Issues with Malaria Screening in the US

Australian experience with malaria antibody screening and feasibility of implementing such a "process" in the US for selected populations versus universal donor screening

FDA Workshop on Testing for Malarial Infections in Blood Donors, July 12, 2006

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Outline

- Current donor questioning process
- Post donation information
- Donor deferrals, 2000-2005
- Australian experience
- US testing options

Donor Questioning

- Question #40: Have you ever had malaria?
  - No: accept the donor
  - Yes: have you been asymptomatic for > 3 years?
    - Yes: accept the donor
    - No: defer the donor

Donor Questioning

- Question #29: In the past 3 years have you been outside the US or Canada?
  - No: accept the donor
  - Yes: in what countries?
    - Only if non-malarial areas, no time in Iraq; accept the donor
    - Yes malarial areas or Iraq; have you lived > 5 yrs in another country?
      - No: defer 12 mos after recent travel or departure from Iraq
      - Yes: what country and what area? Determine how long since donor departed from malarial area
        - Defer for 3 yrs after departure (resident) or 12 mos after travel/departure from Iraq
        - Non-malarial area: defer 12 mos from travel or after departure from Iraq

Assessment of Donor Eligibility Based on Travel/Residence to a Malarial Area

- Health historians provided:
  - Reference Listing: countries by region to assist in identifying general areas
  - Reference Tables (drop down menus; eBDR): alphabetized listing by country of risk, destinations within a country
    - Not all inclusive; questions: refer to CDC's Health Information for International Travel
    - Countries with no risk listed by name
    - Many countries have cities of the same name in several different provinces or states
    - If more information is needed, consult
      - Hammond Atlas (distributed to all collection staff)
      - If cannot determine, defer donor and consult with BHQ

Acceptance of an Ineligible Donor—Malaria
by Month of Occurrence
N=1176

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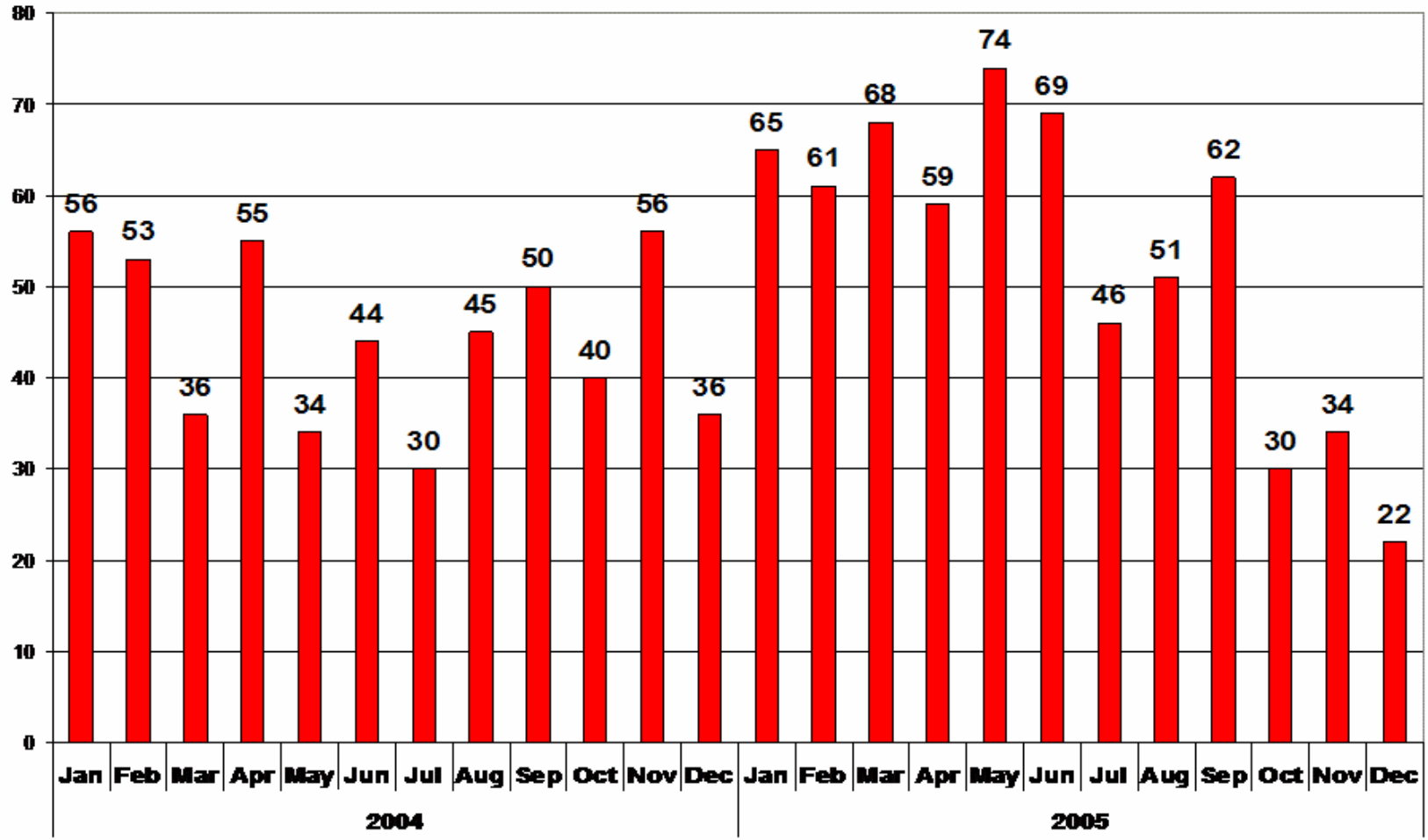

Acceptance of an Ineligible Donor
by Month of Occurrence
N=1176 Malaria (47%); Other 1344 = 2520 Total

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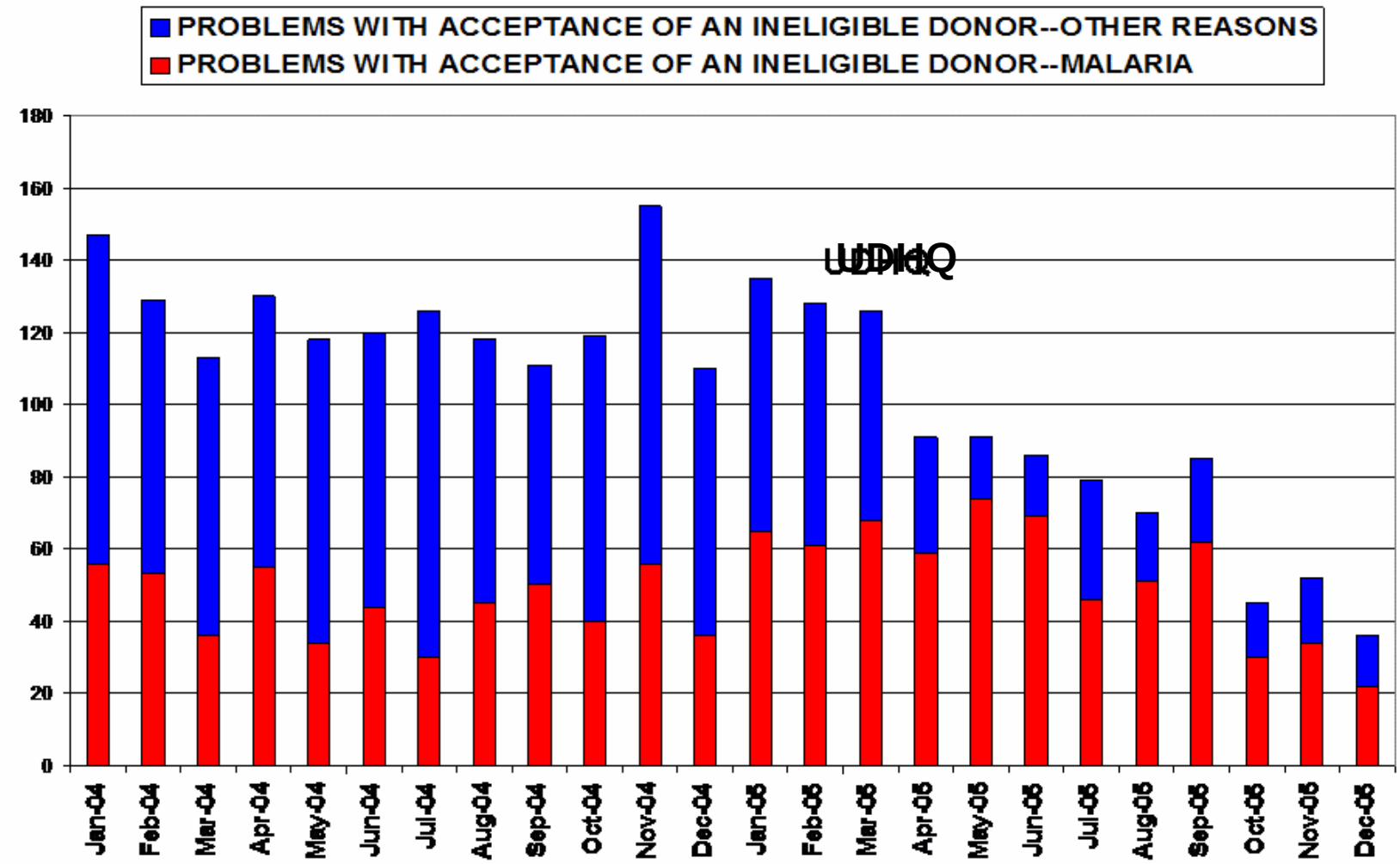

Violative BPD Reports—Acceptance Of An Ineligible Donor—Malaria—
by Month of Occurrence
N=144/1176 (12%)

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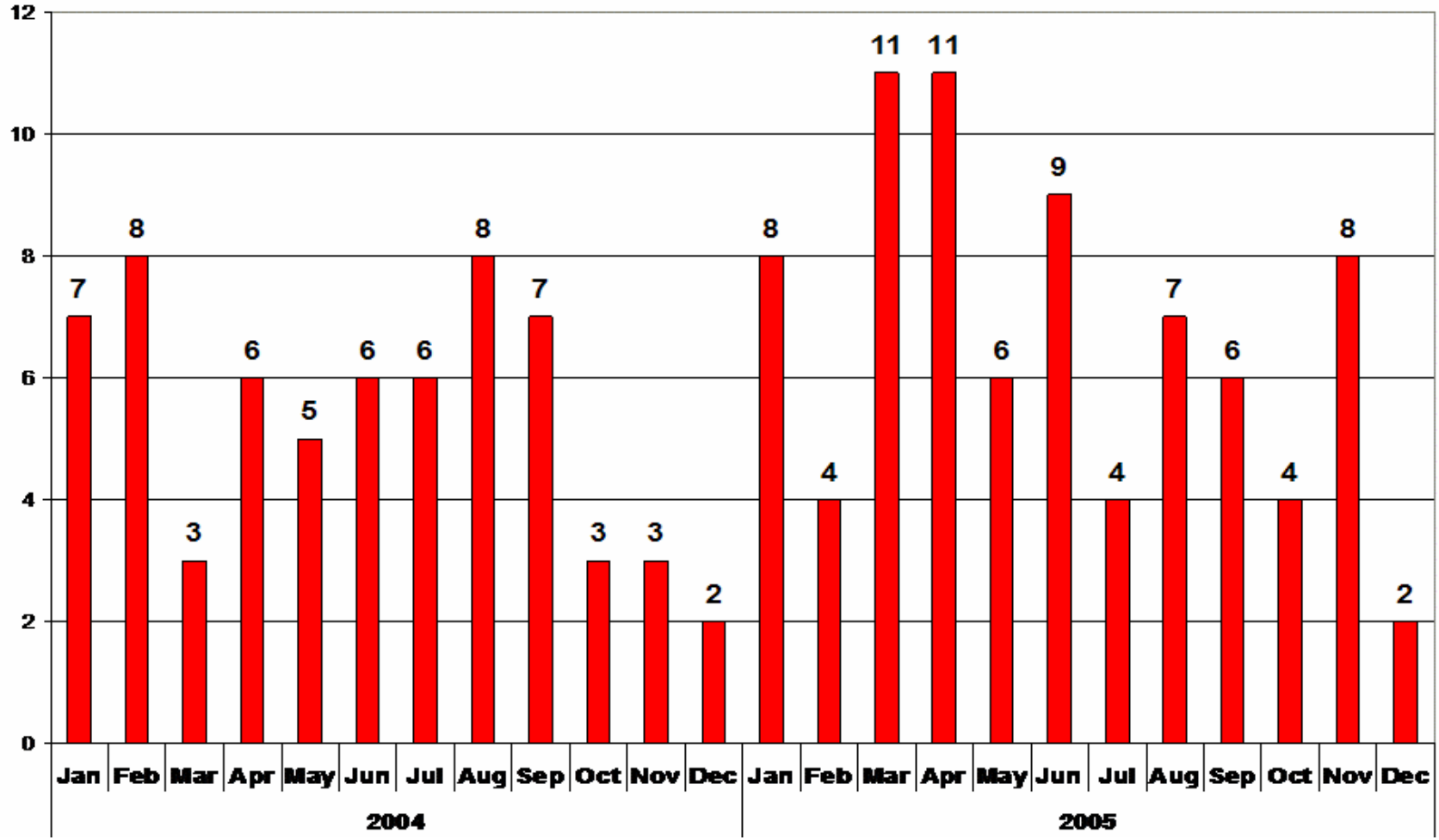

