STOLLERY CHILDREN'S HOSPITAL

# Neonatal Transfusion: Irradiation and CMV

6th Annual Blood Matters Conference

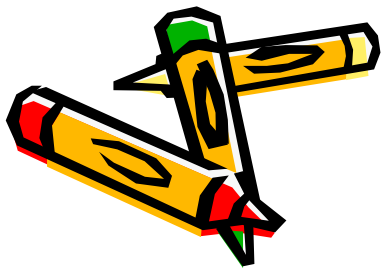
November 6th, 2015

Alberta Health Services

# Disclosures

- Member of NAC (National Advisory Committee on Blood and Blood Products)

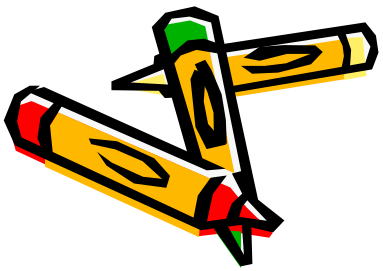
- Co-investigator – CBS Small Project Fund – Transfusion Transmitted CMV in Solid Organ Transplant Recipients



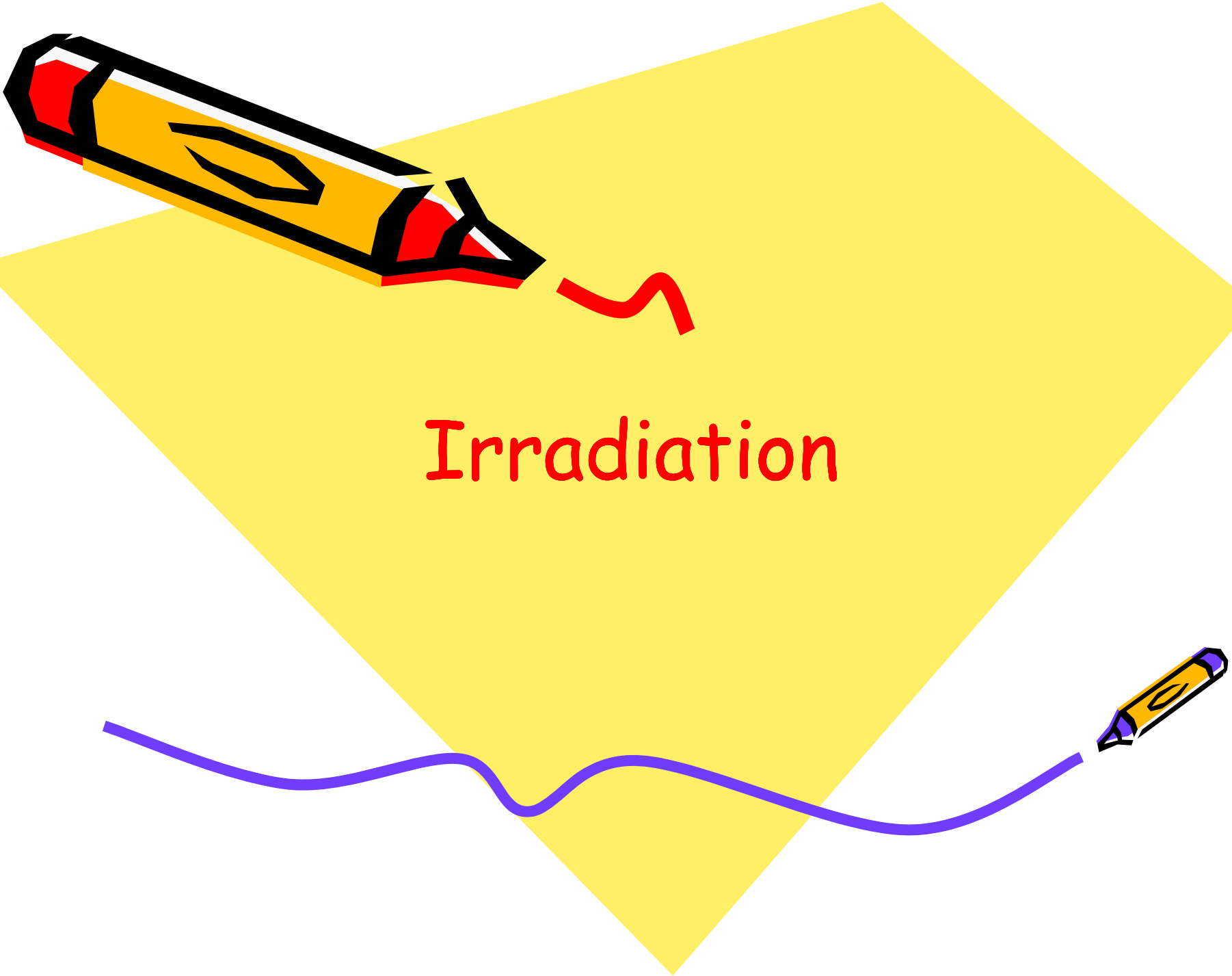
# AHS / Stollery Edmonton Zone- Definitions

- Neonates
  - Birth to 4 months, regardless of gestational age

- Pediatric Patient
  - Less than 16 years of age



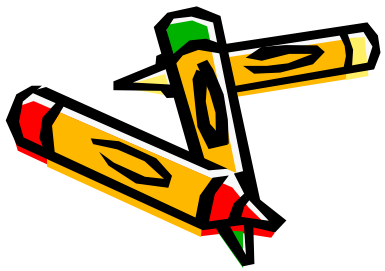
On an annual basis, >20 000 transfusions occur between the two NICUs, the intermediate care nursery and our PICU.


