A Fine Balance: Infection Prevention and Control in Infants

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BUILDINGconnections 2015 to 2020
acceleratingIMPACT

SickKids

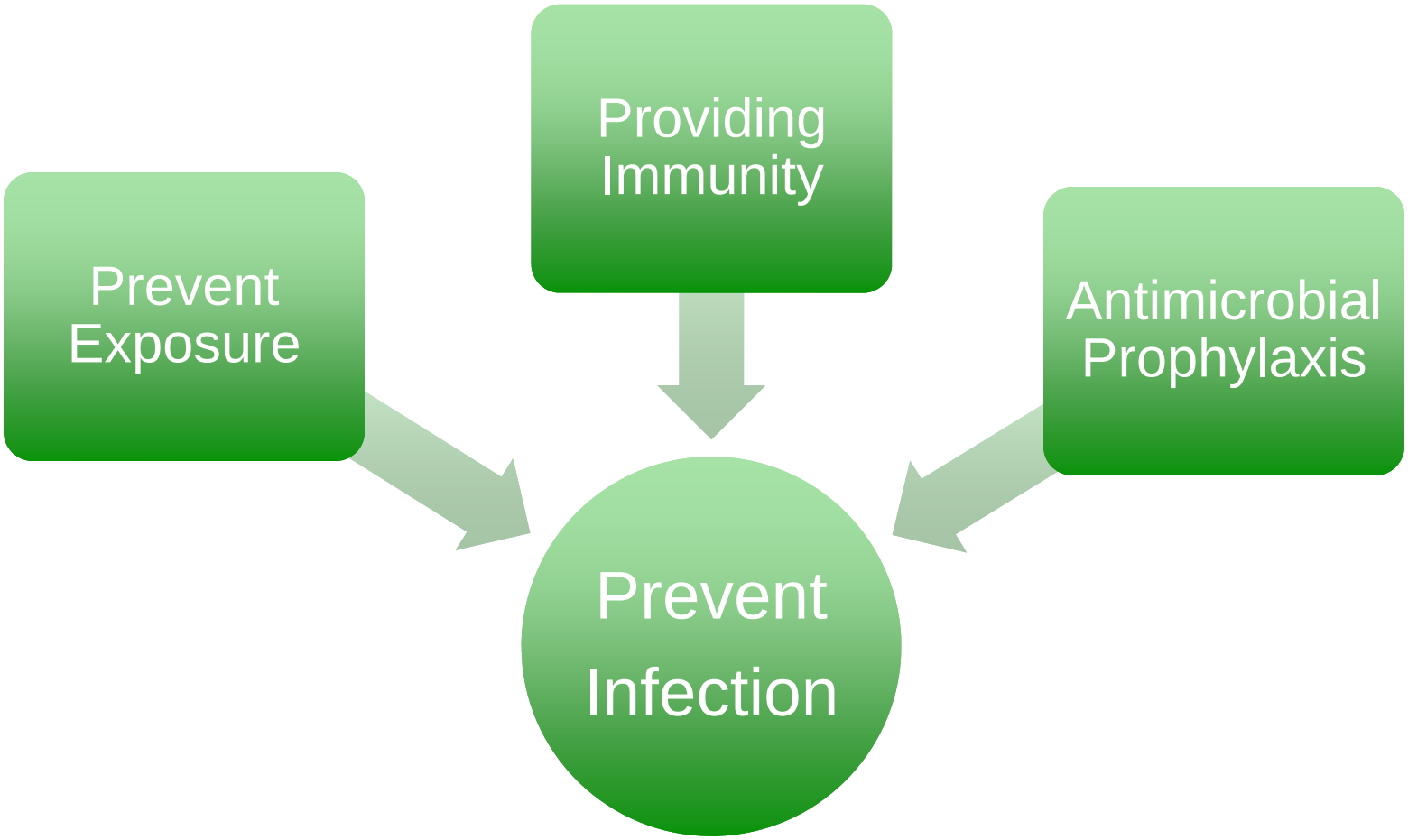
Disclosures

I have no actual or potential conflict of interest in relation to this presentation.

