American Red Cross

Infection transmission risk and different testing strategies

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Outline

- Rationale for testing
- Nature of infection
- Markers for testing
- Test properties
- Need for confirmation
- Assessment of risk
- Fitting test program to environment

Rationale for testing

- Identify those prospective donors whose blood would infect recipients
- Compensate for failures of selection and questioning
- Avoid undue wastage from non-specific selection procedures

What to test for?

- Agent itself
- Component of agent
  - Antigen, nucleic acid
- Host response to agent
  - Specific e.g. antibody
  - Non-specific e.g. disease marker (ALT)
  - Other surrogate

Surrogate tests

- Generally neither sensitive nor specific
- Cannot be confirmed
- Difficult to interpret for affected donor
- Have been controversial in the past
  - e.g. anti-HBc and HIV/AIDS
- Little used currently
  - China: ALT as a rapid pre-test for hepatitis

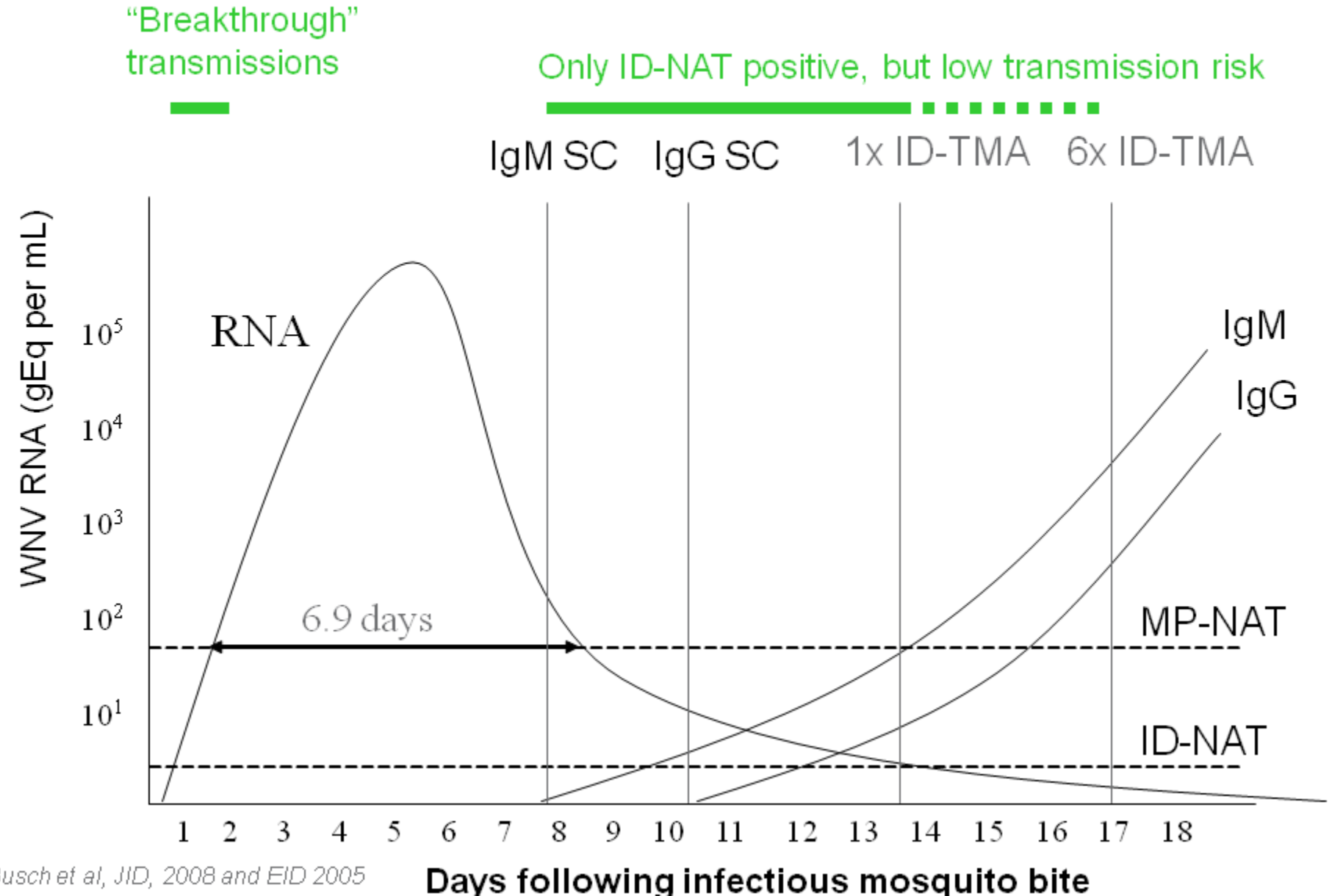
Nature of infection

- Time
  - Acute, chronic
- Symptomatic/Asymptomatic
- Intensity
  - High titer, low titer
- Sequence
  - Infection, nucleic acid, symptoms, antigen, antibodies