Irradiation

# Irradiation

- Gamma irradiation at 2500 rads/cGy renders lymphocytes incapable of mitosis and thus unable to proliferate preventing Transfusion Associated-GVHD

- Irradiation of PRBC
  - will decrease outdate to 28 days post irradiation
  - must wash within 24 hours of irradiation for neonatal transfusion due to concern for increased potassium levels

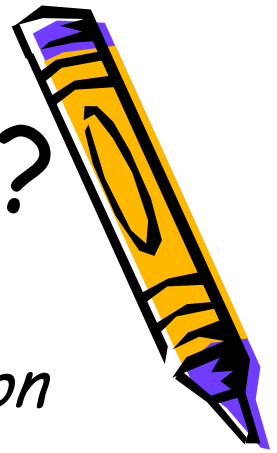


# Irradiation

- Generally Accepted indications:
  - Intrauterine or post IUT exchange transfusion
  - Directed donation/HLA matched
    - Includes platelets!
  - T Cell immune deficiency
    - Includes Congenital Cardiac anomalies
  - Hodgkin lymphoma
  - BM or SC transplantation (allo & auto)
  - Purine analog therapy (ie. fludarabine)
  - low birth weight babies (<1200g)

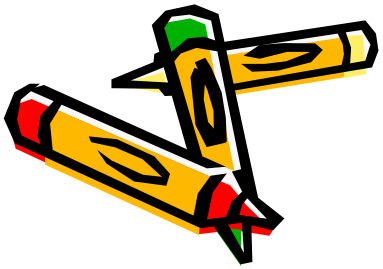
BCSH Guidelines on the use of irradiated blood components BJH 2010
A&NZ Society of Blood Transfusion Guidelines for Prevention of Transfusion Associated Graft versus Host 2011

# What do we do in Edmonton?

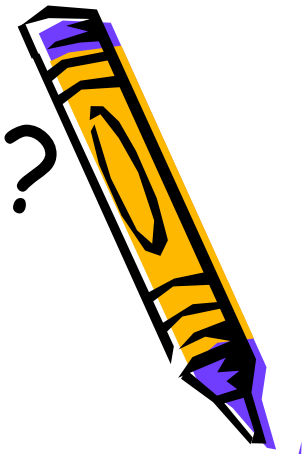


We irradiate for:

- *Intrauterine or post IUT exchange transfusion*
- Directed donation/HLA matched products
  - Includes platelets!
- **T Cell immune deficiency**
  - Includes "Complex" Congenital Cardiac anomalies
    - Up to 6 months of age at which time thymic presence or testing for 22q11.2 is should be completed
- Hodgkin lymphoma
- BM or SC transplantation (allo & auto)
- Purine analog therapy (ie. fludarabine)



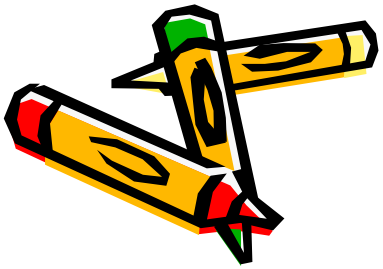
# What do we do in Edmonton?



We do not irradiate for:

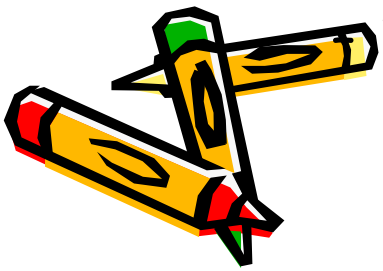
- Exchange transfusion that are not post IUT

- Neonatal top up transfusions regardless of gestational age or birth weight



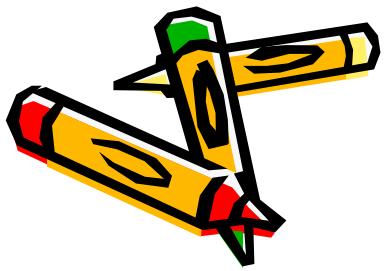
# Why ?

- Neonatologist concerns:
  1. Hyperkalemic arrest
     - No irradiator on site at the Royal Alexandra site where the "medical" NICU is.
     - Holding pre irradiated units will increase the potassium
  2. Delay in transfusion versus Increased donor exposure
     - We have transfusion policy to provide a "limited" donor program in eligible neonates
     - To ship aliquots to University Hospital for irradiation has a turn around time of at least 4 hours



