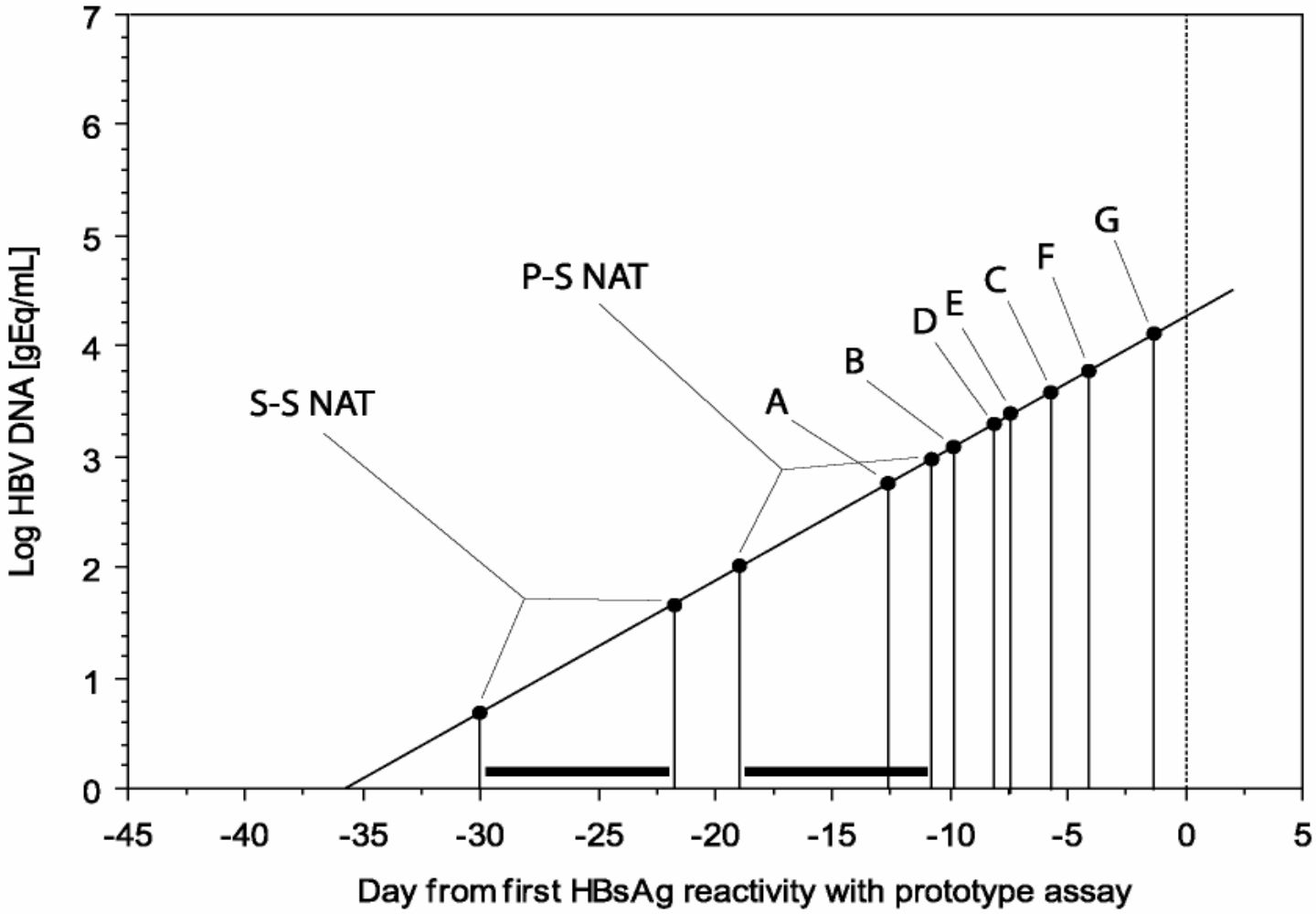
Presentation to ACBSA on HBV NAT

Michael Busch, MD, PhD
Blood Systems Research Institute
August 27, 2004

- Yield and value (cost-effectiveness) of MP and ID-NAT, incl. HBV NAT
- If we implement HBV-NAT:
  - Can we discontinue anti-HBc?
  - Can we discontinue HBsAg?
- What studies are needed?

Estimated WP differences between 7 HBsAg assays (A-G) and Pooled (P-S) vs Single-Sample (S-S) NAT



Biswas et al. FDA/REDS HBV Study

Window Period Reduction (Days) by NAT Assays Compared to HBsAg Assays

HBsAg Assay	Single Unit NAT			Pooled NAT		
	Plasma	WB	WB	Plasma	WB	WB
A	19.8*	19.7*	10.9*	–3.3	2.4	–12.5
B	30.2*	33.0*	23.3*	8.1*	8.2*	0.1
D	31.6*	34.6*	24.6*	8.9*	9.1*	1.3
F	34.0*	36.4*	26.9*	9.8	11.2*	3.0

Positive values represent WP reductions achieved by the use of NAT
*$p<0.05$

Biswas et al. FDA/REDS HBV Study

FDA/REDS study of HBV panels

Benefit of New HBV Detection Methods As Compared to Licensed HBsAg Assays

	WP Reduction in days	Yield/ 10^7 donations
New HBsAg Tests	11 – 15	15 – 21
MP NAT	9 – 11	13 – 15
ID NAT	25 – 36	35 – 50

HBV DNA Concentration and Serological Reactivity

Minegishi K, et al. Vox Sang 84:287-91, 2003

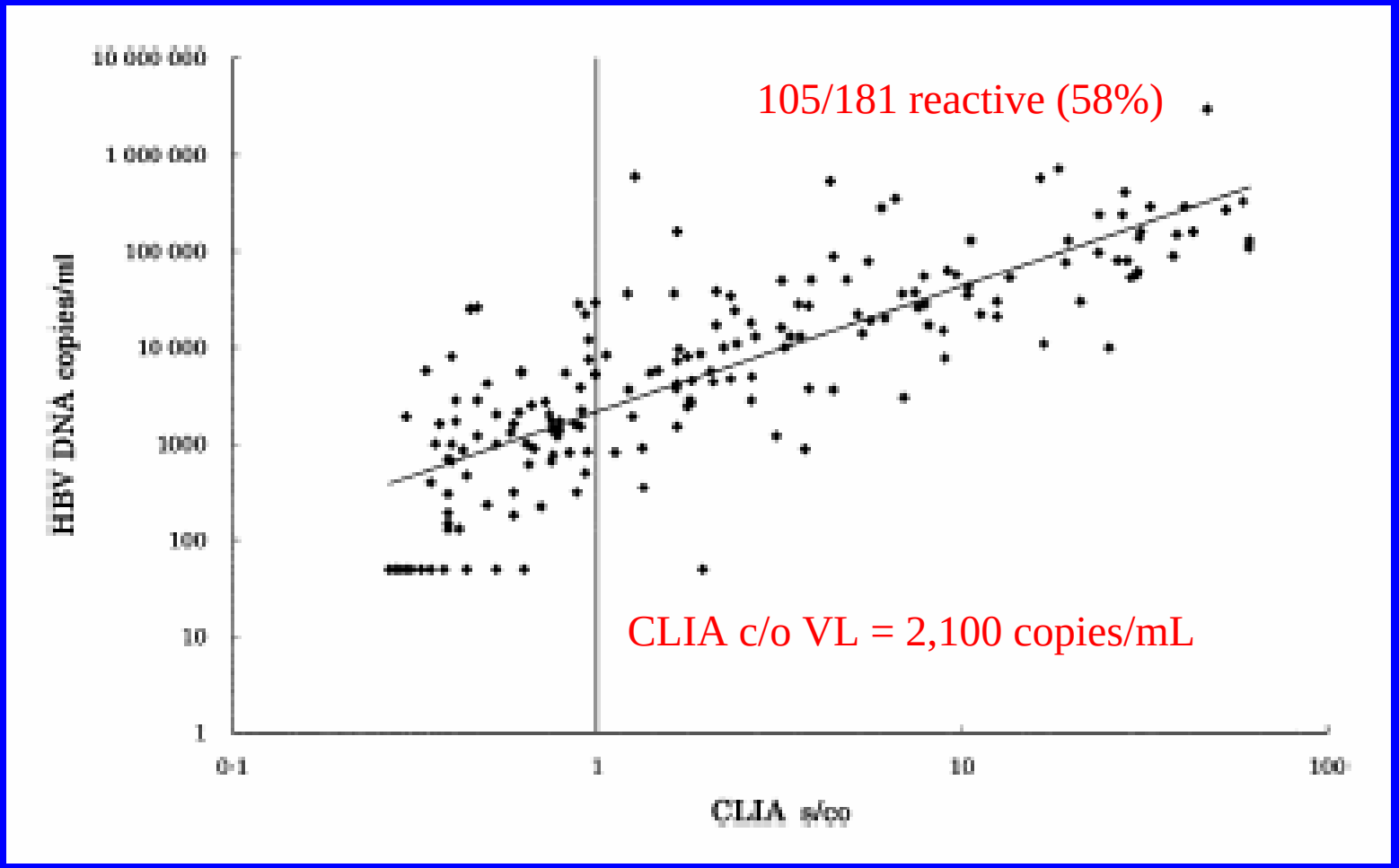
- >11 million donations tested in pools of 50
- Screened by RPHA HBsAg (~13,500 gEq/mL c/o) and anti-HBc
- 181 HBV DNA positive RPHA negative donations found (early phase)

HBV DNA		HBsAg (CLIA)[A]		HBsAg (EIA)[B]	
Copies / mL [C]	No.	Neg (%)	Reactive (%)	Neg (%)	Reactive (%)
$<10^2$	14	13 (93)	1 (7)	14 (100)	0 (0)
10^2 - 10^3	28	24 (86)	4 (14.4)	25 (89)	3 (11) [D]
10^3 - 10^4	59	33 (56)	26 (44	47 (80)	12 (20)
$\geq 10^4$	80	6 (7.5)	74 (92.5)	10 (12.5)	70 (87.5)
Total	181	76 (42)	105 (58)	96 (53)	85 (47)

A. PRISM™
B. Auszyme overnight method
C. HBV DNA quantified by using primers to HBsAg
D. 1 sample CLIA-neg, EIA-pos.

HBV DNA Levels, CLIA S/C Values

Minegishi K, et al. Vox Sang 84:287-91, 2003



NAT Yield in German Red Cross Studies, 1998 - 2002

Roth et al., Transfusion 2003

Virus	NAT only positive	Tested donations (n)	Rate	Yield/ Million
HCV	16	20 566 482	1 : 1 285 405	0,78
HIV-1	5	18 567 943	1 : 3 717 586	0,26
HBV	42 *	18 592 863	1 : 489 676	2,04

*2/3 of HBV DNA pos/HbsAg neg units tested anti-HBc reactive

Summary of WP yield by HBV MP-NAT

	Japan (Minegishi)	Germany (Roth)	U.S. (Roche)
MP size	50	96	24
HBsAg/anti-HBc-neg units screened	11 million	18.6 million	1.2 million
HBV DNA+ units confirmed	76	12	4
Rate of WP units detected	1 in 145,000	1 in 1.5 million	1 in 260,000

Clinical impact of transfusion transmitted HBV

- 50% of recipients do not survive past 3 yrs.
- Estimate of 5% chronic carrier rate in adults; may be lower with low-dose inocula, or in setting of HBV vaccination
- 15-25% of chronic carriers develop significant clinical disease after decades
- 0.25% of transfusion transmissions (1 in 40) will result in chronic carrier state and 1 in 200 in long term disease