Simple, acute infection

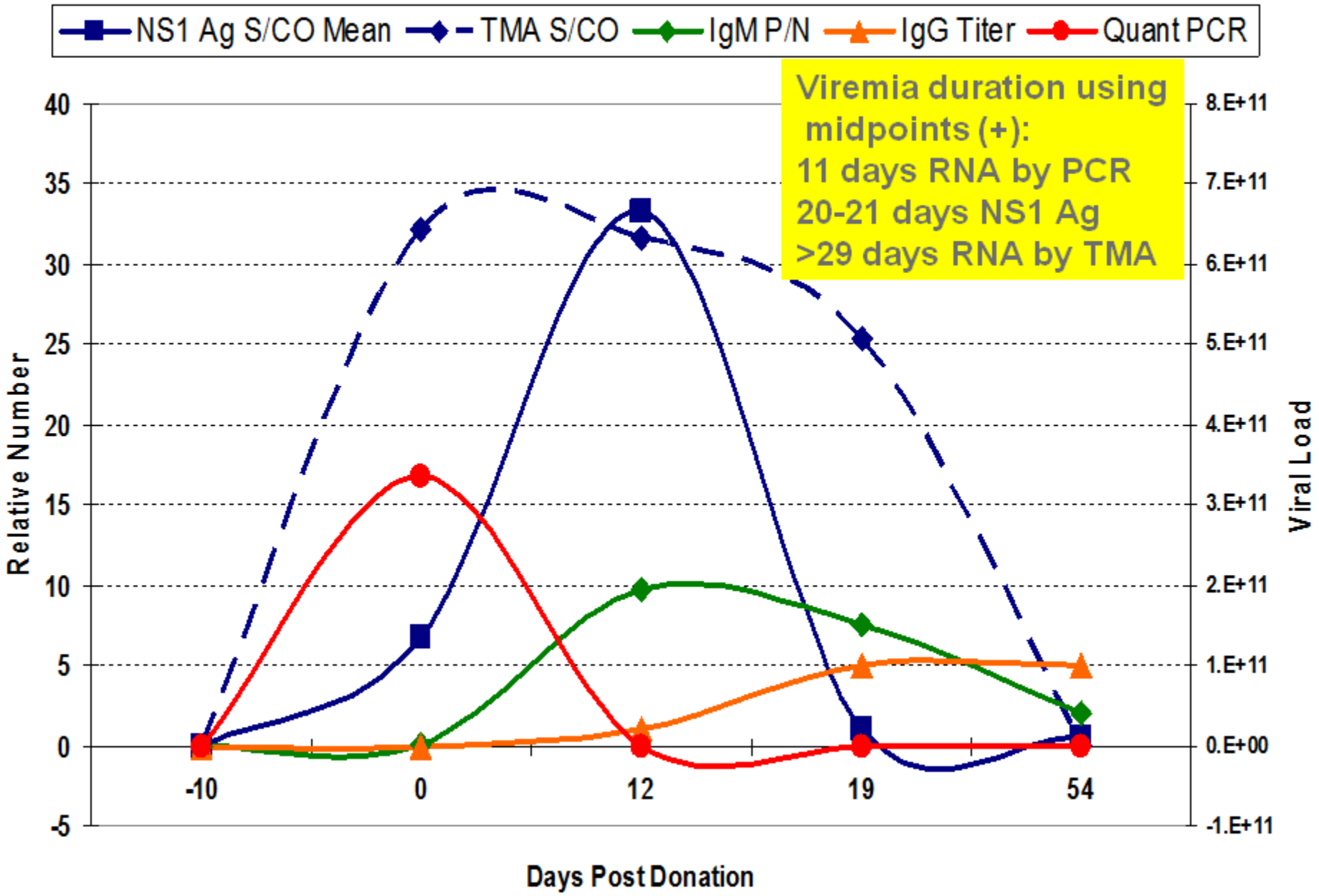
- Examples; WNV, DENV, CHIKV, HAV, HEV
- Virus (RNA) is first marker
- Antigen may follow
- Peaks rapidly
- Declines as symptoms, Ab occur
- Generally non-infectious once IgG is apparent

Acute WNV infection parameters, based on follow-up of 290 infected donors



Busch et al, JID, 2008 and EID 2005

Dengue Seroconverter (DENV-1)



Testing strategy for simple acute infection

- Viral nucleic acid
- Viral antigen
  - Tends to be less sensitive – i.e. detects fewer infectious donations
- Some IgM –positive donations may be infectious, but IgM testing would miss the majority of cases

Simple chronic infection

- Example: Chagas disease, (HTLV)
- Early (childhood) infection
- Few, if any new infections among donors
- Lifelong infection/infectivity
- Coexistence of pathogen and corresponding antibody

