HEV: the journey from decision to test implementation and the importance of universal screening

Alan Kitchen, PhD

Clinical Scientist

Consultant, Transfusion Transmitted Infectious Agents

Hepatitis E – another challenge?

- HEV is an infectious agent which is transmitted through blood and components and may pose a significant risk to immunocompromised recipients
- HEV (genotypes 3 & 4) has appeared as a zoonosis, now present in the general population, and consequently in blood and other donated substances, in a number of countries where HEV had not previously been endemic
- Response of blood services to the appearance of HEV in previously unaffected countries varies from ‘no action’ to ‘universal screening’
- What response should there be?

HEV, hepatitis E virus

Hepatitis E virus

- Small, non-enveloped RNA virus, assigned to the *Hepeviridae* family
  - enterically transmitted, self-limiting, acute viral hepatitis; chronicity can occur in immunosuppressed individuals
  - global distribution has distinct epidemiological patterns based on ecology and socioeconomic factors
  - HEV variants whose primary hosts are terrestrial mammals are classified in the genus *Orthohepevirus*
  - *Orthohepevirus* genus includes 4 families, of which HEV-A includes variants known to infect humans

- Currently 5 genotypes infecting humans – G1, G2, G3, G4, G7
  - genotypes differ in route of transmission and distribution
  - G1 and G2, found only in humans, associated with outbreaks
  - G3, G4 found in human and other mammals, can be transmitted via foodborne zoonotic transmission and via blood and components
  - G3 and G4 are primarily infections of pigs, deer, boar
  - G7 primarily infects camels

HEV infections

- Although usually an acute self-limiting infection, symptoms vary according to genotype
  - asymptomatic or only mild symptoms in most healthy individuals
  - can have more significant symptoms in immunocompromised individuals, giving rise to chronic hepatitis
  - G1/2 infections can give rise to serious consequences in pregnant women
  - G3/4 appear to be less pathogenic than G1/2

- G1 and G2 primarily spread through poor hygiene/sanitation
  - large epidemics, primarily waterborne, faeco-oral transmission
  - mortality rate 1-4% , can reach 20% in pregnancy in some endemic areas

- G3 and G4 zoonosis spread (primarily) from pigs (+boar & deer) to humans
  - G3 predominant genotype found in Europe
  - G4 predominant genotype found in South East Asia – China, Japan

