WHO Guideline on Estimation of Residual Risk of HIV, HBV or HCV Infections via Cellular Blood Components and Plasma

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GL project leader

GL draft version (May 2016)

World Health Organization

WHO Achilles Project (WHA 63.12)

Recovered plasma from whole blood donations

- Disposed as biological waste in many low and middle income countries
- **> 9.3 million liters / year**
- Plasma derived medicinal products (PDMPs) are imported at high cost
- Could be used as source for manufacture of PDMPs

WHO Achilles Project

- Plasma quality acceptable for fractionation
  - Good Manufacturing Practice (GMP)
  - Strengthening of Regulatory Oversight
  - Residual virus input in pools versus virus inactivation capacity

- Virus content in plasma pools dependent on
  - Screening tests
  - Virus epidemiology of donor populations
  - Biological features of viruses

WHO Achilles Project

- Measures for improvement of plasma quality
  (e.g. GMP introduction, screening for infectious markers)
  - Affect all blood products
  - Impact virus safety of cellular blood components

WHO Achilles Project

"WHO Guideline on Residual Risk Estimation"

- Requested by blood transfusion services in LMIC
- Endorsed by WHO ECBS in Oct 2012

Goals

- Impact of screening algorithms on blood safety
- Cost benefit of different testing algorithms

- Risk estimations (also on less detailed data base)
- Comparability between different blood establishments

- Has to be kept relatively simple, but *state of the art*

Residual Risk of HIV, HBV, HCV

Sources for residual risk for viruses in blood

- Assay failures
  - Malfunction instrument, software
  - Design non-detection of viral variants

- Diagnostic window period
  (= phase elapsing between the time point of infection and first detectability of the viral marker by the screening assay)
  - All screening technologies, each assay
  - Differential size
  - Different viraemic levels