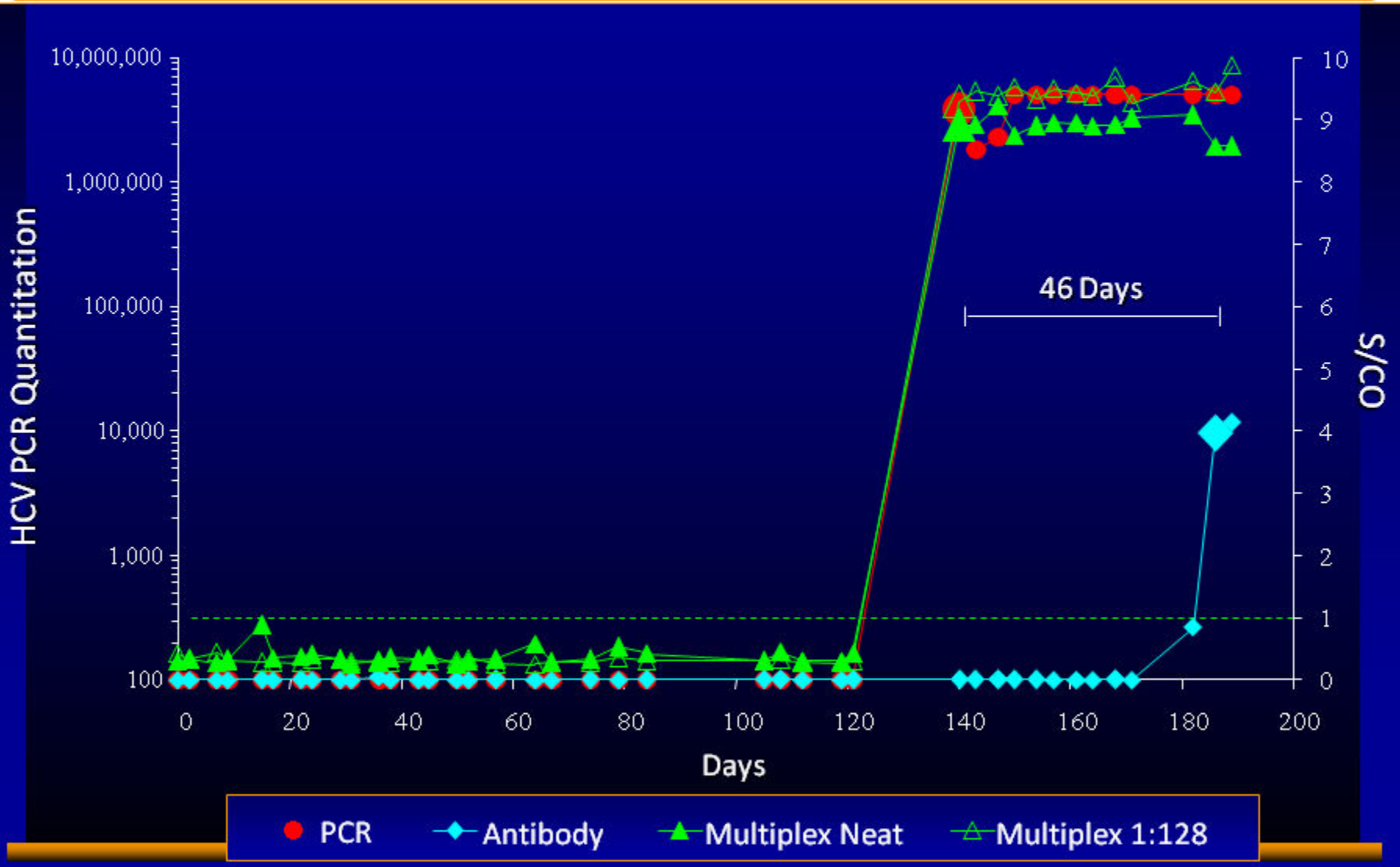
Testing strategy for simple chronic infection

- Direct detection of pathogen
  - Usually not sensitive enough, as levels tend to be low or variable
- Antibody testing
- In the absence of incident cases, one-time testing may be acceptable
  - With adequate data management

