Transfusion-transmitted Cytomegalovirus

Can you confidently abandon CMV seronegative products in the modern era of pre-storage leukoreduction?

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Really?

Are we still talking about this in 2017?

Disclosure

- I am not:
  - A virologist
  - A microbiologist
  - An expert researcher on transfusion-transmitted cytomegalovirus
- I am:
  - A reasonable person
  - An early adopter of leukoreduction as a sole strategy for CMV prevention
- No “official disclosures”

Sunnybrook, UHN & Partners

- Neonates: in 2001 we (in conjunction with Hospital for Sick Kids) stopped dual coverage (breast milk contamination studies)
- Rest of high risk populations:
  - Complete abandonment at Sunnybrook: 2012
  - [Note: Ottawa abandoned for HSCT in 2009]
  - Complete abandonment at 27 sites: 2015
- We have HSCT, solid organ transplants, pregnant women, HIV patients, neonates
- The only thing we don't do is intrauterine transfusions

Outline

- Biology & epidemiology of CMV
- History of transfusion-transmitted CMV
- Blood donor CMV science
- Modern day leukoreduction failure rates
- Systematic review from AABB CTMC
- Larger clinical reports – HSCT, SOT, neonates
- When you need to test HSCT and SOT patients
- Review the National Advisory Committee Recommendation
- Conclusion

Basic Biology of CMV

- CMV or HHV-5 is a herpes virus
- Infected via mucosal epithelial cells
  - Vertical, breast milk, sexual contact (any), transfusion, HSCT, solid organ transplant, iv drugs
- Remains latent in myeloid cells for life
- Primary infection and the risk of reactivation (usually during illness including postpartum)
  - 4-8 week from infection to CMV Ab
  - DNA+ > IgM > IgG
- Seropositive: women, older patients, lower economic status, MSM
- About 40% of Canadians are seropositive (much lower than most other countries)
- 1% annual seroconversion rate in healthy blood donors

Epidemiology of CMV

Blood transfusion

History of TT-CMV prevention

Warm whole blood 1 in 2

Refrigerated whole blood 1 in 100

Seronegative non-LR 1 in 66,000

Pre-storage LR only 1 in 13,575,000

Seed et al. Vox Sang 2015; 109: 11-17
Allain et al. Biologicals 2009; 37: 71-77

If the risk is 1 in 13 million why am I speaking about this today?

I think because blood bankers are neurotic about accepting any possible risk

Compared to other viruses

Virus	Risk
HIV	1 in 21 million
CMV	1 in 13.5 million*
HCV	1 in 13 million
HBV	1 in 7.5 million

* But remember half of recipients already infected!

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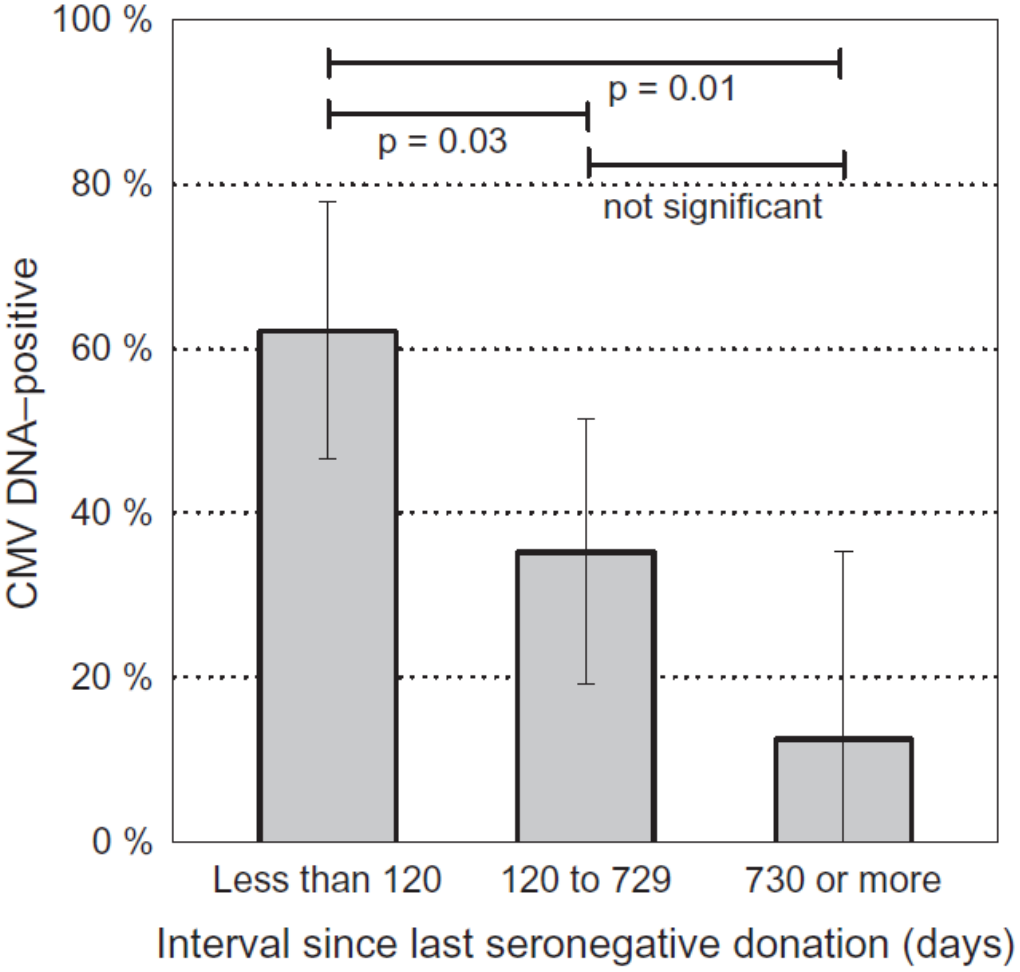
CMV Donor Science