Violative BPD Reports
Acceptance of an Ineligible Donor — Malaria
CY 2004 and 2005—Involved Country

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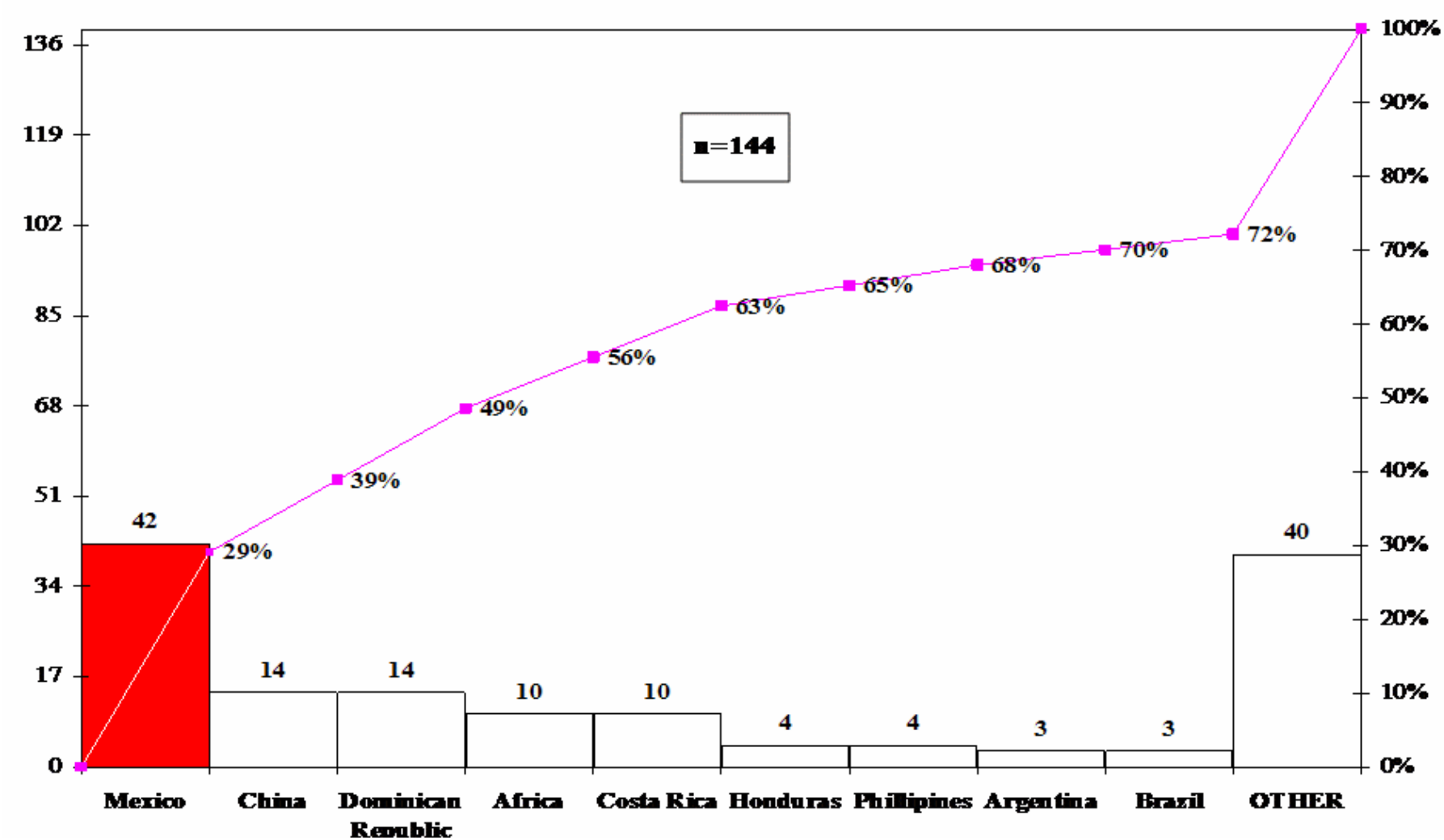

Complexity of Questioning

- Chinese Provinces with risk in rural areas: Hainan, Yunnan, Fujin, Guangdong, Guangxi, Guizhou, Sichuan, Xizang (Zangbo River valley only), Anhui, Hubei, Hunan, Jiangsu, Jiangxi and Shandong
  - Defer if area visited was:
    - <1500m only during warm weather
    - N of latitude 33ºN, July-Nov
    - Between latitude 25ºN and 33ºN, May-Dec
    - South of latitude 25ºN, year round
- Complexity leads to deferral of all donors

Complexity of Questioning

- Mexico; do donors know states of travel?

Location	States	Malarial Risk
Monterrey (in 7 states)	Nuevo Leon	No
	Campeche	Risk
	Chiapas	Risk
	Durango	No
	Sinaloa	Risk
	Sonora	No
	Tabasco	Risk

Post Donation Information-- Malaria
by Month of Occurrence
N=6918 total with or without associated products