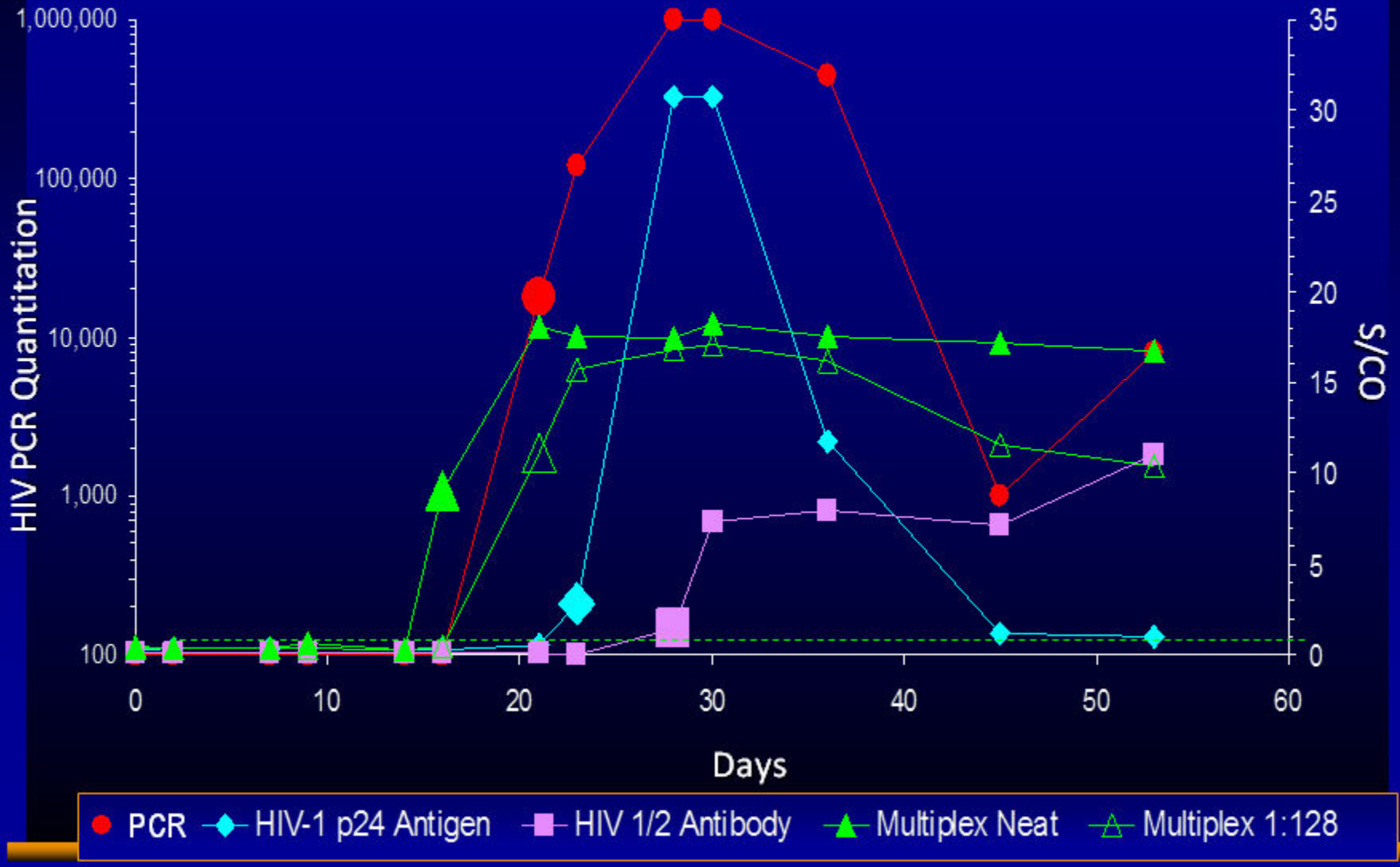
Simple chronic infection with adult incidence

- Examples: HCV, HIV, malaria, babesia
- Early infection asymptomatic, but infectious with "window" in which serologic tests are nonreactive
- Subsequent prolonged infectivity with circulating pathogen
- Most infectious donors can be detected with antibody tests

