Sanquin
Blood Supply

HEV NAT screening update: Effect of screening sensitivity on residual risk

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Hepatitis E virus

- Most common cause of viral hepatitis worldwide
- Genotype 1+2 are human viruses spreading via fecal-oral route
  - May cause severe/fatal infection
- Genotype 3+4 are zoonotic
  - Generally mild symptoms
  - May cause chronic infection in immunesuppressed patients

- Incidence of gt3+4 infection varies widely worldwide
- Screening of blood donors not mandatory
- Many countries perform screening, usually in pools

- Unlike HBV/HCV/HIV this does not fully protect the recipient of blood products

- The dilemma is still: how sensitive is sensitive enough?

Residual risk of transmission (1)

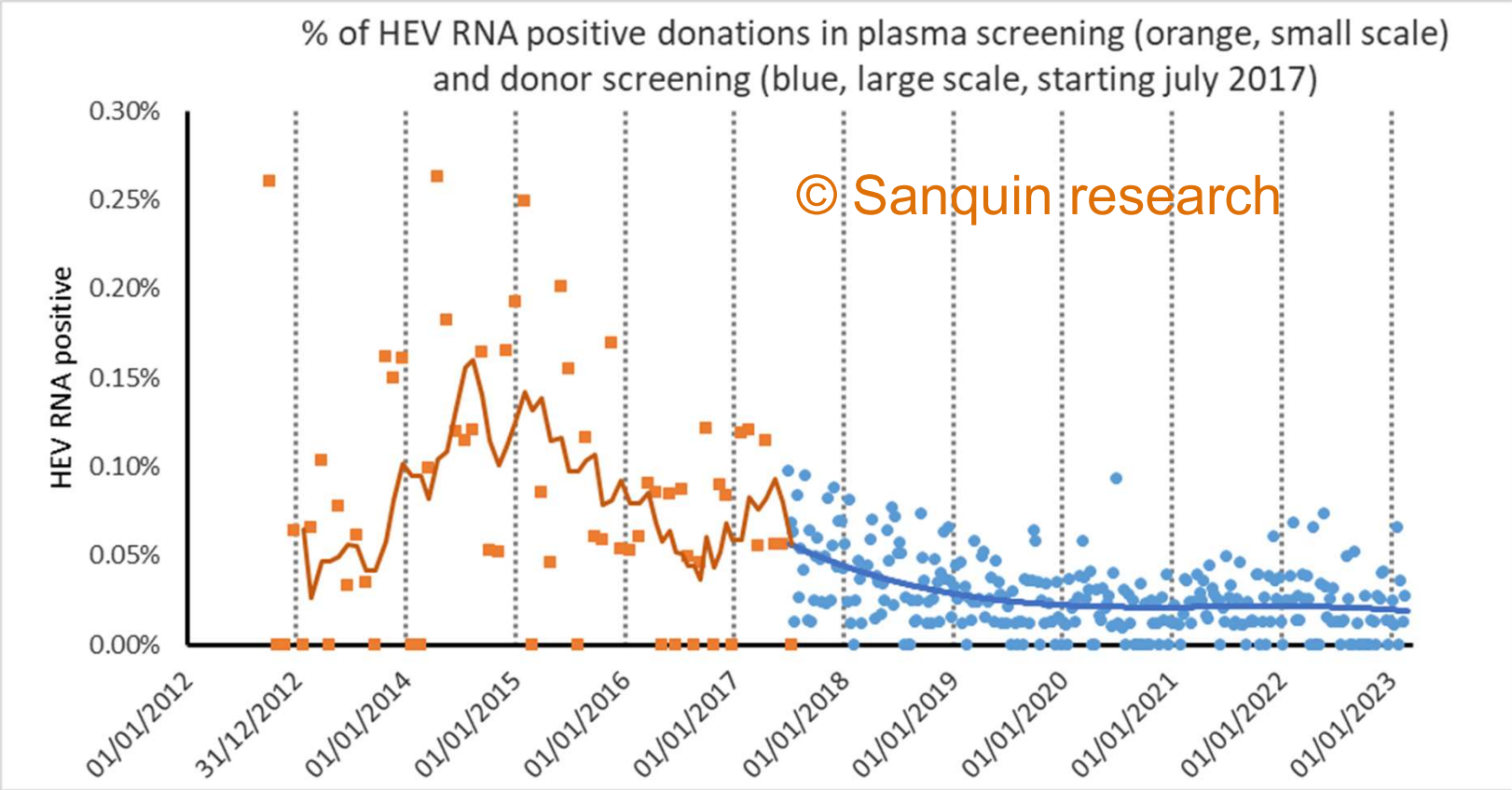
- Estimate of risk and cost effectiveness based on De Vos et al (2017)

  Transfusion 57 258-266

- **Key parameters:**
  - Number of HEV-RNA positive donations
  - Sensitivity of screening test
  - Viral load distribution
  - Probability of transmission (based on viral *dose*)
  - Volume of plasma in product
  - (Progression of disease)