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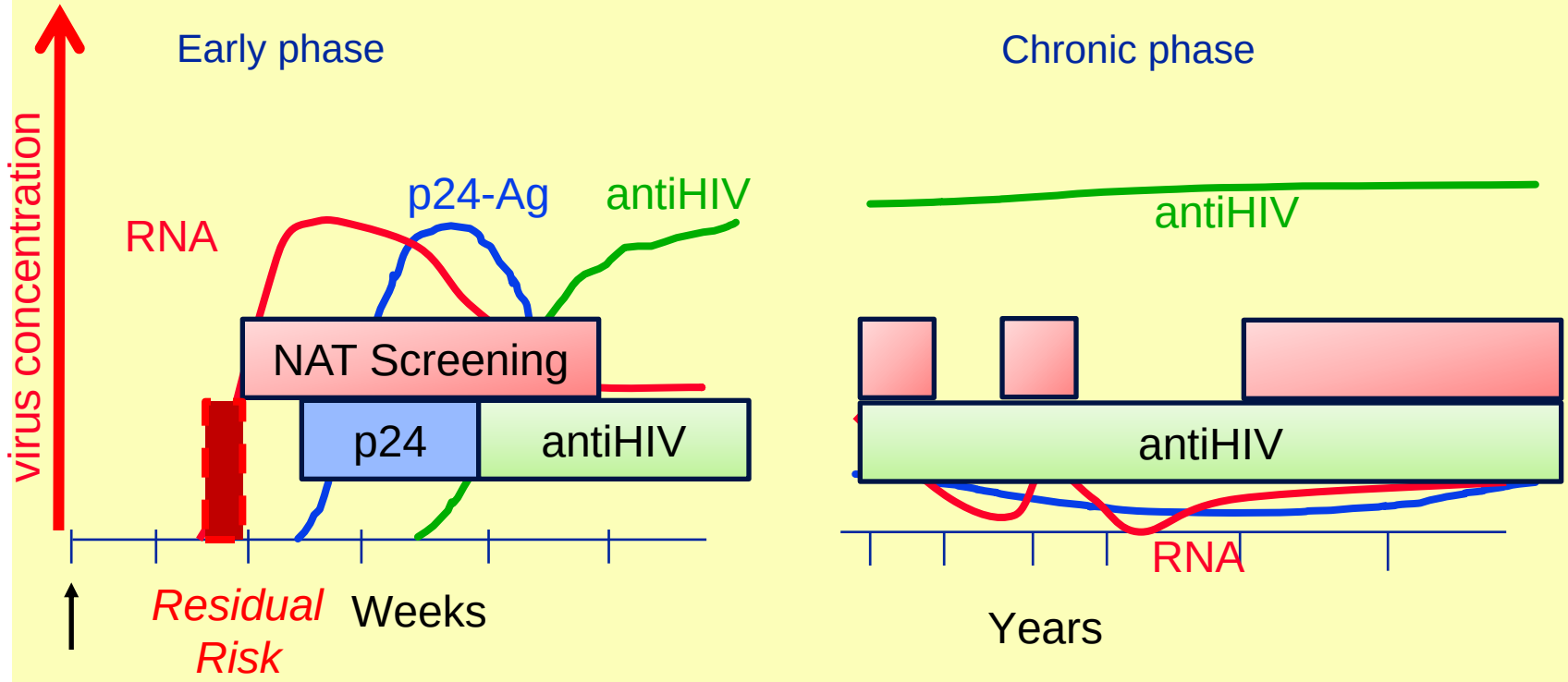