- Presence of HEV in the population leads to risk of HEV in donations

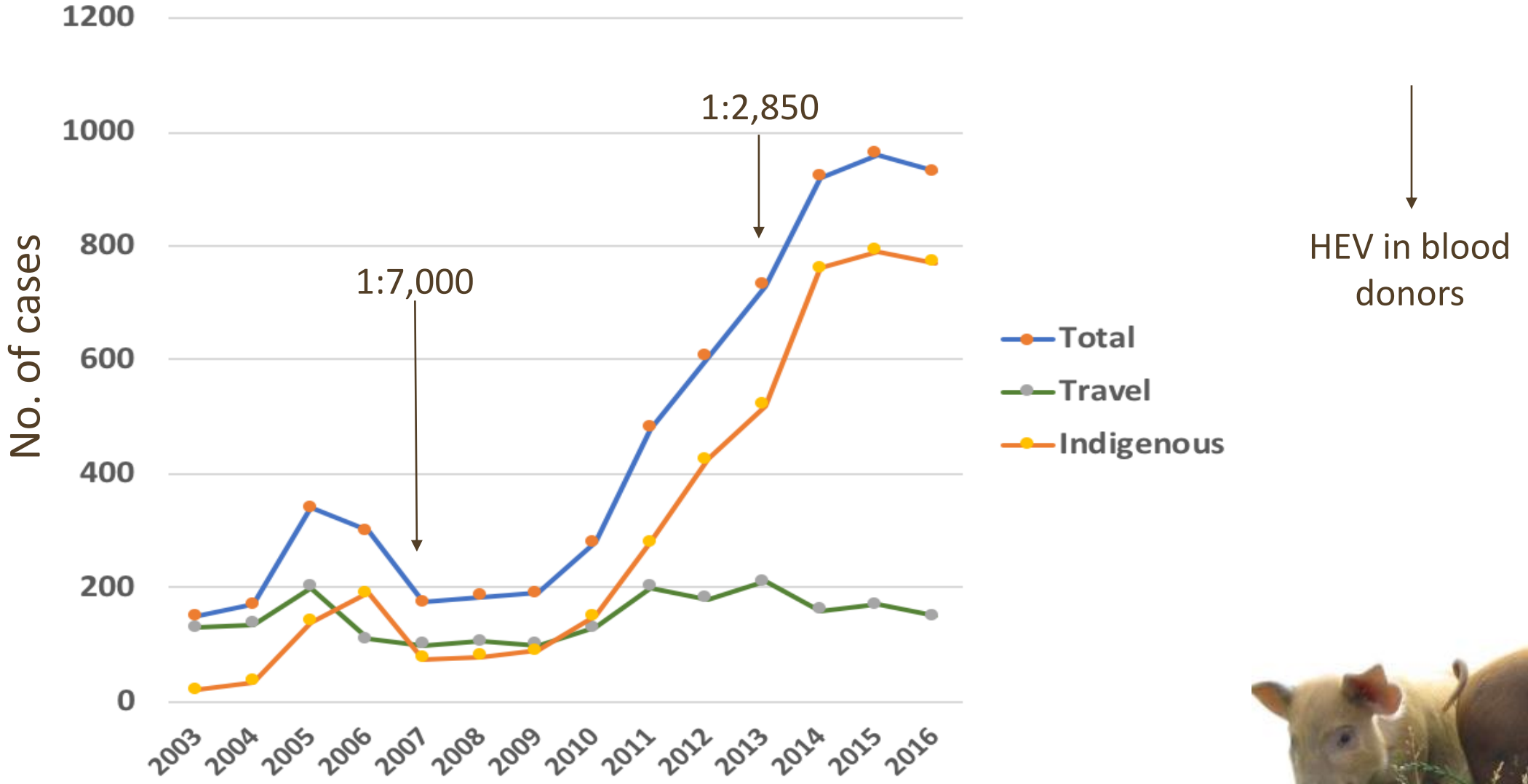
Identification of HEV infections

- An acute infection, presence of HEV RNA is definitive in the diagnosis of current HEV infection
- Presence of HEV IgM often used in diagnostic laboratories
  - may not identify recent infections
  - assays may demonstrate non-specific reactivity
- Presence of HEV IgG in absence of HEV RNA and HEV IgM indicates a resolved infection
- The only effective screening target to ensure ***donation safety*** is HEV RNA

Persistent, chronic hepatitis E

- Defined as persistence of plasma HEV RNA for >3 months
- Infections can be difficult to identify
  - patients have no clear symptoms and are anicteric
  - modestly raised ALTs
- Diagnosis may be overlooked or mistaken for drug-induced liver injury or graft rejection
- Rapid progressive liver disease with 10% of patients developing cirrhosis within 2 years
- Majority of reported persistent cases in G3, although cases of G4 and G7 have been reported

Enhanced surveillance of HEV, England and Wales



Slide courtesy of Dr S Ijaz, Public Health England

HEV in populations

- Appearing as an important and widespread infection in humans in EU/EEA countries
  - likely to be present in many countries, although currently unseen
- HEV RNA incidence (G3/4) in donor populations[1]:
  - Denmark, 2015 — 1:2,331, ID screening
  - France, 2012/3 — 1:2,218, pooled screening (96), TTI identified
  - Germany, 2012 — 1:1,241, pooled screening (6), TTI identified
  - Ireland, 2016 — 1:2,778, ID screening
  - Netherlands, 2016 — 1:726, pooled screening (96)
  - Spain, 2014 — 1:3,333, ID screening, TTI identified
  - UK, 2016 — 1:1,340-1:5,000, pooled screening (24), TTI identified
  - Poland, 2018[2] — 1:2,109, ID screening
  - China, 2017[3] — 1:1,511, ID screening
  - Japan, 2016[4] — 1:15,075, pooled screening (50)
  - Germany (North), 2018[5] — 1:815, pooled screening (24)

[1] Domanovic D et al. Euro Surveill; 2017: [2] Grabarczyk P et al. Transfusion; 2018: [3] Wang M et al. Transfusion; 2017

