

# **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

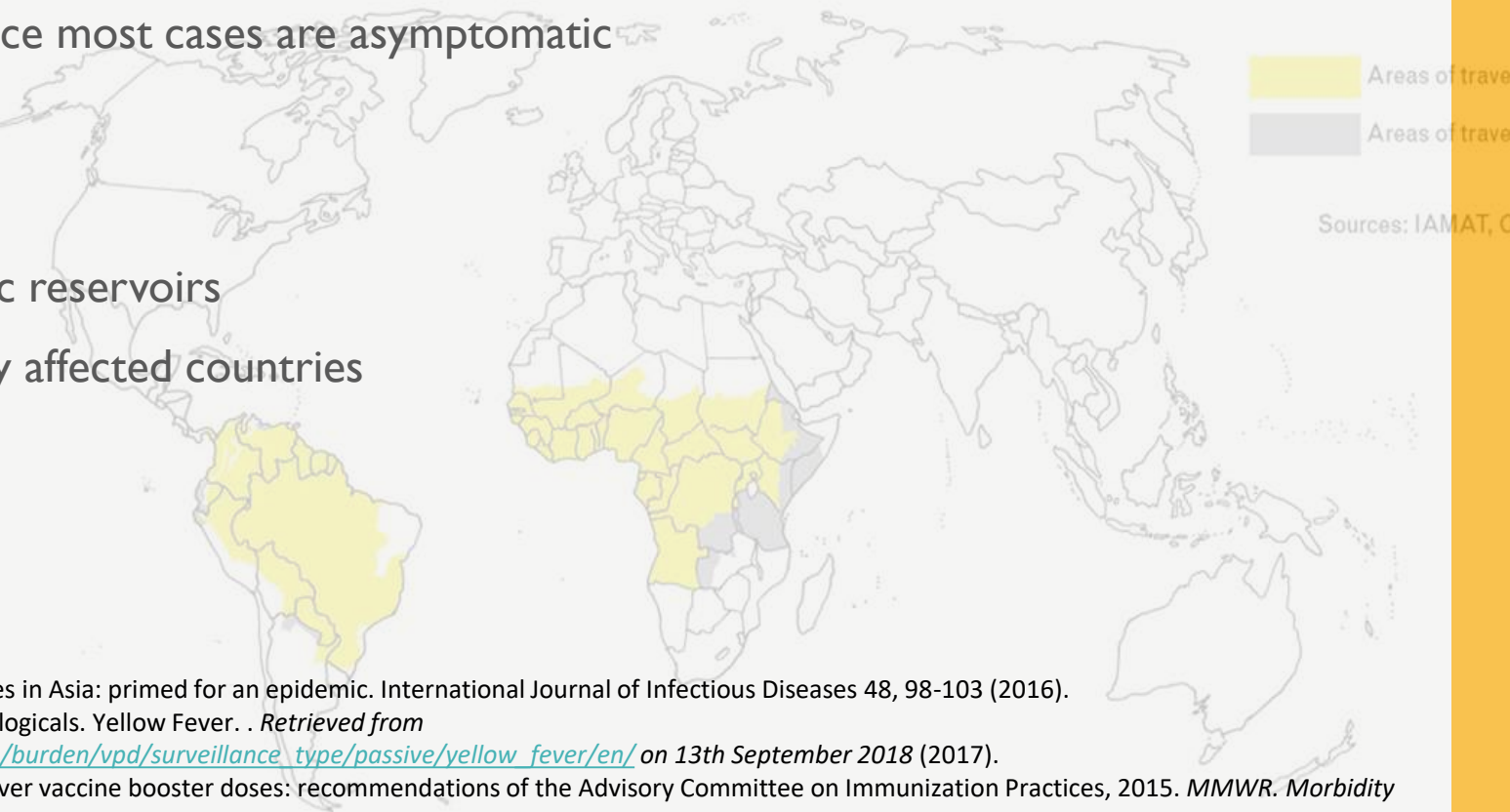
- RNA flavivirus
- Mosquito vector
- 2/3 asymptomatic
- 1/3: headache, fever, myalgia, vomiting
- 12% will have severe disease<sup>1</sup>
  - haemorrhagic symptoms
  - multi-organ dysfunction
  - case fatality rates 15-50%<sup>2,3</sup>
  - Natural immunity accumulates with age – highest risk in infants/children<sup>4</sup>



