ADIEU HBsAg?

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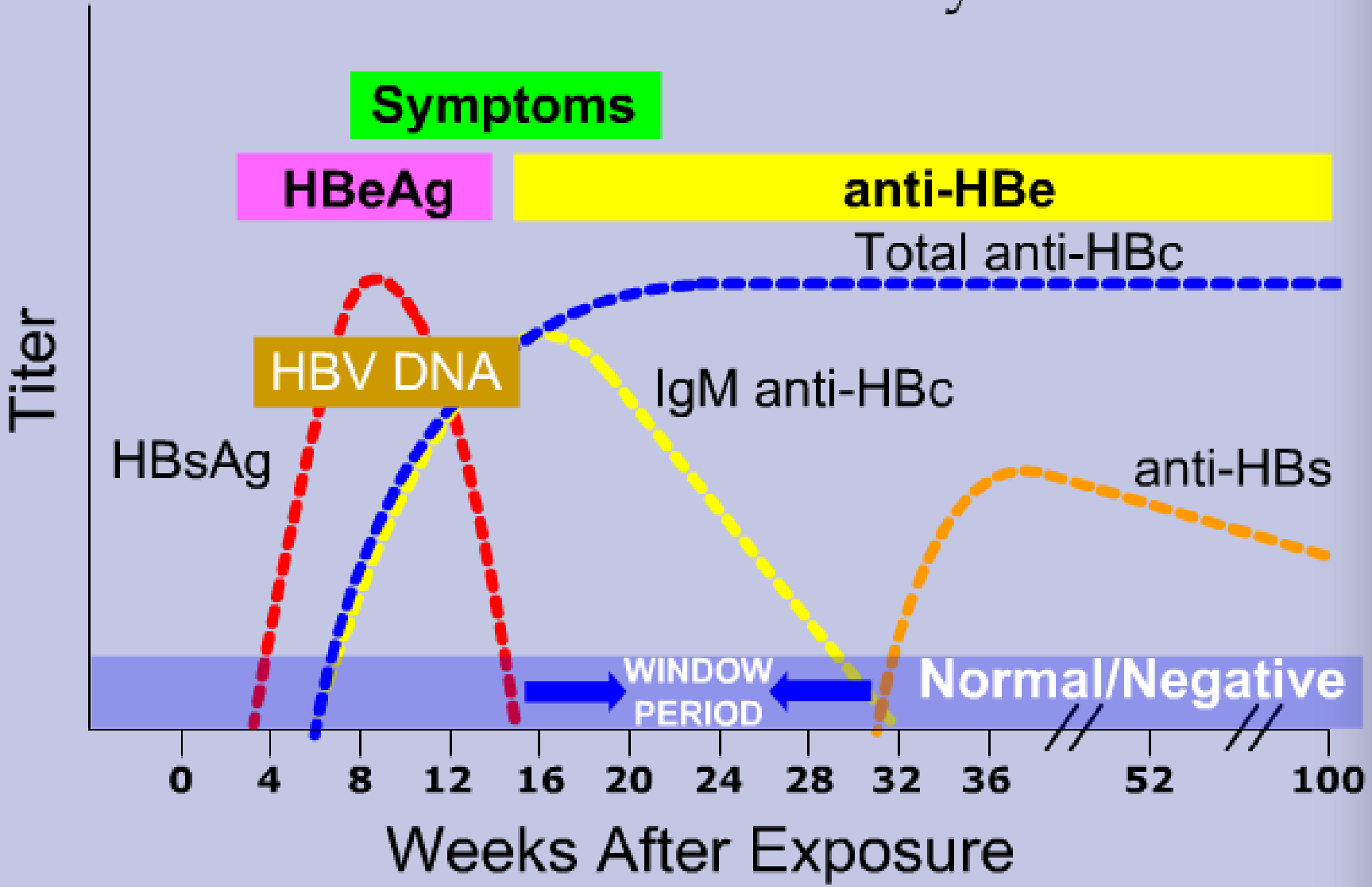
Key questions

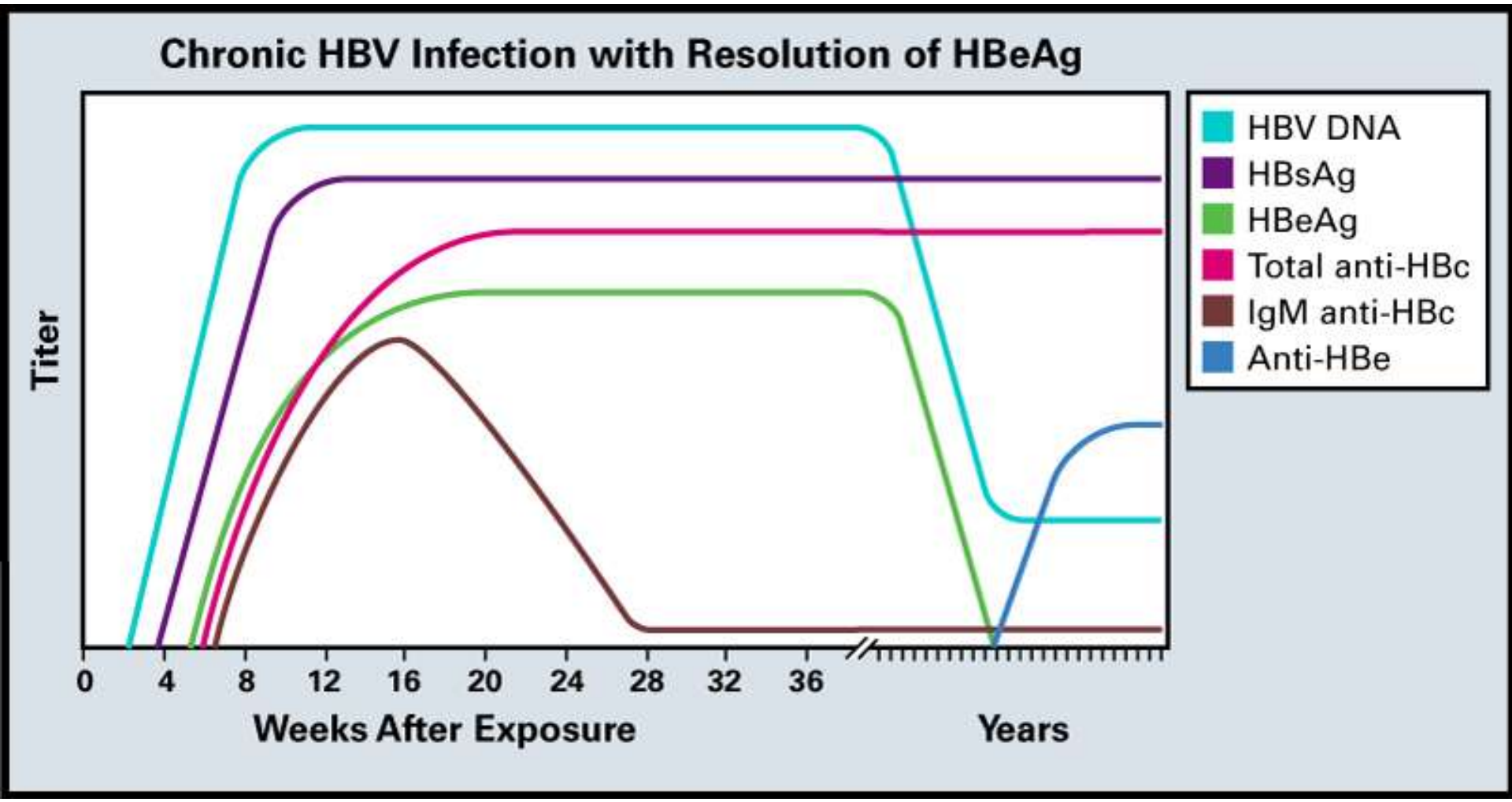
- Is there evidence that, in the presence of routine NAT (DNA), donor testing for HBsAg can be eliminated?
- If so, does this apply uniformly, irrespective of prevalence and incidence?
- If not, are additional data needed?

