1. Introduction

Syphilis is still a public health problem in the world. The World Health Organization estimated that approximately 12 million new cases are reported each year in the world with more than 90 percent from developing countries (Centers for Disease Control [CDC], 2007; World Health Organization [WHO], 2001). Moreover, syphilis has acquired a higher potential of morbidity and mortality with the increasing prevalence of HIV infection. If syphilis is rare in developed countries, it is much more common in developing countries where prevalence can reach 25% amongst blood donors (Tagny & al., 2009, 2010). The infection is transmitted from person to person through contact with a syphilis ulcer (during vaginal, anal, or oral sex). An infected mother can infect her fetus via the placenta. Furthermore, intravenous drug addicts or other infected person can transmit syphilis through infected blood products i.e. through blood transfusion or use of infected needles for example (Workowski & Berman, 2006).

2. Transfusion transmissibility of syphilis

Fordyce reported the first case of transfusion-transmitted syphilis in 1915. More than 100 cases have subsequently been reported in different countries including USA and Great Britain (CDC, 2004; Henneberg M. & Henneberg R.J., 1994; Lobdell & al., 1974). However, the numbers of transfusion-transmitted syphilis cases has decreased all over the world. In the past 35 years, only three cases of transfusion-transmitted syphilis have been reported in the English literature and the last one was reported since more than forty years ago in USA (Brant & al., 2007; CDC, 2004; Chambers & al., 1969; Hook & Peeling, 2004). The absence of transfusion-transmitted syphilis in many developed countries leads to question the rationale for continuing syphilis testing of blood donors.

Syphilis is a transfusion-transmitted infection (TTI) due to a spirocheta called *Treponema pallidum*. The germ is present in the blood of a contaminated blood donor and infects the recipient. The transmissibility of syphilis by blood transfusion has been frequently reported, chiefly based on animal experiments. Cases of syphilis transmitted by blood have been described in literature, with more than a hundred cases since the first description. The main cases reported were shown to occur when donors were in the primary or secondary stage of the disease. (Gardella & al., 2002; Orton, 2001; Risseeuw-Appel & Kothe, 1983; Singh & Romanowski, 1999; Soendjojo & al., 1982). *T. pallidum* may be found in the blood stream, but
levels are variable, and bacteremia is often short-lived even in recent contamination. Moreover, the treponemes are relatively fragile and sensitive to cold; storage below +20°C for more than 72 hours destroys the organism and reduces dramatically the infectious risk. Although clearly potentially infectious, the risk of transmission through the transfusion of blood and blood components stored below +20°C is very low (Orton, 2001; Wendel, 1994). Platelet concentrates usually stored at a temperature above +20°C or blood directly transfused few hours after collection comprises a higher risk of transmitting syphilis. This is the case in many developing countries with limited blood supply where blood is collected from family donors and frequently transfused in the following hours or days. Thus, the screening test is considered essential as most blood transfusion services are concerned by storage of blood products stored either above +20°C or not stored below +20°C for more than 4 days. Furthermore, it is actually shown that the deferral of blood products screened positive also reduces the risk of contamination from HIV and HBV. When the germ is transmitted to the recipient, some signs appear a few weeks later notably macular lesions on the palms, headache, arthralgia, fever, headache, peripheral lymphs nodes and more rarely jaundice. For all the reported cases, there was neither a history of venereal disease nor presence of sores on the blood donor at the time of donation. However, many cases were associated with appearance of a sore on the blood donor few days after the donation. Thus, syphilis can be transmitted from donors who are clinically and biologically negative. It is clear that medical selection and mainly information and questioning are essential to identify those who have been exposed to infection during the preceding two months.

Some other diseases are caused by other species or subspecies of Treponema: Yaws (Treponema pertenue), Pinta (Treponema carateum) and Bejel (Treponema endemicum). Yaws and pinta may potentially be transmitted by transfusion, but few data is available. Bejel is unlikely to be transmitted and infect individuals (Chambers & al., 1969; Wendel, 1994). These diseases usually have clear symptoms that would lead to donor deferral.

Strategies of safety were proposed and modified during the years until the adoption in 1987 by the WHO of a common international strategy. Several steps and strategies were elaborated as well by the international organizations (WHO, the International Society of Blood Transfusion, the American Association of Blood Banks) and the blood banks. Their general recommendations focus on the control of the bacterial dissemination of the disease through blood transfusion by the selection of low risk blood donors and the screening of the disease by efficient lab tests. The strategies of reduction of this risk of transfusion transmissible infections associates the natural medical selection the effective biological qualification, the reduction of pathogens by a physico-chemical treatment of the products and the rational use of the prepared products. However, blood safety begins by the implementation of organized blood centres, of a quality system, hemovigilance, and application of safety measures in transfusion. The organization of blood centres is related to the implementation of blood supply programs and blood safety strategies by a well-organized centre, national or regional. Blood banks are frequently used as a base of transfusion. A Quality system includes management, training, norms, documentation traceability and evaluation. Haemovigilance is defined as a set of organized surveillance procedures relating to adverse or unexpected events or reactions in donors or recipients. In the transfusion chain, the first to be considered is the safe blood donor.
3. Syphilis and blood donor

Blood donors with high-risk sexual behaviour and other risk factors may be infected by syphilis and compromise the safety of blood used for transfusion. The medical selection of the blood donors consists of information of the donor, the finding of the risk factors in the behaviours and the medical history using a questionnaire, the physical examination in order to find clinical signs of the infection. Donor deferral follows identification of any risk. Medical selection is crucial because it could permit to defer more than half of infected donors, especially the ones in the early period of infection here laboratory tests are not efficient (de Almeida Neto & al, 2007; Tagny, 2009).

In some European countries, the prevalence of *T. pallidum* infection in the general population and thus in blood donors has been increasing since last two decades. An increase in syphilis infections has been associated to the high incidence of HIV. Moreover, an infected blood donor with syphilis is more than 5 times more likely to be HIV-positive. However, the prevalence of syphilis is still very low in developed countries and the very rare cases of recipient contamination raised the question of whether syphilis screening was still necessary for blood donors. In developing countries, the prevalence of positive serologic tests for syphilis can reach 25%. The prevalence is however very variable from one area to another and from a country to another. In such settings, the poor quality of laboratory screening due to the lack of equipment, training personnel, reagents and standard procedures highlights the need of the systematic and better screening for syphilis to help ensure a safer blood supply. Very little systematic information is available on the profile of positive blood donors including differences between donors with recent versus past infection. The exclusion of donors with past and treated infection is still a matter of discussion. Abusive exclusion reduces the blood supply and could be problematic in developing countries. However, past history of syphilis may be high-risk sexual behaviour associated to transmitted transfusion infection such as syphilis itself and HIV. The transfusion risk of syphilis is closely related to risk factors in the blood donor, in particular the sexual behaviours, the disease being primarily transmitted by sexual route. The rates of infection are highest amongst homosexual (gay) men - or men who have sex with men (Vall-Mayans & al, 2006). Recent syphilis infections have been shown to be associated with younger age, male-male sex, two or more sex partners, past syphilis treatment, past syphilis history, HIV seropositivity. Risk factors usually associated with transfusion transmitted syphillis also include more than one sexual partner, prostitution, bisexuality (men having sex with both men and women), intravenous drug use, and skin scarification (tattooing, blood rituals).

In developing countries, most blood donors infected are first-time donors. The prevalence of syphilis is one of the highest amongst the TTI screened in developing countries. The problem of this disease, first of all, is its high prevalence in blood donors in various areas of Africa. The recent prevalence were 3.7 % in Congo (Batina & al 2007), 7.9 % in Ghana (Adjei & al., 2003; Ampofo & al., 2002) and 9.1 % in Cameroon (Mbanya & al., 2003; Tagny & al., 2009). It is just as high in females as in males, in the different age groups and in voluntary donor as well as family donors. The family blood donation and remunerated blood donation, mostly found in developing countries is statically associated with higher prevalence of the disease (Batina & al., 2007; Tagny & al., 2010). The donors who have been positive for syphilis during the previous donation are less likely to donate again, whereas donors who were negative for the presence of syphilis in the past would be more likely to
donate again. In countries, which use a medical questionnaire for selection of blood donor, there are usually questions related to infection with syphilis. These questions concentrate particularly on sexual behavior (a number of sexual partners, use of condoms, past history of sexually transmitted diseases) and sometimes on specific symptoms observed during clinical examination. However, medical selection remains ineffective for several reasons:

- Difficulty of understanding the questions due to the level of education (ignorance of the transmissible infections by blood transfusion) (Nébié & al., 2007; Agbovi & al., 2006), linguistic and cultural (taboos) barriers;
- Discrete expression of the disease in its primary phase. The syphilitic rosella is not clearly visible on dark skin.
- Suppression of clinical signs and symptoms by the various antibiotics following self-medication (ampicilline, penicillin). Thus, the biological screening of this disease remains essential to defer blood donors at risk.