- CMV-neg units can transmit CMV because the window period after infection until Ab positive is 4-8 weeks
  - Unknown how long the infectious window is (some donors may self defer “don’t feel well”)
  - LR **may** not help as 0.13% have detectable CMV DNA
  - Unclear how efficient cell free CMV DNA is at transmission
- LR units can transmit CMV because of the incomplete removal of white blood cells in **rare** units due to failure
  - I could not find a single case report of confirmed transfusion transmission from pre-storage LR only
- Some experts recommend the safest CMV product would be from selection of CMV seropositive donors at least 1 year after seroconversion
  - You also get “passive immunity” from donor IgG

Ziemann et al. Transfusion 2007; 47: 1972-83
Visconti et al. Blood 2004; 103: 1137-39
Zanghellini et al. J Infect Dis 1999; 180: 702-7

CMV DNA in recent seroconverters



TRANSFUSION 2007;47:1972-1983.

CMV DNA in different donors

Donor status	N	CMV DNA+	CMV DNA-
Seronegative	150	0	150
Seropositive>1 yr	450	0	450
Sero “negative”	68	2	64
New SP “first”	82	36	43
New SP “second”	71	4	66

62% of SC are DNA+

TRANSFUSION 2007;47:1972-1983.

CMV positive donors

- 2 studies including 1,086 CMV+ donors
- No DNA+ donations in follow-up

Ziemann et al. Transfusion 2007; 47: 1972-83.
Drew et al. Transfusion 2003; 43: 309-13.

- 1 study including 7,303 CMV+ donors
- 1 DNA donations in follow-up – low IgG and very low CMV DNA (<30 IU/mL)

Ziemann et al. Transfusion 2013; 53: 2183-89.

- Led to the common recommendation that CMV+ donors >1 year out = lowest risk donor

Ziemann et al. Transf Med Hemo 2014; 41: 40-44.

Many CMV-neg donors are DNA+

- 41% of CMV+ donors have CMV DNA in their WBCs
  - If you enrich the sample with monocytes then 71% CMV DNA+
- 13% of CMV- donors have CMV DNA in their WBC
  - If you enrich the sample with monocytes then 55% CMV DNA+

TRANSFUSION 1998;38:271-278.

Pre-storage LR in 2015

Variable	B1 RBC	B2 RBC	BC-platelet	A-platelet
# tested	5045	3401	1210	1116
WBC median	0.063×10^6	0.080×10^6	0×10^6	0×10^6
Pass rate	99.88%	99.76%	100.00%	100.00%