Outline

- Brief review of HBV infection stages
- Relevance of marker patterns
- Extended testing algorithm
- Relevant data from ~35 million US donations
- Comments on non-US environments
- Future prospects

Acute Hepatitis B Virus Infection with Recovery




Chronic HBV Infection with Resolution of HBeAg
Titer
HBV DNA
HBsAg
HBeAg
Total anti-HBc
IgM anti-HBc
Anti-HBe
0
4
8
12
16
20
24
28
32
36
Weeks After Exposure
Years

Screening marker progression

• DNA only	Yield
• DNA + HBsAg	Early Acute
◦ HBsAg “alone”?	????
• DNA+ HBsAg + anti-HBc	Later acute/chronic
◦ HBsAg + anti-HBc	????
• DNA + anti-HBc	Occult
• Anti-HBc	Late chronic?

- Note that single markers can be false-positive

ARC testing algorithm

- Screening
  - MP-NAT (Ultrio/Ultrio + pools of 16)
  - HBsAg, anti-HBc ChLIA (PRISM)
- Resolution
  - ID-NAT + dHBV
- Confirmatory
  - NAT yield: Independent sample and follow-up as needed
  - Serology + NAT – No further action
  - Serology and NAT nonreactive
    - HBsAg Neutralization, RT-PCR (UltraQual 1000 NGI)
    - Anti-HBc alone 3X RT-PCR (Roche cobas)
- Retained samples further re-tested if necessary

Hepatitis B virus testing by minipool nucleic acid testing: does it improve blood safety?

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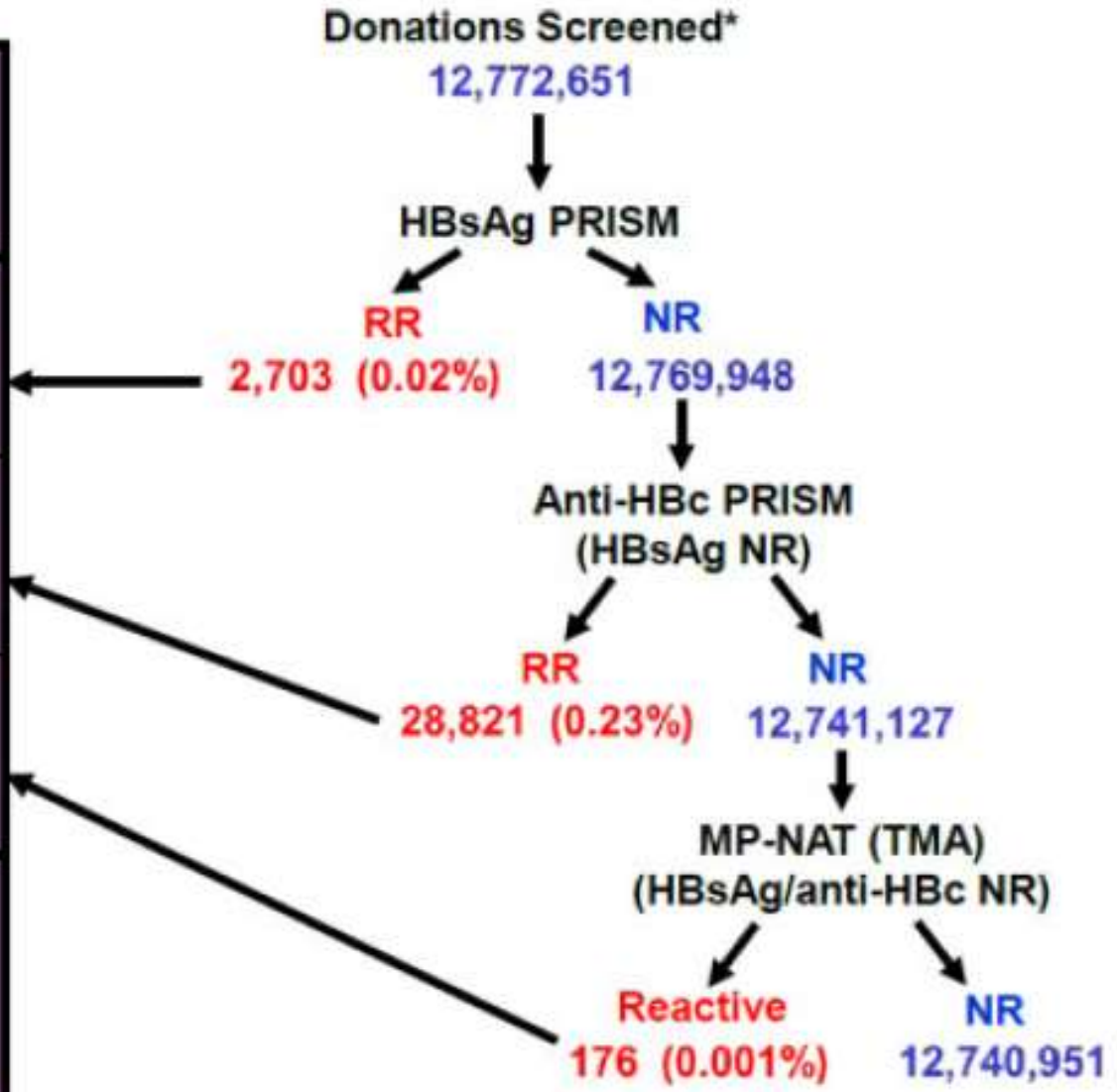
Susan L. Stramer, Edward P. Notari, David E. Krysztof, and Roger Y. Dodd