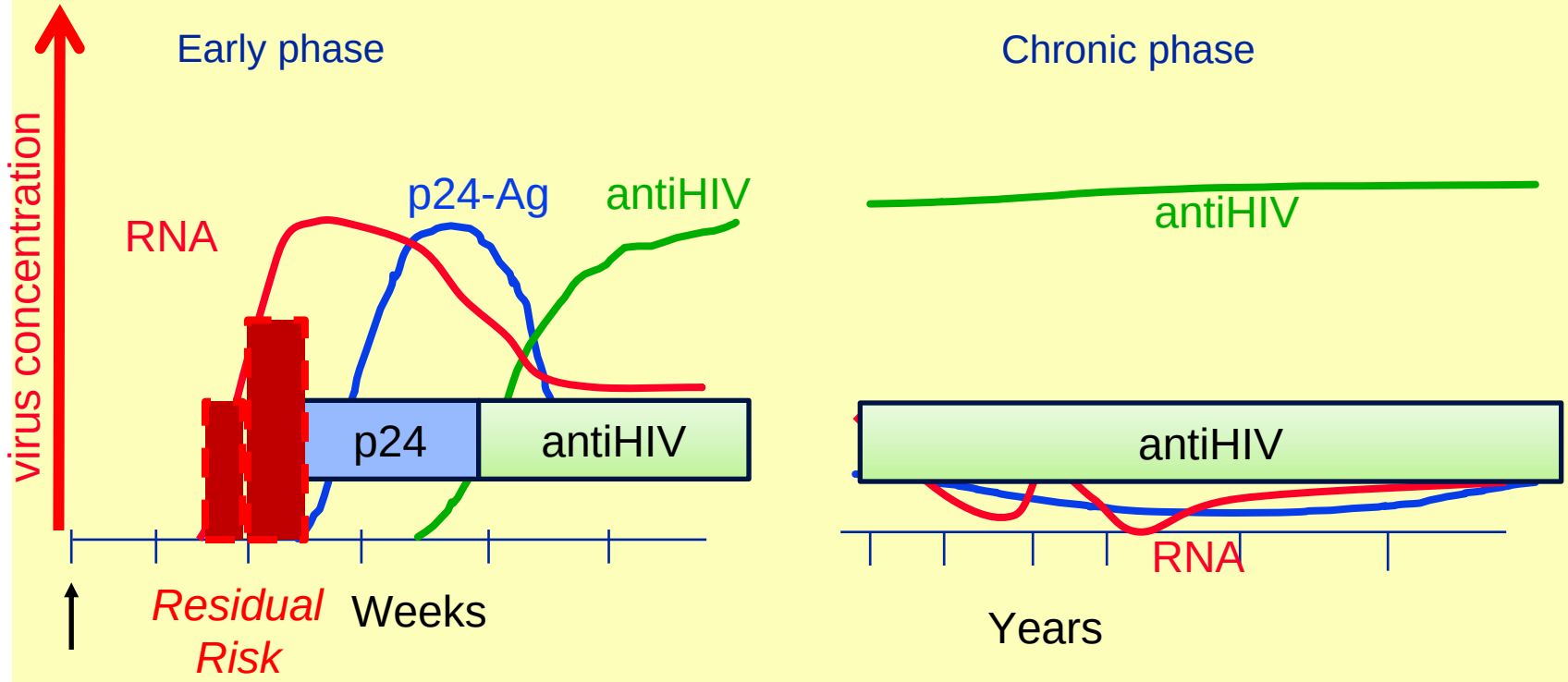
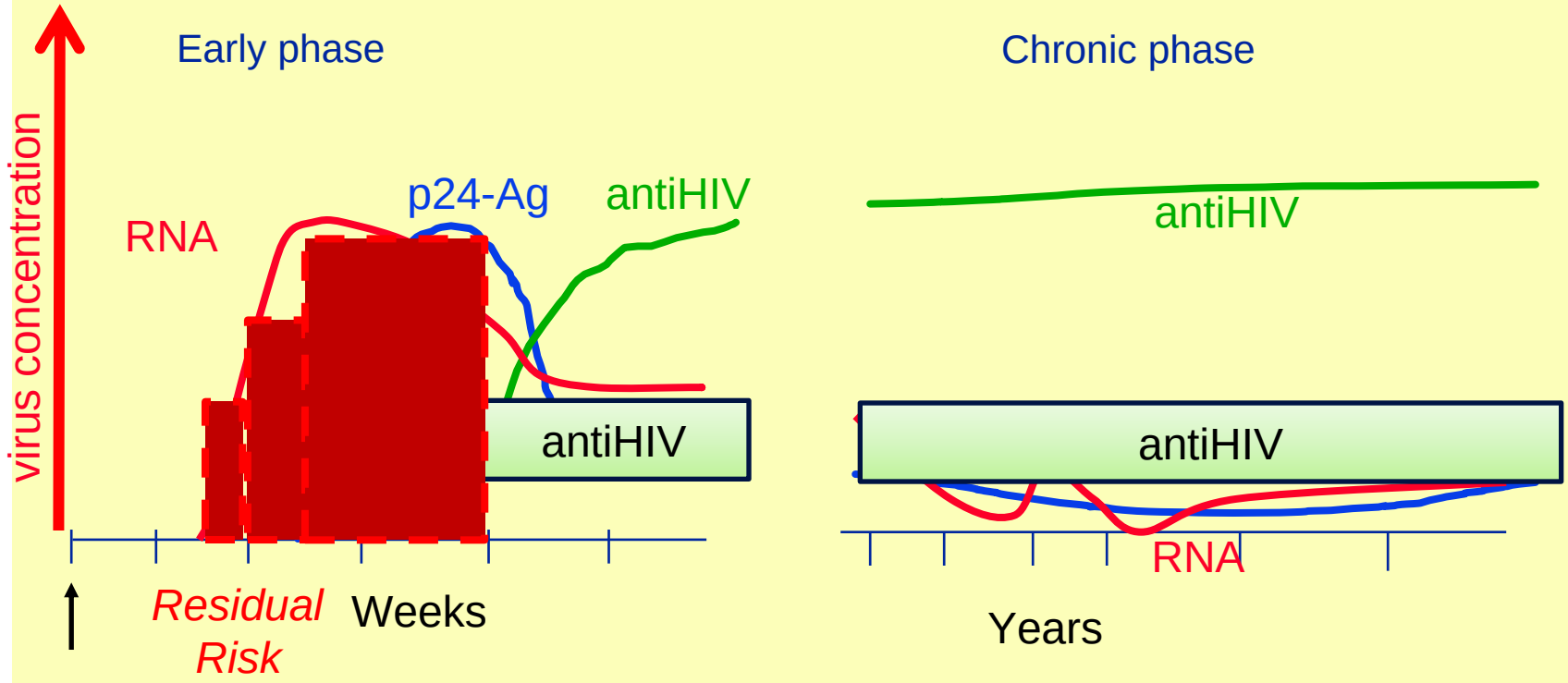
Diagnostic Window of HIV Infection



