Case 1

- **HPI:** 35 year old male receives the influenza vaccine while living in Canada in year 2000.
- 6 hours after receiving vaccine, develops red eyes, cough, wheeze, chest tightness, difficulty breathing, sore throat, and facial swelling
- Had repeat reaction in 2001 with no increase in severity
- **PMH:** Seasonal allergic rhinitis and mild intermittent asthma, Negative for food allergies
  - Never hospitalized for asthma
- **Meds:** Loratidine prn, Albuterol inhaler prn
- **FHx:** Mom with nasal allergies; negative for angioedema
- **SHx:** Denies smoking or drug use, 2 alcoholic drinks/week

Q1: What is the most likely diagnosis?

A. Allergic conjunctivitis
B. Asthma exacerbation
C. Egg allergy
D. Oculorespiratory syndrome

A1: What is the most likely diagnosis?

A. Allergic conjunctivitis
B. Asthma exacerbation
C. Egg allergy
D. Oculorespiratory syndrome (ORS)
Oculorespiratory syndrome “ORS”
- Presence of bilateral red eyes, and/or facial edema, and/or any of the “ORS-defining respiratory symptoms”:
  - Coughing, wheezing, tightness of the chest, difficulty breathing, or sore throat
- Begins within 2–24 h after influenza vaccination
- Resolves within 48 h after symptom onset

History of influenza vaccine
- Influenza affects ~10% to 25% of the population/year.
- Predominant cause of serious respiratory illness in a community (especially children <2, elderly >65, chronic medical conditions including asthma)
- Current vaccines: inactivated trivalent split-virion products (parenteral); live attenuated (intranasal)
- US and Canada Vaccine Safety Surveillance
  - Serious adverse events are rare
- US updates on adverse events: updated Dec 11, 2012
  - http://www.cdc.gov/flu/professionals/acip/adversetiv.htm#ocular
- Guillain–Barré Syndrome (GBS), hypersensitivity, ORS

US Experience with Trivalent Inactivated Influenza Vaccine and ORS
- ORS reported within 24 hours after TIV immunization
  - Typically mild, resolve without Rx
- US Trials: Frequency, causality undefined
  - Red eyes: 1-6%; Cough: 1-7%;
  - Wheezing (6%); chest tightness 1-3%
- Placebo controlled effectiveness study: 2006–7 Fluzone
  - Red eyes in 2% compared to none in controls (p=0.03)
  - 2005–6: 3% versus 0% (not statistically significant)
- Cause: not definitively established but product/year associations and with aggregates proposed as cause
  - Reformulation of vaccine resulted in marked decrease in frequency and severity (side effect rather than adverse event)
  - http://www.cdc.gov/flu/professionals/acip/adversetiv.htm#ocular

Q2: Which of the following regarding the pathophysiology of ORS is true?
A. The complement system may be involved in the “red eyes”
B. ORS is not a life-threatening anaphylactic reaction
C. Risk of ORS recurrence is not a contraindication to future influenza immunization nor a predictor of future more severe anaphylaxis
D. All of the above


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ORS: New or previously unrecognized?
- Ocular and respiratory sxs following influenza vaccination occurred in the past in Canada, U.S., and several European countries
- Remained unrecognized until 2000
- Reports of ORS later found in Canadian AEFI database prior to 2000 AND in Italy during 1995-1996 season (Spila)
- Also observed in current influenza seasons but not associated with prolonged severe reactions or mortality

http://www.cdc.gov/flu/professionals/acip/adversetiv.htm
Back to our patient...

- Since the reactions in 2000 and 2001, he has avoided getting the influenza vaccine.
- He moved to the US in 2005 but over the past few years, his asthma has worsened.
- His new allergist recommends that he receive the annual flu vaccine but he refuses.
- What are the best strategies for enhanced benefit-risk communication?

Risk of Recurrence of ORS

- Retrospective cohort study
- N= 2070 (57 had ORS in 2000, 2013 previously unaffected) received either Fluviral or Vaxigrip vaccine.
- 107 (16 previously affected, 91 new cases) reported ORS sxs.
- Risk btw Fluviral & Vaxigrip not significant (5.6 vs 4.8, p=0.43).
- Individuals previously affected by ORS had:
  - Overall increased risk ⇒ 6.3 fold higher of developing ORS on revaccination (28% vs 4.5%, P < 0.001).
  - Developed higher number of ORS sxs (≥ 3) on revaccination (13% vs 5%) usually sore throat, cough + another.
- Risk with newer formulations and US products significantly less than earlier reports.


Q3: What do you tell him?

A. The risks of serious illness, hospitalization and mortality from influenza infection are increased in patients with chronic lung disease, including asthma.
B. Oculo-respiratory symptoms in the absence of cardiovascular anaphylaxis are not associated with an increased risk of more serious reactions with future TIV immunization.
C. ORS is less frequent in the TIV vaccines produced in the US and in reformulated products in Canada. Revaccination with this history is NOT a contraindication to current vaccine use.
D. Prolonged duration of ORS symptoms (>48h) may be seen among those with previous history of influenza vaccination, lung disease, or allergies but are not associated with increased risk of mortality or morbidity.
E. All of the above.

http://www.cdc.gov/flu/professionals/acip/adverse.htm

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http://www.cdc.gov/flu/professionals/acip/adverse.htm

Case 2

- **HPI:** 13 month old Caucasian female with a history of DiGeorge syndrome presents with intermittent low grade fever and cough x 2 weeks.
- Two days prior to presentation she developed decreased oral intake and one episode of hematemesis.
- **PMH:** DiGeorge syndrome diagnosed at 7 months of age, FISH for chromosome 22 microdeletion positive.
- **Past surgeries:** Underwent heart surgery for Tetralogy of Fallot at 10 months of age.
- **Meds:** Calcium, Vit D supplements, Bactrim pxp.
- **Family Hx:** Mom with nasal allergies, no siblings.
- **Social Hx:** no sick contacts, does not attend daycare.


