# Strategies for reducing viral transfusion risk

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## Lisbon 2016

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# Conflict of Interest statement

- Paid consultant for Cerus
- Paid consultant for Blood Systems Research Institute for work on the International Multicenter NAT Efficacy Study (funded by Grifols and previously by Novartis)

# Advanced Conflict of Interest statement

- Some of the ideas and data interpretation presented in this talk are opinions and may reflect my unconscious and unperceived biases.
- This probably (undoubtedly?) applies to others who also discuss how to make policy based on available data.

# Talk objective

- Question for myself:
  - After hearing a day and a half of talks on viral safety, what can this talk hope to accomplish?

- Answer:
  - Bring together different observations and different ways of thinking about the issues
  - Formulate questions for a provocative panel discussion and something to continue to talk about during the cocktail hour

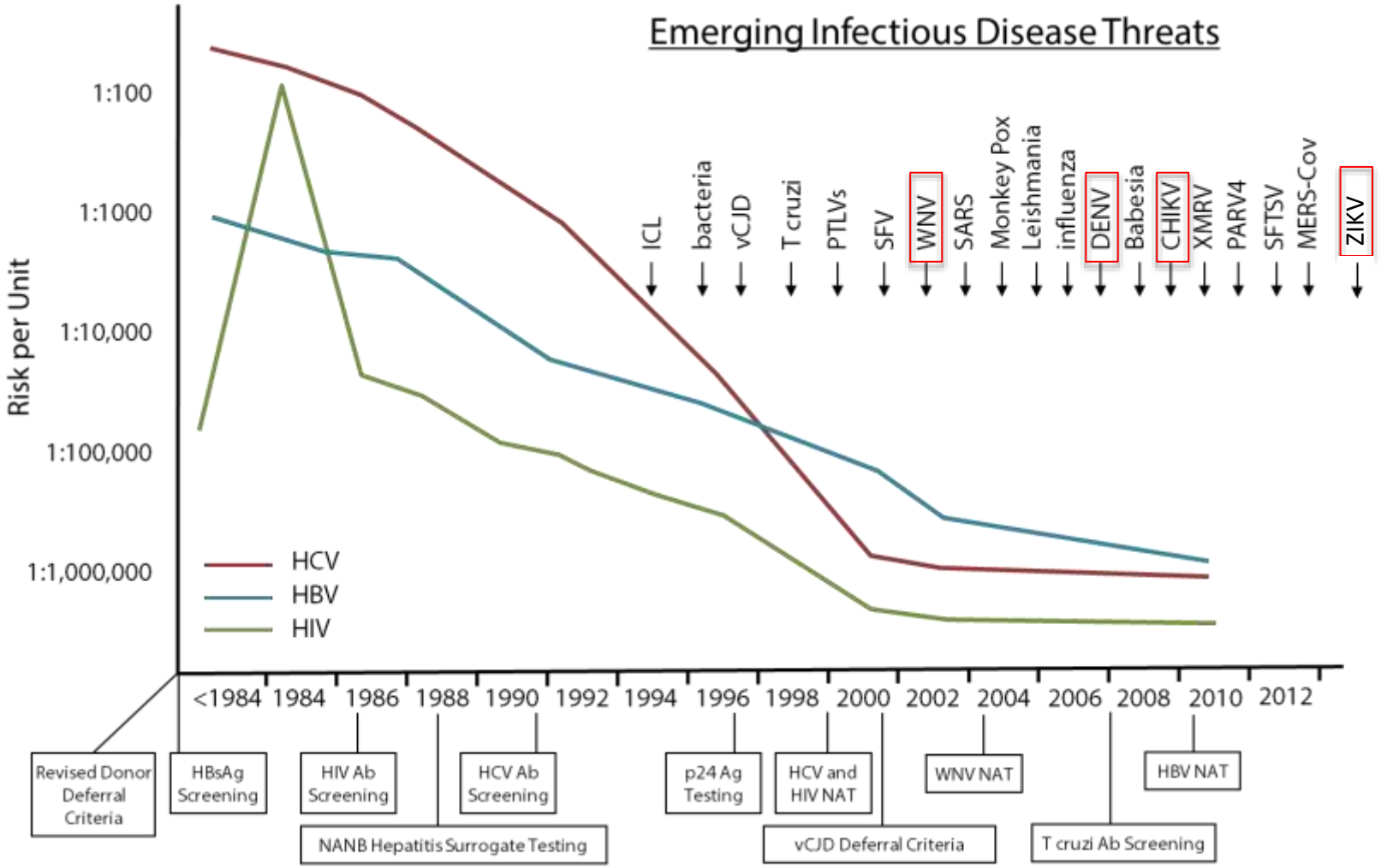
# Basic issues

- When do we intervene?
  - Do we make internally consistent safety decisions in a given jurisdiction and across jurisdictions? Should we?
- What intervention should we use?
  - Potentially robust methods include serology, NAT and PI: how do we choose?
- What role does financial cost play?
  - Can we afford to intervene?
  - Can we afford multiple overlapping interventions?

