Expert Report to the Infected Blood Inquiry: Virology (Hepatitis Supplementary)

Infected Blood Inquiry

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Introduction

This report was produced by members of the hepatitis expert group in response to a further supplementary letter of instruction from the Inquiry on further aspects of viral hepatitis and other viral infections. The letter of instruction is provided at the end of this report; numbered sections in this report correspond to the numbered paragraphs in the letter.

Questions taken from the letter of instruction

4. Further to the reports about hepatitis and HIV dated January 2020, the Inquiry would be grateful for further information about the following viruses:

a. other hepatitis viruses: hepatitis A, hepatitis D, hepatitis E

b. other retroviruses: human t-lymphotropic virus (HTLV)

c. other viruses: cytomegalovirus (CMV), human papillomavirus (HPV), parvovirus

in particular:

i. clinical features

ii. when the virus was first recognised

iii. when testing became available

iv. when screening (if applicable) became available and was introduced

v. whether any other risk reduction methods, such as leucodepletion, are effective.

Hepatitis A

Hepatitis A was not addressed in the initial report as its primary route of transmission is through faecal-oral contamination (via food, water) rather than blood. A form of infectious hepatitis, which came to be known as “type A”, was recognised long before the virus responsible was first identified in 1973[1,2] and serology assays developed by 1975.[3] The virus is endemic in many parts of the world with weaker sanitation infrastructure. It remains relatively rare in the UK, usually resulting from imported infection, though outbreaks have been reported in specific risk groups (e.g. men who have sex with men[4]).

Acute hepatitis A is mild and self-limiting in over 99% of cases. Chronic infection has not been described.[5] Infection may be asymptomatic, and symptomatic infection is more common with increasing age. When present, symptoms are usually mild and non-specific (low-grade fever, malaria, anorexia, vomiting, nausea, abdominal pain and diarrhoea). Serum aminotransferases are typically elevated prior to symptoms developing and jaundice usually begins within 1 week of symptoms, along with dark urine and mild hepatomegaly. Jaundice usually lasts for less than 2 weeks with blood results returning to normal within 2–3 months.[6]

Transmission through blood transfusion is rare but has been described.[7,8,9,10,11] Because the virus is sporadic, has a short period of infectivity and does not lead to chronic infection, molecular screening is not generally recommended. However, following documented cases of transmission from plasma-derived products, some countries require plasma pools to be tested.[12]

Acute liver failure is very uncommon (<0.5%) in acute infection, but a poor outcome is associated with older age and existing chronic liver disease.[13] Occasionally, patients may develop prolonged cholestasis and a relapsing form of hepatitis is described where symptoms and viraemia may return, but this usually resolves within six months of initial infection.

Hepatitis A is preventable through vaccination, with the first vaccine approved in 1995. Vaccines now exist for hepatitis A alone ("monovalent") or commonly combined with other vaccines (e.g. Hepatitis B, typhoid). Vaccination is recommended for those with advanced liver disease from other causes.

Hepatitis E

Hepatitis E was first identified in the 1980s as being responsible for a proportion of those with non-A, non-B hepatitis[14] transmitted by the faecal-oral route. Serological testing became available for research purposes by the late-1980s.[15] Today, there are a rising number of cases, with approximately 2 million cases in Europe each year, caused by 4 main viral genotypes[16] which differ in their transmission. The majority of infections globally are due to genotypes 1 and 2, which are transmitted through faecal-oral contamination (food and water rather than blood or blood products) and have been associated with major outbreaks. Genotypes 3 and 4 are mainly found in animal reservoirs and thought to be transmitted to humans largely through undercooked meat.[17]

Hepatitis E infection is most often mild and self-limiting. Acute infection is not distinguishable from other causes of viral hepatitis. It is usually associated with jaundice with malaise, vomiting, abdominal pain, low grade fever and liver enlargement. Progression to liver failure (fulminant hepatitis) is rare (0.5-3% infections) and occurs more often in pregnancy, particularly third trimester. Severe disease has been reported in those with advanced liver disease/cirrhosis.

