

Should the HBV testing strategy be dependent on the geographical region?

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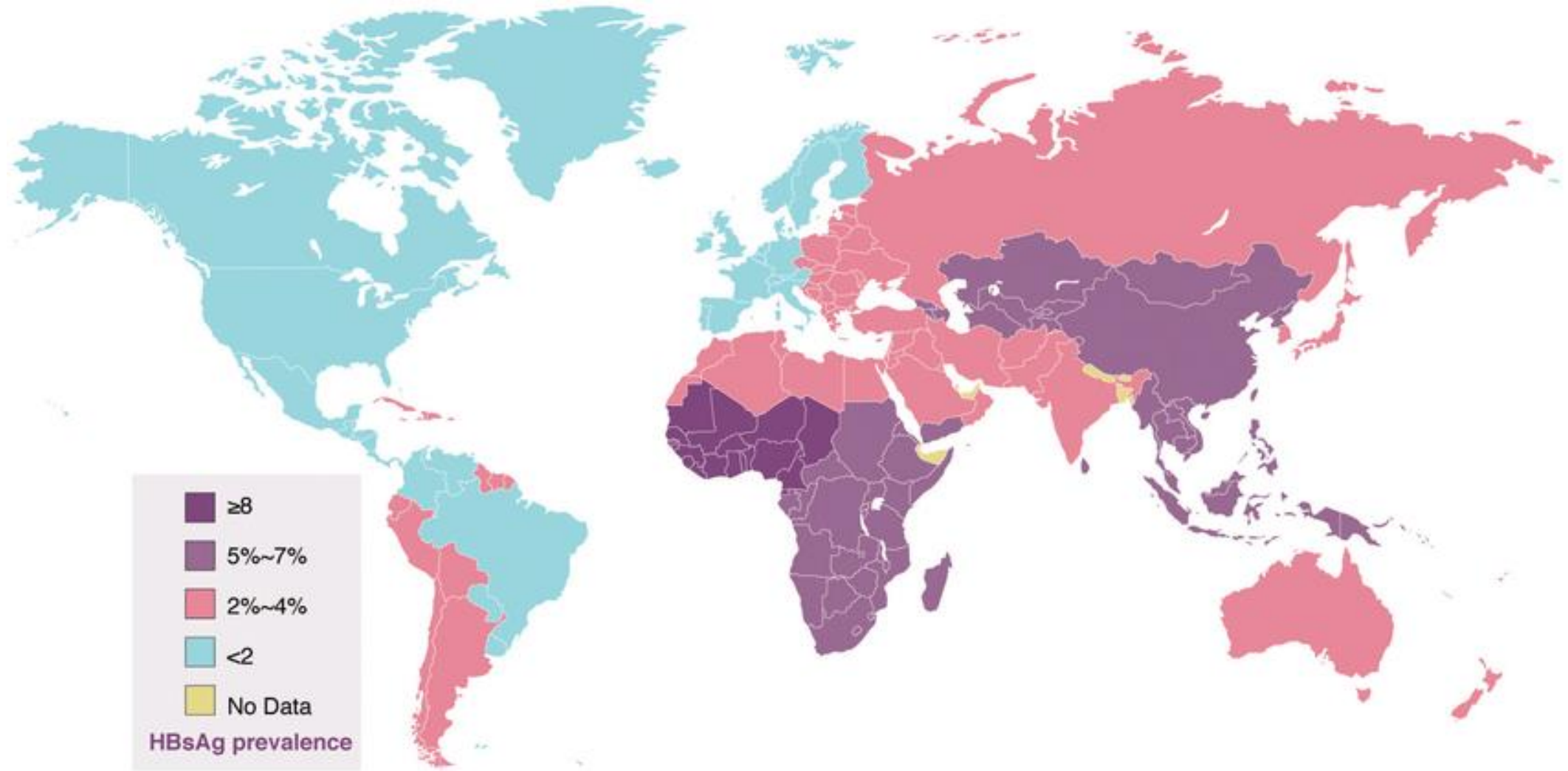
**Should the HBV testing strategy be
dependent on the geographical
region?**

