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Canadian Immunization Conference
Conférence canadienne sur l'immunisation

**Public Health Driven Initiative in the Development of a
Haemophilus influenzae a Polysaccharide- Protein
Glycoconjugate Vaccine**

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Disclosure Statement

Disclosure of Relationship	Company/Organization
I am a member of an Advisory Board or equivalent with a commercial organization.	McMaster / Maastricht U., PREVENT, NSERC-PSAB
I am a member of a Speaker Bureau.	
I have received payment from a commercial organization (including gifts or other consideration or 'in kind' compensation).	
I hold a patent for a product referred to in the CME/CPD program or that is marketing by a commercial organization	
I hold a patent for a product referred to in the CME/CPD program or that is marketing by a commercial organization	
I hold investments in a pharmaceutical organization, medical devices company or communications firms.	Sanofi
I am currently participating in or have participated in a clinical trial within the past two years.).	

Glycoconjugate Vaccines

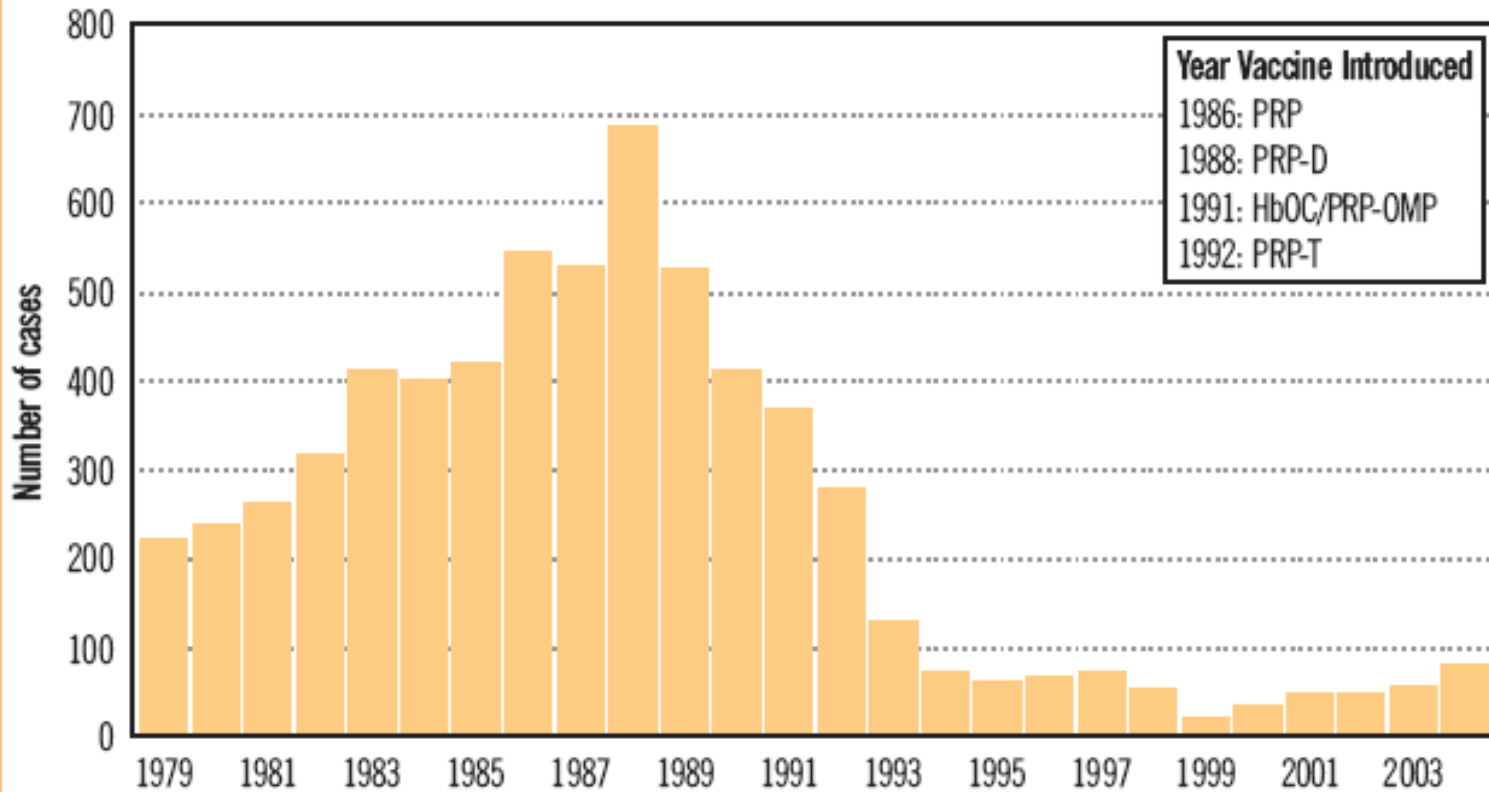
- Glycoconjugate vaccines have a track record of success since their inception in the 1980's.
- Diseases such as *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* type C (MenC) have been virtually eliminated wherever their glycoconjugate vaccines have been administered.
(In Canada there were 1000 Hib cases in 1989 pre-vaccine, <20 cases in 1999 post-vaccine)¹.
(In Canada there were 180 MenC cases in 2001 pre-vaccine, 5 cases in 2010 post-vaccine)¹.
- NRC has a rich history in glycoconjugation technologies with the first Hib and MenC patents issued originating from research at NRC, Ottawa and \$30M of royalties / revenue generated.
- *Hia* is an emerging pathogen and currently prevalent in North America's aboriginal populations.
- Will a glycoconjugate vaccine based on Hia polysaccharide be as successful as the Hib glycoconjugate?