HCV Panel 6211 – Virologic/Serologic Profile



HIV Panel 6240 – Virologic/Serologic Profile



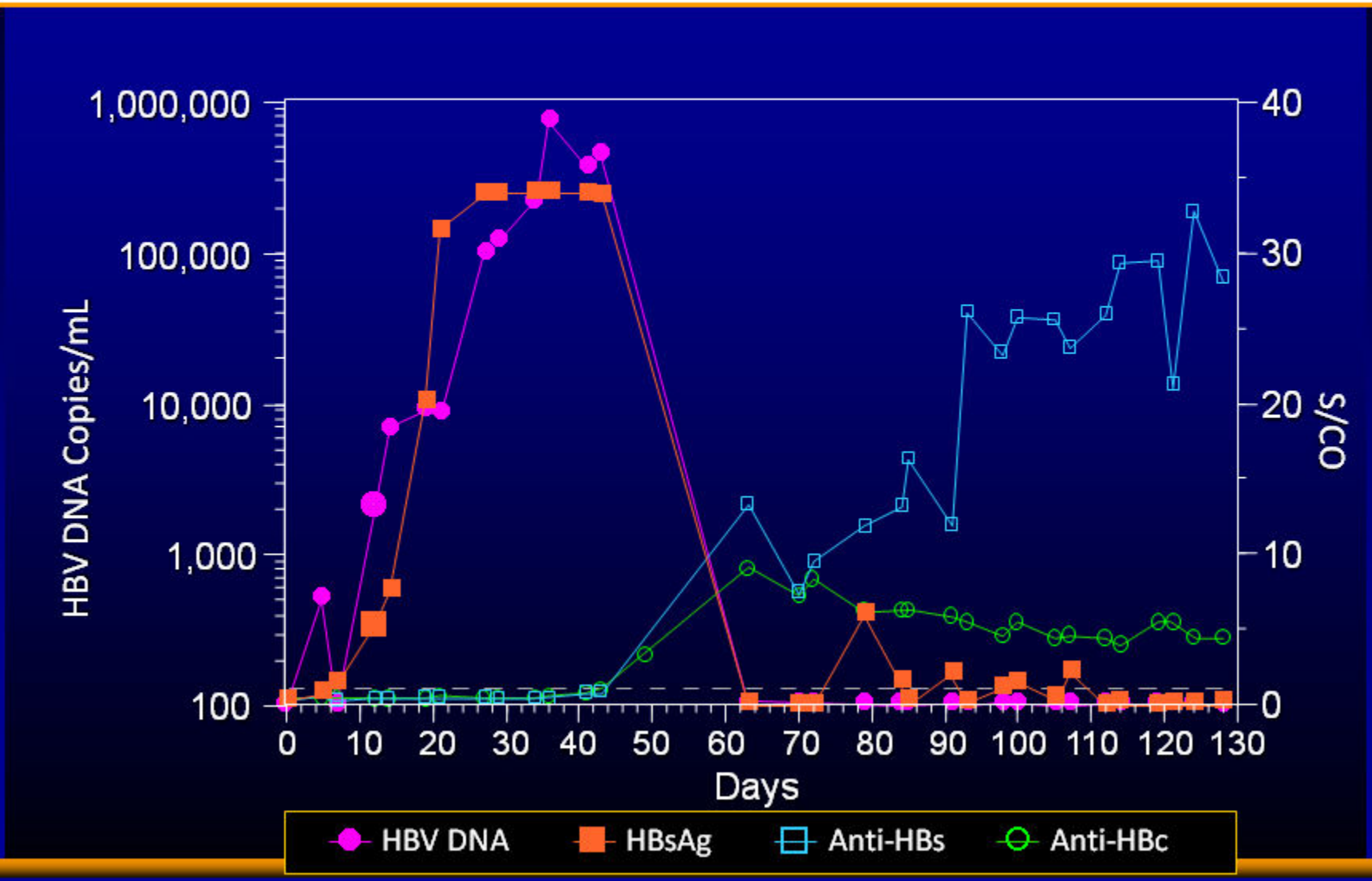
Testing strategy for chronic infection with adult incidence

- The majority of infectious donors will be detected by an antibody test
- Residual infections from window period
  - Improve sensitivity of Ab tests
  - Add Ag detection if appropriate or
  - Add NAT
- NAT alone will not detect all infectious units

Hepatitis B is unusual

- Chronic, with childhood and adult onset
- Overproduction of viral antigen (HBsAg)
- Two key antibodies
  - Anti-HBs – not associated with viral persistence
  - Anti-HBc may signify viral persistence
- DNA tends to parallel HBsAg

