Immunization for the Whole of Life
We’ve only just begun.....

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We’ve only just begun.....

Vaccines are changing......

- New vaccines tailored to fit specific populations
  e.g. flu vaccine for elderly
  RSV vaccine- pregnant women, infants, elderly
  Malaria vaccine

- New understanding of an AEFI
  narcolepsy and H1N1 pandemic vaccine Pandemrix

- New vaccines for cancer treatment not just prevention
Conflicts of Interest

No financial conflicts to declare

My Biases:

- Consultant to Canadian Peadiatric Society Imm/ID Cmt
- Advisor to WHO Immunization/Vaccines and Biologicals
- Consultant WHO EURO on Vaccinology
- Canadian Centre for Vaccinology: Health Policy and Translation Group
Vaccines for Seniors:
Setting the Record Straight on Influenza

![Bar chart showing influenza vaccination rates by age group from 2009-10 to 2013-14. The chart indicates a 61% vaccination rate.](chart.png)
Does influenza vaccine make a difference in morbidity and mortality in frail elderly?

Lee WJ et al. The impact of influenza vaccination on hospitalizations and mortality among the frail older patients. J Am Med Dir Assoc 2014;15: 256-60
Influenza Vaccines for the Elderly

Table 2. Efficacy of High-Dose Vaccine Relative to Standard-Dose Vaccine against Confirmed Influenza Caused by Any Viral Type or Subtype.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laboratory-Confirmed Influenza</th>
<th>Culture-Confirmed Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IIV3-HD (N = 15,990)</td>
<td>IIV3-SD (N = 15,993)</td>
</tr>
<tr>
<td>Protocol-defined influenza-like illness</td>
<td>228 (1.4)</td>
<td>301 (1.9)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>190 (1.2)</td>
<td>250 (1.6)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>8 (&lt;0.1)</td>
<td>9 (0.1)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>171 (1.1)</td>
<td>223 (1.4)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>38 (0.2)</td>
<td>51 (0.3)</td>
</tr>
<tr>
<td>Modified CDC-defined influenza-like illness</td>
<td>96 (0.6)</td>
<td>121 (0.8)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>86 (0.5)</td>
<td>104 (0.7)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>3 (&lt;0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>77 (0.5)</td>
<td>95 (0.6)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>10 (0.1)</td>
<td>17 (0.1)</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>316 (2.0)</td>
<td>387 (2.4)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>262 (1.6)</td>
<td>313 (2.0)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>14 (0.1)</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>231 (1.4)</td>
<td>281 (1.8)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>54 (0.3)</td>
<td>74 (0.5)</td>
</tr>
</tbody>
</table>

* CDC denotes Centers for Disease Control and Prevention.
† Laboratory confirmation of influenza was accomplished by a positive result on culture of a nasopharyngeal swab, a positive polymerase-chain-reaction assay, or both.
‡ The primary endpoint of the study was the occurrence, at least 14 days after vaccination, of laboratory-confirmed influenza caused by any influenza viral types or subtypes, in association with a protocol-defined influenza-like illness.

Respiratory Syncytial Virus Vaccine

RSV major cause ALRI in infants
33.8 M new episodes ALRI <5 yr
3.4 M RSV associated hosp’n
0.2 M RSV associated deaths

-most common etiological pathogen
for pneumonia in 192 countries,
followed by influenza virus

RSV current prevention for infants
– passive immunity
  humanized neutralizing AB against RSV Fusion protein

RSV also problem in elderly esp COPD, congestive heart Failure

RSV Data USA

Children <2 years of age (US data):
- 8.4 million US population <2 years
- 1.5 million RSV infections
- 69,000 RSV hospitalizations/year
- 230 RSV deaths/year

Adults ≥65 years of age (US data):
- 40 million US population ≥65 years
- 1.2 million RSV infections
- 50,000 RSV hospitalizations/year
- 10,000 RSV deaths/year
RSV Vaccine: Target Populations

At least 4:
- RSV naïve young infant,
- RSV naïve infant >4-6 months of age
- Pregnant women
- Elderly adults- esp with low AB titers

Vaccine development impeded by
- 1960’s experience: enhanced disease following natural RSV infection post formalin-inactivated alum-adjuvanted RSV vaccine (FIRSV)- immune mediated
- need to create robust immune responses BUT not cause vaccine-enhanced illness
- vaccines in animal models not replicated in humans
RSV Vaccines: 2014

a. Live-attenuated and live-vectored—9 candidates
b. Protein-based—26 candidates total
   i. Whole-inactivated virus—1 candidate
   ii. Particle-based—13 candidates
   iii. Subunit antigens—12 candidates*
c. Nucleic acid—4 candidates
d. Gene-based vectors—10 candidates*
e. Combination of approaches —2 candidates

http://www.who.int/immunization/research/meetings_workshops/WHO_PDVAC_RSV.pdf

Novavax- Phase II Study Elderly- US

1600 older adults (>60yrs):
  RSV F Vaccine compared to placebo
detected seasonal attack rate of 4.9% for
symptomatic RSV disease (95% LRI signs)
robust serological response in >90%
vaccine efficacy:
  prevention all -symptomatic RSV – 44%
    - RSV LRT disease – 46%
Phase III study to start soon – seniors
  and also one in pregnant women

Vaccines in Pregnancy

Many other vaccines with recommendations for use in pregnancy and new ones in development

Tetanus, Influenza, Pertussis
Ebola, Hep E, JEE
Cholera
Others.......CMV, Group B Strep,
Chlamydia, RSV

WHO examining barriers to immunization of pregnant women: trials, product monograph, recommendations etc

Vaccines in Pregnancy

Questions....... 

How many vaccines can/should be given?

How can future trials be conducted when the standard of care is already to administer at least one vaccine?

What new targets should receive priority?

If multiple new maternal vaccines developed and are safe and effective, which vaccine(s) should have priority?

Need more data

on vaccine safety, immunogenicity, and efficacy

epidemiology of the target pathogen in representative countries or populations,

ture burden of disease in the mother and infant
Vaccines & AEFI In Pregnancy

- AEFI surveillance
  - active and passive systems focus on pregnant women
  - very few and little published – systematic review in 2014 – only 17 studies!!

Malaria

- Life-threatening parasitic infection transmitted by infected mosquitoes.
- 2013 WHO estimated # deaths: 584,000 mostly among African children.
- Prevention and control measures - pyrethroids
  - **Insecticide-treated mosquito nets (ITNs)**
  - **Indoor spraying with residual insecticides (IRS)**
    - MR by 47% globally since 2000, by 54% in WHO African Region.
- Also problem for non-immune travelers to endemic areas

http://www.who.int/mediacentre/factsheets/fs094/en/
Malaria Vaccine: RTS,S/AS01

- Developed in partnership:
  - GlaxoSmithKline Biologicals (GSK)
  - PATH Malaria Vaccine
- Vaccine against *Plasmodium falciparum*,
  - no protection against *P. vivax* malaria.
- **Phase 3 trial** - 15,460 infants and young children
  - 7 sub-Saharan African countries
    - Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Tanzania
  - 2 age groups
    - a) infants  malaria vax at same time other routine childhood vaccines at 6, 10 and 14 weeks of age
    - b) older infants - aged 5 to 17 months at first dose

http://www.who.int/immunization/research/development/malaria_vaccine_qa/en/
Malaria Vaccine Efficacy: Highlights

April 2015

- **Infants 5 -17 mo** at first dose (0, 1, 2, 20mo):
  vs clinical malaria **39%**
  vs severe malaria **31.5%**
  if NO 4\textsuperscript{th} dose- **no protection vs severe disease**
    – shifted disease to older age

- **Infants 6-12 weeks** at first dose (0, 1, 2, 20 mo):
  vs clinical malaria **27%;** only **18%** if no 4\textsuperscript{th} dose
  BUT- **no significant efficacy against severe malaria, with or without a fourth dose**