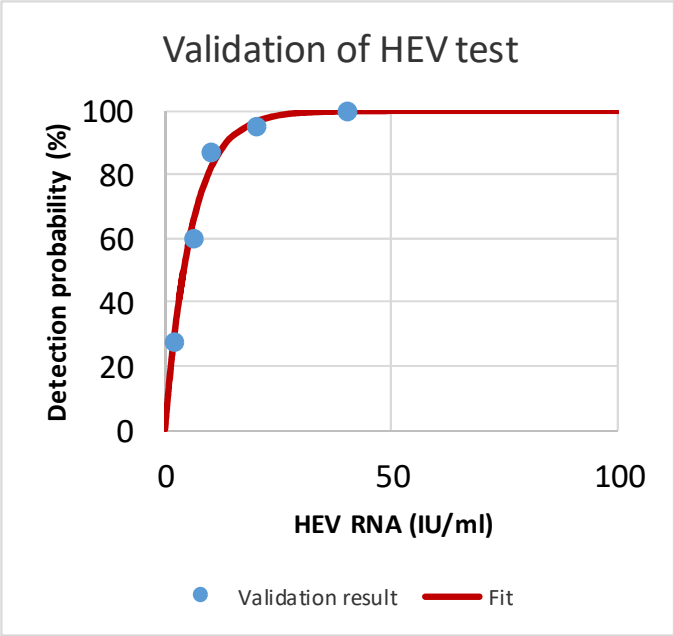
Yield of HEV donorscreening

- The incidence of HEV infection may strongly vary in time and differs between countries
- When screening started, the HEV incidence in the Netherland was perhaps the highest worldwide, with ~1/760 donations positive (despite screening in pools)
- Overview of prevalence of HEV positive donations in the Netherlands in time:



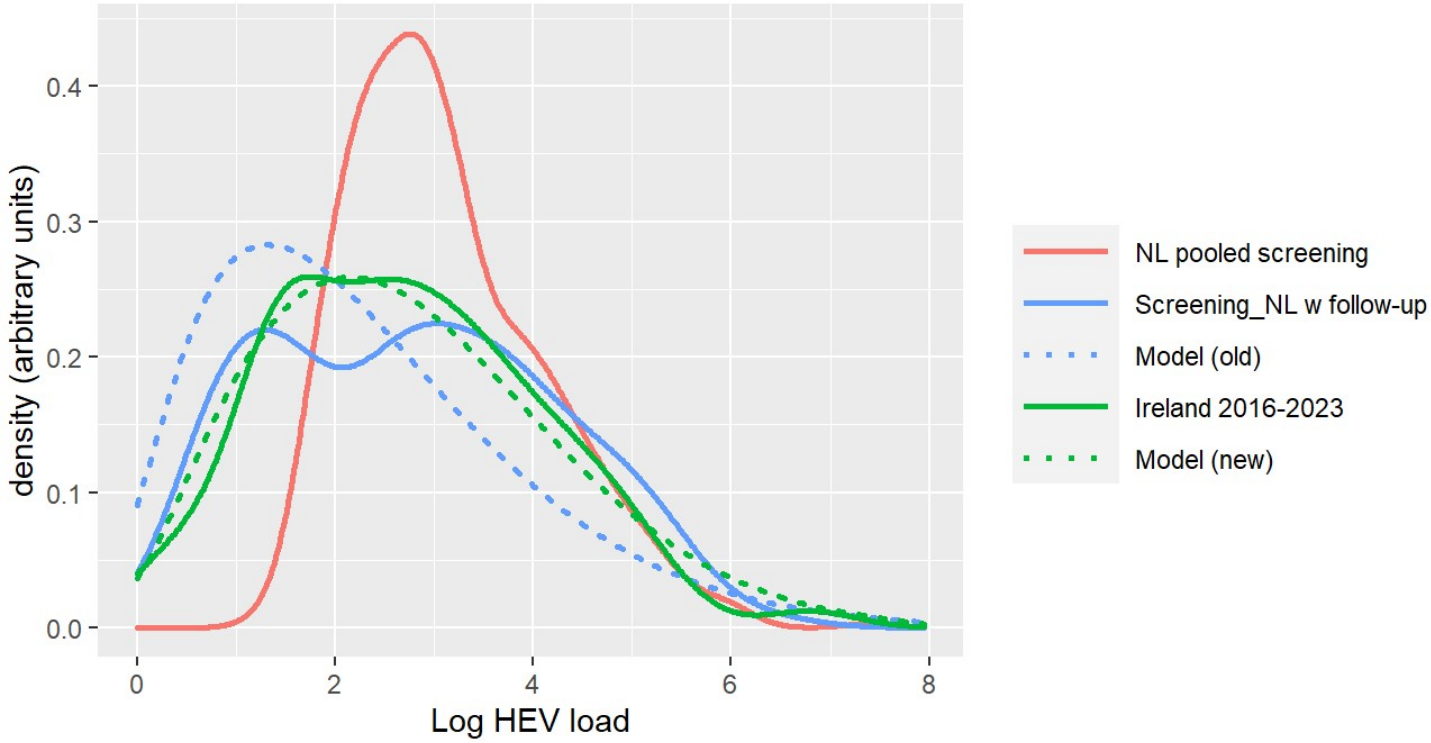
Probability of detection

- Most of the HEV screening is performed in pools using tests from Roche or Grifols.
- 95% limit of detection of these tests is similar (Grifols 7.9 IU/mL, Roche 18.6 IU/mL)
- Probability of detection can be easily calculated based on validation data in combination with the pool size
- Percentage of donations missed depends on the loads in donors