¹<http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hea-eng.php>





Figure 3. *Haemophilus influenzae* type b (Hib) Disease —
Reported Cases, Canada, 1979–2004*



* 1979–1985: reported Hib meningitis only
1986–2004: all invasive forms (meningitis and septicemia)





Haemophilus influenzae a (Hia) Conjugate Vaccine Initiative

- Invasive *Hia* disease is an emerging infectious disease that affects Aboriginal populations in the post-*Hib* conjugate vaccine era.
- *Haemophilus influenzae* serotype *a* as a cause of serious infections.

Lancet Infectious Diseases, 2014; 14: 76-82.

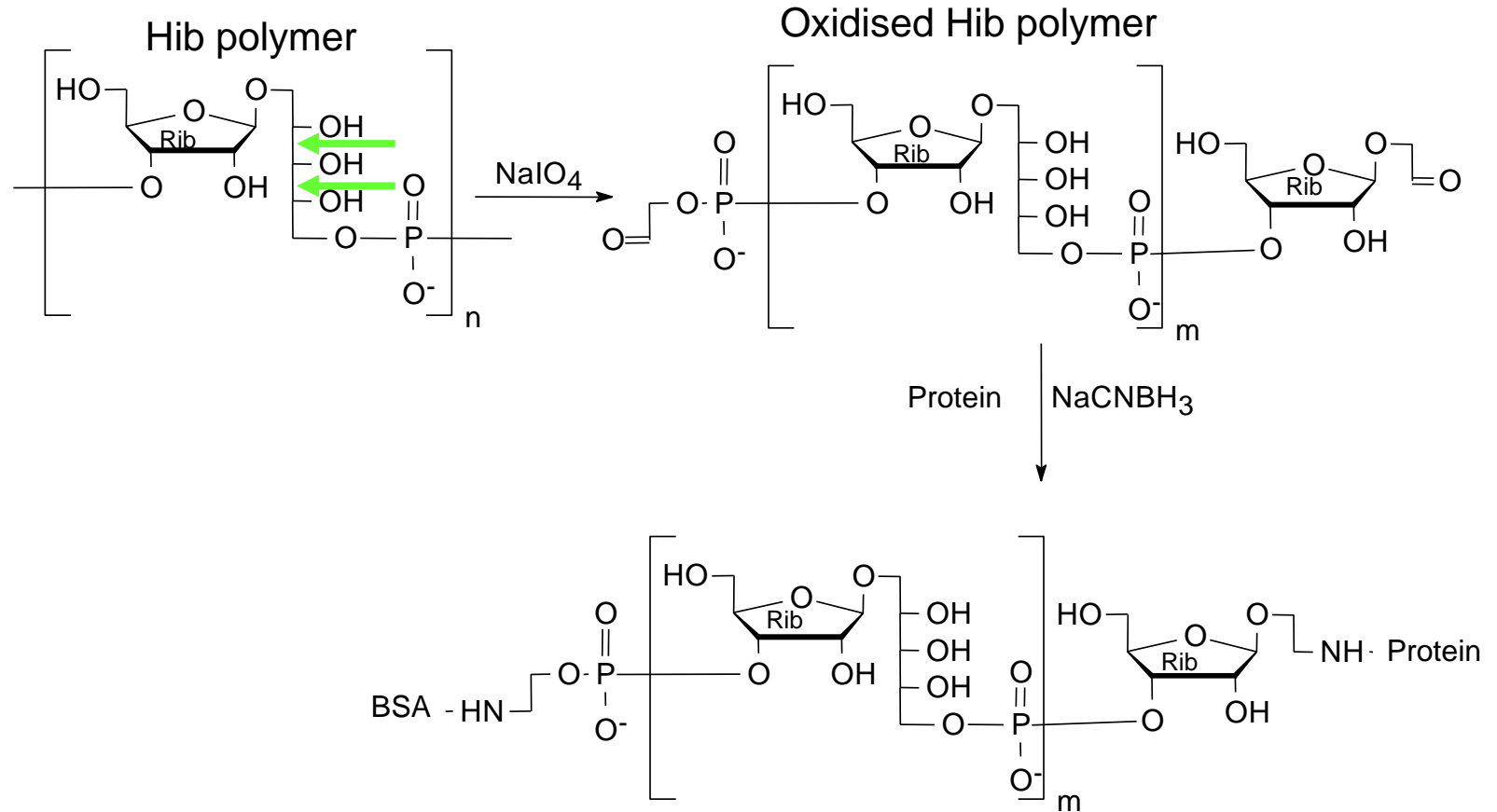
- In collaboration with federal and provincial partners, PHAC has been tracking invasive *Hia* disease over the last several years, and has the largest collection of invasive *Hia* strains in Canada (possibly in the world).



Hib conjugate

->3-β-D-Rib-> 5-ribitol-1-PO₄->

Periodate oxidation / reductive amination conjugation strategy for Hib



Periodate treatment **will** reduce size of Hib polymer.