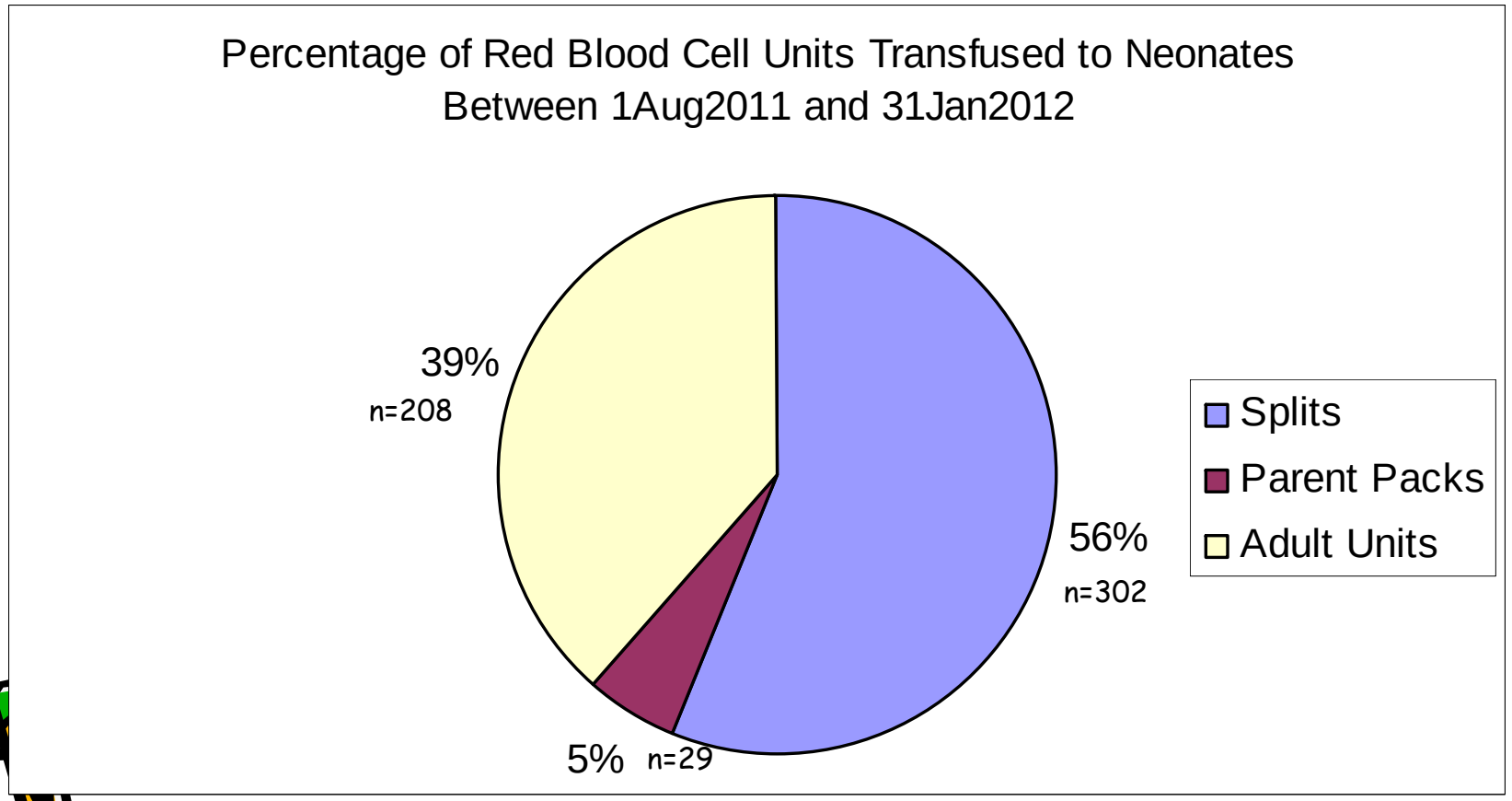
For top up transfusions, attempts are made to limit donor exposure by designating an allogeneic red cell unit to an infant for it's 42 day lifespan

- Red cell aliquots are obtained using Ped-Paks or by sterile docking additional bags to the parent unit



# Data from 2011- Jan 31st 2012

539 red blood cell transfusions in 107 neonates.



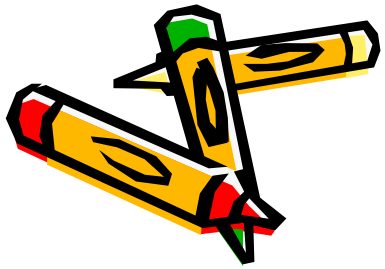
# Donor Exposure in Neonates Receiving Only One Donor Unit

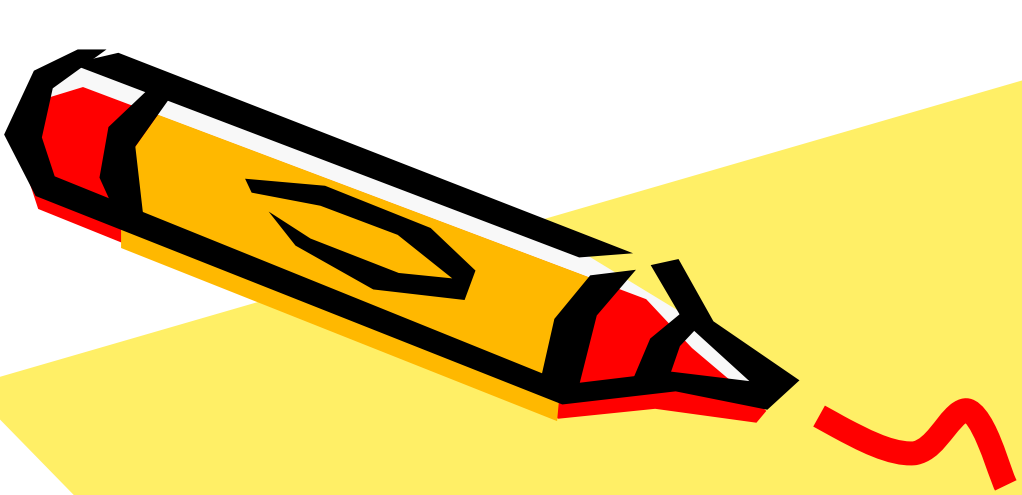
- 60% (32 of 53) of the neonates who were only exposed to the one donor unit took only one split.

- 40% (21 of 53) of the neonates that were only exposed to one donor unit received multiple splits from the same pack.

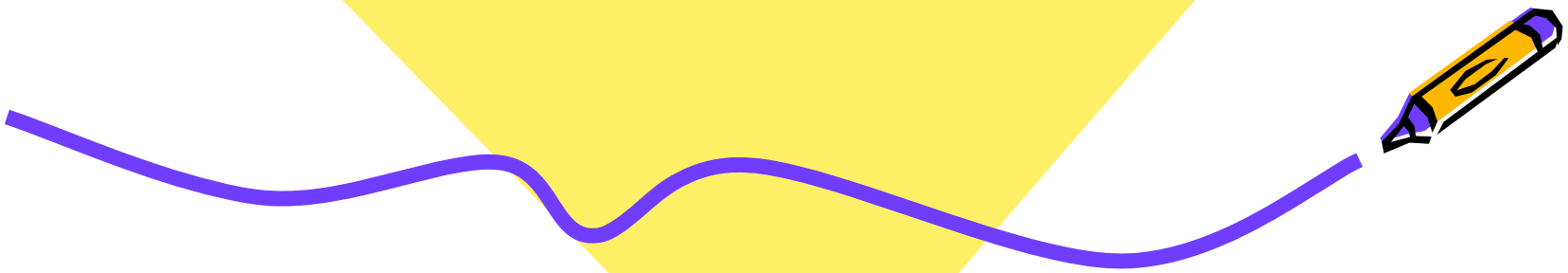
The average received 2 splits with a range of 1 to 8 splits transfused.