# Historical context for blood safety decisions

- Pre-HIV (pre 1983-1985):
  - Clinical significance of risks were minimized; interventions were slow to be implemented
- Post-HIV (1985 – early 2000s)
  - Blood safety given high priority  without regard to cost
  - Legal and political consequences of HIV tx-transmission influenced decision-making
  - New techniques developed (high throughput NAT)
  - PI development seen as important goal
- Post – “post HIV”
  - Paradigm is less clear; “tolerable risks/tolerable costs”
  - Accelerated rate of detecting emerging infectious agents (EIAs)

# Accelerating rate of EIAs of concern to blood safety



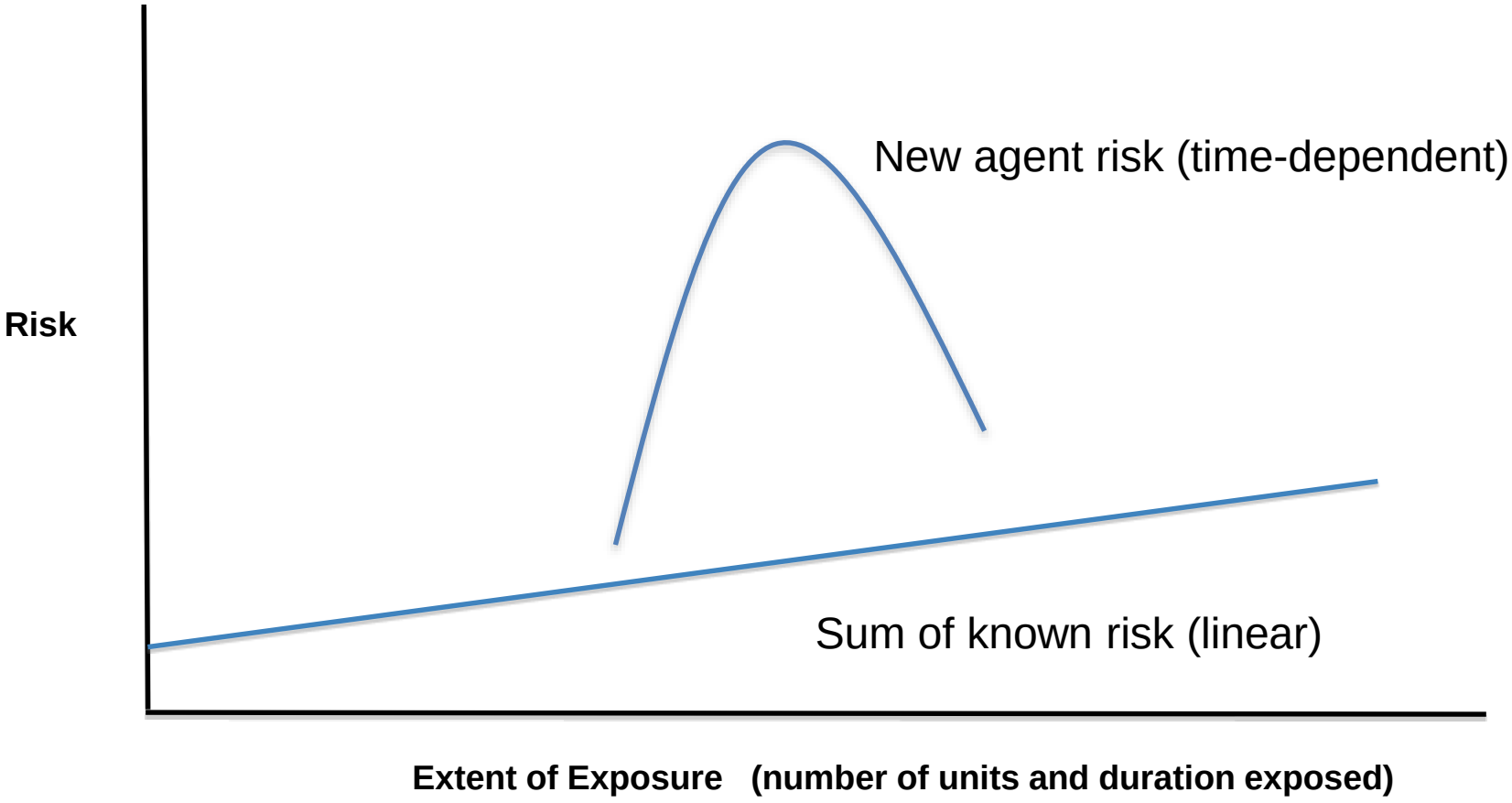
# TTI risk assessment has progressed substantially