FDA recommendation = $<5 \times 10^6$
Other countries = $<1 \times 10^6$

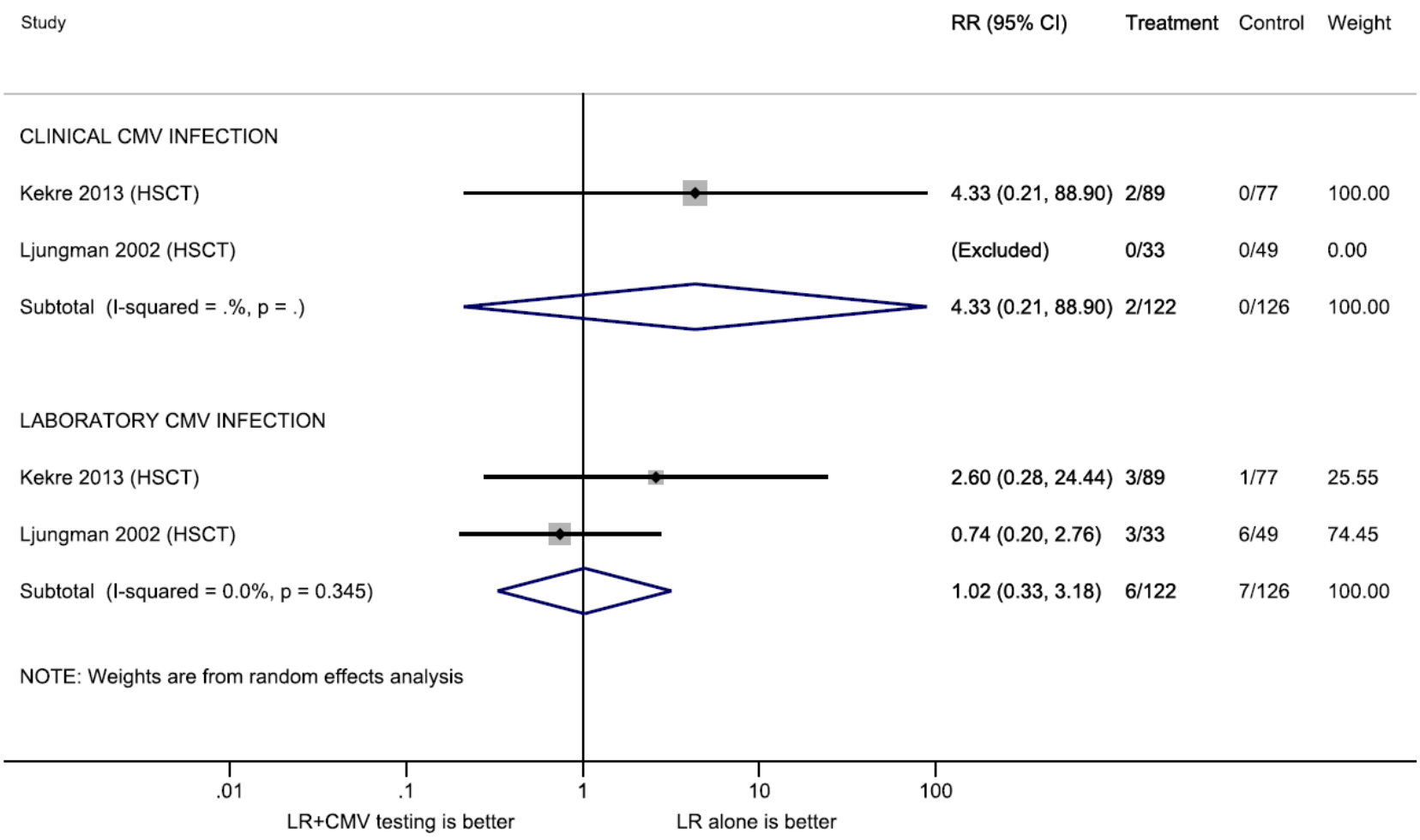
CBS, personal communication

Systematic Review of Clinical Studies

- 11 studies (7 observational with 949 pts; 4 RCTs with 680 pts)
- 7 chemo/HSCT; 4 infants
- Only 3 studies “modern” with pre-storage leukoreduction (677 pts; 2002/2003/2013)
- Infant studies problematic as infants fed CMV+ infected breast milk included
- No attempt to link donor to recipient
- Only 2 looked at LR vs. LR plus seronegative

Mainou et al. Transfusion 2016; 29 January 2016

Systematic Review



Mainou et al. Transfusion 2016; 29 January 2016

Thiele – Germany HSCT

- 23 CMV -/- HSCT patients
- 3180 donor exposures of pre-storage LD only
- No seroconversions
- 17 of 23 had passive IgG detected (IgM neg, DNA neg)

Thiele et al. Transfusion 2011; 51: 2620-26.