[4] Minagi T et al. Vox Sanguinis; 2017: [5] Westhölter D et al. J Hepatol; 2018

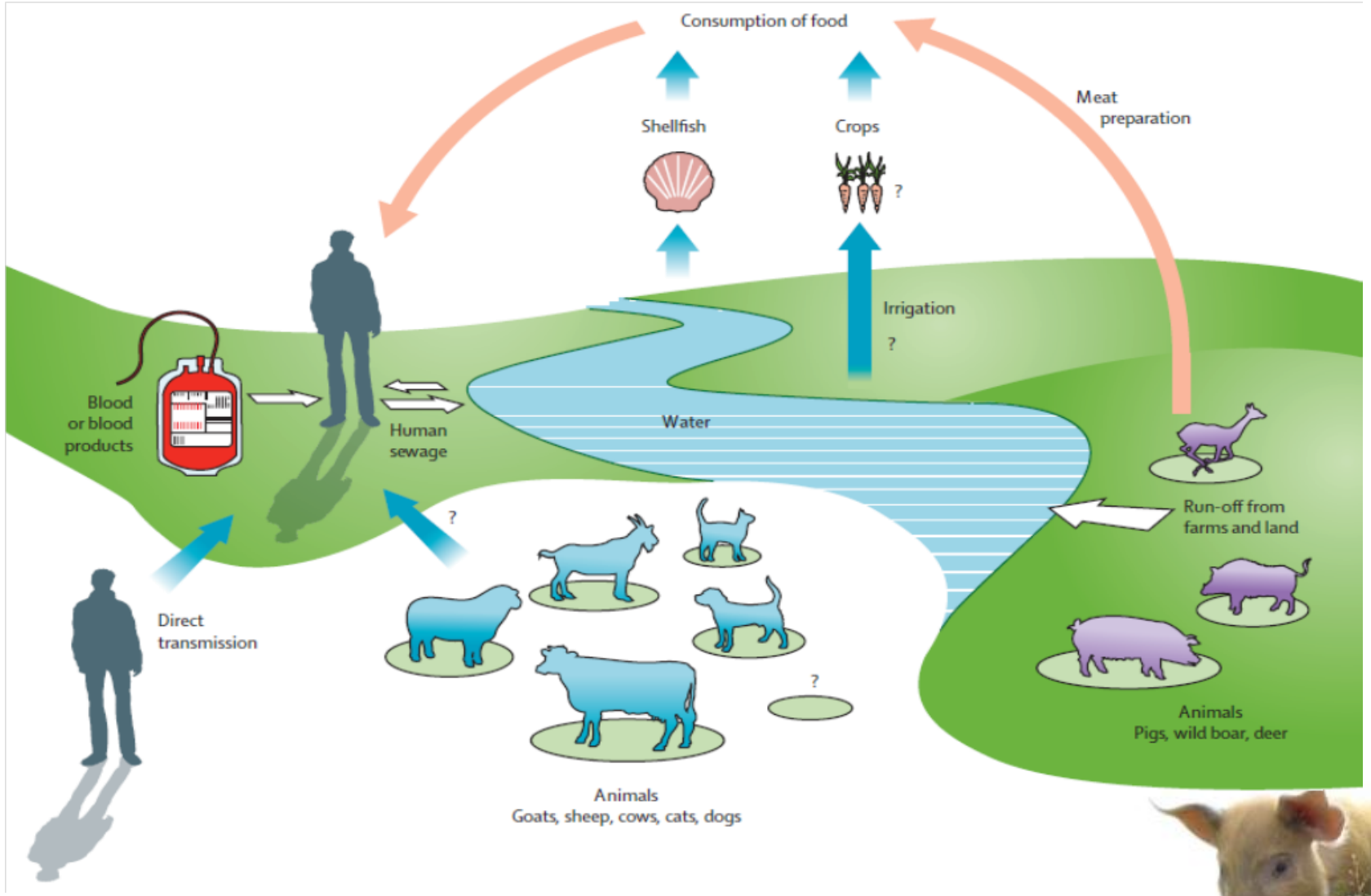
(Original) Sources of HEV

- Only a small percentage of the population have transfusions/receive blood components or other components of human origin

- HEV G1/2 are human infections
  - contamination of water and food by other humans and by animals

- HEV G3/4 are (primarily) zoonoses
  - food is considered to be the original source (raw/undercooked pork, deer, boar)
  - ***everyone eats***
  - transmission via blood/components is an incidental infection

HEV transmission



From Kamar N et al. Lancet; 2012

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How much is enough?