- No case of TA-GVHD has been identified to date in these patient categories
  - Study is planned to review all neonates for past 5 years and ensure not missing any
  - Historically (before I was a MD!)
    - 1 case in a pediatric B-ALL
    - 1 case in a pediatric congenital cardiac patient





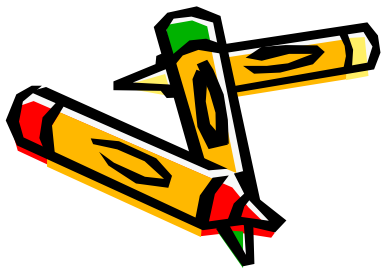
# CytoMegaloVirus



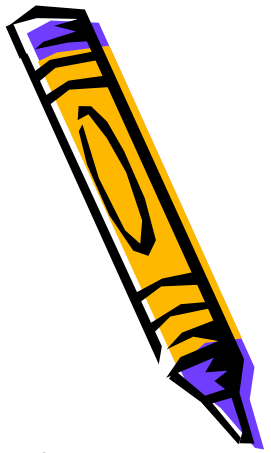
# CMV

- Cytomegalovirus is an intracellular DNA virus that can be transmitted by transfusion of leukocytes

- Many centres have indications for "CMV negative" cellular components for :
  - Intrauterine/exchange transfusion
  - ? Neonates weighing less than 1200g born to seronegative, or unknown status, mothers
  - Seronegative, or unknown status, pregnant women



# CMV Negative/Safe



**CMV Safe = prestorage leukoreduced**

All cellular products in Canada are prestorage leukoreduced and are considered CMV safe

**CMV Negative = CMV SERO-negative**

Misnomer as it only indicates the absence of an antibody response to CMV not the lack of virus.

- 0.13% of CMV seronegative units have detectable CMV DNA due to primary seroconversion

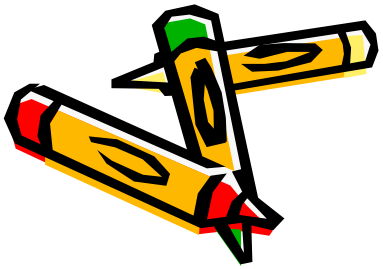
- window period after infection until antibody screening becomes positive is approximately 6 to 8 weeks.

Ziemann M et al Krueger S, Maier AB, Unmack A, Goerg S, Hennig H. High prevalence of cytomegalovirus DNA in plasma samples of blood donors in connection with seroconversion. *Transfusion.* Nov 2007;47(11):1972-1983

# NAC CMV Statement: posted August 2014

"The National Advisory Committee recommends that CMV safe and CMV IgG seronegative products be considered equivalent for the majority of patient populations including adult and pediatric Hematopoietic stem cell recipients, CMV seronegative patients who may require future transplant and immunodeficient patients.

Due to significant controversy and lack of evidence on the need for the provision of CMV seronegative products in addition to leukodepletion in the following 3 patient groups - intrauterine transfusion, neonates under 28 days of age and in elective transfusion of CMV seronegative pregnant women, NAC recommends to follow local policies".



# New evidence?

TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
Transfusion Medicine | SHORT COMMUNICATION

## Transfusion in CMV seronegative T-depleted allogeneic stem cell transplant recipients with CMV-unselected blood components results in zero CMV transmissions in the era of universal leukocyte reduction: a UK dual centre experience

S. Hall,[1] R. Danby,[2] H. Osman,[3] A. Peniket,[2] V. Rocha,[2] C. Craddock,[4] M. Murphy[1] & S. Chaganti[4]

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*Received 8 March 2015; accepted for publication 3 June 2015*

SUMMARY

**Objectives:** To establish rates of cytomegalovirus (CMV) transmission with use of CMV-unselected (CMV-U), leukocyte-reduced blood components transfused to CMV-seronegative patient/CMV-seronegative donor (CMV neg/neg) allogeneic stem cell transplantation (SCT) recipients including those receiving T-depleted grafts.

**Background:** CMV infection remains a major cause of morbidity following SCT. CMV-seronegative SCT recipients are particularly at risk of transfusion transmitted CMV (TT-CMV) and until recently they have received blood components from CMV-seronegative donors with significant resource implications. Although leukocyte reduction of blood components is reported to minimise risk of TT-CMV, its efficacy in high-risk situations, such as in T-depleted transplant recipients, is unknown.

**Methods:** We retrospectively analysed the incidence of TT-CMV in CMV neg/neg allogeneic SCT recipients transfused with CMV-U, leukocyte-reduced blood components in two transplantation centres in the UK. Patients were monitored for CMV infection by weekly CMV polymerase chain reaction testing. Leukocyte reduction of blood components was in accordance with current UK standards.

**Results:** Among 76 patients, including 59 receiving *in vivo* T-depletion, no episodes of CMV infection were detected. Patients were transfused with 1442 CMV-unselected, leukocyte-reduced components, equating to 1862 donor exposures.

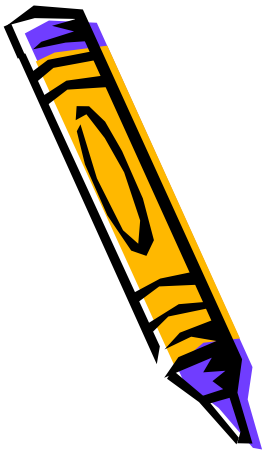
**Conclusions:** Our findings confirm the safety of leukocyte reduction as a strategy in preventing TT-CMV in high-risk allogeneic SCT recipients.

Key words: allogeneic stem cell transplant, cytomegalovirus, leukocyte reduction, T-cell depletion, transfusion.