Identified safe donors must be retained in the pool of repeated donors and frequently informed and educated to avoid risky behaviours.

4. Syphilis and screening of blood donation

Serological tests for syphilis contributed greatly to the detection of *T. pallidum* infection in blood donors and especially in those who were not identified during the medical selection. Wasserman (Henneberg M. & Henneberg R.J., 1994; Rose & al., 1997) developed the first test of syphilis in 1906. Although it had some false positive results, it was a major advancement in the prevention of syphilis because it helped to diagnose the disease before the clinical manifestation and thus prevent its spread. In the 1930s the Hinton test, developed by William Augustus Hinton, and based on flocculation, was shown to be more specific than the Wassermann test. At the beginning of the 20th century newer tests were developed. Present-day, several labs tests, treponemic or not treponemic exist, among which rapid tests, immunological tests, and genomic (Young & al., 2000). Neither there is a specific type of method absolutely indicated, nor is there any confirmatory algorithm for testing based on the different assays available. In fact, the laboratory assessment of syphilis is generally based on the detection of antibodies against *T. pallidum* antigens in blood by the use of either specific or nonspecific reagents. The detection of genomic particle are more specific but not affordable for most of laboratories (Marfin & al., 2001; Orton & al. 2002).

The detection of specific Treponema antigens is possible using methods as passive agglutination, as *T. pallidum* hemagglutination (TPHA) assay or the *T. pallidum* particle agglutination (TPPA) assay, indirect immunofluorescence as the fluorescent treponemal antibody absorbed (FTA-ABS) assay or enzyme immunoassay (EIA) for the detection of specific IgG and IgM or total Ig. Non-treponemal methods are based on non-treponemal lipid antigens (cardiolipin), using frequently the flocculation technique. Of these, the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are the most commonly used. These tests are cheap, fast and more sensitive (Montoya & al. 2006; WHO, 2006). They are able to identify the contaminated blood donors few days before the treponemal test and thus useful for acute infection. However, VDRL and RPR cannot be automated and are time-consuming if used for large scale testing. Moreover, they produce more false positive results. These tests are routinely used to screen blood donors. False positives on the rapid tests can be seen in viral infections such as hepatitis, tuberculosis, malaria, or varicella. Thus, non-treponemal tests should be followed up when possible by a
The treponemal test. The treponemal tests are based on monoclonal antibodies and immunofluorescence; they are more specific and more expensive. The tests based on enzyme-linked immunoassays are the more specific and are usually used to confirm the results of simpler screening tests for syphilis. According to the guidelines published by the U.S. Centers for Disease Control and Prevention, the diagnosis of syphilis should be based on the results of at least two tests: one treponemal and the other non treponemal (CDC, 2006; CDC, 2004). According to WHO, blood banks may choose Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR), or enzyme immunoassay (EIA). VDRL and RPR are sensitive for recent syphilis infection, but not for past infection. Screening should be performed using a highly sensitive and specific test for treponemal antibodies: either TPHA or enzyme immunoassay. In populations where there is a high incidence of syphilis, screening should be performed using a non-treponemal assay: VDRL or RPR. EIA can detect past or recent infection, but may result in rejecting non-infectious blood with distant past infection (Cole & al., 2007). However, one should remember that the reliability of the screening and the diagnosis include the performances as well as the quality assessment notably the use of standard operating procedures, norms, training of the personnel and management of quality.

