SEROLOGICAL TESTING: WHAT DOES IT MEAN IN THE CONTEXT OF VACCINE

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AMMI
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### CONFLICT OF INTEREST DISCLOSURE SLIDE

| In the past 2 years I have been an employee of: |  |
| In the past 2 years I have been a consultant of: |  |
| In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms: |  |
| In the past 2 years I have been a member of the Scientific advisory board of: |  |
| In the past 2 years I have been a speaker for: |  |
| **In the past 2 years I have received research support (grants) from:** | Co applicant on GSK investigator driven collaborative grant (SOS network for influenza and vaccine effectiveness) |
| In the past 2 years I have received honoraria from: |  |
| I agree to disclose approved and non-approved indications for medications in this presentation: | N/A |
| I agree to use generic names of medications in this presentation: | YES |

There are no relationships to disclose ☐
DIFFERENT TECHNOLOGIES

IFA

EIA

- Plate
- Micro/EIA
- Color vs chemiluminescent
- New technologies

Neutralization assays

- PRNT
- Microneutralization

Hemaglutination Inhibition
Contains all different types of antigens
Synthetic or from culture

Mix of viral antigens

Patient serum containing IgG

anti-human IgG
EIAS MAY NOT MEASURE “NEUTRALIZING ANTIBODIES”
HEMAGGLUTINATION INHIBITION

- Influenza serology
- Arboviral serology
  - Lots of cross reactivity
Antibodies inhibit a virus from infecting a cell monolayer
VACCINES

- VZV
- Measles
- Mumps
- Rubella
- Hepatitis A
- Hepatitis B
- Diphtheria
- Tetanus
- Pertussis
- Polio
- Influenza
- N. meningitidis
- S. pneumoniae
- HiB
- Yellow fever
- Japanese encephalitis
- Rabies
- Cholera
- BCG
- HPV
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• anthrax
JUST BECAUSE YOU CAN MEASURE IT
WHAT DOES IT MEAN?
WHAT CORRELATES WITH PROTECTION?
INFLUENZA

HAI > 1:40

Hobson et al 1972
Study in Rural Senegal Children
Titer less that 125 mIU/ml had high attack rates compared to those with < 125
(Samb et al., 1995 JPID)

Outbreak among students at BU in 1985
Chen et al., 1990

### Table

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<th>Subject(s)</th>
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<th>PRN titer Post-exposure</th>
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• O’Shea et al., 1983
  • Experimentally infected volunteers
  • Seronegative – 80% became viremic
  • >15 IU/ml – 0% were viremic
  • <15 IU/ml natural infection – 0% viremic
  • <15 IU/ml vaccine Abs – 5% viremic
STANDARDIZATION OF METHODOLOGY

• EIA and other methods have multiple components
• Different viruses
• Different antigens
• Different conjugate antibodies
• Different dilutions and methodology

• HOW DO YOU ENSURE EQUALITY BETWEEN TESTS
STANDARDS

Measles
- WHO standard > 120 mIU/ml

Rubella
- WHO standard > 10 IU

HBV
- WHO standard > 10 IU

Rabies
- 0.5 IU/mL

Diptheria
- WHO standard 0.1 IU/mL
STANDARDS CAN BE TRICKY
• They can change with time
  • The protective level estimated to be
    – 200 mIU/mL based on 1st International Reference
    – 120 mIU/mL when based on 2nd International Reference
• Correlations of ELISA and PRNT are still not perfect
  • IgG antibody detected by EIA kits are not necessarily neutralizing
Rubella serology

- All tested with the HAI gold standard
- The IOU may not make all things equal
- TALK TO YOUR LAB!

Dimech et al., 2008
WHAT DOES THE CANADIAN IMMUNIZATION GUIDE SUGGEST?
• Serological testing may be indicated to confirm the diagnosis of measles or to determine immune status.

• Serologic testing is not recommended before or after receiving measles-containing vaccine.

  “If serology is inadvertently done subsequent to appropriate measles immunization and does not demonstrate immunity, measles re-immunization is NOT necessary.”

NACI 2012
• Presumed immune
  • born before 1970 (NACI) but others say 1957*
  • Documented vaccination with 2 doses
  • Lab evidence of immunity
  • Lab evidence of infection

* PICNet BC 2001
WHAT IS LAB EVIDENCE OF IMMUNITY?

- **Measles**
  - WHO standard exists.
  - >120 mIU/ml is WHO recommendation
  - >200 mIU/ml considered a safe cutoff in BC

- **Mumps**
  - No WHO standard
  - MN titer of >1:2 is protective
  - EIA IgG pos a surrogate for protection
    - BUT may not be measuring neutralizing antibodies

(Mauldin et al., 2005. J Clin Microbiol. 43:4847-4851; Chen et al., JID 1990)
Pre-immunization
- History of immunization = immunity
- DO NOT need to prescreen before deciding on immunization

Post-Immunization
- Not Necessary

Prenatally
- Only screen those who have no evidence of immunization
- If \( < 10 \text{ IU}^* \) vaccinate immediately post partum
- No need for further serologic testing
Individuals who do not have ANY of the following are considered susceptible to VZV:

- Self-reported history of VZV if born before 2004 (except for health care workers)
- For those born in 2004 or later and for health care workers, a health care provider diagnosis of VZV or herpes zoster
- Documented evidence of immunization with two doses of a VZV containing vaccine
- A history of laboratory confirmed VZV infection
- Laboratory evidence of immunity
• **Prevaccination:**
  - 12 months to 12 years of age: NOT RECOMMENDED
  - 13 to < 50 years of age: if immunity unknown – Test
    - majority of such individuals will be immune and will not require varicella vaccine.
  - >50 years of age: NOT RECOMMENDED - unless known to be varicella-susceptible based on serology previously drawn for other purposes.

• **Post immunization**
  - NOT RECOMMENDED
  - Commercial EIAs are not sensitive

Holmes et al., 2004 CMAJ; Holmes et al., CFP 2005
VZV SEROLOGY

• FAMA – Fluorescent antibody to membrane antibody test
  • >1:4 titre = protection

• gpELISA – Proprietary
  • 5gpELISA units or 10mIU/ml is thought to = protection

• Commercial ELISA
  • Sensitivities 63% - 76% compared to FAMA or gpELISA

Breuer et al., JID 2008:s147-15
• No indication for pre-post vaccination serology
• IWK measures PT / filamentous Hemaglutinin (FHA)
  • No correlate of protection
• Serology is available but no indication for pre-post immunization serology
• Still requested for “immune status”
• But true level for protection is not known

< 0.01 IU/ml non-protective
> 0.01 IU/ml may provide some protection
≥ 0.1 IU/ml are considered protective.
≥ 1.0 IU/ml associated with long-term protective immunity.
**HBV**

- **Pre immunization**
  - Not cost effective for the general populations

- **Post immunization**
  - Only in circumstances where exposure is likely
  - 1 - 6 months after completion of series
  - If < 10 mIU/mL give another booster and if still <10 1 month later give second series
- No serology available (and not indicated)
- Travelers to polio-endemic countries or areas who have previously received ≥3 doses of OPV or IPV should be
  - offered another dose of polio vaccine as a once-only
  - dose before departure.
• Serology and vaccines is complex
• We often measure antibody levels but correlates to protection not always there
• Different assays have different cut-offs
• May be reasonable in some circumstances
• Better to have documented vaccination history

NACI guidelines: