# Penicillin Allergy-
# Are we denying our children optimal care?

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# Outline

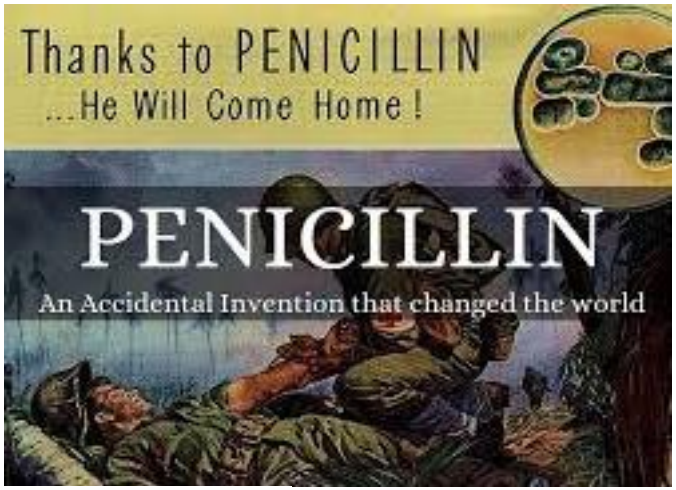
- Antibiotics and antibiotic allergies in general
- Antibiotic allergy labels and its clinical impact

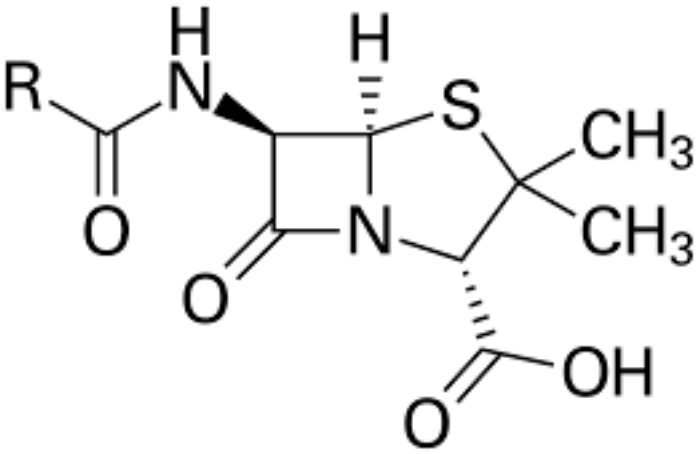
Research undertaken at PMH/PCH:

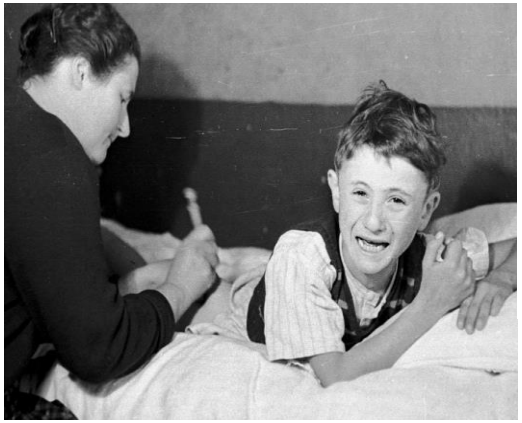
- Retrospective audit
- CHAD (Children Antibiotic De-labelling project)
- SPECIAL (Safely Preventing Errors and Complications due to Inappropriate Allergy Labelling


One sometimes finds, what one is not looking for. When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer. But I suppose that was exactly what I did.

