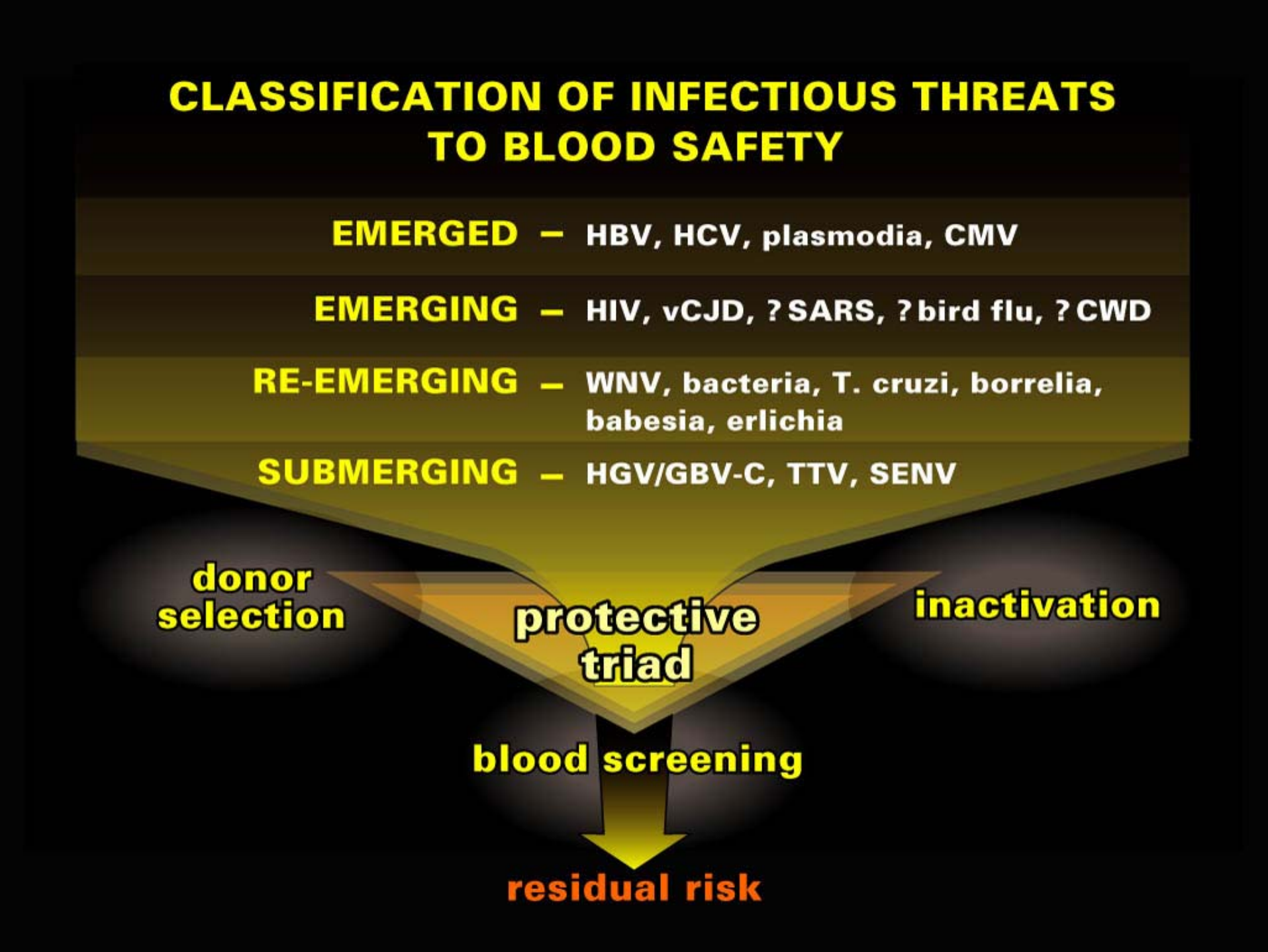
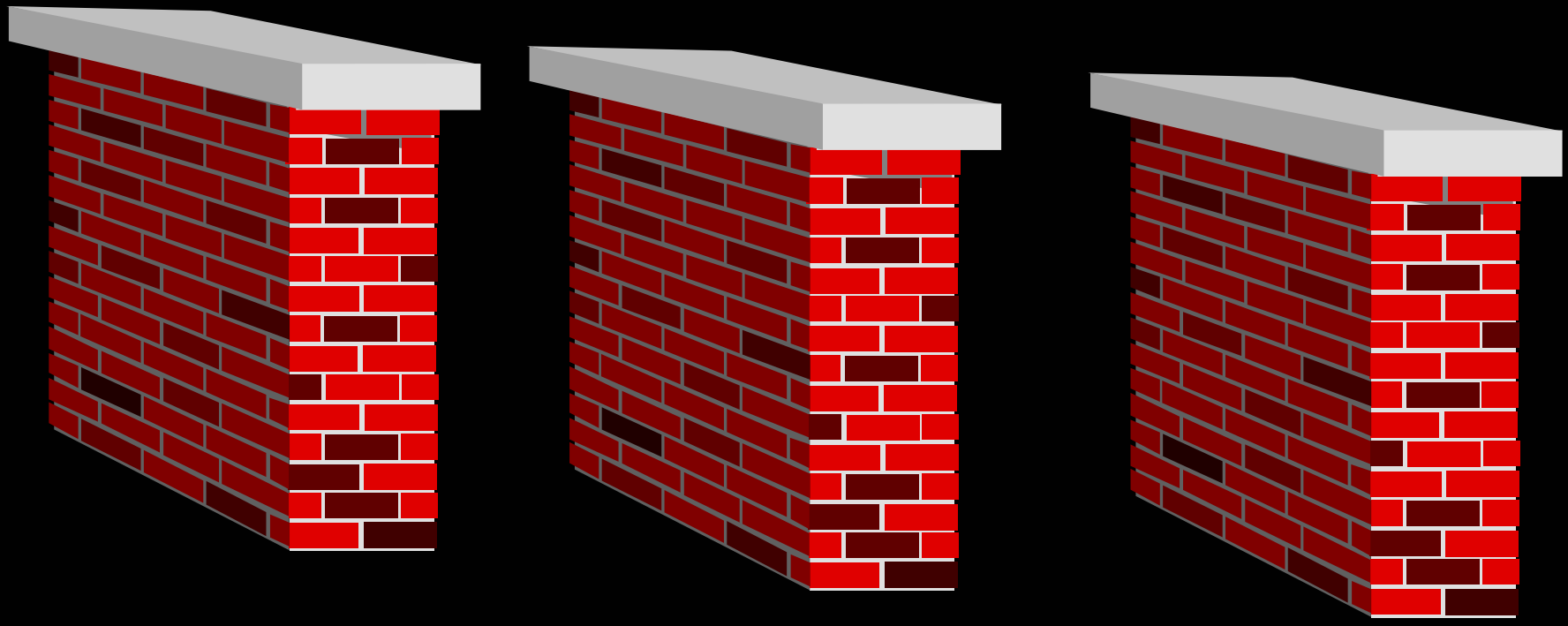

CLASSIFICATION OF INFECTIOUS THREATS TO BLOOD SAFETY
EMERGED – HBV, HCV, plasmodia, CMV
EMERGING – HIV, vCJD, ? SARS, ? bird flu, ? CWD
RE-EMERGING – WNV, bacteria, T. cruzi, borrelia, babesia, erlichia
SUBMERGING – HGV/GBV-C, TTV, SENV
donor selection
protective triad
inactivation
blood screening
residual risk

PROTECTIVE BARRIERS AGAINST TRANSMISSION OF PATHOGENS



Donor Selection/Exclusion

Testing

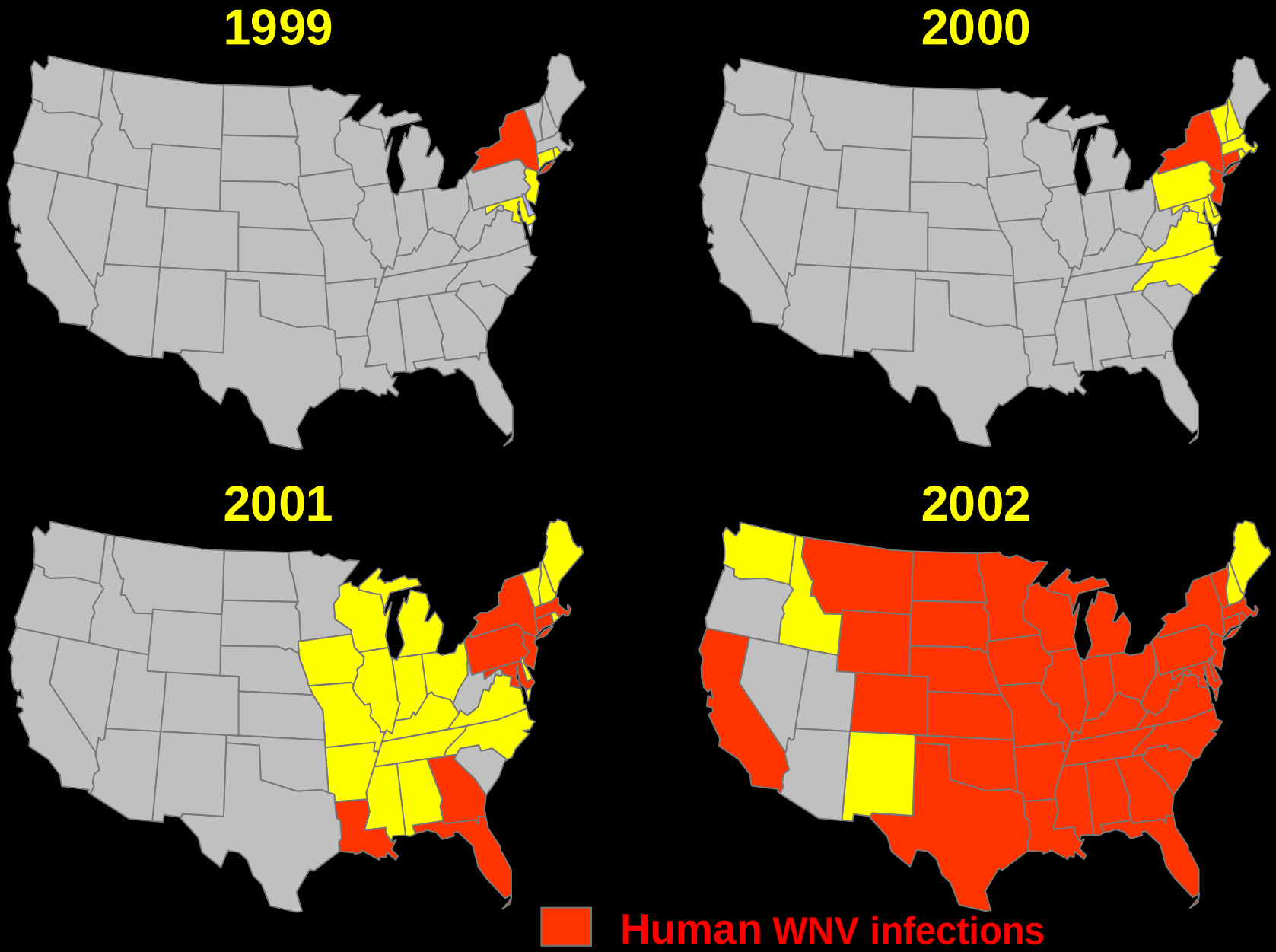
Inactivation Removal

PERILS OF A REACTIVE APPROACH TO EMERGING PATHOGENS

TIME INTERVAL BETWEEN RECOGNITION OF RISK AND IMPLEMENTATION OF A DONOR SCREENING ASSAY

Agent	Recognized As Transfusion Risk	Screening Introduced	Interval (Years)
HBV	1940	1970	30
NANB/HCV	1975	1990	15
HIV	1982	1985	3
WNV	2002 (1999)	2003	1 (4)
CHAGAS	2002	2007	5

West Nile Virus Activity: 1999-2002



TRANSFUSION-TRANSMITTED WNV

Year	Documented Clinical Disease	Projected Infections*
2002	23 (16 WNND)	3220
2003	6	840
2004	1	140
2005	0	0
2006	2	280
Total	32	4480

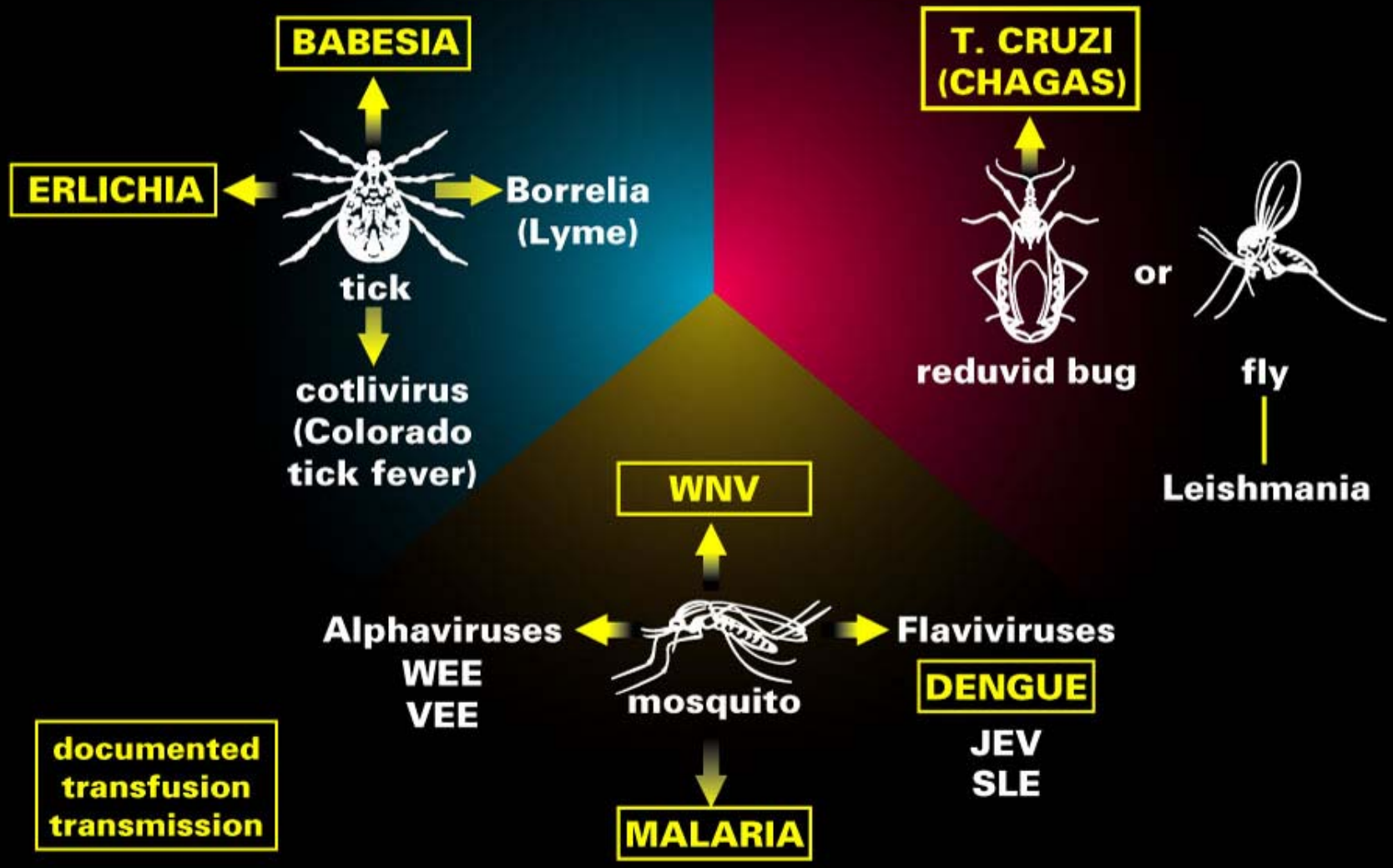
Approx. 1400 donors (2100 components) interdicted in 2003-2005