Improved estimate of viral load distribution

- First estimate for our model used pooled data from pooled screening combined with follow-up in positive donors
- Screening 59,474 donations in pools of 96 yielded 45 donations from 41 donors. 33/90 additional donations from these donors remained undetected (Hogema et al, Transfusion 2015)
- Viral load distribution was corrected for probability of not detecting donations and extrapolated
- New viral load distribution was made based on Irish donor screening data from 2016-2022
- Distribution based on quantitative HEV RNA test on 141 yield cases
- Old model apparently overestimated number of donations that was undetected



Percentage of undetected donations

- Based on viral load distribution the percentage of undetected donations can be calculated for any sensitivity of the screening method

	Pool size		
Test	Individual	24	96
Grifols	2.3%	24.4%	38.0%
Roche	5.6%	32.5%	43.6%

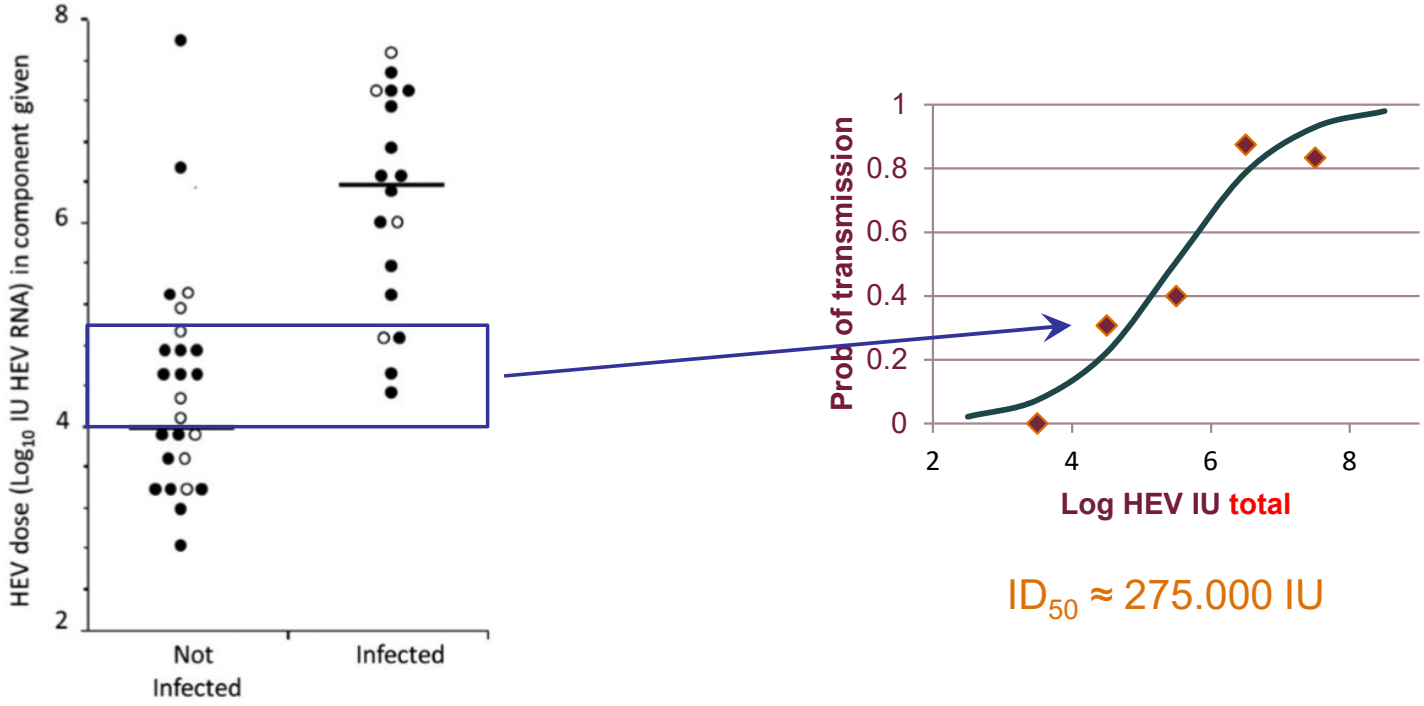
Dose-dependent probability of HEV transmisison

Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

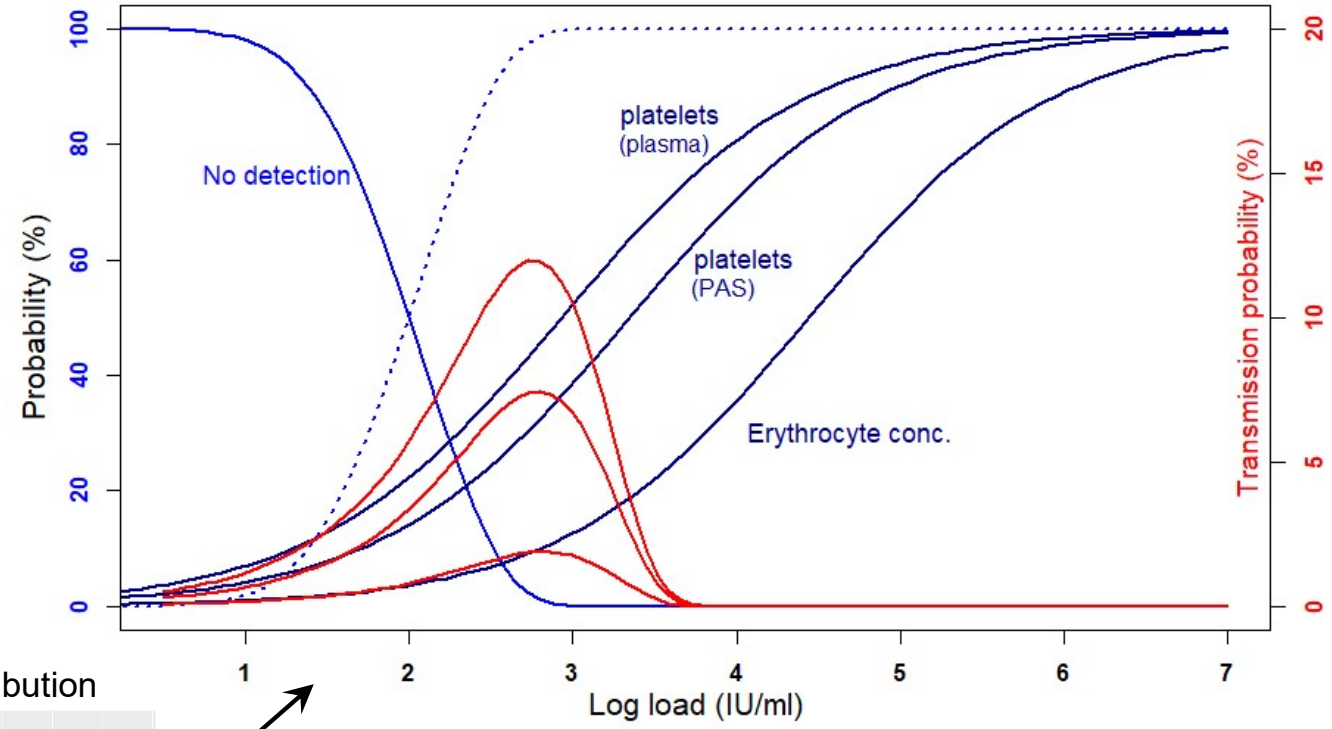
Lancet, 2014

- 42% of transfused HEV positive blood products caused transmission (43 recipients tested)
- Infectious dose is high
- Estimated probablitly of transmission can be calculated based on dose range:

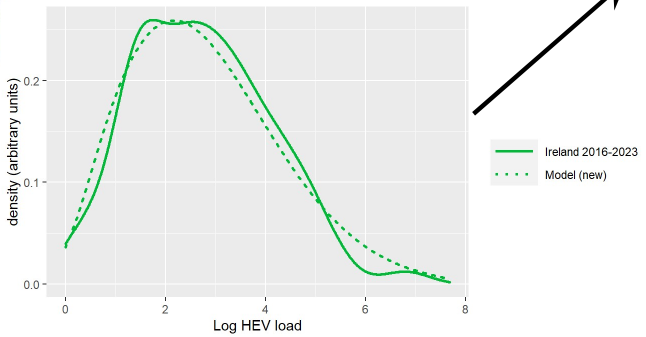


$ID_{50} \approx 275.000$ IU

Residual risk of HEV transmission via blood products



Viral load distribution



Plasma volumes:

- 10 ml (ery)
- 124 ml (platelets stored in PAS
- 322 ml (platelets stored in plasma)

- Unknown what products would have been made from HEV+ donations
- We do know the percentage of donations processed into each type of blood product

Residual risk of HEV infection

- The residual risk of HEV infection by blood products was estimated for different screening scenario's

Probability of transmission of HEV-RNA positive donations (%)`

	Erythrocyte concentrate	Buffycoat	Trombocyte concentrate or Q plasma	Trombocyte concentrate PAS-E
Volume of plasma	10	2	322	115.5
No screening	19.7	12.2	44.6	36.1
Pools 96 (Roche)	1.6	0.66	9.1	5.7
Pools 24 (Roche)	0.68	0.27	4.3	2.6
Pools 24 (Grifols)	0.38	0.15	2.5	1.5
ID NAT (Grifols)	0.03	0.01	0.20	0.11

Corresponding risk reduction (%)

Screening type	Erythrocyte concentrate	Buffycoat	Trombocyte concentrate or Q plasma	Trombocyte concentrate PAS-E
No screening	0	0	0	0
Pools 96 (Roche)	92	95	80	84
Pools 24 (Roche)	97	98	90	93
Pools 24 (Grifols)	98	99	94	96
ID NAT (Grifols)	100	100	100	100

What risk is acceptable?