SBA of D70 rabbit sera vs. Hib strain Eagan

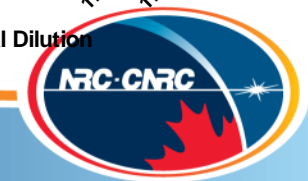
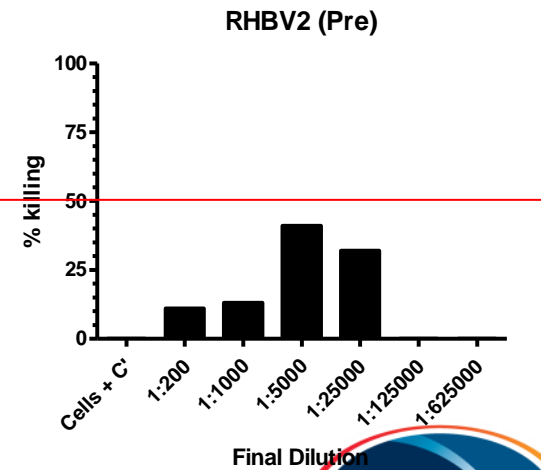
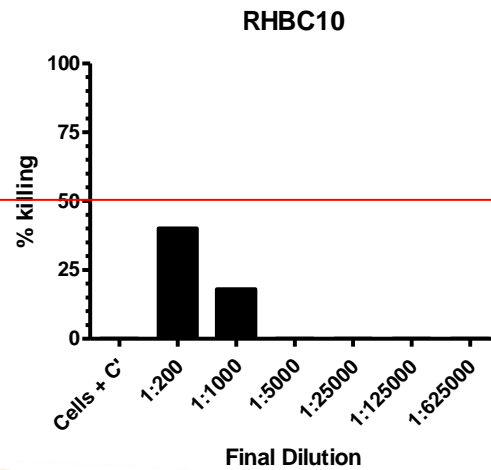
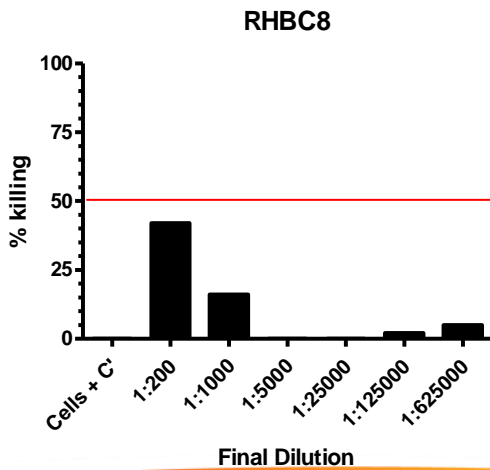
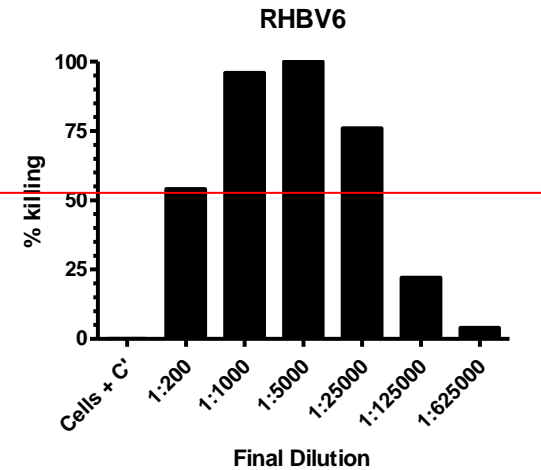
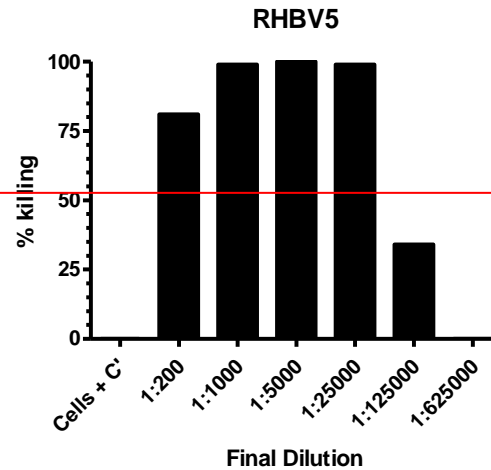
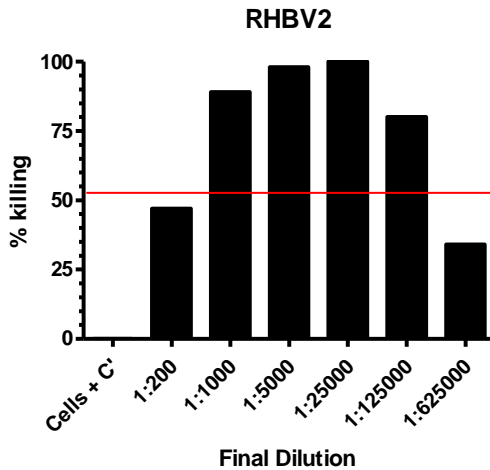
RHBV2: *H. influenzae* B-HSA; Dose 50ugCHO, 50ugHSA;

RHBV5: *H. influenzae* B-HSA; Dose 25ugCHO, 25ugHSA

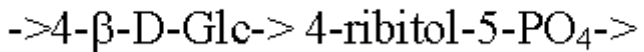
RHBV6: *H. influenzae* B-ProD; Dose 25ugCHO, 25ugProtein D