Lower immune response in younger: ? Age, ? Co admin vac

http://www.who.int/immunization/research/development/malaria_vaccine_qa/en/
Malaria Vaccine – next steps

European Medicines Agency (EMA)
- scientific evaluation (European scientific opinion)
  - positive:
    “quality of the vaccine and the risk/benefit is favourable from a regulatory perspective”
NOT equal licensure but African NRAs may use when consider Oct 2015
- WHO meeting to propose recommendations for use
  – expect official policy Nov 2015
• Who, when, where and with what else?
• Role in travellers?

http://www.who.int/immunization/research/development/malaria_vaccine_qa/en/
New Understanding an AEFI:
Narcolepsy with Pandemrix™

2011-2012

- 17-25 fold ↑ narcolepsy cases after large-scale H1N1 pandemic vaccination programs
  – # varied by country (Finland, Ireland, Norway, Sweden highest)
- absolute number very small
  e.g. Finland (largest #) 6/100,000
  Canada (Quebec) 1/1,000,000
- NOT with all pandemic flu vaccines

Narcolepsy-1

neurological disorder: affects control of wakefulness

• ↓ in hypocretin: -neurohormone modulates sleep, wakefulness, and eating behavior

• HLA-DQB1*06:02 - majority cases, different ethnicities, - imp in CD4+ T helper cell development/function

• Concordance rate in monozygotic “identical” twins both narcolepsy- only 1 in 4 (25%), thus genetic contribution fairly low

• Nongenetic (e.g. environmental) factors must have an essential role in triggering narcolepsy

• Research complicated as NO animal models
Narcolepsy -2

1918 pandemic influenza & “Encephalitis Lethargica”
temporal overlap:
limited to the height of the influenza pandemic
Oliver Sachs- gave Ldopa- awoke ..... 

2010 H1N1 pandemic: in China
temporal overlap pandemic and ↑ narcolepsy
– not vaccine related
Autoimmune Concept of H1N1-related Narcolepsy: 4 Stages Linked to HLA-DQB1*0602

Wekerle, H. Science Translational Medicine 2015, 7; 294-7
| Human hypocretin receptor 1_{22-42} | P | V | P | P | D | Y | E | D | F | - | L | R | Y | L | W | R | D | Y | L | Y | P |
| Human hypocretin receptor 2_{29-50} | L | N | P | T | D | Y | D | E | E | F | L | R | Y | L | W | R | E | Y | L | H | P |
| Influenza nucleoprotein_{106-126} (wild/X-179A strain) | R | E | L | L | Y | D | K | E | E | - | ! | R | R | ! | W | R | Q | A | N | N | G |
| e value= 0.026 (HCRT{1}) 0.0061 (HCRT{2}) | | | | | | | | | | | | | | | | | | | | |
| Influenza nucleoprotein_{106-126} (X-181 strain) | R | E | L | L | Y | D | K | E | E | - | M | R | R | ! | W | R | Q | A | N | N | G |
| e value= 0.025 (HCRT{1}) 0.0045 (HCRT{2}) | | | | | | | | | | | | | | | | | | | | |
| Cross-reactive residues | | | | | | | | | | | | | | | | | | | | | Y | D | E | E | ! | R | ! | W | R |

Implications Narcolepsy as AEFI

- Still a hypothesis- but backed by elegant experiments
- Need another independent group to verify findings
- *First example of autoimmune AEFI albeit very rare*
- Anti NP AB with wild influenza may explain observation narcolepsy in China – not due to vaccine but wild influenza
- If hypothesis proven correct
  need influenza vaccines *low* NP content
  prevent wild influenza in those with risk HLA type
Implications Narcolepsy as AEFI-2

Not know

• If similar mechanism for non vaccine related narcolepsy

• Role, if any, for adjuvant in development narcolepsy with NP containing vaccines