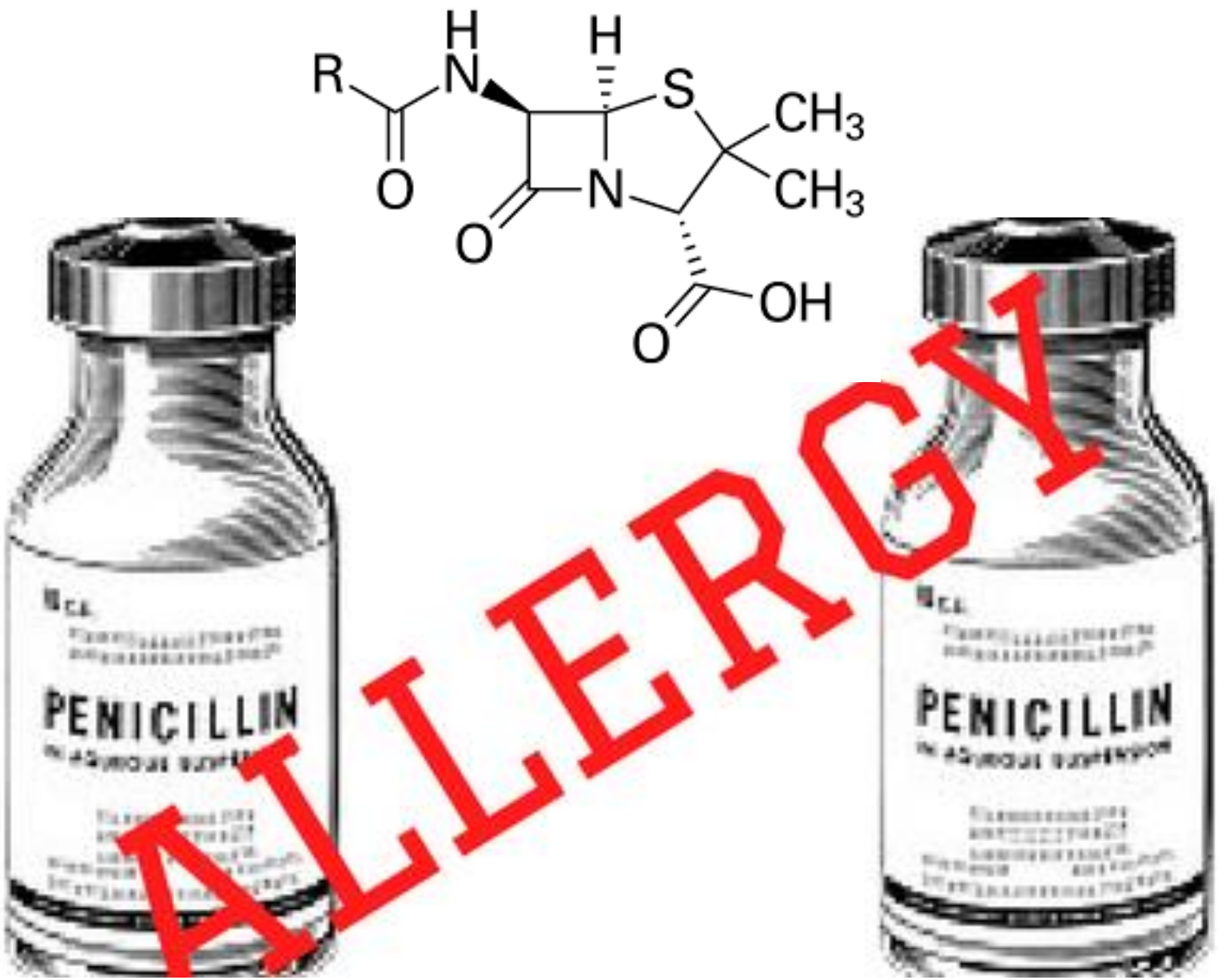
— *Alexander Fleming*


Since 1940th antibiotics have greatly reduced reduced morbidity and mortality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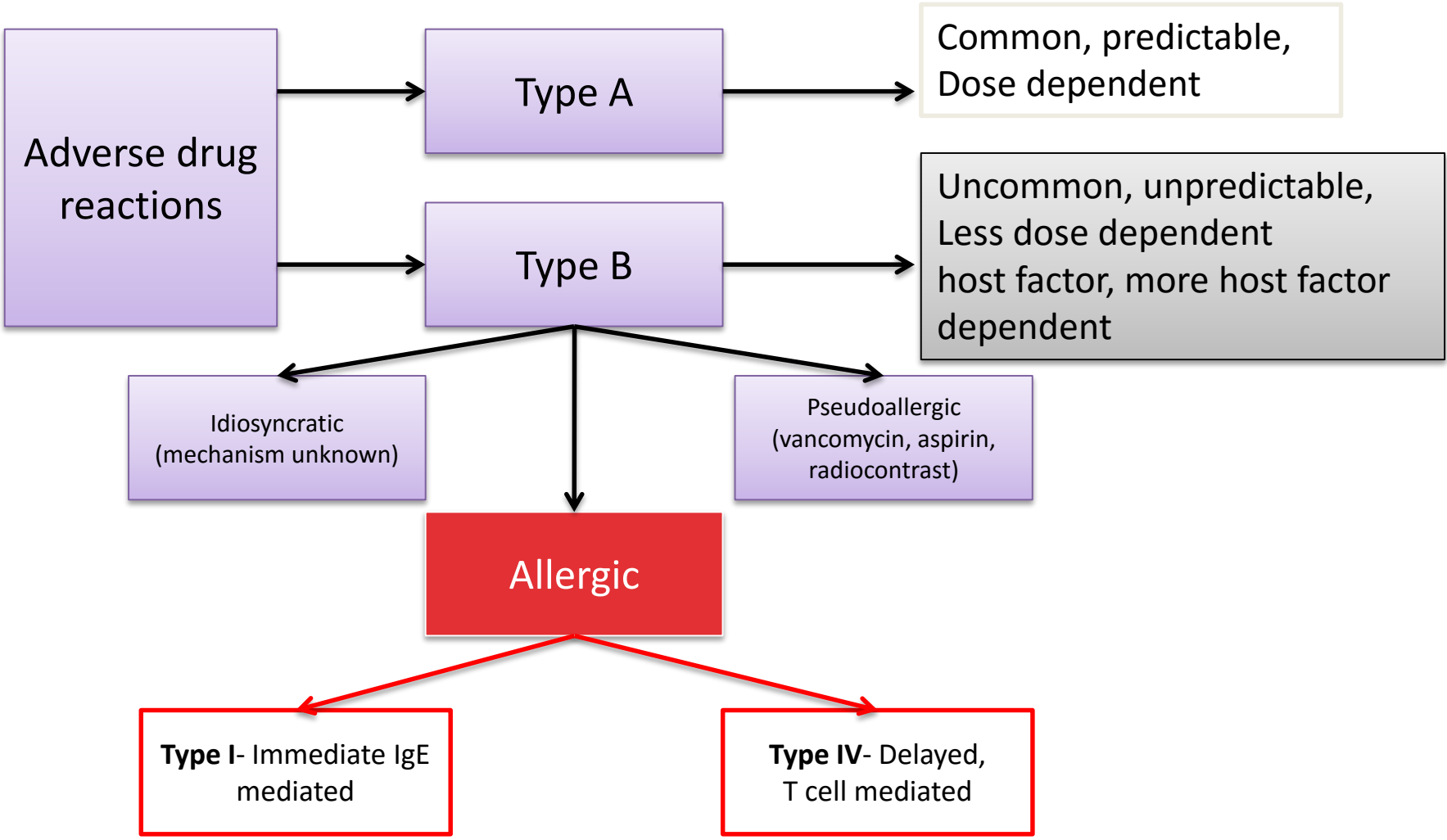
# Adverse Drug Reaction (ADR) classification



# Classification of DHR: TYPE I Reactions

Drug allergy/ hypersensitivity (DHR) reactions are heterogeneous.

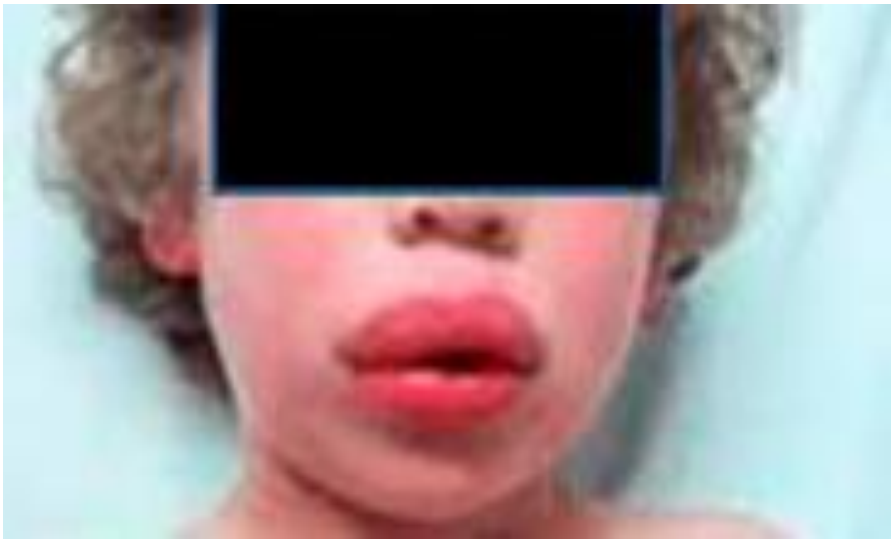
**Immediate reactions:**

–Result of IgE production by antigen-specific B cells after sensitisation

–**urticaria, angioedema,** rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain), **anaphylaxis**

– typically occur within 1–6 h after the last drug administration.

# What do we see in ED?



# What do we see in ED?

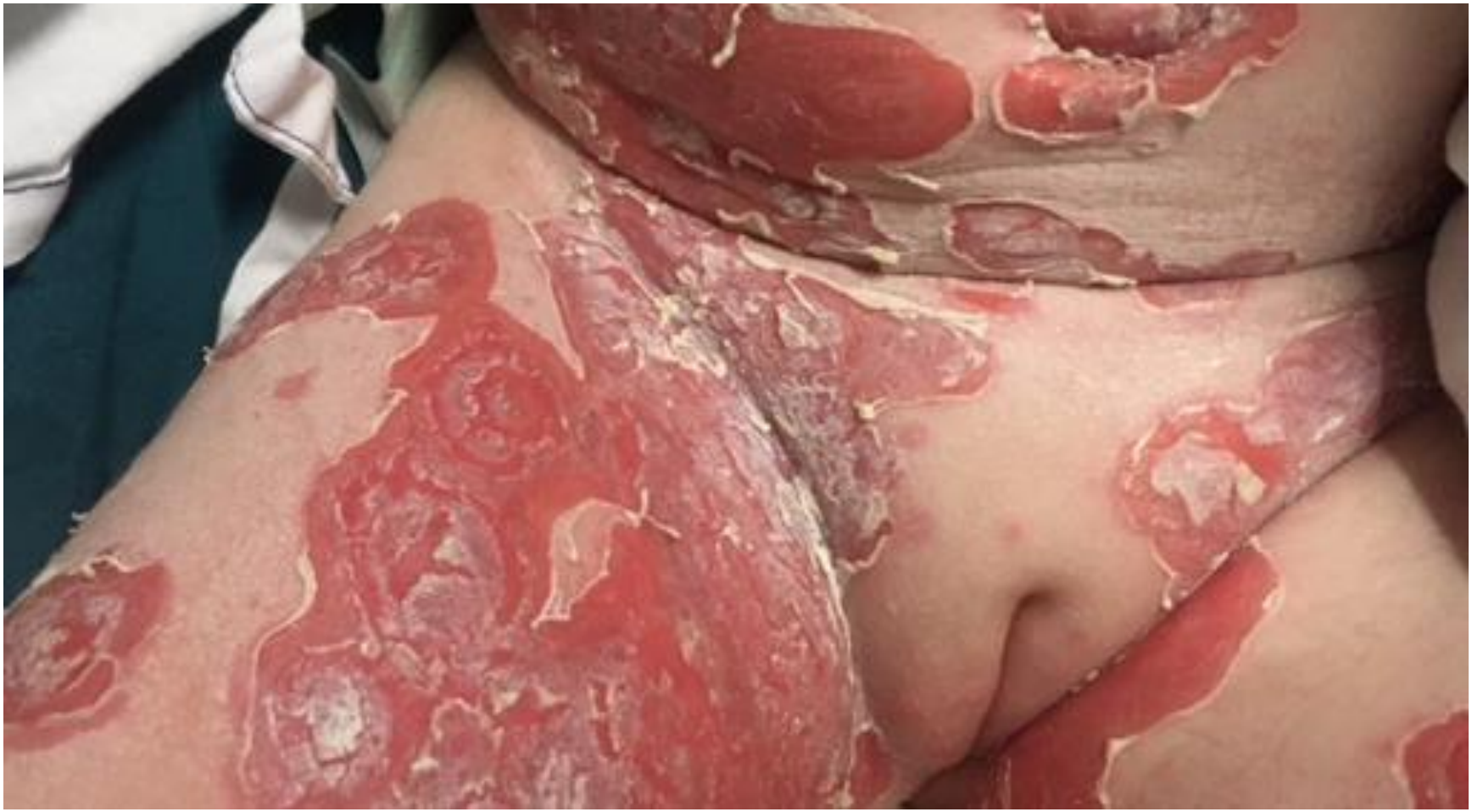
# Classification of drug DHR
# Type IV Reactions

**2. Non-immediate reactions**

– heterogenous clinical picture
  - **delayed urticaria**, **maculopapular eruptions**, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, and **Stevens–Johnson syndrome**, drug reaction with eosinophilia and systemic symptoms (**DRESS**), acute generalized exanthematous pustulosis and symmetrical drug-related intertriginous and flexural exanthemas; internal organs can be affected either alone or with cutaneous symptoms (DRESS, vasculitis) and include hepatitis, renal failure, pneumonitis, anemia, neutropenia, thrombocytopenia;

– Spectrum of disease with varying pathogenesis
– they may occur at any time as from 1 h after from the initial drug administration.