- We now know how to assess/estimate viral tx risk
  - Incidence-window period model (or variation thereof) for HIV, HCV, HBV
  - Arbovirus transfusion risk model for emerging or endemic arboviruses
- Our risk models are very sophisticated
  - We calculate 95% CIs, perform Monte Carlo simulations selecting from multiple distributions, and/or select worst case scenarios
  - On-line tools are available (e.g. ***E****uropean* ***U****p-****F****ront* ***R****isk* ***A****ssessment* ***T****ool)* **- eufrattool.ecdc.europa.eu/**

# Multiple assumptions influence model outcomes

- Duration of “viremia”
- Infectivity
  - 100% is assumed in early infection; not known once Ab develops
  - Can we generalize from one arbovirus to the next?
- Clinical severity of tx-transmitted cases is unknown
  - Inferred from other modes of transmission and usually assumed to be worse due to immunocompromise
    - WNV (worse) versus dengue (not as bad?)
- Models for travel related risks have been developed but have even more assumptions:
  - These include donor travel history, rate of infection acquisition by travelers, donation behavior upon return

# Influence of an EIA on total TTI risk



# Different types of emerging viral agents

- Tx risk has been modeled for 2 types of EIAs, determined by agent characteristics in a particular donor:
  - HIV-like: asymptomatic infection with persistent viremia
  - WNV-like: transient viremia that resolves quickly
- Could also define risk based on EIA population dynamics:
  - Dengue-like: recurrent periodic outbreaks (endemic?)
  - CHIKV-like: massive outbreak that infects most of the population in a rapid timeframe then disappears
  - HEV-like: transient viremia but continued new transmission in the donor population
- **The EIA type could affect the decision to develop a NAT or serology assay but would not be relevant to PI adoption**

# Decision-making frameworks

- Regulatory model of zero-based risk (as the goal):
  - Has been the predominant model in some jurisdictions
  - Uses risk assessments
  - Includes multiple “pillars of safety”
    - Corollary is we continue to add increased safety measures without discontinuing existing measures
- Risk based decision-making (RBDM) from the ABO group
  - Allows for tolerable risks
  - Includes other factors such as cost, societal values, contextual issues
  - It is resource intensive to conduct the full process
  - Does anyone know how to apply it?

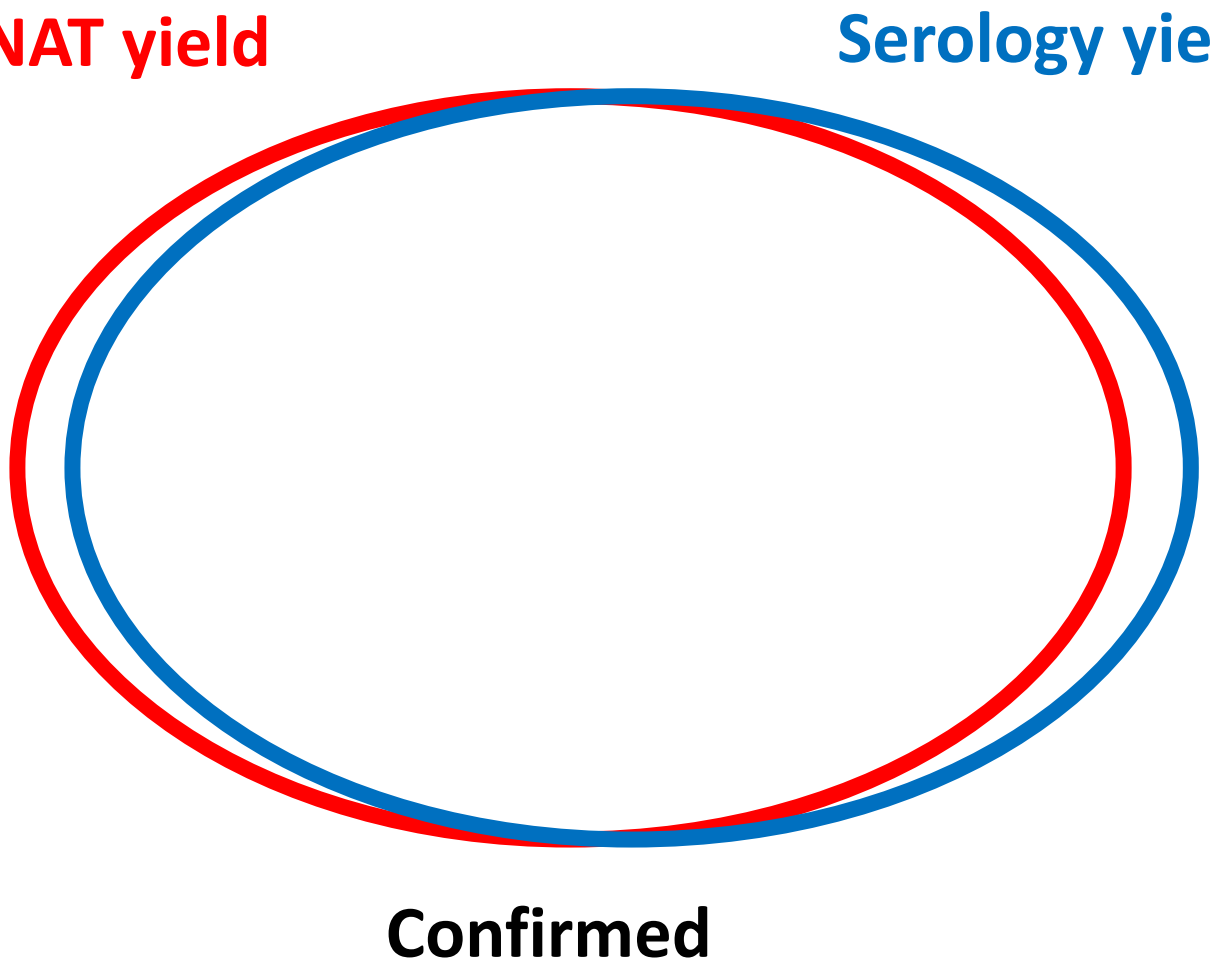
# Risk matrix used by HemaQuebec

| | | | SEVERITY | | | |
|---|---|---|---|---|---|---|
| | | | **Low** | **Moderate** | **High** | **Catastrophic** |
| | | | Transient morbidity with minimal impact on well-being: no need for hospitalisation (or prolongation thereof); minimal or no investigation required; minimal (symptomatic) or no treatment required. | Significant morbidity with some impact on well-being: need for hospitalisation (or prolongation thereof), and/or; some specific investigation and treatment required. No significant risk of death or long term disability. | Significant morbidity as defined previously, with some significant (but less than 50%) risk of death or long term disability. | Significant morbidity as defined previously, with a high risk (50% or more) of death or long term disability. |
| **FREQUENCY** | **Very Low** | **Less than 1:5,000,000** | **Acceptable** | **Acceptable** | **Tolerable** | **Tolerable** |
| | **Low** | **1:1,000,000 to 1:5,000,000** | **Acceptable** | **Tolerable** | **Tolerable** | **Intolerable** |
| | **Moderate** | **1:250,000 to 1:1,000,000** | **Tolerable** | **Tolerable** | **Intolerable** | **Intolerable** |
| | **High** | **1:1 to 1:250,000** | **Tolerable** | **Intolerable** | **Intolerable** | **Intolerable** |