In contrast to hepatitis A, hepatitis E can cause chronic infection, though this is rare and usually associated within genotypes 3 and 4 in those with a weakened immune system (e.g. in the setting of immunosuppressive therapy, HIV).[18] Chronic infection does not lead to fibrosis/cirrhosis of the liver, however there are rare non-liver complications such as arthritis and neurological conditions.[19] Treatment options are limited but there is some evidence of benefit from ribavirin, most notably in transplant recipients.[20]

Hepatitis E is preventable through vaccination. The vaccine (HEV 239) has high efficacy[21] and gives durable protection[22] but is not approved for use in the UK and its uptake outside China is relatively low.

In the UK, it was recognised from 2012 that there were an increasing number of transfusion associated transmissions of hepatitis E, and in 2015 the Advisory Committee on Safety of Blood, Tissues and Organs (SaBTO) recommended screening for hepatitis E in order to provide blood components to individuals receiving allogeneic stem cell transplants and solid organ transplants.[23] In recognition of the risks, costs and complexity of this approach a change to universal testing was recommended in 2016.[24] HEV is now screened for routinely, as part of UK blood donation policy.[25]

Hepatitis D (HDV,delta)

Hepatitis D, which can only cause chronic infection in the setting of hepatitis B, was addressed in the initial report of the expert group as an important pathogen transmissible through blood and blood products (Expert Report to the Infected Blood Inquiry: Hepatitis, 2020, p3). Since that report was written, there has been some progress with the development of the first therapeutic for HDV. Bulevirtide (Myrcludex B) is a drug which prevents the entry of HDV

into liver cells by blocking the receptor the virus uses for entry (sodium taurocholate co-transporting polypeptide, NTCP). It can lead to reductions in the levels of HDV virus in the blood.[26] There is strong evidence that bulevirtide can reduce the levels of hepatitis D virus when used in combination with standard therapy for hepatitis B, but viral levels rebounded if treatment was stopped after 24 weeks.[27] Full results from a Phase III trial (MYR 301) are awaited, but provisional data suggest some improvement with prolonged treatment up to 48 weeks.[28]

Rights to drug commercialisation were bought by Gilead Inc (Foster City, USA) in 2020 and it is now marketed as Hepcludex. The drug was given conditional marketing authorization in the EU in 2020.[29] However, in 2022 it was turned down for approval by the FDA.[30] The drug is currently under consideration by NICE in the UK, but it is not yet known if it will be approved based on its cost-effectiveness at current prices.

Human T-lymphotrophic virus

HTLV-1 and -2 (Human T- lymphotrophic viruses) were discovered in the early 1980s (before HIV) and have been estimated to infect 20-30,000 people in the UK.[31,32] Serological testing for HTLV became available in the UK in 1986;[33] in 2015 the prevalence in UK donors was 5.2/100,000.[34] Prevalence is higher in populations which have migrated from areas of endemic infection, notably the Caribbean, South America, Southern India, Iran, Japan, Melanesia and much of Africa. Prevalence in blood donors of black or black British origin is approximately double that of other groups.[35]

In the UK HTLV cohort, the main risk exposures are mother-to-child transmission and heterosexual sex, though transmission through infected blood is recognised. HTLV-1 is more prevalent than HTLV-2 and the virus is associated with more severe disease. Infection is usually asymptomatic (in about 90% of those infected) but in a small proportion of individuals it can result in severe complications including adult T-cell leukaemia (ATLL, c. 5%) which has median survival less than 1 year, and HTLV-associated myelopathy (HAM, c. 3%), also known as tropical spastic paraparesis (TSP) – a progressive, chronic, disabling neurological condition[33] with high impact on quality of life. Progression to both conditions is slow (mean 25 years for ATLL and 10 years for HAM/TSP). Infection is also associated with a range of rarer clinical presentations (e.g. bronchiectasis, encephalitis, uveitis, polymyositis, arthritis). Infection with HTLV-1 is associated with a 57% increase in adjusted mortality rate.[36] There is no vaccine for HTLV, no treatment that will slow progression of disease development in the event of HTLV-1 infection, and very limited treatment options for HAM/TSP and ATLL.

