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Donor Epidemiology

**Cees L. van der Poel, MD, PhD
Secretary Medical Affaires Sanquin
Julius Center, Epidemiology, Univ. Utrecht**

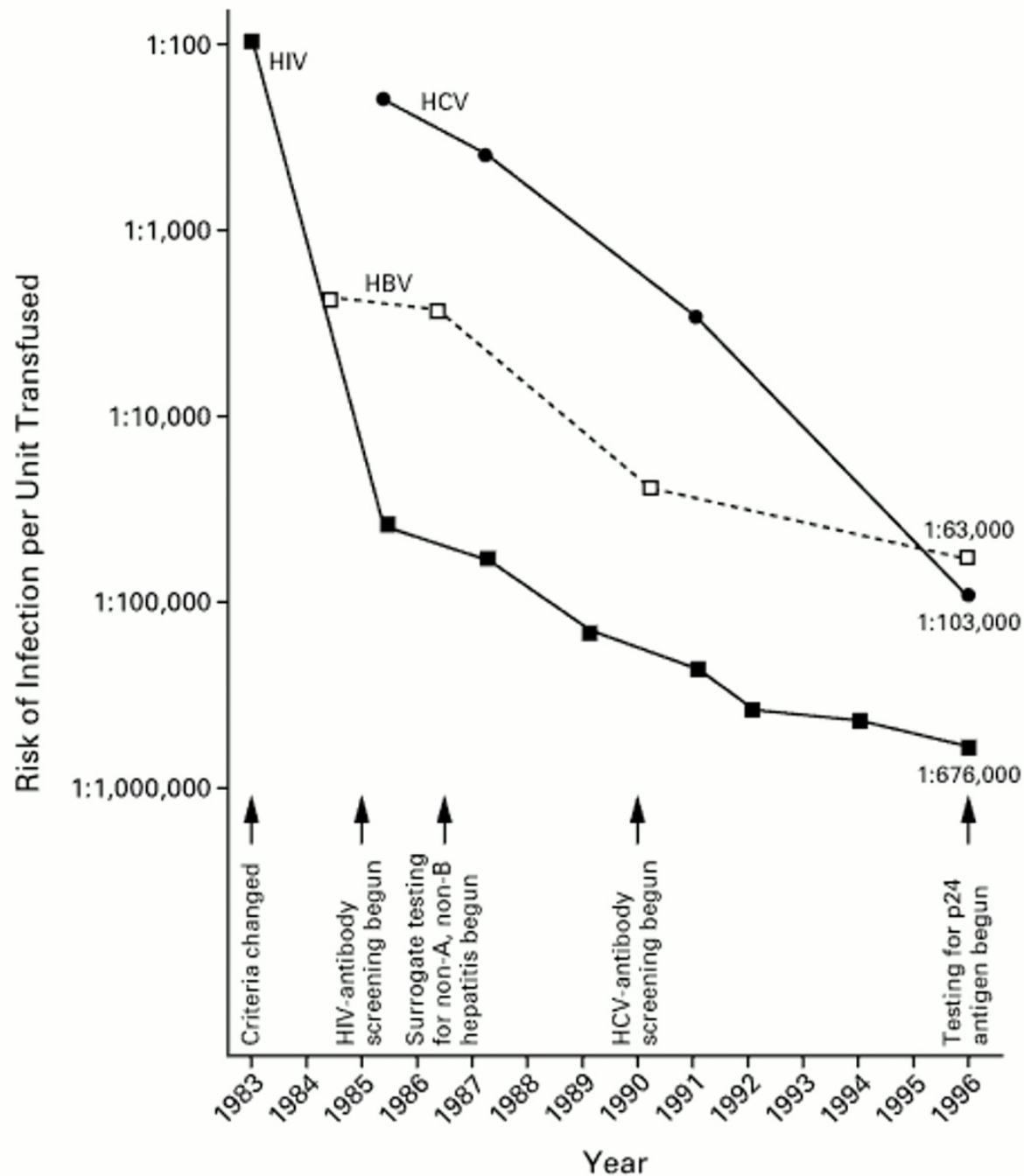
**10th European Haemovigilance Seminar
February 28 – march 1, 2008
Frankfurt am Main**

Epidemiology and donors

Outline of the talk

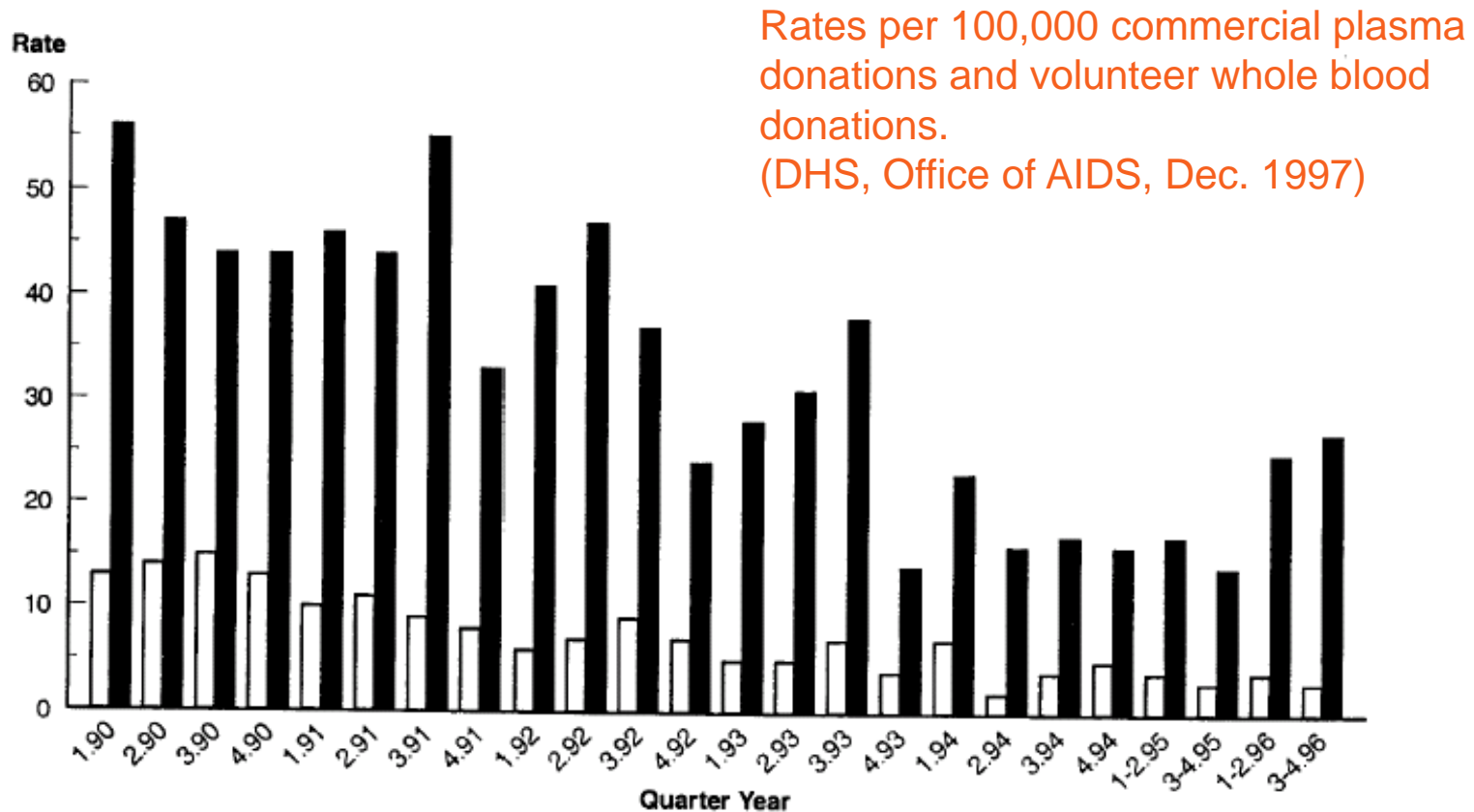
- Epidemiology of VNRD
- Incidence of infections in donors in Europe
- EU Commission Directives and EMEA Guidelines
- Monitoring incidence rates (SPC)
- Surveillance of risk factors in infected donors
- Incidence rates and safety of plasma products
- Incidence rates, look-back procedures and impact on hospitals