Blood transfusion has features that are characteristic of complex systems…… and it is sensitive to major effects from small remote perturbations—witness the origins of HIV, bovine spongiform encephalopathy, or the consequences for transfusion in the United States of the arrival in New York of what was possibly a single West Nile Virus-infected mosquito.

William Murphy

Transfusion 2006;46:2011-13

VECTOR BORNE AGENTS THAT ARE OR MAY BE THREATS TO BLOOD SAFETY



Any agent capable of causing disease in man that has an asymptomatic "viremic" phase is a threat to be transfusion-transmitted. The likelihood of that transmission is highly dependent on the duration of viremia and the level of concern is dependent upon the severity of the ensuing disease.

Unscreened Threats

vCJD	HAV
Malaria sp.	HEV
HHV-8	HPV
Dengue (Other Arbov)	
Parvo-B-19	
B. Microti (Babesia)	
Rickettsia (Q-Fever)	
B. Burgorferi (Lyme)	
Chikengunya	

XMRV

Future Threat to Blood Suppy

The next really bad one (HIV-X)

Comments on the Agent Du Jour - XMRV

- The data in the Lombardi, et al Science manuscript are extremely strong and likely true, despite the controversy. Not only have they detected gag and envelope XMRV sequences, but they have infected prostate cell lines and recovered gamma retrovirus particles and have transmitted XMRV to rhesus macaques by the IV route and demonstrated infectivity
- Although blood transmission to humans has not been proved, it is probable
- The association with CFS is very strong, but causality not proved
- XMRV and related MLVs are in the donor supply with an early prevalence estimate of 3%-7%.
- We (FDA & NIH) have independently confirmed the Lombardi group findings

THE PRECAUTIONARY PRINCIPLE

For situations of scientific uncertainty, the possibility of risk should be taken into account in the absence of proof to the contrary

Corollary: The precautionary principle asserts that measures need to be taken to face potential serious risks

Alter Corollary: Pathogen reduction is the ultimate precautionary principle by eradicating almost all potential for infectious disease transmission even before risk has been conclusively established, and possibly, even before the agent has been recognized

PRECAUTION VERSUS PREVENTION

The precautionary principle ….forces society to think that it is possible to make decisions in the absence of definitive knowledge. It also focuses undue attention on the potential risks of transfusion while ignoring other (non-transfusion) risks prevalent in society.

Important to address the question as to whether it is worth investing resources to deal with hypothetical risk in situations where proven risks are not sufficiently resourced

Eric Hergon: TMR 2005;19:273

ADVANTAGES OF PATHOGEN REDUCTION

- Effectively inactivates most clinically relevant viruses whether RNA or DNA, ss or ds, enveloped or non-enveloped, intra-cellular or extra-cellular
- Inactivates clinically relevant gm.+ and gm.- bacteria
- Inactivates all the spirochetes, rickettsia and protozoa of known transfusion relevance
- Prevents transfusion associated GVH
- Offers probable preemptive protection against pathogenic, potentially lethal, agents that will inevitably emerge in the future

IMPEDIMENTS TO PATHOGEN REDUCTION

- Decreased Yield (10-20%): clinical effect marginal
- Insufficient kill of some hi-titer agents (HAV, Parvo B-19)
- Toxicity: None known for riboflavin; theoretical for psoralens at low residual doses transfused; wide safety margin
- No single process for all blood products
- Cost

OFFSETS TO COST FOR A PATHOGEN REDUCTION SYSTEM APPLICABLE TO ALL BLOOD COMPONENTS

- Eliminate some current assays (RPR, anti-HBc, Chagas, ?WNV,)
- Preempt future testing (HHV-8, babesia, dengue, malaria)
- Eliminate bacterial testing
- Eliminate radiation
- Allow for continued mini-pool testing
- Reduce donor exclusions based on geography (malaria)

Perceptions and Realities

- **Perception: Everyone wants safer, better blood**
- **Reality: No one wants to take a risk or incur the cost of new approaches to achieve this in the absence of either a crisis or a major push by the healthcare community or public at large**
- **Perception can become reality only if costs are low**