Infection with cytomegalovirus (CMV) remains a major cause of morbidity and mortality after allogeneic stem cell transplantation (SCT), especially in recipients of T-depleted grafts (van Burik *et al.*, 2007; Schmidt-Hieber *et al.*, 2010). Primary infection may follow infusion of stem cells or blood products from a CMV-seropositive donor as well as through direct contact with actively infected individuals. CMV-seronegative SCT recipients are particularly at risk of transfusion transmitted CMV (TT-CMV) and until recently have received blood products from CMV-seronegative donors with significant resource implications. Since the introduction of leukocyte-reduced blood components in many countries, there has been a debate on the continuing need to transfuse cellular blood components from CMV-seronegative donors to high-risk patients. Given CMV achieves latency in leukocytes, rigorous leukocyte reduction is likely to reduce or even eliminate the presence of virus in blood donated by CMV-seropositive donors. In the UK, universal leukocyte reduction, initially introduced to reduce the risk of variant Creutzfeldt–Jakob disease, has been in routine use since 1999. Stringent leukocyte-reduction methods are used to achieve the target of $<5 \times 10^6$ white cells per unit, result-

Further support for the first part of the NAC recommendation

# New Evidence?



Original Investigation

## Blood Transfusion and Breast Milk Transmission of Cytomegalovirus in Very Low-Birth-Weight Infants

### A Prospective Cohort Study

Cassandra D. Josephson, MD; Angela M. Caliendo, MD, PhD; Kirk A. Easley, MS, MApStat; Andrea Knezevic, MS; Neeta Shenvi, MS; Michael T. Hinkes, MD; Ravi M. Patel, MD, MSc; Christopher D. Hillyer, MD; John D. Roback, MD, PhD

**IMPORTANCE** Postnatal cytomegalovirus (CMV) infection can cause serious morbidity and mortality in very low-birth-weight (VLBW) infants. The primary sources of postnatal CMV infection in this population are breast milk and blood transfusion. The current risks attributable to these vectors, as well as the efficacy of approaches to prevent CMV transmission, are poorly characterized.

**OBJECTIVE** To estimate the risk of postnatal CMV transmission from 2 sources: (1) transfusion of CMV-seronegative and leukoreduced blood and (2) maternal breast milk.

**DESIGN, SETTING, AND PARTICIPANTS** A prospective, multicenter birth-cohort study was conducted from January 2010 to June 2013 at 3 neonatal intensive care units (2 academically affiliated and 1 private) in Atlanta, Georgia. Cytomegalovirus serologic testing of enrolled mothers was performed to determine their status. Cytomegalovirus nucleic acid testing (NAT) of transfused blood components and breast milk was performed to identify sources of CMV transmission. A total of 539 VLBW infants (birth weight, ≤1500 g) who had not received a blood transfusion were enrolled, with their mothers (n = 462), within 5 days of birth. The infants underwent serum and urine CMV NAT at birth to evaluate congenital infection and surveillance CMV NAT at 5 additional intervals between birth and 90 days, discharge, or death.

**EXPOSURES** Blood transfusion and breast milk feeding.

**MAIN OUTCOMES AND MEASURES** Cumulative incidence of postnatal CMV infection, detected by serum or urine NAT.

**RESULTS** The seroprevalence of CMV among the 462 enrolled mothers was 76.2% (n = 352). Among the 539 VLBW infants, the cumulative incidence of postnatal CMV infection at 12 weeks was 6.9% (95% CI, 4.2%-9.2%); 5 of 29 infants (17.2%) with postnatal CMV infection developed symptomatic disease or died. A total of 2061 transfusions were administered among 57.5% (n = 310) of the infants; none of the CMV infections was linked to transfusion, resulting in a CMV infection incidence of 0.0% (95% CI, 0.0%-0.3%) per unit of CMV-seronegative and leukoreduced blood. Twenty-seven of 28 postnatal infections occurred among infants fed CMV-positive breast milk (12-week incidence, 15.3%; 95% CI, 9.3%-20.2%).

**CONCLUSIONS AND RELEVANCE** Transfusion of CMV-seronegative and leukoreduced blood products effectively prevents transmission of CMV to VLBW infants. Among infants whose care is managed with this transfusion approach, maternal breast milk is the primary source of postnatal CMV infection.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00907686

*JAMA Pediatr*. 2014;168(11):1054-1062. doi:10.1001/jamapediatrics.2014.1360
Published online September 22, 2014.

Supplemental content at jamapediatrics.com

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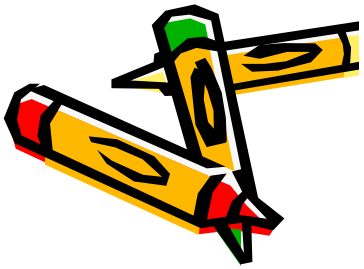

# New evidence?

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion

Vox Sanguinis (2015)

ORIGINAL PAPER


DOI: 10.1111/vox.12250

## The residual risk of transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components

C. R. Seed,[1] J. Wong,[2] M. N. Polizzotto,[3] H. Faddy,[4] A. J. Keller[1] & J. Pink[4]

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[3]Department of Clinical Haematology, Monash University, Melbourne, Vic., Australia
[4]Australian Red Cross Blood Service, Brisbane, Qld, Australia

Vox Sanguinis

**Background and Objectives** Cytomegalovirus poses a risk to transfusion safety as its transmission to an immunocompromised recipient may lead to significant clinical sequelae. Once infection is established, it is lifelong and generally asymptomatic. Strategies to reduce the risk of transfusion-transmitted CMV (TT-CMV) include donor serological testing and blood component leucodepletion to deplete the transmissible reservoir. We estimate the residual risk for non-CMV antibody screened, leucodepleted (LD-only) fresh blood components.