# What do we see in ED?



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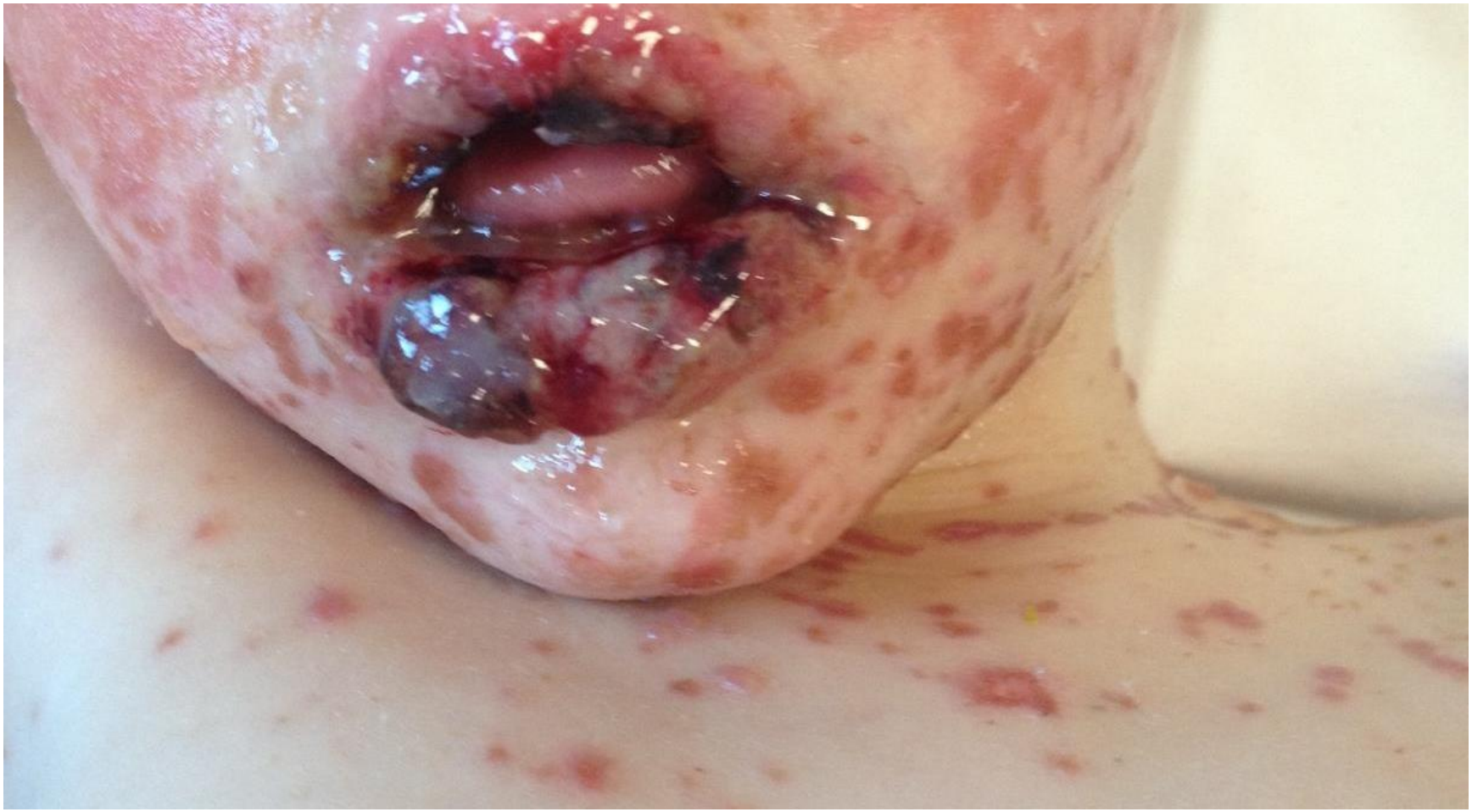
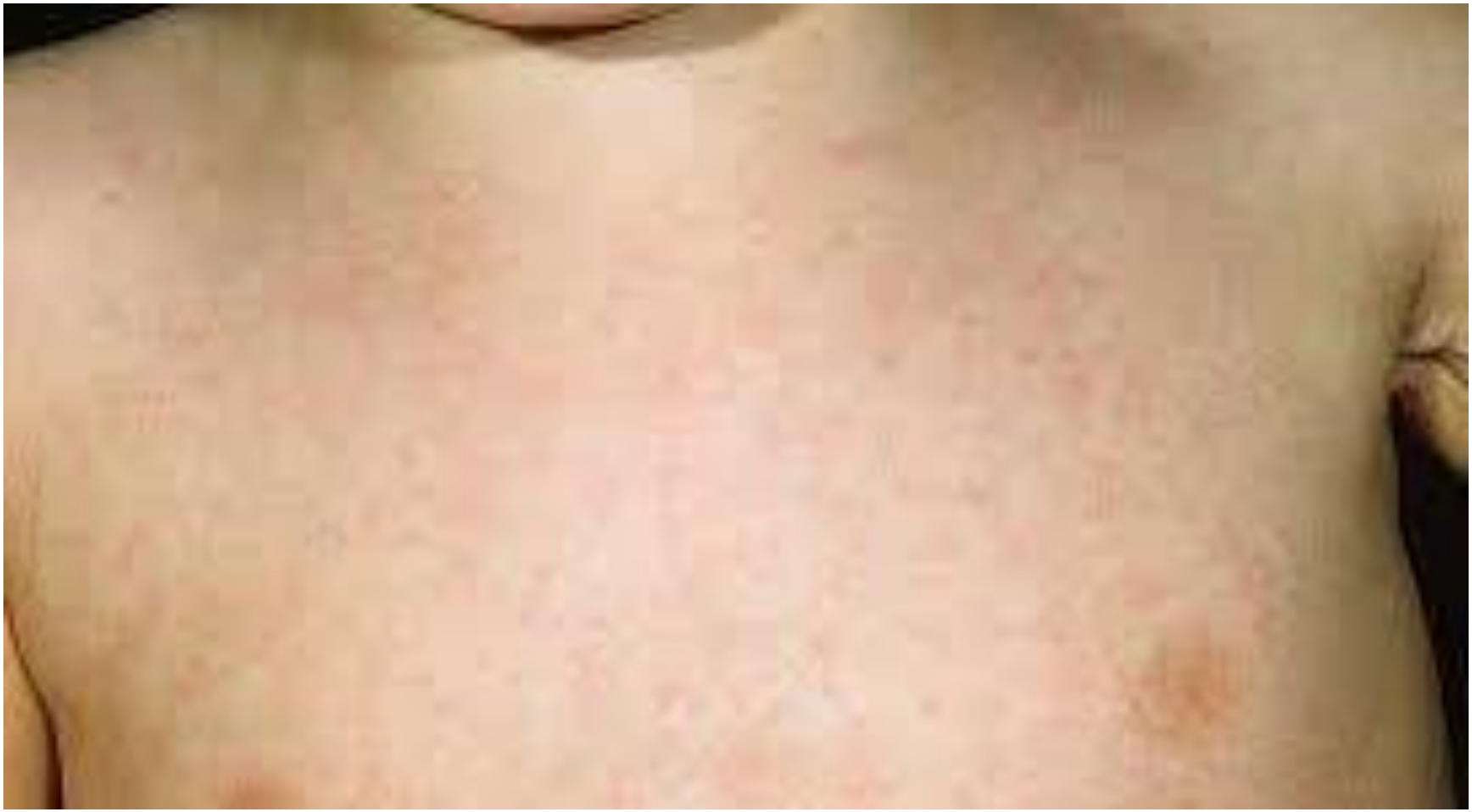


# What do we see very often in ED Antibiotic Allergy???



# Diagnosis-Skin tests and Oral drug provocation

**Immediate reactions**

- Serum specific IgE testing (aka RAST)
- Skin prick testing (SPT)
- If negative, intradermal testing (IDT) which provides increased sensitivity
- Oral provocation (OPC) testing
    - Gold standard for the identification of drug allergy
    - Can confirm DHR or demonstrate tolerance
    - Important for assessment of beta-lactam allergy when skin tests are negative
    - Oral route is preferred when possible

# Antibiotic allergy label

- Patients frequently report antibiotic allergies (**antibiotic allergy label, AAL**) when presenting to ED

  What does this mean?

- The patient (probably) had an adverse reaction to an antibiotic in the past, but commonly:
  - cannot recall to which antibiotic they reacted to
  - is unsure of the type of the reaction
  - cannot recall how long ago the reaction occurred

?