- HEV needs not only to be present, but also at a level sufficient to transmit infection
  - approximately 1–5x10^4 IU/product required to transmit[1,2], Dreier et al calculated specific figures of 7.05x10^3 for platelet preparations, 3.16x10^4 for red blood cells and 3.6x10^4 for fresh frozen plasma
  - infectivity varies with product type (volume of plasma present)
  - *infectivity may also be influenced by presence of HEV Ab in the recipient*

- Donors with low viral loads less likely to transmit
  - what are the viral loads in viraemic donors?
  - some countries (e.g. Denmark) report finding viraemic donors, but all low level and no cases of transmission via transfusion have been identified

[1] Tedder R et al. Transfusion; 2017

[2] Dreier J et al. Frontiers Med; 2018

HEV presence and transmissibility

- Original English donor study in 2012
  - 225,000 donations screened for HEV RNA in pools of 24
  - donations collected in the South-East of England
  - screened using an in-house assay with 95% LoD 22 IU/mL

- 79 viraemic donations identified – 1:2,848 donations tested
  - 57 were seronegative at pick-up
  - 64% male
  - median age: male 51.5 years, female 49.5 years; majority in 40–60 year group

Hewitt P et al. Lancet; 2014

LoD, limit of detection

HEV presence and transmissibility

- Viral loads in donations 50–2.37x10^6 IU/mL
  - median viral load 3,900 IU/mL
  - viral loads 0.5 log10 higher in donations which were antibody negative

- 54 (68%) of the 79 donor samples could be genotyped
  - all G3
  - 80% of which are G3, Gp2

Hewitt P et al. Lancet; 2014

HEV in UK recipients

- 129 blood components identified, prepared from the 79 donations
  - 62 components transfused to 43 recipients

- 25 recipients (58%) had no evidence of infection
  - seronegative 16 weeks post-transfusion
  - seronegative and HEV RNA negative 8 weeks post-transfusion

- 18 recipients (42%) had evidence of infection (RNA and/or Ab)
  - absence of detectable antibody and high viral load in the donation rendered transmission more likely
  - spontaneous clearance of viraemia without clinical disease was common despite delayed seroconversion

Hewitt P et al. Lancet; 2014

HEV in UK recipients

- 18 recipients (42%) had evidence of infection (RNA and/or Ab)
  - 8 no or mild immunosuppression, 3/8 had detectable RNA
  - 6 moderate, 5/6 had detectable RNA
  - 4 high, 4/4 had detectable RNA
  - 10 recipients developed prolonged or persistent infection; transaminitis was common, but short-term morbidity was rare
  - recipient immunosuppression delayed or prevented seroconversion and extended the duration of viraemia

Hewitt P et al. Lancet; 2014

HEV in recipients

- A number of countries have reported cases of transfusion transmitted HEV but a recent review[1] has determined that not all reported cases have complete and/or convincing data

- Provenanced reports include:
  - Satake[2] reviewed cases of transfusion of HEV RNA positive components in Japan, approximately 50% of recipients became infected with HEV
  - Andanov[3] reported HEV transmission 2/17 Canadian thrombotic thrombocytopenic purpura patients treated with single donor platelets
  - Hauser[4] reported 2 cases of transmission in France from Intercept plasma
  - Huzly[5] reported one confirmed and one probable transmission from a single apheresis platelet donor

[1] Dreier J et al. Front Med; 2018

[2] Satake M et al. Transfusion; 2017

[3] Andanov A et al. Transfusion; 2014

[4] Hauser L et al. Blood; 2014

[5] Huzly D et al. Euro Surveill; 2014

Acceptable level of risk

- When challenged by an infectious threat blood services need to respond – but this does not automatically mean implementing screening!

- Blood services/governments need to decide an acceptable level of risk
  - what is the level, in the general and donor populations, of an infectious agent which may be transmitted via transfusion and transplantation?
  - what is the risk of an infectious agent entering the supply of donated products?
  - what is the risk of transmission to a recipient?
  - what is the probability of recipients already having been exposed and infected?
  - what is the risk of subsequent disease in the recipient?

- Zero risk is not achievable
  - what level do we need to achieve?
  - what is achievable?

Why do blood services start screening for HEV?