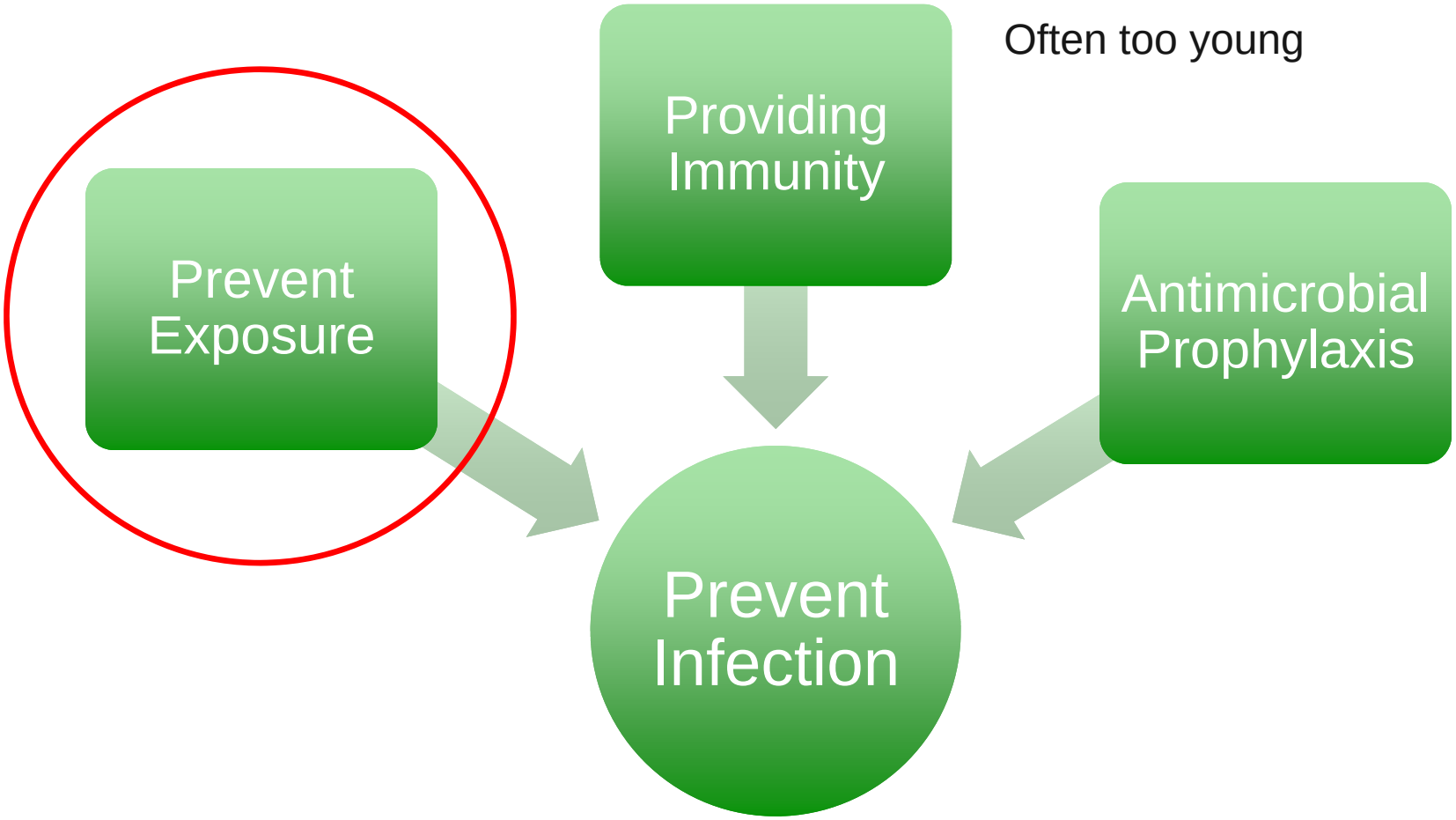
Outline

- Three cases highlighting infection prevention and control issues in Infants
  - Influenza
  - Measles
  - Varicella