HBV Panel 13867
Virologic/Serologic Profile

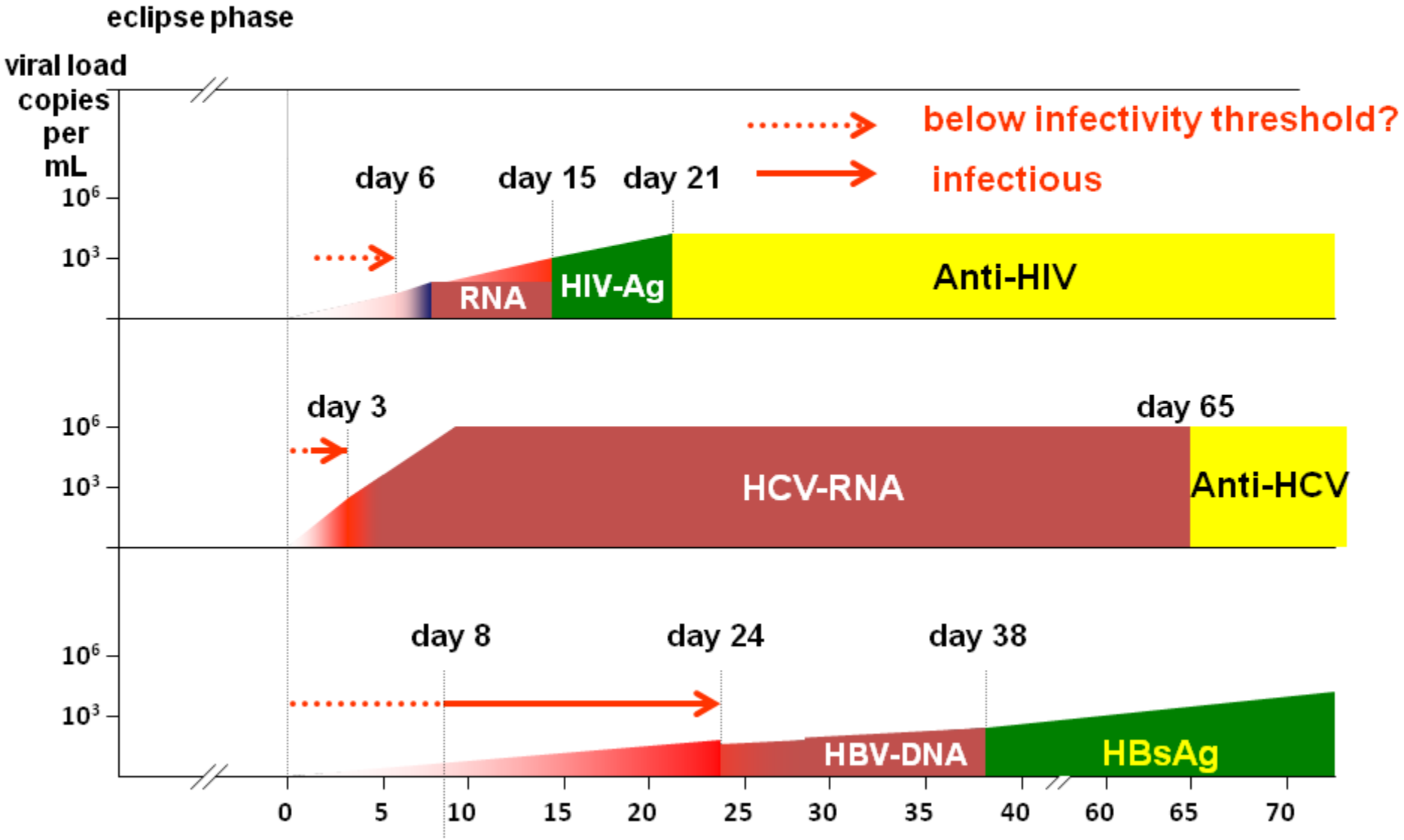


Testing strategy for HBV

- Minimum strategy is to test for HBsAg
  - Identifies the majority of active infections, but not OBI or WP
- Additional testing improves safety
  - Anti-HBc and/or
  - HBV DNA
- Anti-HBc inappropriate for high-prevalence areas

Closing the Infectious Window by NAT

Kleinman, Lelie, Busch; Transfusion 2009;49:2454-89



Infectivity (days) based on 1 infectious copy/20 mL

Test performance characteristics

- Sensitivity
  - Shorten window, minimize false negatives
- Specificity
  - Reduce false positives
- Values should approach 100%
- Should be cited in product insert

Positive predictive value (PPV)

- Proportion of reactive results that are truly positive
- Even a test with high specificity may have a poor PPV when the prevalence is low
  - If test has specificity of 99.8%, then 20/10,000 samples will be false-positive
  - If prevalence of positives is 0.01%, then only 1/10,000 will be true positive
  - PPV will be 1/21= 4.8%!

Confirmatory testing

- Counselling requires accurate information
- Ideally, a different test method should be used for confirmation
- Minimal approach would be a second EIA
- Some methods suffer from generation of “indeterminate” results (e.g. western blot)

How to define risk of TTI

- Risk is the chance that a blood recipient will be transfused with an infectious blood unit
  - A direct function of the proportion of donations that are infectious and the number of units received
  - May be impacted by survival of agent in blood and the susceptibility of the recipient

Assessing the risk of TTI

- Determine frequency of new infection in transfused patients
  - Slow
  - May not be possible because of low frequency
- Estimate from available data
  - Donor populations – prevalence, incidence, window period