Diagnostic Window of HIV Infection



Diagnostic Window of HIV Infection



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Definitions chosen in the RR GL

- **Assay categories**

  - NATs (ID, MP16)
  - Antigen assays (HIV, HBV, HCV)
  - Combo assays (HIV, HCV)
  - Antibody assays (HIV, HCV)
  - Rapid diagnostic tests (HIV, HBV, HCV)

Limitation:

Features of individual assays within category vary

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Definitions chosen in the RR GL

- **Length of viraemic phase of diagnostic window for assay categories**
  - Viraemic phase: ≥ 1 virus particle / 20 ml plasma
  - Mean for respective assay category (CE, FDA, WHO PQ IVD, …)

→**Table 1 of the GL**

Limitation

Worst case of potential infectivity of blood components

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Lengths of viraemic phase of diagnostic windows with reference to screening test categories (Table 1)

	Length of the viraemic phase of the diagnostic window period (vDWP) for test categories (in days)							
	NAT ID	NAT MP (16)	antigen ELISA / CLIA	combo ELISA / CLIA	antibody ELISA / CLIA	antigen RDT	combo RDT	antibody RDT
HIV	8	11	14	16	21	---	20	28
HBV	27	37	42	---	---	55	---	---
HCV	5	7	9	38	60	---	---	80

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Lengths of viraemic phase of diagnostic windows with reference to screening test categories (Table 1)

These estimates should be used for risk calculation unless there is more detailed information available for the sensitivity and corresponding window period of the assay

							od (vDWP)	
	N						o	antibody RDT
HIV	8	11	14	16	21	---	20	28
HBV	27	37	42	---	---	55	---	---
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Residual Risk per Blood Donation

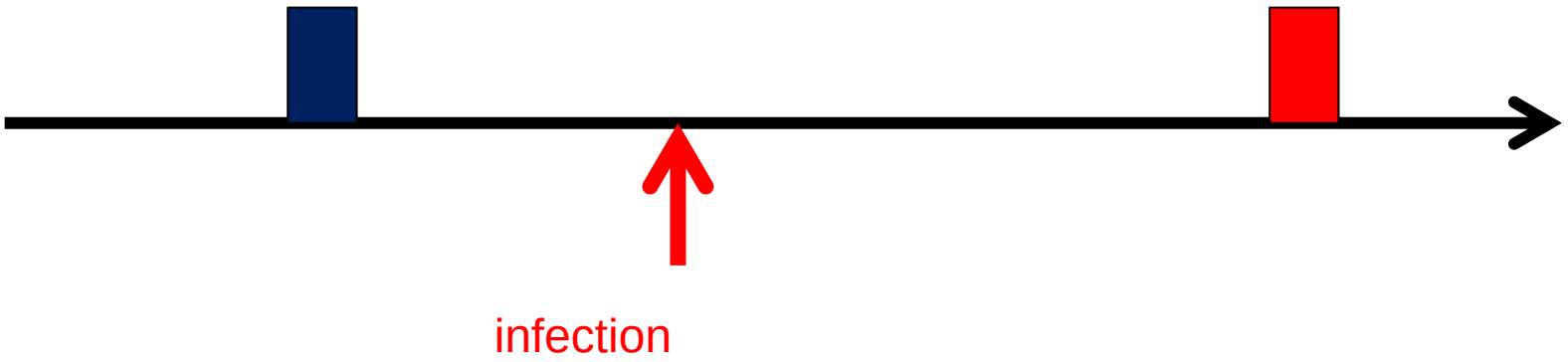
- Frequency of window phase donations depends on the virus epidemiology of the donor population

- Donor populations
  - First time donors
  - Repeat donors

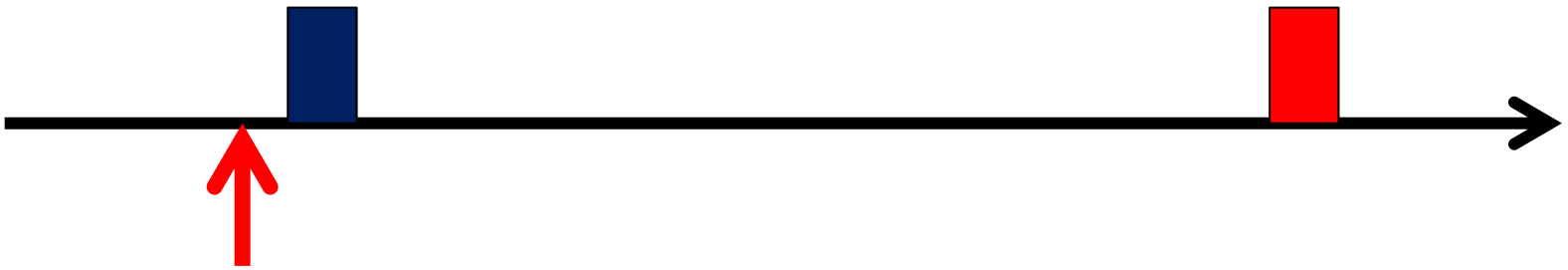
- Positive test results in repeat donors provide information on incidence = rate of new infections in a certain time period