Preventing Infections



Preventing Infections – Infants



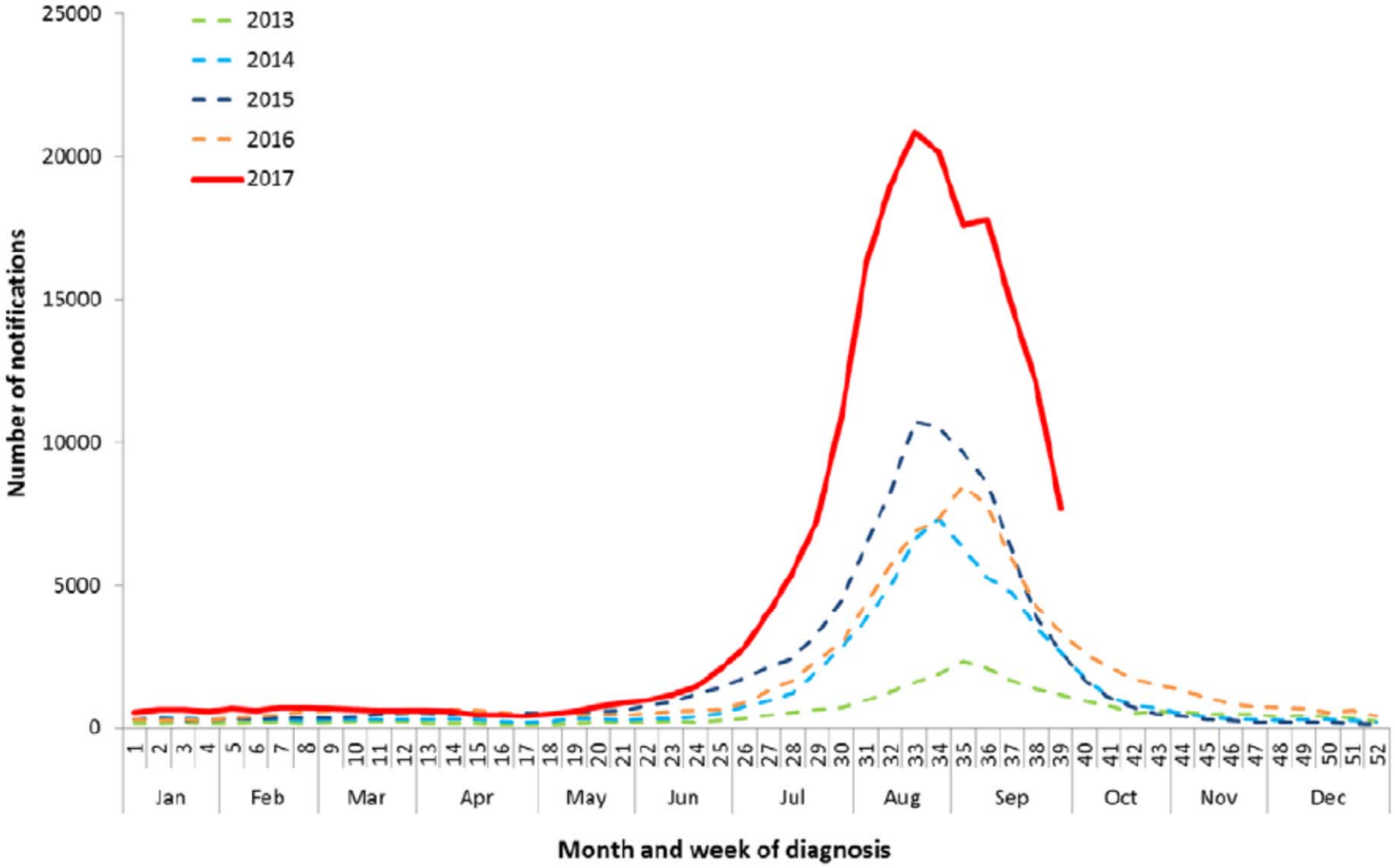
Case #1

- 8 month old boy with infant ALL
- Parents concerned about Influenza
- He has a 4 year old sister at home who started JK this year

Case #1

- Can the infant be vaccinated ?
- Which vaccine would you use ?
- What is the optimal timing ?
- What vaccine would you give the parents and sibling ?

Australian Experience

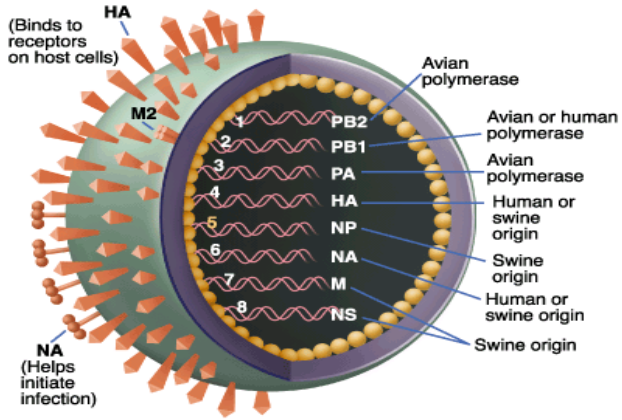


Source: NNDSS

http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/ozflu-surveil-no07-2017.pdf

Influenza viruses

- Influenza A and B viruses cause seasonal epidemics, while type C causes mild respiratory illness
- Influenza A viruses are classified into different strains or subtypes based on two proteins or antigens on the virus surface:
  - Hemagglutinin (H)
  - Neuraminidase (N)



- Influenza B viruses can be classified into two antigenically distinct lineages: Yamagata and Victoria-like viruses
- Influenza A and B strains are included in each year's influenza vaccine

How strains change each year

- Small changes in influenza viruses occur continually
  - New virus strains may not be recognized by the body's immune system
- A person infected with a specific influenza virus strain develops antibodies against that specific strain
- In most years, some or all of the virus strains in the influenza vaccine are updated to align with the changes in the circulating influenza viruses
- Annual influenza vaccine is recommended to protect against infection from these changing influenza viruses

Influenza vaccine development

- Each February, the World Health Organization (WHO) provides a recommendation on the strains to be included in the influenza vaccine for the northern hemisphere
- Two influenza “A” viruses and one (trivalent vaccine) or two (quadrivalent vaccine) influenze “B” viruses are selected based on the characteristics of the current circulating influenza virus strains
- A new vaccine is reformulated each year to protect against new influenza infections

Vaccine strains in 2017-2018 Vaccine

- H1N1 A/Michigan/45/2015
- H3N2 A/Singapore/INFIHM-16-0019/2016
- B strain (Yamagata), B/Phuket/3073/2013

Case #1

- Can the infant be vaccinated ?

Recommendations for Oncology Patients

- Children with cancer or immune compromising conditions are at high risk of influenza-related complications or hospitalization due to underlying disease and/or therapy
- Vaccination is recommended for all patients >= 6 months of age
- No additional safety concerns (compared to non-immunocompromised patients)
- Efficacy concerns:
  - Children on immunosuppressive chemotherapeutic agents may have less of an immune response compared to healthy children

An Advisory Committee Statement (ACS) - National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2017-2018; https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2017-2018.html. Accessed September 25, 2017, 201

Case #1

- Can the infant be vaccinated ?
  - YES
- Which vaccine would you use ?

Types of Influenza Vaccines

- Trivalent
  - Inactivated vaccine
  - Intramuscular
- Quadrivalent
  - Inactivated (IM) vaccine and live attenuated (intranasal) vaccine
  - Recommended for children 6 months to 17 years
  - Live attenuated (intranasal vaccine)
    - >= 2 years

Recommendations for Oncology Patients

- Children should be given inactivated quadrivalent vaccine
- Intranasal vaccine (live attenuated) is contraindicated

- Administration
  - Intramuscular vaccine
  - 6 months to less than 9 years:
    - First time vaccinated – two doses (minimum 4 weeks apart)
    - Previously vaccinated – one dose
  - Greater than or equal to 9 years: 1 dose

Case #1

- Can the infant be vaccinated ?
- Which vaccine would you use ?
  - Quadrivalent Inactivated Vaccine
- What is the optimal timing ?