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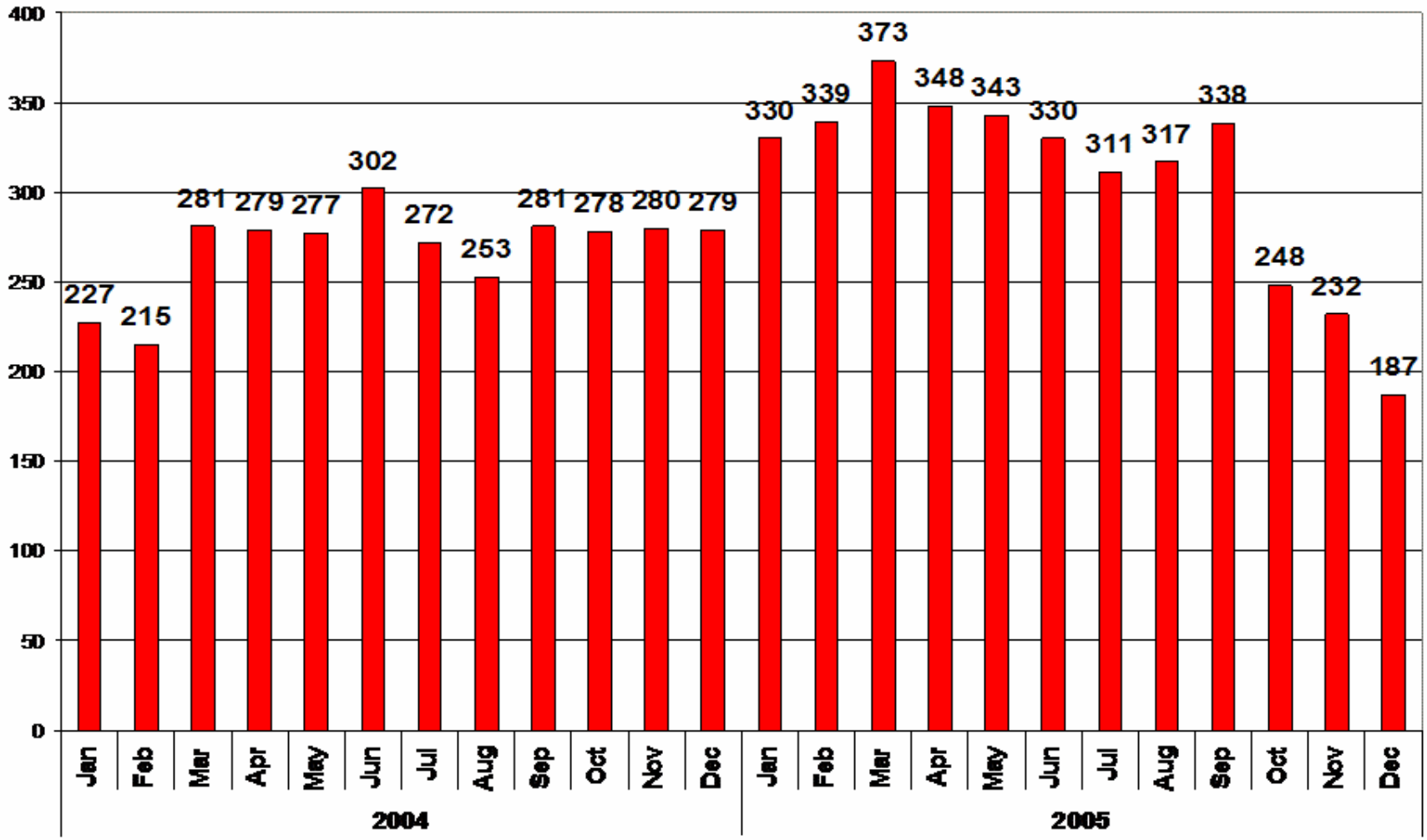

Post Donation Information Related to Behavior/History
by Month of Occurrence
N=6918 Malaria (39%); Other 11,018 = 17,936 Total

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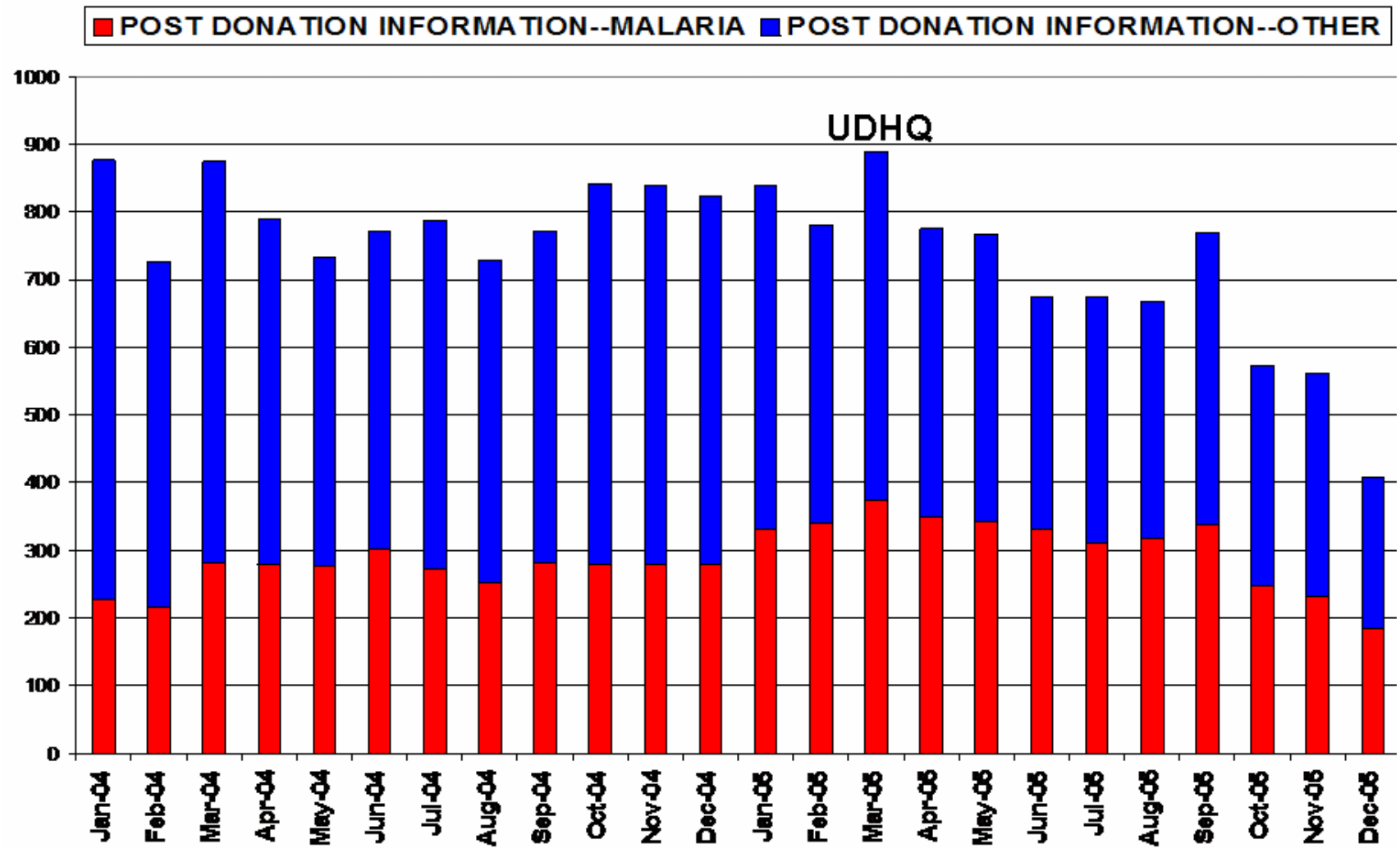