Repeat Donors

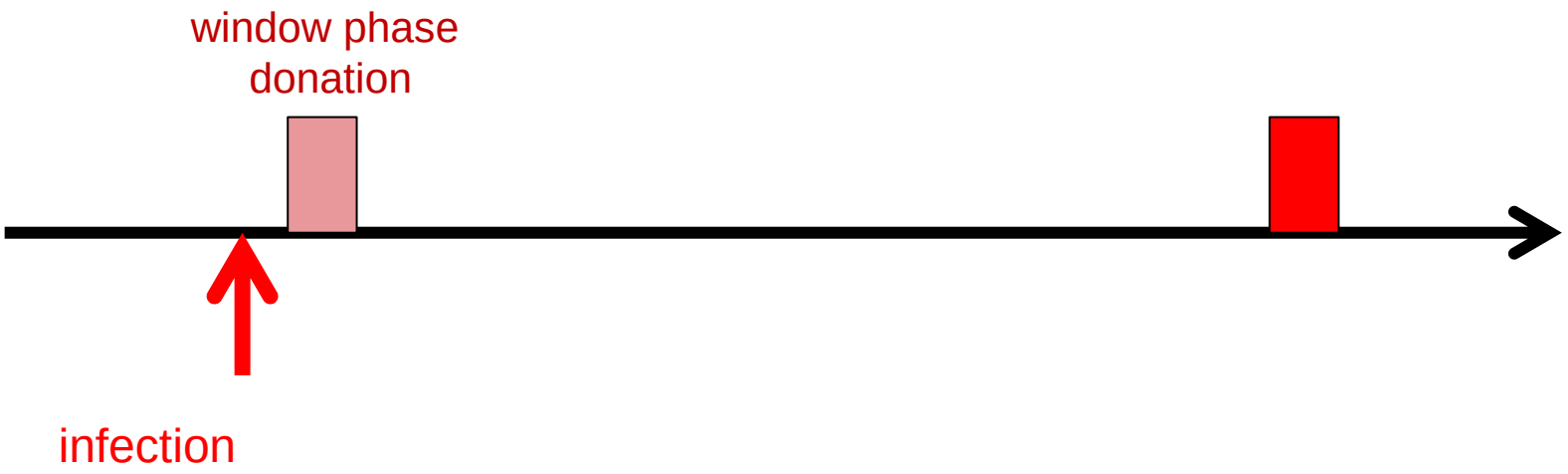
Repeat Donors



Repeat Donors



Repeat Donors



Incidence (Repeat Donors)

Repeat Donors (RD)

- Probability of viraemic window phase donations dependent from
  - Infection rates in the population **(incidence)**

$$\text{Incidence} = \frac{\text{number of repeat donors tested positive during one year}}{\text{total number of repeat donors in the year}} \text{ x } 100\,000$$

Calculation of Residual Risk (Repeat Donors)