RHBC8: *H. influenzae* B; Dose 50ugCHO

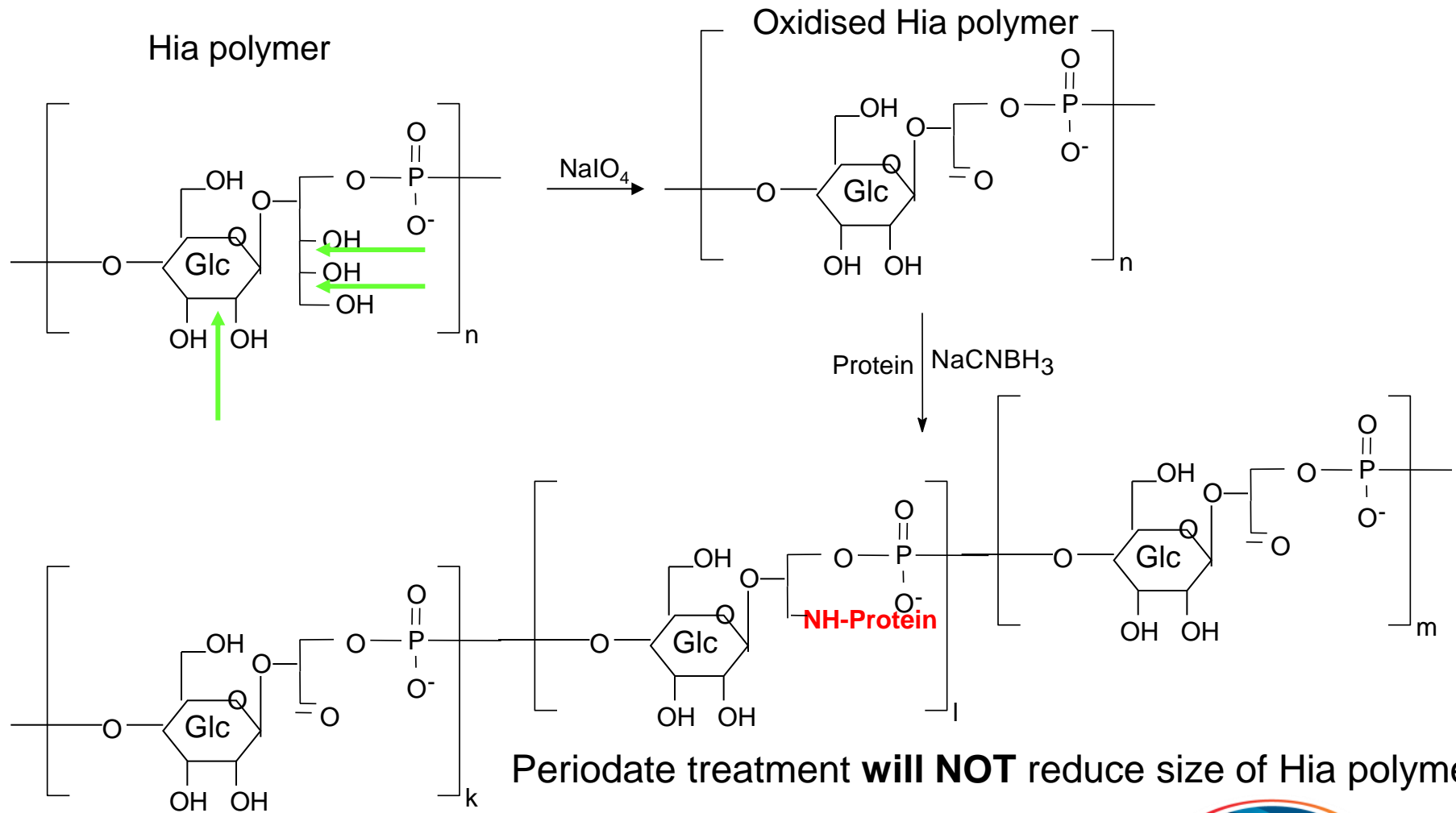
RHBC10: Protein D; Dose 50ugCHO



Hia conjugate



Periodate oxidation / reductive amination conjugation strategy for Hia