**→ Penicillin allergy labels often lead to the avoidance of all beta-lactam antibiotics**

# Self-reported antibiotic allergy in Australia: A growing problem !

- The number of self-reported antibiotic allergy (AAL) in Australia is about 18% in adult patients admitted to hospital

  (Trubiano JA et al. J Antimicrob Chemother. 2016; Knezevic B et al., IMJ 2016)

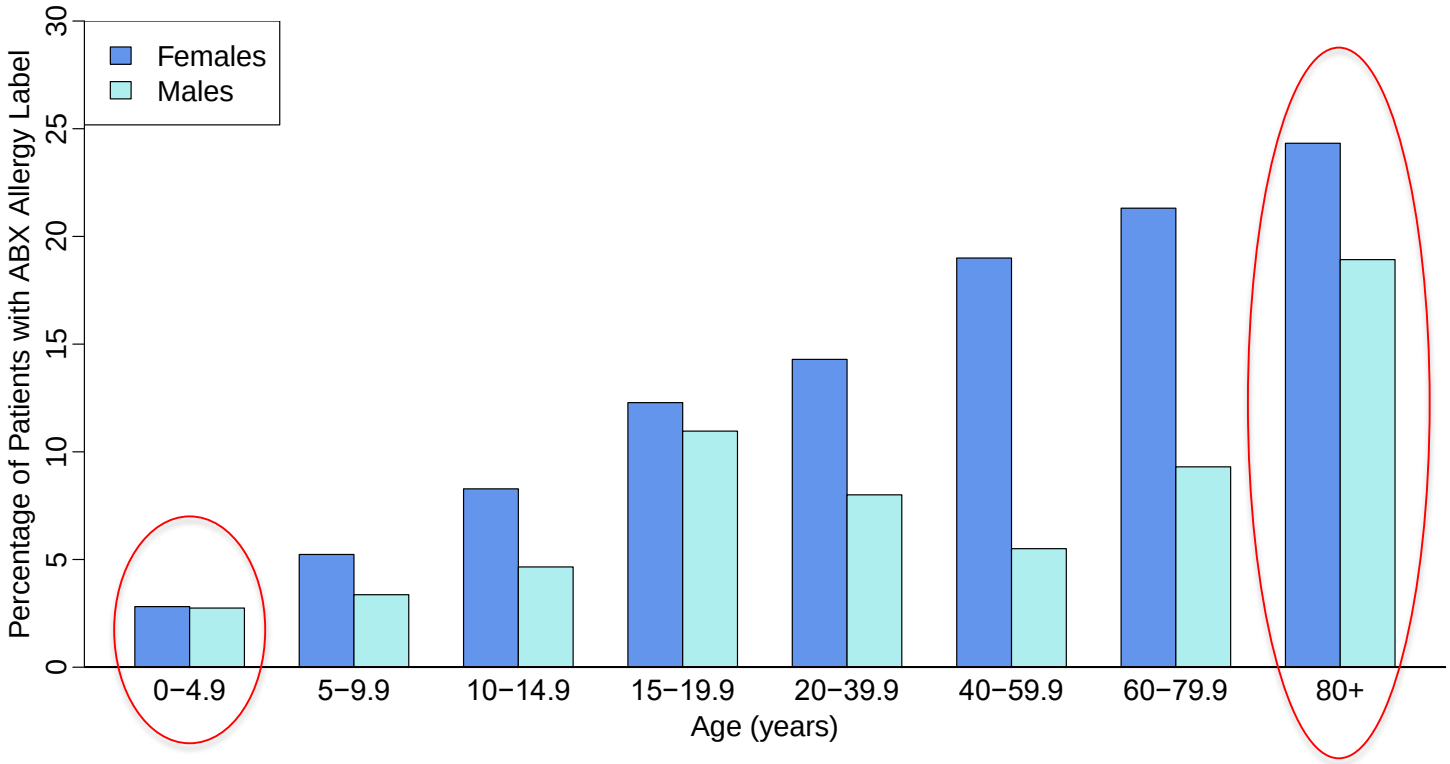
- The rate of patients with self-reported allergy in the primary care setting in Australia is unknown

- Self-reported antibiotic allergy in admitted General Medicine patients is common: 21-24%

  (Trubiano JA et al. MJA 2016; Knezevic B et al., IMJ 2016)

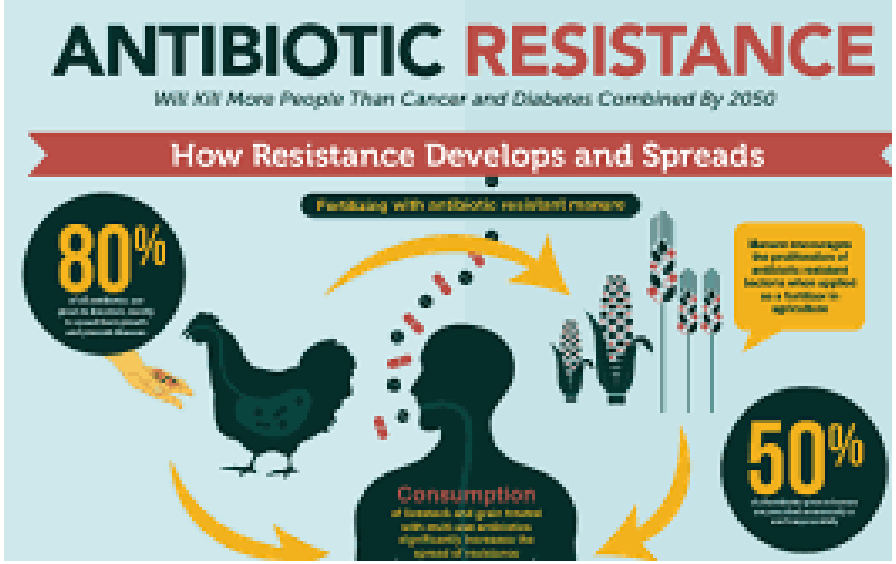
- The rate of self-reported antibiotic allergy in Australian children is not well studied

# Self-reported antibiotic allergy- age and gender




Lucas M unpublished data

# Key Problem behind AAL:




- Antibiotic resistance in both -children and adults- is increasing rapidly, globally and in Australia due to widespread use
  (Shaban RZ, Australian Health Protection Principal Committee, 2013)

- National Alert system for Critical Antimicrobial Resistance (NAS CAR) detected that more than 1000 ED cases resistant to Abs between 2016 and 2017

- Further 75% increase in total number in 2017

- At least one strain of bacteria with critical antimicrobial resistance reported from each territory in Australia

# Key problem : use and abuse of antibiotics

- Australia has one of the highest antibiotic exposures worldwide and prescription rates have increased by 230 % in the last decade

  Exposure to antibiotics is the greatest in early childhood

  (Pan Y, Respir Med 2006; Schneider- Lindner V., J Antimicrob Chemother 2011)

- Australian children are exposed to considerably more antibiotics than the majority of international counterparts (Anderson H; J Paed Child Health 2017)

# Antibiotic Allergy Labelling and


**Aim:**

➔Critical role of using the right antibiotic in the right way in every case

➔Preservation of all antibiotic choices whenever possible

- AAL are:
  - a barrier to Antimicrobial Stewardship
  - linked to increased antimicrobial resistance
  - lead to the use of alternative antibiotics which may be less effective
  - linked to increased infection with resistant pathogens (MRSA, VRE, C. diff)

# AAL and Clinical Care

- AALs are associated with higher rates of inappropriate prescribing and increased use of broad-spectrum antimicrobials (Multiple international studies; Australia: Trubiano JA et al.; J Antimicrob Chemother. 2016 Jun; Knezevic B et al.; IMJ 2016 Nov)

- A small Australian study reported that patients with penicillin allergy labels, hospitalized with community acquired pneumonia, had longer lengths of stay (Irawati L et al.; J Res Pharm Pract. 2006).