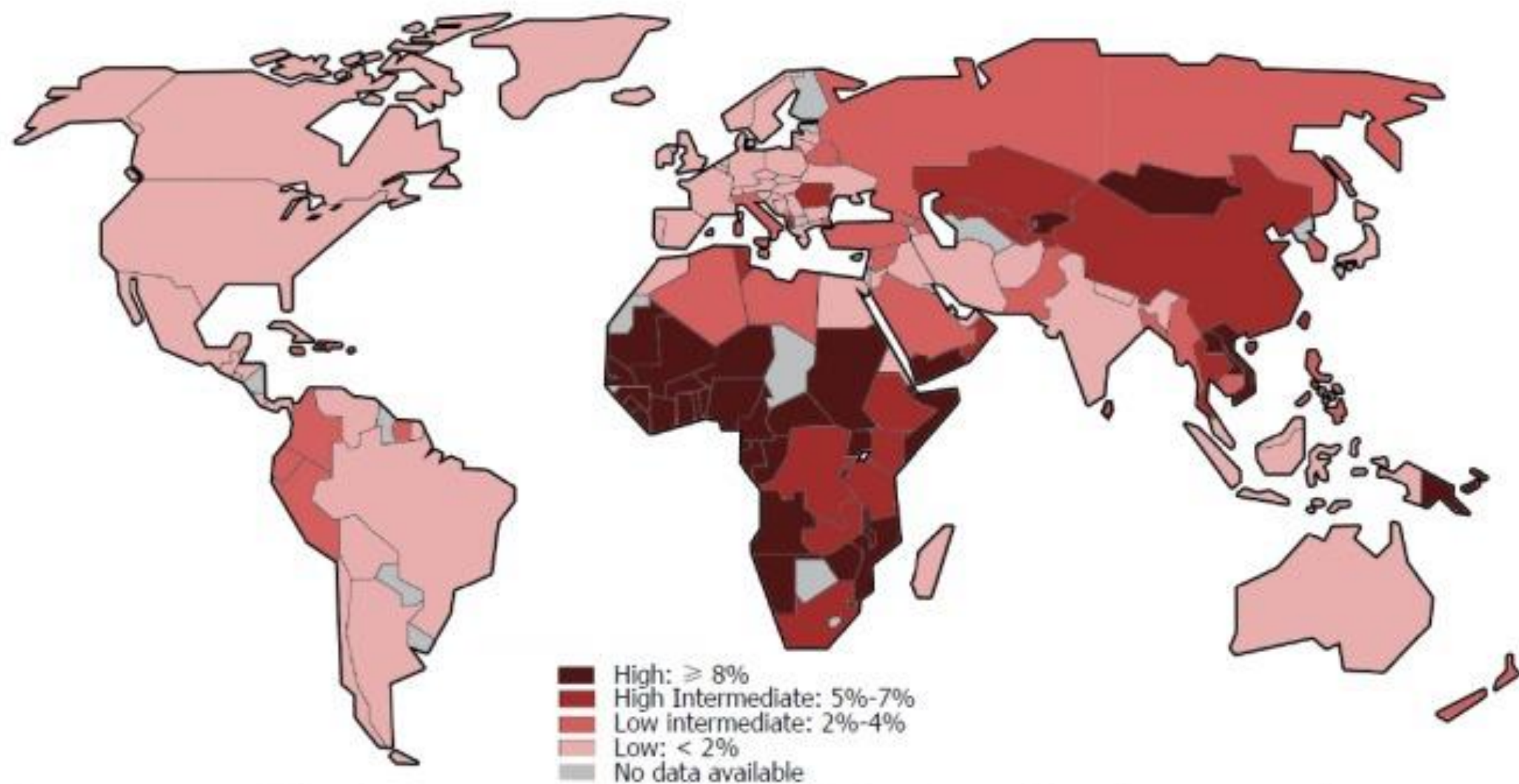
NO

YES

MAYBE

Global prevalence of chronic HBV infection in adults
U.S. Centers for Diseases Control and Prevention, 2010
350 million global infections



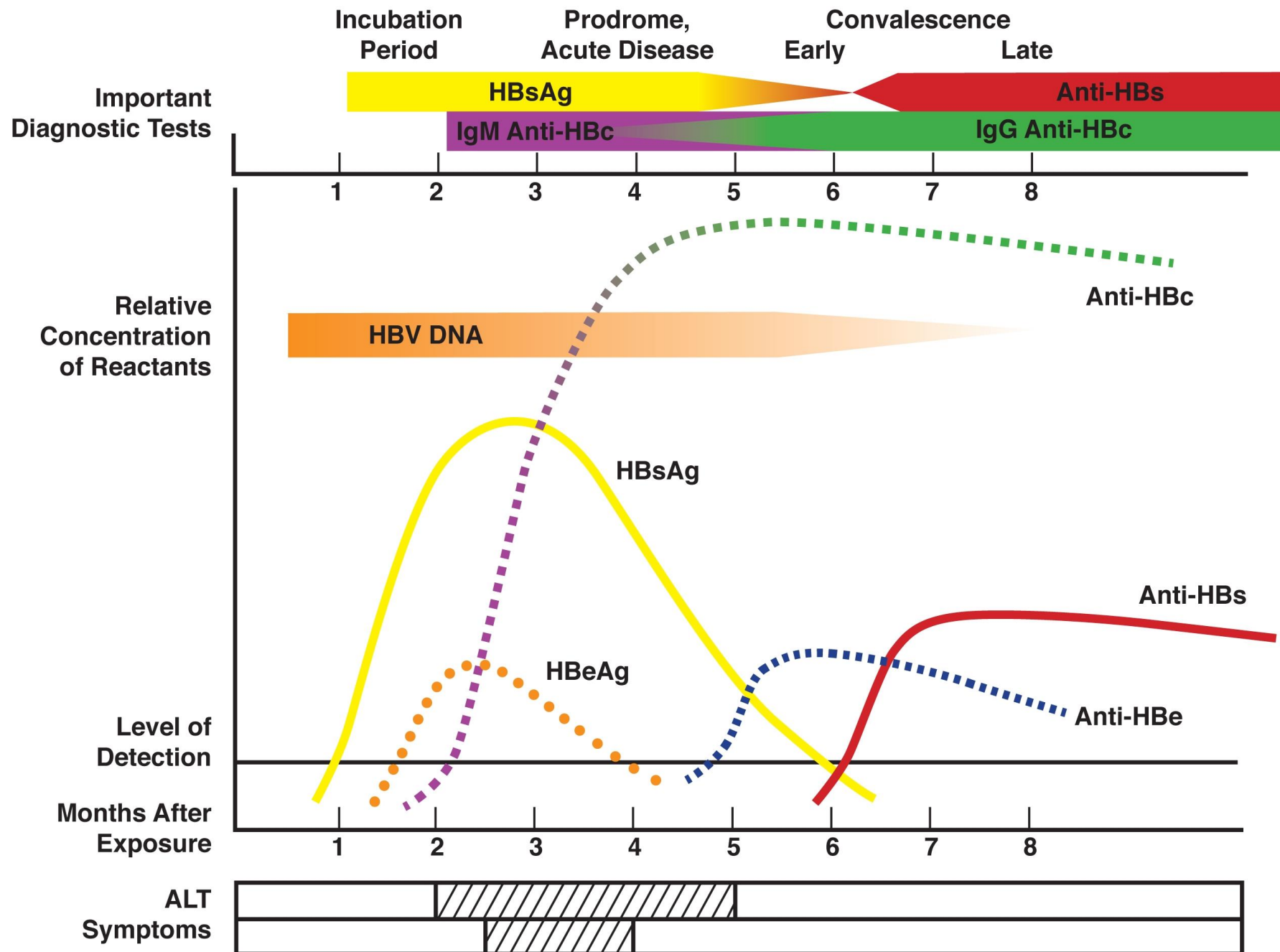


Source: Schweitzer A, Horn J, Mikolajczyk R, Krause G, Ott J. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *The Lancet*. 2015 Jul 28; 386(10003): 1546-1555.