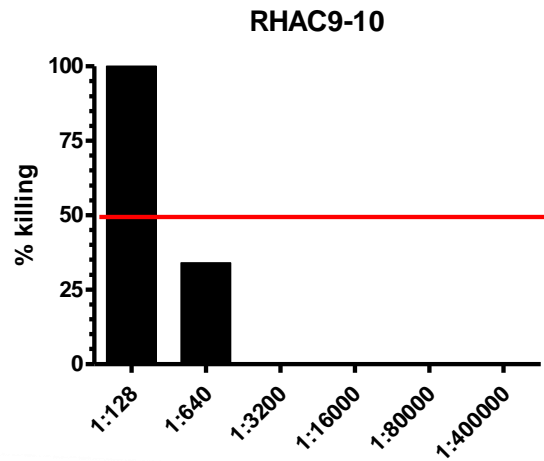
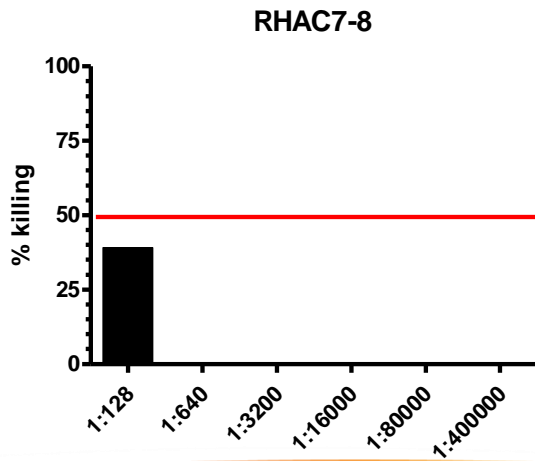
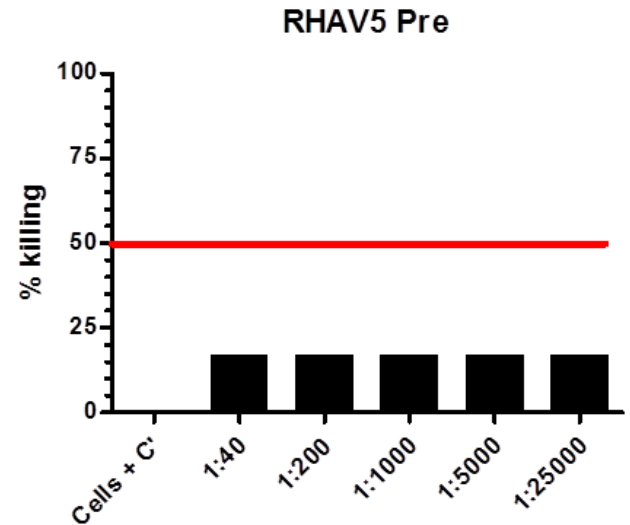
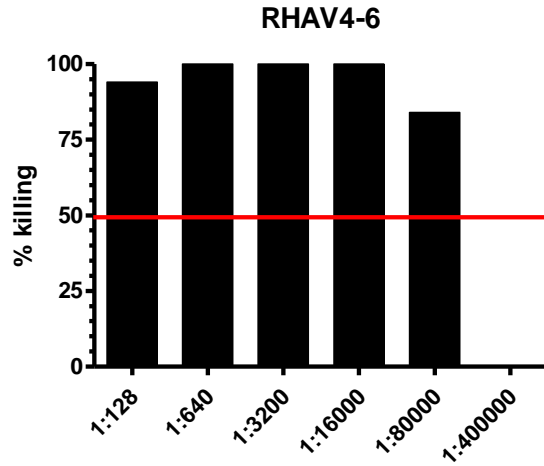
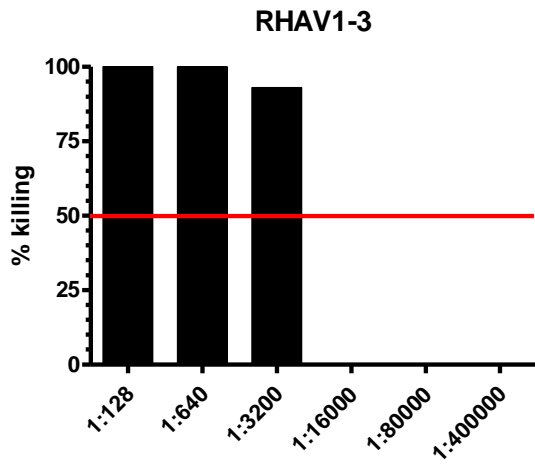
SBA of D70 rabbit sera vs Hia strain 6753