**Materials and Methods** We established an approach to estimate the risk of TT-CMV under various scenarios. We estimated the probability of an infectious component, for both red cells and platelets, as a function of the observed WBC filter failure rate and the probability that such a unit was also contaminated with infectious virus.

**Results** Using this model, the estimated combined residual risk of LD-only red cell and platelet units was very low, 1 in 13 575 000 (95%CI:1 in 1 344 167 000–1 in 1 730 000) as was the individual residual risk estimate for LD-only red cells, 1 in 7 790 000 (95%CI: 1 in 771 307 000–1 in 993 000) and LD-only platelets, where a zero risk was estimated (95%CI: 0–1 in 1 074 000).

**Conclusion** We describe a novel approach to assess the residual risk of LD-only components. This can be applied generally using local data. Our risk estimate for LD-only blood components in Australia is below the threshold of 1 in 1 million, generally considered negligible. This provides a useful indicator of the relative safety of LD-only components to assist clinical decisions when serologically screened inventory is unavailable.

Received: 4 November 2014,
revised 17 December 2014,
accepted 17 December 2014

**Keywords:** blood safety, leucodepletion, residual risk estimation, transfusion-transmissible infection.

# New Evidence?

Residual risk of transfusion-acquired cytomegalovirus (CMV) infection in CMV seronegative solid organ transplant recipients receiving CMV seronegative organs and leukodepleted cellular blood products

Jutta Preiksaitis, Susan Nahirniak, Curtis Mabilangan, Margaret Fearon, Sheila O'Brien

**Background :** Universal leukodepletion of all cellular blood products (in place in Canada since July 1999) significantly reduces the risk of transfusion-acquired ( TA)- cytomegalovirus ( CMV ) infection but the residual risk in is uncertain. We studied TA-CMV incidence in transfused CMV seronegative (R-) solid organ transplant recipients ( SOTR) receiving CMV seronegative organs (D-).

**Methods:** Transfusion records and post-transplant ( Tx) CMV antigenemia/PCR and serology results were extracted from the laboratory information system for all CMV D-R- SOTR transplanted at the our center between Jan 2000 and Dec 2011, identified using a Tx database. Patients were non-infected only if no detectable antigenemia/PCR was detected and they remained CMV seronegative ≥ 1 year after last transfusion. Possible TA-CMV cases were defined occurring < 1 year after transfusion; infections>1 year were considered community-acquired (CA).

**Results:** Among 474 D-R- SOTR, 323(68.1%) received cellular blood products (Tr)[study group], 151 (31.8%) did not ( non-Tr) [control group]. Assignment of CMV infection status was possible for 49.2% of the Tr and 48.3 % of the non-Tr group. Blood product use and CMV infection events are summarized in table 1. One possible case of TA-CMV infection was observed in a pediatric heart Tx child receiving 33RBC, 14 platelet and 6 plasma units who remained asymptomatic , was seronegative at 9 months but had seroconverted by 16 months; CA-infection could not be ruled out. During follow- up CA-CMV infection was observed in 5 SOTR (2 Tr, 3 non-Tr) .

| Allograft type | Number of transfused patients (child/adult) | Transfused units median (range) [total] | | | Number CMV-infected ≤1 yr | Number CMV-infected >1 year | Number of non-transfused patients (child/adult) | Number CMV-infected ≤1 yr | Number CMV-infected >1 year |
|---|---|---|---|---|---|---|---|---|---|
| | | RBCs | platelets | plasma | | | | | |
| Kidney | 37<br>3/34 | 2 (1-45)<br>[179] | 0 (0-14)<br>[15] | 0 (0-85)<br>[99] | 0 | 0 | 50<br>(3/47) | 0 | 2 (adults) |
| Heart | 43<br>8/35 | 8 (0-76)<br>[488] | 2 (0-21)<br>[171] | 2 (0-21)<br>[171] | 1 (child)* | 2 (1 child, 1 adult) | 7<br>(1/6) | 0 | 0 |
| Lung | 24<br>1/23 | 9.5 (1-44)<br>[289] | 1 (0-11)<br>[54] | 1 (0-6)<br>[40] | 0 | 0 | 1<br>(0/1) | 0 | 0 |
| Liver | 55<br>14/41 | 6 (0-54)<br>[483] | 1 (0-16)<br>[159] | 2 (0-36)<br>[266] | 0 | 0 | 15<br>(4/11) | 1 (child ) | 0 |
| Total | 159<br>26/133 | 6 (0-76)<br>[1439] | 1 (0-21)<br>[399] | 2 (0-85)<br>[612] | 1 ( child)* | 2 (1 child, 1 adult) | 73<br>8/65 | 1 (child) | 2 (adults) |

*possible case of TA-CMV

**Conclusions:** No symptomatic CMV disease could be attributed to TA-CMV in D-R- SOT recipients receiving leukodepleted blood products. The incidence of CA- CMV infection exceeds the risk of TA-CMV in this population.

Poster presentation CST 2015

# Variable Practice - Globally

VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2013)

INTERNATIONAL FORUM


DOI: 10.1111/vox.12103

## Prevention of transfusion-transmitted cytomegalovirus (CMV) infection: Standards of care

L. Lieberman, D. V. Devine, H. W. Reesink, S. Panzer, J. Wong, T. Raison, S. Benson, J. Pink, G. C. Leitner, M. Horvath, V. Compernolle, P. S. Prado Scuracchio, S. Wendel, G. Delage, S. Nahirniak, X. Dongfu, T. Krusius, E. Juvonen, S. Sainio, J.-P. Cazenave, P. Guntz, D. Kientz, G. Andreu, P. Morel, E. Seifried, K. Hourfar, C. K. Lin, J. O'Riordan, E. Raspollini, S. Villa, P. Rebulla, P. Flanagan, D. Teo, S. Lam, A. L. Ang, M. Lozano, S. Sauleda, J. Cid, A. Perreira, B. Ekermo, C. Niederhauser, S. Waldvogel, S. Fontana, M. J. Desborough, R. Pawson, M. Li, H. Kamel, M. Busch, L. Qu, D. Triulzi