- Large American study reported increased lengths of stay, intensive care admission rates and higher mortality rates for patients with AALs (Charneski L.; Pharmacotherapy 2011

- Significant extra costs of using alternative antimicrobials for beta-lactam allergy labelled patients (Sade K.; Clin Exp Allergy 2003; Picard M.; JACI IP 2013); not found in our WA study (Knezevic, IMJ 2016 Nov)


# aspects and AAL

There are ensuing costs to:

- **The individual**
  - Increased complexity of care leads to greater propensity for error
  - Alternative treatment may not provide optimal outcomes
  - Increased risk of ARI (AB resistance and Infection) which has been shown to lead to longer hospital stays, higher mortality and significantly greater health care costs
- **The community**
  - The increase in ARI is potentially a public health crisis given the potential for treatment failure and/or death and the consequent financial impact on the health system

➔The associated benefits of de-labelling will be long-term for individuals and the community

# Collecting labels?
# Address the problem before it starts!

# Antibiotic allergy research in ED at PMH/ PCH

1. **Retrospective audit on patient care: completed**

1675 patients surveyed

**2. Children Antibiotic De-labelling - ChAD:**

**ongoing**

Funded by WA Health and Telethon Kids Institute

Recruitment started July 2016, completed

500 patients (children) recruited through various hospital sources

**Reported beta-lactam** antibiotic allergy **only**

Allergy testing includes skin testing, oral provocation challenge, extended course, blood testing

**3. Safely Preventing Errors and Complications due to Inappropriate Allergy Labelling – SPECIAL:**

**ongoing**

Funded by PMH Foundation and SPANZA

Started April-2018.

3000 patients to be randomised in intervention group and control group.

**All antibiotic allergies**

Allergy testing dependant upon history of allergy.

Government of Western Australia Department of Health

Retrospective audit:
**Antibiotic allergy labels and its clinical impact**

## AIM

To examine if parentally/self-reported antibiotic allergy labelling in children significantly impacts on their clinical care

M Lucas….K Rueter, in press JACI i Pr in press

# Methods

- Retrospective study of all inpatient admissions in April 2014 and April 2015 at Princess Margaret Hospital, Perh
- Patients admitted to hospital wards (medical and surgical specialties, PICU, psychiatry and rehabilitation wards)
- Data collected by chart review included:
    - patient demographics
    - admitting specialty and principal diagnosis on admission
    - documented antibiotic allergy labels
    - antibiotic prescriptions and/or infections during the stay
    - hospital length of stay
    - hospital readmissions within 4 weeks and 6 months of discharge

# Results

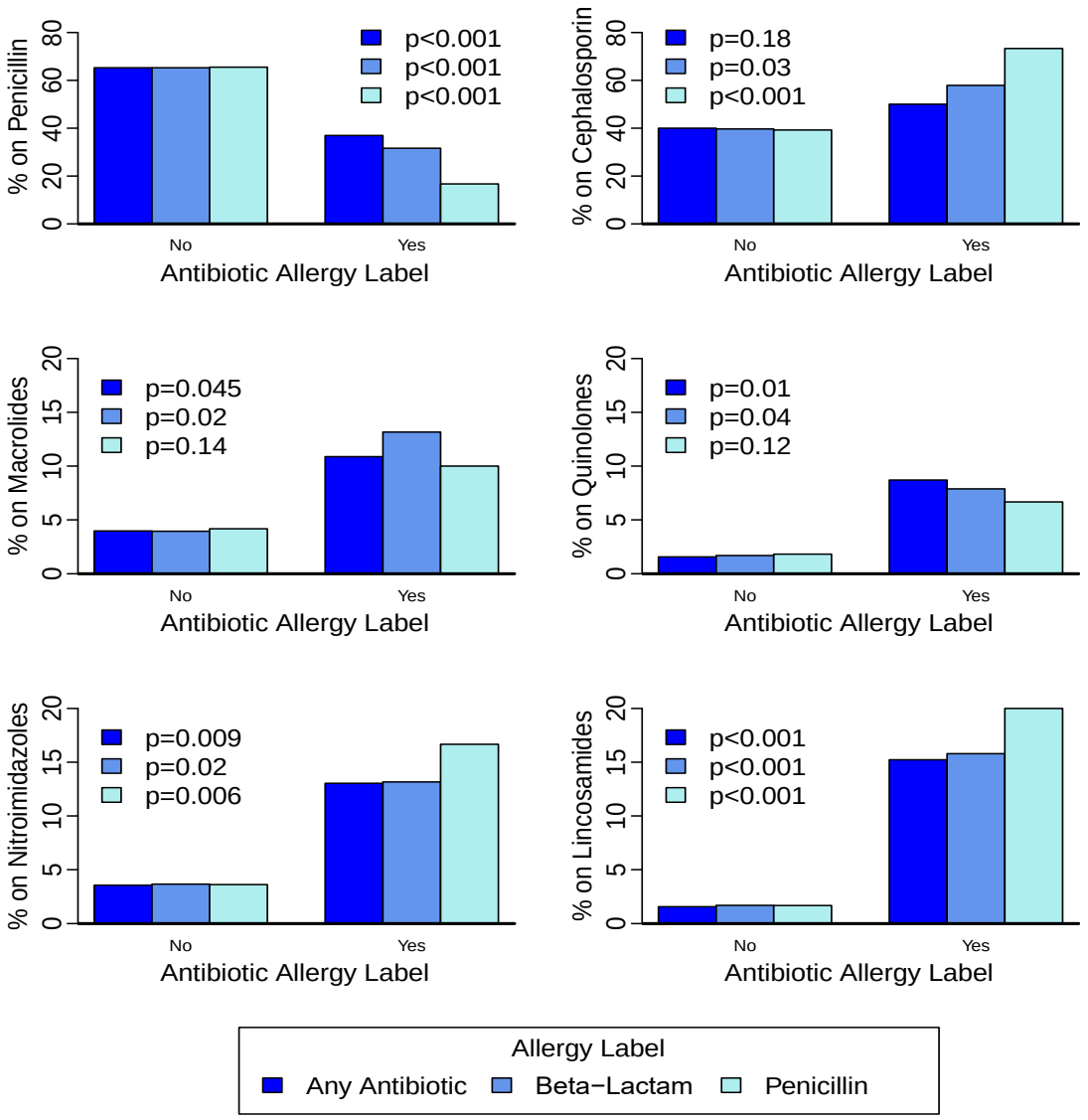
- 1672 admitted children ( 0- 18 years, 58% male) surveyed
- 44.8% prescribed antibiotics
- 5.3% labels recorded
- 85% beta-lactam labels, mostly to unspecified penicillins