1. Johansson, M. A., Vasconcelos, P. F. & Staples, J. E. The whole iceberg: estimating the incidence of yellow fever virus infection from the number of severe cases. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **108**, 482-487 (2014).
2. World Health Organisation. WHO report on global surveillance of epidemic-prone infectious diseases. (Geneva: World Health Organization, 2000).
3. Woodall, J. & Yuill, T. Why is the yellow fever outbreak in Angola a 'threat to the entire world'? *International Journal of Infectious Diseases* **48**, 96-97 (2016).
4. Centers for Disease Control and Prevention. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017. (2018)

# EPIDEMIOLOGY

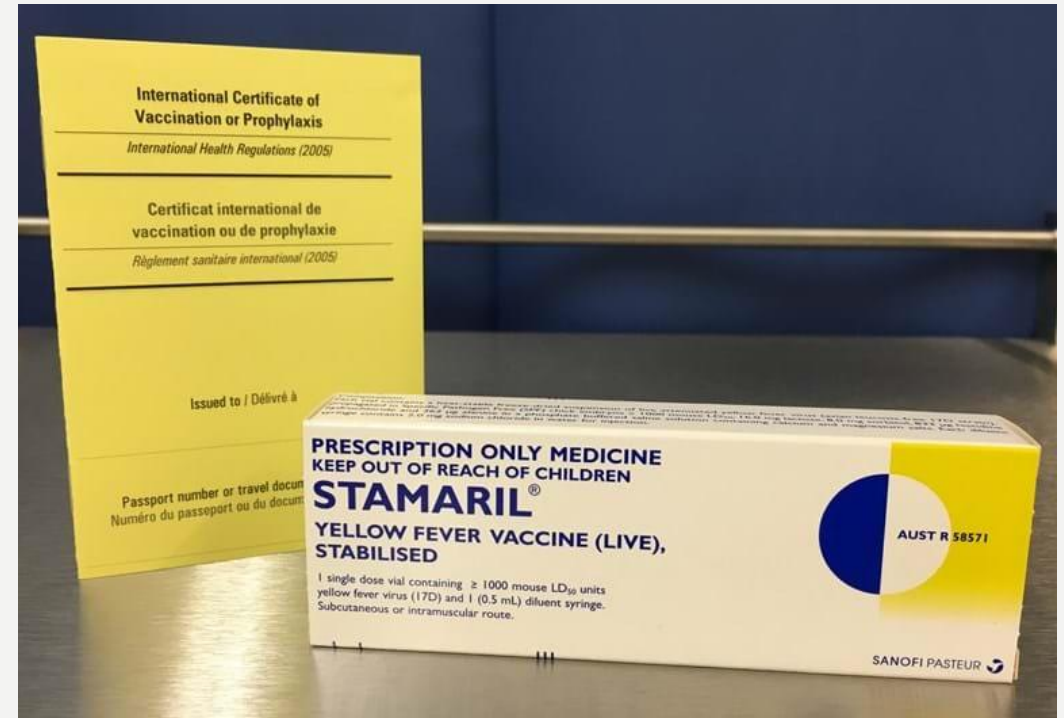
- Endemic to 44 countries across tropical Sub-Saharan Africa & South America
  - Cases reported in China for the first time<sup>1</sup>
- Estimated 200,000 cases & 30,000 deaths per year<sup>2,3</sup>
  - Actual burden likely higher since most cases are asymptomatic
- Large, unpredictable outbreaks
- Elimination not possible-
  - Maintenance of virus in sylvatic reservoirs
  - Poor vaccine coverage in many affected countries
  - Global vaccine shortage
  - Increasing migration