Goodnough 1999



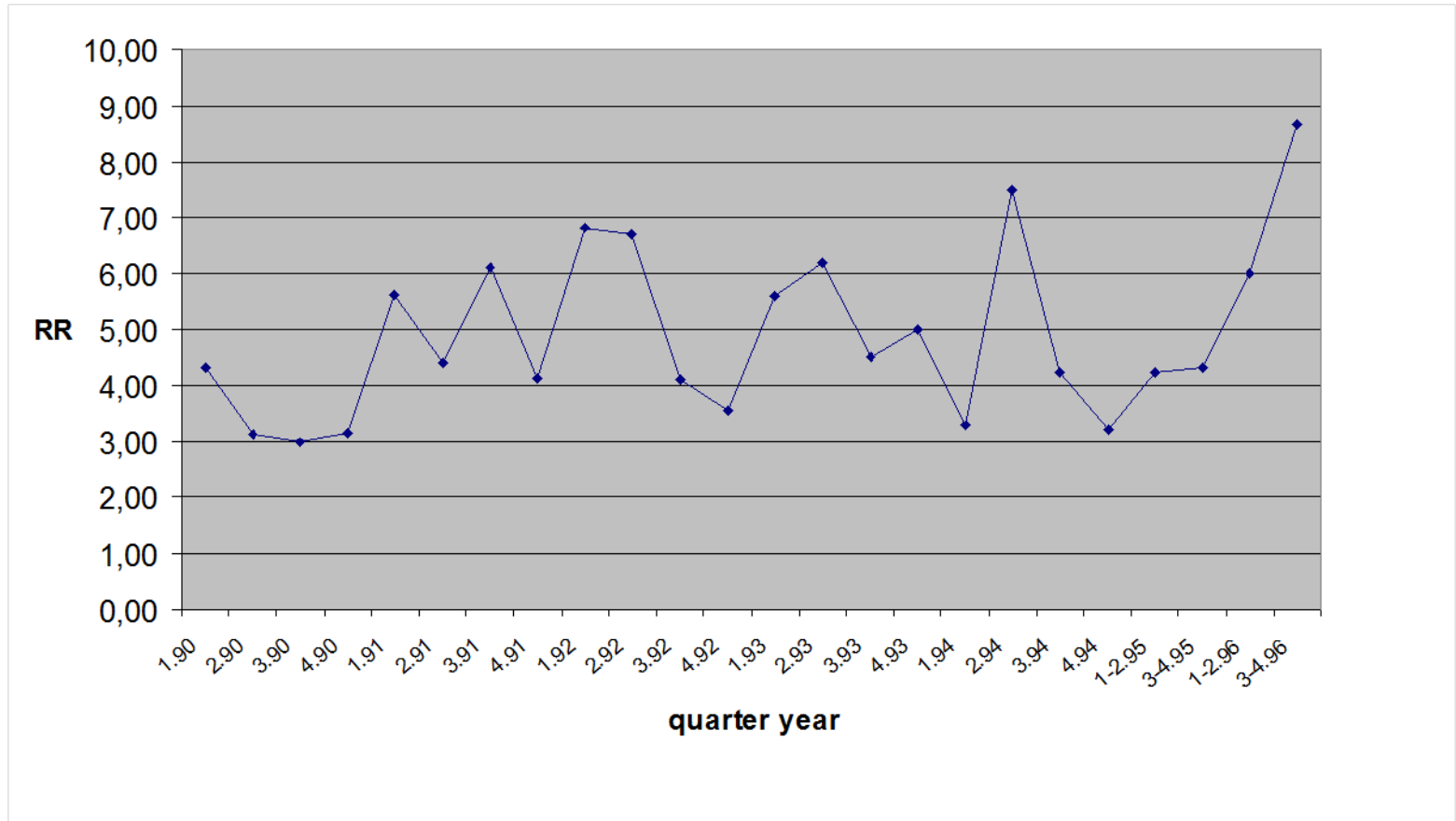
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Reported Confirmed HIV Rates Among Donations in California, 1990 to 1996



Relative Risk or Risk Ratio

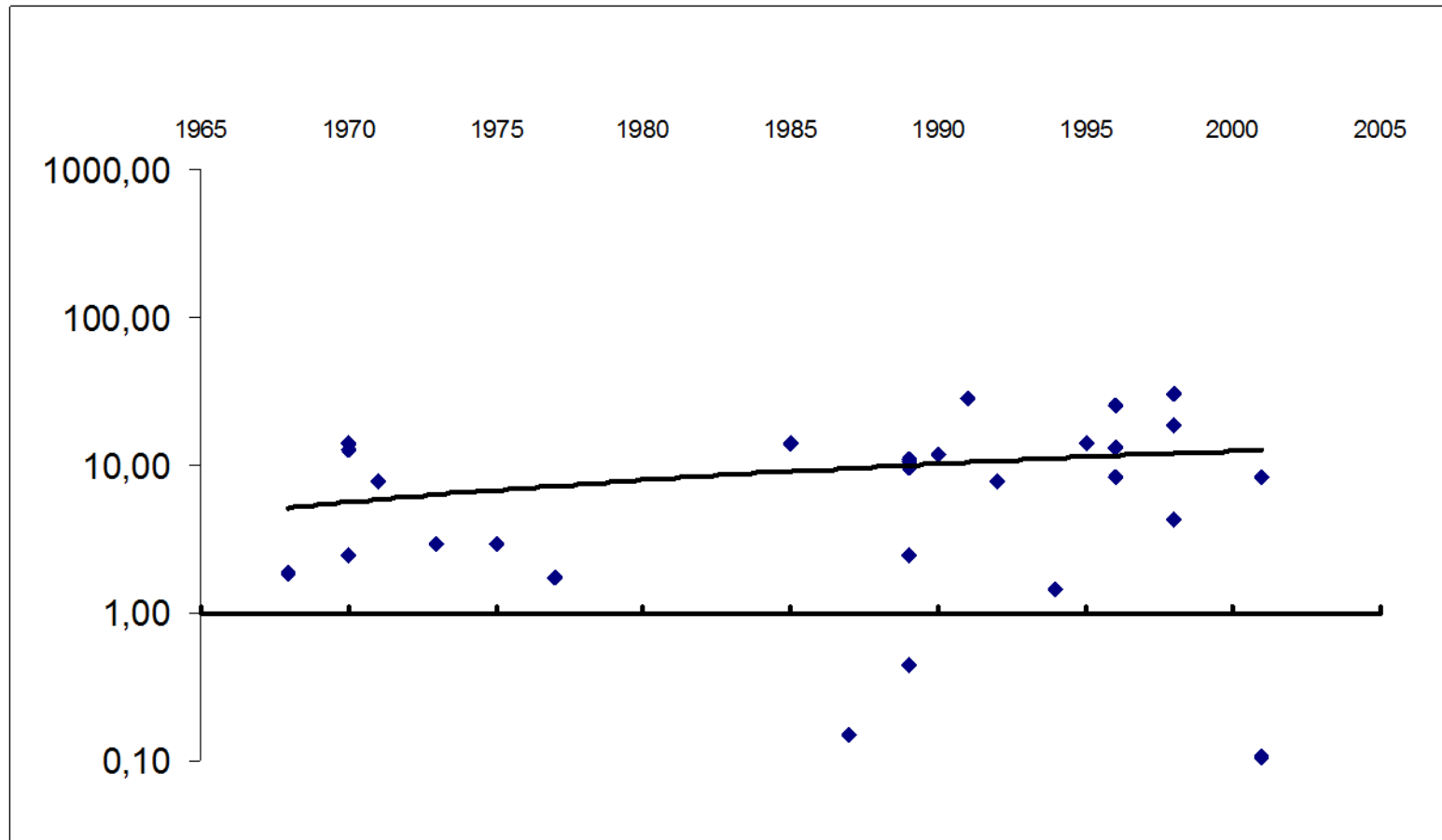
HIV rates in commercial plasma donations / volunteer whole blood donations in California, 1990 - 1996



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(adapted from GAO report 1998)

Trend analysis RR infectious disease markers of paid v.s. unpaid blood donors in studies between 1968 and 2001 ($p = 0.128$, NS)



Lithuania, a real-time experiment

- After the fall of the Iron Curtain, Lithuanian Government decided to pay for each whole blood donation
- Since 2005 the policy is to phase out payment

Profile of blood donors National Blood Center, Lithuania 2005 (53% natl dons

	Total donations		HBV		HCV		HIV	
	first time	repeat	first time	repeat	first time	repeat	first time	repeat
paid	5904	34456	2,388	0,012	2,541	0,131	0,017	0,006
unpaid	7383	965	1,043	0,000	0,610	0,104	0,000	0,000