• Role, if any, for co-infections, e.g. GAS in development of narcolepsy (GAS- ARF, PSGN, PANDAS)  


• If DR1 host susceptibility gene (facilitates replication flu A viruses) also found in those who develop narcolepsy

Therapeutic Vaccines

Vaccines developed to PREVENT infections – including cancer e.g. HPV, HBV vaccines

New era- therapeutic vaccines – designed to TREAT cancer

Cancer immunotherapy: 4th treatment modality

surgery, chemotherapy, radiotherapy & immunotherapy

Science in 2013 – immunotherapy – the breakthrough of the year

Therapeutic Vaccines

Anti-tumour immunization:

• complex, multi-component task,
• optimal combinations: ?????
  antigens, adjuvants, delivery vehicles,
  routes of administration, timing
• beware – patient maybe immunocompromised
  not able to respond well to vaccine

Both innate and adaptive immunity involved in cancer surveillance
Dendritic cell Vaccines

Curran E et al. Targeting the innate immune system as immunotherapy for acute myeloid leukemia. Frontiers in Oncology 2015; 83-93.
Expression of NKG2D ligands on human tumor cells

Innate immune system
- recognize Ags through germline-encoded receptors
- discriminate self from non self by 3 mechanisms:

Recognize-
  a) conserved microbe products
  b) “missing self” – not in microbe
  c) altered –self **

**NKG2D** receptor- functions to recognize cells expressing induced self-proteins in NK and T cells

- **NKG2D** ligand expression:
  tightly regulated in healthy adult tissue to prevent self-recognition, autoimmune reactivity and cell death

## Expression of NKG2D Ligand on Human Tumor Cells

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ovarian</td>
<td>AML</td>
</tr>
<tr>
<td>bladder</td>
<td>ALL</td>
</tr>
<tr>
<td>breast</td>
<td>CML</td>
</tr>
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<td>lung</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>colon</td>
<td>Multiple myleoma</td>
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<tr>
<td>renal</td>
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<td>prostate</td>
<td>Ewing’s Sarcoma</td>
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<tr>
<td></td>
<td>Glioma</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma</td>
</tr>
</tbody>
</table>
Immunotherapies Targeting NKG2D Ligands
Melanoma GVAX-

- GM-CSF secreting allogeneic melanoma cell vaccine
- 20 patients – 18 completed 4 vax (intra dermal)

Results:
Biopsies injec sites: complex inflam infiltrates
  ↑ eosinophils, PD-1 + lymph
Serum GM CSF ++↑ 48 hours post vax
  ↑ activated monocytes, ↓ myeloid suppressor cells

Lipson E et al. Safety and immunologic correlates of Melanoma GVAX, a GM-CSF secreting allogeneic melanoma cell vaccine administered in the adjuvant setting. J Transl Med 2015 13:214
Immunotherapy for Melanoma

PD-1 inhibitors
- Pembrolizumab
- nivolumab

CTLA-4 inhibitor
- Ipilimumab

Target PD-1: protein T cells that normally help keep these cells from attacking other cells in the body.

Boosts the immune response as blocks CTLA-4, another protein on T cells that normally helps keep them in check.

Melanoma: From Incurable Beast to a Curable Bet. The Success of Immunotherapy”
Gi et al. Dendritic Cells as Danger-Recognizing Biosensors. Sensors 2009, 9(9), 6730-6751
Immunization for the Whole of Life

Indeed we have only just begun…….

**Preventive Vaccines**

**Tailored to fit**
- across the ages
  - pregnancy, baby, child, adult, senior….whole of life
- our genetic background
- our context – environment, travel

**Growing understanding AEFI – impact on vaccine design**

**Therapeutic Vaccines**
- for cancer

We as HCP need to be up to date, be able to knowledgably offer advice to our patients; refer on when not in our area expertise.
“Vaccines are the tugboats of preventive health.......maybe even become for therapeutic care e.g. cancer”

William Foege – devised global strategy for small pox eradication