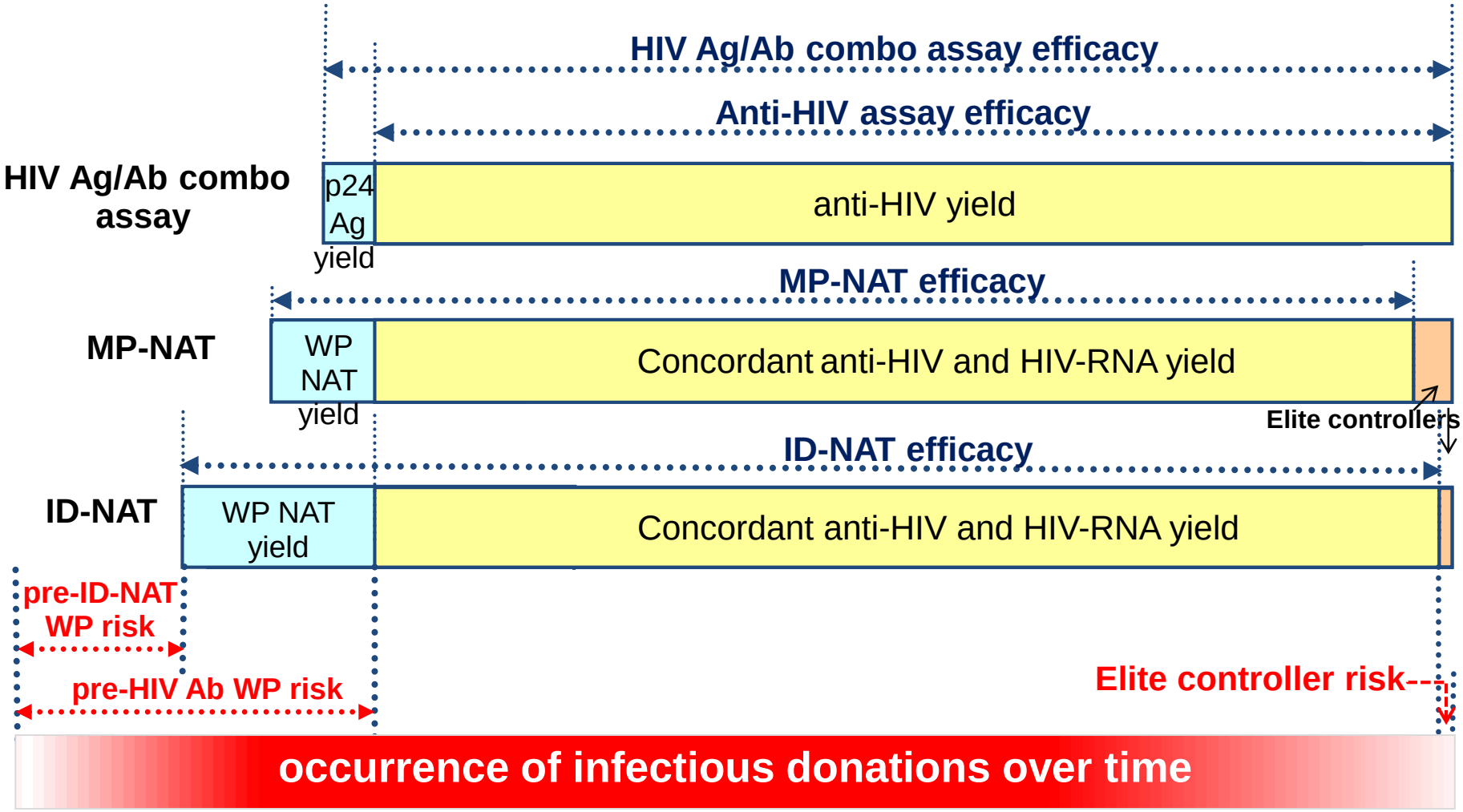
# So which intervention should we choose?

- NAT (MP or ID)
- Serology (antibody, antigen, combo)
- PI (selected component, all component/whole blood)
- Combination of these techniques
- If we implement a new technology, what is needed to eliminate a prior safety method?
  - Blood safety is a conservative field so this has not been an inherently attractive approach
  - How can we afford to pay for innovation unless we are able to reengineer our approach?

# NAT and serology yield for HIV, HCV, and HBV



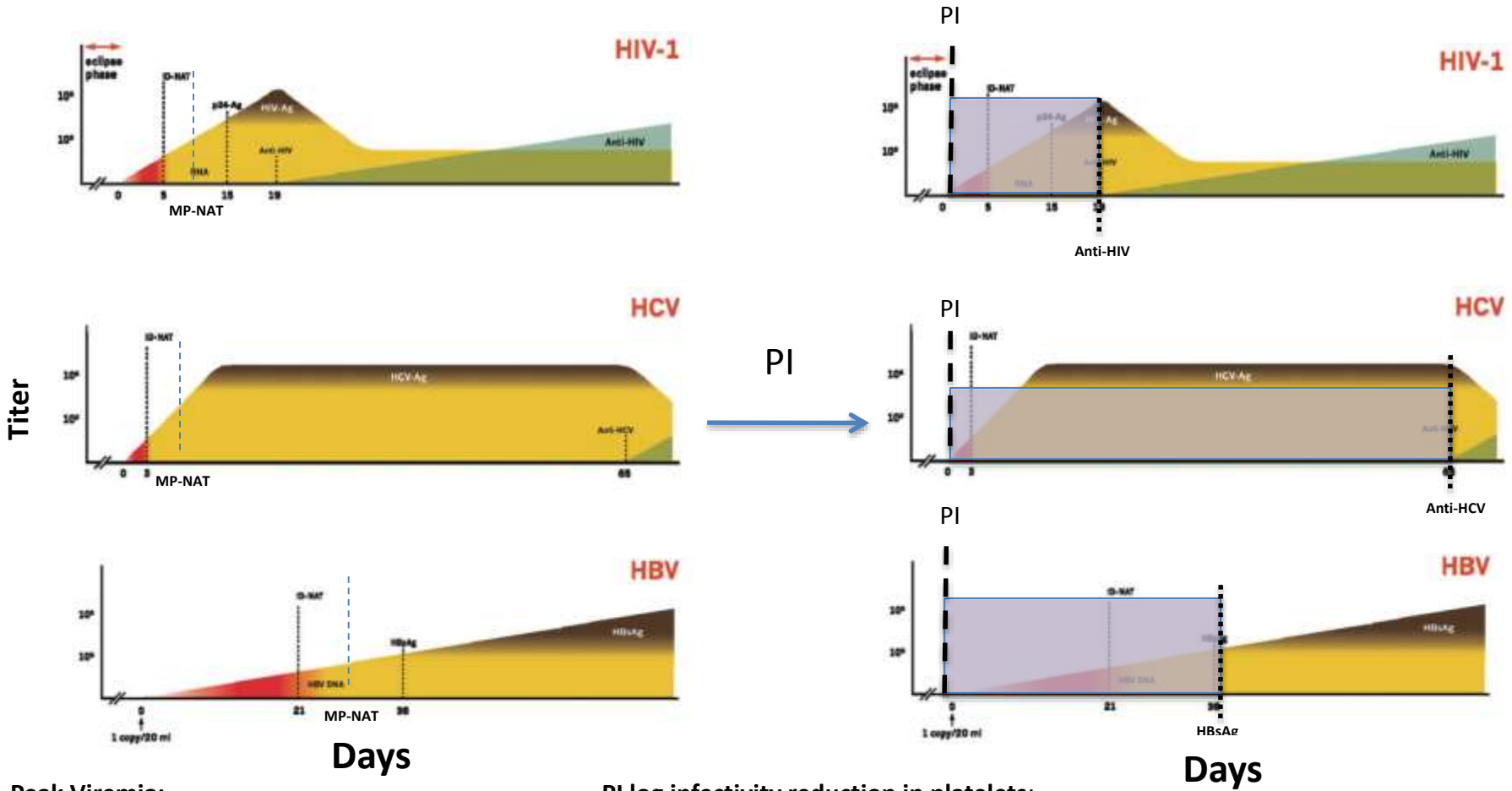
# Model to evaluate efficacy of HIV screening assays




Bruhn et al. Transfusion 2013:53:2399-2412

LELIE RESEARCH

# Effect of NAT and PI on HIV, HCV and HBV risk




**Peak Viremia:**
HIV: ~$10^8$ geq/mL
HCV: ~$10^8$ geq/mL
HBV: ~$10^9$ geq/mL

**PI log infectivity reduction in platelets**:
HIV: >6.6 pfu/mL
HCV: >4.5 $CID_{50}$
HBV: >5.5 $CID_{50}$

Adapted from Kleinman S *et al.* Transfusion 2009;49:2454-2489;