Post Donation Information--Malaria
by Month of Occurrence
N=6281 with associated products/6918 total = 91%

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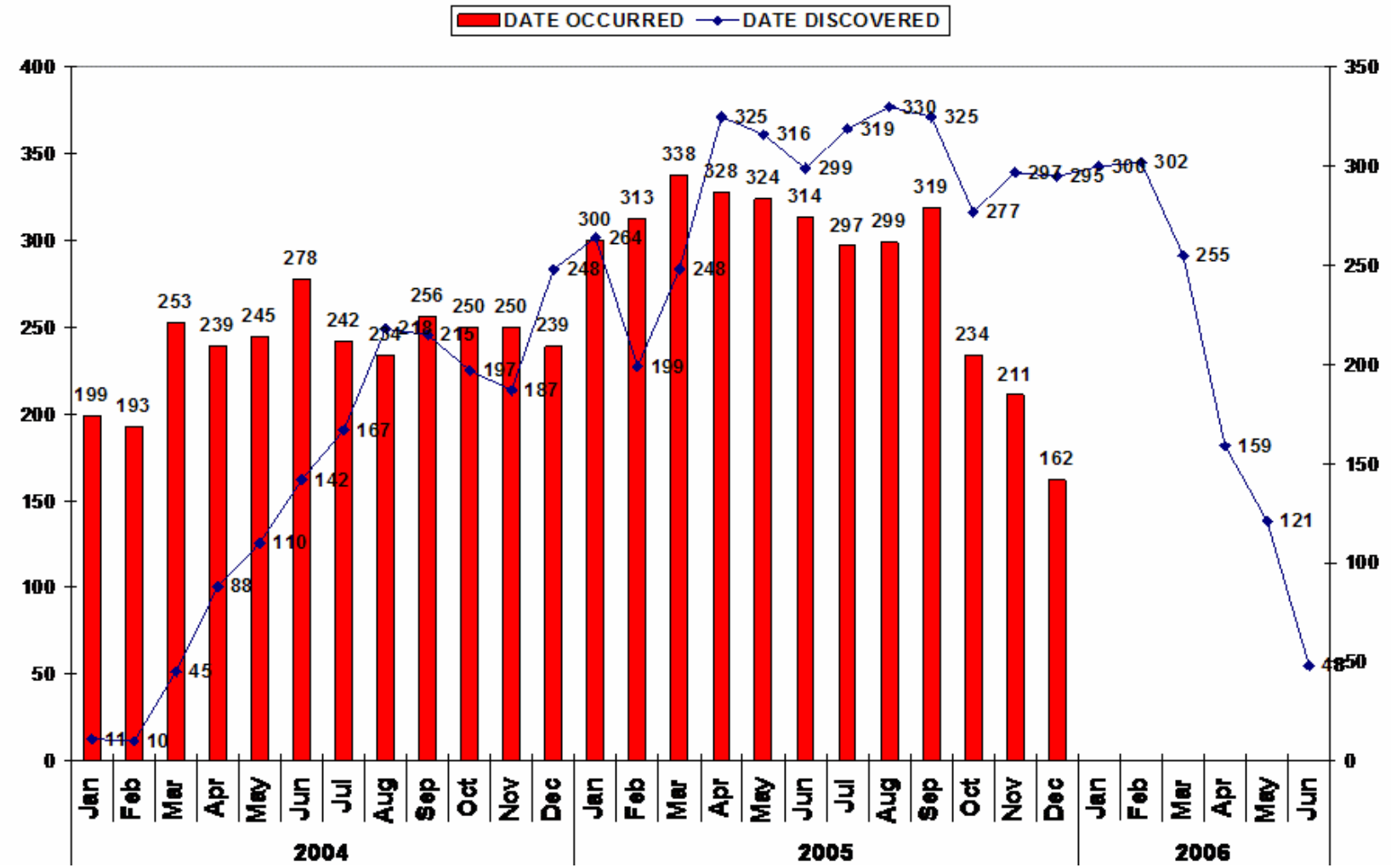
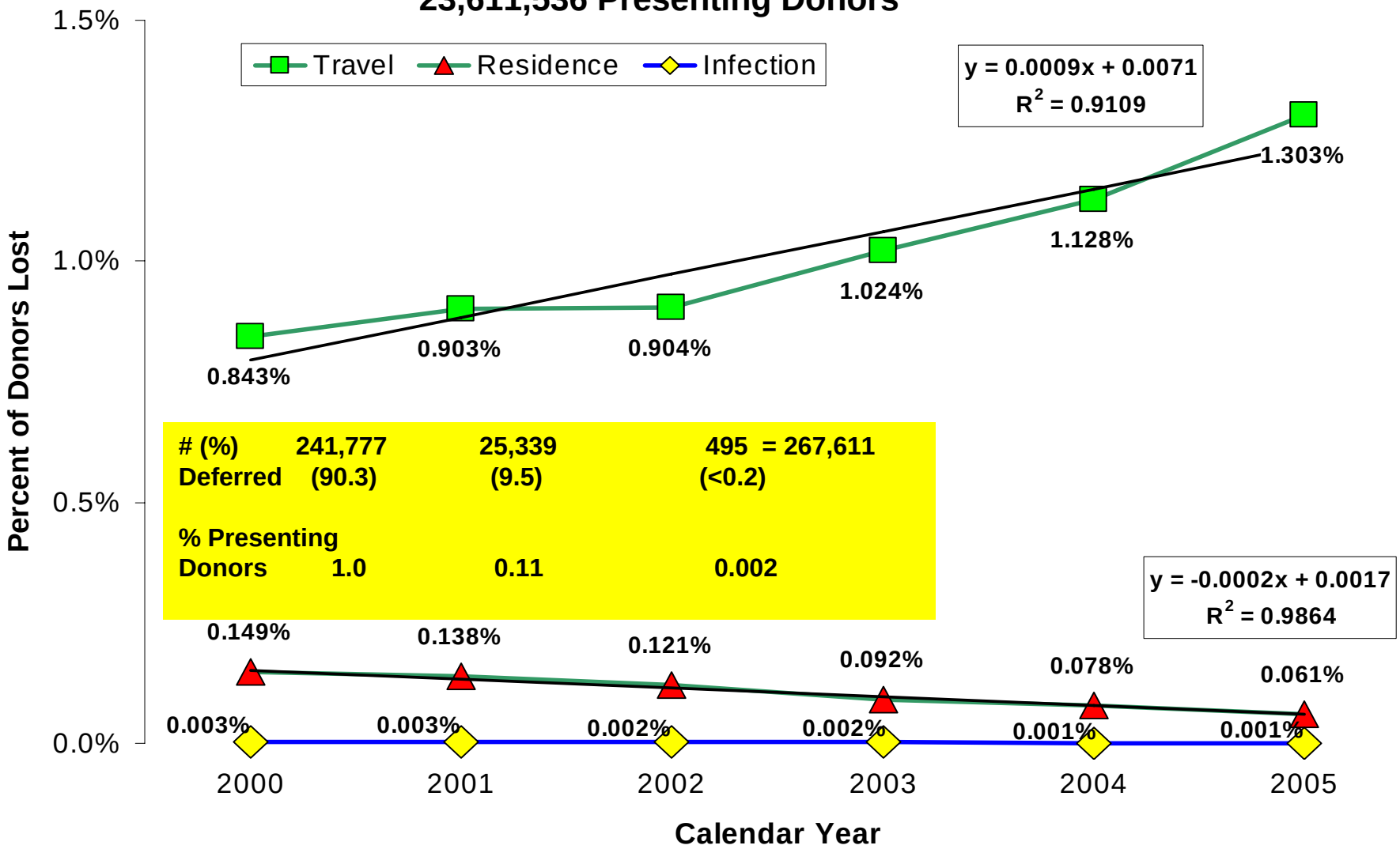