- Cost effectiveness estimate for HEV screening in the Netherlands (De Vos et al, Transfusion, 2017)

Screening	HEV transmissions per year	Chronic HEV cases / year	Testing costs / year	Costs per chronic case averted	Costs per incurable case averted
No testing	187	4.94	0	n.a.	n.a.
Pools 24	13.4	0.42	1.4 million	310,000	3 million
ID NAT	1.33	0.04	13.3 million	2.7 million	26.7 million

- Estimate of costs per quality adjusted life year was not made, but costs per QALY exceed the norm
- The observed decline in HEV incidence obviously reduced the cost effectiveness of the screening

- Estimated yield of screening based on positive donations:
  - Prevented transmissions 34.8 /year
  - Chronic HEV cases prevented 1.0 /year
  - Transmissions despite screening 2.1 / year

What risk is acceptable (2)?

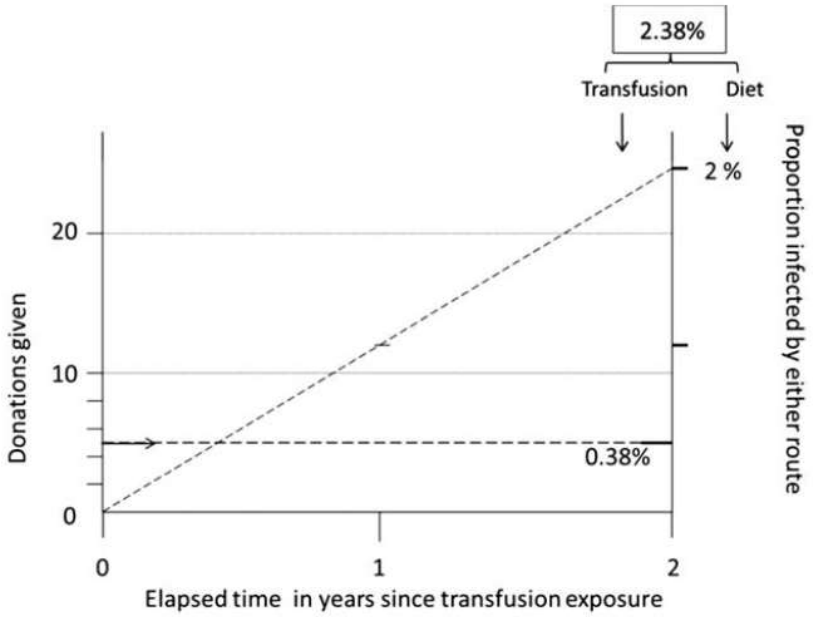


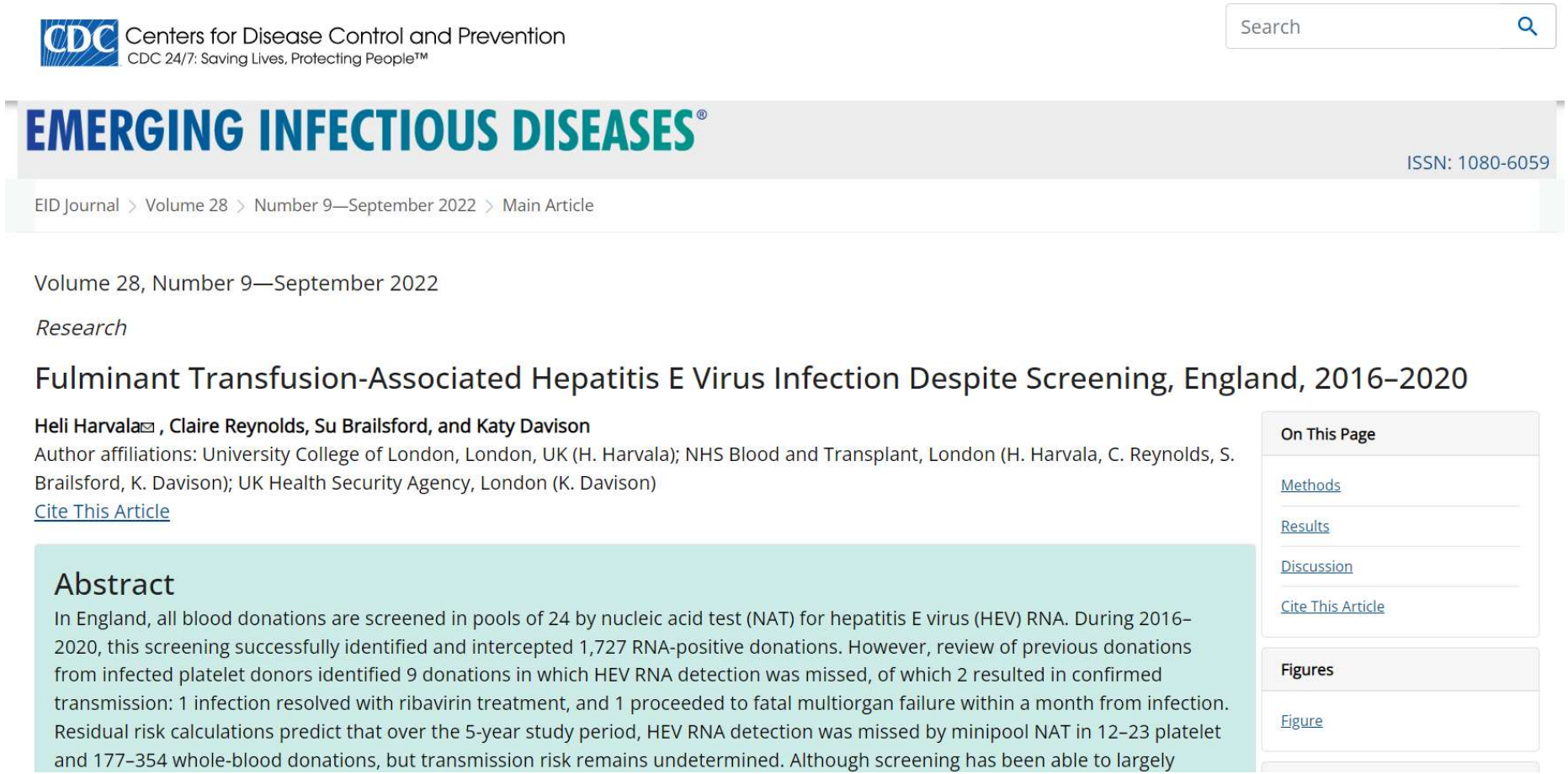
Fig. 3. Outcome 2 years after receiving five components in a country with an annual seroconversion rate of 1%. The combined infection risk is 2.38% comprising both dominant cumulative dietary and smaller transfusion risks.

Tedder et al
Transfusion 2017, 57:267-272

- We estimated that without HEV screening 0.14% of HEV infections is caused by use of blood products
- This percentage is independent of HEV incidence!
- 29% of chronic HEV in transplant patients caused by blood products
  (in the year of transplantation)

What risk is acceptable (3)?