**Table 1** Policies for testing and risk reduction in TT-CMV

| Country | Universal LR | CMV Ab testing | NICU | IUT | Pregnancy[a] | SCT[b] | Solid organ transplant[b] |
|---|---|---|---|---|---|---|---|
| Australia | Y | Y | **1** | **1** | **1** | **1** | **1** |
| Austria | Y | Y | **1** | 4 | 4 | **1** | 2 |
| Belgium | Y | Y | 2 | **1** | 2 | **1** | 2 |
| Brazil | Y | Y | 2 | 2 | 4 | 2 | 2 |
| Canada | Y | Y | 2 | **1** | **1** | **1** | 2 |
| China | Y | Y | 4 | 4 | 4 | 4 | 4 |
| Finland | Y | N | 2 | 2 | 2 | 2 | 2 |
| France | Y | Y | 3 | 4 | 3 | 3 | 3 (lung only) |
| Germany | Y | Y | **1** | 4 | **1** | **1** | 4 |
| Hong Kong | N | Y | **1** | **1** | **1** | **1** | 2 |
| Ireland | Y | Y | **1** | **1** | **1** | **1** | **1** |
| Italy | Y | Y | **1** | **1** | **1** | **1** | 2 |
| New Zealand | Y | Y | **1** | **1** | **1** | 2 | 4 |
| Singapore | Y | N | 2 | 2 | 2 | 2 | 2 |
| Spain | Y | Y | **1** | 4 | **1** | 2 | 4 |
| Sweden | Y | Y | 2 | 4 | 4 | 2 | 2 |
| Switzerland | Y | N | 4 | **1** | **1** | 2 | 2 (lung only) |
| UK | Y | Y | **1** | **1** | **1** | 2 | 2 |
| USA (clinical) | N | Y | 2 | 2 | 2 | 2 | 2 |

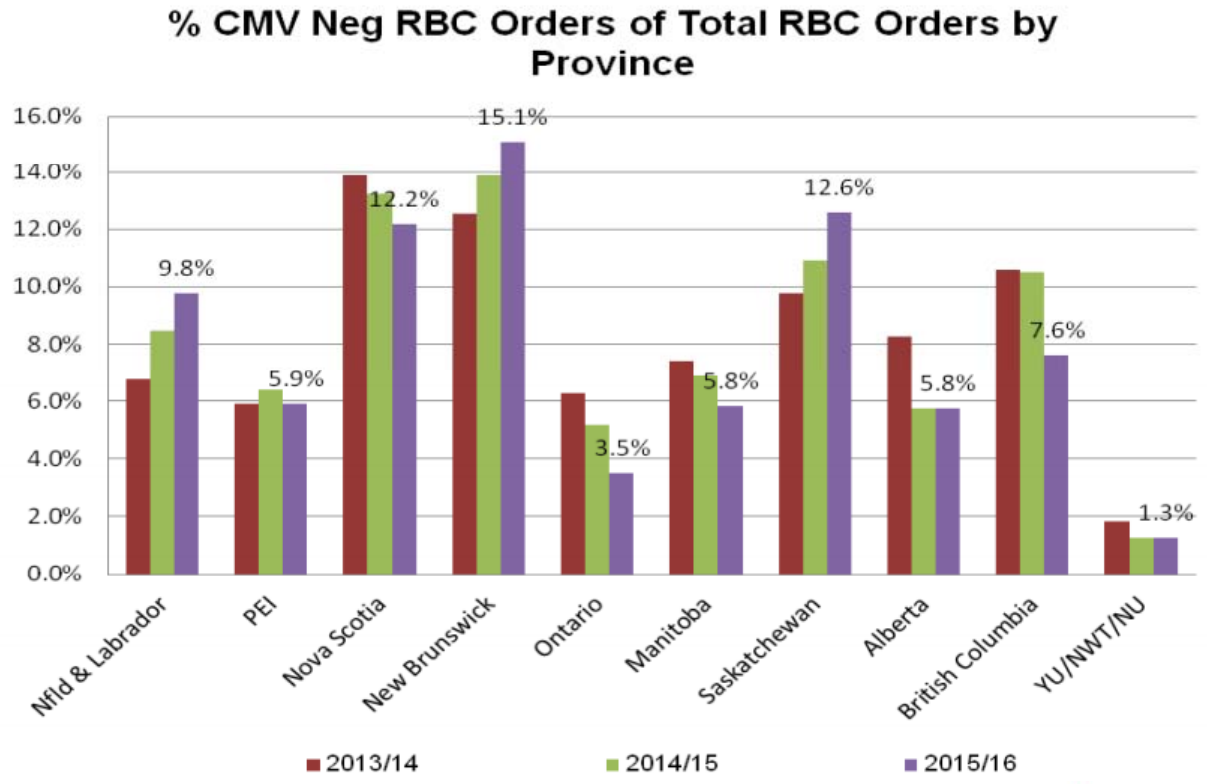
PRBC, packed red blood cell; LRK, leucoreduced; Plt, platelet; TT, transfusion transmitted; SD, single donor; Y, yes; N, no; Ab, antibody; NICU, neonatal intensive care unit; IUT, intrauterine transfusion; SCT, stem cell transplant; CMV, cytomegalovirus; LR, leucoreduced; TT-CMV, transfusion-transmitted cytomegalovirus.

Numerical legend: **1**: Provides CMV-negative and leucoreduced product; 2: provides leucoreduced product or CMV alone; 3: provides LR and either CMV-negative or pathogen-inactivated product; 4: practice unspecified or unknown.