Percent of Donor Loss Due To Malaria Deferral
Calendar Years 2000 to 2005
23,611,536 Presenting Donors



Total Malaria Deferrals Donors 2000-2005 23,611,536 Presenting

	No.	%	Annual mean donation rate	Projected no. total lost donations
Travel	**241,777**	**1.01**	**1.69**	**410,844**
Residence	**25,339**	**0.11**	**1.69**	**42,635**
Malaria	**495**	**0.002**	**1.69**	**831**
Total	**267,611**	**1.13**		**454,310**

Total Malaria Deferrals
2005
3,795,204 Presenting Donors*

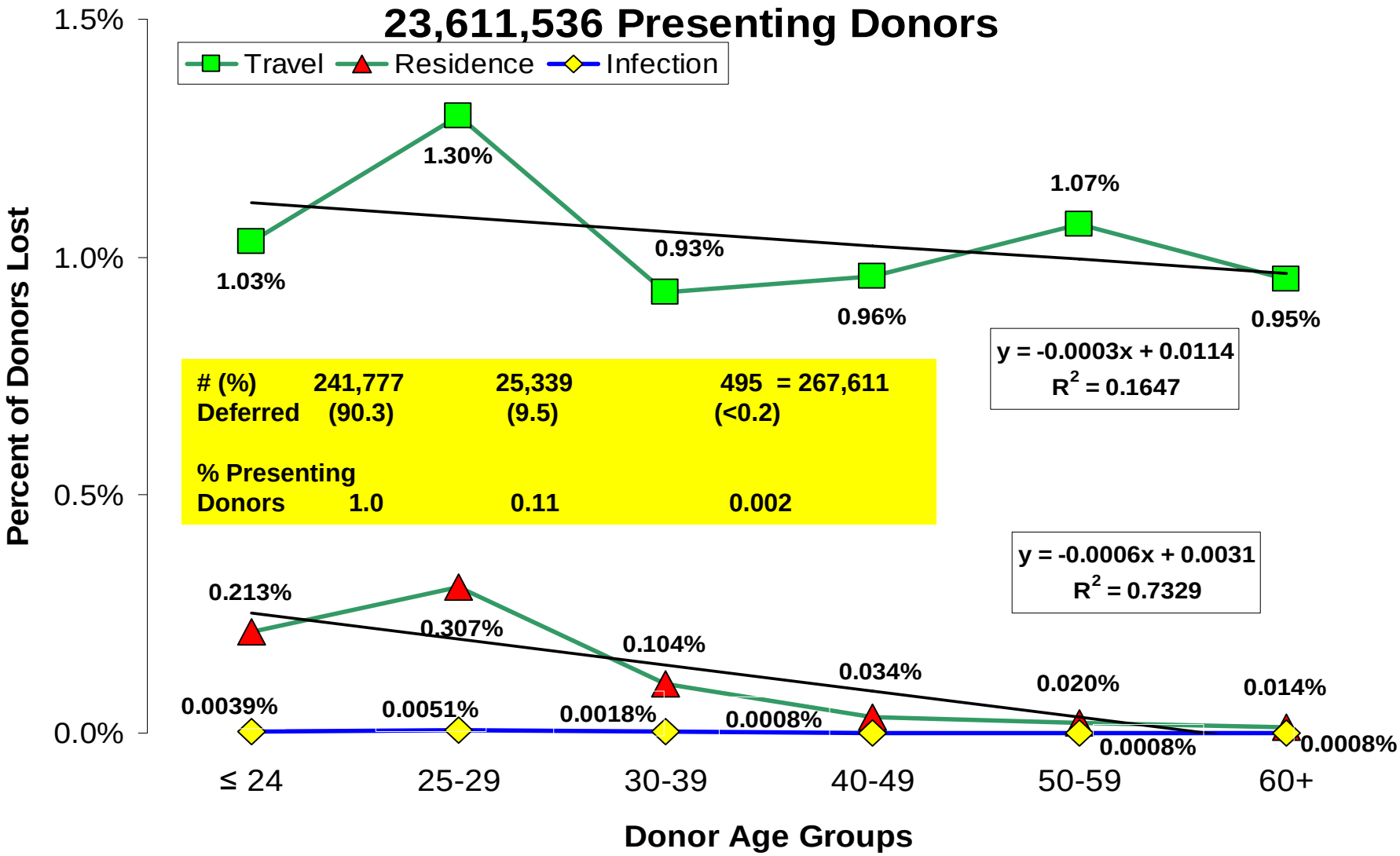
	No.	%	Annual donation rate	Projected no. total lost donations
Travel	**50,119**	**1.303**	**1.725***	**86,455***
Residence	**2309**	**0.061**	**1.725**	**3983**
Malaria	**53**	**0.001**	**1.725**	**91**
Total	**52,481**	**1.365**		**90,529**

*** 6,546,727 donor presentations projected 86,455 lost donations due to travel deferrals; US ABC 2005 data = 7, 133,005 donor presentations with 83,066 (1.2%) malaria travel deferrals**

Opportunity Losses Lifetime

- 2005 total losses, 52,481 presenting donors
  - Will show that most are FT donors in all categories (>80%) and most (<10%) never return over observed period
- 10-year follow up FT donors to determine return frequencies (assuming same pattern for malaria deferred donors); 1995-2005
  - 505,695 of 1,016,110 FT donors returned (50%)
  - Median 3.3/mean 5.7 career donations
    - 2-226 range
    - 4.34 years
- Convert 2005 travel deferrals of 50,119 into lifetime donors = 285,678 career donations (mean)