2 years data

TABLE 1. Reactivity defining HBV-infected donors

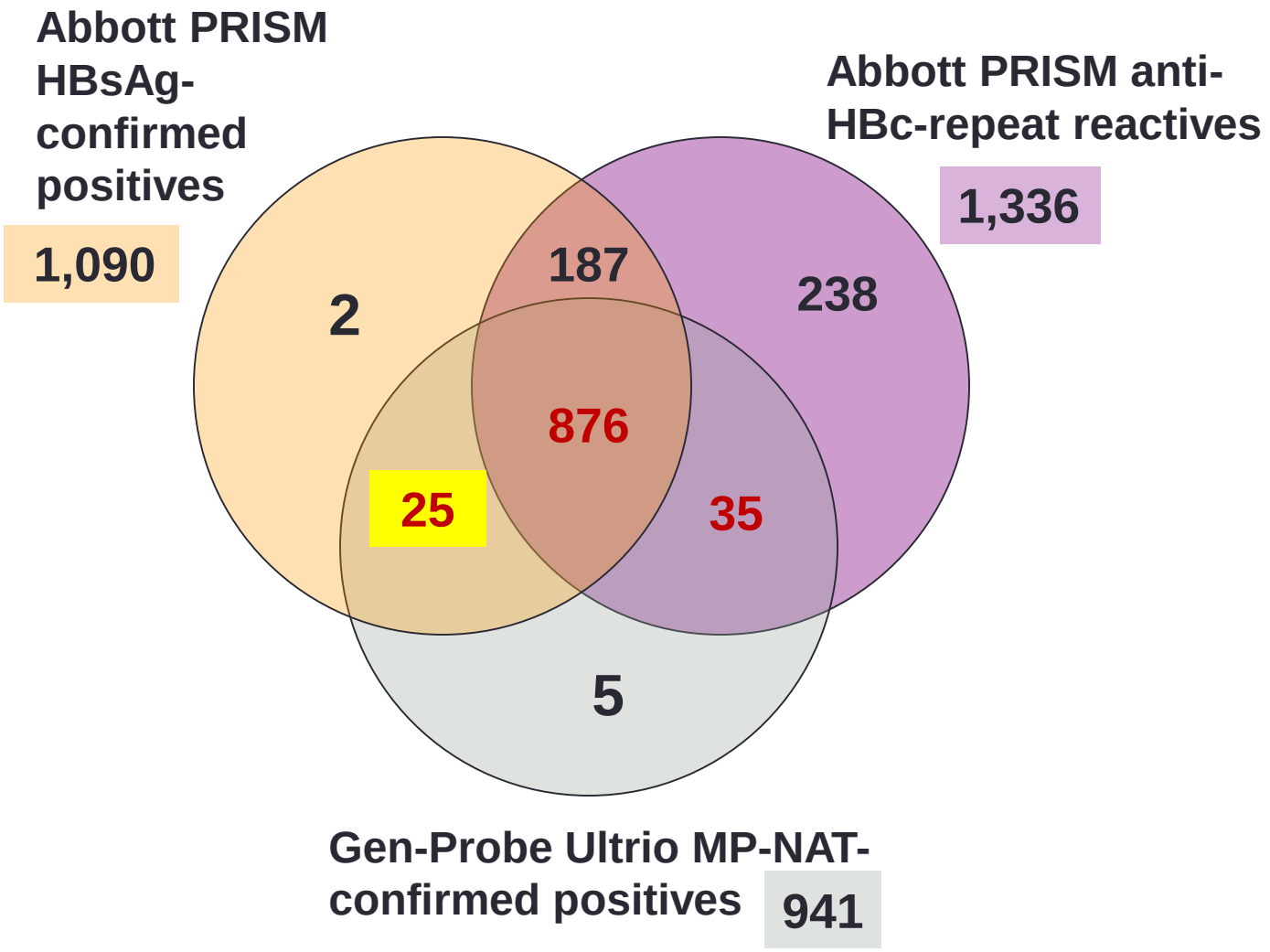
HBsAg	Anti-HBc	MP/ID-NAT (Ultrio)	ID-PCR
+	+	+	Not done
–	–	+	+
+	+ or –	–	+
–	+	–	+
–	+	+	Not done
+	-	+	Not done

Not Currently Infected**	True Positive (Infected)
1,613	1,090 (40%)
28,548	273 (0.95%)
171	5 (2.8%)
30,332 (0.24%)	1,368 (0.011%; 1:9337)
99.76% Specificity	4.32%*** PPV