Recommendations for Oncology Patients

- There is no specific contraindication to administering the inactive influenza vaccine to neutropenic patients
- Practical considerations (i.e. need for admission if develops fever) may contribute to preference to wait until neutropenia resolved
- Adverse affects:
  - Less than 12% of children 1 to 5 years develop transient fever (less common in older children)
- Anticipated course of neutropenia and amount of circulating virus should contribute to decision regarding optimal timing

Case #1

- Can the infant be vaccinated ?
- Which vaccine would you use ?
- What is the optimal timing ?
  - As soon as vaccine available – if brief neutropenia expected, may delay until neutropenia resolved
- What vaccine would you give the parents and sibling ?

Recommendations for family members

- The influenza vaccine is strongly recommended for family members in contact with H/O and HSCT patients
- These individuals should receive the inactivated influenza vaccine
- No specific recommendation from NACI regarding family members and live attenuated influenza vaccine:
  - Recommend to avoid for healthcare workers caring for patients
  - Live influenza vaccine should generally be avoided given possible virus shedding

Case #1

- Can the infant be vaccinated ?
- Which vaccine would you use ?
- What is the optimal timing ?
- What vaccine would you give the parents and sibling ?
  - Parents – trivalent influenza vaccine
  - Sibling – quadriavlent inactivated influenza vaccine

Case #2

- 2 month old infant new diagnosis of AML
- Exposed to patient in the ED with measles
- Mom immune to measles – vaccination
- Currently breastfeeding

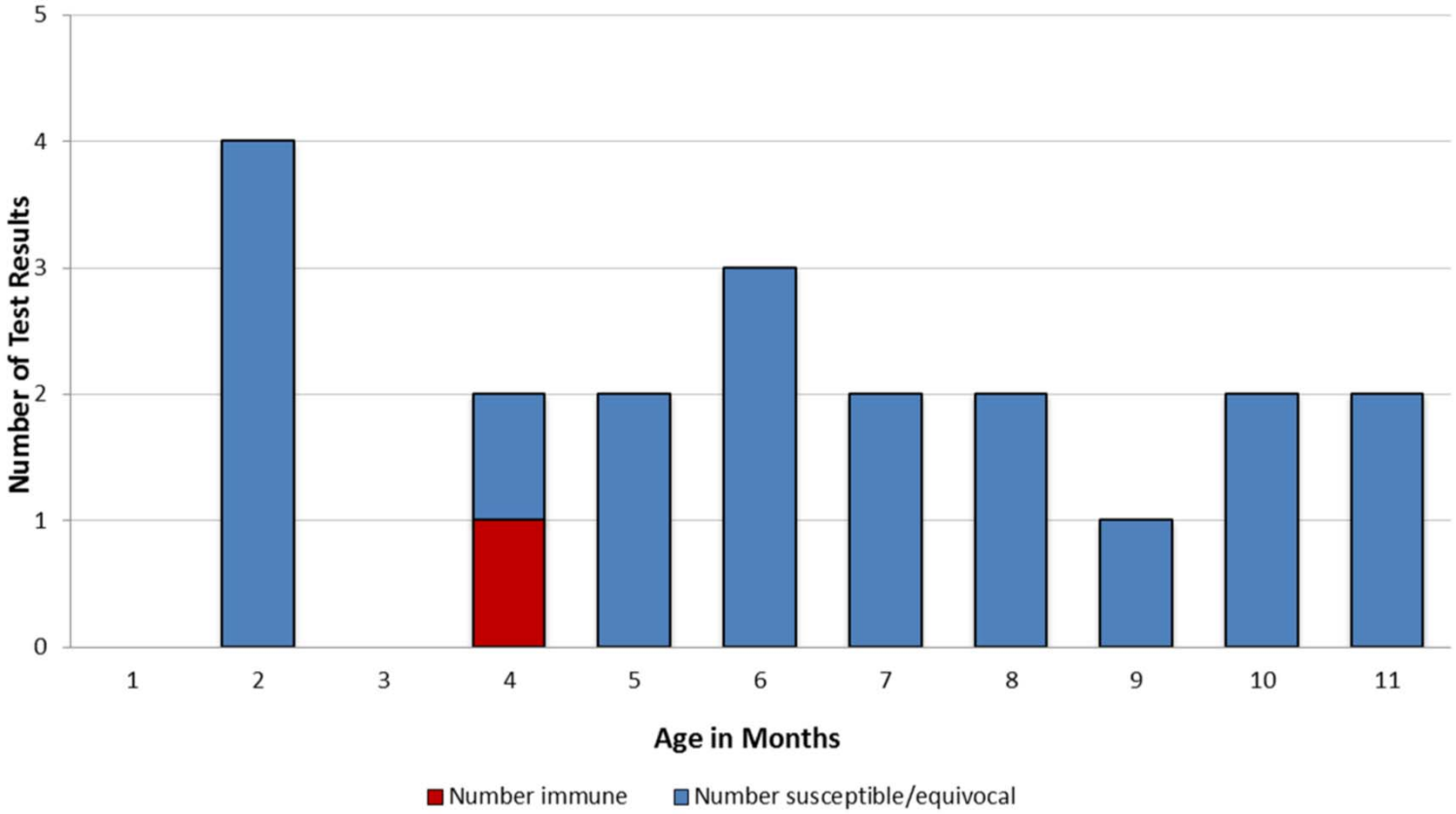
Case #2

- Is the infant considered immune / susceptible ?