Percent of Donor Loss Due to Malaria Deferral By Age Groups 23,611,536 Presenting Donors



Malaria Deferred Donor Characteristics Infection, 2000-2005 23,611,536 Presenting Donors

Total	**492 (3 deferred twice) = 495 presentations**
FT	**479 (97.4%)**
RPT	**13 (2.6%); 2 donors with 2 prior donations**
Males	**290 (58.9%)**
Returned	**4 (0.8%); 1-2 donations/donor**

Malaria Deferred Donor Characteristics Residence, 2000-2005 23,611,536 Presenting Donors

Total	**25,169 (167 deferred 2-3X) = 25,339 presentations**
FT	**24,253 (96.4%)**
RPT	**916 (3.6%); 226 donors with 2 prior donations**
Males	**15,392 (61.2%)**
Returned	**338 (1.1%); 2-7 donations/donor**

Malaria Deferred Donor Characteristics Travel, 2000-2005 23,611,536 Presenting Donors

Total	**237,307 (4302 deferred 2, 3 or 4X) = 241,777 presentations**
FT	**196,398 (82.8%)**
RPT	**40,909 (17.2%); 11,892 donors with 2-21 prior donations**
Males	**118,145 (49.8%)**
Returned	**13,274 (5.6%); 2-23 donations/donor**

Malaria Deferred Donor Collection Regions 2000-2005 23,611,536 Presenting Donors

- High by collections: Oakland/Tulsa (infection), LA/Oakland (residence), Oakland (**2.4%**)/LA (**1.6%**) (travel)
- Low by collections: Omaha/PR (**0**) (infection), Toledo/PR (residence), Birmingham (**0.4%**)/PR (**0.3%**) (travel)
- US ABC data range (2005): min **0.7%** Gulf coast area to **2.0%** max on the East coast

Top Ten Deferral Categories, 2005, N (%)

Low hemoglobin	691,950	**65.22%**
Unacceptable blood pressure	46,575	**4.39**
Travel-malaria	**50,120**	**4.72**
Rapid pulse rate	26,007	**2.45**
Current infection/antibiotics	25,983	**2.45**
12 mo, other blood exposure; e.g., needle stick, tattoo, body piercing, snorted cocaine	19,085	**1.80**
Cancer ever	17,280	**1.63**
3 mo outside US;1980-96 (UK)	13,722	**1.29**
Don't feel well today	11,874	**1.12**
Chest pain (6 mo)	10,151	**0.96**

Impact of Malaria Deferrals by Country of Travel 6 REDS-II Centers, 12,310 deferrals/1.25 million allogeneic donations, 30-day travel recorded

Travelers to: (x 10^6) in 2003	# Imported Malaria Cases (US civilians)	Rate Imported Malaria/10^6 travelers	Malaria Travel by Area	Projected # Deferred Donors/Year
Africa (0.21)	561 (94x)	2683 (8000x)*	2.3%	3400
Mexico (17.56) (84x)	6	0.34	41.1%	59,650
Central America Caribbean (6.78)	59	8.71	38.4%	55,700 (80%)
S America (1.85)	21	11.38		
Asia/W Pacific (4.26)	109	25.57	16.0	23,250
	756	*91x Amer	97.8	142,000

Spencer et al., AABB 2006

Donors Implicated in Transfusion Transmitted Malaria, US, 1963-99

N=64 (of 67) imp.donors	1963-69 (N=11)	1970-79 (N=24)	1980-89 (N=17)	1990-99 (N=12)
	Number (%)			
Resident mal area	4 (36)	5 (21)	15 (88)	10 (83)
US civilian traveler	0	2 (8)	0	1 (8)
Visit friends/rel	1 (9)	4 (17)	2 (12)	1 (8)
US military	6 (55)	13 (54)	0	0

Mungai et al., NEJM, 1999

Region of Acquisition; Imported US Malaria by species (2002)

Plasm.	falcip	vivax	mal	ovale	unk	mix	Total
Africa	613	71	30	30	153	6	903
Asia	18	130	3	3	14	3	171
Cental Am/Carib	23	62	1	1	9	0	96
N Amer	2	7	0	0	1	0	10
S Amer	8	19	2	1	5	0	35
Oceania	5	23	1	0	7	0	33
unk	29	24	0	1	24	2	80
Total	698	336	37	37	213	11	1332

MMWR ss-1 2004

Australian (ARCBS) Experience

- 1991 - Last case of TTM; fatal
  - At 1 million donations per year, risk is < 1 per 10 million
- Donor deferral rate due to questioning infection/residence/travel = appr.5%
  - 20,000 deferred/472,000 presenting donors per year (x1.92 dntns/year=908,000/yr + other =1.08 million)
  - 50% of current discard of red cells
  - Yes to question: **in all cases, distribute frac plasma only** (so donors are still donating)
  - Deferral = cessation of distribution of cellular components
    - 95.5% travelers (within past 12 mos but stayed < 6 continuous mos; i.e., not a resident); 12-mo deferral
      - Risk area defined by WHO
    - 4.4% residents (≥6 continuous mos within the past 3 years; i.e., to detect significant recent exposure); 3-yr deferral
    - <0.1% infection (but recovered); 3 yr-deferral
  - Questioning as protection, **"Any process reliant on assessors eliciting and recording accurate information has a significant error rate"**

Australian (ARCBS) Experience

- July 17, 2005 implement "testing in" strategy for any deferred donor
  - Modeled after the UK NBS (*Kitchen et al., 2004 Vox Sang*)
  - ≥ 4 mos elapsed since leaving a malarial area or recovery/cessation of symptoms of prior infection (compliant with Council of Europe)
    - If >3 years passed, no testing required
  - Collect donation (quarantine red cells)
  - Test recombinant malaria Ab test for Pf/Pv (Newmarket EIA, Newmarket Labs, Ltd, UK)
    - Pm/Po detection by cross reactivity (50-70% for Po)
    - Pm/Po represent 3% and 1% of malaria cases in Australia
      - Last TTM Pm case 1956
    - TGA approved based on low frequency of Pm/Po; cross rx; and 4-month "embargo"
  - If test neg: release red cells for transfusion; donor deferral removed unless re-visit other malarial areas
- Note, logistical challenges (IT and collection staff) to trigger testing and quarantine red cells; one process recall to date