Ray Goodrich ; Caridian BCT

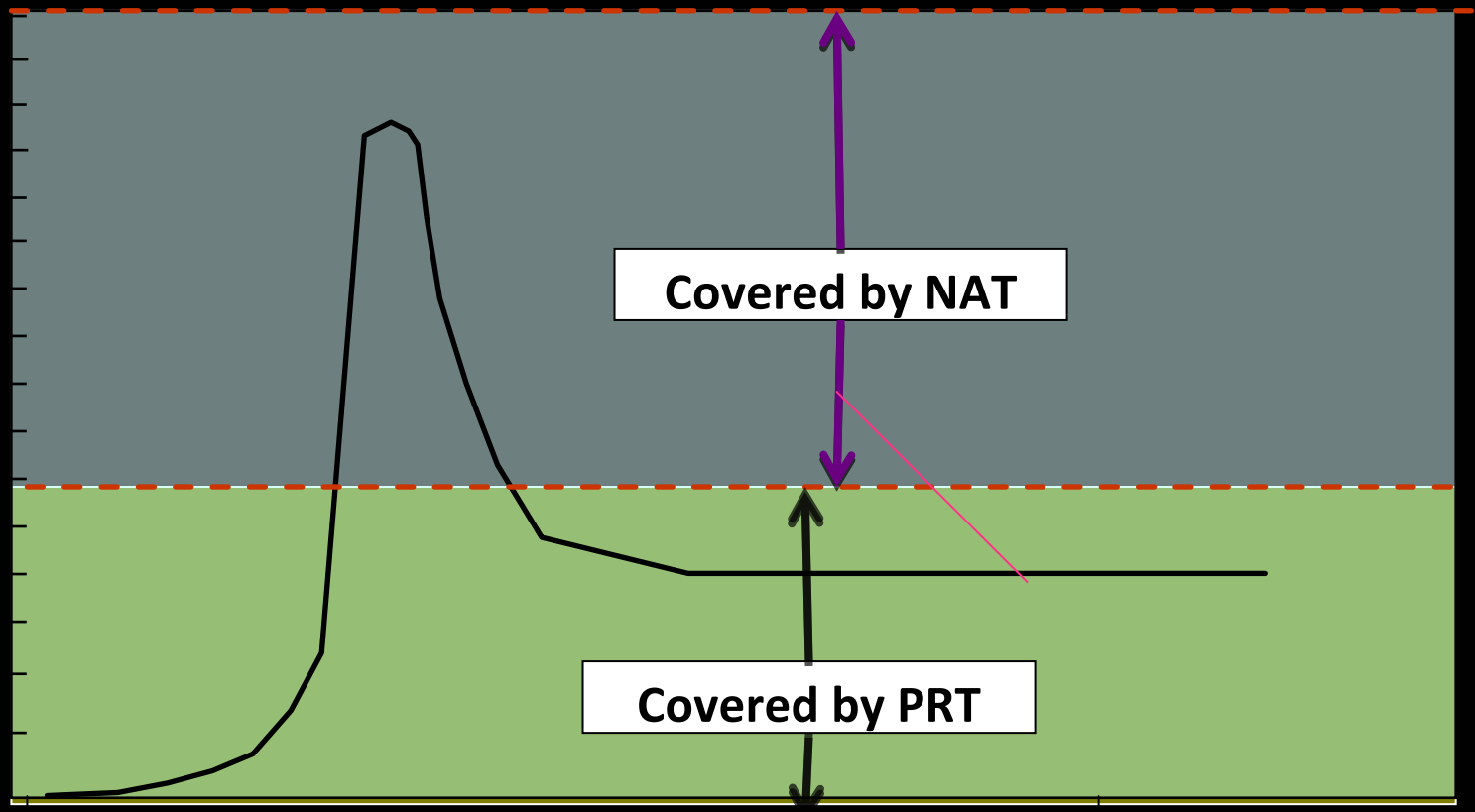
Thinking Orthogonally

An Alternative Strategy

Use the strengths of both approaches (testing and PR) to offset potential individual weaknesses

Ray Goodrich, Caridian BCT

Covering The Windows: An Orthogonal Process Approach



PATHOGEN REDUCTION: WHERE ARE WE NOW?

- Currently, only two options :
  - Psoralen UVA (Cerus) & Riboflavin UVA (Caridian)
  - No alternative method known to be in pipeline

- Psoralen SPRINT trail raised safety issues for the FDA including pulmonary toxicity and grade 2 bleeding : while no adverse event reached statistical significance, the trends were in the same negative direction. FDA requires a second, larger, phase III clinical trial that will delay licensure for at least 5 yrs

- No high through-put RBC/whole blood PR method for civilian use is on the immediate horizon

Personal Pessimistic Prediction Pertaining to Pathogen Preventive Paradigms

- **Timing & Probabilities**
- **Platelets: > 5 years**
- **Red Cells: > 5 years**
- **HJA Retires: < 5 yrs**
- **Chance that HJA is inactivated before pathogens: 100%**
- **Chance that HJA is inactivated by pathogens: 50:50**