Transmission of HTLV through blood transfusion requires cell-to-cell interaction of white blood cells. The significance of blood transfusion related HTLV-1 and development of HAM/TSP was known since 1986.[37] A pilot study to determine HTLV-1 infection rates in UK (North Thames Region) was conducted in 1991,[38] following which the case for introduction of routine blood donor screening for HTLV-1 was made, and rejected, at least twice during the 1990s i.e. prior to the introduction of leucoreduction. Prior to the introduction of leucoreduction of blood in the UK, the HTLV transmission rate from infected blood components was estimated at 29.4%.[39,40] A subsequent lookback study found evidence that leucoreduction had led to an estimated 93% reduction in HTLV transmission[40] before routine serological testing for HTLV blood donations was finally introduced in 2002.

HTLV testing in the UK was conducted in pools until 2013 when singleton testing was implemented in England. Scotland switched to singleton testing in 2015, Northern Ireland in 2016 and Wales switched in 2018. Republic of Ireland used singleton testing from 2002. This decision was reviewed in 2015[34] and in 2017 NHSBT moved to testing donations from new donors and those used for non-leucodepleted components only.[41]

Cytomegalovirus (CMV)

Cytomegalovirus is a member of the herpes virus family first identified in 1956.[42] The first serology studies were reported in 1956[43] and by the 1970s seroprevalence had been characterised in many populations.[44] CMV transmits widely in the community and seroprevalence is associated with age, rising from 18.3% in UK children aged 11-14[45] to 59% in those aged 40-79.[46]

In healthy individuals, infection is usually asymptomatic or mild, most typically associated with a mild fever, and glandular fever- like illness. CMV can establish latent infection and usually remains asymptomatic, but can reactivate when an individual's immune system becomes weakened (e.g. by HIV, or medical immunosuppressive therapy most commonly associated with transplantation). Rarer clinical manifestations such as hepatitis, colitis, retinitis, pneumonitis are well-recognised and can be associated with a poor outcome. As with other viruses of the herpesvirus family, an infected individual remains both infected, and potentially infectious, for life.

Transmission is largely through close contact, particularly with saliva and other bodily fluids. Mother to child transmission (either in utero or post-natally) remains a key route of infection and CMV infection in utero is responsible for up to 12% of all sensorineural deafness in children.

CMV vaccine development is an area of active research, but there is no product yet licensed. Treatments are available (e.g. ganciclovir, valganciclovir, foscarnet and marabivir) but they are associated with significant adverse events and are generally only used in severe infections.

It was recognised in the 1970s[47] that CMV can be readily transmitted through blood and can be a risk to recipients without an antibody response to the infection and/or significantly immunosuppressed. The main mechanism for transmission is thought to be through latently infected white blood cells.[48] Evidence suggests that antibody screening of donors and leucodepletion has similar, substantial effects in preventing transmission (over 90% reduction from each).[49,50,51] However, with either approach the potential for transmission still exists, particularly from donors who have been recently infected where antibody testing can miss recent infection in the 'window period' before antibodies develop.[52] It has been proposed previously that an approach should be taken to use leucodepleted blood only from donors who had been infected more than a year previously.[53] In 2012, SaBTO conducted a detailed review and made a number of recommendations on testing for CMV, concluding that leucodepletion provided adequate risk reduction without the need for provision of seronegative blood, including in patients with HIV, and blood or solid-organ transplantation. However, the requirement for seronegative blood remains for specific recipient groups including in utero transfusion, neonates, and elective transfusion in pregnancy and granulocyte transfusion.[54, 55]

Only a proportion of donors are therefore now tested for CMV IgG to provide 'CMV negative' red cells and platelets to hospitals on request. Blood services use validated enzyme immunoassays (EIA) to detect total CMV antibody (IgG and IgM) with a sensitivity of >99.5% and a specificity between 98.1% and 99.3%.[55]

Human Papilloma Virus (HPV)

There are over 170 members of the papilloma virus family. Infections are common and usually asymptomatic but it is the well-recognised association between specific persistent papilloma virus infection and human cancers which make them a major public health challenge. An association with cervical cancer was first reported in 1983, and persistent infection is a prerequisite for disease.[56] Approximately 75% of cervical cancers are attributable to either