- Fatal HEV infection despite pooled screening observed in Germany and the UK



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EID Journal > Volume 28 > Number 9—September 2022 > Main Article

Volume 28, Number 9—September 2022

Research

Fulminant Transfusion-Associated Hepatitis E Virus Infection Despite Screening, England, 2016–2020

Heli Harvala✉, Claire Reynolds, Su Brailsford, and Katy Davison

Author affiliations: University College of London, London, UK (H. Harvala); NHS Blood and Transplant, London (H. Harvala, C. Reynolds, S. Brailsford, K. Davison); UK Health Security Agency, London (K. Davison)

Cite This Article

Abstract

In England, all blood donations are screened in pools of 24 by nucleic acid test (NAT) for hepatitis E virus (HEV) RNA. During 2016–2020, this screening successfully identified and intercepted 1,727 RNA-positive donations. However, review of previous donations from infected platelet donors identified 9 donations in which HEV RNA detection was missed, of which 2 resulted in confirmed transmission: 1 infection resolved with ribavirin treatment, and 1 proceeded to fatal multiorgan failure within a month from infection. Residual risk calculations predict that over the 5-year study period, HEV RNA detection was missed by minipool NAT in 12–23 platelet and 177–354 whole-blood donations, but transmission risk remains undetermined. Although screening has been able to largely