# Should NAT be done for newly discovered arboviruses? How long does it take for assay development?

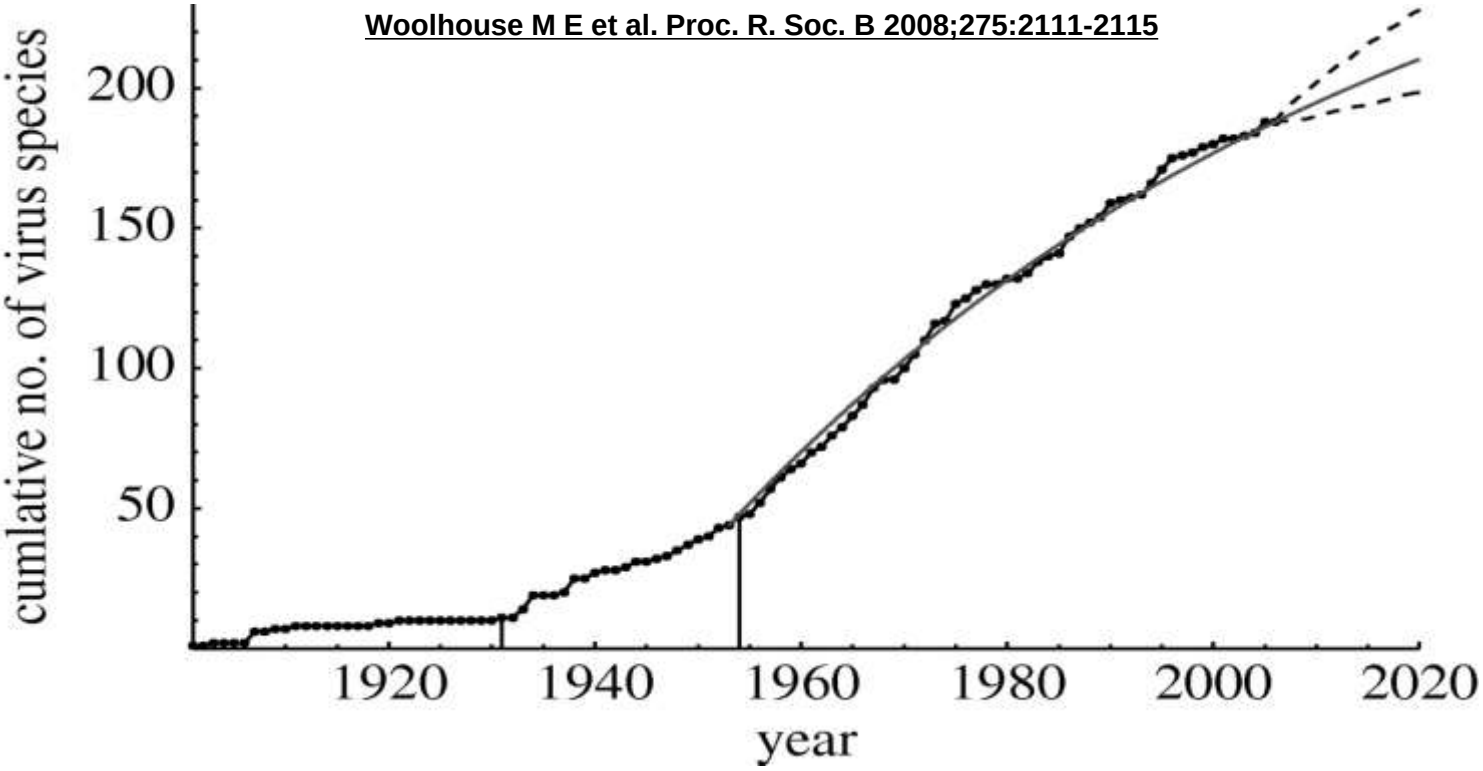
| Agent | % with symptoms | Severe clinical outcomes | Demonstrated TTID (#) | RNA screening (timing) |
|---|---|---|---|---|
| WNV | 20 | Neuroinvasive Disease | Yes (36) | MP/ID (US- 9 mos) |
| DENV | 50 | Plasma Leakage/DHF | Yes (15) | No |
| CHIKV | 85 | Chronic painful arthralgias | No | No |
| ZIKV | 20 | Guillain Barre; Congenital infection | Probable (2) | ID (select US – 3 mos) |

- Would PI be a better solution for the next arbovirus if it were already in place?
  - Depends on the robustness of the PI method and the maximal viral titres

# Is PI a viable future direction?

- Transfusion carries multiple risks, each of which is small
  - Deterrent to assay development
- PI is an intervention that addresses multiple risks but has limitations:
  - Will not inactivate some agents
  - What about units with very high “viral” titers?
  - Each PI technology has its own properties
- Changes paradigm from reactive to proactive
  - Consistent with plasma fractionators approach
  - Maintains trust in blood system when a new real or potential tx-transmitted virus emerges