Infant Immunity to Measles

Population	CCDR	Toronto Public Health
< 6 months	Immune if maternal history of adequate vaccination	Susceptible
6 – 12 months	Susceptible	
12 months – 17 years	2 doses of vaccine (given on or after 1st birthday) given at least 4 wks apart (MMR) or 6 weeks (MMRV)	
>= 18 years	1 dose if born 1970 or later No doses if born before 1970	1 dose if born 1970 or later (excluding health care workers and students in post-secondary education settings)

Measles susceptibility in infants < 1 year



The Hospital for Sick Children 2015-2016, N=20

Infant Immunity to Measles

Age Band (d=day, m=months)	Immune (≥192 mIU/mL)	Equivocal (112-191 mIU/mL)	Negative (<112 mIU/mL)	Total
0 – 30 d	20 (80%)	3 (12%)	2 (8%)	25
31 – 60 d	17 (68%)	3 (12%)	5 (20%)	25
61 – 89 d	8 (33%)	7 (29%)	9 (38%)	24
90 – 119 d	2 (8%)	2 (8%)	20 (83%)	24
4 m	2 (8%)	4 (17%)	18 (75%)	24
5 m	4 (16%)	0	21 (84%)	25
6 – 8 m	0	0	25 (100%)	25
9 – 11 m	0	1 (4%)	24 (96%)	25

Infant Susceptibility to Measles

- Patients are considered immune if they have IgG at, or before cancer diagnosis or documented age-appropriate vaccination
- Immune status may be lost on therapy
- Immunity during induction impacted by lack of cell-mediated immunity

Pediatric Oncology Group Ontario. Satellite Manual. Section 4.6 Immunization of Children with Cancer.

Case #2

- Is the infant considered immune / susceptible ?
  - Likely susceptible and will be once started induction
- How would you manage?

Susceptible patients

- Isolation in airborne precautions during the incubation period
  - Day 5 – 21 (Day 28 if IG)
- Post-exposure prophylaxis
  - Immune globulin within 6 days of exposure

Case # 3

- 4 month old infant ALL
- Brother has been diagnosed with chickenpox
- Mom has a history of chickenpox

Case # 3

- Is the infant considered immune / susceptible ?

Infant Susceptibility to Varicella

- Likely similar to measles
- More mothers now vaccinated, less immune boosting
  - Lower maternal antibody levels
  - Lower infant antibody levels

Case #3

- Is the infant considered immune / susceptible ?
  - Likely susceptible
- How would you manage?

Management of Susceptible individuals

- Isolation in airborne precautions
  - Day 8 – 21 (Day 28 if VZIG)
- Post-exposure prophylaxis
  - VZIG within 10 days of exposure
  - Acyclovir

Case #3

- Is the infant considered immune / susceptible ?
  - Likely susceptible
- How would you manage?
- Could this have been prevented ?

Family Member Management

- Important to ensure family member vaccinations are up to date
- Varicella vaccine can be safely administered to family members of immunocompromised patients
  - Small risk of transmission if rash develops in vaccinated person
  - Risk associated with natural infection more significant

SUMMARY

- Infants are often too young to be vaccinated leaving them vulnerable to a number of vaccine preventable illnesses
- Maternal antibodies in infants may wane faster than previously described
- Vaccination of close contacts and family members remains a key strategy to prevent exposures and infection

QUESTIONS ?

Reactions to inactivated influenza vaccine

	Adverse effects *associated* with influenza vaccination		**Adverse effects *prevented* by influenza vaccination**	
	Rate	Description	Rate	Description
Common	< 1 in 2	Sore arm (usually mild)	1 in 4 to 1 in 16	Acute respiratory illness
Uncommon	1 in 5,000 1 in 10,000	Allergic reaction Oculorespiratory syndrome	1 in 35 to 1 in 100	Illness requiring antibiotics
Rare	1 in 500,000 1 in 1 million 1 in 30 million	Anaphylaxis Guillain Barre Syndrome Death	1 in 200,000 1 in 1 million 1 in 1.5 million 1 in 3.5 million	Hospitalization for influenza Guillain Barre Syndrome ICU admission for influenza Death due to influenza

Healthcare Worker Influenza Immunization. Report and Recommendations of the TAHSN Healthcare Worker Influenza Immunization Working Group. 2014

Transfusion-transmitted Infections: How Safe Is the Blood Supply?

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Professor of Pathology & Laboratory Medicine
University of British Columbia

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Disclosures

Research funding received from TerumoBCT, Macopharma and Hemanext (New Health Sciences)

Member of the medical advisory committee of Fresenius Kabi Deutschland GmbH

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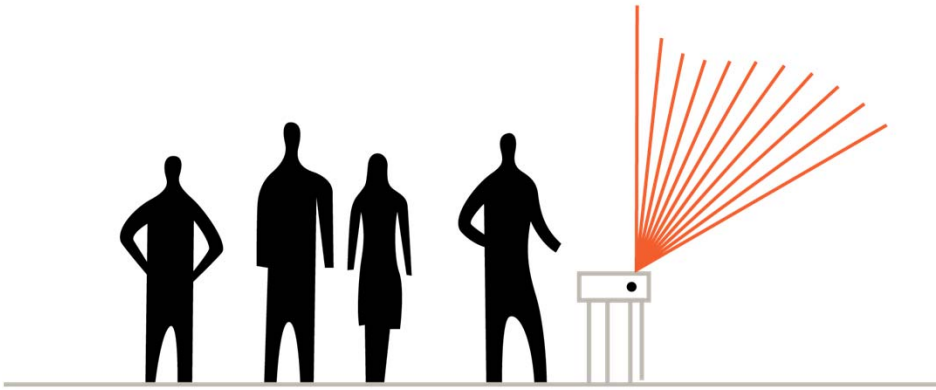
Overview