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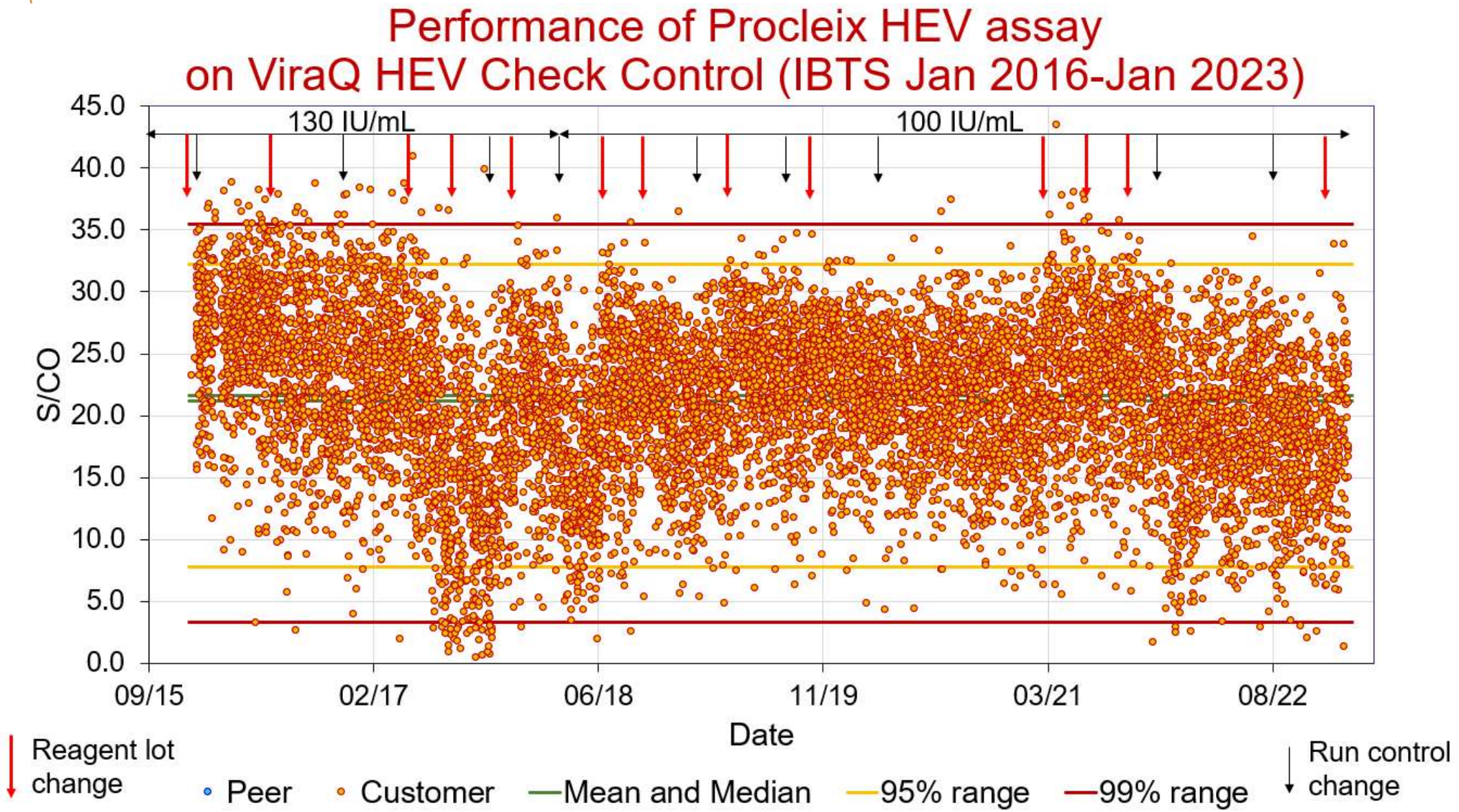
How robust are these estimates?

- Detailed sensitivity analysis has been published (De Vos et al, 2017 Tranfusion)

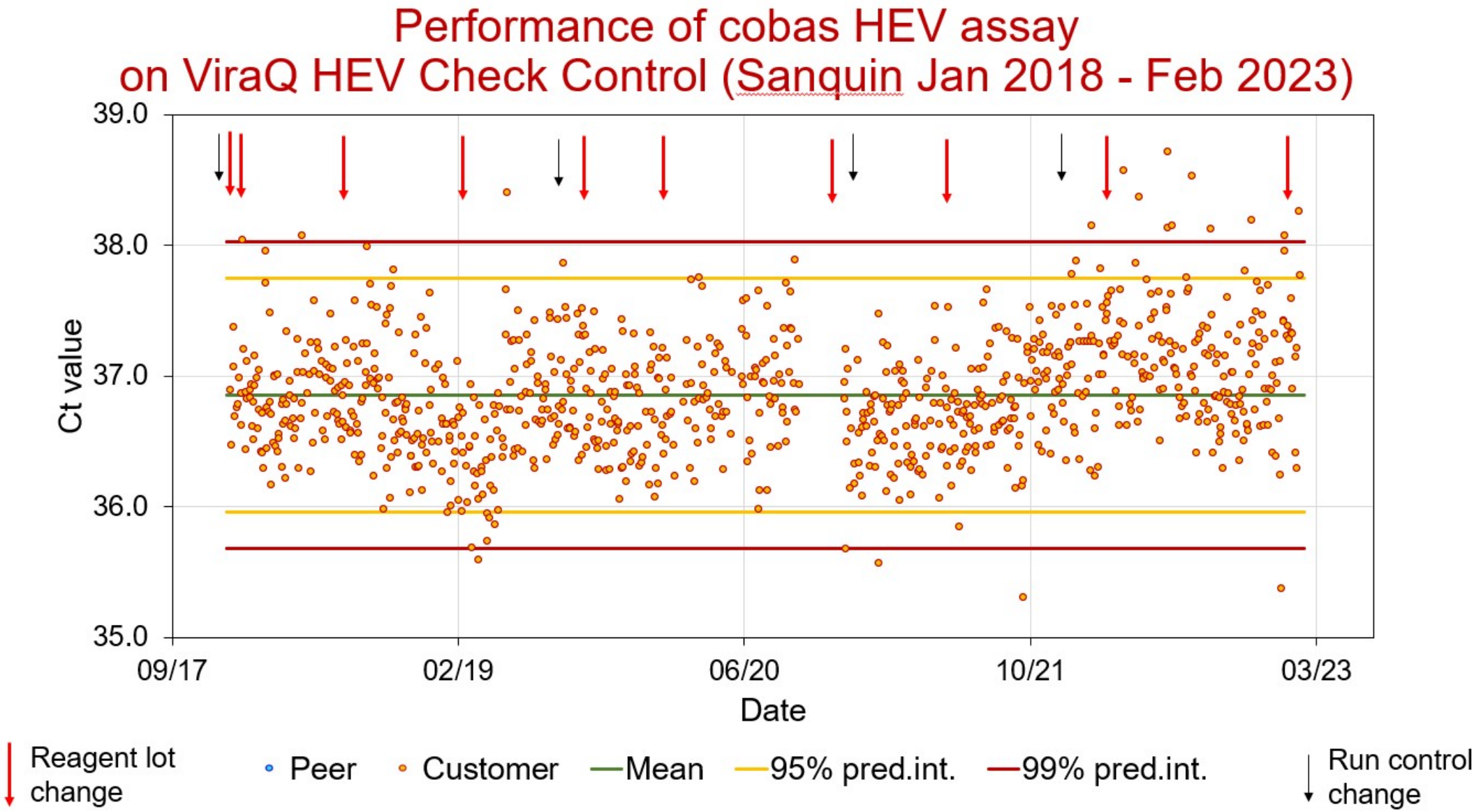
Most critical parameters:

