetology , 2022..https://doi.org/10.1111/bjh.18313
50. Bolcatoa, M., Russoa, M., Rodrigueza, D., Aprile, A. Patient blood management implementation in light of new Italian laws on patient's safety. Transfusion and Apheresis Science (2020). https://doi.org/10.1016/j.transci.2020.102811
51. Mabunda, N., Augusto, O., Zicai, A.F., Duaja, A., Oficiano, S., Ismael, N., Vubil, A., Mussa, T., Moraes, M., Jani, I. Nucleic acid testing identifies high prevalence of blood borne viruses among approved blood donors in Mozambique. PLoS ONE, (2022), 17(4): e0267472. https:// doi.org/10.1371/journal.pone.0267472
52. Bala Bhasker, P.M., Williams, S. Ensuring safe blood supply: A 2-year retrospective study on seropositivity of transfusion-transmitted infections among blood donors. J Clin Sci Res 2022;11:197-9. DOI: 10.4103/jcsr.jcsr_64_21
53. Haass, K.A., Sapiano, M.R.P., Savinkina, A., Kuehnert, M.J., Basavaraju, S.V. Transfusion-Transmitted Infections Reported to the National Healthcare Safety Network Hemovigilance Module. Transfusion Medicine Reviews 33 (2019) 84–91. https://doi.org/10.1016/j.tmrv.2019.01.001
54. Kracalik, I., Mowla, S., Basavaraju, S.V., Sapiano, M.R.P. Transfusion-related adverse reactions: Data from the National Healthcare Safety Network Hemovigilance Module — United States, 2013–2018. Transfusion. 2021; 61: 1424–1434. https://doi.org/10.1111/trf.16362
55. Gemechu, G., Abagez, W.E., Alemayehu, D.H., Tesfaye, A., Tadesse, D., Kinfu, A., Adane Mihret, A., Mulu, A. Occult Hepatitis B Virus Infection Among Blood Donors in the Capital City of Addis Ababa, Ethiopia: Implications for Blood Transfusion Safety. Front. Gastroenterol., 06 July 2022 Sec.Hepatology https://doi.org/10.3389/fgstr.2022.887260

56. Dean, C.L., Wade, J., Roback, J.D. Transfusion-Transmitted Infections : an Update on Product Screening, Diagnostic Techniques, and the Path Ahead. Journal of Clinical Microbiology, Vol. 56, july 2018. DOI: https://doi.org/10.1128/JCM.00352-18
57. Alkhateeb, Z. D., Maleek, M. I., & Faraj, A.. Applying RT-PCR standard detection procedures of HBV and HCV in Wasit blood bank. International Journal of Health Sciences, (2022), 6(S5), 1668–1679. https://doi.org/10.53730/ijhs.v6nS5.9676
58. Uche EI, Chukwukaodinaka NE, Akinbami AA, Adeyemi OI, Hassan AO, Bamiro RA, Ibrahim IN, Suleiman AM, Augustine B, Anaduaka DC. Common hepatitis B virus genotypes among blood donors in Lagos, Nigeria. Niger Postgrad Med J 2022;29:228-35. **DOI:** 10.4103/npmj.npmj_19_22

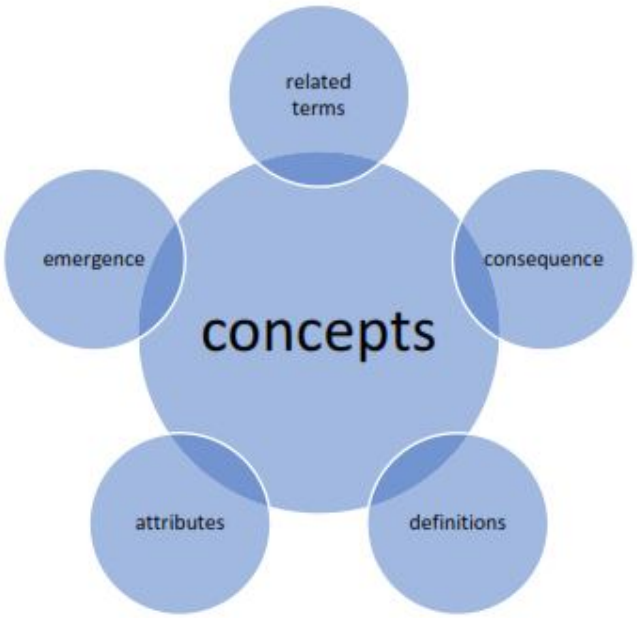

Figure 1 : Concept themes for the extraction of text passages.