Donations tested for HBV 2009-2011

HBV reactivity of 1,368 infected ARC donations, July 1 2009 to June 30 2011*



*defined as HBV MP- or ID-NAT reactive

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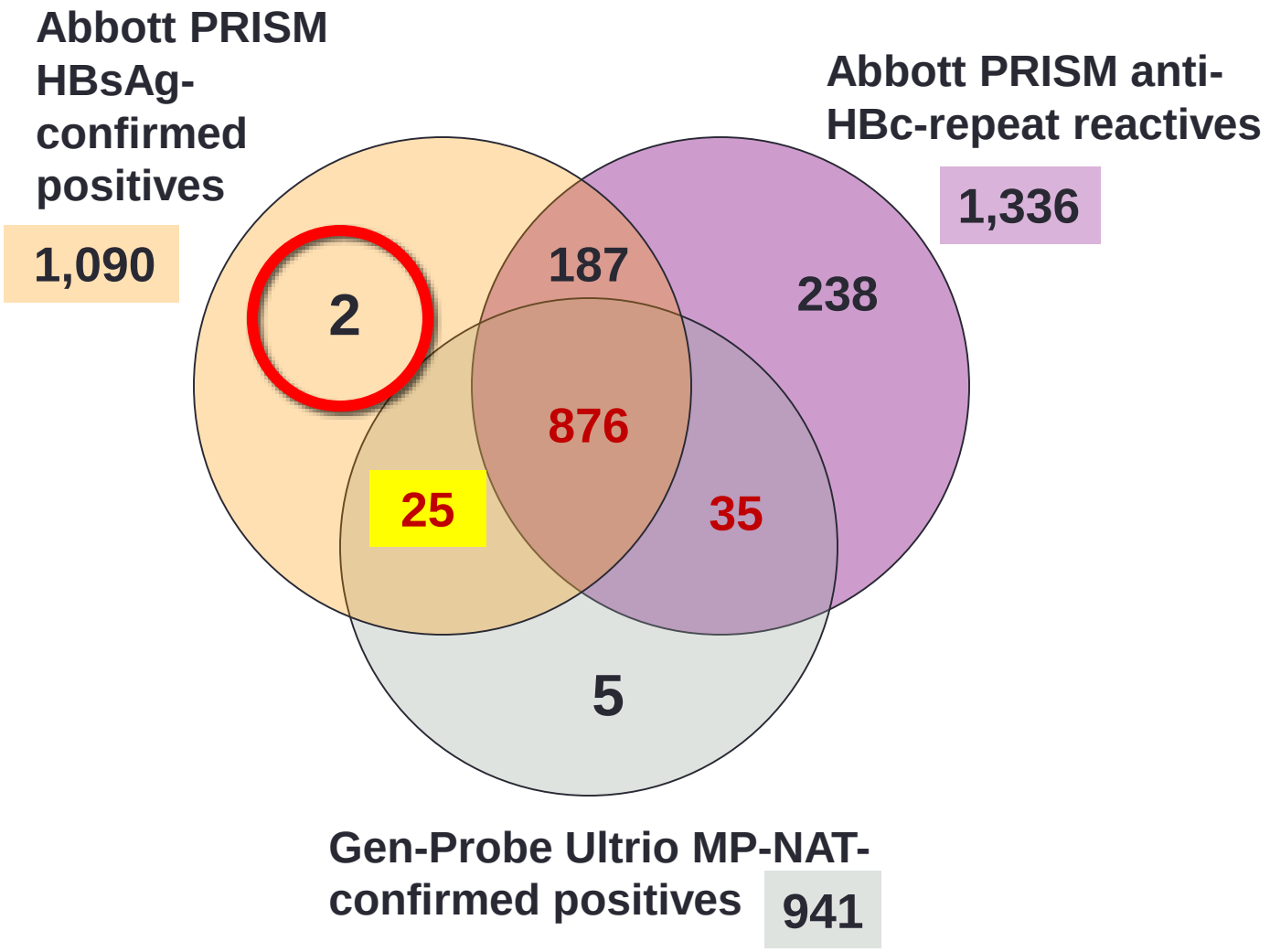

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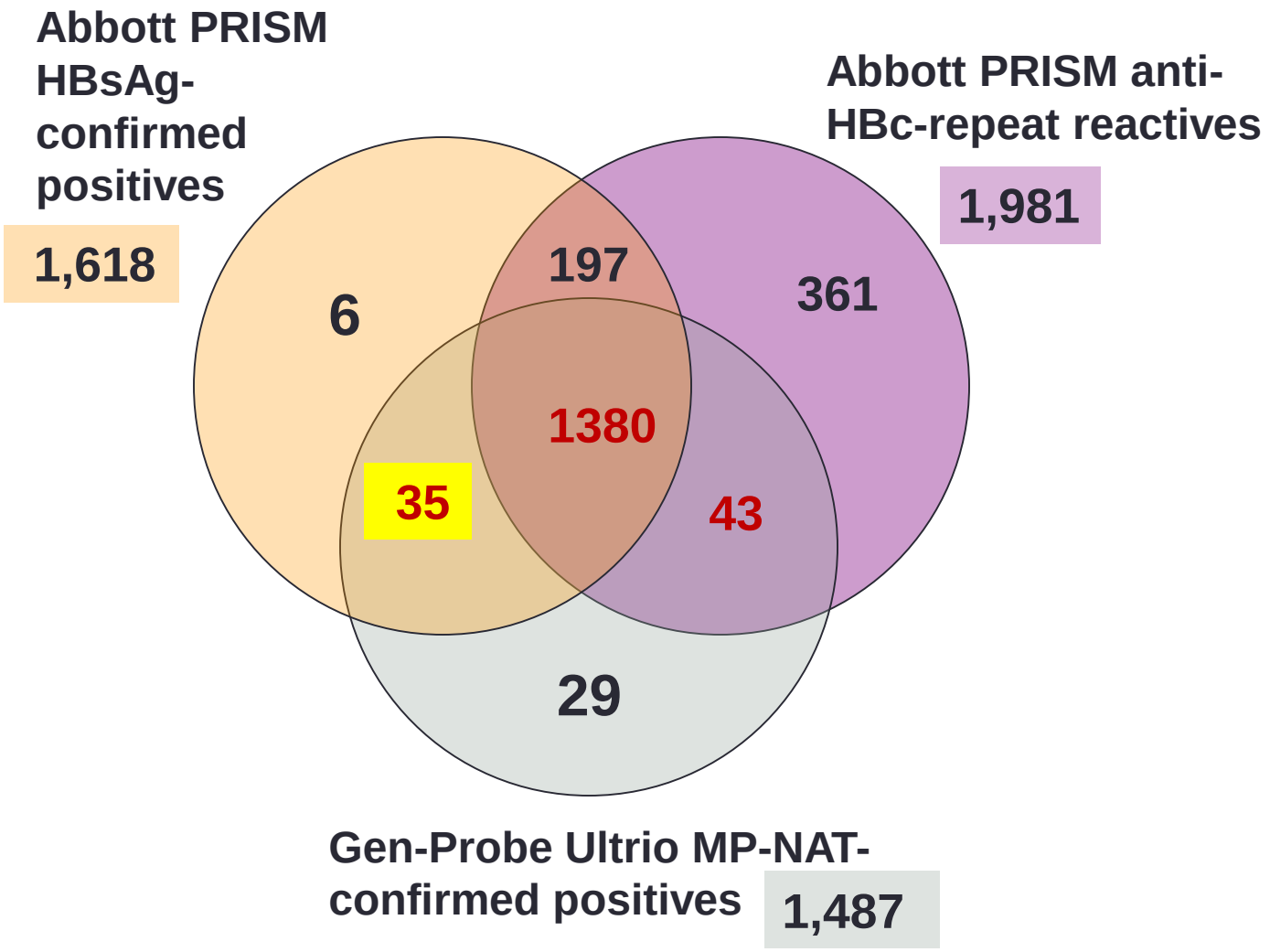
HBsAg-only?