Cost-Effectiveness of NAT for HIV, HCV & HBV

Jackson, Busch, Stramer, AuBuchon. Transfusion, 2003

	QALY per Infection Avoided		Infections Avoided per Year (QALYs)		
			Serology to MP		Serology to ID
HIV	7.1		5.0 (35)	56%*	8.9 (63)
HCV	0.60	44x	77 (47)	95%	81 (49)
HBV	0.16	4x	15 (2.3)	23%	64 (10)
Total			(84)		(122)

* - % of ID-NAT yield detected by MP-NAT

Screening Test Costs*

Scenario	Cost
Routine Screening (RS)	$15
RS + MP NAT †	$29-$30
RS + MP NAT – p24†	$26-$27
RS + ID NAT – p24‡	$33-35

*** Based on estimates from BSL, ARC, Chiron Corp.**
† Estimate includes labour, materials and indirect costs.
‡ Estimate based on additional cost of reagents.
$5 per unit cost for adding HBV NAT to HIV/HCV NAT

Cost-effectiveness of adding NAT to serologic testing to detect WP donations

Strategy	Cost-effectiveness [range based on cost ranges]
MP-NAT for HIV/HCV, discontinue HIV p24 Ag	$4.3 million/QALY [2.7-5.8]
SD-NAT for HIV/HCV, discontinue HIV p24 Ag	$7.3 million/QALY [6.2-8.4]
MP-NAT for HIV/HCV/HBV, discontinue HIV p24 and anti-HBc.	$4.9 million/QALY [2.3-8.7]
SD-NAT for HIV/HCV/HBV, discontinue HIV p24 and anti-HBc.	$7.3 million/QALY [5.5-9.9]

Incremental CE of ID over MP-NAT: $15 million/QALY without HBV

$12 million/QALY with HBV

Jackson, Busch, Stramer, AuBuchon. Transfusion, July 03

Screening Test & Disease Cost Offsets

Marshall et al. Vox Sanguinis, 2004

Scenario	Screening Test Costs ($000's)	HBV Costs ($000's)	HCV Costs ($000's)	HIV Costs ($000's)
RS	209,500	14	223	1,574
RS + MP NAT	403,100	12	29	984
RS + MP NAT - p24	363,763	12	29	984
RS + ID NAT – p24	461,063	9	22	688

Incremental Cost Effectiveness

Marshall et al. Vox Sanguinis, 2004

Scenario	Comparator	Incremental Cost (millions)	Incremental QALYs gained*	$/QALY
RS + MP NAT - p24	RS	$155	102	$1.5 million
RS + ID NAT - p24	RS +MP NAT – p24	$97	13	$7.5 million
RS + MP NAT	…	…	…	…

… more expensive strategy with less or equal health benefit (dominated).

"in sensitivity analysis, HBV NAT had minimal benefit ($66 million/QALY) because a large proportion of HBV infections (97.5%) do not progress to a chronic symptomatic state"

Rate of HBV DNA detection in anti-HBc-only U.S. blood donors

Parameter	REDS	ARC	Roche
Sample dates	1991-95	2001	2002-03
No. tested	395	3,000	2,900
No. DNA-pos	4	19	12
Rate:	calculate	direct	direct
per HBc-pos	0.24 %	0.63 %	0.41 %
per tx unit	1:49,000	1:37,000	1:49,000
Viral Load (copies / mL)	all ≤ 100	68 % ≤ 100	92% MP-NAT (-)

Anti-HBc-only units implicated or proven to be the source of transfusion/transplant HBV infections

- Case reports from late 1970s
- Mosley/TTVS (US): 6 probable cases
- Allain (UK): 2 probable transmissions from HBsAg EIA(-), anti-HBc(+) units,
- Matsumoto (Japan): 2 donors to pts with post-tx HBV were HBsAg EIA(-), anti-HBc(+), HBV DNA (+) (one at 400 copies/ml)
- Roth (Germany): probable Tx cases identified from lookback of HBV NAT(+) donor
- Multiple studies of liver transplantation have documented high rates of HBV transmission from HBsAg EIA (-), anti-HBc (+) donors to anti-HBc (-) recipients