HPV16[56] or HPV18[57] but at least 12 other HPVs have been associated with disease including oropharyngeal, skin, anal, vulval, vaginal and rectal cancers. Robust serological testing was first developed for HPV16 (associated with cervical cancer) in 1994.[58]

Effective vaccination against HPV has been available since 2006. Three highly effective and safe vaccines are now available that protect against 2, 4 or 9 HPV types respectively. Vaccines are now used widely across the world, with policies differing between countries with some choosing to vaccinate only younger females.

The vast majority of HPV transmission occurs through sexual contact, and blood is not routinely screened for HPV. The potential for transmission of HPV in blood remains an area of scientific inquiry. Evidence for transmission is indirect, stimulated by a report of detectable HPV in children who had received blood transfusions or blood products[59] and a recognition that HPV can be found in deep seated tissues within the body. HPVs, including those associated with cervical cancer, have since been identified in blood samples from adults[60,61] with evidence that the virus may be attached to a range of peripheral blood mononuclear cells (PBMCs). The presence of HPV DNA in PBMCs does not necessarily mean infection is possible through blood, but if it were, it would be likely that leucodepletion would be effective.

HPV can only infect humans, however, the potential for transmission of other papilloma viruses through blood has been demonstrated in animal models, using papilloma viruses that differ from those causing infection in humans.[62] The relevance of these findings to human transmission has not been established.

Parvovirus

Within the family of parvoviruses, the most important for human health is the common pathogen, human parvovirus B19 (B19V) discovered in 1975.[63] In healthy individuals, B19V infection is usually asymptomatic or a mild disease with a seasonal variation. In children it is associated with “fifth disease” characterised by fever, runny nose, headache and a rash and less frequently with joint pain and swelling. Joint pain is more common in adults, usually in the hands, feet, knees and can occur as the only symptom of infection.

B19V infection can be a more severe disease in those with immunosuppression,[64] where chronic infection over months or years can be established. In pregnancy, particularly second trimester, infection can have severe consequences for the foetus, associated with hydrops fetalis and foetal death in approximately 16% of infections.[65,66] Uncommonly, infection can lead to a reduction in production of red blood cells and can have a major impact in those with existing anaemia, most notably those with sickle cell disease who have life-long requirements for red blood cell transfusion.[67] No virus-specific treatment exists, but intravenous immunoglobulin (IVIG) is used successfully for some infections.[68]

The dominant mode of B19V transmission is usually via aerosol and respiratory secretions. In the absence of a vaccine, prevention relies on the basics of good hand hygiene and reducing exposure to respiratory secretions. Transmission from mother-to-child is well recognised as above.

B19V can be transmitted through blood and blood products;[69] its presence in blood and blood products has been extensively reviewed.[70] B19V is resistant to common methods of viral inactivation and thus products made from large donor pools (e.g. immunoglobulin, clotting factor concentrates) are screened for high levels of B19 DNA in many countries. A recent detailed analysis of B19V risk has been undertaken to inform B19V screening strategies for the UK.[71]

In contrast to some European countries,[72] routine donor testing is not carried out in the UK, but only one case of confirmed transmission was identified between 1996-2012. It has recently been suggested that donor testing of red blood cells should be introduced for transfusions into high risk groups.[73]

5. Please explain if there is evidence of an infective cause transmissible by blood for primary biliary cirrhosis.

Primary Biliary Cirrhosis and Human Betaretrovirus (HBRV)

Primary Biliary cirrhosis is a progressive liver disease characterised by cholestasis (where the passage of bile is blocked through the liver), specific auto-antibodies (anti-mitochondrial antibodies, AMA) and evidence of bile duct destruction on liver biopsy.[74] The cause of PBC is not fully understood. Human genetic variation plays a role, and there is some suggestion that a transmissible factor, potentially an infection, contributes in some patients. No infection has yet been clearly demonstrated to be responsible.