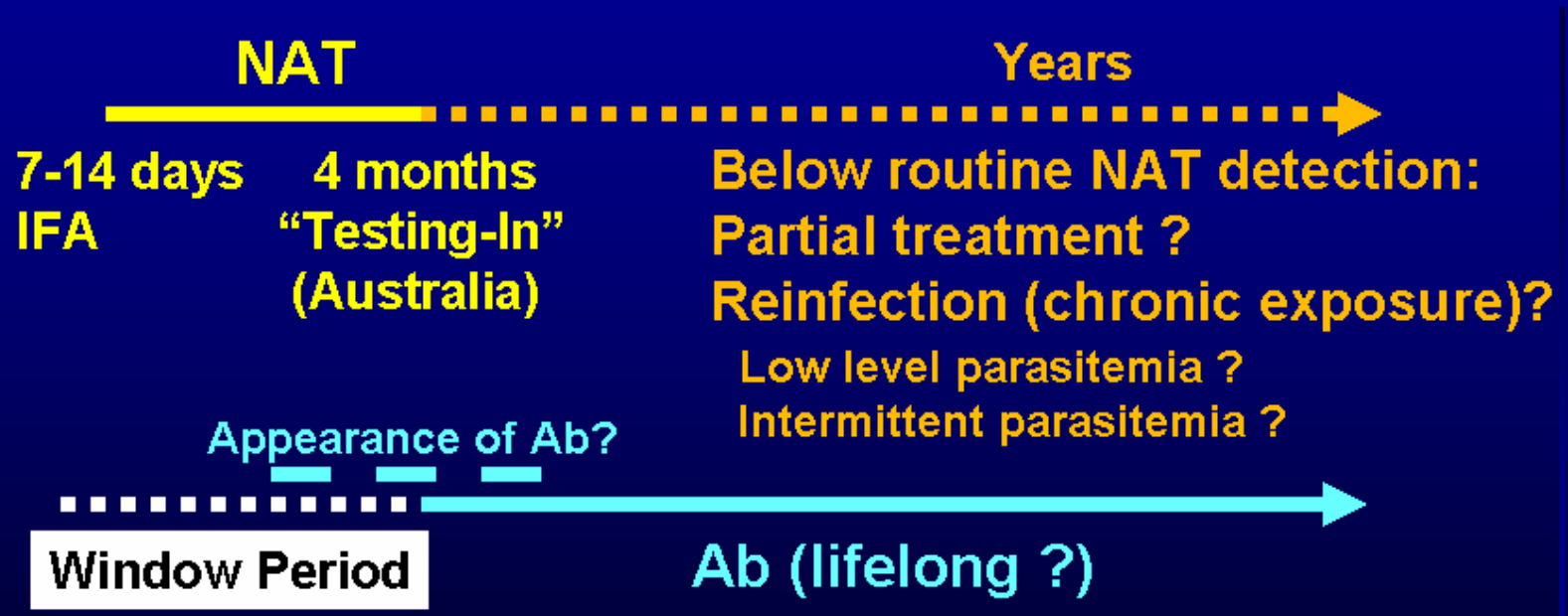
Australian (ARCBS) Experience

- Results (7/17/05-3/30/06)
  - 26,356 donors screened (visitors/residents/prev infection); Sydney
    - + 18,145 (77%) subsequent donations
  - RR rate = 2.28% (602); pilot 2.3%; *Seed et al., 2005 Vox Sang 88*
  - Each RR tested to determine evidence of parasitemia
    - Binax (Portland, ME)/NOW Pf/Pv Ag dipstick (sens 100 parasites/uL)
      - 93.4% sens (100% Pf, 89% Pv); Pm/Po cross rx
      - 96-98% spec
      - Whole blood w/in 72h
    - Artus RealArt Rotorgene PCR (Artus Biotech, Germany) (sens 1 parasite/uL)
    - Pos Ag (+/-PCR) referred for clinical assessment: probable parasitemic
  - Each RR notified (letter for MD stating Ab RR to explain any febrile illness); again restricted to donating only frac plasma until Ab nonreactive
  - No Ag or PCR positives to date

Australian (ARCBS) Experience

- July 2006 (first week), first probable parasitemic donor
  - Indian resident who migrated to Australia in 2005, completely asymptomatic
    - RR Newmarket EIA (high signal)
    - Ag weak Pf band (repeated)
    - PCR negative
    - Follow up pending
    - Referred to ID specialist
    - Within predicted rate
- Of analyzed data: RR/total tested
  - **Travel: 216/20,780 (1.0%)**
  - **Residence: 138/1550 (8.9%)**
  - **Infection : 15/50 (30%)**
- Recovery: to May 06 = 32,000 index red cells (minus Queensland, 20% of supply)
  - Exceeds predictions of 26,000 (included Queensland)
  - Hidden deferrals (donors not retained as frac plasma donors)

Testing Options: Universal Screening (Ab only vs Ab + NAT) Ab "Testing In" (Australian model)



Current deferrals based on:

- **97% of malaria cases in travelers occur within 1 year of living in the risk area**
- **99% of malaria cases in residents occur within 3 years**

Testing Options: Ab "Testing In" (Australian Model)

PROS

- Shortens deferral period (from 12 mos-3yrs to 4 months)
- Aus model: 4 month return visit is a donation, where if Ab negative, the RBCs used and donor automatically reinstated
  - US model; sample only or donation; if test neg, could donation be used?

CONS

- **COMPLEX**; doesn't alter current questioning process
- Donor loss likely equivalent
- Costs:
  - IT
  - Process development including donor management and testing algorithm
  - Reagents (if any interest in US)

Testing Options: Universal Screening (Ab only vs Ab + NAT)

PROS

- Eliminates travel deferral; 1.2-1.3% presenting donors
- Increase donations; convert 83% FT presentations into donors
- Improved donor retention
- May reduce self deferrals

CONS

- Required algorithm uncertain (Ab only ?)
- Cost
- Test performance
  - Sensitivity to all 4 P. spp.; versus cross rx?
  - Specificity
- Donor management
  - Ab pos deferral period ? (would there be permanent deferral since Ab testing would be in place)

Testing Options: Universal Screening (Ab only vs Ab + NAT)

- Donor question: have you had malaria?
  - Yes: no test, permanent deferral
- Donor question: In the past 3 years have you lived (> 5 yrs) outside the US or Canada? (drop down menus to determine malarial areas)
  - Yes: no test, deferral period (3 years as current or permanent based on minuscule yield/risk of donors)?
- Test all donations
  - 4 spp test, or Pf/Pv specific (with Po/Pm via cross reactivity)
  - Ask donors with recent travel to self defer during window period
  - Additional testing; PCR or Ag for counseling

Collaborators

- ARC
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