# Demographics

**Increasing incidence of antibiotic allergy labels with age (p<.001)**

| | Any Antibiotic Allergy Label | | Any Beta-Lactam Allergy Label | | Overall (n=1675, 58% m) |
|---|---|---|---|---|---|
| | No (n=1587) | Yes (n=88) | No (=1600) | Yes (n=75) | |
| **Age Group** | | | | | |
| **0 - 4.99 years** | 714 (96.8%) | 24 (3.3%) | 719 (97.4%) | 19 (2.6%) | 738 (44.1%) |
| **5 - 9.99 years** | 417 (95.6%) | 19 (4.4%) | 418 (95.9%) | 18 (4.1%) | 436 (26.0%) |
| **10-18 years** | 456 (91.0%) | 45 (9.0%) | 463 (92.4%) | 38 (7.6%) | 501 (29.9%) |

Antibiotic use depending on having an antibiotic allergy label or not



# Results

- Patients with antibiotic allergy labels received more macrolides ($p=0.045$), quinolones ($p=0.01$), lincosamide antibiotics ($p<0.001$) as well as more metronidazole ($p=0.009$) than patients without an antibiotic allergy label (Figure 1)

- After adjusting for patient age, sex and admitting specialty, children with any antibiotic or beta-lactam allergy label, had longer hospital lengths of stay (OR 1.62, 95% CI 1.05-2.5, $p=0.03$).

- Mean length of hospital stay of 3.8 days for those without and 5.2 days for those with beta-lactam allergy label

# Conclusions

- This is the first study to demonstrate the negative impact of antibiotic allergy labels on clinical outcomes in children including:
    1. Significant alternate antibiotic use
    2. Longer hospital lengths of stay

➔ Childhood de-labelling may reduce the use of alternative antibiotics and the associated increase in bacterial resistance to antibiotics

➔ Early de-labelling may be beneficial from a health economic point of view, by reducing the prevalence and negative impact of allergy labels among children, and the future adult population

(Lucas M…..Rueter K, JACI i Pr 2018, in press)

# THE CHAD STUDY

➔Assessing Antibiotic allergies in children:

- The role of skin testing
- Serum testing
- Immediate provocation and
- Extended provocation

# Background

- Current international guidelines diagnose a beta-lactam allergy from a positive skin test, positive specific IgE or positive OPC

- Recent studies in adults conclude that skin testing and/or specific IgE, have poor sensitivity and specificity ➔ proceeding directly to oral challenge with the culprit antibiotic can be safe (Tannert LK, Journal of Clinical Immunology: in Practice 2017)

Very limited data in children, no data in Australia:
(Mill C, JAMA 2016 Jun)

➔ 1. To investigate the role of skin testing, specific IgE testing in predicting the outcome of OPC in children with a reported beta-lactam allergy.

➔ 2. Prospectively evaluate the rate of true antibiotic allergy

# CHAD
# Methods

- 411 children with a reported **beta-lactam allergy** (any history) were assessed, 2 children with a well documented history of anaphylaxis were excluded

(a) Skin prick testing (SPT) and/or intradermal testing (IDT)

(a) Gold standard oral provocation challenge (OPC) of 1/10$^{th}$ dose followed by full dosing.

(a) 5 day extended course of Abs to observe for a delayed reaction.

(b) Blood sampling for serum specific IgE collected post oral challenge

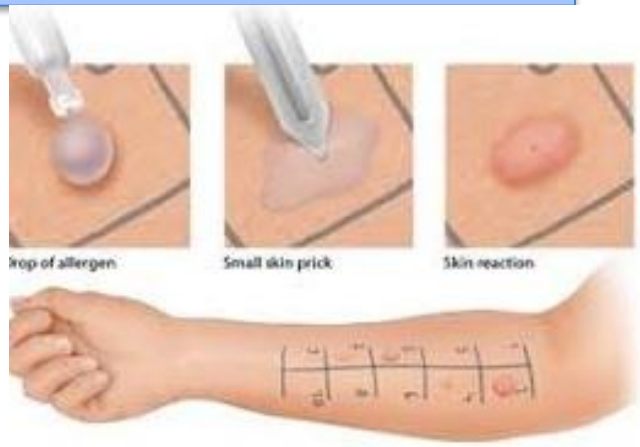
# Demographics (1)

| Demographics | Total n=370 | Male n=194 (52%) | Female n=176 (48%) |
|---|---|---|---|
| **Age at Challenge (years)** | 8.4 (1.0-18.1) | 7.7 (1.0-16.6) | 8.5 (1.0-18.1) |
| **Age at Reaction (years)** | 3.4 (0.0-16.7) | 3.5 (0.0-15.0) | 3.4 (0.0-16.2) |
| **Time between Challenge and Reaction** | 4.7 (0.0-16.7) | 4.2 (0.0-15.1) | 5.3 (0.0-16.7) |

# Demographics (2)

| Culprit Antibiotic | Total | Male | Female |
|---|---|---|---|
| | n=370 | n=194 (52%) | n=176 (48%) |
| Amoxicillin, n (%) | 237 (64.0) | 113 (47.7) | 124 (52.3) |
| Penicillin, n (%) | 76 (20.5) | 45 (59.2) | 31 (40.8) |
| Cephalexin, n (%) | 31 (8.4) | 23 (74.2) | 8 (25.8) |
| Flucloxacillin, n (%) | 5 (1.4) | 4 (80.0) | 1 (20.0) |
| Augmentin, n (%) | 19 (5.1) | 9 (47.3) | 10 (52.7) |
| Cefazolin, n (%) | 1 (0.2) | 0 (0.0) | 1 (0.0) |

# Results (1)




**All children had skin testing**

- 2 (0.5%) had positive skin-prick,

✓ one passed OPC and EC, one failed EC

- 8 (2.0%) had positive intradermal testing:

✓ 1 reacted at the 1/10th dose

✓ 1 passed the OPC but reacted on day 5 of the EC

✓ 6 passed OPC and EC

??