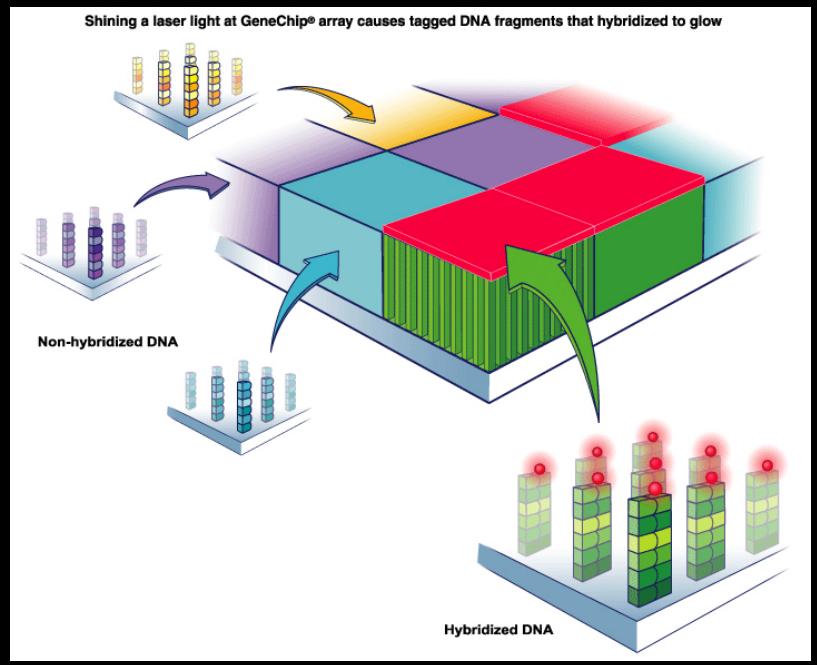
PATHOGEN REDUCTION: WHAT CAN WE DO WHILE WE WAIT?

- **Hedge our bets: existing technologies may never be optimal for RBCs. We should simultaneously support basic and applied research to develop new strategies for PR of red cell products.**

- **Explore novel testing strategies e.g. gene arrays for 20 or more agents of clinical relevance and current concern**

DNA microarrays

Designed to simultaneously detect (and quantify) multiple specific nucleotide sequences present in a sample

