Protective Immunity After Vaccination

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Overview

1) Models of long-term humoral immunity
2) (All) Vaccines require booster shots
3) The Yellow Fever conundrum
4) Imprinted Model of long-term humoral immunity
Predictions based on various models of humoral immunity

Persisting antigen/Immune complexes
Repetitive stimulation
PC competition for BM
Long-lived Immunity (long-lived PC)

Smallpox vaccination induces antibody responses that are maintained essentially for life

$T_{1/2} = 92$ years
Predictions based on various models of humoral immunity

Virus-specific antibody responses are unaltered by heterologous infections
Maintenance of serum antibody levels appears to be largely determined by the antigen.

Results of longitudinal analysis of serum antibody production indicate that antibody half-life differs between antigens.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>T_{1/2} (years)</th>
<th>95% CI (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td>11</td>
<td>10-14</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>19</td>
<td>14-33</td>
</tr>
<tr>
<td>VZV</td>
<td>50</td>
<td>30-153</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>92</td>
<td>46-∞</td>
</tr>
<tr>
<td>Rubella</td>
<td>114</td>
<td>48-∞</td>
</tr>
<tr>
<td>EBV</td>
<td>11,552</td>
<td>63-∞</td>
</tr>
<tr>
<td>Mumps</td>
<td>542</td>
<td>90-∞</td>
</tr>
<tr>
<td>Measles</td>
<td>3,014</td>
<td>104-∞</td>
</tr>
</tbody>
</table>
Imprinted Lifespan model of humoral immunity

Maintenance of serum antibody levels appears to be largely determined by the antigen

Amanna et al., NEJM, 2007
Longitudinal analysis of antibody responses to *B. pertussis* toxin

Serum Antibody Titer

Age (years)

$T_{1/2} = 16$ years

Longitudinal analysis of antibody responses following pertussis vaccination or infection

Serum Antibody Titer

Age (years)

$T_{1/2} = 16$ years

$T_{1/2} = 13$ years
Longitudinal analysis of antibody responses following pertussis vaccination or infection

\[ T_{1/2} = 16 \text{ years} \]

Serum Antibody Titer vs. Age (years)

Longitudinal analysis of antibody responses following pertussis vaccination or infection

\[ T_{1/2} = 16 \text{ years} \]

Serum Antibody Titer vs. Age (years)
Maintenance of serum antibody levels appears to be largely determined by the antigen.

Amanna et al., NEJM, 2007
Approximately 97% of the total adult population has protective immunity against tetanus (99% of people <60 years of age)
Monovalent antigens, tetanus and diphtheria, induce long-term immunity that decays slowly over time.

Tetanus

$T_{1/2} = 14$ years (95%CI = 11-17 years)

Diphtheria

$T_{1/2} = 27$ years (95%CI = 18-51 years)

Which vaccines offer “One Shot and Lifelong Immunity”?
Wild-type viruses induce long-term immunity but artificially attenuated viruses require booster vaccination

<table>
<thead>
<tr>
<th>Wild-type Virus</th>
<th>Artificially attenuated vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>MMR</td>
</tr>
<tr>
<td>Mumps</td>
<td>MMR</td>
</tr>
<tr>
<td>Polio</td>
<td>OPV</td>
</tr>
<tr>
<td>Smallpox, Cowpox, Vaccinia*</td>
<td>MVA</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>YFV-17D**</td>
</tr>
<tr>
<td>Varicella Zoster Virus</td>
<td>VZV-Oka</td>
</tr>
</tbody>
</table>

*Vaccinia represents a naturally attenuated virus (likely horsepox)

**YFV vaccination induces long-term immunity in only about 60-70% of subjects

Longitudinal analysis of antiviral antibody responses following measles infection
Vaccine-induced measles-specific antibody is long-lived, but often resides at or below the protective threshold.

Relationship between long-lived immunity and long-term protection.
The Yellow Fever
Conundrum

Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA

M. Niedrig, M. Lademann, P. Emmerich and M. Lafrenz

The eye is drawn to the durable immunity in the upper portion of the graph

...but 25-30% lose immunity within 5 years
Conclusion: Protective immunity can be maintained for 30-35 years after vaccination – but 30-40% of individuals may be left unprotected without administering a booster vaccination

Why are some individuals endowed with lifelong immunity against yellow fever and others are not?
Smallpox vaccination induces antibody responses that are maintained essentially for life.

Antibody responses to MVA decline rapidly even after two doses.

Does this mean that *All* vaccines elicit only short-lived immunity?

(The answer: No.)

Antibody responses to inactivated Hep A virus are maintained for *decades* after two doses

H. Theeten *et al.* Long-term antibody persistence after vaccination with a 2-dose Havrix™ (inactivated hepatitis A vaccine): 20 years of observed data and long-term model-based predictions. Vaccine, 2015
Imprinted Lifespan model of humoral immunity

**Vaccine Class**
- Multivalent Antigen (e.g., measles virus particle)
- Intermediate Antigen (e.g., tetanus toxin)
- Multivalent Non-Protein Antigen (e.g., Pseudomonas
type 23)

**Outcome**
- +Reaches antigenic threshold
  - Increased BCR clustering
  - Increased antigen presentation
  - Increased dwell time with $T_H$ cell
  - Long-term immunity
- -Does not reach antigenic threshold
  - Little or no BCR clustering
  - Intermediate antigen presentation
  - Shorter dwell time with $T_H$ cell
  - Intermediate to long-term immunity

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**Conclusions**

- Monovalent protein antigens are less likely to induce life-long immunity but if high titers are reached (e.g., tetanus/diphtheria) then protective immunity may be maintained for decades as long as antibodies remain above the protective threshold.

- Active infection or addition of adjuvants that induce inflammation (e.g., CpG/LPS from *B. Pertussis*) are unlikely to increase the durability of the immune response to specific antigens.

- Multivalent antigens (e.g., viruses or VLPs) typically induce long-term immunity, especially if antigen persists due to modestly prolonged infection or by addition of alum to maintain an antigen depot.

- Based on these points, vaccination against influenza could be improved by switching from “split virus” to whole-virus formulations, preferably with an alum-containing adjuvant.
  - *note that safety/reactogenicity issues would need to be resolved*
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