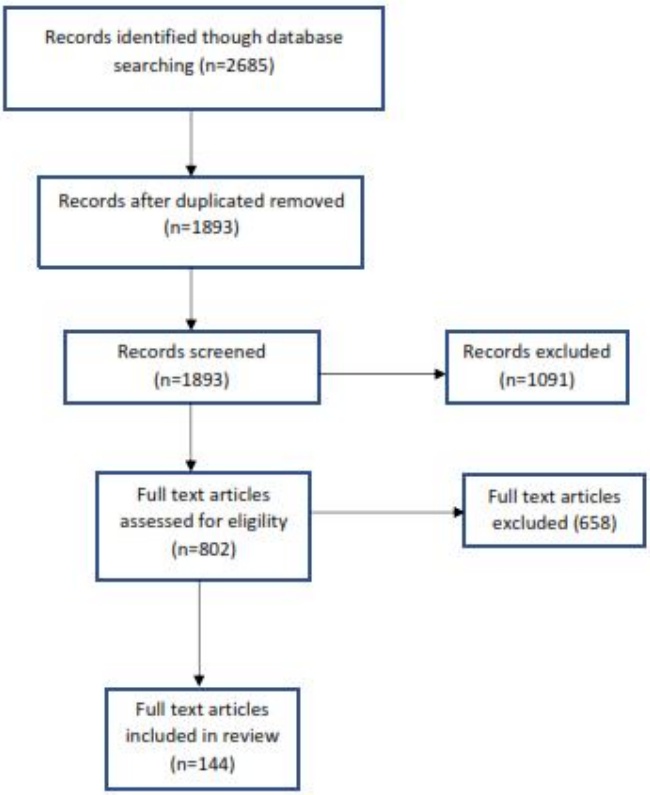

Figure 2 : Prisma flow chart of study selection.

Table 1 Text passages extracted from 144 publications, sorted by concept theme.

	Number of text passages			
Concept theme	**HBV**	**Genetic diversity**	**Transfusion**	**Transmission risks**
Definition	86%	27%	66%	66%
Attributes	-Viral Hepatitis -Cryptic HBV infection -Overt and Occult HBV infection -Incident and prevalent HBV infections	-Phylogenetic analysis - Molecular characterization -Sequencing -Genetic recombination	-Blood donation testing -Pre donation and Post donation screening -TTIs screening -Blood safety	-HBV window period -HBV Undetectable -Likelihood of HBV infection -Residual risk of HBV
Empirical referents	-HBsAg -HBcAb -HBV DNA viral load	-Escape mutations -Genotypes - Subgenotypes -Vaccine escape -Antiviral escape	-SSP -PDS -Questionnaire -RDTs -ELISA -PCR -PRT -Lookback strategy	-Negative serology -Positive viral load
Consequences	-Chronic infection -Liver cirrhosis -HCC	Affect diagnostic assays and therapeutic interventions	Virus infecting both donor and recipient	Extrahepatic manifestations occur

TTIs : transfusion-transmitted infections ; SSP : standard selection procedure ; PDS : selection pre donation and donation screening ; RDTs : Rapid diagnostic tests ; PRT : Pathogen reduction
technology ; ELISA : Enzyme- linked immunosorbent assay ; HCC : hepatocellular carcinoma ; HBsAg : Hepatitis B surface antigen ; HBcAb : Hepatitis B Core Antibodies ; HBV
DNA : Hepatitis B viral DNA

Table 2. Characteristics of included full texts

Countries/regions of origin	Full texts (N=144)	%
African countries	59	41
Asian countries	50	34.7
American countries	21	14.6
European countries	11	7.6
Oceanian countries	3	2,1

Types of Research Questions	Number of authors	inter-rater reliability score
Definition		
Hepatitis B virus	123	0.6
Genetic diversity	38	0.68
Transfusion safety	94	0.88
Transmission risks	94	0.93
Relationship between variables		
Blood donation-Transmission risks	19	0.95
Demographic factors-Transmission risks	25	1
HBsAg-Transmission risks	36	0.89
Anti-HBc-Transmission risks	22	0.92
Viral load-Transmission risks	17	0.91
Measurement errors-Transmission risks related	5	1
HBsAg-viral load related	2	1
Anti-HBc-viral load related	1	1
Sequencing-viral load related	2	1
Genotype-Transmission risks	5	0

Table 3. Relative reliability in coding and identifiying the use of key terms

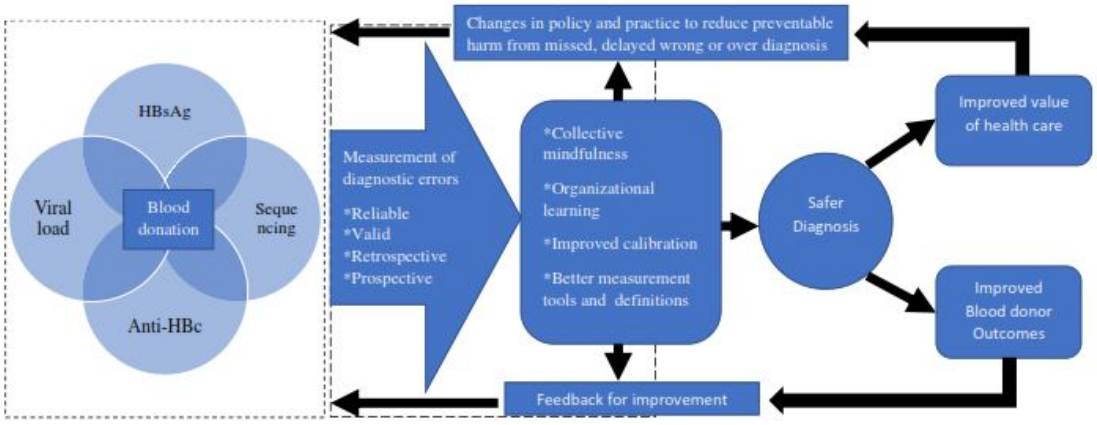

Figure 3 : Integrative model of Blood donor-transfusion safety (adapted from Singh et Sittig, 2015)