- 2 samples (2 donors) of 12.8 million were HBsAg reactive (and neutralized pos) and ID-PCR reactive; anti-HBc nonreactive
  - First donor had 5 copies/mL DNA, but retrieved plasma was dHBV TMA non-reactive in 10X replicates and HBsAg nonreactive on subsequent retest (but S/CO was 0.94). Also, anti-HBs negative. Judged HBsAg and PCR false-reactive (20 yo female repeat donor; nonCaucasian); no follow-up
  - Second donor was ID-PCR positive (100 copies/mL DNA), but retrieved plasma was DNA nonreactive in 10X replicate. Low-level HBsAg on subsequent retest of donor (S/CO was 1.4; also neutralized). Anti-HBs positive (90 IU/L). Judged HBsAg and PCR false-reactive? (20 yo male FT donor; Caucasian); no follow-up
- In this series, no donor was HBsAg definitively positive in the absence of any other marker

Additional data, 2011-2015

- 22,370,273 donations tested (~ 50% each Ultrio and Ultrio +)
  - Total of 2051 active infections
    - confirmed by DNA (if MP-NAT non-reactive => ID-NAT)
  - 29 HBV Yield
  - 35 HBsAg/anti-HBc non-reactive Incident infections
  - 6 HBsAg/anti-HBc non-reactive with Low-level DNA
  - 197 HBsAg/anti-HBc reactive (MP-NAT non-reactive)
  - 1380 HBsAg/anti-HBc reactive (MP-NAT reactive)
  - 361 OBI (MP-NAT non-reactive)
  - 43 OBI (MP-NAT reactive)

HBV reactivity of 2051 infected ARC donations, July 1 2011 to June 30 2015*



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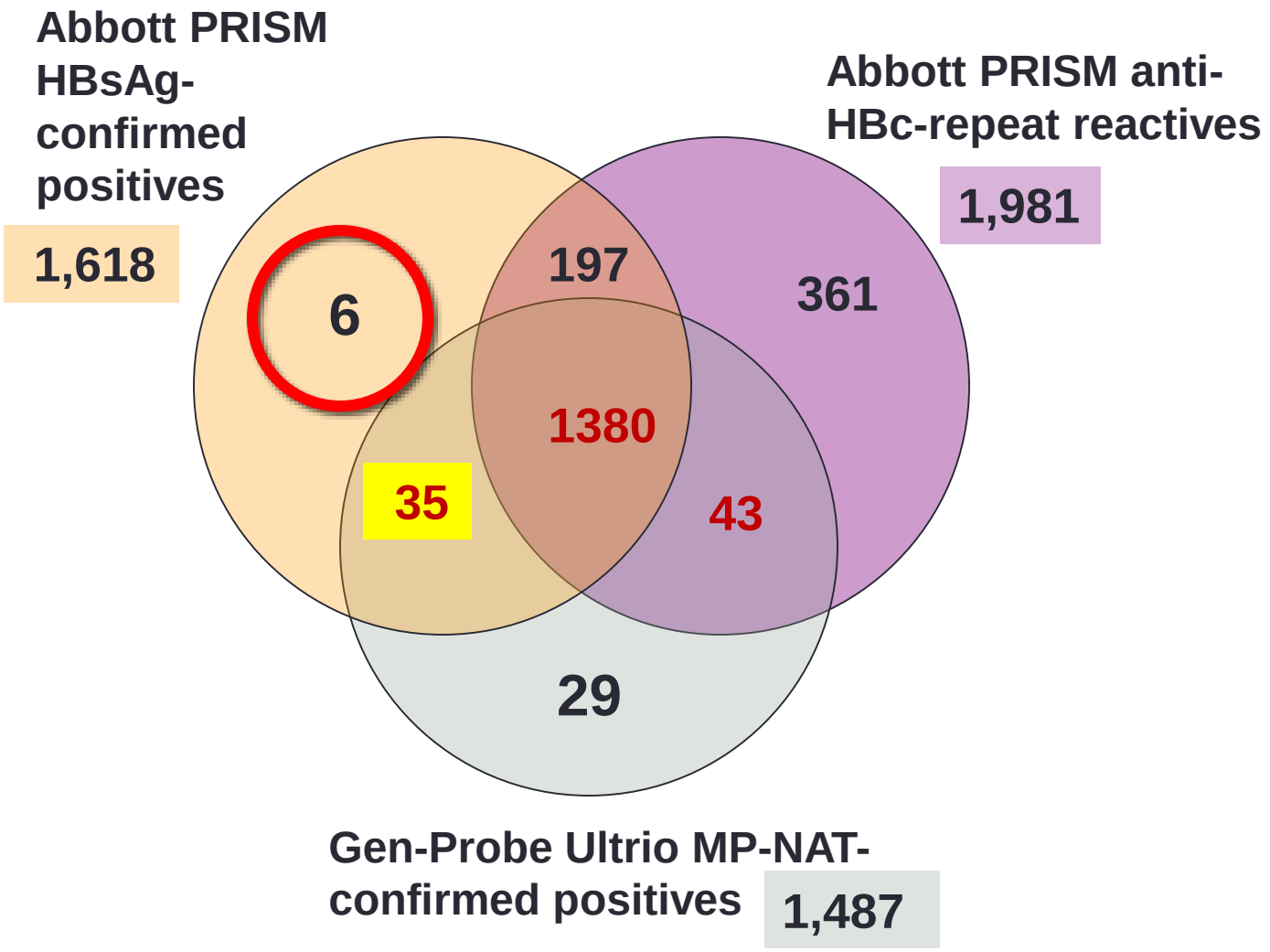
HBV reactivity of 2051 infected ARC donations, July 1 2011 to June 30 2015*