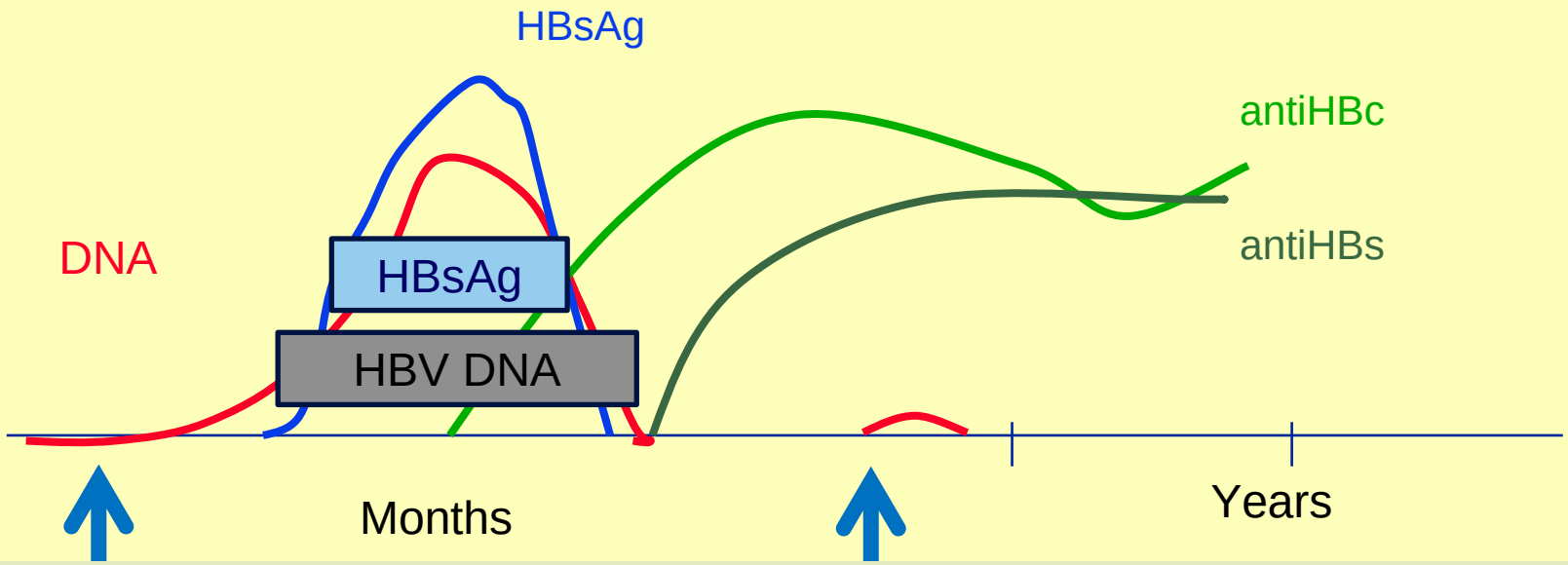
Residual Risk (RR) per donation

- Number of seroconversions (one year observation period)
- Donation frequency: interdonation intervals (IDI)
- Screening test category: length of viraemic diagnostic window phase (vDWP)

$$RR = \frac{vDWP}{IDI} \times \frac{\text{number of seroconverters among repeat donors}}{\text{number of donations from repeat donors}}$$

HBV Incidence Adjustment Factor

70% **transient**
25% **transient (no detectable HBsAg**
5% **chronic**



HBV incidence adjustment factor

- underestimation by transient direct screening marker(s)
- assay sensitivitity / interdonation interval

Interdonation Interval (IDI) Adjustment

- Length of IDI determines probability for window phase donations

- Adjustment for IDIs significantly different between seroconverting and non-seroconverting donors

Residual Risk Estimation (First Time Donors)

First Time Donors (FTD)

- Positive test result may reflect past (prevalent) or recent (incident) infection
- Investigations (NAT, detuned antibody assays) needed to estimate recent infections (incidence) in FTD
- Investigations of different donor populations show 2 – 3 fold incidence in FTD compared to RD

FTD incidence adjustment factor of 3 (worst case)

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- Calculation of frequency of viraemic donations
- Comparisons between donor populations
- Impact of testing algorithms on transfusion and plasma safety
  - Cost benefit analysis for different testing algorithms

Limitation: ***worst case: "each viraemic donation infectious"***

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- Maximal virus concentration during diagnostic window
  - For risk modelling of plasma pool contamination
  - Dependent on assay categories

- Contamination frequency and contamination level of manufacturing plasma pools
  - Inventory hold
  - Virus inactivation capacity

worst case

"each viraemic donation with maximal virus concentration"

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Maximal virus concentration in window phase donations

	Maximal concentration of viral genomes in the viraemic phase of the diagnostic window period (vDWP) (in International Units per millilitre (IU/ml))							
	NAT ID	NAT MP (16)	antigen ELISA / CLIA	combo ELISA / CLIA	antibody ELISA / CLIA	antigen RDT	combo RDT	antibody RDT
HIV	150	2400	2×10^4	10^5	10^7	---	10^7	10^7
HBV	24	384	10^3	---	----	3×10^4	---	---
HCV	30	480	10^4	5×10^6	10^8	---	---	10^8

WHO Guideline on Residual Risk Estimation

- **Annexes**
  - Recommendations for targeted performance evaluation of screening tests
  - Examples for RR calculations

WHO Guideline on Residual Risk Estimation

Current status (05/2016)

- Draft guideline prepared by group of experts
- Presented to ECBS and BRN 2015
- Guideline consultation phases, comments still welcome
- Will be proposed for adoption by ECBS 2016

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Conclusions

- Differential benefit of screening options
  - Virus transmissions by blood components
  - Plasma pool contamination
- Consistency of calculations between establishments
- Decisions on testing strategies
- Consistent with EMA PMF approach to estimate plasma pool contamination

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Thanks to …

RR Working Group

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Blood Regulator Network Members

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THANK YOU