Hepatitis B prevalence

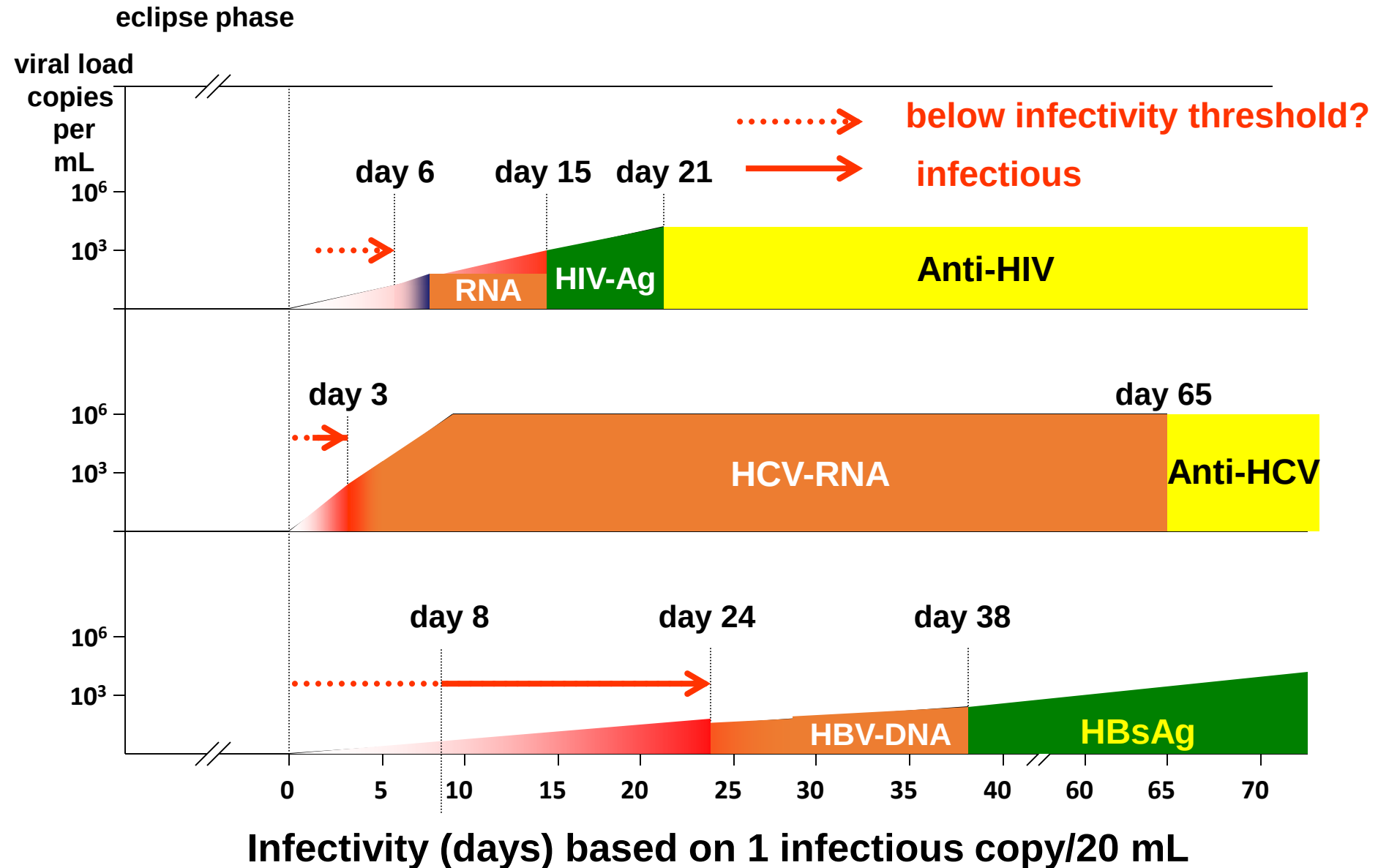
Considerations

- Regional epidemiology (chronic HBV):
 - Assume frequency of chronic HBV parallels that of incident infection (infected source without effective use of mitigations)
 - High (sub-Saharan Africa, SE Asia)
 - Moderate (North Africa, Middle East, rest of Asia, parts of S America)
 - Low (Europe [for the most part], N, Central and parts of S America, Australia)
- Interventions available (resource dependent/availability variable by geography):
 - Vaccination; genotype specific (e.g., US [A2] first available in 1981; plasma-derived => recombinant; now combined with HAV)
 - Testing for blood safety
 - Incident/acute infection (HBV DNA, HBsAg)
 - Chronic/resolved infection (anti-HBc, anti-HBs determines protection)
 - Inactivation
 - Combination of above



Closing the Infectious Window by NAT

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



Testing by Region - Europe

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- France

- HBsAg since 1971, anti-HBc since 1988, ID-NAT since 2005 (**Ultrio => Ultrio Plus**); anti-HBc reactives with anti-HBs >500 IU/mL => fractionation
- HBV-pos donations further tested by HBV diagnostic tests and viral loads
- **NAT 95% LOD: 10.4 IU/mL and 3.4 IU/mL; confirmation by cobas TaqScreen, 95% LOD 4.8 IU/mL**
- NAT yield: **1:975,000 (excludes OBI)**
- Donation samples archived for 3 years and tested when a seroconversion is identified; recipients tested in case of positivity
- Pre- and post-NAT residual risks: **1:1.1 million pre- and 1:4.1 million post**
- No TT-HBV cases since NAT

Testing by Region - Europe

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- England
 - HBsAg, no anti-HBc, MP-NAT since 2009 (**MPs of 24; cobas MPX on the 6800/8800**)
 - HBV-pos donations further tested by HBV diagnostic tests and viral loads
 - **NAT 95% LOD: 1.4 IU/mL; confirmation by Ultrio Elite, 95% LOD 4.3 IU/mL (if neg, repeat with sample concentration)**
 - NAT yield: **1:660,000 (18/27 OBI)**
 - Donation samples archived for a minimum of 3 years; if DNA pos => lookback
 - Pre- and post-NAT residual risks: **1:971,000 pre- and 1:2.1 million post**
 - 2 probable TT-HBV cases since NAT (probable => genotyping couldn't be done; SHOT)
 - 2011 WP – FFP recipient developed clinical hepatitis; LB revealed RBC co-component recipient also with clinical hepatitis; archived donor sample ID-PCR pos by 1 of 2 tests
 - 2012 OBI – RBC recipient developed clinical hepatitis; archived donor sample anti-HBc pos

Testing by Region - Europe

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Ireland
 - HBsAg since 1973, anti-HBc since 2002, ID-NAT since 2009 (**Ultrio => Ultrio Plus**)
 - HBV-pos donations further tested by HBV diagnostic tests and viral loads
 - Donation samples archived; lookback for all repeat donors (none for OBI since all in FT donors)
 - Pre- and post-NAT residual risks: **1:892,000 pre- and 1:2.1 million post**
 - 1 TT-HBV cases since NAT (WP); ID-NAT neg, but disc HBV pos in archived sample; donor and recipient had identical C2 sequences
- Spain
 - HBsAg, no anti-HBc; ID-NAT since 2007 (**Ultrio**) (*Catalonia*)
 - NAT-yield donations tested by 5-rep Ultrio; PCR with 9.6mL enrichment
 - Donation samples archived (but < 1mL); lookback performed including OBI with 0 yield
 - NAT yield: **1:14,000 (OBI)**
 - Pre- and post-NAT residual risks: **1:74,000 pre- and 1:200,000 post**
 - 3 TT-HBV cases, 2 since 2005 (both OBI)