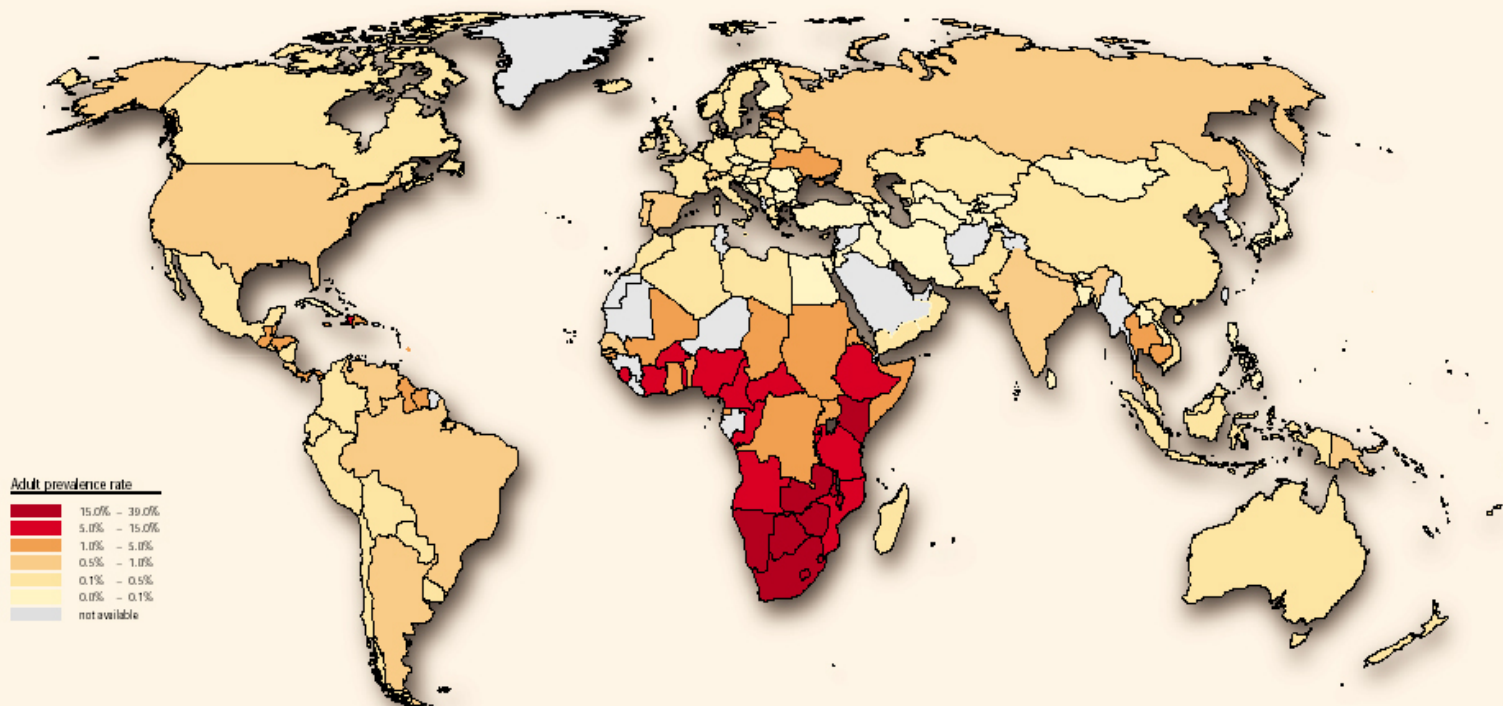
HIV endemic



UNAIDS
The United Nations Programme on HIV/AIDS
UNICEF • UNDP • UNFPA • UNHCR
ILO • UNESCO • WHO • WORLD BANK

