YELLOW FEVER VACCINATION IN EGG ALLERGIC PATIENTS

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OUTLINE

• Background
  – Yellow fever
  – Epidemiology
  – Yellow fever vaccine
  – Ovalbumin content

• Recommendations in egg allergy

• Case series
  – Methods
  – Results
  – Conclusions
**BG: YELLOW FEVER**

- RNA flavivirus
- Mosquito vector
- 2/3 asymptomatic
- 1/3: headache, fever, myalgia, vomiting
- 12% will have severe disease
  - haemorrhagic symptoms
  - multi-organ dysfunction
  - case fatality rates 15-50%
- Natural immunity accumulates with age – highest risk in infants/children

EPIDEMIOLOGY

• Endemic to 44 countries across tropical Sub-Saharan Africa & South America
  – Cases reported in China for the first time\(^1\)

• Estimated 200,000 cases & 30,000 deaths per year\(^2,3\)
  – Actual burden likely higher since most cases are asymptomatic

• Large, unpredictable outbreaks

• Elimination not possible-
  – Maintenance of virus in sylvatic reservoirs
  – Poor vaccine coverage in many affected countries
  – Global vaccine shortage
  – Increasing vaccine shortage

YELLOW FEVER VACCINE

- Live attenuated 17D strain
- Effective
- Well tolerated, adverse events usually mild
- Rare adverse events: neurotropic or viscerotropic disease
- Anaphylaxis: 1 in 131,000
  - Contains ovalbumin
  - YF-VAX contains gelatin
- Can be administered intramuscularly or subcutaneously

VACCINE RECOMMENDATIONS

• People aged ≥ 9 months living in or travelling to areas with a risk of yellow fever transmission

• Occupational risk

• Single dose provides long term protection for most
  – Booster dose at 10y recommended for special groups

• International Health Regulations (2005)
  – International Certificate of Vaccination or exemption letter needed for entry into some countries

• Entry into Australia
  – Travellers > 1y strongly recommended to have valid ICVP if entering Australia within 6 days of leaving a yellow-fever declared country and stayed in the area overnight or longer
OVALBUMIN CONTENT

• Stamaril (Sanofi-Aventis Australia)
  – AIH: May contain traces of egg protein
  – <5ug per 0.5mL dose (personal communication)

• Stamaril (Sanofi Pasteur, UK)¹
  – Mean 0.105ug/0.5mL dose
  – Range 0.067 – 0.306 ug/0.5mL

• YF-VAX (Sanofi Pasteur, USA)²
  – Mean 3.11 ug/mL (range 2.43 – 4.42)

• YFV is not heated at any stage

• Safe limit of ovalbumin in a parenteral vaccine has not been established

OTHER VACCINES

• MMR: nanograms to picograms
  – Can be safely given to patients even with anaphylaxis to egg

• Influenza vaccines: < 1 ug per dose in Australian formulations
  – Previously was contraindicated in egg allergy
  – Then proceeded to skin testing, split dosing protocols
  – Over time and multiple published reports (> 4000 patients), guidelines were relaxed
  – AIH:

<table>
<thead>
<tr>
<th>Allergy</th>
<th>Vaccine administration and setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain (eg positive skin test but not yet eaten egg)</td>
<td>Vaccinate with full age-appropriate dose in any immunisation setting</td>
</tr>
<tr>
<td>Non-<strong>anaphylaxis</strong> egg allergy</td>
<td>Vaccinate with full age-appropriate dose in any immunisation setting</td>
</tr>
<tr>
<td>Anaphylaxis egg allergy</td>
<td>Vaccinate with full age-appropriate dose in a medical facility with staff experienced in recognising and treating <strong>anaphylaxis</strong></td>
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</table>
YFV IN EGG ALLERGY

- Australian Immunisation Handbook
  - CI: anaphylaxis to eggs
  - Egg allergy: refer to immunologist or specialist immunisation clinic

- Product Information
  - Stamaril (Sanofi-Aventis, AU): CI in persons with a history of severe allergic reaction to eggs or chicken proteins
  - Stamaril (Sanofi Pasteur, UK): CI in persons with hypersensitivity to eggs
  - YF-VAX (Sanofi Pasteur, US): CI in persons with hypersensitivity to egg. “However, if a subject is suspect as being an egg-sensitive individual, the following test can be performed before the vaccine is administered”
    - SPT with 1:10 dilution; if negative, IDT with 1:100. If positive → desensitisation protocol
    - The following successive doses should be administered subcutaneously at 15- to 20-minute intervals: 1. 0.05 mL of 1:10 dilution 2. 0.05 mL of full strength 3. 0.10 mL of full strength 4. 0.15 mL of full strength 5. 0.20 mL of full strength
METHODS