# Results (2)

**370 children underwent oral provocation challenges**

- 4 (1.1%) reacted immediately to 1/10$^{th}$ dose
- 3 (0.6%) reacted to the full dose
- All reactions were urticarial rashes

**351/370 (94.8%) went home on a 5-day EC**

- 23 reacted (6.6%) reacted (all rashes)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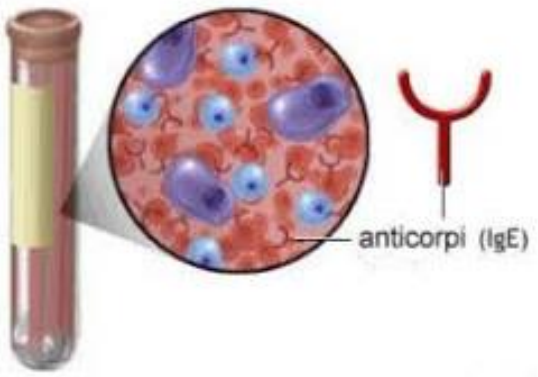
# Results (3)

**<u>346 (93.5 %) underwent blood sampling post challenge</u>**

- 13 (4.7%) children out of 346 had a positive serum-specific IgE for at least one beta-lactam, →all of these children passed the oral provocation and EC challenge

- 30 children reacted at OP(
  →all had a negative serum-specific IgE

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# Conclusion

- Skin testing and serum beta-lactam sIgE were poor predictors of the outcomes of OPC in children
- Immediate (7/370; 1.7% ) and delayed (23/253; 6.6% ) adverse reactions were rare and only presented with mild (rashes)

**Proceeding directly to oral provocation is safe and effective in de-labelling children from antibiotic allergy.**

# Consensus statement of the Australian Society of Clinical Immunology and Allergy (ASCIA)

Skin testing can be omitted in “presumed low risk”cases

# Safely Preventing Errors and Complications due to Inappropriate Allergy Labelling (SPECIAL Study)
# A Randomised Controlled Trial

PRINCESS MARGARET HOS
foundation

**WHY** to start the SPECIAL STUDY?

Our retrospective paediatric data have shown:

- an increased readmission rate in children with antibiotic allergy labels compared to children with no antibiotic allergy labels

- a significantly higher use of broad spectrum antibiotics in those with allergy labels [2, 3]

Hypothesis:

➔ Unverified antibiotic allergy labels lead to poorer clinical outcomes for patients and increased health care costs

Government of Western Australia Department of Health

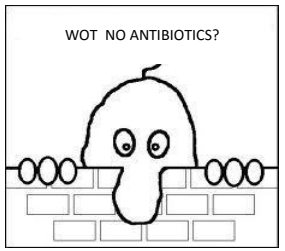
THE UNIVERSITY OF WESTERN AUSTRALIA

# How?

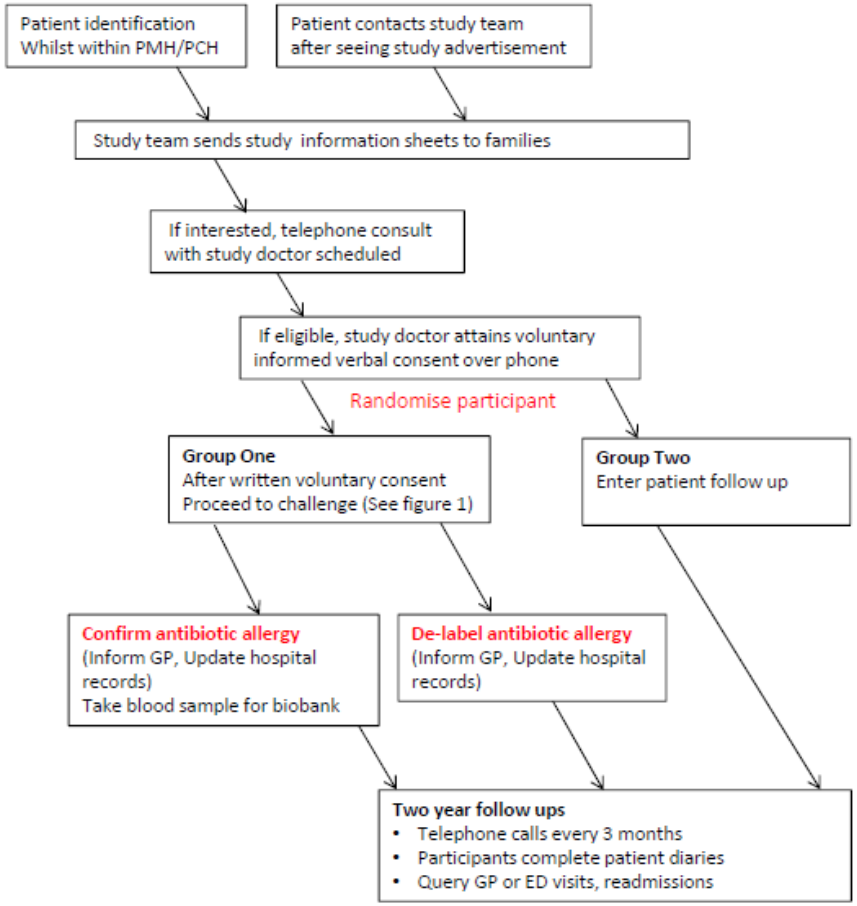
➔By safely de-labelling patients and comparing their health outcomes and costs to patients under normal care

- Better health outcomes for de-labelled patients
- Optimised emergency care
- Highlighting the true economic costs of inaccurate labelling
- Reduced spread of multiresistant bacteria

# Safely Preventing Errors and Complications due to Inappropriate Allergy Labelling (**SPECIAL Study**)




- 3000 participants recruited at PMH/PCH randomised across two groups
  - All 3000 patients will be followed up for 2 years
  - 1500 patients will receive de-labelling assessment challenge
  - 1500 patients will receive no intervention at first (control group), and then de-labelling assessment challenge after the 2 years follow up.

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# The SPECIAL study

- Self enrolment
- Enrolment from any Health Service

Every child 6 months-16 years with an antibiotic allergy label or a family history with antibiotic allergies leading to avoidance

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# Summary

- The burden of self-reported antibiotic allergy in Australia is high, however the rate of antibiotic allergy overall is low

- Over-labelling can set up a negative cycle of restricted access to antibiotics, poorer clinical outcomes, increased admission rate and hospitalisation

- Systematic drug allergy de-labelling may mitigate these clinical and economic burdens

➔The solution to this problem requires a collaborative approach and consensus opinion between different subspecialties

# A global challenge
# always requires a global solution !



# Thank you!

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