- Impact on immunocompetent individuals minimal, but impact on immunocompromised individuals may be significant
  - up to 60% of HEV-infected immunocompromised individuals may develop chronic/persistent infection
  - progressive fibrosis & cirrhosis

- Although the decisions to screen were made at different times, blood services that have implemented screening have done so for the same reasons

- Pathogen inactivation is currently ineffective
  - non-enveloped virus, resistant to solvent detergent treatment
  - not reduced by current pathogen inactivation technologies

National screening decisions

- UK: Committee for the Safety of Blood Tissues and Organs (SaBTO) in 2015 recommended that:

  "Recipients who are immunosuppressed or likely to receive immunosuppression and who require blood or blood products should be given HEV RNA screened products"

  - implemented in March 2016 with selective HEV RNA screening of blood donations in pools of 24
  - Nov 2016 universal screening implemented and SaBTO advised that all tissue and stem cell donations screened
  - Nov 2016 SaBTO advised that organ donor should be screened
  - SaBTO also advised that recipients should be advised about dietary risk of HEV

- Ireland: HEV became a notifiable disease in Ireland in December 2015, universal ID screening implemented Jan 2016

- Netherlands: universal pooled screening (pools of 24) implemented July 2017

SaBTO reports and guidance documents, 2016, updated 2017. Available at: https://www.gov.uk/government/collections/sabto-reports-and-guidance-documents (accessed Oct 2019)

National screening decisions

- Germany: PEI requirements, cellular blood components and therapeutic fresh plasmas (including lyophilising fresh plasmas), and stem cell preparations, which have been put into circulation after 30/09/2019, must be produced from HEV RNA screened donations
  - the assay used must detect HEV RNA in an individual donation at 2,000 IU/mL

- Switzerland[1] : universal pooled screening (pools of 24) implemented Nov 2018

[1] Niederhauser C et al. Euro Surveill; 2018

PEI, Paul Ehrlich Institute

When should donation screening start?

- What do you know about HEV and your blood supply?
  - data on clinical cases of HEV in Czech Republic (Prevalence of Ab against HEV, Němeček et al, 2017; HEV in South Moravia, Mihalcin et al, 2019)
  - no published data found on HEV in Czech Republic blood donors/donations

- What do you know about HEV and your blood supply?
  - is HEV present in the general population?
  - is HEV present in the donor population?
  - what are the viral loads of viraemic donors?
  - what is the likely source of the HEV?
  - are there other sources of HEV which may have a greater significance?
  - have there been any reports of possible transmissions of HEV via transfusion?
  - what is the size of the ‘at risk’ recipient population?

What screening strategy to adopt?

- Selective or universal screening – depends on:
  - estimated needs for recipients who should receive screened products
  - ability of laboratory systems to select the donations which require screening
  - ability of hospitals to ID eligible recipients
  - ability of hospital blood banks to be able to segregate and maintain the segregation

- ID or pooled screening
  - pooled screening may be sufficiently sensitive to identify all donations which have high enough viraemia to transmit (does depend on component types)
  - HEV RNA screening of whole blood donations in pools of 24 would prevent 4.52 of the 4.94 transfusion-associated chronic HEV infections expected annually[1]

[1] de Vos AS et al. Transfusion; 2017

Roche cobas® HEV assay performance

- 95% LoD of 18.6 IU/mL; a 50% LoD of 3.9 IU/mL
  - in most cases sensitivity is quoted in relation to the 95% LoD of an assay
  - the lowest level of detection may be a lot lower although detection is less reliable
  - a component would need to contain at least 10^4 IU of HEV to be likely to transmit

- Using the assay 95% LoD
  - screening in pools of 24 will have a working sensitivity of 446.4 IU/mL
  - approximately 22 mL plasma would contain 10^4 IU of HEV RNA

- Using the assay 50% LoD
  - screening in pools of 24 will have a working sensitivity of 93.6 IU/mL
  - approximately 107 mL plasma would contain 10^4 IU of HEV RNA

