

A NEW COMPUTATIONAL STRATEGY FOR ESTIMATING RESIDUAL VIRAL TRANSMISSION RISK BY NAT- SCREENED BLOOD COMPONENTS

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Risk-analyses transfusion-mediated infections

- Previous studies:
risk due to donors in window phase (WP),
in early ramp-up phase of viremia

TRANSFUSION COMPLICATIONS

Transfusion 42 (2002) 537-548

**Mathematic modeling of the risk of HBV, HCV,
and HIV transmission by window-phase
donations not detected by NAT**

Jos J.A.M. Weusten, Harry A.J. van Drimmelen, and P. Nico Lelie

DONOR INFECTIOUS DISEASE TESTING

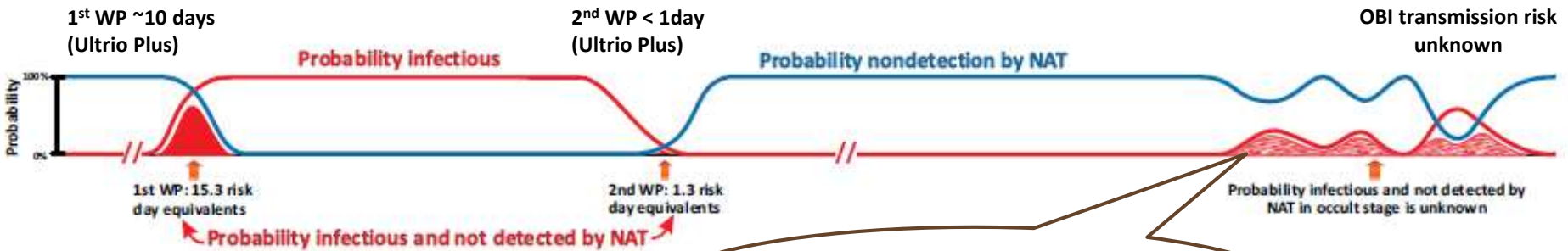
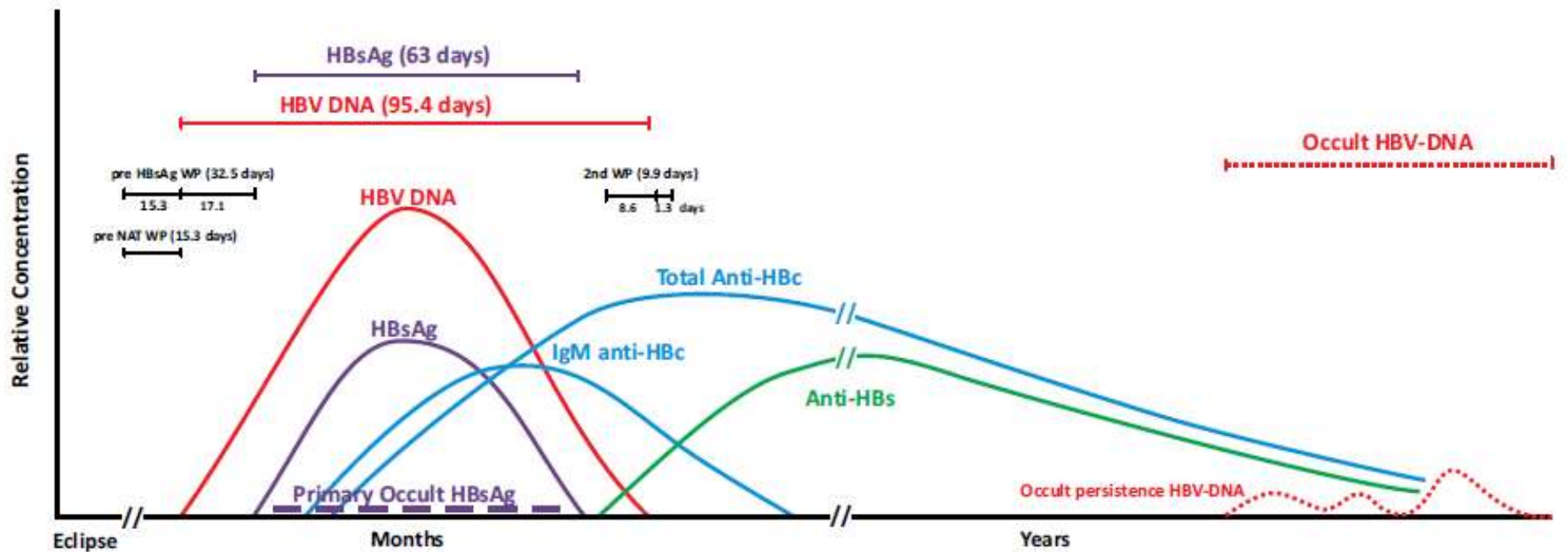
Transfusion 51 (2011) 203-215

**Refinement of a viral transmission risk model for blood
donations in seroconversion window phase screened by nucleic
acid testing in different pool sizes and repeat test algorithms**

Jos Weusten, Marion Vermeulen, Harry van Drimmelen, and Nico Lelie



Course of HBV markers and residual transmission risk of NAT-screened blood



How safe is NAT screened OBI blood

Issues for current presentation

Given the donor has occult HBV infection (OBI):

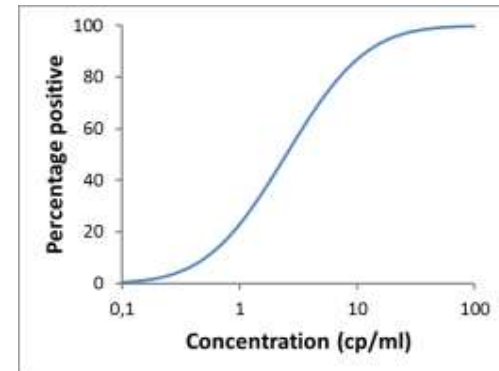
- What is the probability that the virus is detected by NAT?
- What about infectivity?
- What do we know about the viral loads in the first place?



Probability that a random donor is occult HBV carrier follows from epidemiologic data (not for current presentation)

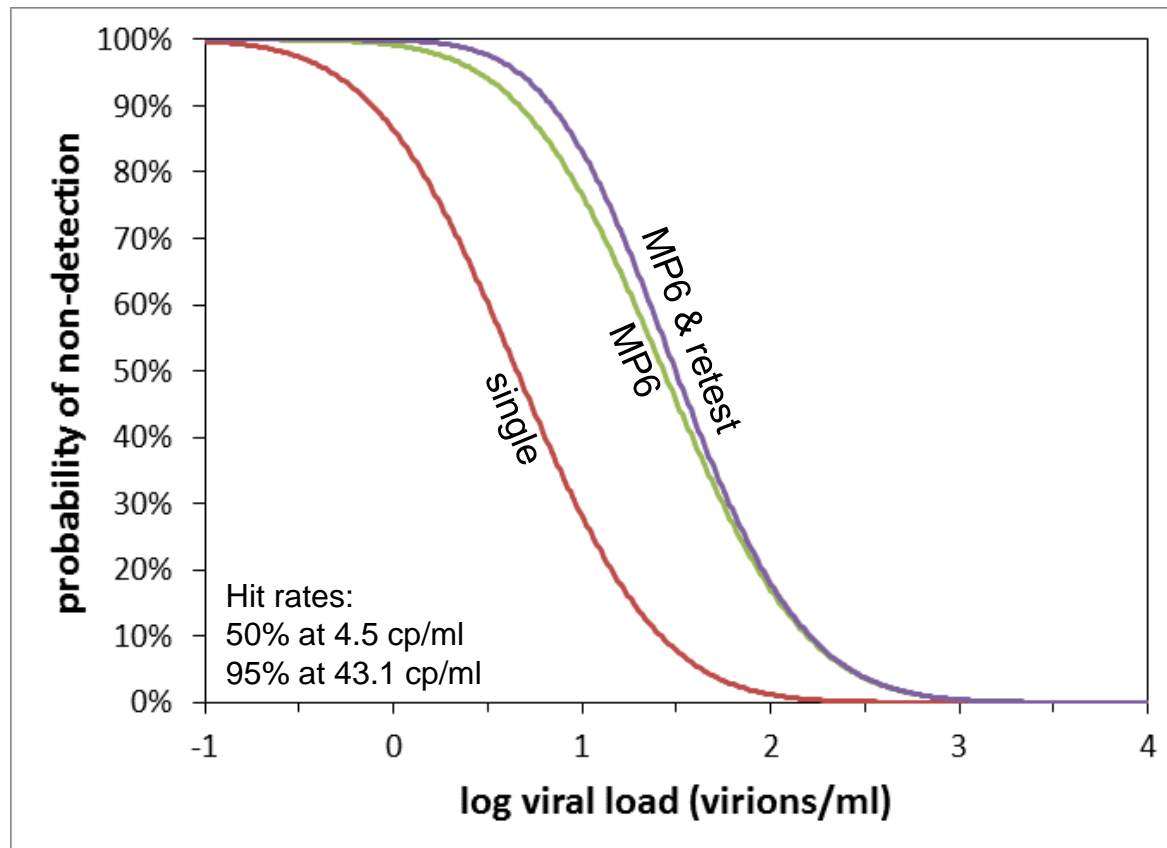
Non-detection

- Detectability in NAT-assays:
characterized by viral loads corresponding to
 - 50% positivity rate
 - 95% positivity rate
- Probit curve to describe the concentration dependency
- Risk is defined by probability of non-detection

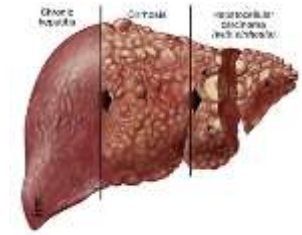


Non-detection

- Single donation testing, MP6, MP6 with single retest of individual samples in minipool



Risk depends on properties of NAT assay and on the screening protocol

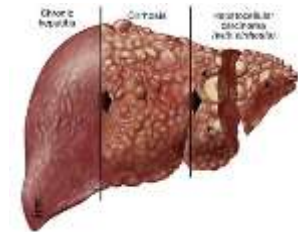


Infectivity

- Depends on *number* of virions in transfusion product, not on the concentration in donor blood
- OBI: 50% infectivity rate at ~316 virions#
(animal¹ and lookback² studies: somewhere between 100 and 1000 HBV-DNA copies)
- One intact virion already causes infection
→ Infection probability can be described by the fraction of intact virions