Nash – Michigan HSCT

- 100 CMV -/- HSCT patients
- Followed weekly for CMV DNA
- Transfused 3690 units of LR-only
- No seroconversions
- 2/100 transient IgG CMV Ab positive (IgM neg, DNA neg) due to passive Ab

Nash et al. Transfusion 2012; 52: 2270-72.

Kekre - Ottawa HSCT

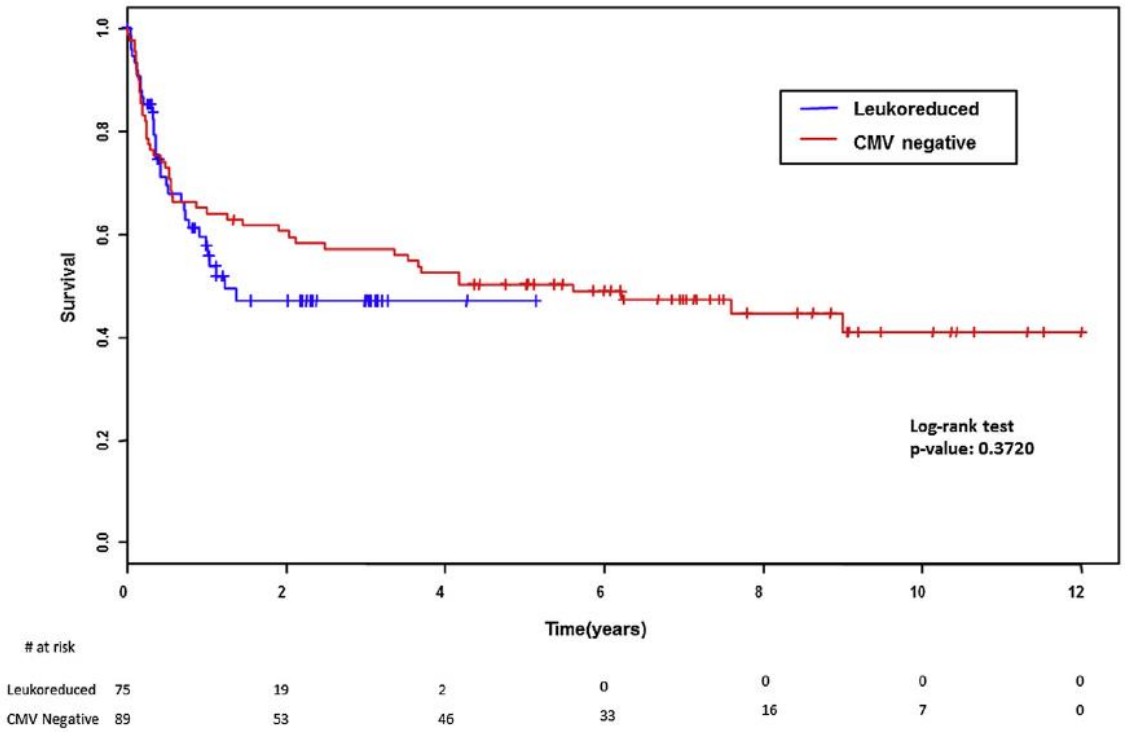


Figure 3. Overall survival by transfusion group.

89 LR and CMV-
77 LR only

Just -/- transplants

4 CMV PCR+
- 3 LR and CMV-
- 1 LR only

2 CMV disease
- Both LR and CMV-

Biol Blood Marrow Transplant 19 (2013) 1719–1724

Hall – Oxford/Birmingham HSCT

- 76 CMV -/- HSCT patients
- Followed weekly for CMV DNA
- Transfused 1862 donor exposures of LR-only
- No seroconversions

Hall et al. Transfus Med 2015; 25: 418-23.

Solid organ transplant

- Non-LR, CMV untested; details fuzzy

Type of allograft	CMV serostatus of recipient and donor	Number of CMV patients infected* (%)	Number of patients who were transfused (%)	Number of R–D– patients who developed CMV/number transfused (%)
Renal	R–D–	0/71 (0%)	57/71 (80.3%)	0/57 (0%)
	R–D+	69/81 (85.2%)	62/81 (76.5%)	
Heart	R–D–	0/29 (0%)	29/29 (100%)	0/29 (0%)
	R–D+	28/32 (87.5%)	32/32 (100%)	
Lung	R–D–	1/7 (14.3%)	6/7 (85.7%)	1/6 (16.7%)
	R–D+	9/10 (90.0%)	10/10 (100%)	
Liver	R–D–	2/20 (10.0%)	20/20 (100%)	2/20 (10.0%)
	R–D+	25/31 (80.6%)	31/31 (100%)	

TRANSFUSION 2002;42:396-402.