Considerations in dropping HBsAg screening after implementation of HBV NAT - Pro

- Combination of highly sensitive direct virus assay and antibody assay *optimal screening paradigm* for major TT pathogens with acute and chronic infection phases (HIV, HCV, HBV)

- HBsAg and HBV NAT are both direct viral detection assays, therefore may be redundant

- HBV NAT is more sensitive than HBsAg for detection of infectious virus during acute phase

Considerations in dropping HBsAg screening after implementation of HBV NAT - Con

- Unusual biology of HBV chronic infection - excess HBsAg production - results in situations where HBsAg detects "chronic infections" missed by MP-NAT and even ID-NAT

- To assure no incremental risk, MP- and ID-NAT must be rigorously compared to HBsAg using donor samples from different stages of infection and epidemiological settings:
  - WP (anti-HBc-) and chronic (anti-HBc+) stages
  - Populations with varying HBV endemnicity and routes of exposure (perinatal, sexual, IDU)
  - Vaccinated populations (vaccine breakthrough infections)
  - Populations with divergent HBV genotypes and mutant strains

HBV Viremia in HBsAg+/anti-HBc+ blood donors

Kuhns, Kleinman, McNamara, Rawal, Glynn, Busch. Transfusion, in press

200 HBsAg+/anti-HBc+ REDS donations

↓ *Roche HBV Monitor Assay*

128 DNA pos. w/ quant VL (72 DNA neg. [< 400 copies/ml])
(64% viremia)

↓ *(low input vol. research PCR)*

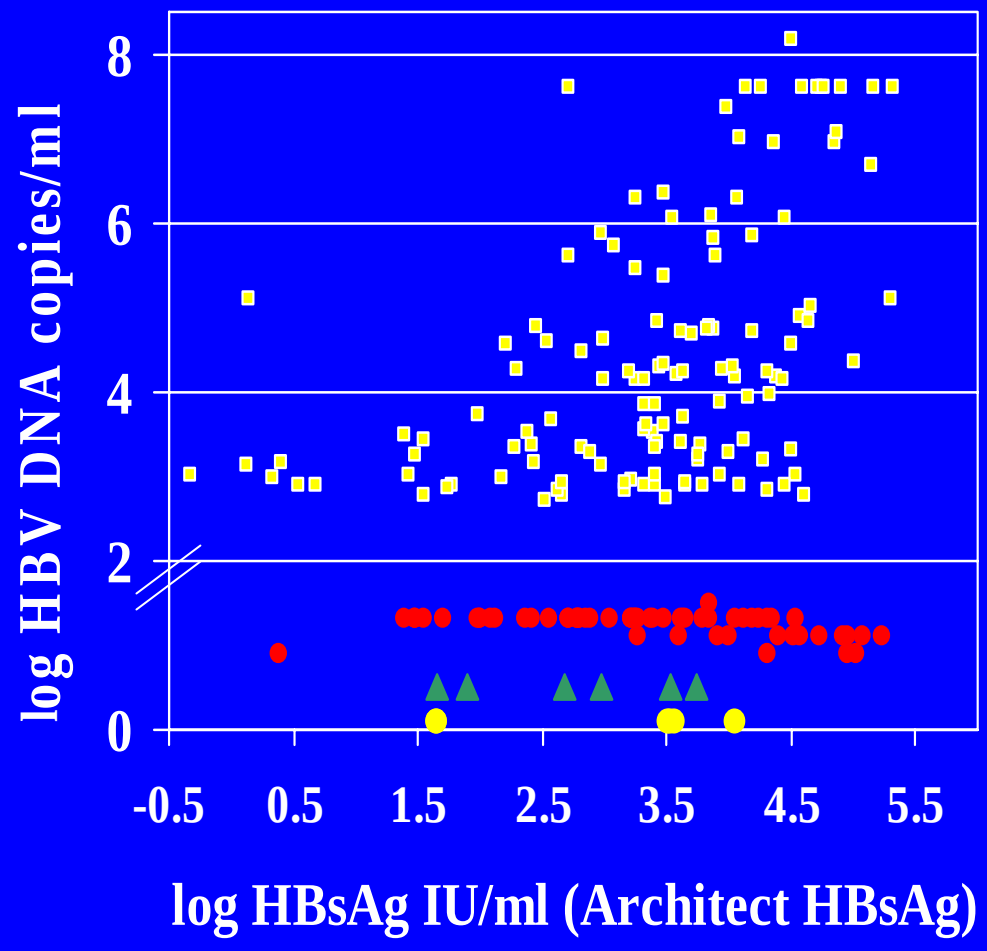
60 HBV DNA pos. (12 HBV DNA neg. [<65 copies/ml])
(94% viremia)