1. Wasserman, S., Tambyah, P. A. & Lim, P. L. Yellow fever cases in Asia: primed for an epidemic. *International Journal of Infectious Diseases* 48, 98-103 (2016).
2. World Health Organization. Immunization, Vaccines and Biologicals. Yellow Fever. . Retrieved from [http://www.who.int/immunization/monitoring\\_surveillance/burden/vpd/surveillance\\_type/passive/yellow\\_fever/en/](http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/yellow_fever/en/) on 13th September 2018 (2017).
3. Staples, J. E., Bocchini, J. J., Rubin, L. & Fischer, M. Yellow fever vaccine booster doses: recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR. Morbidity and mortality weekly report* 64, 647-650 (2015).

# 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<sup>1</sup>
  - Contains ovalbumin
  - YF-VAX contains gelatin
- Can be administered intramuscularly or subcutaneously



1. Kelso, John M., Gina T. Mootrey, and Theodore F. Tsai. "Anaphylaxis from yellow fever vaccine." *Journal of allergy and clinical immunology* 103.4 (1999): 698-701.

# VACCINE RECOMMENDATIONS

- People aged  $\geq 9$  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)<sup>1</sup>
  - Mean 0.105ug/0.5mL dose
  - Range 0.067 – 0.306 ug/0.5mL
- YF-VAX (Sanofi Pasteur, USA)<sup>2</sup>
  - 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



Rutkowski, K., Ewan, P. W. & Nasser, S. M. Administration of yellow fever vaccine in patients with egg allergy. *International Archives of Allergy & Immunology* **161**, 274-278.

Smith, D., Wong, P., Gomez, R. & White, K. Ovalbumin content in the yellow fever vaccine. *The Journal of Allergy & Clinical Immunology in Practice* **3**, 794-795.

# OTHER VACCINES

- MMR: nanograms to picograms
  - Can be safely given to patients even with anaphylaxis to egg
- Influenza vaccines: < 1ug 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. Recommended administration of influenza vaccine in people with egg allergy**

Allergy	Vaccine administration and setting
Uncertain (eg positive skin test but not yet eaten egg)	Vaccinate with full age-appropriate dose in any immunisation setting
Non- <a href="#">anaphylaxis</a> egg allergy	Vaccinate with full age-appropriate dose in any immunisation setting
Anaphylaxis egg allergy	Vaccinate with full age-appropriate dose in a medical facility with staff experienced in recognising and treating <a href="#">anaphylaxis</a>



# 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

Age/Sex	Egg allergy history	Egg SPT result
14m M	Diagnosed on SPT	'Large positive'
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 17mm
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