RHAV1-3 *H. influenzae* A-ProD; Dose 50ug CHO, 50ug ProD

RHAV4-6 *H. influenzae* A-ProD; Dose 25ug CHO, 25ug ProD

RHAC7-8 *H. influenzae* A; Dose 50ug CHO

RHAC9-10 *H. influenzae* A + ProD; Dose 50ug CHO + 50ug ProD



***Hia* glycoconjugate vaccine conclusions:-**

- *Hia* capsular polysaccharide can be isolated and purified from flask and fermenter growth.
- Capsular polysaccharide structure has been confirmed by NMR.
- Glycoconjugate vaccines have been prepared using several carrier proteins including human serum albumin (HSA), diphtheria toxoid cross reacting material (CRM) and protein D.
- Mice and rabbits have been immunised with conjugates and good serum titers produced
- Mice and rabbit sera has facilitated bactericidal killing thus illustrating the proof of concept.



Steps in the vaccine development

Phase	Goal	Current status
Surveillance of invasive Hia disease Hia carriage Natural immunity against Hia	Understand current immuno-epidemiology Identify target populations	Ongoing (NOSM)
Collecting Hia isolates	Identify vaccine candidate	Ongoing (NOSM)
Molecular characterization of Hia strains	Selecting strains for vaccine composition	Ongoing (NML)
Isolation of the antigen, purification, large scale production	Prepare an immunizing agent	Ongoing (NRC)
Selection of the protein carrier, conjugation, testing immunogenicity	Preclinical vaccine development	Ongoing (NRC)
Production of GLP / GMP vaccine lots	Prepare for animal / human clinical trials	Next 1-2 years (NRC & CMO / Industry)
Clinical trials	Test safety, immunogenicity	Next 3-5 years (NOSM and CDC)

Collaboration on *Haemophilus influenzae* (Hia)

Collaborative approach involving Canada, US, PAHO, Brazil and Columbia

- **International Circumpolar Surveillance**
- **Improved tools for Hi characterisation:**
 - genome sequencing of 40 Hia strains— 38 from Canada and 2 from Brazil
 - development of monoclonal antibodies to Hi capsular polysaccharides
- **Public Health Agency of Canada (PHAC)** providing expertise to PAHO in typing Hia strains
- **CDC proposal to 20 states** for enhanced lab-based surveillance on non-Hib
- **Arctic Investigations Program (CDC)** to initiate severity study
- **Protein polysaccharide conjugate vaccine (NRC)**
- **Lakehead University's Northern Ontario School of Medicine:** serology & protective immunity studies.



Proposed Federal-Led Action Plan on Vaccine Research, Innovation and Development:

Addresses needs and opportunities for enhanced and accelerated research, innovation and development of vaccines of interest to Canada:

- human and animal vaccines for preventive applications
- vaccine technologies—e.g., adjuvants, vaccine platforms, biomarkers for safety and efficacy
- entire vaccine development life cycle along the value chain
- social and market factors—e.g., factors affecting vaccine acceptance
- domestic and global markets
- whole-of-government federal leadership and support to focus, enhance coordination, and leverage available resources and expertise

Preliminary proposal has been presented to and endorsed by Assistant Deputy Ministers of Health and Industry and they have provided guidance on further development of the Action Plan



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