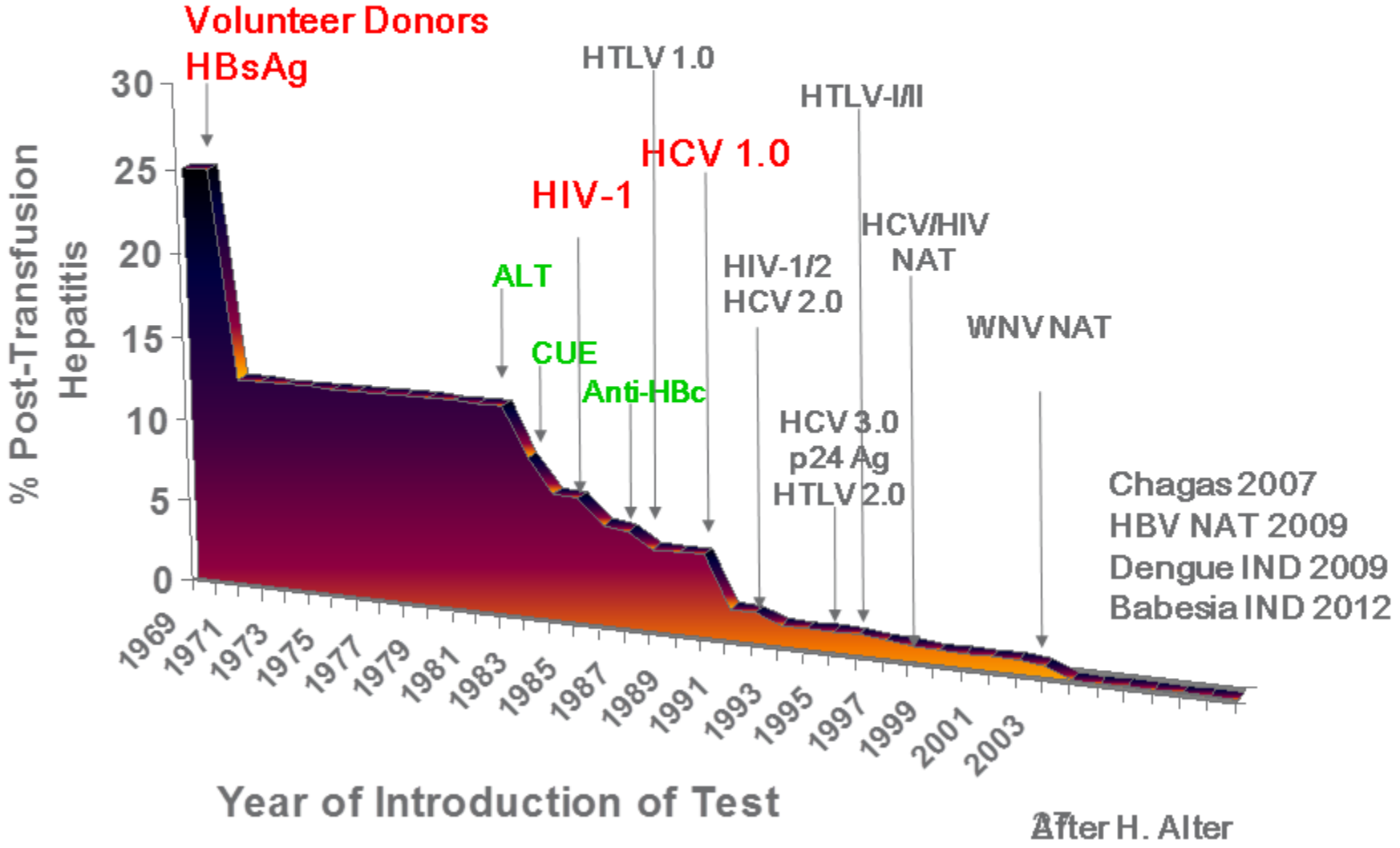
Then: Risks when testing began

American Red Cross System data

Blood Safety in the New Millennium; "Germs, gels, genomes", R. Dodd; AABB Press 2001

Marker	Method	Year	Rate
HBsAg	CEIP	1971	1:855
Anti-HIV-1	EIA	1985	1:2,631
Anti-HCV	EIA	1992	1:222

Transfusion-Transmitted Disease
Post –Transfusion Hepatitis Risk: 1969-2005 observed at NIH



Now: Estimated Incidence and Residual Risk

(ARC estimates; Transfusion: Zou et al., 2009, 2010; Stramer et al., 2013)

Study Period	Agent	Incidence per 10^5 PY	Infectious Window Period (days)	Residual Risk per Donated Unit
2007-2008	HIV	3.1	9.1	1:1,467,000
2007-2008	HCV	5.1	7.4	1:1,149,000
2006-2008	HBV	3.4†	38-30	1:280,000-1:357,000*
2009-2011	HBV	1.6	38-30	1:592,000-1:754,000*
			29.2 - 21.2	1:765,000-1:1,006,000*

PY = Person-Years of observation

†Estimated by two independent methods both based on HBsAg

*Range combines estimates for the HBsAg-negative window period (38 vs 30 days)

HIV Window Period Transmissions in the US: during the 9-day WP (with NAT)

All identified by Lookback

Year	State	Component	No. Pos Recipients
2000	TX	RBC	1
2002	FL	RBC/FFP	1/1
2002	**MD**	RBC/FFP	0/1
2006	**GA**	RBC/FP24	0/1
2008	CO	FFP	1

Thus, in total there were **5 wp donors** from which **6 of 8 recipients** of their products tested HIV pos (2 RBC and 4 FP with 2 RBC testing negative)

Window period risk

- Window period X incidence
  - Window period for key infections is known
- Incidence is the frequency of new infections, per person, per time
  - Can be determined directly for repeat donors
    - Seroconversions per person-year
  - Methods are available for first-time donors but most are relatively complex