Premature neonates

- 462 mother and 539 LBW infant “pairs”
- 76.2% of mothers were CMV antibody positive
- CMV infection rate among infants was 7% at 12 weeks
- A total of 2061 CMV-seronegative and LR transfusions administered
  - No cases of transfusion-transmitted CMV
- 96% of cases were from breast milk (1 other route)
- What is the point of CMV seronegative and leukoreduced if breast milk feeds are continued?

Josephson et al. JAMA Ped 2014; 168: 1054-62.

Why can't clinical trials answer this question?

Product	Probability	95% confidence
RBC	1 in 7,790,000	1 in 771,307,000 1 in 993,000
Platelets	0	0 1 in 1,074,000
Combined	1 in 13,575,000	1 in 1,344,167,000 1 in 1,730,000

$$\begin{aligned}\text{RBC unit } [p(Inf)] &= p(f) \times p(viraemia) \\ &= 0{\cdot}001083 \times 0{\cdot}0011850538 \\ &= 1{\cdot}2837 \times 10^{-7} (95\%\ \text{CI}: \\ &1{\cdot}297 \times 10^{-9} - 1{\cdot}007 \times 10^{-6}) \text{ or,} \\ &1 \text{ in } 7\,789\,519\ (95\%\ \text{CI}: \\ &1 \text{ in } 771\,306\,874 - 1 \text{ in } 992\,979).\end{aligned}$$

Seed et al, Vox Sang 2015; 109: 11-17

Criticism of Seed et al.

- They excluded infections from cell free DNA…but the authors argued:
  - Theoretical only
  - No reported cases of CMV transmission by FFP
  - Cell free DNA is highly fragmented
  - Studies in mice fail to demonstrate any infectivity

Seed et al, Vox Sang 2015; 109: 11-17

Logistical issue

- You **MUST** draw CMV Ab testing for potential HSCT and SOT patients before their 1st platelet transfusion!
- Observational study of 31 HSCT patients
  - 35.5% did not have their CMV Ab checked before 1st transfusion
  - 93.5% had multiple CMV Ab tests pre-transplant
  - 27.6% had “flipping” results suggesting passive Ab detection
  - 1 CMV-neg donor had a CMV-pos donor selected in error

Morton, et al. Transfusion Med 2015; 25: 411-13

Overall conclusion

Patient population	Recommendation	Justification
Neonates	LD only	74% of CMV+ mother have CMV in breast milk
Solid organ	LD only	CMV transmission from "LR only" never detected in -/- SOT; monitoring plus preemptive therapy routine*
HSCT (allogeneic)	LD only	CMV transmission from "LR only" rare unproven cases in -/- HSCT; preemptive therapy and screening routine*
Pregnant women (not in delivery)	LD only	40% seropositive and 3.9% seroconversion rate in pregnancy[1]
HIV	LD only	High baseline rates of CMV infection (>90%)
Intrauterine	CMV+>1 year CMV DNA-	Highly unlikely that the CMV DNA step adds additional safety…but perhaps after a large HSCT cohort study we can abandon this

* Must do CMV Ab testing before 1st platelet transfusion or IVIG administration

1. Lamarre et al. Epidemiolog Infect 2015; epub ahead of print

Cost to Canadian Blood Services?

$700,000

(just the testing kit cost)