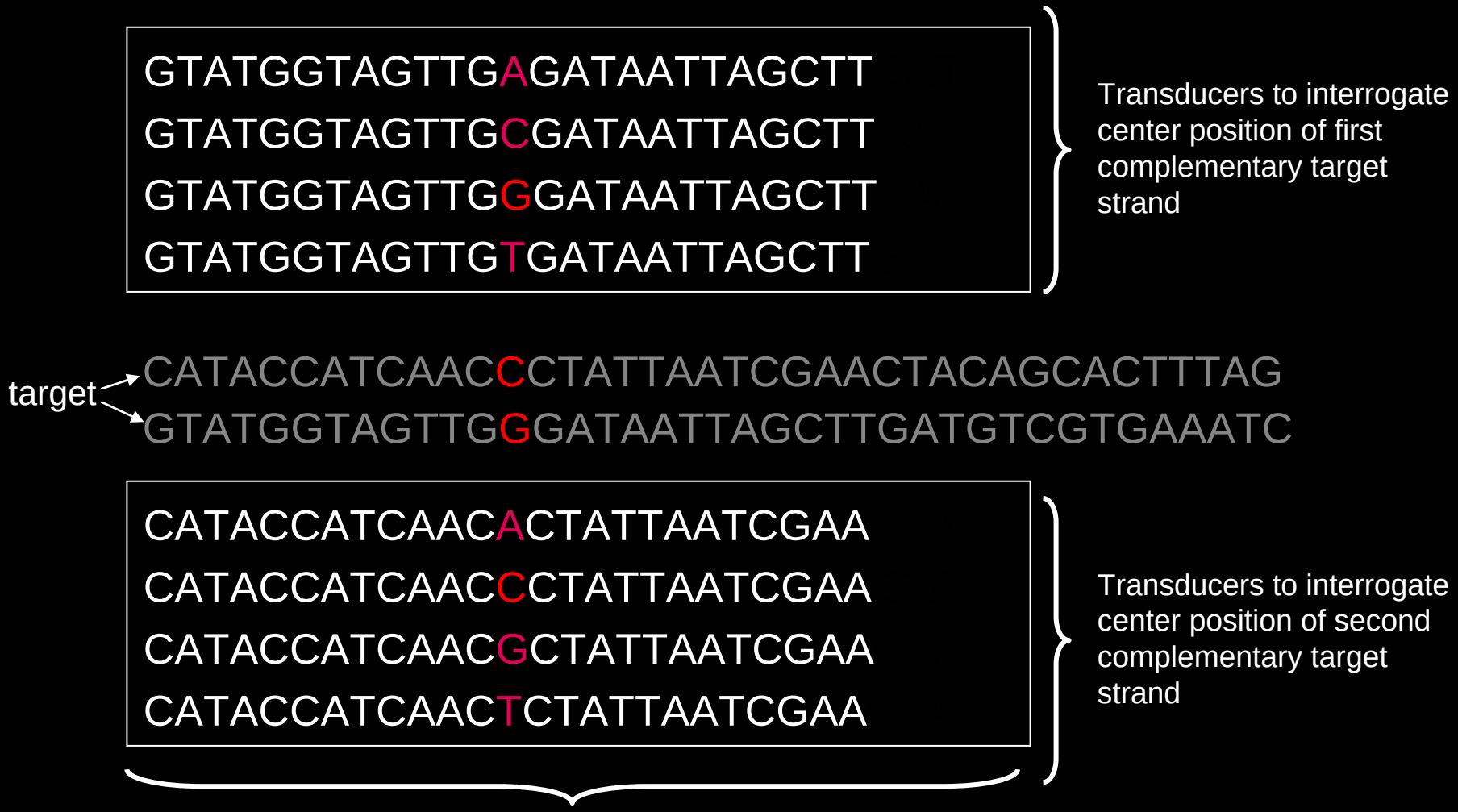


HIGH MULTPLICITY RESEQUENCING PATHOGEN MICROARRAYS (RPM)

- Extract total nucleic acid from small blood sample
- Amplify in a very relaxed way using degenerate random primers. No attempt to make PCR specific
- Place amplicons on chip containing 100,000 – 1 million probes
- Uses 4 probes to interrogate each base on opposite strands with 96% overlap
- The array directly sequences the amplicon providing extreme specificity and allowing comparisons with the universe of stored sequences.
- Detects down to 10-30 virions

TessArae: Clark Tibbetts

Resequencing by Hybridization - 1



Resequencing by Hybridization - 2

Resequencing by Hybridization - 3