- Pediatric blood use
- Blood transfusion safety: mitigation strategies and residual risk
- Cytomegalovirus risk mitigation



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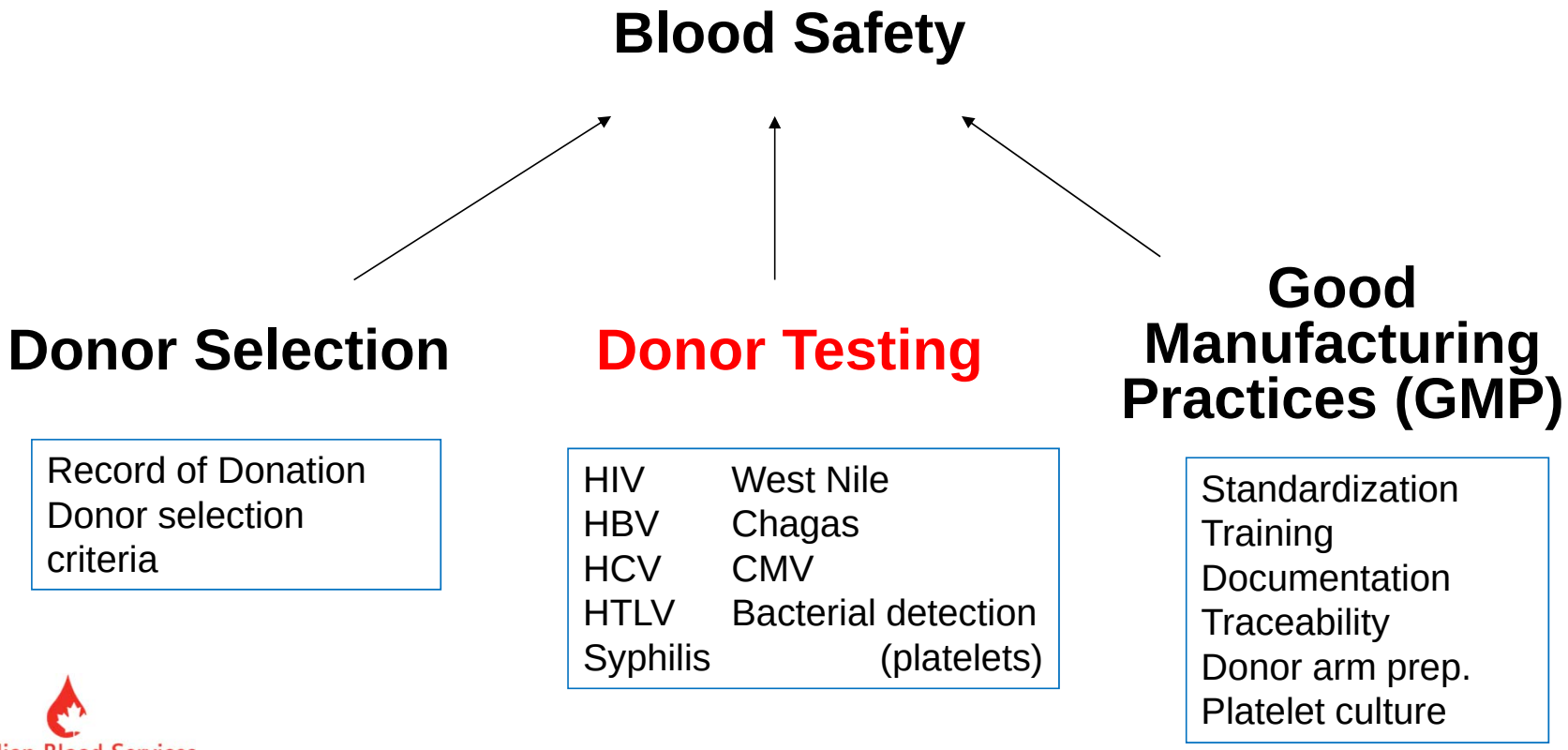
Unique Features of Pediatric Blood Use

- Last year, Canadian Blood Services issued over 20,000 units of red blood cells to pediatric hospitals.
- Due to potassium leakage from RBCs during storage, fresh RBCs are used for some neonatal and pediatric procedures such as cardiac surgery.
- Concern over total number of donor exposures led to (1) dedicated RBC units; and (2) favouring apheresis platelets over pooled platelets, although apheresis platelets have higher risk of reduced efficacy.

Transfusion-transmitted Infection Risk Mitigation



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Blood Donor Testing

Donor testing		Implementation Date
– Syphilis	Ab	1949
– HBV	HBsAg, anti-HBc and NAT[1]	1972, 2005, 2010
– CMV	Ab (selected units)[3]	1984
– HIV1/2	Antibody (Ab) and	1985
	nucleic acid testing (NAT[1])	2001
– HCV	Ab and NAT[1]	1990, 1999
– HTLV1/2	Ab	1998 (HTLV 1 – 1990)
– WNV	NAT (pools of 6)	2003[2]
– *Chagas*	*Ab (selective donor testing)*	*2010*

[1]NAT testing for HIV, HCV and HBV performed on Roche Cobas TaqScreen MPX 2.0 (Multiplex NAT) in pools of 6 – March 2010.