↓ *(high input vol.research PCR)*

6 HBV DNA pos. (6 HBV DNA neg.[<1.3 copies/ml])
(97% viremia)

HBV DNA relative to HBsAg in "chronic carriers"

Kuhns et al. Transfusion, in press



Correlation coefficient = 0.33

}<Amplicor LOD

● , Amplicor negative but positive by the standard PCR assay

Δ , negative by both Amplicor and standard PCR assay but positive by enhanced PCR

● , negative by all three NAT assays; all 3 units anti-HBc IgM- and anti-Hbe+

Detection of HBV DNA in HBsAg (+) donations lacking anti-HBc

- 2-5% of HBsAg (+) U.S. donors lack anti-HBc
- Most of these units contain high levels of HBV DNA and represent acute HBV infections
- But a small proportion test HBV DNA negative
  - True HBV infection
    - mutant not detected by NAT
    - Failure to develop detectable anti-HBc
  - Lab contamination (HBsAg carryover)
  - Biological false positive (persistent non-specific HBsAg reactivity)
  - Recent vaccine recipient

HBsAg+, anti-HBc- donors lacking HBV DNA

- **Japan - Sato et al. Transfusion 2001; 41:1107-1113**
  - 3/65 HBsAg+/anti-HBc- donors PCR+ only with enhanced sensitivity PCR (1 ml, nested PCR, core primers)
  - no history of vaccination
  - no anti-HBc SC or change in PCR reactivity after >1 year follow-up
- **France - Leperche et al. Vox Sang. 2001 Feb; 80(2):90-4**
  - 2 FT donors from Africa (0.1% of HBsAg+ donors)
  - persistent HBsAg w/o anti-HBc and very low-level HBV DNA
  - no vaccination or immunosuppression
  - no mutations in pre-C or C regions
- **U.S. - REDS unpublished data**
  - 20 HBsAg+ (Auszyme, PRISM, Architect) but anti-HBc- units
  - 16 DNA+ by Amplicor or Abbott "standard" PCR assays
  - 4 negative by Amplicor and Abbott "standard" PCR
    - 3 negative for HBeAg/anti-HBe (carryover HBsAg or early SC)
    - 1 anti-HBe(+) could represent atypical chronic carrier
    - no donor follow-up

Conclusions

- HBV MP-NAT will offer very small yield and clinical benefit, and is unlikely to allow discontinuation of either anti-HBc or HBsAg screening

- HBV ID-NAT may allow discontinuation of HBsAg (or less likely anti-HBc) screening, but only after large scale studies to assure no incremental risk
  - Parallel testing to acquire units of plasma for lab and chimp infectivity studies for following marker categories:
    - HBsAg-, anti-HBc+, HBV DNA+/-
    - HBsAg+, anti-HBc+, HBV DNA-
    - HBsAg+, anti-HBc-, HBV DNA- or +/-
      - for last category, follow-up of donors critical to rule out contamination and establish persistence and biological basis anti-HBc- chronic carrier state