Proposed RPM-EID Chip by TessArray

AABB – Prioritized EID Threats (August 2009)

Viruses

- **Chikungunya**
- **Dengue 1, 2, 3, 4**
- HAV
- HBV
- HCV
- HIV
- HTLV I, II
- Herpesvirus
  - HSV
  - CMV
  - VZV
  - EBV
  - KSV
  - HHV-8
- Influenza A/H5N1
- LCMV
- Parvovirus B19
- Rabies
- Spumavirus
- **St Louis Encephalitis**
- West Nile Virus
- XMRV

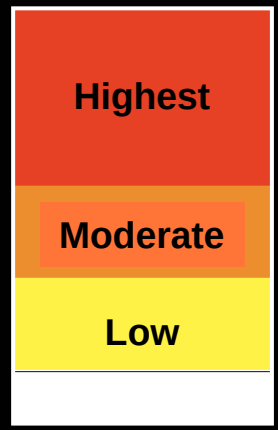
Prokaryotes

- *Clostridium*
- *Mycobacterium*
- *Streptococcus*
- ***Borrelia burgdorferi***
- *Ehrlichia*

Eukaryotes

- ***Plasmodium spp.***
- ***Babesia spp.***
- *Trypanasoma*
- *Leishmania spp.*

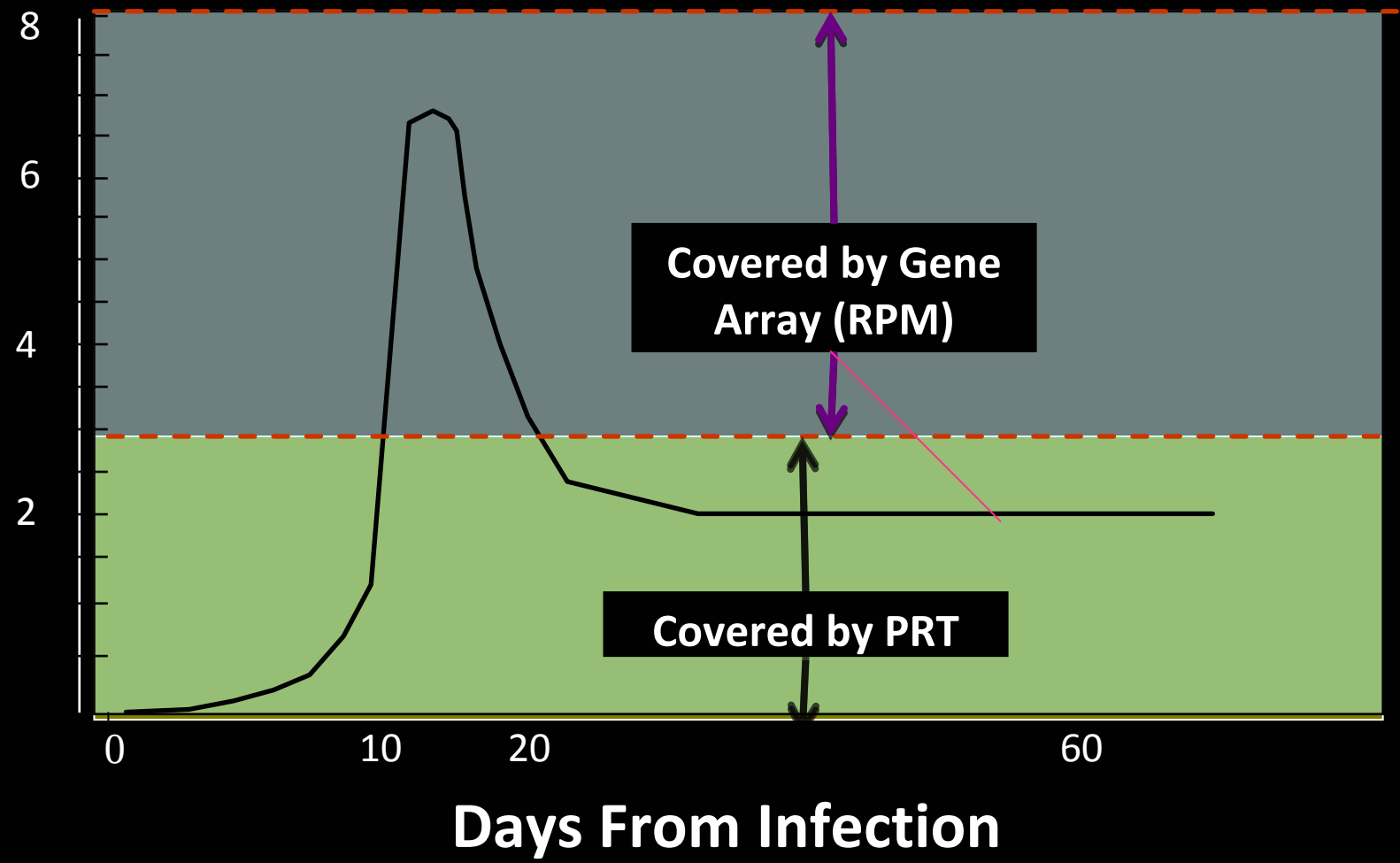
Blood Product & Tissue Safety Priority Level