• Audit of Specialist Immunisation Clinics (SIC) at two Australian tertiary paediatric hospitals
  – The Children’s Hospital at Westmead, Sydney
  – Royal Children’s Hospital, Melbourne
• Identified patients with egg allergy who presented for yellow fever vaccination
• We reviewed:
  – history of clinical reactions to egg
  – SPT results for egg
  – details of skin testing that was performed prior to vaccination
  – protocol used to administer the vaccine
  – adverse events recorded during the post-vaccination observation period & at phone follow up
# Patient Characteristics

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Egg allergy history</th>
<th>Egg SPT result</th>
</tr>
</thead>
<tbody>
<tr>
<td>14m M</td>
<td>Diagnosed on SPT</td>
<td>‘Large positive’</td>
</tr>
</tbody>
</table>
| 19m M   | Generalised rash, angioedema, resp distress | EW 10 x 6 mm  
EY 14 x 7 mm |
| 2y M    | Generalised urticaria | EW 9 x 7 mm  
EY 9 x 6 mm |
| 13y F   | Itchy throat, difficulty swallowing, cough | EW 5 x 3 mm  
EY 4 x 5 mm |
| 2y M    | Generalised urticaria, wheeze, rhinorrhoea, vomit | EW 3 x 3 mm  
EY 1 x 1 mm |
| 12y M   | Oral symptoms, nausea | EW 17 mm |
| 15m M   | Vomiting            | Unavailable   |
| 4y M    | Generalised urticaria | EW 8.5 mm    |
| 23m M   | Anaphylaxis         | EW 4.5 mm    |
RESULTS

• SPT with neat yellow fever vaccine was performed in 5/9 patients and was negative in 4/5
  – 4 pts with negative SPT → 2 dose protocol: 10% then 90% with 60 min interval, then 60 min observation period
  – 1 patient with borderline positive SPT (2x3mm)
    • 10% dose given SC → large erythematous flare
    • Given antihistamine
    • 20% dose given SC → no adverse events
    • Remaining 70% given intramuscularly
• 4/9 patients did not have any skin testing
  – 2 patients proceeded to 2 dose protocol (as above)
  – 2 patients were given a full dose
• IDT was not performed on any patient
• All 9 patients were successfully vaccinated with the full dose
## COMPARISON OF PROTOCOLS

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Skin testing (dilution)</th>
<th>Approach if skin testing positive</th>
<th>Approach if skin testing negative</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutkowski</td>
<td>3 adults 3 children</td>
<td>SPT (1:1) IDT on adults (1:10)</td>
<td>7-step protocol</td>
<td>2 dose protocol</td>
<td>1 ISR 1 generalised urticaria</td>
</tr>
<tr>
<td>Juliao</td>
<td>5 children (1-9yo)</td>
<td>SPT – all IDT if &gt; 5yo</td>
<td>5 step protocol</td>
<td>Single dose</td>
<td>1 urticaria</td>
</tr>
<tr>
<td>Munoz-Cano</td>
<td>1 (42y)</td>
<td>SPT (1:10) IDT (1:100)</td>
<td>3 step protocol</td>
<td>N/A</td>
<td>ISR urticarial</td>
</tr>
<tr>
<td>Catelain</td>
<td>1 (14y)</td>
<td>SPT (1:10) IDT (1:1000 then 1:100)</td>
<td>N/A</td>
<td>2 step protocol</td>
<td>Nil</td>
</tr>
<tr>
<td>Ruiz</td>
<td>2 (4y, 23m)</td>
<td>SPT (2000 IU/mL) IDT (20 IU/mL)</td>
<td>N/A</td>
<td>3 step protocol</td>
<td>Nil</td>
</tr>
<tr>
<td>Mosimann</td>
<td>1 (40y)</td>
<td>SPT (1:10) IDT (1:100)</td>
<td>N/A</td>
<td>Single dose</td>
<td>Nil</td>
</tr>
</tbody>
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ISSUES WITH SKIN TESTING

• Skin testing:
  – Low sensitivity & specificity for predicting reactions to MMR and influenza vaccines¹
  – No evidence to support positive predictive value for yellow fever vaccine hypersensitivity reactions

• IDT:
  – Painful
  – Time consuming, technically difficult (requires training)
  – 1/5th of dose provides 10y of immunity²

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CONCLUSION

• Largest case series of yellow fever vaccine administration in egg allergic children
• YFV has been safely administered to egg allergic patients, including those with severe or anaphylactic egg allergy
• Skin testing protocols & administration protocols vary widely
• Ovalbumin content of YFV not known but is higher than influenza vaccine
  – Risk of anaphylaxis is possible
  – Safe threshold not known
• Referral to a Specialist Immunisation Clinic or immunologist is recommended