Testing by Region - Europe

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Poland

- HBsAg, no anti-HBc, NAT since 2005
 - **Ampliscreen (MPs 24) TaqScreen MPX (MPs 6) => TaqScreen v2 (MPs 6) => Ultrio => Ultrio Plus => Ultrio Elite**
- NAT yield donations tested by 2- or 3-reps (dHBV or GFE-Blut) to sensitivity of < 1IU/mL, anti-HBc and anti-HBs
- NAT yield: **1:130,000** (all OBI)
- Donation samples archived; 6-month lookback if ID-NAT pos
- Post-NAT residual risk (OBI): **1:172,000-1:769,000**; varies by component; WP: **1:6 million**
- No TT-HBV cases based on recipient HBsAg or DNA positivity; other recipients infected from OBI donors previously described

- Germany

- HBsAg, anti-HBc mandated in 2006, MP-NAT since 1996 (voluntary), **MPs 96 at a sensitivity of 98.4 IU/mL (GFE Blut)**
- NAT-yield donations tested in reps 3 and sequenced
- Anti-HBc RRs tested for anti-HBs
- Donation samples archived; recipient is tested if ID-NAT pos
- NAT yield: **1:1.14 million**; OBI yield: **1:1.15 million**
- Post-NAT residual risk: **1:360,000**
- 2 TT-HBV cases due to OBI prior to anti-HBc testing

Testing by Region - Africa

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Egypt
 - HBsAg, ID-NAT since 2007 (**Ultrio => Ultrio Plus => Ultrio Elite**)
 - NAT-pos tested by anti-HBc
 - Most donors FT
 - Donation samples archived; no lookback
 - No hemovigilance system
- South Africa (*SANBS*)
 - HBsAg, ID-NAT since 2005 (**Ultrio => Ultrio Plus => Ultrio Elite**)
 - NAT-pos further tested for HBV markers including replicate dHBV
 - NAT yield: **1:20,000** (1st 4 years); acute NAT yield: **1:26,000** (back-end WP yield +anti-HBc: **1:84,000**)
 - No archive; lookback performed including for OBI donors
 - Post-NAT residual risk: **1:40,000** (estimated that 6.5% of OBI infectious)
 - TT-HBV cases: 1 WP (1:2.9 million) and 1 OBI (identified by lookback); both from RBCs with low viral loads (~30 copies [virions]/dose)

Testing by Region - Asia

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

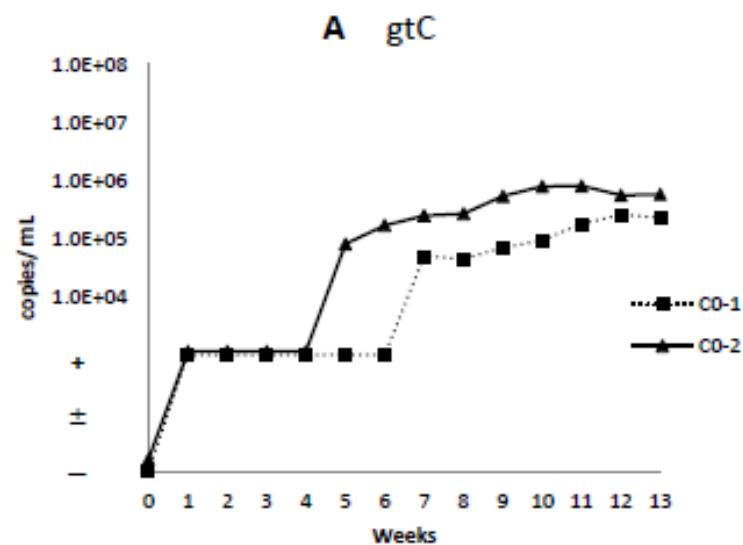
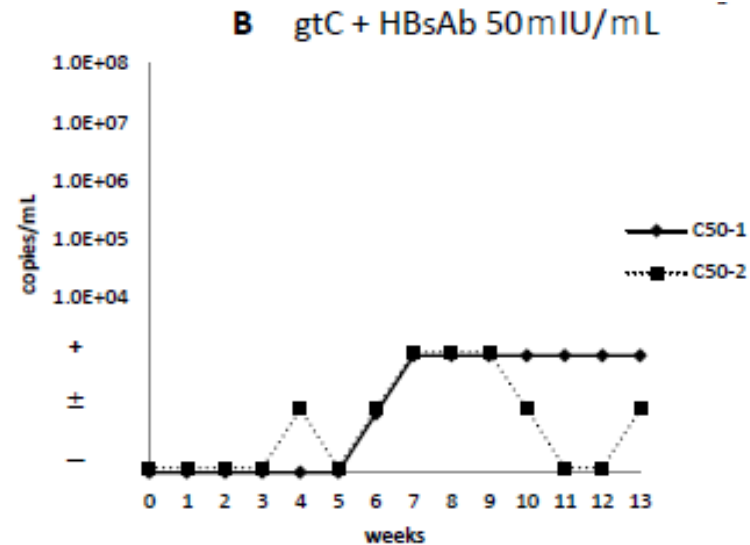
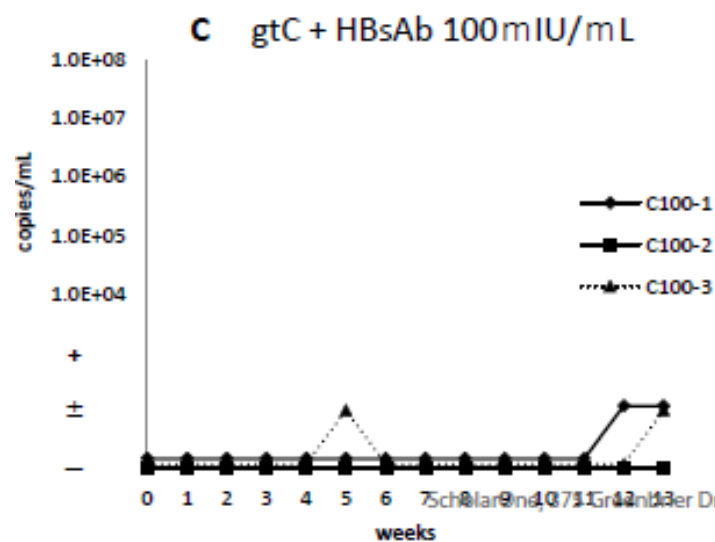
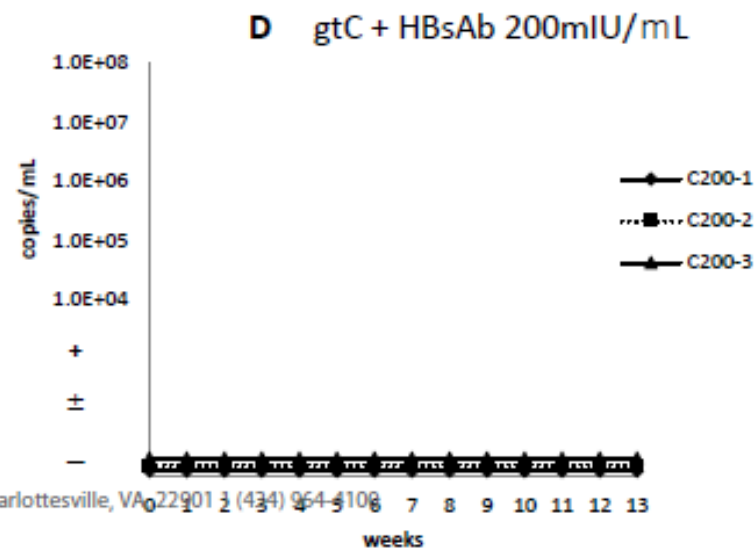
- Korea
 - HBsAg and ID-NAT (**Ultrio Plus**) since 2012
 - No screening for anti-HBc (background prevalence >10%)
 - Majority of NAT yield cases are OBI (75%)
 - Further testing to confirm NAT yield
 - NAT yield: **1:8800 (overall)**
 - Donation samples archived for 10 years and tested once a DNA-pos donor is identified; recipients tested in case of positivity
 - Pre-NAT residual risks (no post data): **1:45,000**
 - Last TT-HBV case 1999
- Hong Kong
 - Universal neonatal HBV vaccination in 1988 reduced FT donor HBsAg rates from 8% in 1990 to 1.2% in 2010; OBI common in donors >35 years old
 - HBsAg and ID-NAT (**Ultrio => Ultrio Plus**) since 2007
 - No screening for anti-HBc (background prevalence >10%)
 - HBV-pos donations further tested by HBV diagnostic tests and viral loads
 - Donation samples archived, but no lookback due to high endemicity
 - Pre- and post-NAT residual risks: **1:22,000 pre- and 1:52,000 post**
 - No TT-HBV reported since NAT