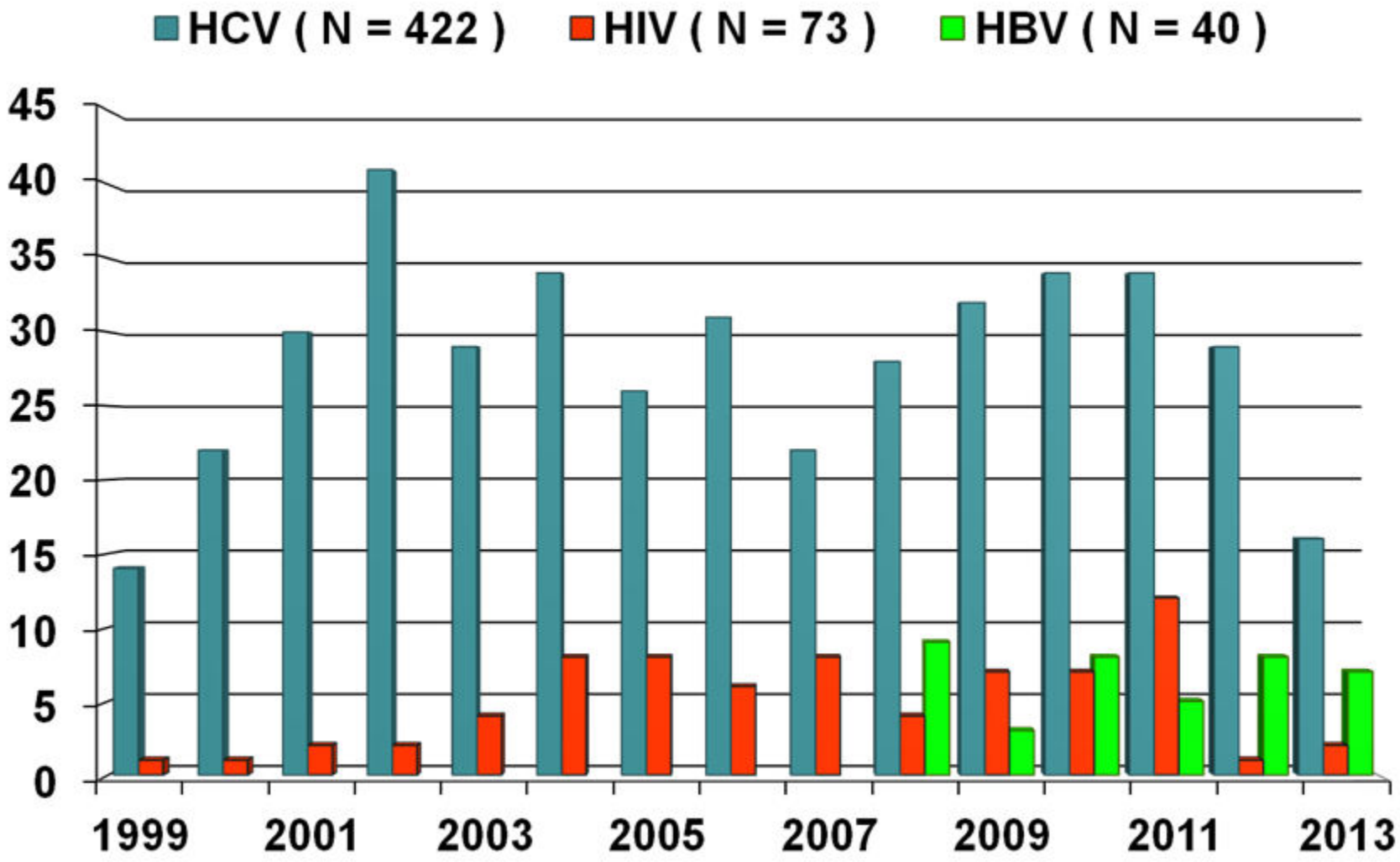
Testing strategies

- Minimum expectations (WHO)
  - Syphilis, anti-HCV, anti-HIV, HBsAg
- Local conditions – endemic infections
  - Chagas in SA, HTLV, malaria, etc
    - Note that some tests may be too wasteful of blood (eg anti-HBc)
- Environment and resources
- Financial
  - Cost-effectiveness

NAT

- Will it have a measurable impact?
- Does the infrastructure support it?
- Could the money be better spent?
- Is there public concern?
- If adopted, are there offsetting economies?
  - No anti-HBc, reduced confirmatory testing, etc

Total Yield Cases by Year, ARC



Approximately 6 million donations per year

Take-home messages

- Testing for ID markers is a vital component of blood safety
- Minimal approach is serologic testing
- Residual risk is a function of window period and incidence
- Additional testing aims to reduce the window period
- Testing should be tailored to local needs and resources