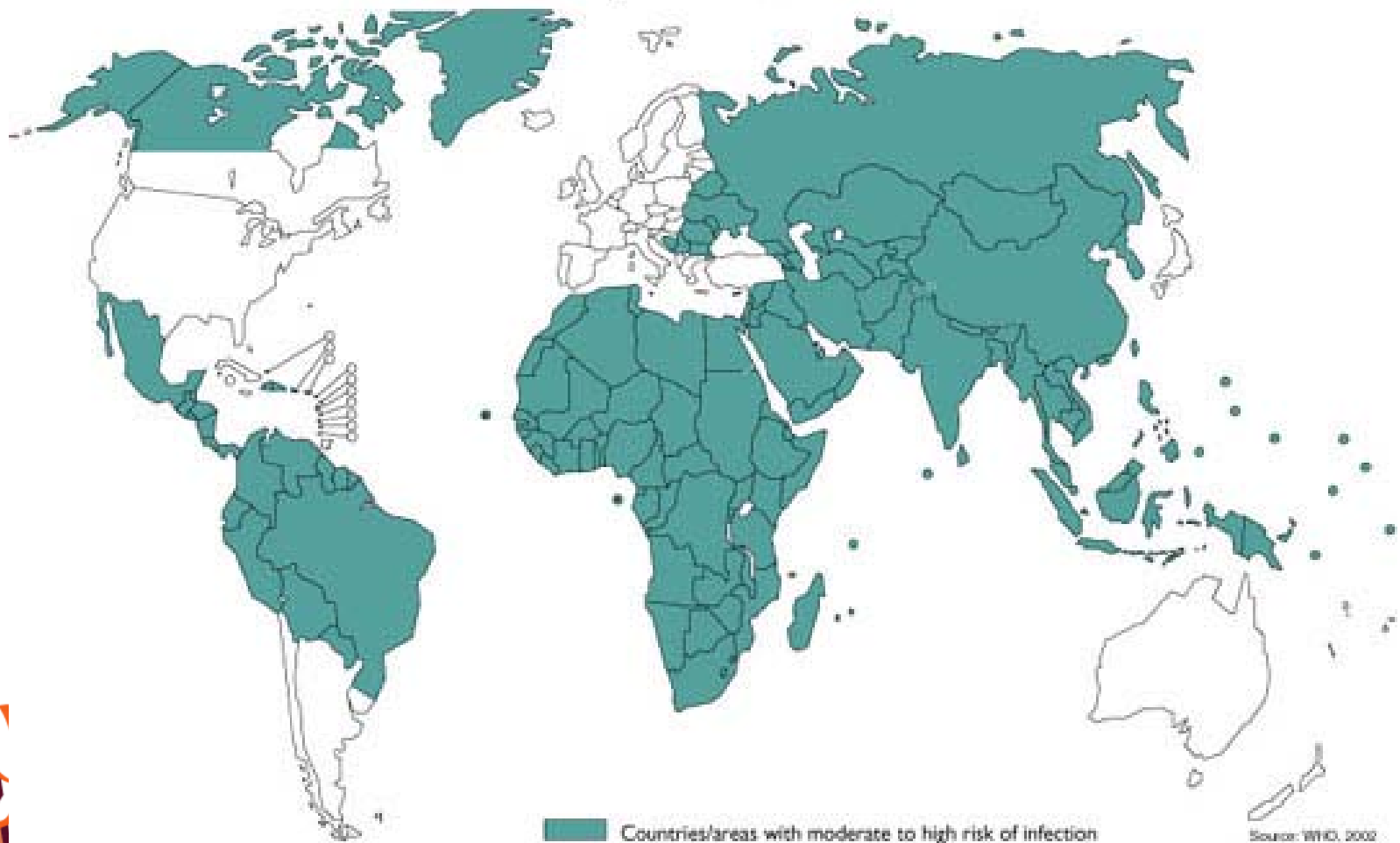
A global view of **HIV** infection

40 million adults living with HIV/AIDS as of end 2001

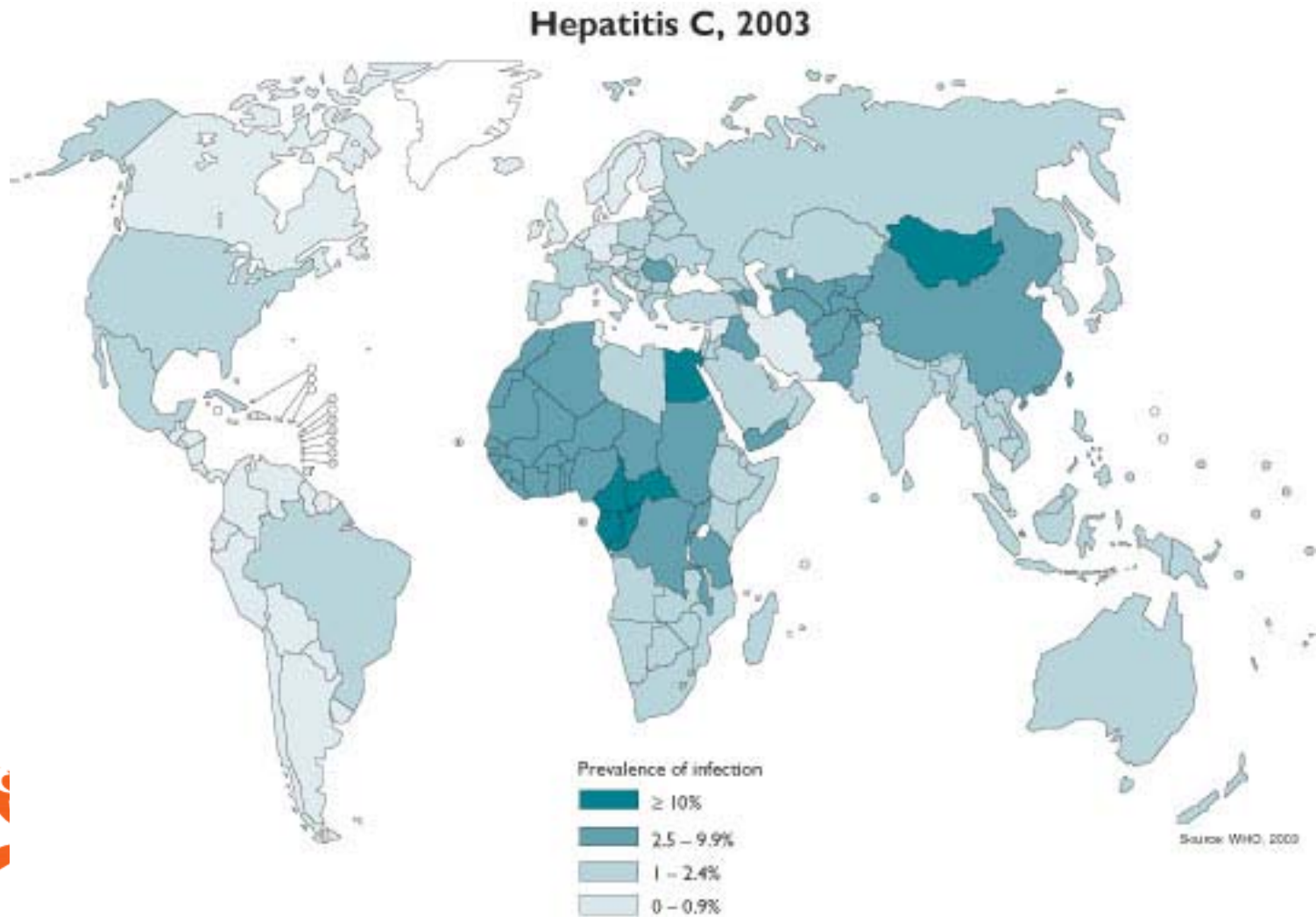


HBV endemic

Hepatitis B, 2003



HCV endemic



**Ranking reported incidence rates (per 100.000 repeat donors) in Europe
(Council of Europe 2005)**

HIV		HBV		HCV	
Denmark	0,00	Denmark	0,00	Finland	0,00
Ireland	0,00	Ireland	0,00	Norway	0,00
Moldovia	0,00	Norway	0,00	Netherlands	0,21
Norway	0,00	Belgium	0,40	Switzerland	0,46
Slovak Republic	0,00	France	0,43	Sweden	0,81
Netherlands	0,43	United Kingdom	0,61	United Kingdom	1,15
Czech Republic	0,64	Hungary	0,67	France	1,21
Finland	0,70	Switzerland	1,85	Denmark	1,31
Belgium	0,79	Netherlands	1,92	Ireland	1,41
Switzerland	0,92	Sweden	2,03	Belgium	1,59
Sweden	1,22	Slovenia	2,09	Germany	3,55
United Kingdom	1,30	Germany	2,24	Spain	4,10
France	1,99	Slovak Republic	5,49	Poland	5,66
Slovenia	2,09	Poland	6,00	Croatia	6,51
Germany	2,62	Spain	6,66	Slovak Republic	8,79
Poland	3,00	Czech Republic	9,58	Hungary	14,33
Romania	3,75	Montenegro	11,27	Czech Republic	17,87
Croatia	3,90	Croatia	15,61	Montenegro	22,53
Spain	5,38	Greece	93,49	Greece	31,38
Greece	6,08	Romania	492,51	Bulgaria	90,94
Latvia	34,19	Bulgaria	705,16	Romania	155,63





European Medicines Agency
Evaluation of Medicines for Human Use

London, 20 January 2005
EMA/CPMP/BWP/125/04

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON EPIDEMIOLOGICAL DATA ON BLOOD
TRANSMISSIBLE INFECTIONS**

For inclusion in the Guideline on the Scientific data requirements for a Plasma Master File
(EMA/CPMP/BWP/3794/03)



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Residual risk calculations Sanquin 2006

EMEA / PMF

Table 2. Residual risk in 2006

A	B	C	D= C/365	E= B x D
Type of virus	incidence among repeat donors (per million donor yrs)	Detection window (days)	Window Risk	Probability of an infected donation in The Netherlands (per million donations)
HIV ½	9,8	11	0,03	0,3
HBV *	36,9	59	0,16	5,9
HCV	12,3	10	0,03	0,4
HTLV III	0,0	51	0,14	0,0

*) Incidence HBV adjusted for non-detection by factor 3.0 (Korelitz et al)



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Residual risk calculations Sanquin 2003-5 EMEA / PMF

Table 1. Residual risk in 2003-2005

A	B	C	D= C/365	E= B x D
Type of virus	mean incidence among repeat donors (per million donor yrs)	Detection window (days)	Window Risk	Probability of an infected donation in The Netherlands (per million donations)
HIV 1/2	5,4	11	0,03	0,2
HBV *	55,1	59	0,16	8,8
HCV	3,1	10	0,03	0,1
HTLV I/II	0,8	51	0,14	0,1

*) Incidence HBV adjusted for non-detection by factor 3.0 (Korelitz et al)



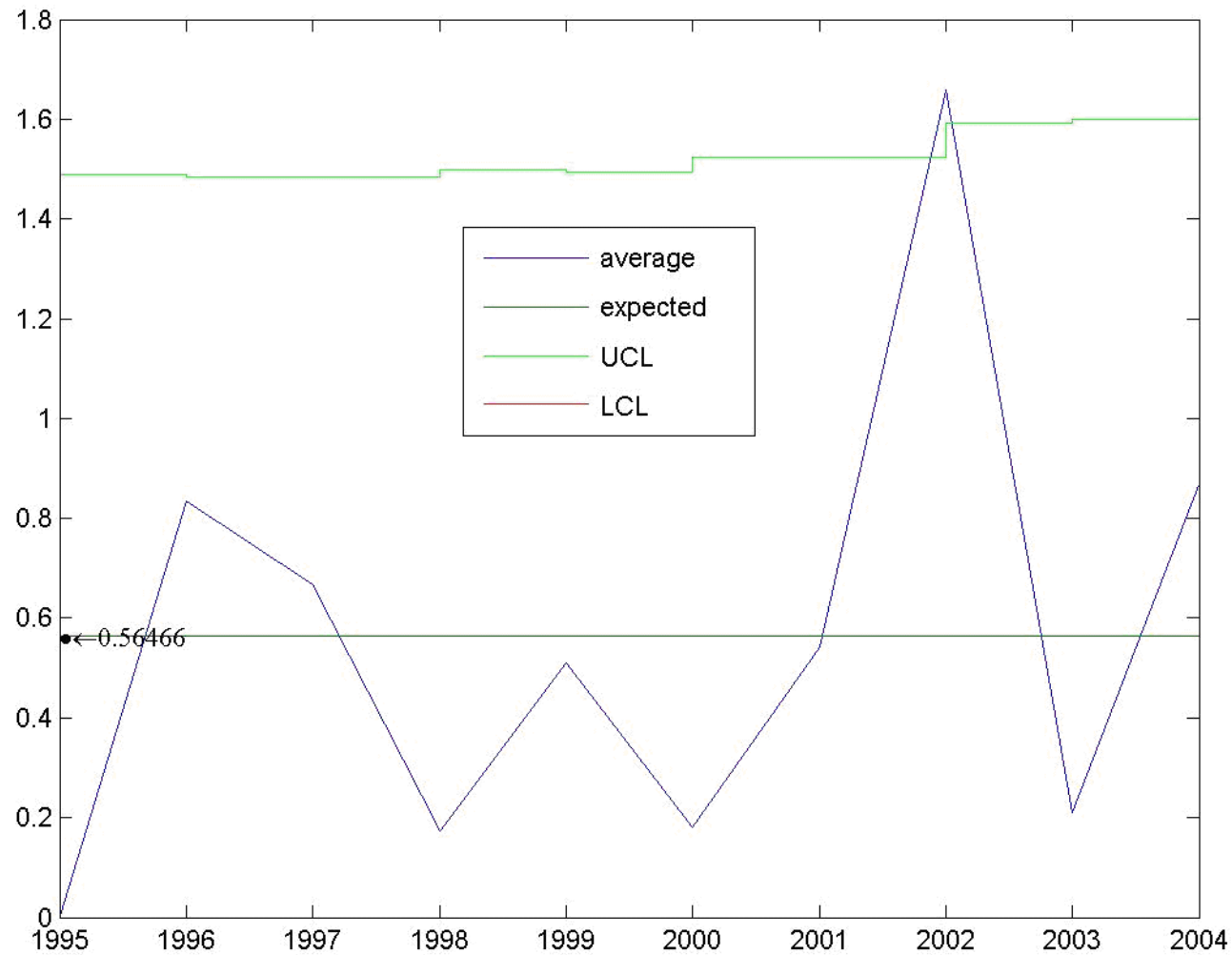
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Incidence monitoring of viral infections in donation centers in The Netherlands

M.P. Janssen
C.L. van der Poel
Julius Center for Health Sciences and Primary Care,
University Medical Center Utrecht
The Netherlands

M.P. Kaleta
E.A. Cator
Department of Probability and Statistics / Department of Risk Analysis
Faculty of Electrical Engineering, Mathematics and Computer Science
Delft Technical University
The Netherlands

U chart for HIV (national data)



Poisson distributions on HIV incidence for collection centres 1995-2004 Netherlands