Testing by Region - Asia

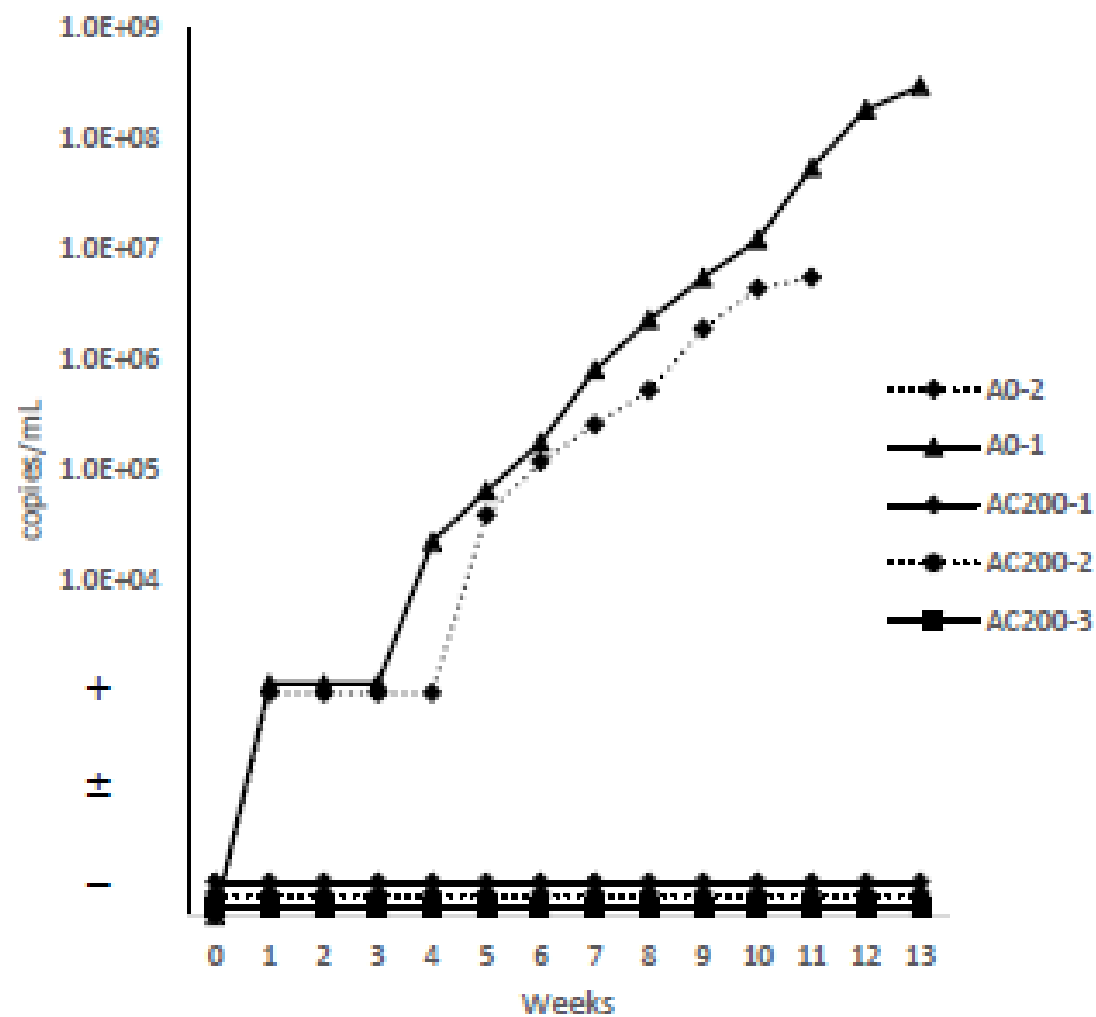
(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Japan