The smallest and least expensive TessArray RPM would enable multiplexed detection and specific identification for all 35 of these pathogens, as a single test of a single specimen with same-day results.

The only barriers to rapid development and implementation of such diagnostic testing capabilities are regulatory, not technical.

Covering The Windows: An Orthogonal Process Approach

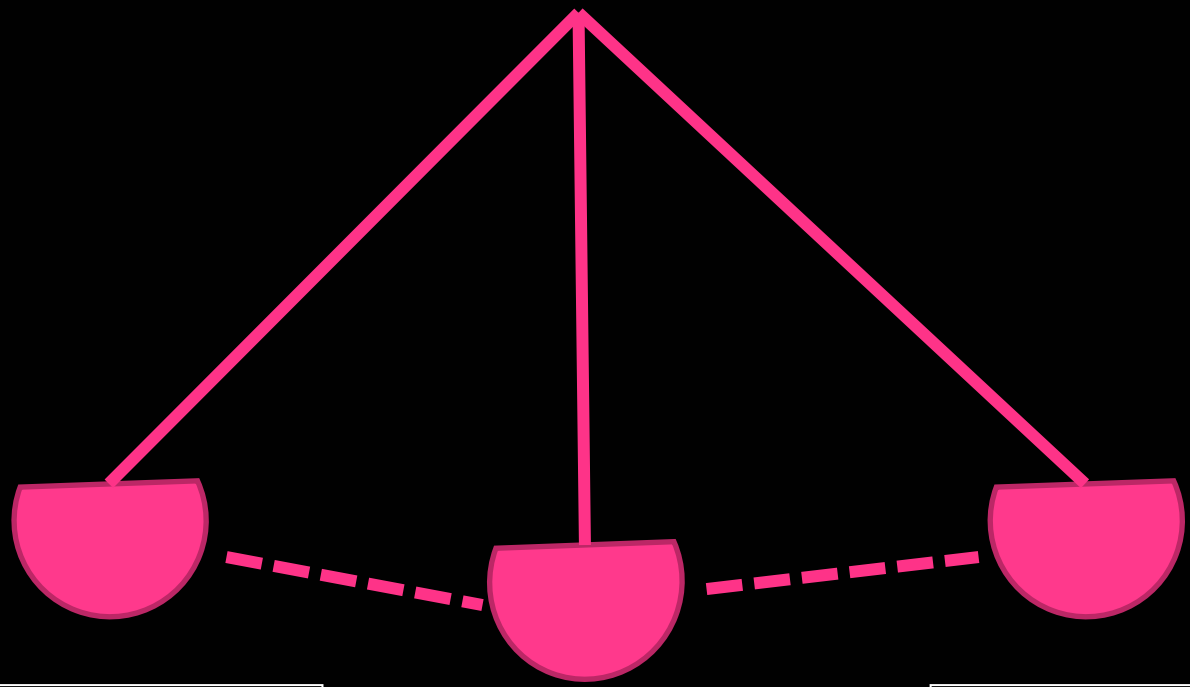


Risk is in the Eye of the Beholder

- Based on Sprint trial FDA fears the psoralen method might add risk to products that are already quite safe
- Based on the European experience, others consider these product risks minimal and feel PR can make a safe blood supply even safer

The consequences of a wrong risk decision are considerable

Pendulum of Blood Bank Responses to Infectious Agents & Pathogen Reduction



Questions + Big 3 + Inactivate

Go directly to poor house

Questions + add new tests when need arises

Status Quo

Ask questions; Test for Big 3

Go directly to jail