- Significant peak of HIV incidence in 2002 on a national level (>3 sigma)
- No significant peaks of HIV incidences for individual collection centres (in 2002 or other years)
- Root-cause not local, but national
 - HIV incidence mainly MSM (van der Bij et al)
 - Lobby in national press for de-selection on MSM started end of 2001

BLOOD DONORS AND BLOOD COLLECTION

Surveillance of risk profiles among new and repeat blood donors with transfusion-transmissible infections from 1995 through 2003 in the Netherlands

Akke K. Van der Bij, Roel A. Coutinho, and Cees L. Van der Poel



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TRANSFUSION 2006;46:1729-1736

Methods Questionnaire 1

Standardised questionnaire completed by blood bank physician at post-test counseling of confirmed positive donors 1995-2003:

- General information
- Endemic country
- Health Care Work
- Bloodtransfusion
- IVDU
- Tatoo /piercing

Questionnaire (cont)

- Ritual operation or medical treatment under poor hygiene
- Endoscopy
- Living abroad
- Sexual behaviours
- Prostitution
- History of STD
- Family history
- Most likely subjective risk factor according to
 - physician
 - donor

Risk profiles repeat donors (N=168)

Sexual behaviour	HBV N (%)	HCV N (%)	HIV1/2 N (%)	HTLV1/2 N (%)	Syphilis N (%)	P
MSM	8 (14%)	2 (11%)	8 (31%)	0 (0%)	2 (4%)	0.010
SC with IVDU	1 (2%)	4 (27%)	1 (4%)	1 (14%)	1 (2%)	0.002
Prostitution	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	0.013
History STD	5 (9%)	2 (11%)	6 (23%)	0 (0%)	16 (27%)	0.062

Concordance most likely risk factor

Donor *versus* physician:

- 72%
- kappa: 0.46 (modest concordance)

Physician *versus* multivariate analysis:

- 50%
- kappa: 0.15 (poor concordance)

Conclusions 1

Effectivity donor selection:

- Lower prevalences in new donors vs general population
 - HCV 2/1000 *versus* 0.6/1000
 - HBV 1/1000 *versus* 0.4/1000
- Risk factors
 - Most (66%) confirmed positive donors have identifiable risk factors

Conclusions 2

Identifiable risk factors

- HBV/HTLV: MSM, endemic countries
- HCV: IVDU, sex with IVDU, blood transfusion
- HIV: mainly repeat donors (!), MSM
- Syphilis: history of syphilis / STD

BLOOD COMPONENTS

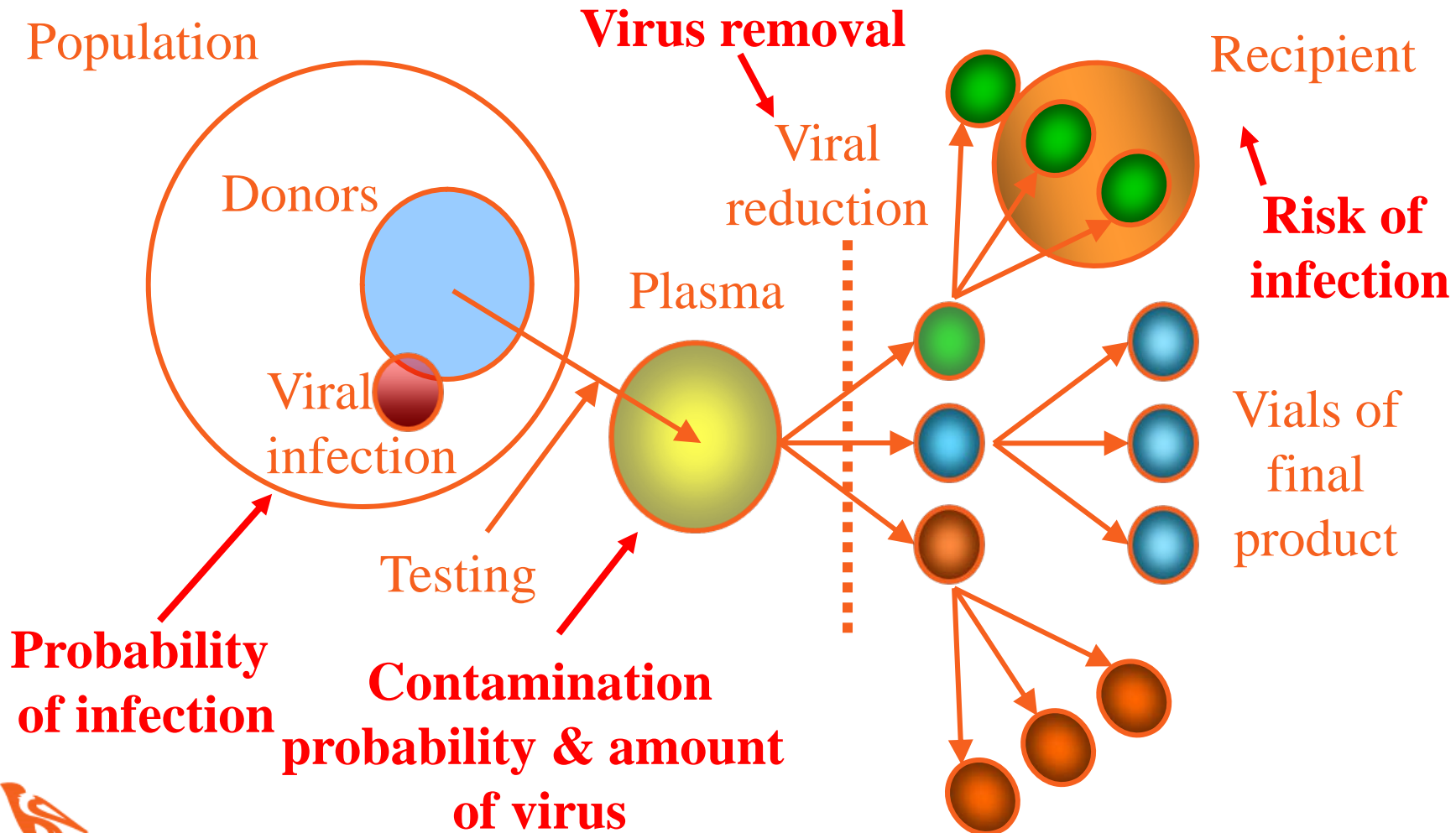
A probabilistic model for analyzing viral risks of plasma-derived medicinal products

Mart P. Janssen, Jan Over, Theo Cuijpers, Cess L. van der Poel, and Ben A. van Hout



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Process highly schematic



Assumptions concerning viral loads

Exponential growth models for description of viral ramp-up during window periods:

$$C = C_0 2^{t/\lambda}$$

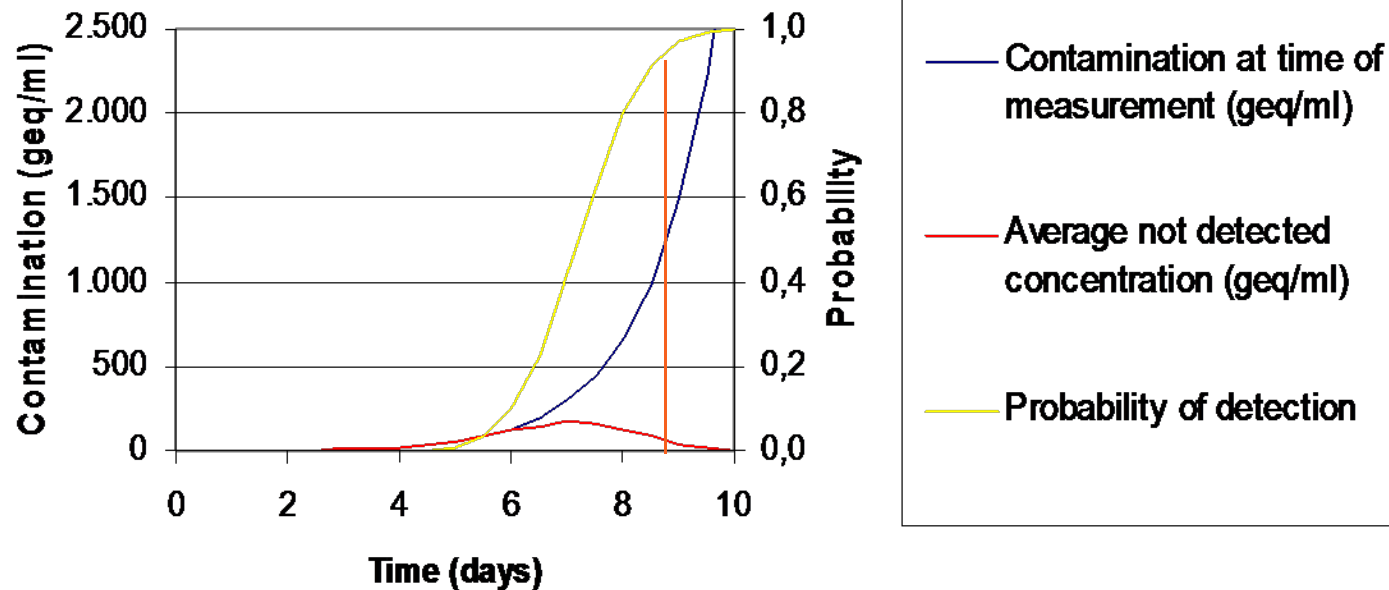
Where:

t = time since infection

λ = viral doubling time

C_0 = initial contamination level

Viral load during seroconversion HIV

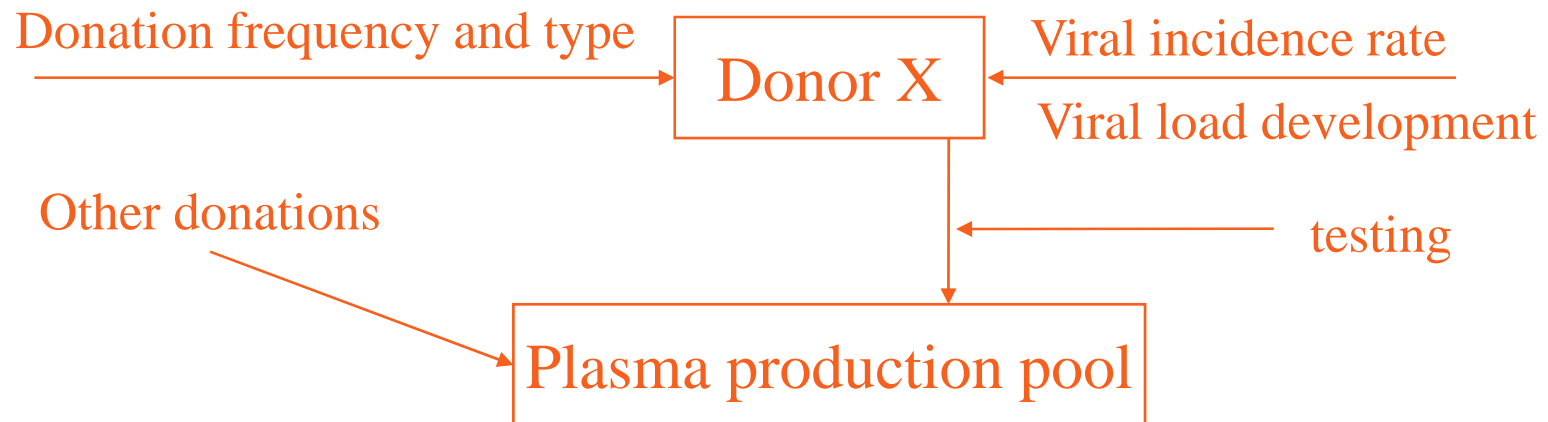


* Viral doubling time: 0,85 days

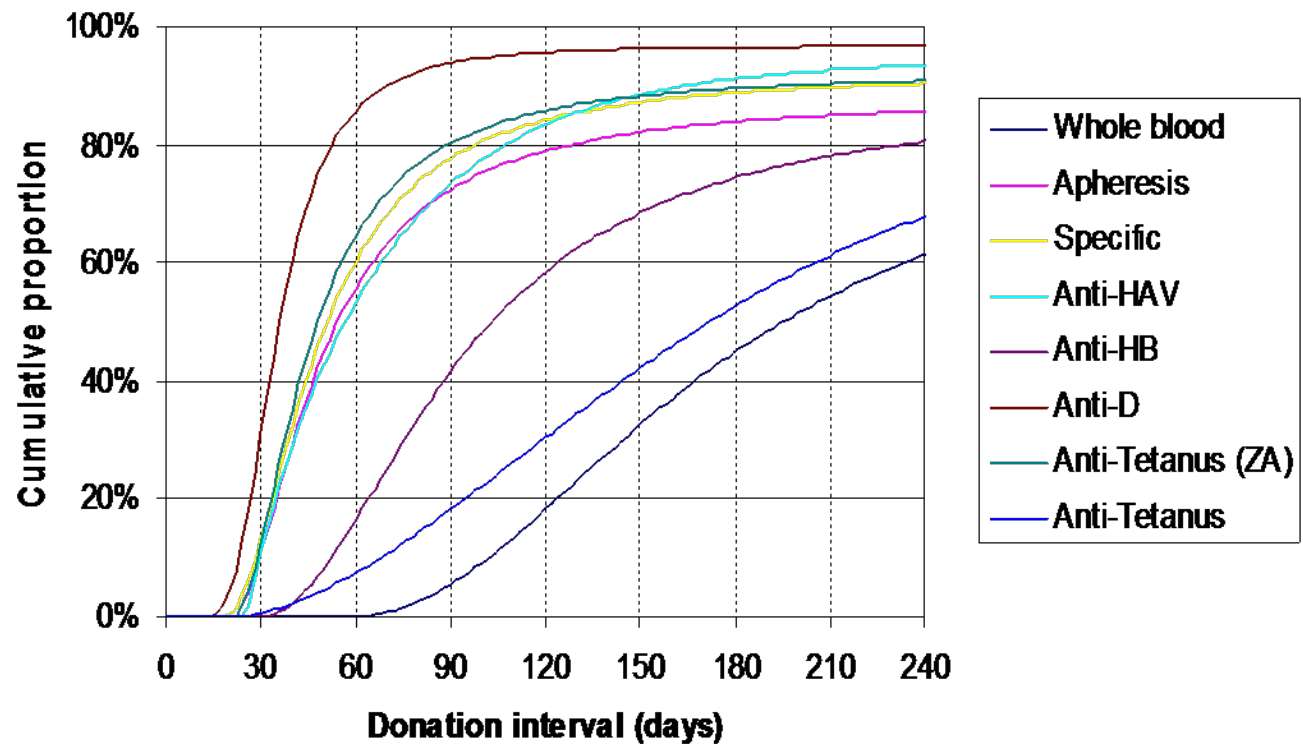
* NAT pool size: 48 donations

* Test characteristics: X95 = 25 gEq/mL
X99,9 = 75 gEq/mL

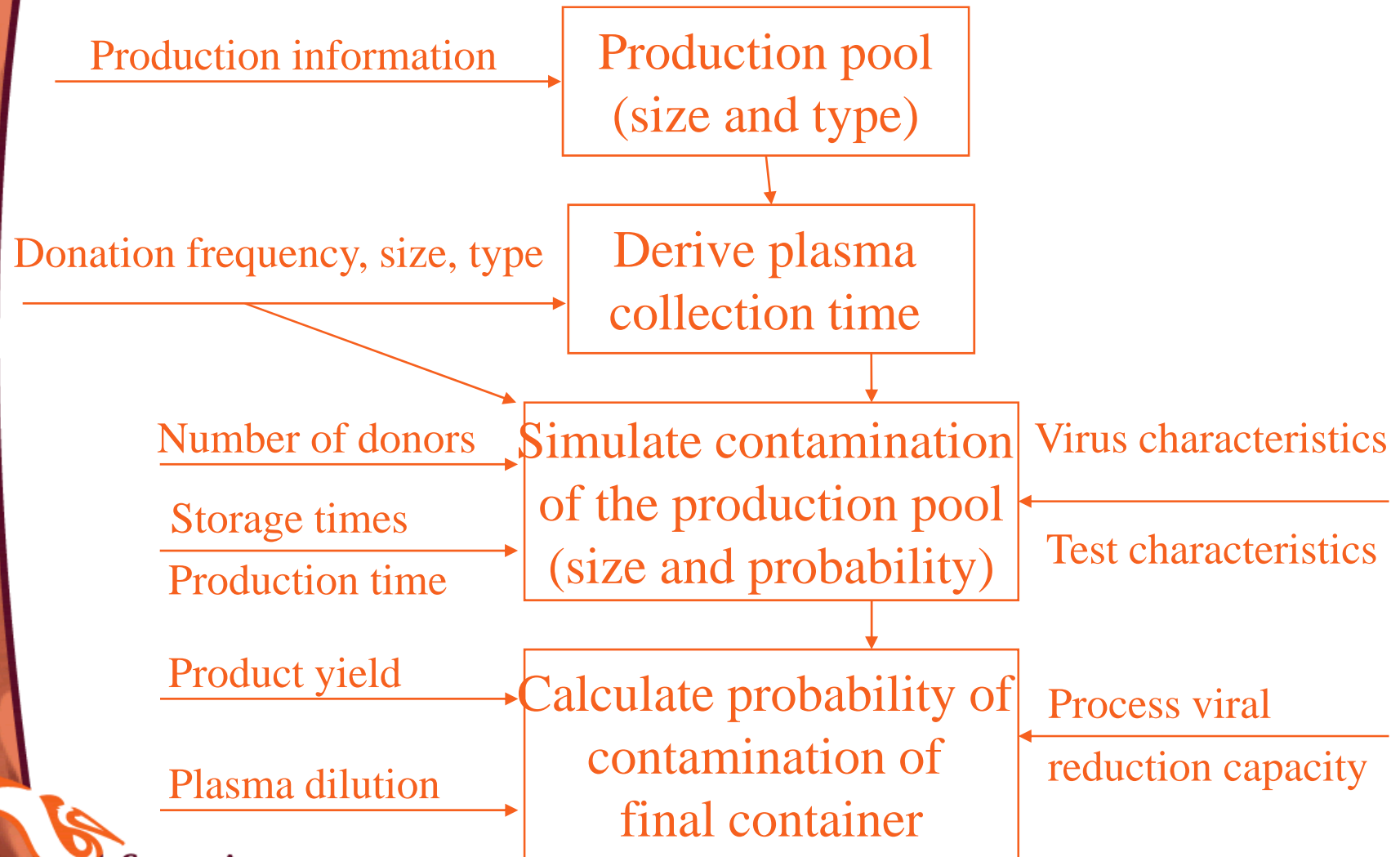
Contamination process



Donation interval per type of donation



Simulation Processing steps



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Final container contamination probability