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Supplementary data, 6 HBsAg-only samples

Sample ID	Anti-HBc	Anti-HBs IU/L	HBsAg S/CO			Neut	NAT	MP-NAT	dHBV retest pos/# tested	dtn status (FT/RPT)	Age	Gender	Race
006LP	N	NT	1.79	1.66	1.60	NT	Ultrio	N	1/1	FT	22	Female	Cauc
007FQ	N	NT	4.10	3.99	3.86	NT	Ultrio	N	1/1	FT	16	Female	nonCau
011LS retest	N	>400	1.02 3.60	1.32 1.87	1.49 1.93	P	Ultrio	N	1/10, 0/10	RPT	28	Female	Unk
032KS retest	N	<5	1.14 0.92	1.17	1.11	P	Ultrio	N	1/10, 0/10	RPT	30	Female	nonCau
W0255 retest	N	<5	2.39 1.71	2.54 1.62	2.61 1.49	P	Ultrio +	N	4/10, 0/10	RPT	19	Male	Cauc
041FQ retest	N	<5	1.45	1.31	1.34	P	Ultrio	N	6/10, 9/10	RPT	56	Male	nonCau

Further comments on HBsAg-only samples

- Within the 2011-2015 study, there were an additional 144 samples characterized as HBsAg-only non-reactive in ID-NAT
- Of these, 47 reported recent HBV vaccination and 96 had HBsAg S/CO of 10 or less
- One donor had a repeatable, high HBsAg S/CO which was still present at follow-up one year later (all S/CO values >34); both NT by neut. ID-NAT at index was clearly non-reactive (S/CO = 0.11)
- A minority (6/102) of donors with reactivity for HBsAg only had HBV DNA at levels that are not detectable by routine MP- or ID-NAT (overall frequency ~1 per 3.7 million)
  - In the absence of 10X replicate NAT, 4 of 6 could not be differentiated from low-signal false-positives

“HBsAg-only”: significant or not?

- Are they real?
  - False-positive/contamination for HBsAg and/or DNA
  - No logical place in recognized marker-sequence
- If real, then:
  - Are they infectious (dilution studies suggest a low infectious dose)?
  - Can they be explained (low-level infection, mutation impacting detectability)?
  - Are they relevant to policy (no breakthrough HBV infections reported, but note absence of lookback)
- Are more studies needed or justified?