Since 2004, a number of publications have reported an association between the presence of human betaretrovirus (HBRV) and PBC, with the strongest evidence finding the virus in 58% of those with the condition compared to 7% of those without.[75] HBRV has been found integrated in the lining of the biliary system of patients with PBC, autoimmune hepatitis and other idiopathic liver disease.[76] HBRV is not known to cause other human disease, but is similar to a murine retrovirus (mouse mammary tumor virus, MMTV) and a possible association with malignancy, particularly breast cancer has been proposed.[77]

There is insufficient evidence to conclude that the virus itself causes PBC. There has not been replication of the original findings by other groups, with some published studies finding no evidence of the infection.[78] It has been suggested that the findings might result from laboratory contamination,[78] a phenomenon recognised in other conditions initially associated with retroviral infection (e.g. chronic fatigue syndrome and xenotropic murine leukaemia virus, XMRV[79,80]).

Studies of existing antiviral therapies are ongoing (e.g. ClinicalTrials.gov NCT03954327) in the hope of a potential effect on disease (and indirect confirmation of a viral aetiology) though none has been observed in small studies previously (e.g. NCT00490620, NCT01614405,[81]).

It remains uncertain as to how HBRV is transmitted, but there is no evidence it is transmitted via blood or blood products. Virus has been detected in saliva, leading to speculation that transmission is via close contact with secretions, or aerosol transmission.[77]

6. Further to the report about hepatitis dated January 2020, please explain if it is possible for hepatitis C to reactivate in a person who has achieved a sustained virological response if they are exposed to illness or treatment that suppresses their immune system.

The question of reactivation is different for hepatitis B and hepatitis C. Hepatitis B is able to establish latent infection and can reactivate many years later. For patients undergoing immunosuppressive therapy or chemotherapy, testing for hepatitis B is routinely recommended and patients may be offered treatment to prevent reactivation.[60] For hepatitis C, this is different as for the great majority of individuals HCV treatment is able to completely eradicate viable virus from the body, however, there is no perfect test to establish this.

The definition of reactivation in the hepatitis C literature varies and can lead to confusion. In many papers it is used to describe patients in whom existing active infection is worsened by chemotherapy, or in whom viral levels increase. For this discussion we do not consider that to be reactivation, but rather evidence of enhanced replication. Here we consider reactivation as the re-emergence of detectable RNA in blood having previously been persistently negative following successful treatment.

Individuals for whom hepatitis C treatment fails to clear the infection usually have detectable virus in their plasma in the first few weeks after treatment completion. The likelihood of virus re-emerging decreases with time, to the point where if no virus is detectable 12 weeks after treatment (so called sustained virological response 12, SVR12), treatment is considered successful. Issues related to the definition of SVR12 and cure were addressed in the previous hepatitis expert report to the Inquiry (pages 54-55).

Later recurrence is uncommon and can be due to reinfection or relapse of the original virus. A study across several trials found a very low incidence of recurrent infection between 12 and 24 weeks after therapy (5/3004, 0.17%).[82] Reports of recurrence after 24 weeks are rare, a recent study of 384 patients found 1 (0.2%) relapsed 60 weeks after completing therapy.[83]

Despite assessment of both their ongoing risks of exposure and genomic sequencing of virus, it might not always be possible to resolve whether recurrence is due to reinfection or late relapse/reactivation. A change in viral genotype from before and after treatment is usually considered evidence of reinfection, particularly where the virus has been characterised with modern, viral deep-sequencing methods. The presence of the same virus at both time points is usually considered evidence of relapse. In the broader population it is not always possible to exclude re-exposure (and reinfection) with the same source, though in the case of transfusion related infection this should be possible to establish.

In this context, where there is little convincing evidence of late relapse, there is little evidence that additional illnesses (at least common ones) on top of hepatitis C are associated with reactivation of infection. In some individuals, viral RNA can be detected in non-liver cells (particularly white blood cells) despite an absence of detectable viral RNA in the blood, and this might represent potential for reactivation. However, there is no evidence that such patients are infectious.[84] There are rare reports of reactivation of hepatitis C in the setting of specific immunomodulatory therapy[85,86] although these are more often patients in whom there is evidence of prior infection (antibody positive but no virus detectable) but who have not received treatment. In contrast to hepatitis B, current guidelines do not recommend

preventative treatment for individuals without active infection (i.e. antibody positive, no evidence of detectable virus in blood) if undergoing chemotherapy. There is no evidence that virus re-emerging in any individual will respond less well to conventional antiviral treatment.