Probability of a particle in a final container given a contamination level of the plasma pool equals:

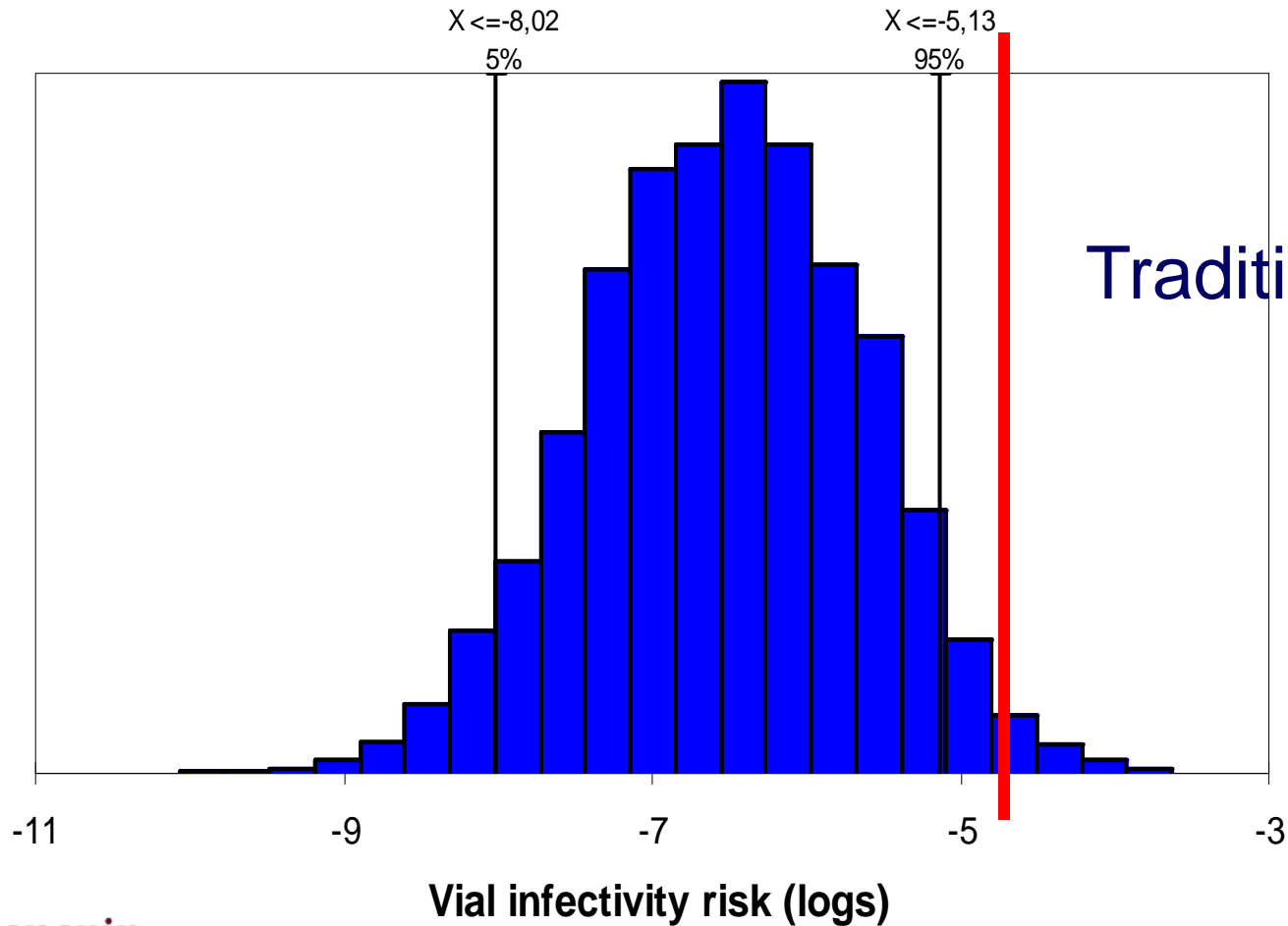
$$P(\text{contamination}) = \frac{np_c x}{W \psi \alpha}$$

Where:

n	=	number of viral particles in production pool
P_c	=	production pool contamination probability
x	=	production pool fraction used for end product preparation
W	=	total pool weight [kg]
ψ	=	production yield [final containers/kg plasma]
α	=	process viral reduction factor