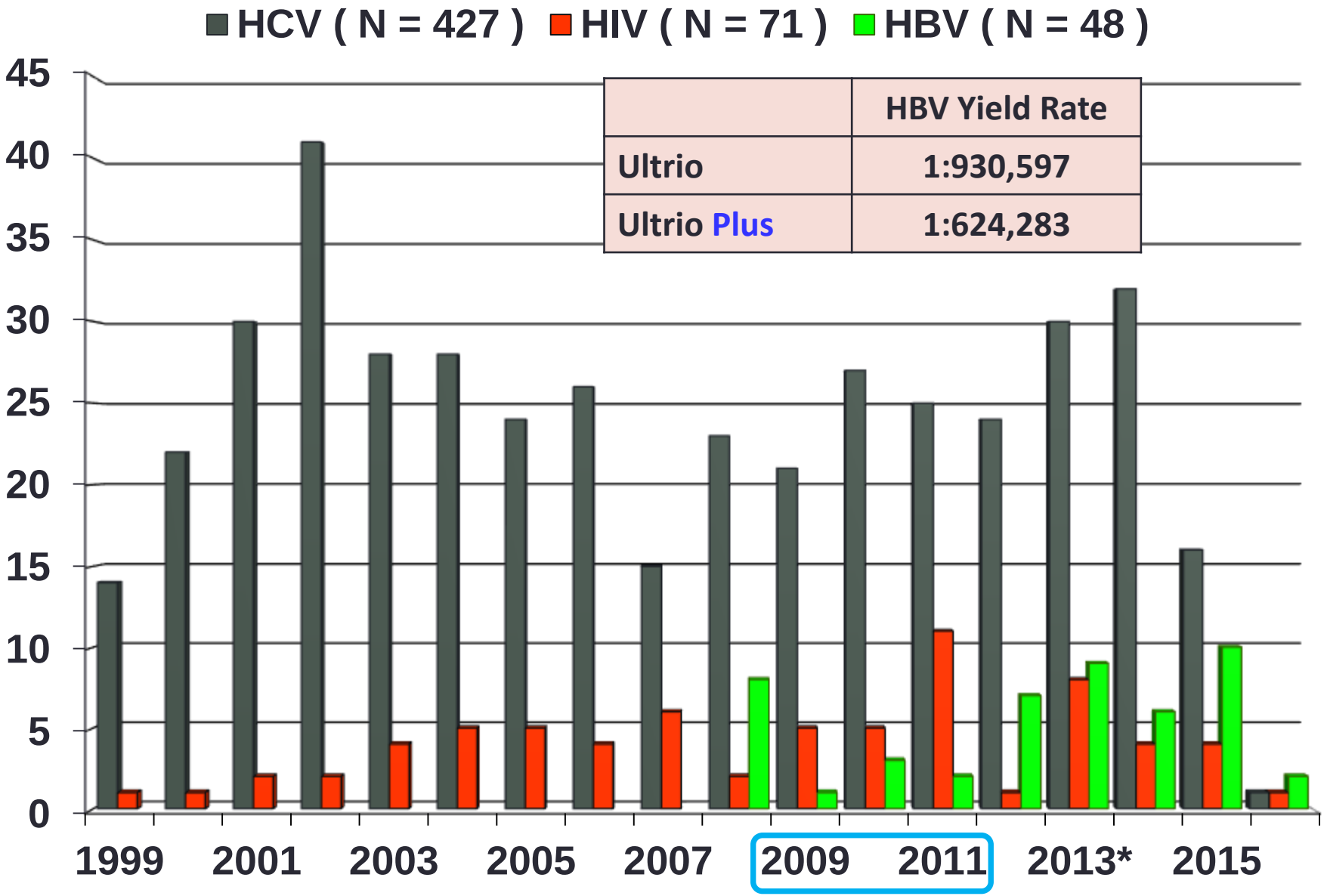
Summary, 2009-11 vs 2011-15

	Number	Rate*	Number	Rate*
Tested	**12,772,651**		**22,370,273**	
Active Pos	**1368**	**1.07**	**2051**	**0.92**
MP-NAT Pos Total	**941**	**0.74**	**1487**	**0.66**
OBI (MP-NAT Neg)	**238**	**0.19**	**361**	**0.16**
OBI (MP-NAT Pos)	**35**	**0.027**	**43**	**0.019**
HBsAg Pos Total	**1090**	**0.85**	**1618**	**0.72**
HBsAg Yield	**25**	**0.020**	**35**	**0.016**
HBsAg Only	**2**	**0.0016**	**6**	**0.0027**
DNA Yield	**5 (1:2,554,531)**	**0.004**	**29 (1:771,389)**	**0.013**
Incidence**		**1.62**		**1.33**