[2]Seasonal WNV testing implemented 2015 (only donors with travel outside Canada tested from December 1 to June 1)

[3] CMV antibody tested negative product for intrauterine transfusion only as of October 2017

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Incidence and Residual Risk of HIV, HCV and HBV in Canadian Blood Services' Donors, 2012-2014*

Virus	Number of incident cases	Person-years of observation	Repeat donors Incidence rate per 100,000 person-years of observation (95%CI)	All donations Incidence rate per 100,000 person-years of observation (95%CI)	Window Period Risk-Day Equivalents (95% CI)	Residual Risk per million donations (95% CI) [1 per number of donations]
HIV	2	854,829	0.23 (0.03, 0.85)	0.28 (0.04, 1.03)	6.1 (4.4, 7.8)	0.047 (0.009, 0.168) **[1 in 21.4 million]**
HCV	7	854,839	0.82 (0.33, 1.69)	1.0 (0.40, 2.06)	2.9 (2.1, 3.8)	0.079 (0.030, 0.170) **[1 in 12.6 million]**
HBV (unadjusted)	1	854,832	0.12 (0.003, 0.65)	0.15 (0.004, 0.79)		
HBV (adjusted for transient viremia)			0.21 (0.01, 1.13)	0.26 (0.01, 1.37)	18.8 (13.3, 24.3)	0.134 (0.020, 0.665) **[1 in 7.5 million]**

* O'Brien, Q. Yi, W.Fan, V.Scalia, M.Goldman, M.Fearon Residual risk of HIV, HCV and HBV in Canada. Transfusion and Apheresis Science 2017;56:389-391

Residual Risk of Clinical Septic Reactions

CBS (2007-2014)

Non-fatal reactions: 0.62/100,000
Fatalities: 1.5/1,000,000

American Red Cross

Non-fatal reactions: ~1/100,000
Fatalities: ~1/1,000,000

National Health Service Blood & Transplant (UK) (2011 – Dec 31, 2014, 7 day platelet storage)

Non-fatal reactions: ~1/1,000,000
Fatalities: 0
3 near misses (abnormal appearance)

Mitigation Other Than Testing

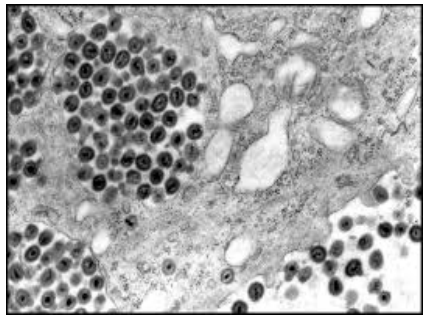
- Donor deferral for travel: zika virus, dengue virus, yellow fever virus, malaria, Leishmania, etc.
  - Deferral period from 4 weeks to 12 months depending on where travel occurred

- Donor deferral for risk behaviour: piercings, tattoos, male to male sex, etc.

- Other deferrals for non-infectious risks: mainly medications

Transfusion-transmitted viral disease

Cytomegalovirus



- CMV is a common herpes virus infection which is frequently asymptomatic or causes mild fatigue, sore throat and general malaise.
- Approximately 40 – 80% of tested populations are CMV seropositive.
  - More common in women, older patients, lower socioeconomic status, MSM
  - Approximately 40% of Canadian blood donors are CMV positive with a 1% annual seroconversion rate.
- The virus is transmitted via direct contact with blood, saliva, urine, breast milk, as well as through organ or tissue transplant. Congenital CMV occurs via transplacental transfer.
- CMV remains latent in myeloid cells for life. Reactivation can occur with illness or immunosuppression.

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Risk Reduction of TT-CMV Prevention with Development of Component Therapy

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 CR, Wong J. et al. The residual risk of transfusion transmitted cytomegalovirus. Vox Sang 2015; 109: 11-17
Allain JP, Stramer SL, et al. Transfusion Transmitted Infectious Diseases. Biologicals 2009; 37: 71-77

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Slide courtesy of Dr. Jeannie Callum, Sunnybrook

The epidemiology of CMV

To Put Things in Perspective.... the Relative Risk

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Slide courtesy Dr. Jeannie Callum, Sunnybrook

Provision of CMV tested negative blood products

National Advisory Committee on Blood and Blood Products | Comité consultatif national sur le sang et les produits sanguins

CMV Statement dated ***February 14, 2017***

NAC's Statement Regarding Appropriateness of Use of Cytomegalovirus (CMV) Sero Negative vs CMV Safe Product

Recommendation #1

The National Advisory Committee recommends that CMV safe (leukoreduced) and CMV IgG seronegative products be considered equivalent ***except*** for Intrauterine transfusion.

Recommendation #2

The National Advisory Committee recommends that Canadian Blood Services 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.

Recommendation #3

The National Advisory Committee recommends that Canadian Blood Services explores the feasibility of providing a small boutique inventory of dually tested (seronegative and NAT) CMV negative blood components for the sole purpose of intrauterine transfusion.

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Provision of CMV tested negative blood products

Recent Changes to Donor CMV Testing

- CBS implemented Recommendation #2 on October 23, 2017
- We provide a small inventory of CMV antibody tested negative (O negative, C negative E negative and Kell negative) red cell components at our distribution sites near hospitals where intrauterine transfusions are performed:
  - Sinai Health System (Mt. Sinai Hospital), Toronto
  - BC Children's and Women's Health Centre, Vancouver
  - Foothills Medical Centre, Calgary
  - Winnipeg Health Science Centre
  - Isaac Walton Killam Health Care Centre, Halifax
- CMV antibody negative Platelets requested for IUT (extremely small number) will be provided on demand basis only.