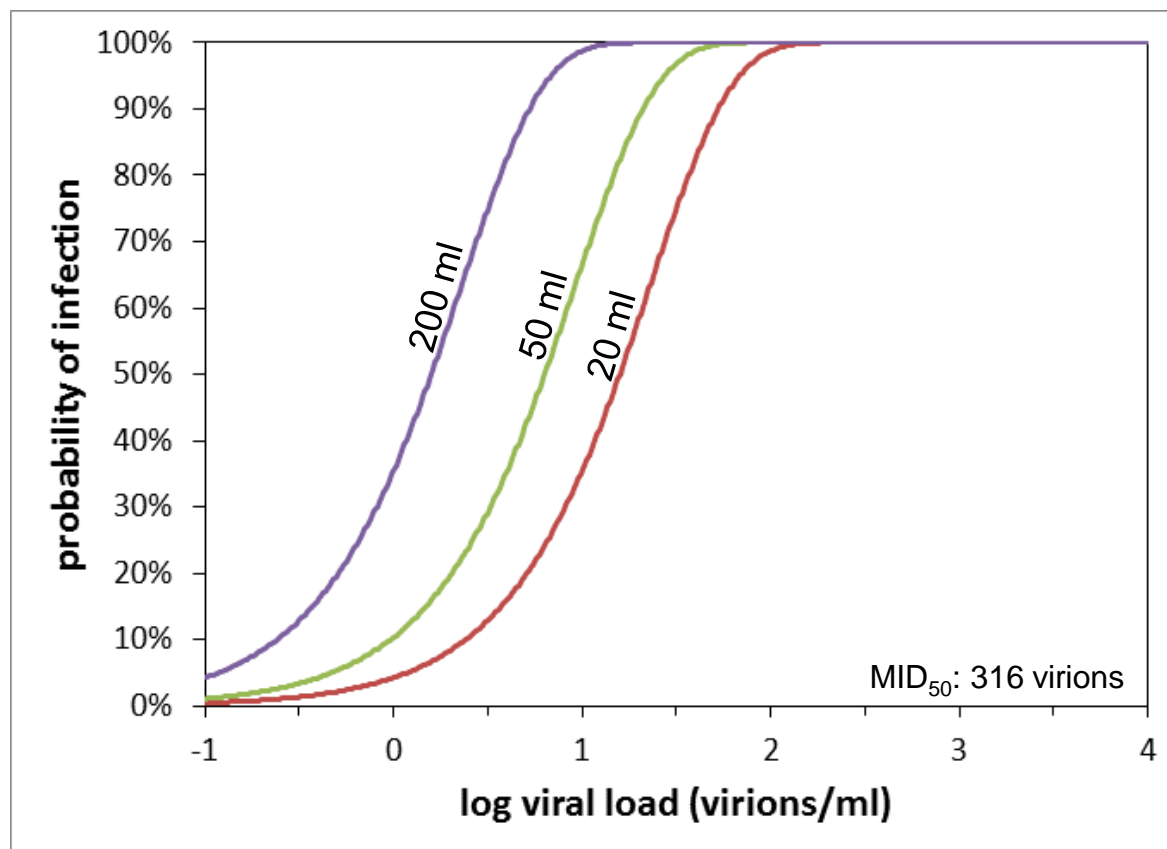
in anti-HBs negative OBI blood

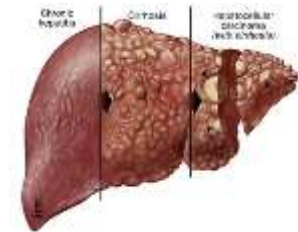
1. Tabuchi A et al. J Med Virol 2008; 80:2064
2. Allain JP et al. Transfusion 2013; 53:1405



Infectivity

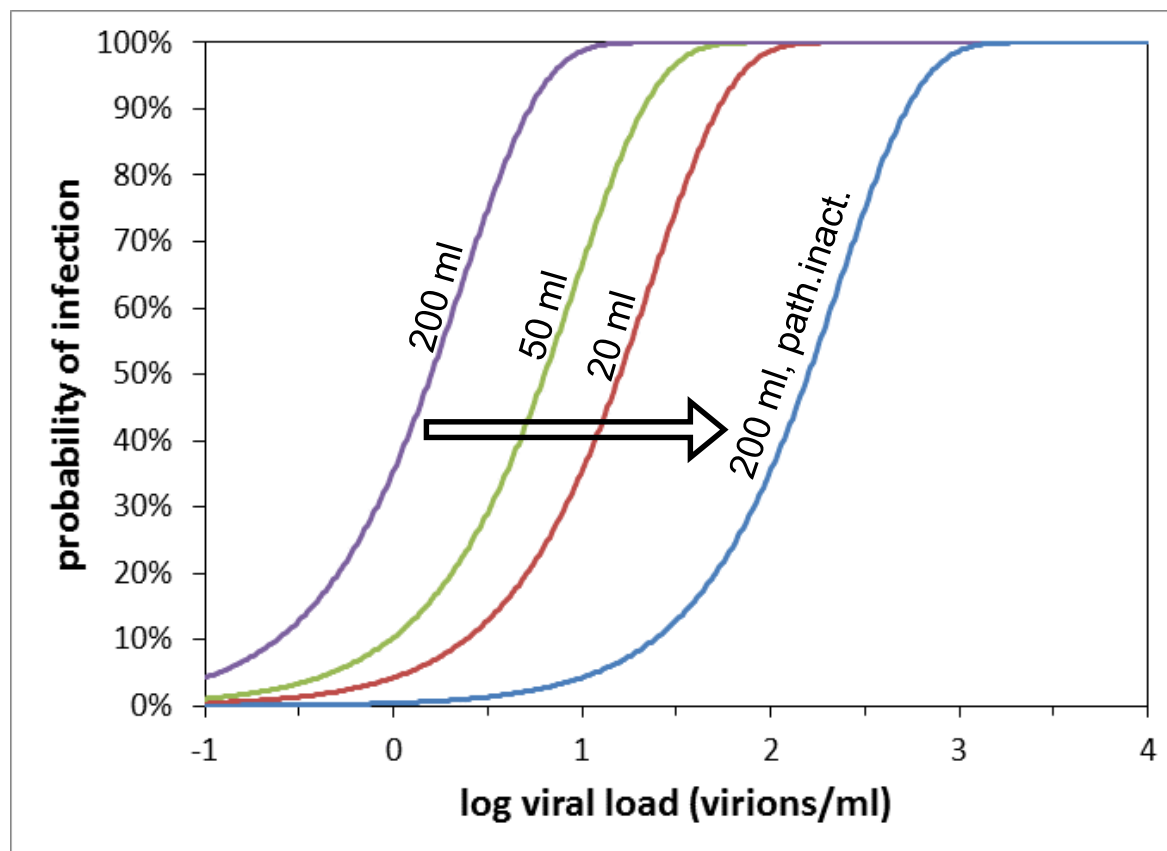
- Blood product with 20 ml, 50 ml, 200 ml plasma
→ risk increases with volume





Infectivity

- Blood product with 20 ml, 50 ml, 200 ml plasma
Pathogen inactivation (factor 100; 2 logs) reduces risk

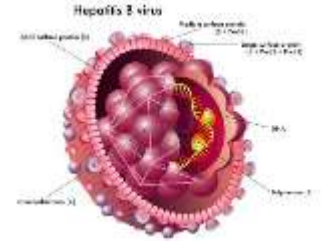


Distribution OBI viral loads

- Given the donor has occult HBV infection (OBI): what do we know about the viral loads?
- Collect OBI samples
- Quantify the viral loads
- Study the distribution of the observed viral loads

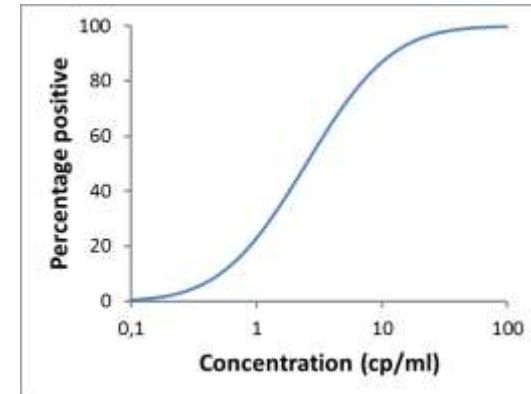


Distribution OBI viral loads



- Assessing viral loads:
Levels are (generally) below limit of quantitation

- Multiple samples analyzed in replicates in Ultrio Plus
→ hit rates in combination with probit curve yield estimates of viral loads^{1,2}

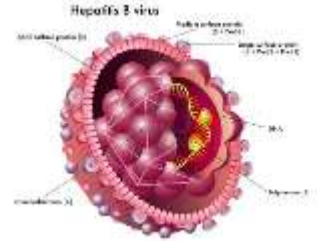


- Results with OBI samples in South Africa (n=217)
 - Detected using: Ultrio (1st study¹) Ultrio Plus (2nd study²)
 - Anti-HBs negative (OBI) n=28 n=89
 - Anti-HBs positive (OBIS) n=27 n=73