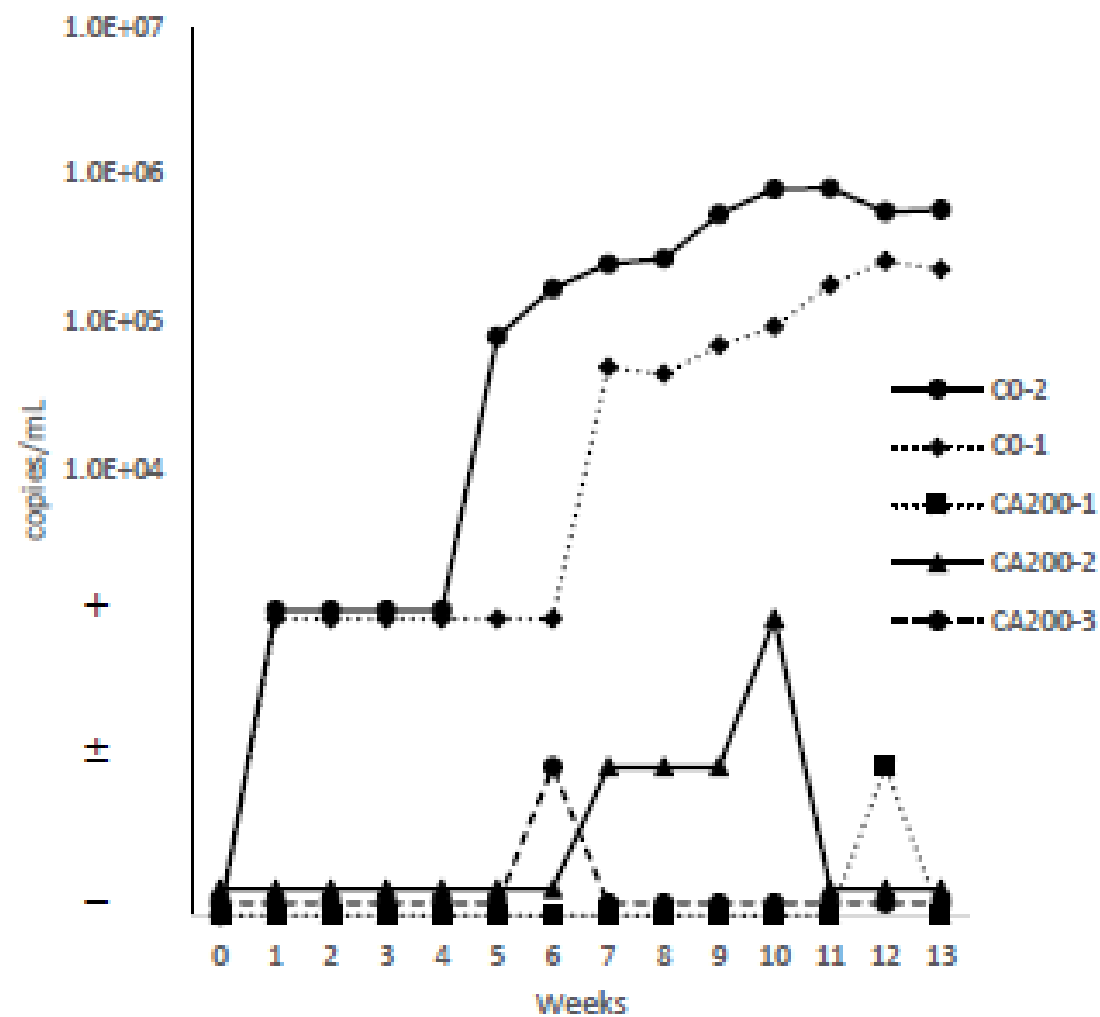
- HBsAg, anti-HBc and anti-HBs since 1989; PA => chemiluminescence since 2008; and NAT in various iterations
 - NAT implemented in MPs of 500 (1999) => 50 (2000) => 20 (2004) => ID-NAT using the Ultrio Elite (2014)
 - Unpublished results using 20-sample MP (cobas s401), 2008-2012
 - **NAT 95% LOD: 18.6 IU/mL (372 IU/mL MPs 20)**
 - High-titer anti-HBc (S/CO ≥ 12) + low titer anti-HBs (<200 mIU/mL) reactive donors rejected
 - Low-titer anti-HBc or high-titer anti-HBs accepted (≥ 200 mIU/mL); >100 mIU/mL “safe”
 - Variability in anti-HBs assays; 200 mIU/mL provides additional safety threshold
 - 23 cases of TT-HBV from anti-HBc reactive donors (15/23 <10mIU/mL anti-HBs; none from ≥ 200)
 - Anti-HBc cutoff reduced (S/CO ≥ 12 to 1) in 2012
 - Anti-HBs (≥ 200 mIU/mL) protective in SCID mice (human hepatocyte-repopulated) even with 10^5 HBV DNA copies/mL
 - HBV vaccination effective between HBV genotypes A and C (C=>A total inhibition; A=> lesser)
- No further testing to confirm NAT yield
- *Donation samples archived for 10 years; lookback*
- ID-NAT residual risk (2008-2012): **1:710,000**
- No TT-HBV case since August 2012



A gtA HBV + gtC anti-HBs



B gtC HBV + gtA anti-HBs



Testing by Region – Australia

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Australia
 - HBsAg and ID-NAT since 2010 (**Ultrio => Ultrio Plus**); selective anti-HBc screening for history of hepatitis or HBsAg/NAT yield or NAT non-discriminated (anti-HBc background 2% of population)
 - Further testing to confirm NAT yield
 - Donation samples archived (*5 years in New Zealand*); lookback for non-OBI (OBI LB limited: “unnecessary based on low-risk donations” as anti-HBs ≥ 10 mIU/mL and HBV DNA neg)
 - Pre- and post-NAT residual risks: **1:664,000 pre- and 1:8.5 million post** based on TTB (below); **1:1.1 million minus NAT and 1:3.2 million with NAT based on modeling (2015-2016)**
 - 2 probable TT-HBV cases pre-NAT (2003), both from same OBI donor
 - 1 probable TT-HBV case post-NAT, also OBI

Testing by Region – S America

(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Brazil
 - HBsAg and anti-HBc mandated; NAT since 2016 (multiple methods)
 - One private large hospital (*Sirio Libanes*) implemented universal plasma/platelet pathogen inactivation (INTERCEPT)
 - ID-NAT (cobas MPX 2.0); 95% LOD 2.3 IU/mL
 - NAT yield donations further tested by HBV diagnostic testing and viral loads (not universal; med director discretion)
 - Overall NAT yield: 1:100,000; OBI yield: 1:43,000 (14/20 OBI)
 - Donation samples archived for 6 months; lookback mandatory for 6 months prior to last seronegative
 - No residual risk data
 - One TT-HBV case from an OBI donor in 2015 (prior to NAT; impetus for NAT implementation); none since NAT (>600,000 donations tested)