The screening for syphilis is frequently carried out on the African blood donor, and national policies often include the disease in the list of ITT to be screened at the time of blood donation. More than 90% of blood collected in Africa in the year 2004 was screened for syphilis (Tapko & al., 2005). The techniques used for screening are different from one country to another: VDRL or RPR alone for some, VDRL + TPHA for others (Tagny, 2009). Developing countries are characterized by a difficult epidemiologic, sociological and economic environment which limits the implementation of a high quality of blood safety. Thus, this context requires that tests and algorithms should be selected so that they correspond with the high prevalence of the disease, limited technical know-how of the personnel and limited availability of reagents and equipments. The selection criteria of screening strategy must include simple techniques, reliability, sustainability and cost effectiveness. Regular supply of electricity, freezer and ELISA kits is mostly found in big cities and barely available in small towns. Several blood banks use rapid test technique as it does not required sophisticated lab materials (Tagny & al., 2009). Screening strategies must also take into account the training of technicians, guarantee their capacity to carry out the test and provide reliable results.

5. Other blood safety issues

The good clinical use of the blood products is an essential stage of blood safety with respect to syphilis. It relates to the definition and the respect of the indications of transfusion, but also recording, analysis and diffusion of adverse reactions due to the infection. Each blood bank or transfusion service (national or regional) is responsible for ensuring blood safety to their patients. They should minimize unnecessary transfusions by prevention of conditions that result in the need for transfusion, reduce blood loss by using good surgical and anaesthetic techniques, or use simple alternatives for volume replacement. These strategies could be done with the help of organisations such as transfusion committees in each hospital, national committee on the clinical use of blood, and a national haemovigilance system.
Blood safety also consists of the use of physico-chemical treatment (filter on blood bag, use of amotosalen or ribavirin). This treatment of donated blood has shown its capacity to reduce the transmissibility of many germs especially in plasma and platelets. Once inside the pathogen, amotosalen or ribavirin docks in between the nucleic acid base pairs and blocks irreversibly the replication of DNA and ARN, thus preventing the proliferation. The physico-chemical treatment cannot be used on erythrocytes and are costly, thus less suitable for resources limited countries where whole blood and red blood cell concentrates are mostly used.

6. Conclusion

The challenge and perspectives of syphilis during transfusion is related to improvement of clinical selection of blood donor (identifying the precise risk factors) and to development of tools for the treatment of red blood cell concentrates. Syphilis was the first infectious agent shown to be transmitted by blood transfusion and, in the past, there was a reasonably significant number of transmissions. Occasional cases still occur even today in some countries with a high incidence of syphilis. However, it is very unlikely that transfusion has ever been a major factor in the spread of the disease. In low incidence countries, the vast majority of cases of syphilis identified in blood donors are due to old infections that have been treated successfully and present no risk of transfusion transmission. With the exclusion of high risk donors, screening for *T. pallidum* and storage of most blood components at or below +4°C before transfusion, makes the risk of post transfusion syphilis almost negligible in many countries. The challenges and the perspectives of the disease during transfusion are related to improvement clinical selection of blood donor (identifying the precise risk factors) and to the development of tools for treatment of red blood cell concentrates.

Prevention of the spread of syphilis is primarily by education and development of effective and treatment programmes. All patients with syphilis should be tested for HIV. Sexually transmitted diseases in general are the major route of infection while transfusion is only a minor route. Eliminating high risk sexual behaviours is very effective in helping prevent Syphilis. Proper and consistent use of a latex condom can also reduce the spread of syphilis. Moreover, donors sexually exposed to a person with primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be assumed to be infected. They should be treated and educated, even if they are seronegative at the time of donation.

7. References


Syphilis, a sexually transmitted disease was first described in 15th century, is caused by Treponema pallidum subsp. pallidum and occurs worldwide. This book is a collection of chapters presenting the novel knowledge about the T. pallidum and some historical and up to date information about venereal disease and syphilis. The collection of articles includes: immunological aspects recognition of T. pallidum by the pattern recognition receptors of the innate immune; the whole genome analysis of treponemes and new targets for its molecular diagnosis; some historical aspects of venereal diseases treatment; natural history of syphilis including clinical manifestation and epidemiology; a clinical aspects dealing with psychiatric manifestations of neurosyphilis; spatial and temporal patterns of primary syphilis and secondary syphilis described by the spatial and space-time scan statistics; a commonly used methods for laboratorial diagnosis, the serological response to treatment of syphilis and safety in blood transfusion. I hope this book will be useful for students and research fellows as well for the wide audience.

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