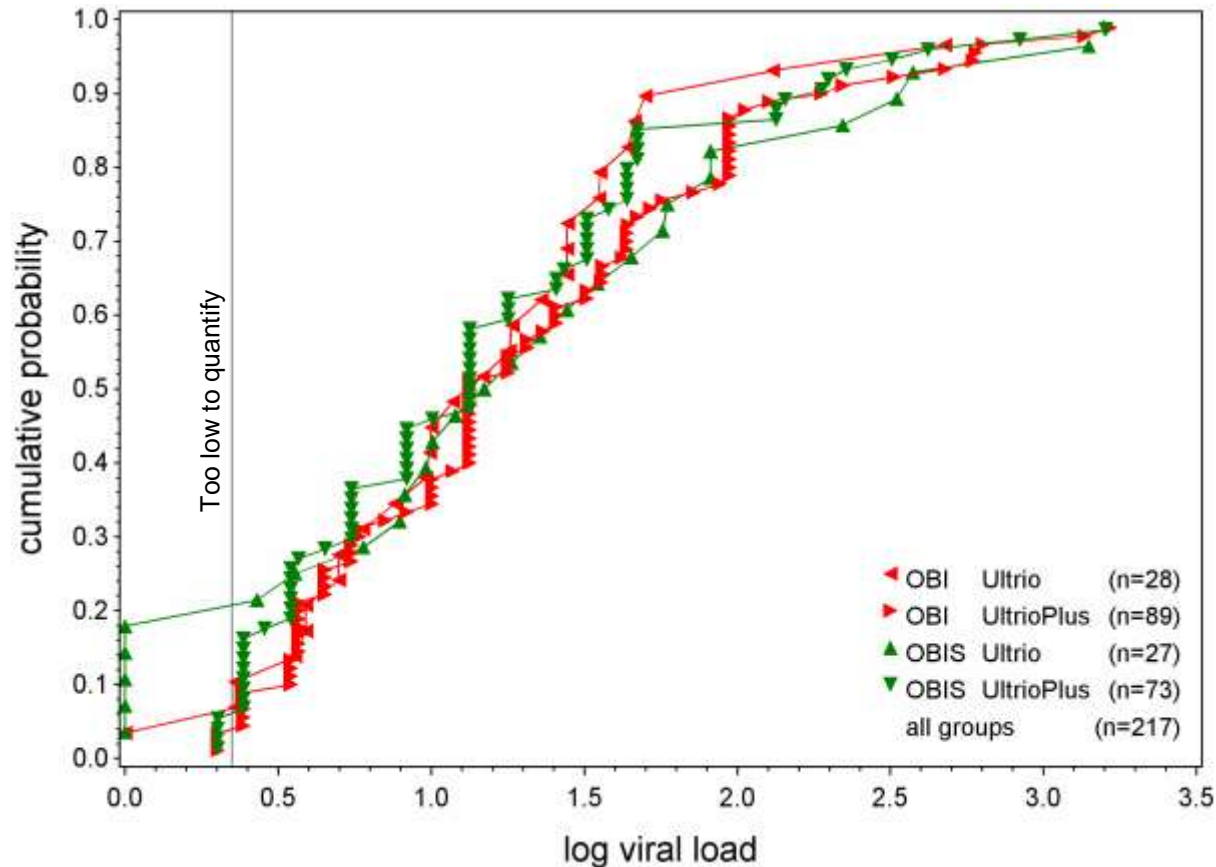
1. Vermeulen M. et al, Transfusion 2014; 54: 2496-2504.

2. Vermeulen M. et al, manuscript in preparation

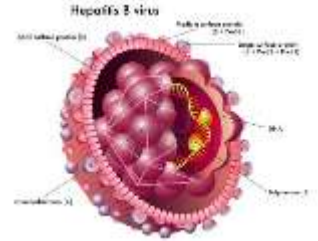
Distribution OBI viral loads



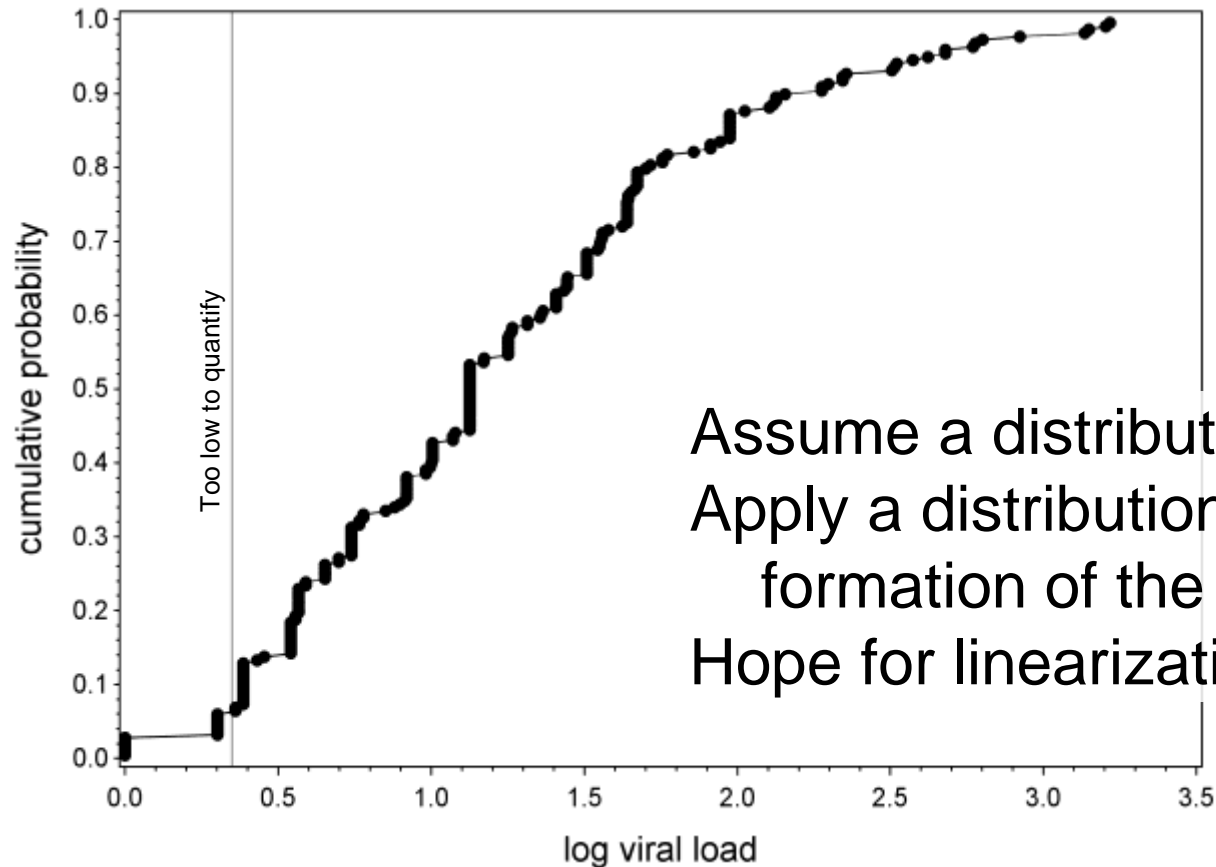
- Empirical cumulative probability distributions
→ all very similar



Distribution OBI viral loads

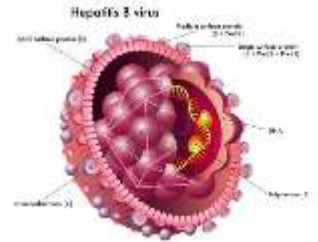


- Empirical cumulative probability distribution
– all data combined

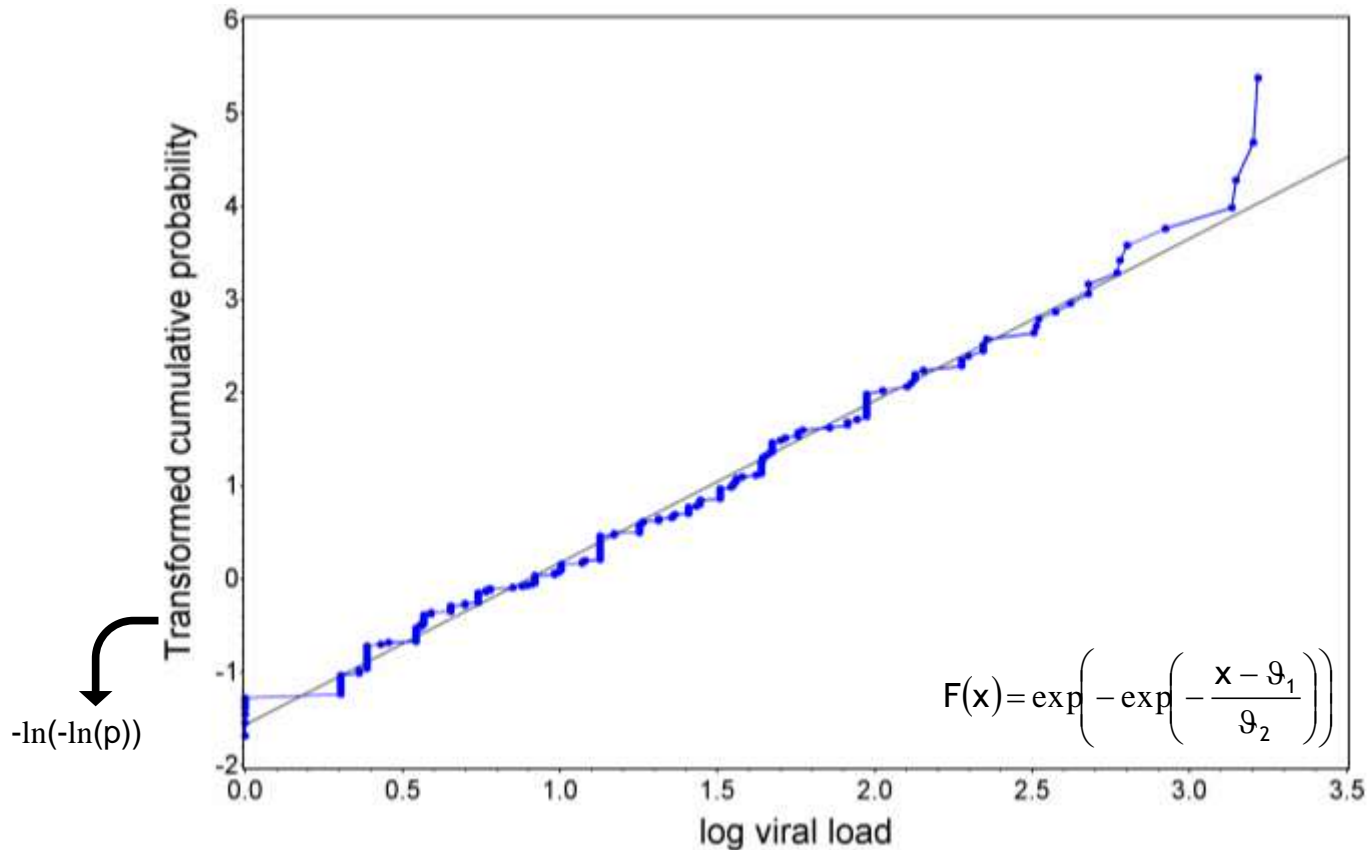


Assume a distribution
Apply a distribution-specific transformation of the vertical axis
Hope for linearization