Testing by Region – N America

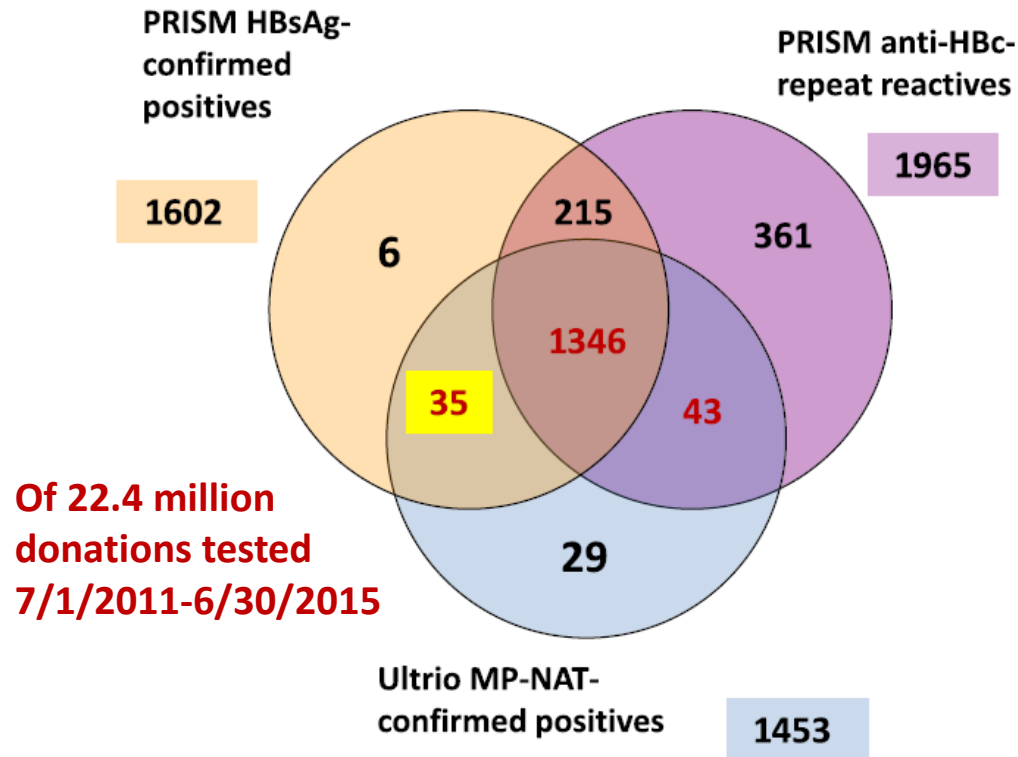
(as summarized by Seed et al., International Forum on OBI and Transfusion Safety)

- Canada
 - HBsAg and anti-HBc; MP-NAT since 2010-11 (**CBS: MPs of 6; cobas MPX 1.0, 2.0 and cobas MPX on the 6800/8800; HQ: converted to MP 16 Ultrio => UP**)
 - Further testing to confirm NAT yield
 - No donation sample archives; lookback required (prior 5 years)
 - Pre- and post-NAT residual risks: **1:1.7 million pre- and 1:7.5 million post**
 - 2 probable TT-HBV cases pre-NAT (2003); none post NAT
- United States
 - Mandated neonatal and high risk vaccination since 1990s (vaccine first available 1981)
 - HBsAg and anti-HBc; MP-NAT since 1999; **MPs 16 (Ultrio => Ultrio Plus => Ultrio Elite) and MPs 6 (Ampliscreen => TaqScreen => cobas MPX on the 6800/8800)**
 - Variable additional testing other than HBsAg neutralization and alternate NAT for potential yields; ARC performs ID-NAT on all anti-HBc reactives to identify OBI (92% require ID-NAT for detection)
 - No donation sample archives; lookback not required (except NAT undiscriminated reactives)
 - Acute NAT yield: **1:781,000**; acute NAT/HBsAg yield: **1:290,000**; OBI yield: **1:60,000** (acute/HBsAg + OBI yield = 26% of total yield; ARC data, 2009-2015)
 - Pre- and post-NAT residual risks: **1:720,000 pre- and 1:3.0 million post** (ARC data)
 - No documented TT-HBV cases since NAT

Blood donor testing for hepatitis B virus in the United States: is there a case for continuation of hepatitis B surface antigen detection?

Dodd et al., Transfusion 2018;58:2166-70

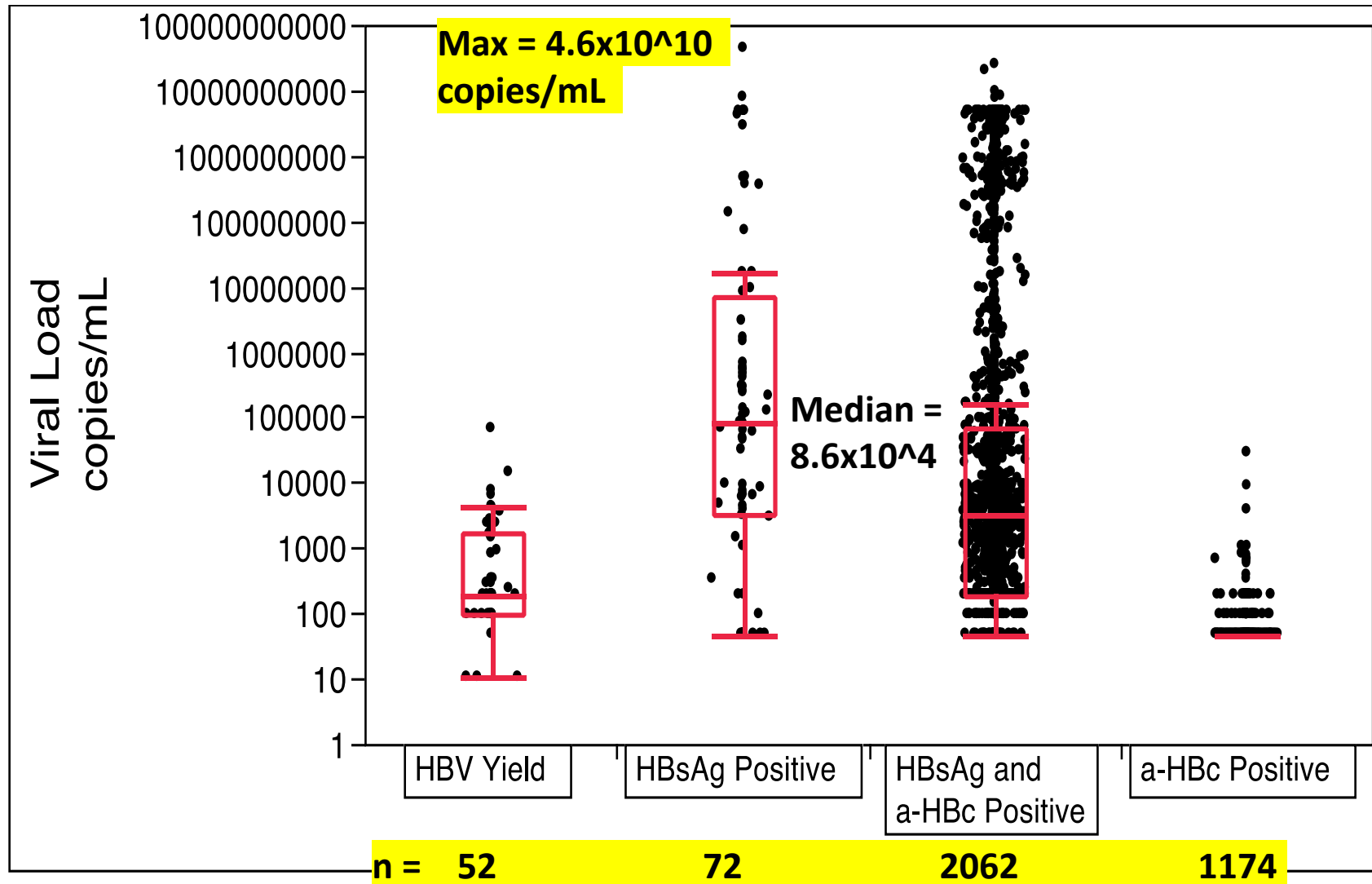
Roger Y. Dodd,¹ Megan L. Nguyen,² David E. Kryzstof,² Edward P. Notari,¹ and Susan L. Stramer²