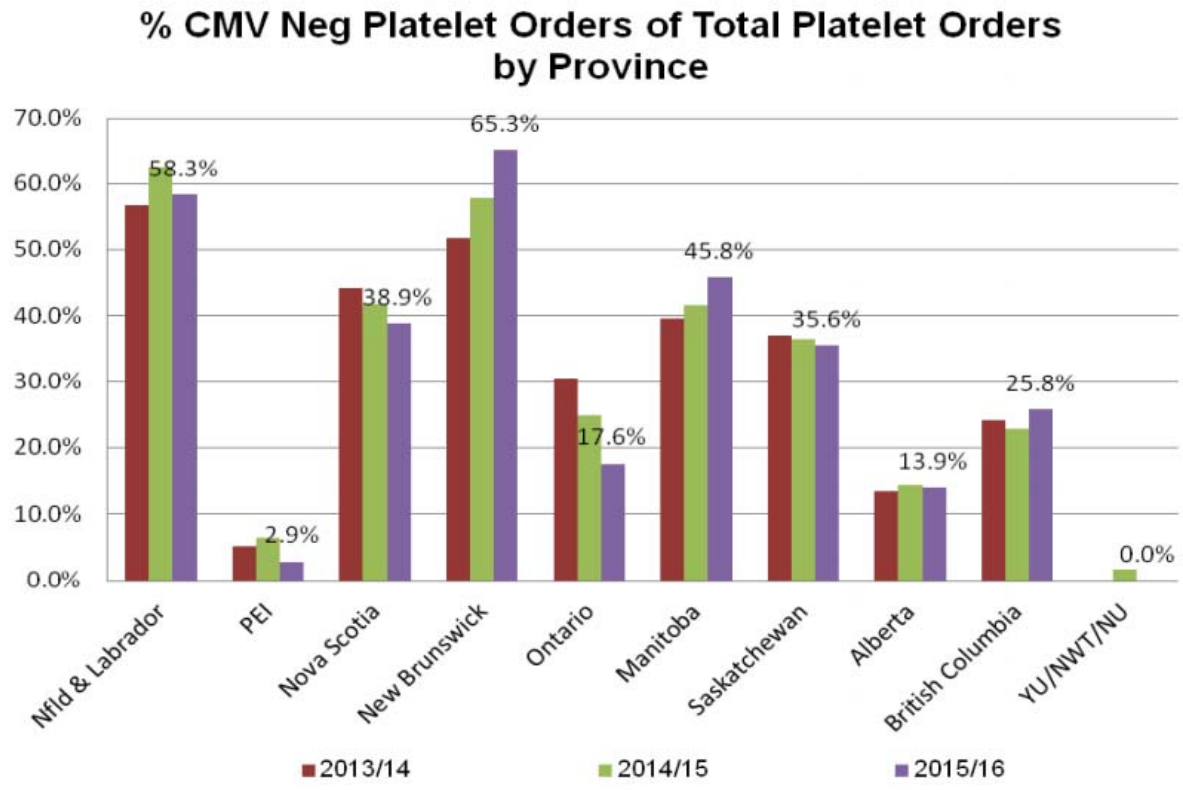
[a]Refers to cases when mother is CMV negative.

[b]Refers to cases when recipient and donor are CMV negative.

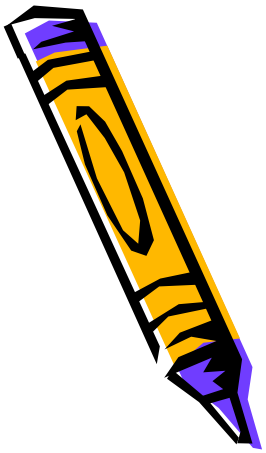
# Variable Practice - Canada



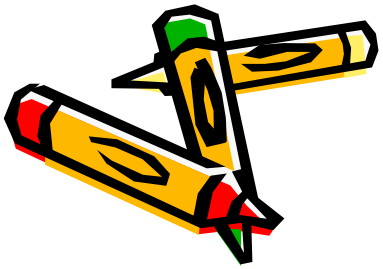
# Variable Practice - Canada



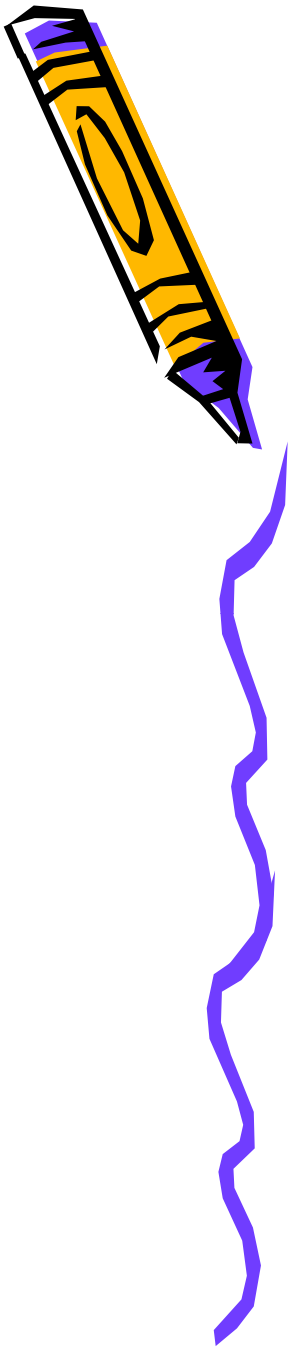
# Revised NAC Statement: Approved October 2015



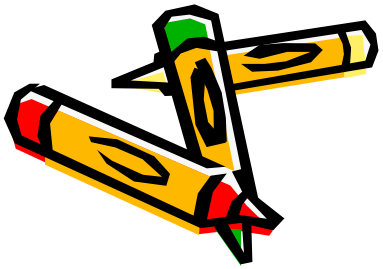
- The National Advisory Committee recommends that CMV safe (leukoreduced) and CMV IgG seronegative products be considered equivalent.
  - White paper to be updated and posted on the website as the evidence summary.



# Specific considerations in Neonates



- Role of breast milk
  - Maternal versus Public bank
- Ongoing need in IUT situation
  - Better to have NAT tested for CMV!



Questions????