- **Percentage of positive donations**
  - Robust estimate if screening sufficiently sensitive
  - Can be adjusted for % of undetected donations
- **Sensitivity of test**
  - Robust estimate, but needs to be monitored
- **Load distribution**
  - Improved estimate. May be subtype dependent and/or change over time
- **Transmission probability**
  - Based on one (large, robust) study
  - Many studies and case reports confirm high infectious dose
- **Progression of disease**
  - Based on case studies, rather rough estimates of number of chronic and fatal cases

Quality control: NAT reagent lot consistency (1)



Quality control: NAT reagent lot consistency (2)



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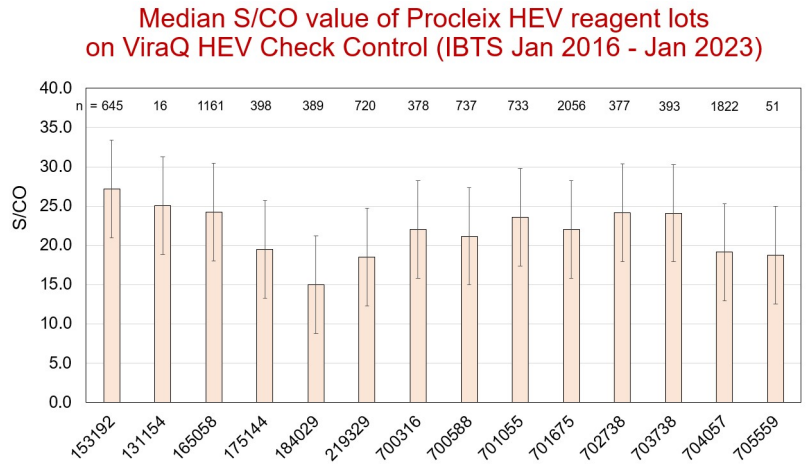

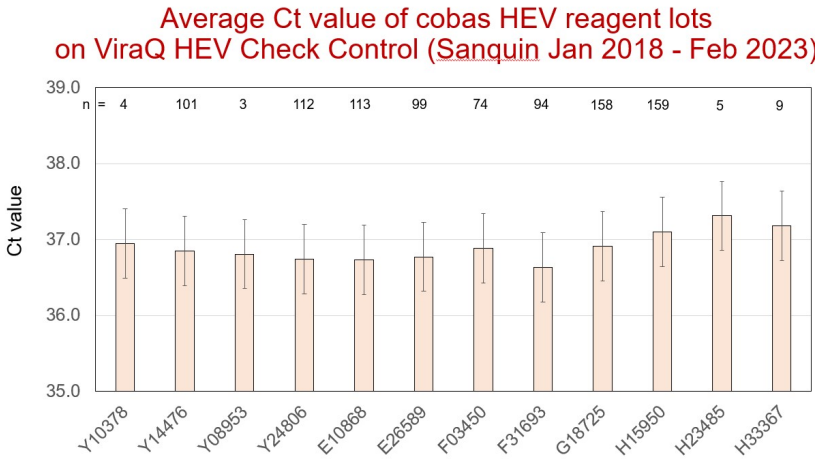

- Overall very consistent results over the years
- Change in S/CO or Ct values not real evidence for change in sensitivity but could be trigger to investigate

Acknowledgements

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