# The discovery curve for human virus species

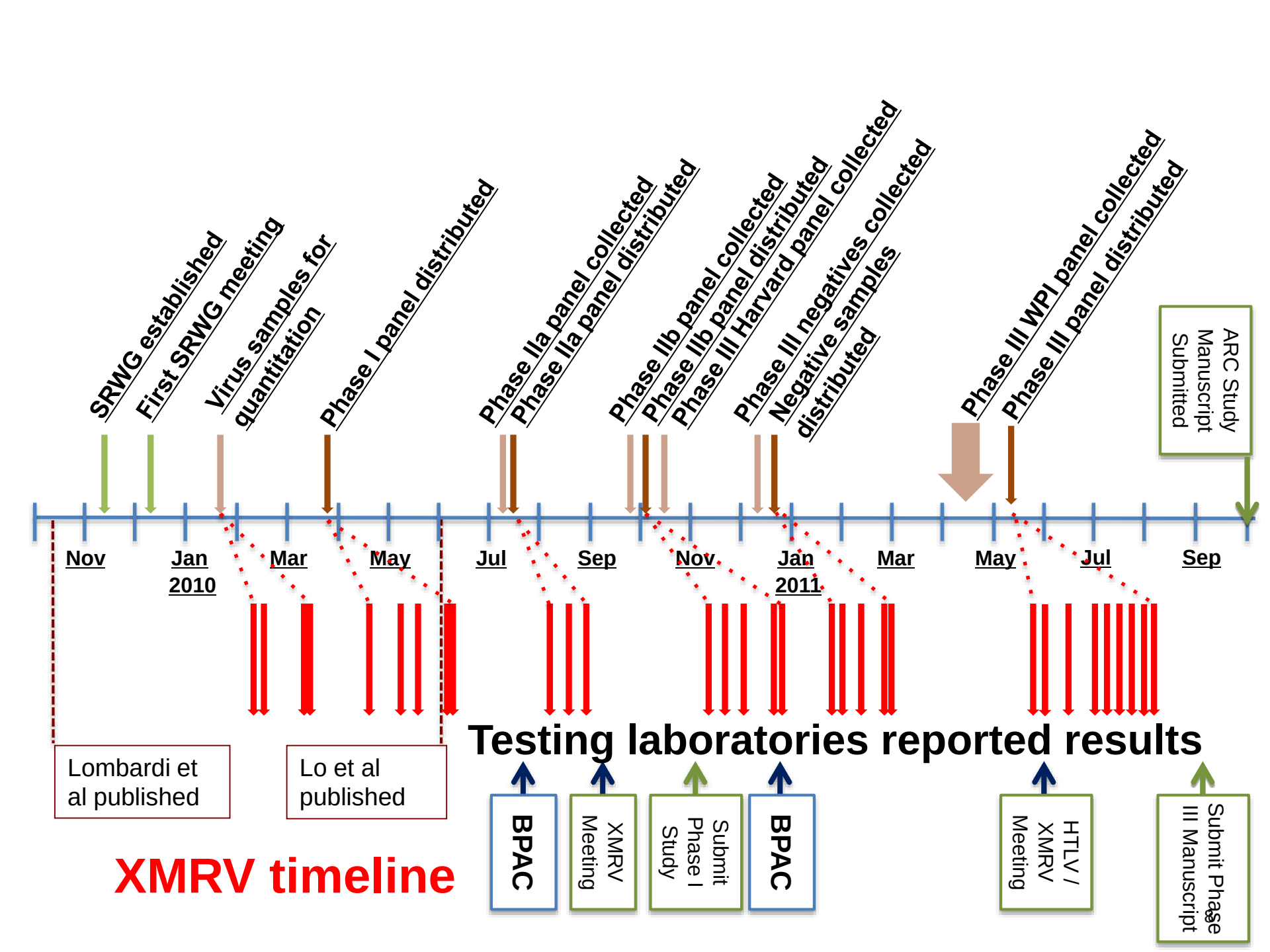


# Viral discovery programs and their impact on blood safety policy and on resource consumption

- Discovering new tx-transmitted agents that cause disease is important
- Deep sequencing techniques are awesome tools

**but**

- There is a sophisticated viral discovery “industry”
- Newly discovered agents that are not associated with a disease consume valuable blood community resources
- Blood transfusion can be used as a marketing tool by research investigators or patient advocate groups to gain funding or publicity


SRWG established
First SRWG meeting
Virus samples for quantitation
Phase I panel distributed
Phase IIa panel collected
Phase IIa panel distributed
Phase IIb panel collected
Phase IIb panel distributed
Phase III Harvard panel collected
Phase III negatives collected
Negative samples distributed
Phase III WPI panel collected
Phase III panel distributed
ARC Study Manuscript Submitted
Nov
Jan 2010
Mar
May
Jul
Sep
Nov
Jan 2011
Mar
May
Jul
Sep
Lombardi et al published
Lo et al published
Testing laboratories reported results
BPAC
XMRV Meeting
Submit Phase I Study
BPAC
HTLV / XMRV Meeting
Submit Phase III Manuscript
XMRV timeline

# Potential changes with all component PI

- Modification of donor testing:
  - Eliminate syphilis, CMV, T. cruzi, some HBV testing, malaria donor requalification testing
  - Eliminate off-season (or all) WNV testing
  - Conduct NAT testing for known agents in larger mini-pools; eliminate ID NAT
- Elimination or modification of donor screening questions:
  - Travel for malaria, WNV, other arboviruses
- Elimination of gamma irradiation and irradiators

# Why do we?

- Perform HIV/HCV/HBV MP NAT in the US but perform ID NAT in most of the rest of the world?
- Have different safety requirements for plasma (FFP) transfusion in the EU (pathogen inactivated or quarantine) than in the US (infectious disease testing only)?
- Have countries with similar donor HEV RNAemia prevalence adopting different donor screening policies?
- Use different travel based deferrals (“universal”vs. known risk areas) for reducing arboviral tx-transmission risk?
- Implement blood component PI in some but not all jurisdictions where a technology is approved/licensed?

# Acknowledgements


- To my wife, Dianne, for suggesting that I take a common sense approach to this lecture rather than show lots of complicated numbers
- To my colleagues who have provided input, slide templates and/or slides for this presentation:
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