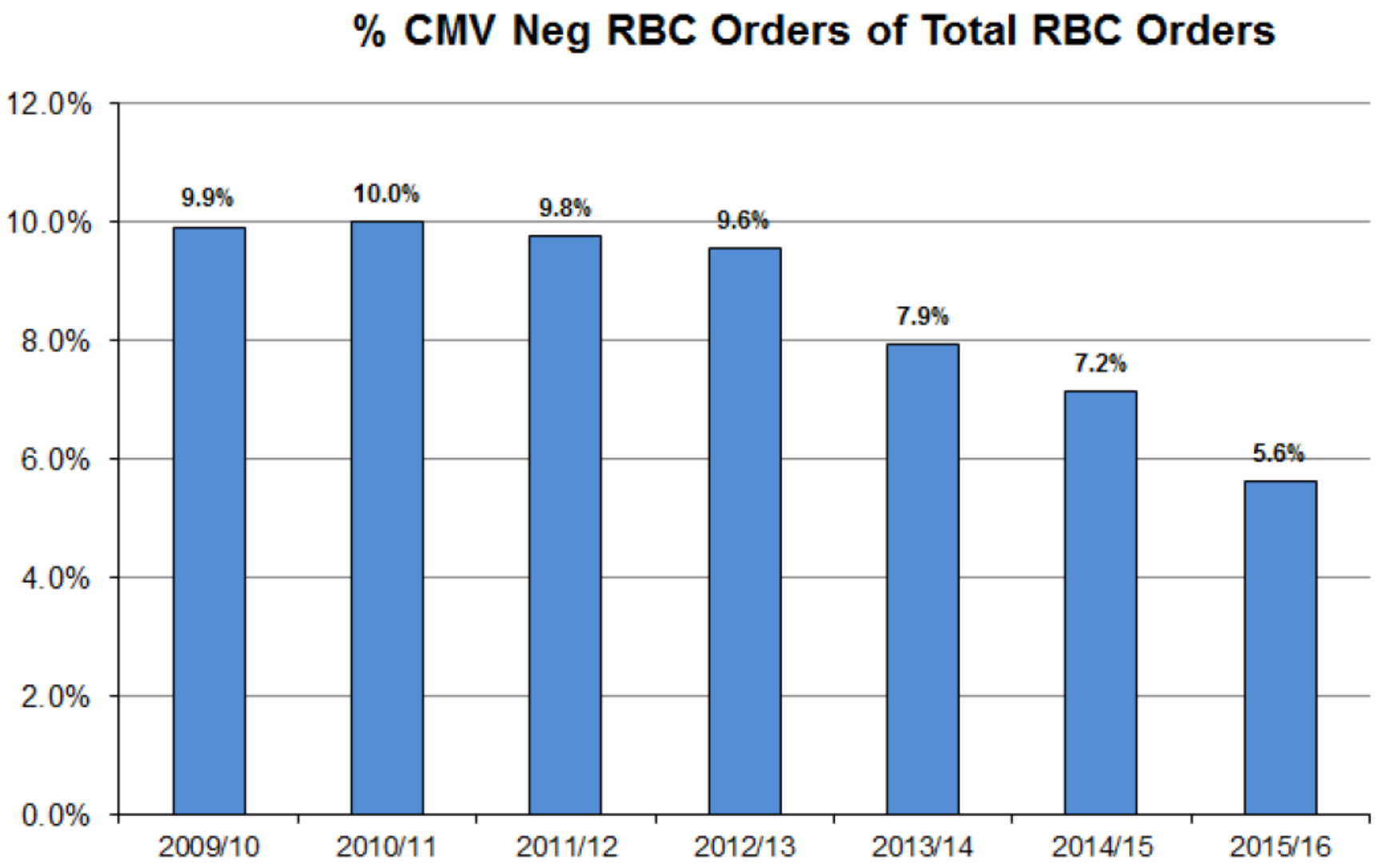
Personal communication, CBS, 2012

Just a guess

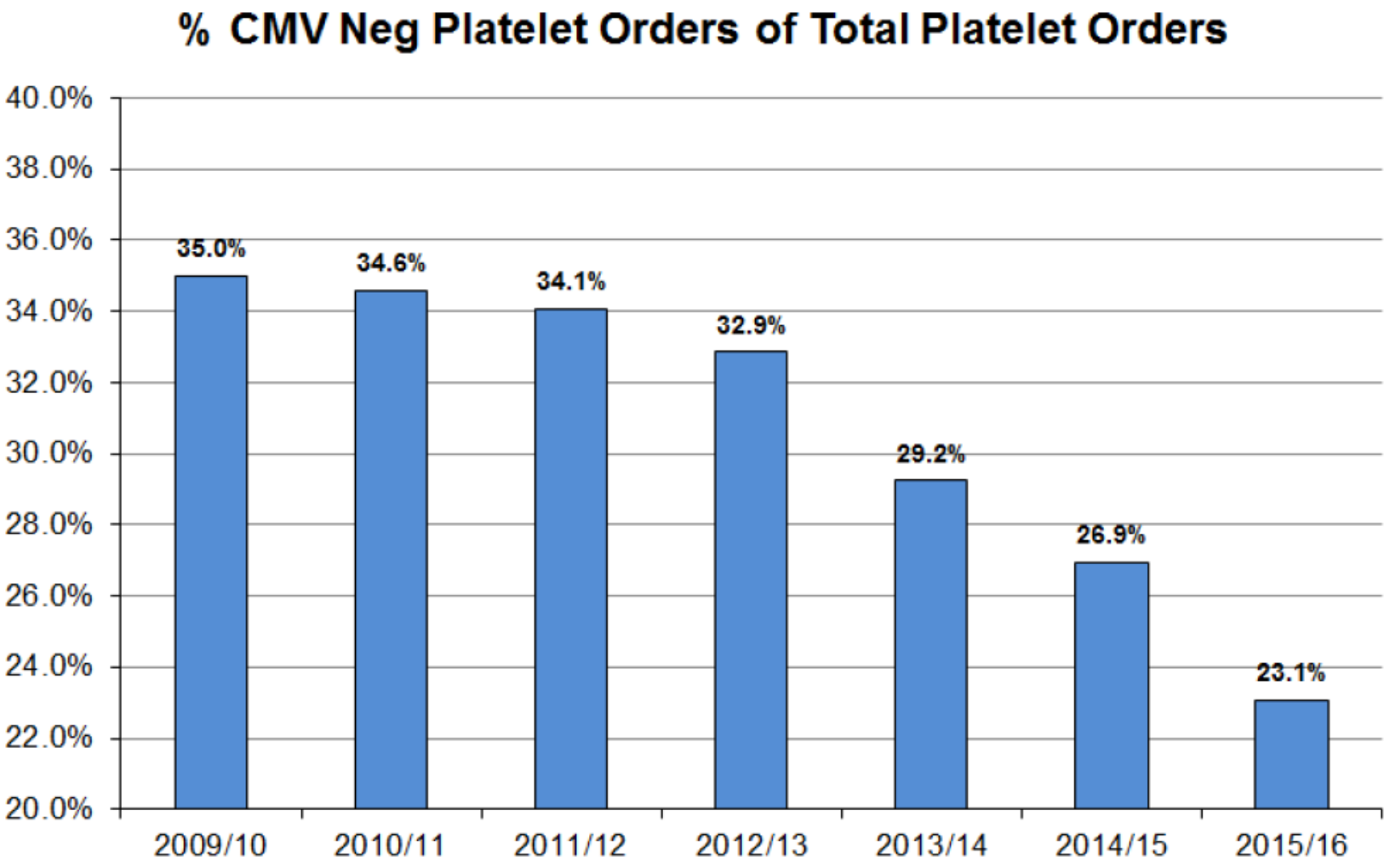
We are probably spending $1-2 million on CMV seronegative testing and distribution

(add labour, transportation, transfusion delays)