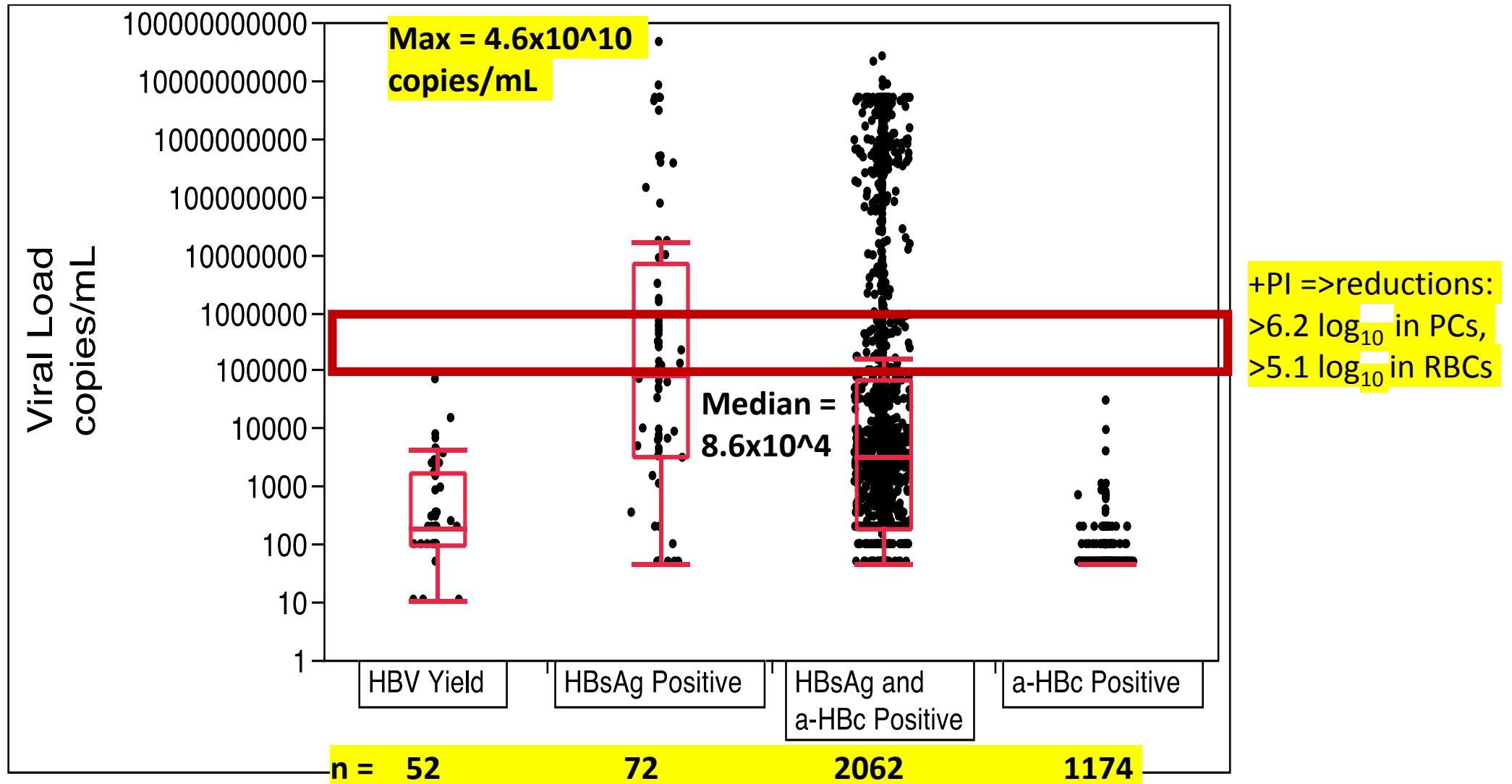
CONCLUSIONS: Point estimates of HBV infection rates among blood donors continue to decline, as do those for incidence and residual risk. Elimination of HBsAg screening would have negligible impact, with a risk less than 1 per 4 million donations.

Fig. 1. Distribution of HBV markers among 2035 samples from blood donors defined as actively infected with HBV. All samples have HBV DNA detectable by MP-NAT of 16 donations (n = 1453) or by testing using ID-NAT (n = 582; 361 + 215 + 6).

Viral Load Distributions - HBV Confirmed Positives n = 3360 (Nov 2006-June 2018)



Viral Load Distributions - HBV Confirmed Positives n = 3360 (Nov 2006-June 2018)



**Should the HBV testing strategy be
dependent on the geographical
region?**

NO

YES

MAYBE

Should the HBV testing strategy be dependent on the geographical region?

YES, as practiced

All countries represented use NAT (ID or MP; HBV endemicity dependent)

Anti-HBc regional; endemic regions do not use (could rescue by ↑anti-HBs; cost component)

Few documented TT-HBV cases since NAT (countries that do not use anti-HBc)

All continue to use HBsAg in face of sensitive (and duplicative) HBV DNA

Could same level of sensitivity be achieved without HBsAg?

Could HBsAg (and anti-HBc) be replaced with PI?