* Rate per 10,000 donations

** Rate per hundred thousand person-years

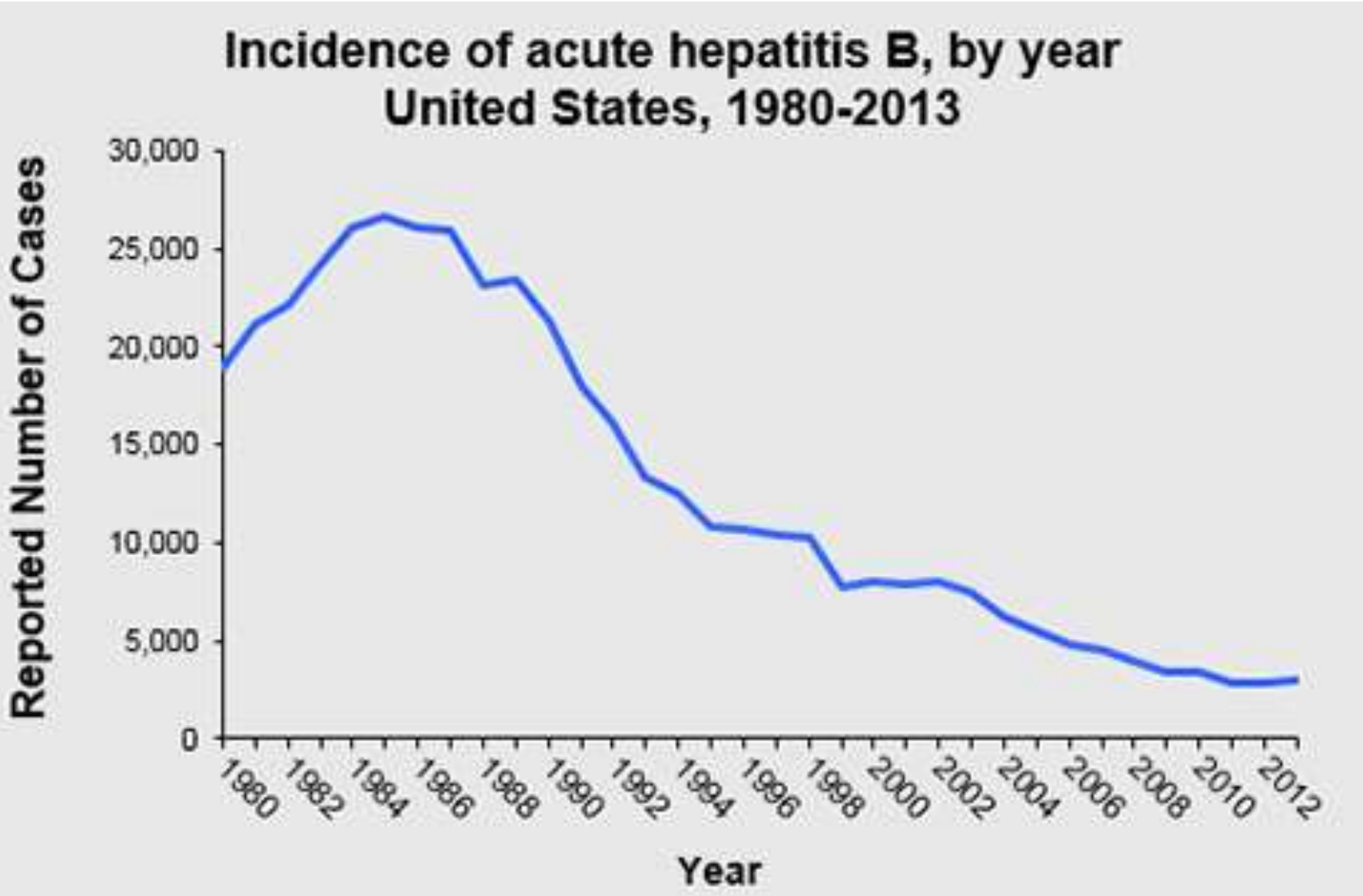
Total ARC Yield Cases by Year



	HBV Yield Rate
Ultrio	1:930,597
Ultrio Plus	1:624,283

*split between U and U+

3/31/2016

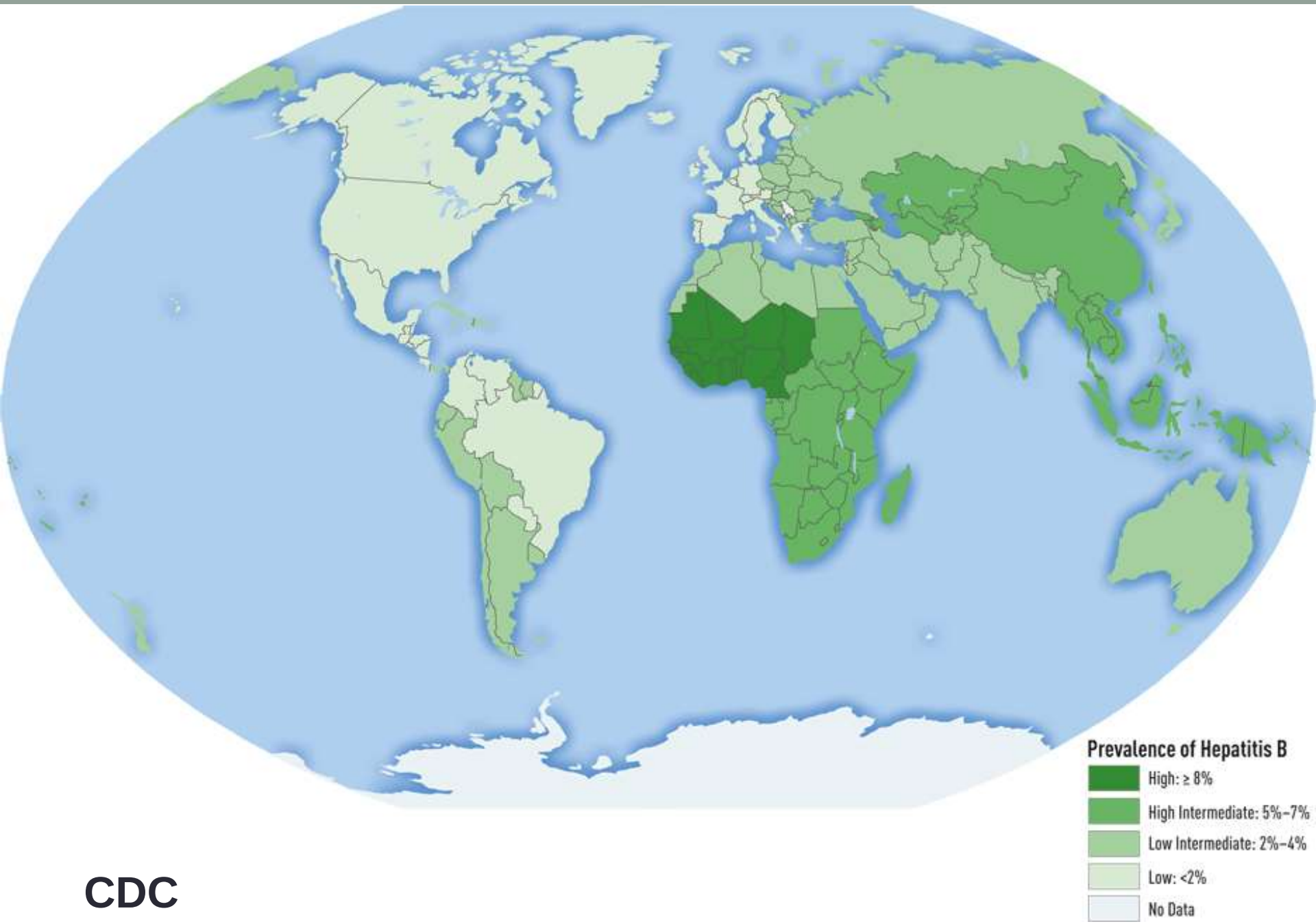

Incidence of acute hepatitis B, by year
United States, 1980-2013
Reported Number of Cases
30,000
25,000
20,000
15,000
10,000
5,000
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
Year

CDC

HBV testing, US and similar

- Currently, HBsAg, anti-HBc and anti-HBc
  - Relatively low donor loss, mostly attributable to anti-HBc
    - 17.5% of all ID-NAT(active) positives detectable by anti-HBc alone
  - Value of HBsAg alone
    - 0.23% of all HBV positives
      - 6 years (8 pos “worst case”/3419 total HBV pos)
    - 0.23/million of all screened donations
  - Infectivity of very low DNA levels is unknown

- Future perspectives
  - Rely on MP-NAT and pathogen-reduced products without HBsAg (or anti-HBc)

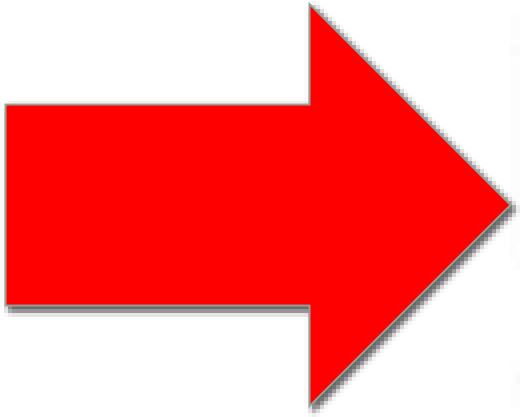

Prevalence of Hepatitis B
High: ≥ 8%
High Intermediate: 5%–7%
Low Intermediate: 2%–4%
Low: <2%
No Data

CDC

Moderate to high HBV rates

- Global expectation of HBsAg testing
  - Very high rates might be managed through rapid pretest (eg China where 60% of all positives may be detected this way)
- Anti-HBc likely of value for OBI, but wasteful of resources because of unacceptably high prevalence rates
  - “Rescue” of anti-HBc-positive with anti-HBs testing (this approach recently abandoned in Japan)
- More pressure on use of NAT for HBV safety
  - Is MP-NAT adequate?
- Complete solutions may not be available in resource-limited environments

The last word goes to Mark Twain:



James Ross Clemens, a
cousin of mine was seriously
ill two or three weeks ago, but
in London,
is well now.

The report of my illness
grew out of his illness, the
report of my death was
an exaggeration.

Mark Twain