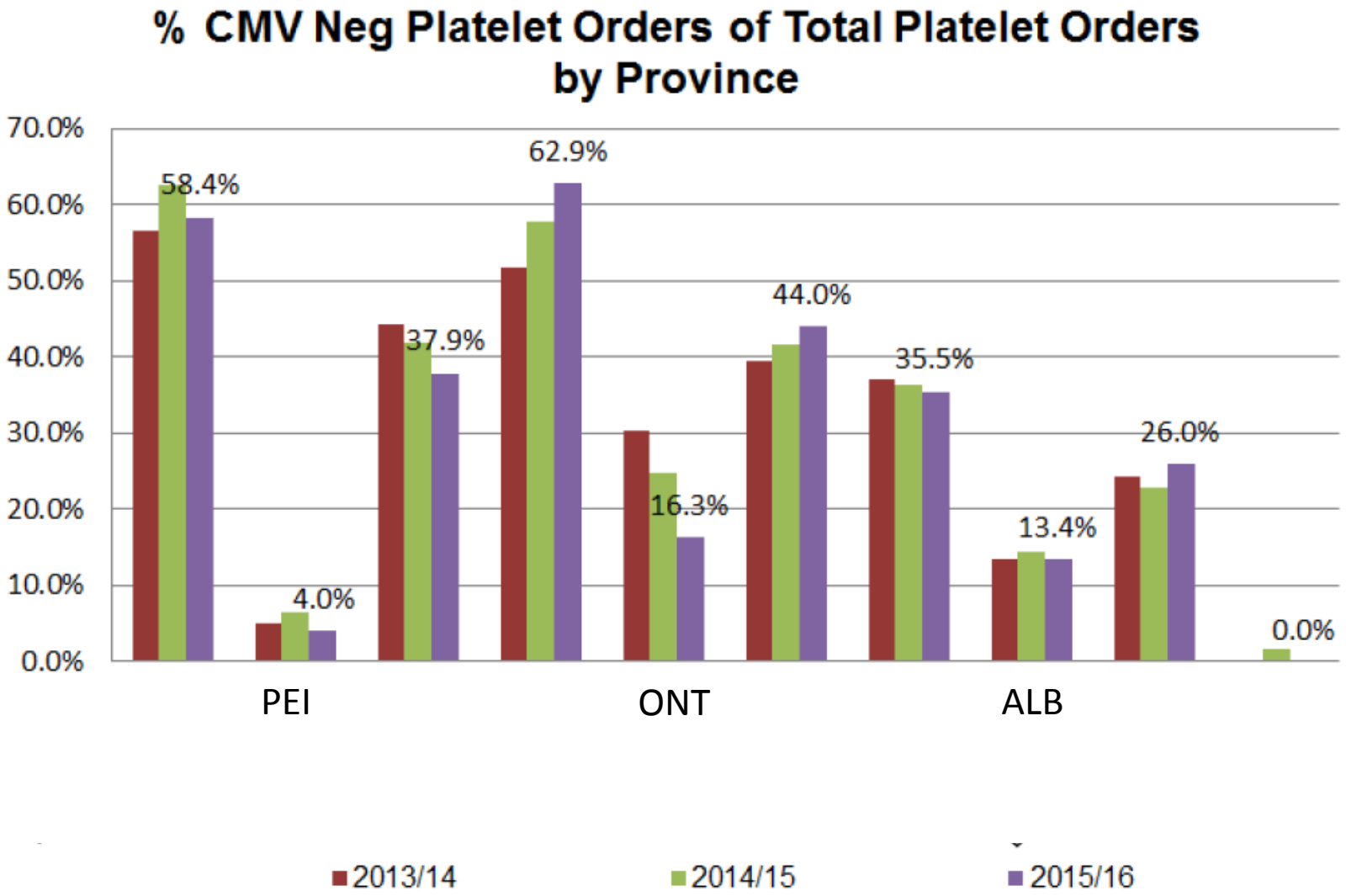
RBCs


% CMV Neg RBC Orders of Total RBC Orders
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
9.9%
10.0%
9.8%
9.6%
7.9%
7.2%
5.6%
2009/10
2010/11
2011/12
2012/13
2013/14
2014/15
2015/16

Platelets


% CMV Neg Platelet Orders of Total Platelet Orders
40.0%
38.0%
36.0%
34.0%
32.0%
30.0%
28.0%
26.0%
24.0%
22.0%
20.0%
35.0%
34.6%
34.1%
32.9%
29.2%
26.9%
23.1%
2009/10
2010/11
2011/12
2012/13
2013/14
2014/15
2015/16

Variability by Province



National Advisory Committee Recommendations on CMV Prevention

- NAC recommends that CMV safe (LR) and CMV IgG seronegative products be considered equivalent ***except*** for Intrauterine transfusion
- NAC recommends that CBS stop their current process for testing and provision of CMV seronegative units issued to hospital facilities and develop a new process to maintain a small inventory of CMV seronegative blood components for the sole purpose of Intrauterine transfusion (IUT)
- NAC recommends that CBS explores the feasibility of providing a small boutique inventory of dually tested (seronegative and NAT) CMV negative blood components for the sole purpose of IUT

http://www.nacblood.ca/resources/guidelines/CMV.html

Summary

- CMV is present in half the population and transfusion (if ever) is NOT a common route of infection
- History of transfusion-transmitted CMV
  - We have decreased the risk from 1 in 2 to about 1 in 13 million
- Blood donor CMV science
  - Evidence suggests long-term CMV+ donors may be the safest
- Modern day leukoreduction failure rates
  - Never for platelets and rare for RBCs
- CMV seronegative and leukoreduction are NOT additive in terms of protection
- Test HSCT and SOT patients before the first platelet transfusion to avoid passive Ab issue
- No proven cases of CMV transmission from LR-only in HSCT or other recipients

If the risk of TT-CMV is
1 in 13.5 million
we will never have RCTs…
so…STOP WAITING FOR THEM