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

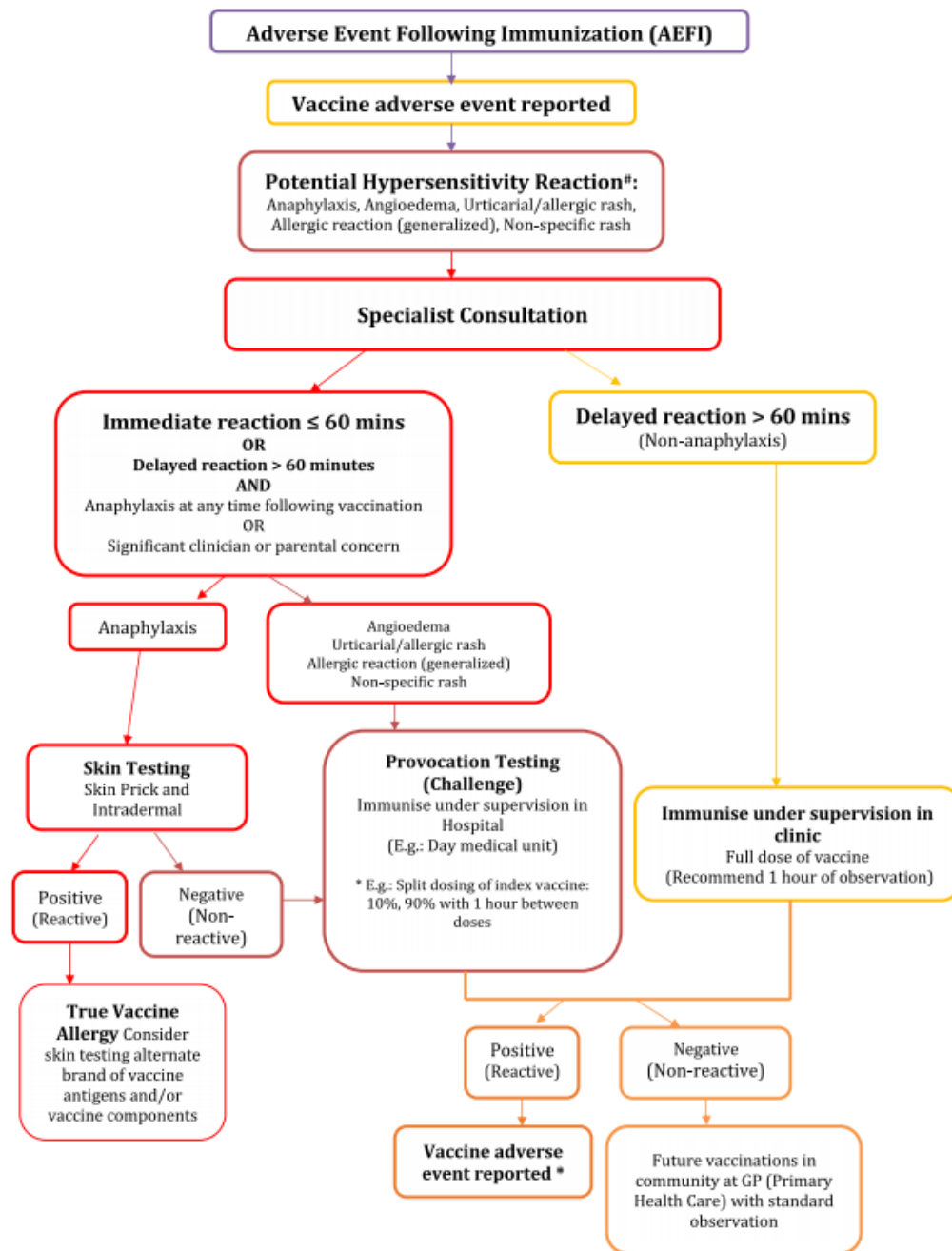
# ISSUES WITH SKIN TESTING

- Skin testing:
  - Low sensitivity & specificity for predicting reactions to MMR and influenza vaccines<sup>1</sup>
  - No evidence to support positive predictive value for yellow fever vaccine hypersensitivity reactions
- IDT:
  - Painful
  - Time consuming, technically difficult (requires training)
  - 1/5<sup>th</sup> of dose provides 10y of immunity<sup>2</sup>

1. Committee on Infectious Diseases, American Academy of Pediatrics. Recommendations for prevention and control of influenza in children, 2012–2013. *Pediatrics*. 2012;130:780–92. 20. Kelso JM. Potential food allergens in medications. *J Allergy Clin Immunol*. 2014;133:1509–18.

2. Roukens, Anna HE, et al. "Long-term protection after fractional-dose yellow fever vaccination: Follow-up study of a randomized, controlled, noninferiority trial." *Annals of internal medicine* 169.11 (2018): 761-765.





Cheung, Abigail, Sharon Choo, and Kirsten P. Perrett. "Vaccine Allergy? Skin Testing and Challenge at a Tertiary Pediatric Hospital in Melbourne, Australia." *The Journal of Allergy and Clinical Immunology: In Practice* (2019).

**FIGURE 2.** Suggested algorithm of suspected hypersensitivity reactions to vaccine. <sup>#</sup>May include any of the major and minor criteria used in the Brighton Collaboration case definition of anaphylaxis. <sup>9</sup> \*If suspected IgE-mediated reaction at 10% dose, seek specialist guidance before proceeding with further doses.

# 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