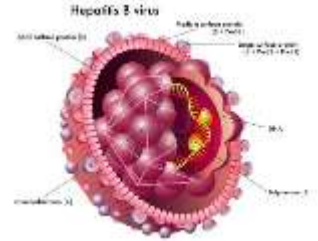
Distribution OBI viral loads: Gumbel



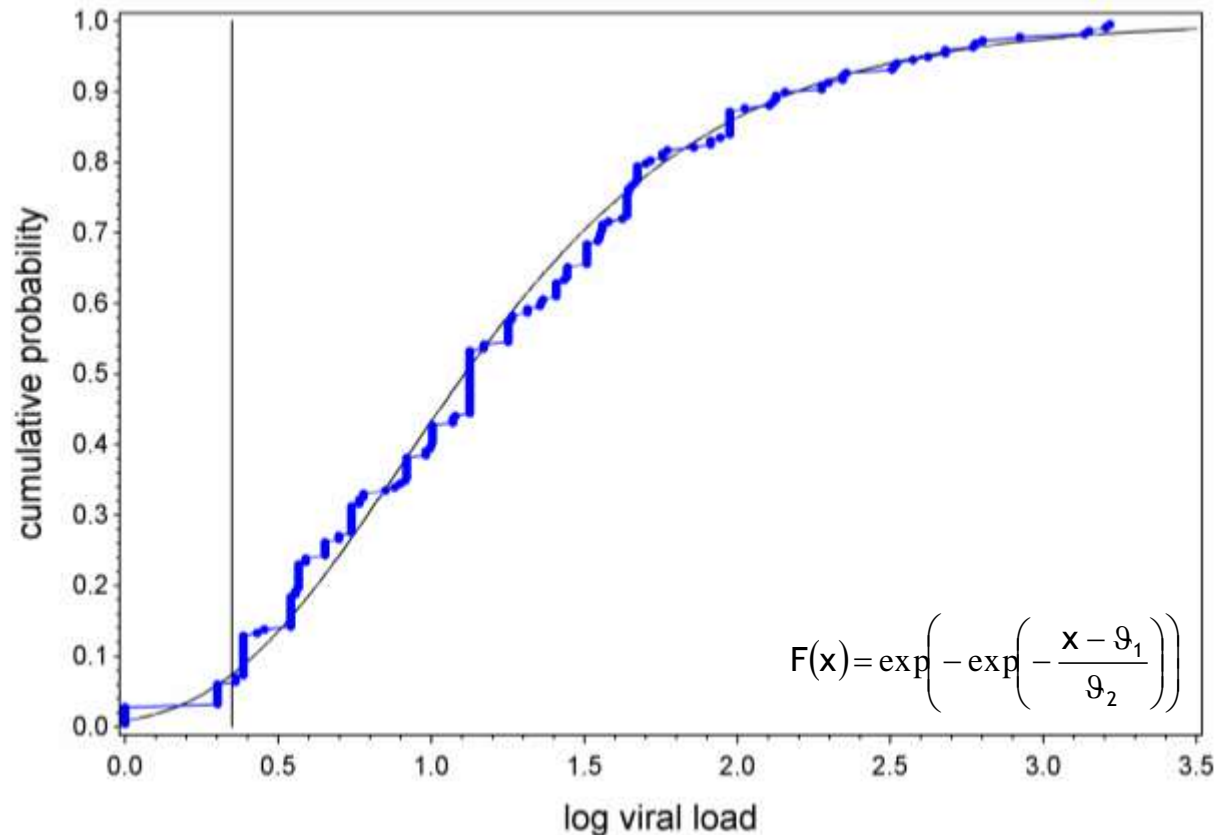
- A Gumbel distribution gives a good description of the data



Distribution OBI viral loads: Gumbel



- A Gumbel distribution gives a good description of the data



Originally 4 groups
(OBI/OBIS, Ultrio/UltrioPlus)

Hypothesis test

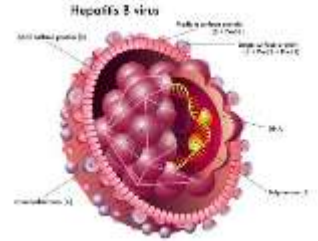
H_0 : all the same

Gumbel

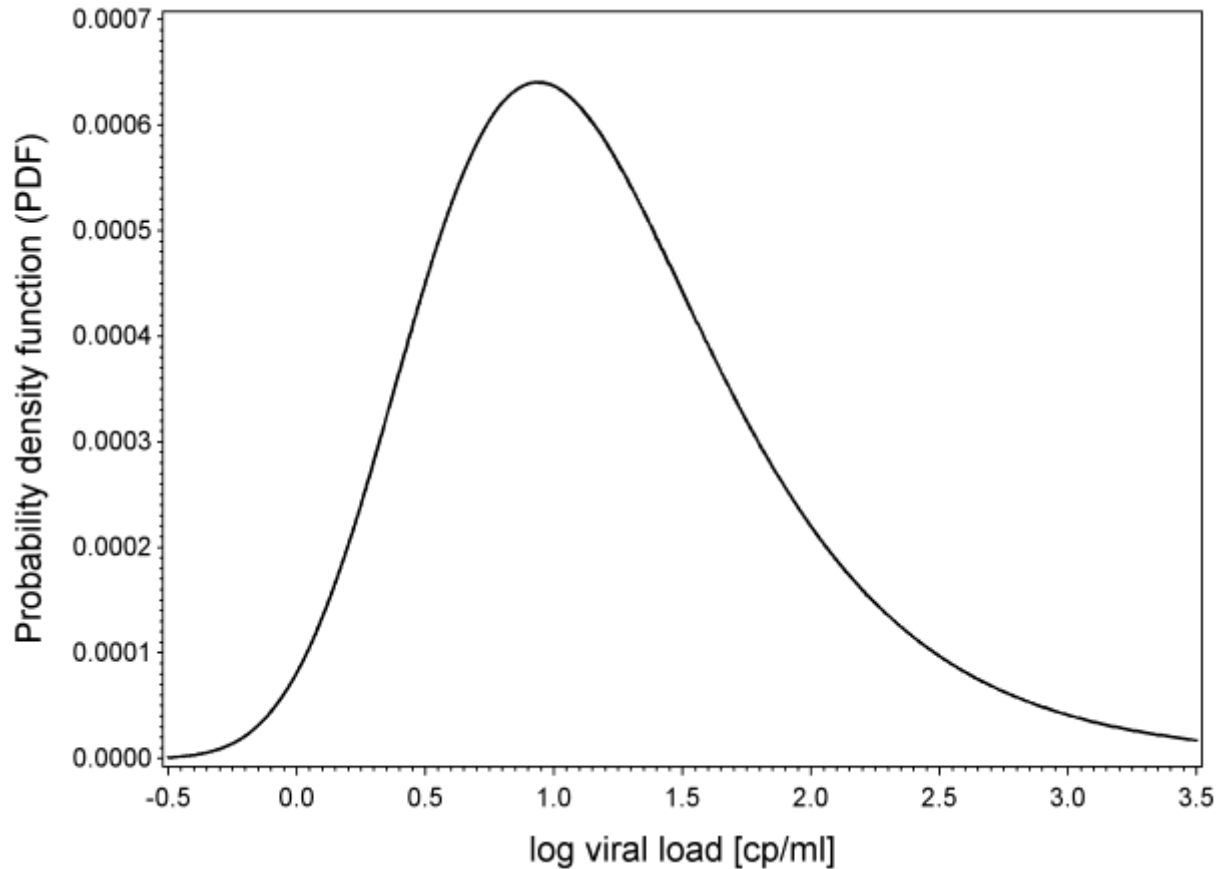
H_1 : each their own

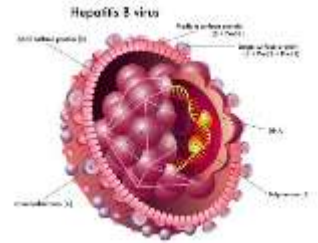
$p=0.34$ (Not significant)

Distribution OBI viral loads



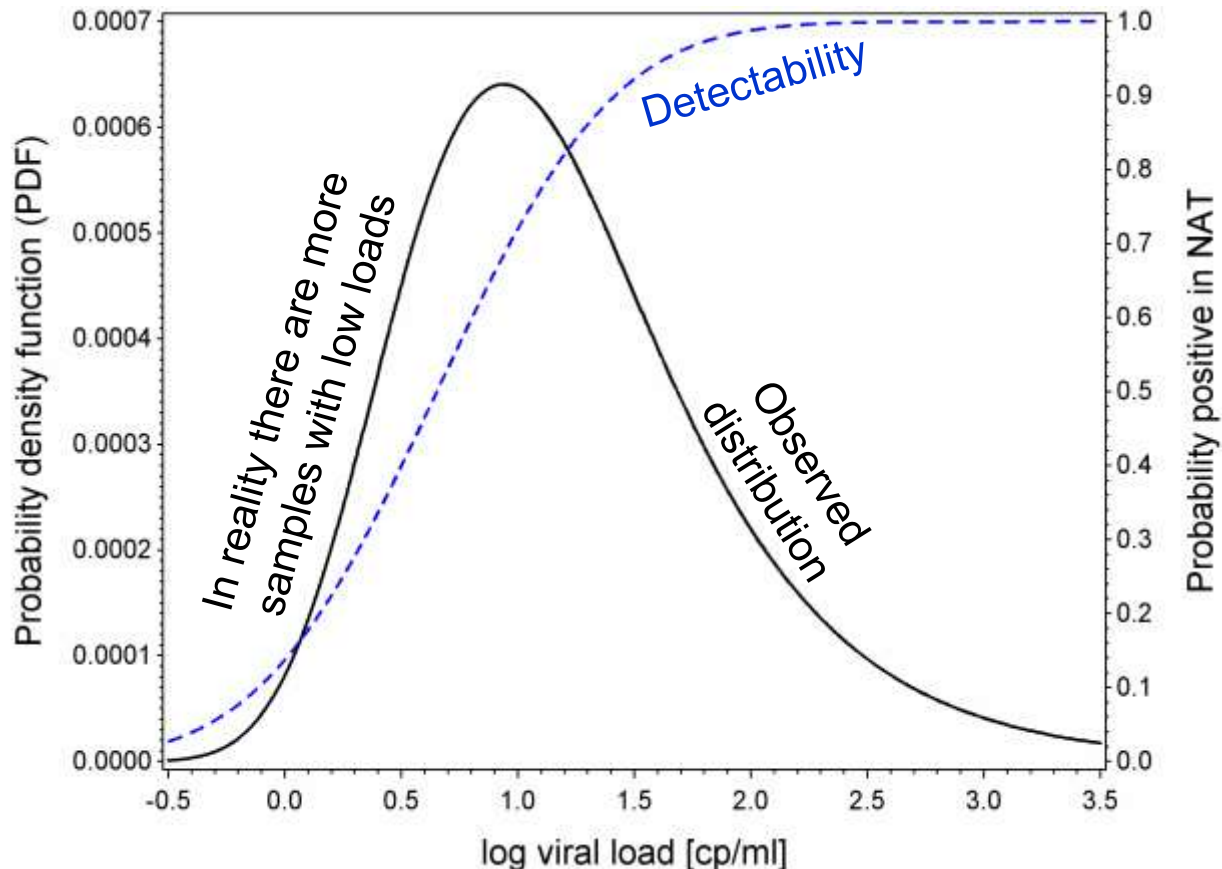
- Gumbel probability density function of observed log viral loads





Distribution OBI viral loads

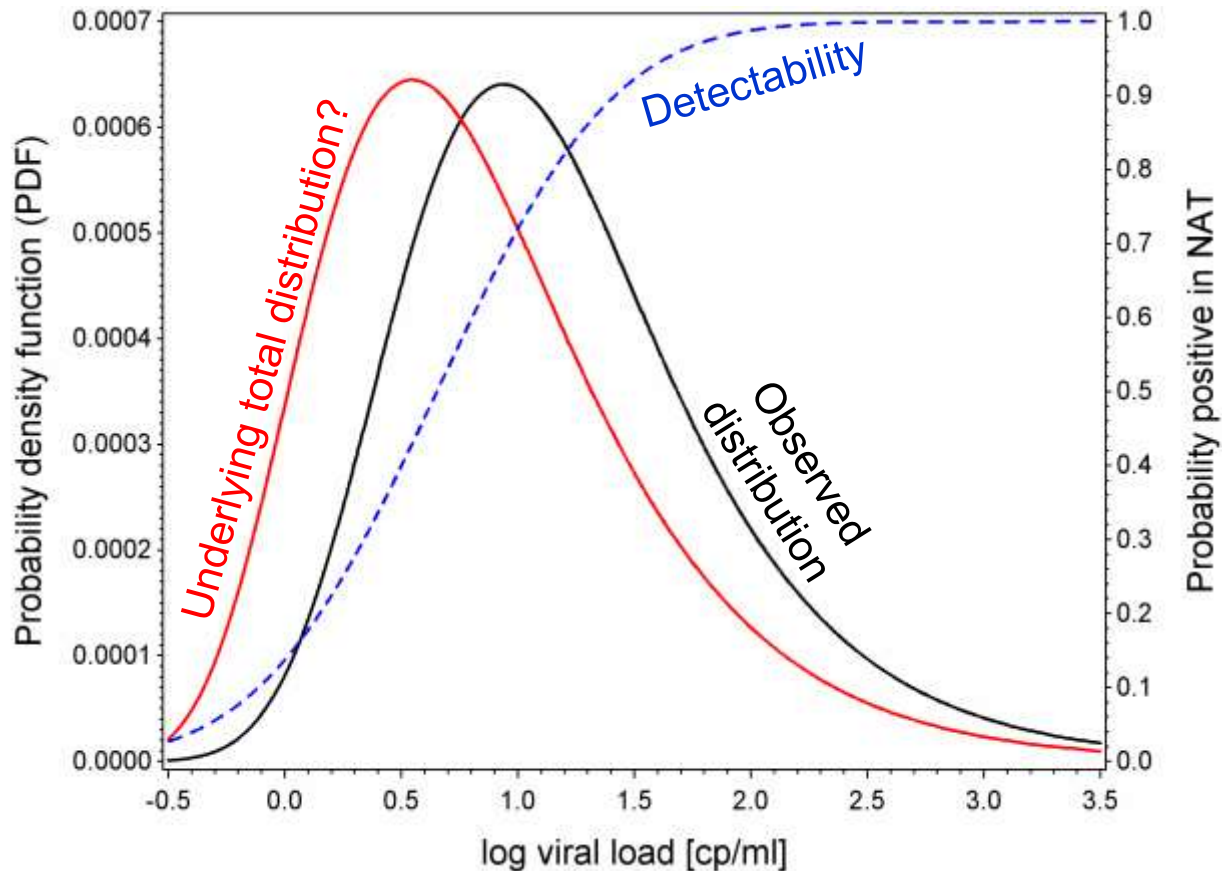
- Gumbel probability density function of observed loads
However: selection due to non-detection



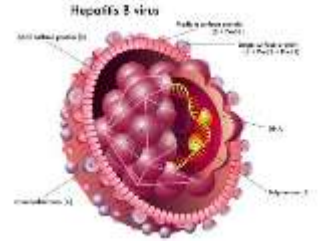


Distribution OBI viral loads

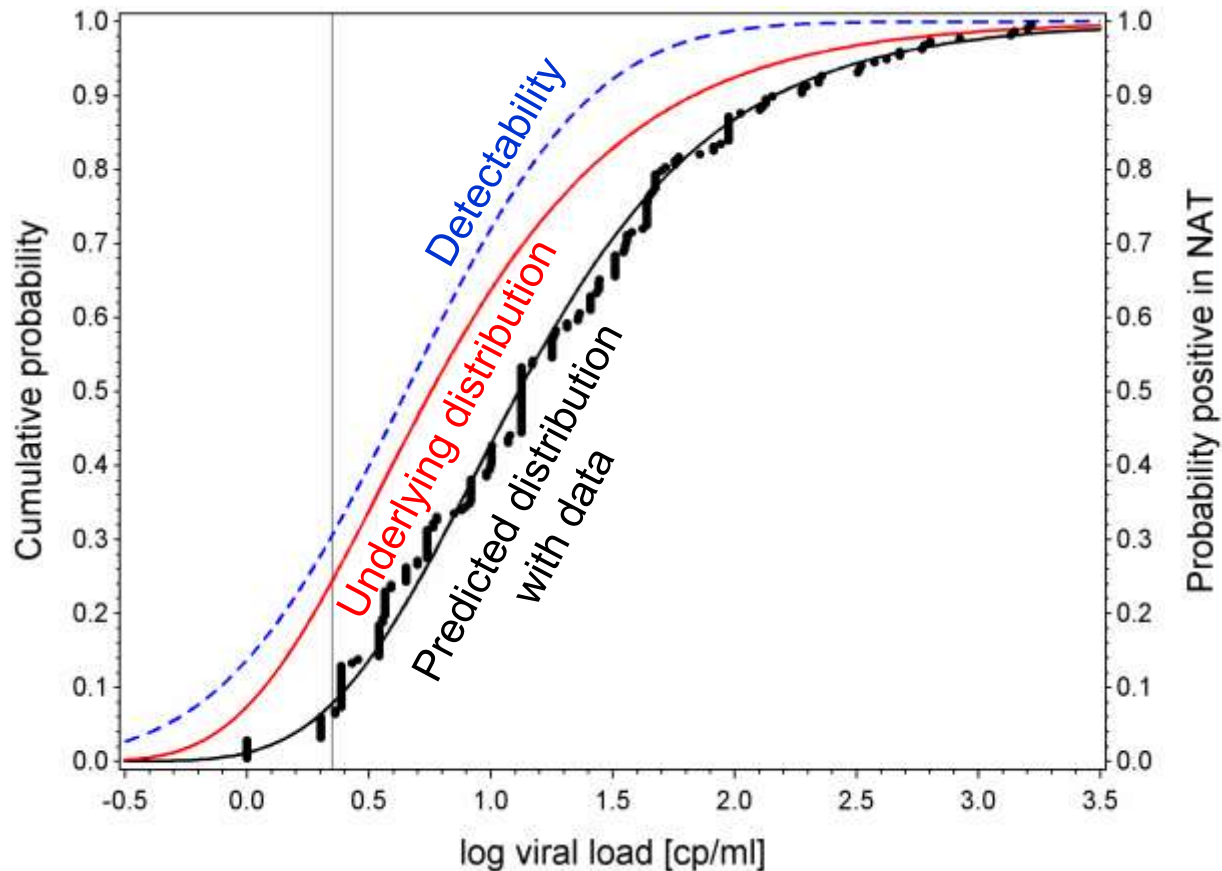
- There is an underlying OBI distribution
- Can we reconstruct this underlying distribution?



Distribution OBI viral loads



- Fitted cumulative Gumbel distribution, detectability curve, predicted and observed distribution for experimental data



Estimated quartiles:

Observed distribution

- Q1: 0.712 logs
5.15 cp/ml
- Q2: 1.11 logs
12.9 cp/ml
- Q3: 1.61 logs
41.2 cp/ml

Underlying distribution

- Q1: 0.361 logs
2.29 cp/ml
- Q2: 0.756 logs
5.70 cp/ml
- Q3: 1.26 logs
18.1 cp/ml

Current status

- Viral load in OBI: Gumbel distribution (2 parameters; ϑ_1 and ϑ_2)

$$F(x) = \exp\left(-\exp\left(-\frac{x - \vartheta_1}{\vartheta_2}\right)\right)$$

parameters can be expressed in terms of first and third quartiles

- Detectability: probit curve (2 parameters; x_{50} and x_{95})

$$\Pr(\text{pos} | x) = \Phi\left(z \cdot \frac{x - \log(x_{50})}{\log(x_{95}) - \log(x_{50})}\right)$$