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Verifying Statements

Each contributing group member confirms that he or she understands his or her duty to provide independent evidence and has complied with that duty.

All contributing group members confirm that in respect of those parts of the report to which they have contributed:

(i) They have made clear which facts and matters referred to in this report are within their knowledge and which are not.

(ii) Those that are within their knowledge they confirm to be true.

(iii) The opinions they have expressed represent their true and complete professional opinions on the matters to which they refer.

Authors

Professor Graham Cooke

Graham Cooke is an NIHR (National Institute for Health Research) Professor of Infectious Diseases at Imperial College London. He leads HIV/hepatitis services at St Mary's Hospital, Paddington and the Infection and AMR theme of the Biomedical Research Centre. Previously, he was based at the Africa Health Research Institute in KwaZulu-Natal. He led the Commission on Accelerating the Elimination of Viral Hepatitis published in 2019 and chairs the WHO Essential Medicines List. His current work focuses on precision medicine for managing infectious diseases and access to medicines, particularly for HIV/viral hepatitis. In 2021 he joined the board of MHRA as a non-executive director.

Professor John Dillon

John Dillon is a Professor of Hepatology and Gastroenterology at the University of Dundee, and a principal investigator at their Medical School. He is the clinical lead for blood-borne viruses with NHS Tayside, and has been an NHS Hepatologist for over 23 years. His research interests include HCV therapies, novel diagnostics and treatments for non-alcoholic fatty liver disease, care pathways for patients with abnormal liver function tests, and treating HCV in people who inject drugs. He has chaired the Testing, Treatment and Care Working Group of phase one of the HCV Action Plan for Scotland and is a member of the Scottish Government's Ministerial advisory board for sexual health and blood-borne viruses.

Professor Katie Jeffery

Katie Jeffery is a Consultant in Clinical Infection in the Department of Microbiology, the Infection Control Doctor (ICD) and Director of Infection Prevention and Control (DIPC) at the Oxford University Hospitals NHS Foundation Trust, and Associate Professor in Microbiology and Hospital Epidemiology at the University of Oxford. She has over 20 years experience of treating patients with viral hepatitis. Her clinical interests include infection prevention and control, laboratory diagnostics, viral hepatitis, and infections in the immunocompromised host. She is the President of the British Infection Association.

Dr Jonathan Wallis

Jonathan Wallis is a Consultant Haematologist. He trained at Oxford University, Westminster Hospital and Medical School, Exeter and Newcastle Hospitals before being appointed consultant in Newcastle in 1990. He is an active member of the British Blood Transfusion Society and the International Society for Blood transfusion. He lectures widely on transfusion topics and sits on a number of national committees relating to transfusion medicine.

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Letter of Instruction

This report answers the following questions, extracted from the further supplementary letter of instruction to the Hepatitis expert group.

Further supplemental instructions

4. Further to the reports about hepatitis and HIV dated January 2020, the Inquiry would be grateful for further information about the following viruses:

    a. other hepatitis viruses: hepatitis A, hepatitis D, hepatitis E

    b. other retroviruses: human t-lymphotropic virus (HTLV)

    c. other viruses: cytomegalovirus (CMV), human papillomavirus (HPV), parvovirus

in particular:

    i. clinical features

    ii. when the virus was first recognised

    iii. when testing became available

    iv. when screening (if applicable) became available and was introduced

    v. whether any other risk reduction methods, such as leucodepletion, are effective.

5. Please explain if there is evidence of an infective cause transmissible by blood for primary biliary cirrhosis.

6. Further to the report about hepatitis dated January 2020, please explain if it is possible for hepatitis C to reactivate in a person who has achieved a sustained virological response if they are exposed to illness or treatment that suppresses their immune system.