Roche internal data, published in assay IFU

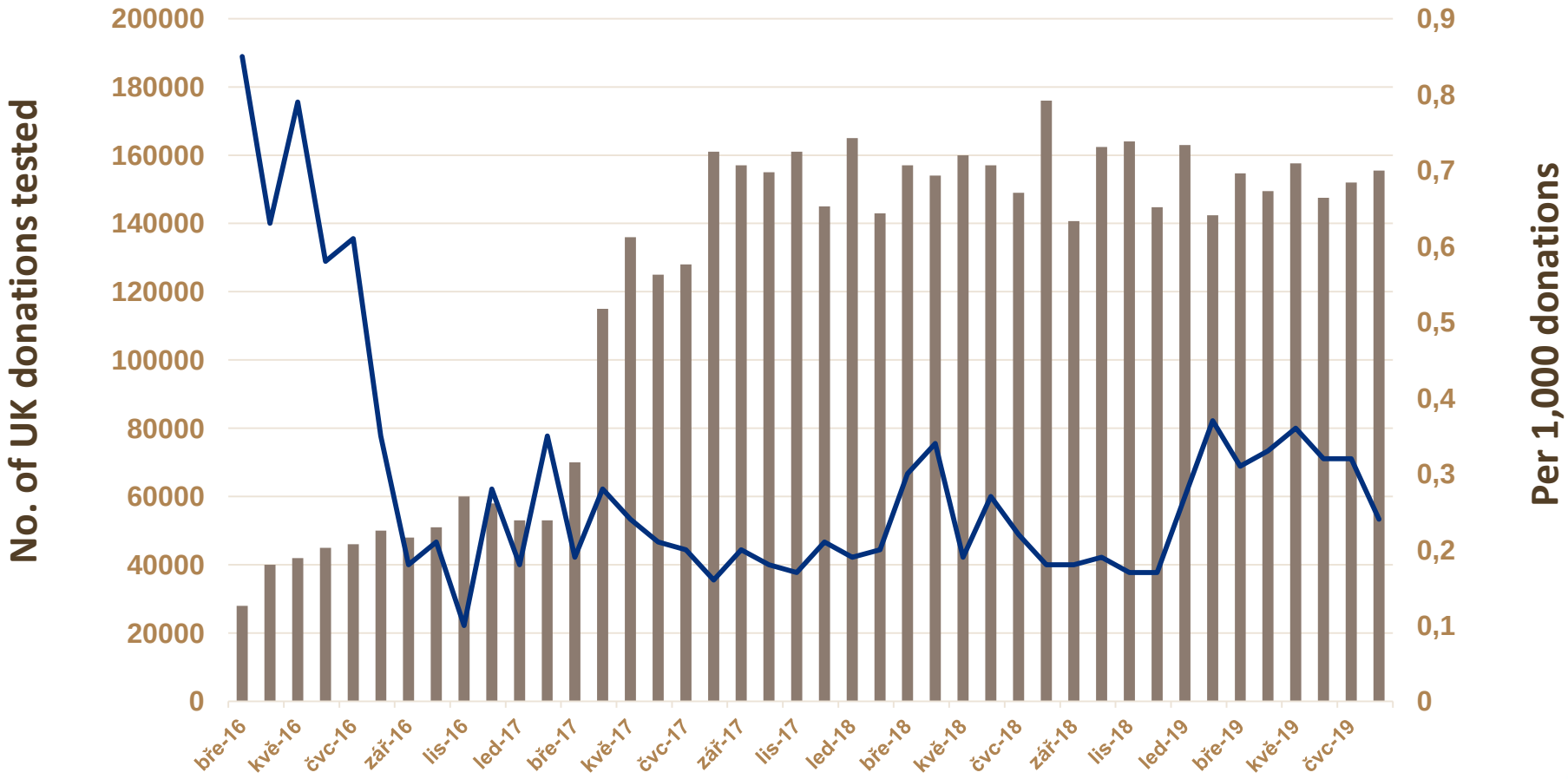
Managing HEV-infected donors

- How should HEV infected (viraemic) donors be managed?

- Should viraemic donors be informed?
  - how should they be informed?
  - what should they be told?

- Should viraemic donors be deferred?
  - permanent or temporary?
  - if temporary, how long?
    - Ireland – 6 months
    - The Netherlands – 3 months
    - UK – 6 months
  - if to be re-instated, is any further laboratory investigation required?

Will the time come to stop screening?



- If the main risk is from food, will the underlying issue be addressed?
  - at what level could screening be considered to no longer be needed?

Original graph courtesy of Dr S Ijaz, Public Health England, updated by AK, Oct 2019

Summary/conclusions

- HEV infection may have significant consequences in recipients of blood and/or components who are immunocompromised

- The provision of HEV RNA negative blood and components would minimise any risk of transmission of HEV
  - screening must identify all donations with sufficient virus to transmit
  - if infected donors have low level viraemia, transfusion transmission may not occur
  - the likelihood of transmission is dependent on the components received…….
  - ….. and the existing HEV status of the recipient
  - universal or selective screening would depend on recipient population needs, complexity of undertaking selective screening, complexity of holding dual inventory