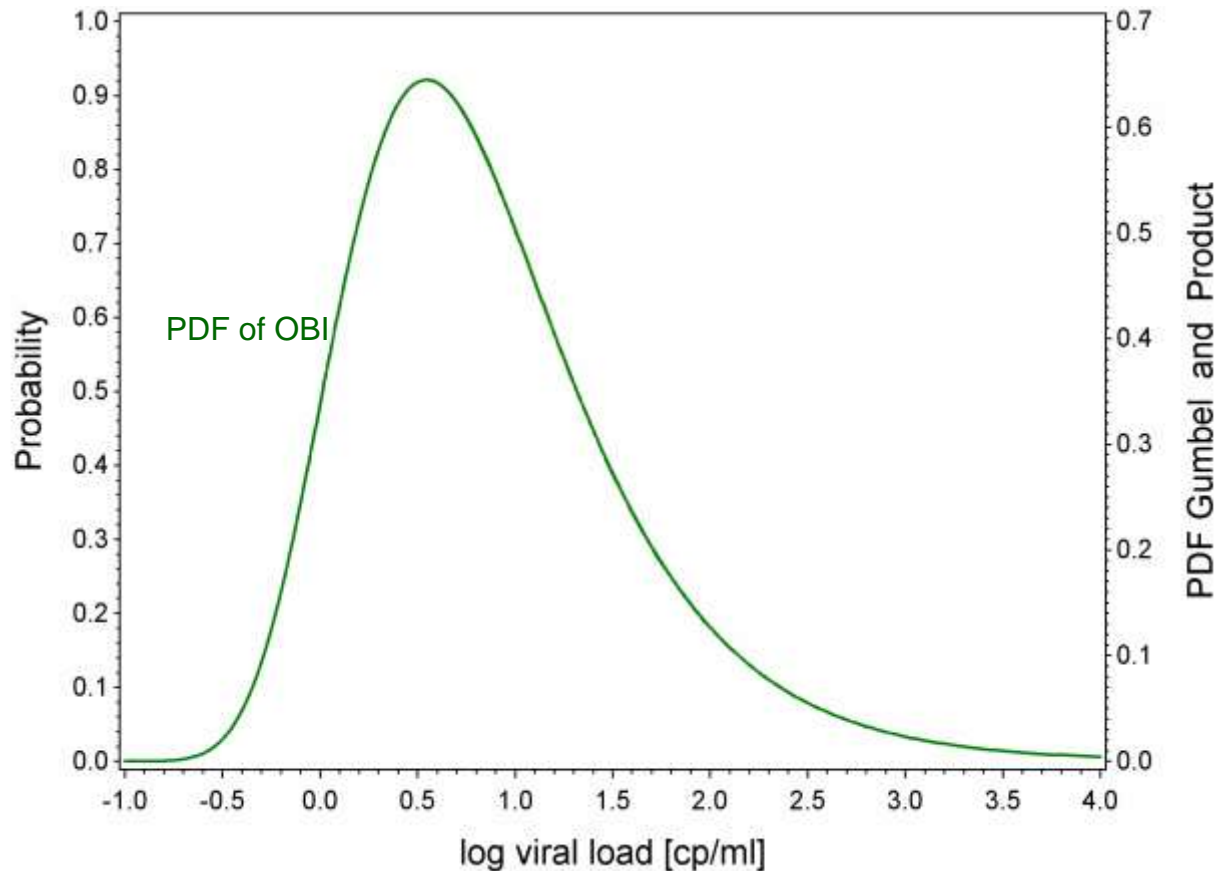
- Infectivity: 50%-infectious dose (1 parameter; N_{50})

$$\Pr(\text{infectious}) = 1 - 2^{-N/N_{50}}$$

- Combine these → Risk calculations

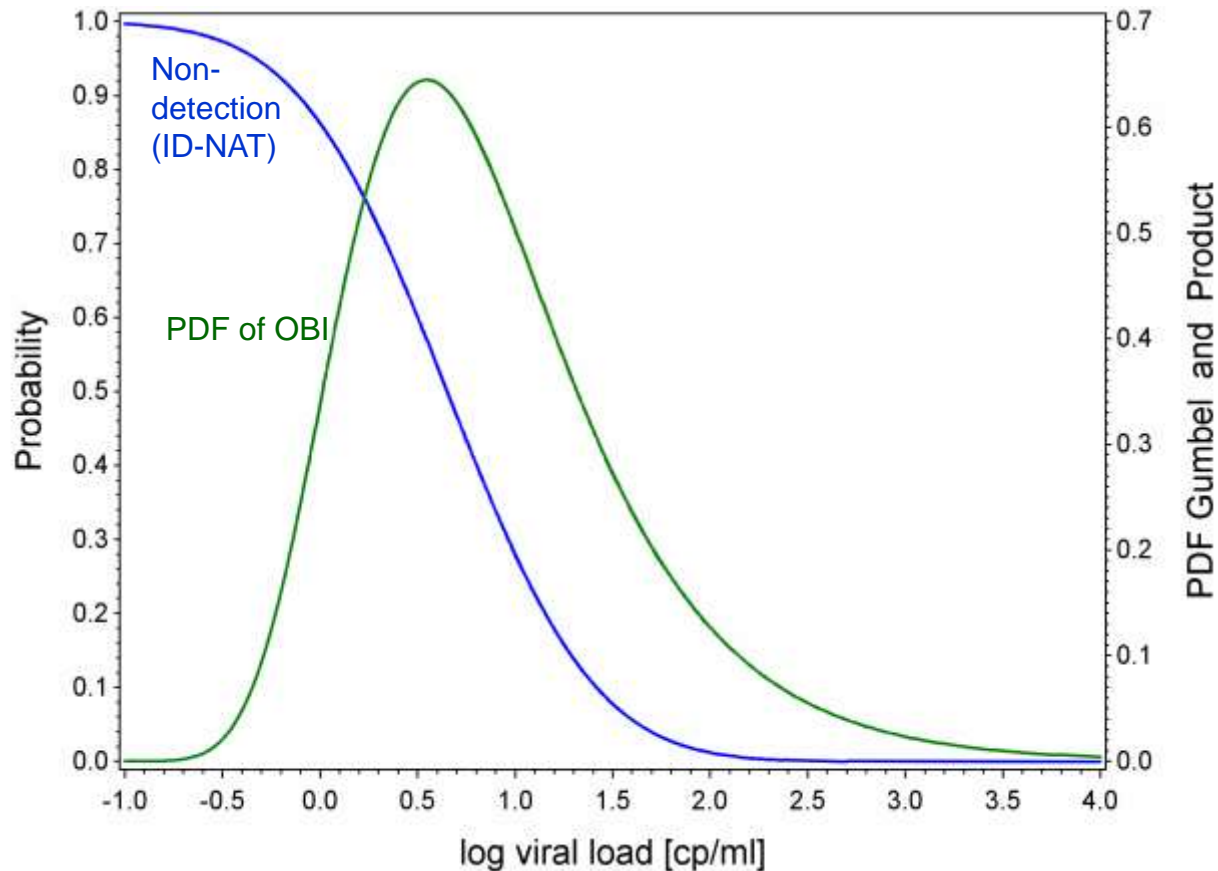
Risk calculation

- Viral loads in OBI donations:
Gumbel distribution (area under curve = 1)