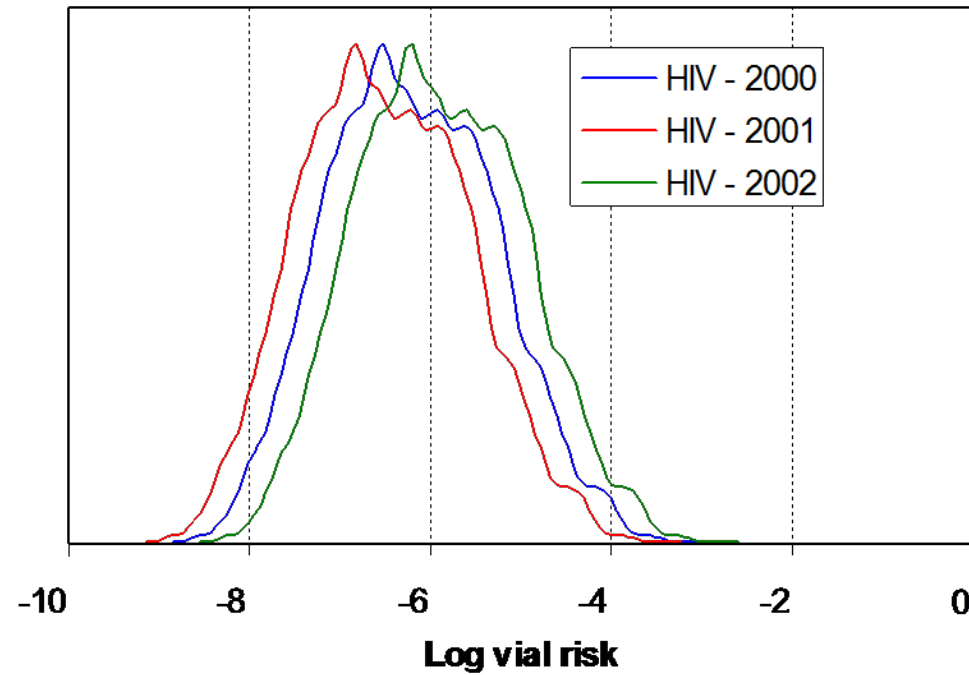
← **Large uncertainties**

Hypothetical end-product infectivity risk



Traditional mode

Differences in annual HIV incidence rates in NL



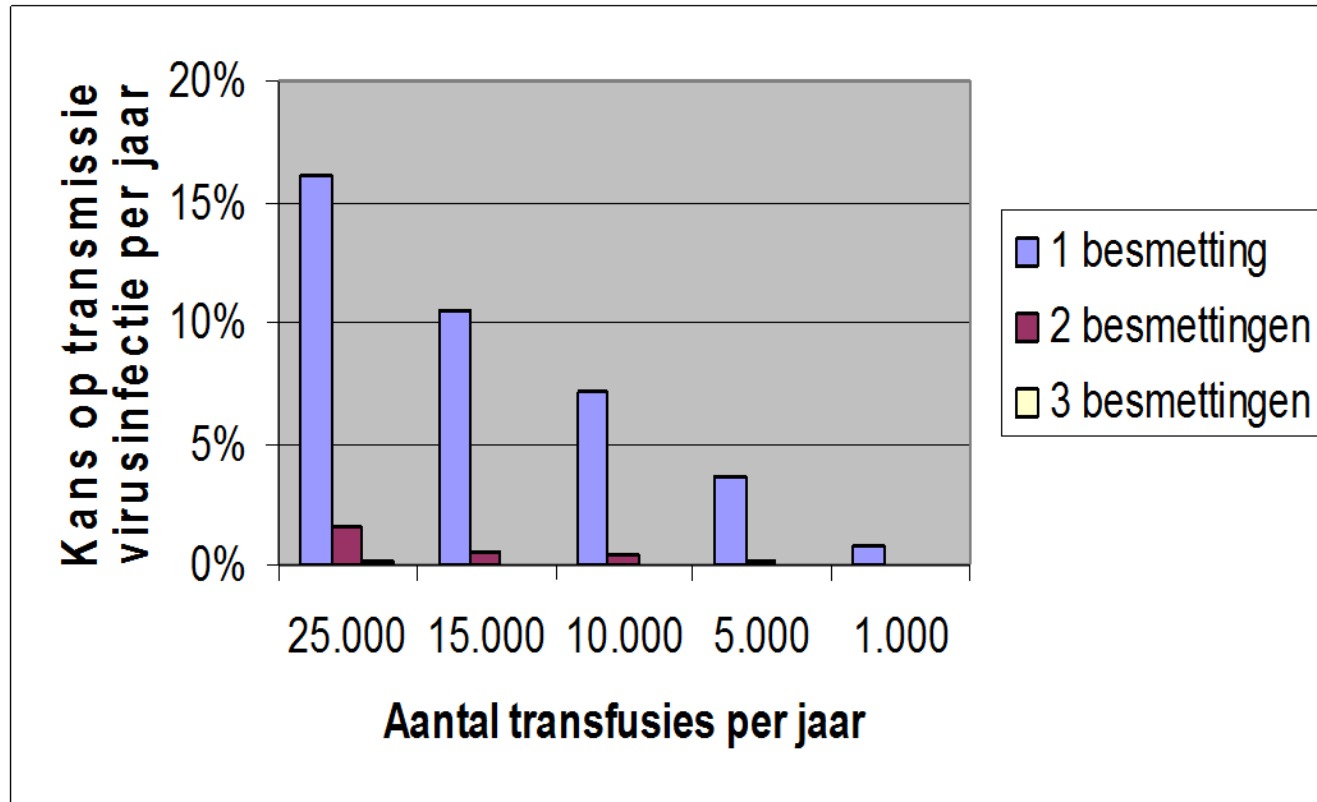
Residual risk end products mainly determined by:

- Viral incidence rate
- Screening test sensitivity
- Process viral reduction capacity
- Product yield

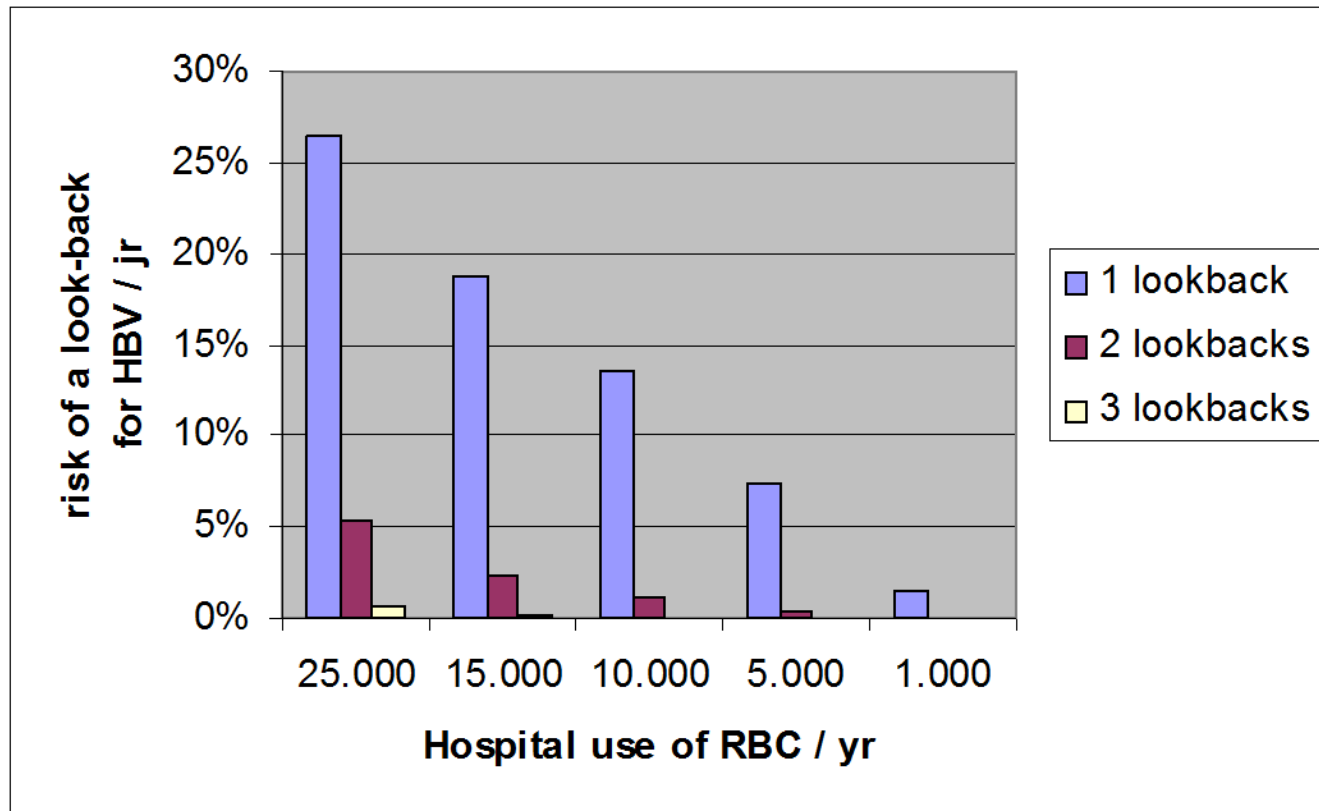
Very limited impact on residual risk :

- Type of donation
 - whole blood recovered plasma vs plasmapheresis plasma
- Production pool size (except B19)
- A modest impact has the length of the on-hold period
 - for HIV and HCV

Annual probability of a HBV transmission by hospital size / RBC use



Annual probability of a HBV look-back report by hospital size / RBC use



Patiënte Bernhoven niet besmet met hiv

SCHAIJK - Een 80-jarige vrouw uit Schaijk die twee weken geleden te horen kreeg dat zij mogelijk hiv-bloed toegediend heeft gekregen bij een transfusie in ziekenhuis Bernhoven in Oss, blijkt niet besmet. Een familielid heeft dat vrijdag desgevraagd gezegd.

Vorige week werd via het lokale weekblad Arena bekend dat het ziekenhuis door bloedbank Sanquin in Amsterdam op de hoogte was gebracht van de mogelijke besmetting door donorbloed dat positief was getest op hiv. De patiënte werd deze week getest en haar uitslag bleek negatief.

Het ziekenhuis doet om privacyredenen geen mededelingen over de uitslag van de hiv-test.

Mogelijk 500 patienten besmet met hiv bij Bernhoven

Vijfhonderd patiënten van ziekenhuis Bernhoven in Oss en Veghel zijn mogelijk besmet met het hiv-virus, hepatitis B of hepatitis C. Door een technische fout in vier nieuwe scopendesinfectoren (wasmachines), zijn slangen die gebruikt worden voor kijkonderzoek aan maag, longen of darmen mogelijk niet goed gereinigd.

Het ziekenhuis benadrukt dat de fout in de machines zit en dat het ziekenhuis geen blaam treft. Bernhoven heeft leverancier Sanamij uit Rotterdam aansprakelijk gesteld. De kans op besmetting is volgens de voorzitter van de raad van bestuur van Bernhoven René Peters 'uiterst gering'. "Maar we nemen het zekere voor het onzekere en willen alles uitsluiten." Daarom krijgen de vijfhonderd patiënten donderdag een brief waarin ze opgeroepen worden binnen een week bloed af te staan.

Daarvoor is het ziekenhuis de komende dagen buiten kantoortijden geopend. Ook wordt extra personeel ingezet.

Het ziekenhuis heeft alle huisartsen in de regio en de Inspectie voor de Gezondheidszorg op de hoogte gebracht. Eind september wordt bekend of er daadwerkelijk mensen besmet zijn.

Kijkonderzoek

Volgens Peters gaat het om driehonderd patiënten die tussen 9 juli en afgelopen maandag in het ziekenhuis in Veghel een kijkonderzoek hebben ondergaan. In Oss gaat het om tweehonderd patiënten die tussen 13 augustus en afgelopen dinsdag een dergelijk onderzoek hebben gehad. Het ziekenhuis nam in die tijd in Veghel en Oss per locatie twee nieuwe wasmachines in gebruik.

Final notes

- Donor epidemiology is a principal tool to assess blood safety
- Donor epidemiology in Europe differs, NW-SE gradient
- EU Commission and EMEA aware impact of incidence,
 - Require monitoring
 - Different test regimes may be needed in different regions?
- Monitoring (changes in) incidence in donors / donor centers
 - quality aspect
 - statistical process control
- Surveillance of risk factors in infected donors feasible and important for re-assessment of donor selection criteria
- Safety level of plasma products is influenced by donor incidence notwithstanding effective inactivation steps
- Probabilistic modelling important to define the upper limit of uncertainty
- Look-back procedures related to incidence require risk communication