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CMV safe blood products

Systematic Review of Clinical Studies*

- 10 studies (7 observational with 949 pts; 4 Randomized Control Trials with 680 pts).
- Only 3 studies are "modern" with pre-storage leukoreduction (677 pts; 2002/2003/2013). These compared leukoreduced to CMV Ab tested and found no statistically significant difference in CMV infection.
- 5 studies compared leukoreduction to transfusing CMV untested, unfiltered product – found no statistically significant difference in CMV infection.
- Infant studies problematic as infants fed CMV-infected breast milk included.
- Certainty in estimates was low for all comparisons.

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*Mainou M, Alahdab F, et al. Reducing the risk of transfusion-transmitted CMV infection: a systematic review and meta-analysis. Transfusion 2016; 56;1569-1580

CMV Positive Donor Studies

- 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.

CMV safe blood products

Data from Hematopoietic Stem Cell Transplants

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

Thiele T, Kruger W, et al. Transmission of cytomegalovirus infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation. Transfusion 2011; 51: 2620-26.

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

Nash T, Hoffmann S,et al. Safety of leukoreduced cytomegalovirus – untested components in CMV negative allogeneic human progenitor cell transplant recipients. Transfusion 2012; 52: 2270-72

CMV safe blood products

Hematopoietic Stem Cell Transplants*

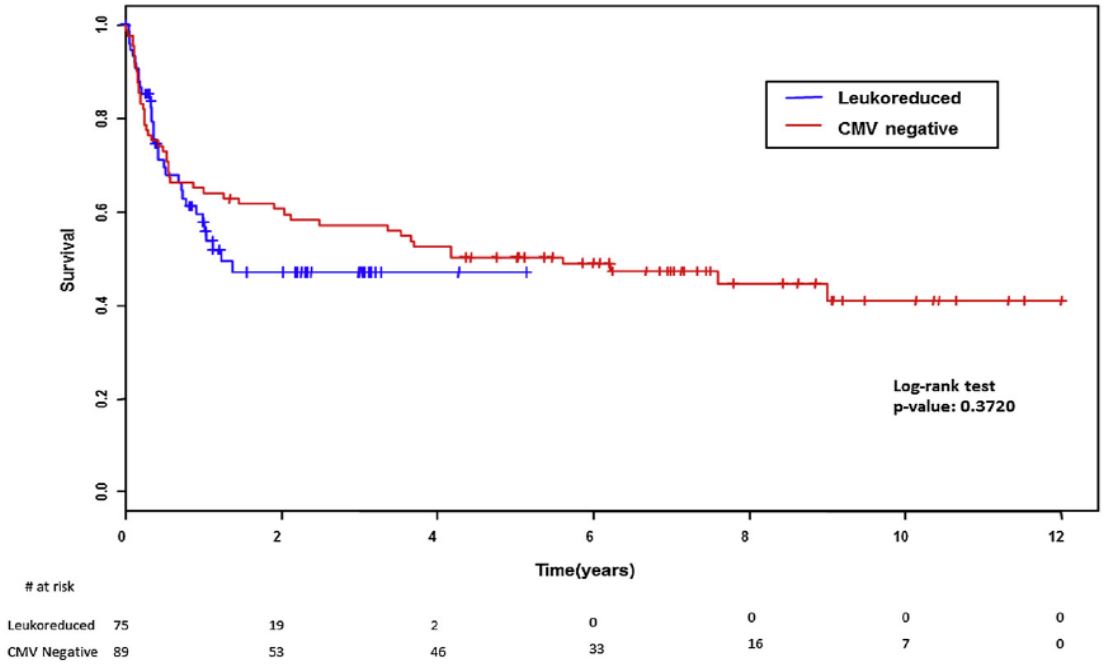

Figure 3. Overall survival by transfusion group.

89 Leukoreduced(LR) and CMV Ab neg; 77 LR only

Just -/- transplants

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

2 CMV disease
- Both LR and CMV Ab neg

*Kekre N, Tokessy M, et al. Is CMV testing of blood products still needed for hematopoietic stem cell transplant recipients in the era of universal leukoreduction? Biol Blood Marrow Transplant 2013;(12):1719-24

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Hematopoietic Stem Cell Transplants*

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

*Hall S, Danby R, et al. 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. Transfus Med 2015; 25: 418-23.

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CMV safe blood products

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 leukoreduced 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 CD, Caliendo AM et al. Blood transfusion and breast milk transmission of CMV in very low-birth-weight infants: A prospective cohort study. JAMA Ped 2014; 168: 1054-62.

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CMV safe blood products

Residual Risk of Transfusion-Transmitted CMV Infection*

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

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

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*Seed CR, Wong J, et al, The residual risk of transfusion transmitted CMV infection associated with leucodepleted blood components. Vox Sang 2015; 109: 11-17

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
- Modern day leukoreduction failure rates: rare
- CMV seronegative and leukoreduction are NOT additive in terms of protection
- No proven cases of CMV transmission from LR-only in HSCT or other recipients

Questions?

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

https://professionaleducation.blood.ca/en/transfusion/best-practices/use-cytomegalovirus-cmv-seronegative-blood-products

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Thanks to Margaret Fearon for data slides!!