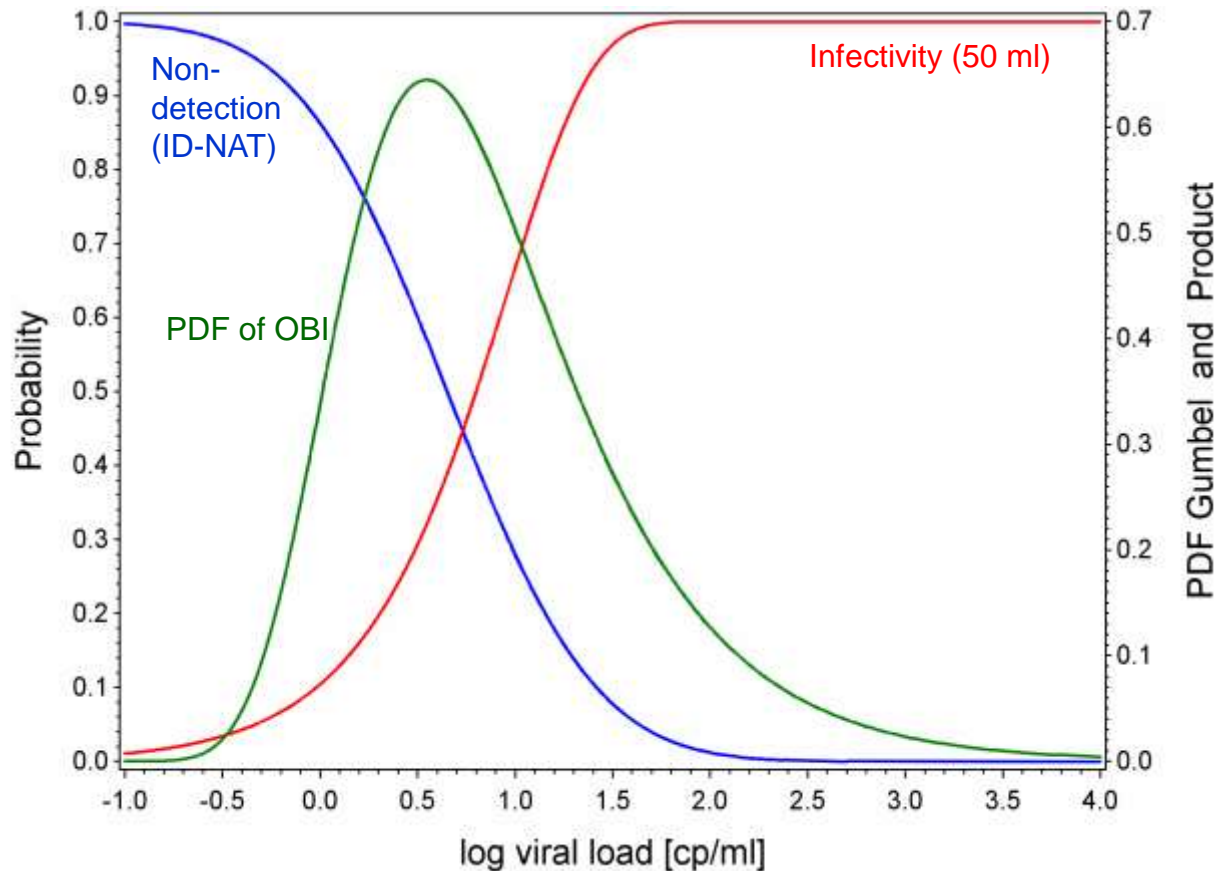
Risk calculation

- Non-detection in single donation testing



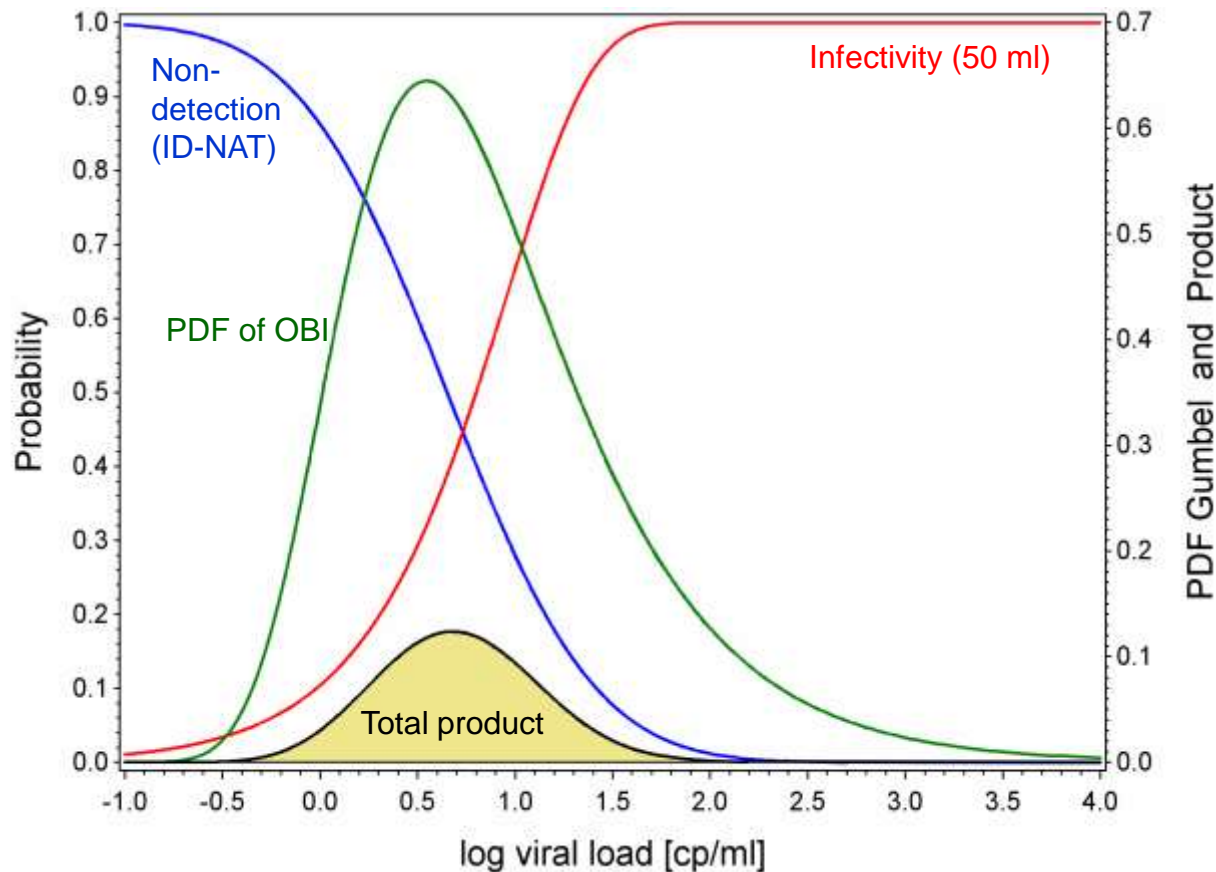
Risk calculation

- Infectivity in 50 ml plasma product



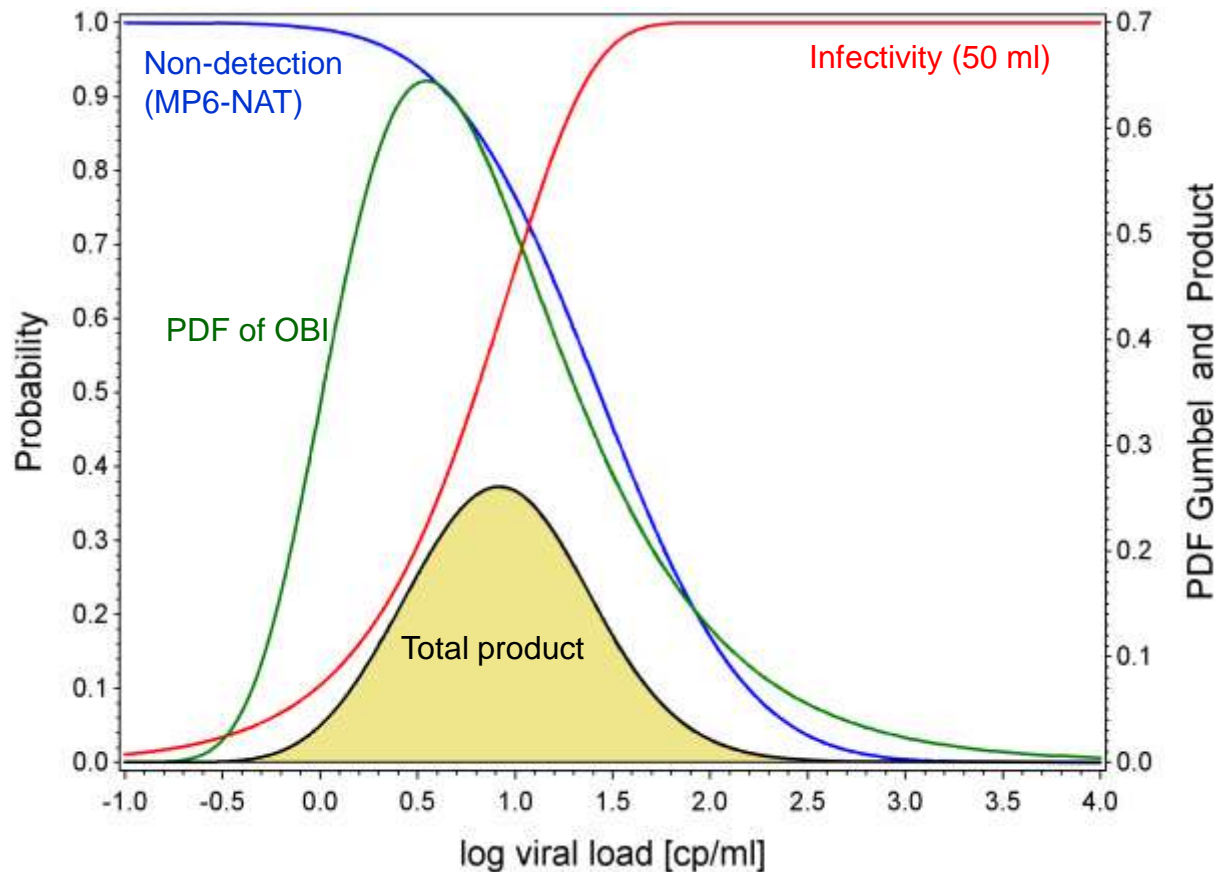
Risk calculation

- Total risk is area under curve: 13%



Risk calculation

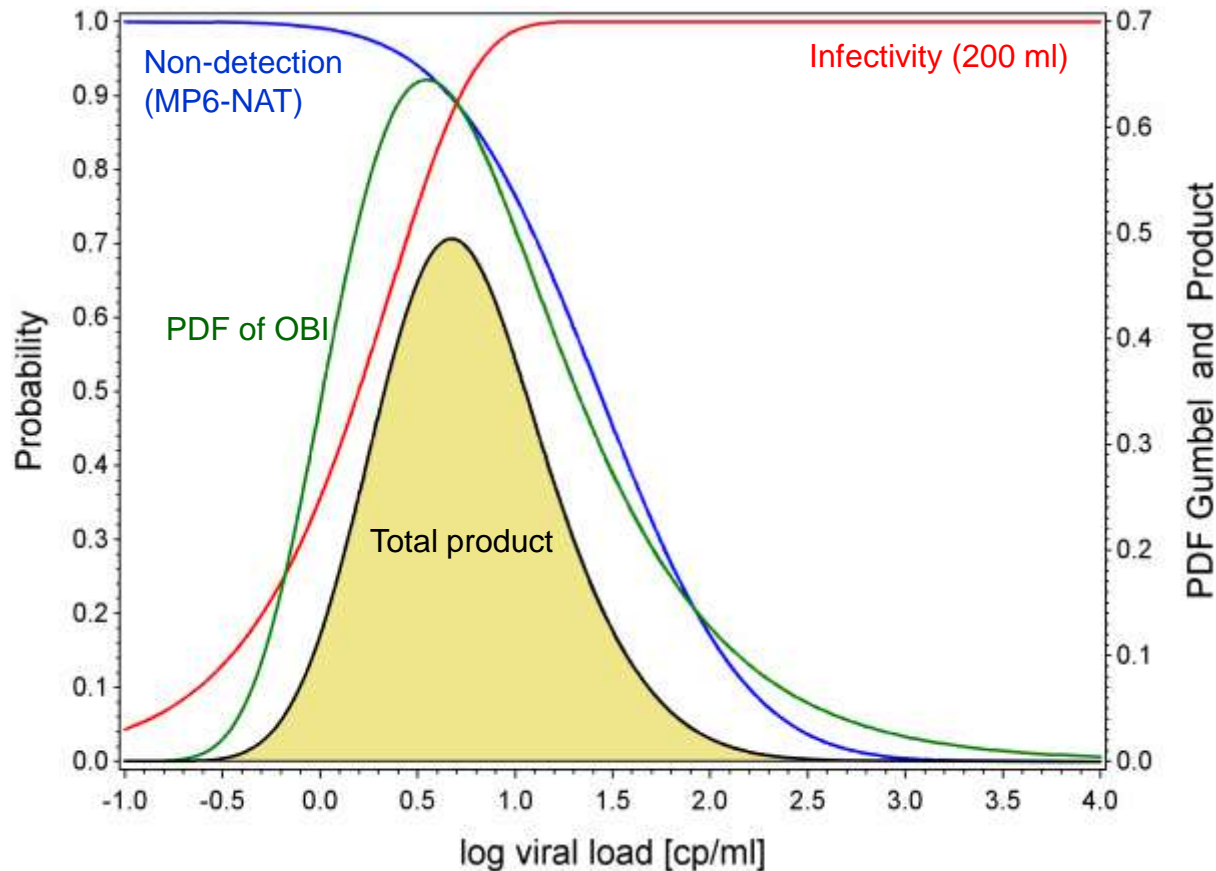
- Risk increases for MP6-NAT: 31%



Risk calculation



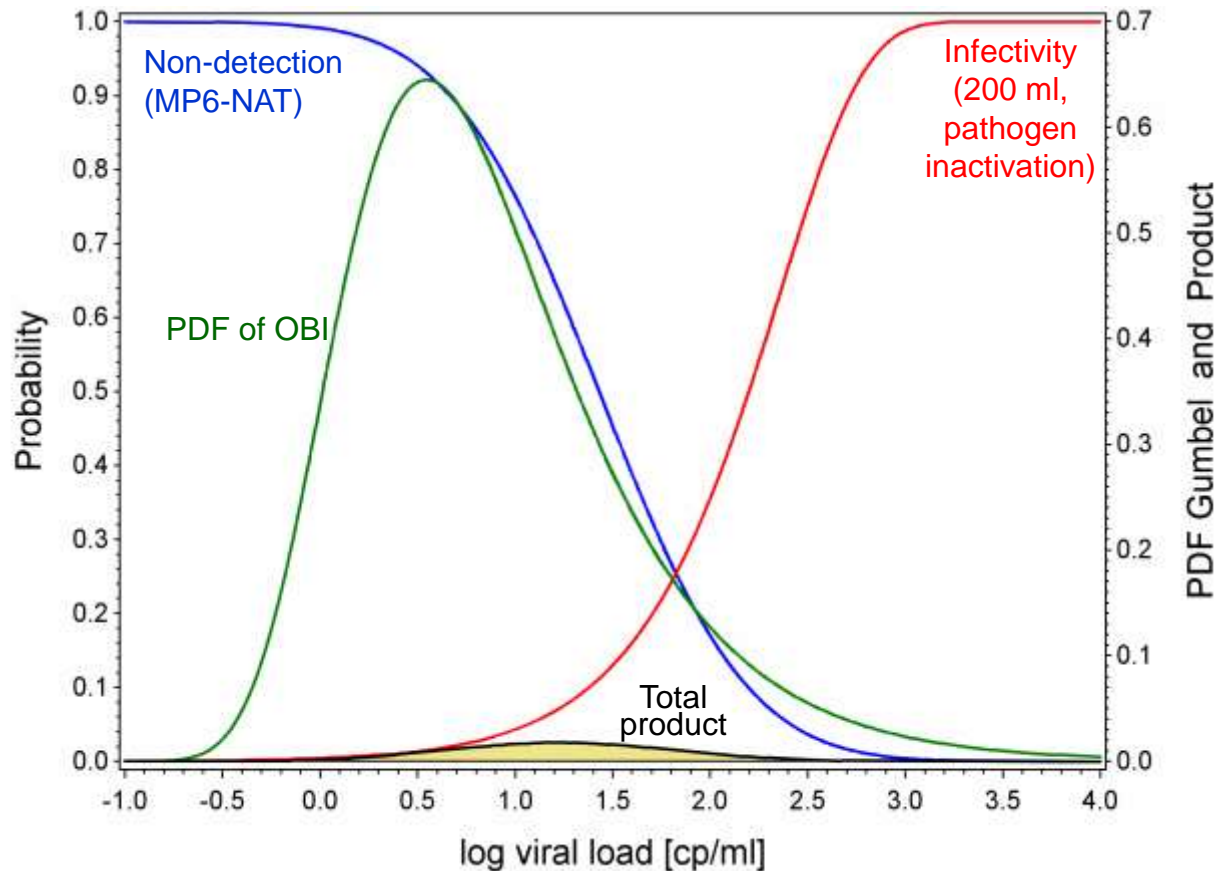
- Risk for MP6-NAT and 200 ml transfusion volume: increases to 55%



Risk calculation



- Pathogen inactivation (2 logs) reduces risk: 2.6%





Risk calculation examples

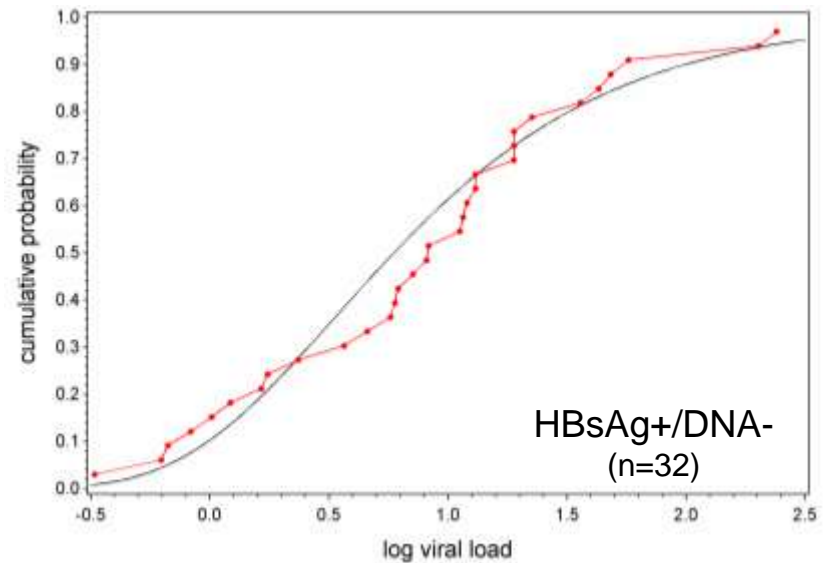
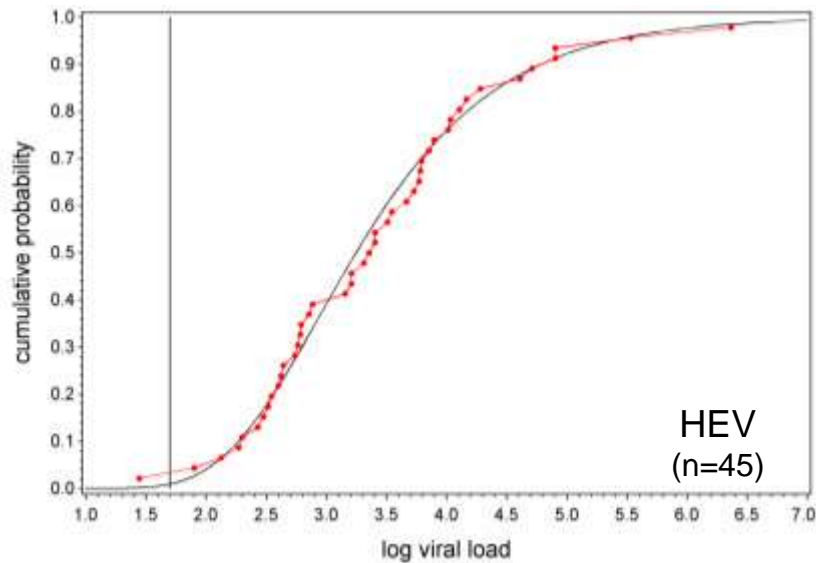
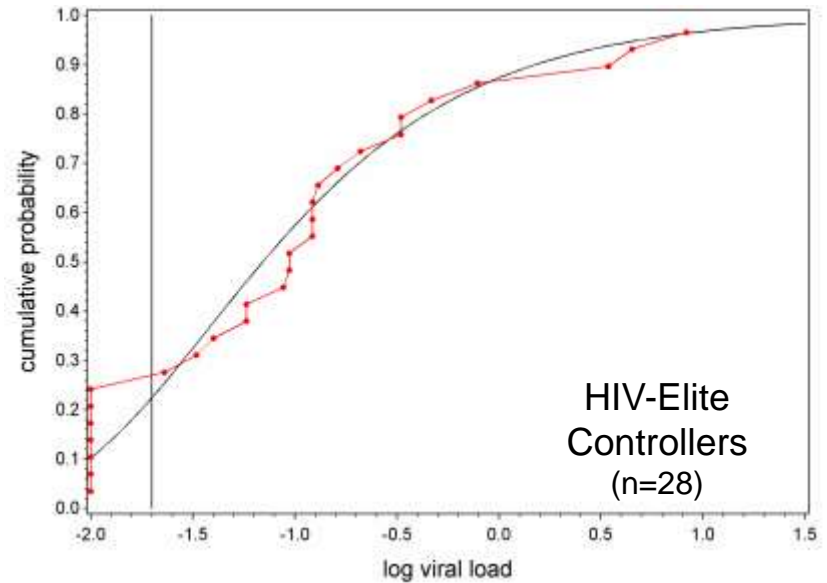
- Examples of risk calculations for infectious OBI donations

Screening method	50% LOD cps/mL	95% LOD cps/mL	PI infectivity reduction	MID ₅₀	Transfusion volume	% residual risk of total number of OBI cases [#]
ID-NAT	4.5	43.1	No PI	316	RBC 20 mL	6.5%
MP6-NAT	4.5	43.1	No PI	316	RBC 20 mL	17%
ID-NAT	2.2	21.4	No PI	316	RBC 20 mL	3.7%
MP6-NAT	2.2	21.4	No PI	316	RBC 20 mL	13%
No NAT	-	-	No PI	316	RBC 20 mL	35%
No NAT	-	-	2 logs	31600	PC 50 mL	3.9%
No NAT	-	-	4 logs	3160000	FFP 200 mL	0.41%

of anti-HBs negative OBI donations

Three other infection categories

- Gumbel distribution appears useful (only detected part)



Data sources

HIV-Elite controllers: Vermeulen M et al Transfusion 2013;53:2384-2398.
HBsAg+/HBV-DNA-: Vermeulen M et al Transfusion 2014;54:2496-2504,
HEV (MPNAT96-192): Hogema BM et al. Transfusion 2016;56:722-728.

Conclusions, Discussion

- Viral load distribution in OBI (and some other categories of viral infections) can be described using a 2-parameter Gumbel distribution
- Combining this distribution with probability calculations on detectability and infectivity allows to estimate risks of transfusion-mediated infections
- Calculations can be used as tool to choose a useful screening program (in combination with options for pathogen inactivation)
- Calculations have been automated in an Excel-tool
 - This can be made available for evaluation of efficacy (or cost effectiveness) of blood safety scenarios