- Vaccines up to date: Received MMR and Varicella at 12 months of age (4 weeks prior presentation).
- **Physical Exam:**
  - Vitals: Weight and height < 5th %, Temp 102, RR 40
  - Gen: Characteristic facies, micrognathia
  - HEENT: Microphthalmia, cleft palate repaired
  - Heart: RRR, nl S1 S2, no murmurs
  - Lung: Bilateral inspiratory crackles
  - Abd: soft, NT/ND, normoactive bowel sounds
  - Skin: no rash

Case 2

- Labs:
  - Calcium 9.0 (9.6-10.6 mg/dL)
  - Ionized Ca 5.0 (5.1-5.9 mg/dL)
  - Absolute lymphocyte count 1200 (660-4600 cell/mm³)
  - CD3: 400 (2100-6200 cells/mm³ normal range)
  - CD4: 300 (1,300-3,400 cells/mm³ normal range)
  - CD8: 100 (620-2,000 cells/mm³ normal range)
  - B cells: 800 (720-2,600 cells/mm³ normal range)
  - IgG: 600 (246-904 mg/dL normal range)
  - PBMC Proliferation to mitogens were normal

Q4: What is the most likely diagnosis?

A. Bacterial pneumonia  
B. Aspergillus pneumonia  
C. Mycoplasma pneumonia  
D. Viral pneumonia

CXR

- Multiple small round calcified lung lesions

Bronchoscopy

- Bronchoscopy specimens demonstrated multinucleated giant cells with nuclear inclusions.

PCR studies

- PCR obtained 6 weeks post-vaccination revealed:
  - Tracheal aspirates: +Varicella (vaccine strain)
  - Vesicular lesions: +Varicella (vaccine strain)
  - Negative for Measles

A4: What is the most likely diagnosis?

A. Bacterial pneumonia  
B. Aspergillus pneumonia  
C. Mycoplasma pneumonia  
D. Viral pneumonia secondary to VZV
Q5: In which of the following immune deficiency disorders is live virus varicella vaccine recommended?

A. Severe combined immune deficiency  
B. DiGeorge's with functional T-cell defects  
C. HIV infection with CD4 count < 200/mm³ or < 15% of total lymphocytes for children < 6 years of age  
D. Cancer under treatment with immunosuppressive or radiation therapy  
E. None of the above

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Varicella vaccine in immunocompromised

- In 1979, the NIAID sponsored the Varicella Vaccine Collaborative Study that looked at effectiveness of the vaccine on 437 children whose leukemia was in remission.
- Results showed seroconversion in 88% and 98% of leukemic children after the first and second dose, respectively
- 46% with rash. treated with Acyclovir
- 4% severe febrile illness, nonfatal reactions linked vaccine lot
- Varicella vaccine was safe in children in remission from leukemia and induced immunity to chickenpox that persists for more than 3 years.


Challenge for the Immunologist: Quantify the Degree of Cellular Immune Deficiency?

- Benefit-risk analysis in the context of primary and secondary immune deficiencies
  - Loss of broad multi-antigen anergy panel for assessment of T-cell function
  - Are in-vitro T-cell studies sufficient?
- What is true incidence of complications from live viral vaccines?
  - Rare that clinicians assess vaccine virus strain
  - Use CDC resources to support your patient evaluation in this setting
- Do NOT forget to take a vaccine history as part of your consideration of drug/vaccine adverse reactions! REPORT!
Q6: According to the 2011 Institute of Medicine Review on Adverse Effects of Vaccines and Causality Evidence, for which of the following is there strong evidence linking varicella vaccine as a cause:

A. Thrombocytopenia
B. Pneumonia
C. Seizures
D. Encephalopathy

A6: According to the 2011 Institute of Medicine Review on Adverse Effects of Vaccines and Causality Evidence, for which of the following is there strong evidence linking varicella vaccine as a cause:

A. Thrombocytopenia (inadequate)
B. Pneumonia (convincingly supports)
C. Seizures (inadequate)
D. Encephalopathy (inadequate)

Back to the patient
- The patient was treated with IV Acyclovir
- However, remained intubated
- Died 2 months later of pulmonary hemorrhage

Conclusions
- Patients who are immunocompromised often experience more severe varicella infection and are at greater risk of fatal infection.
- Evidence convincingly supports a causal relationship between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in pneumonia in individuals with significant cellular immunodeficiencies.
- Allergists-immunologists need to be familiar with the 2011 Institute of Medicine Report on Causality Evidence related to vaccines and adverse reactions.

Questions?
AAAII Annual Meeting 2013: Difficult Cases: Vaccine Reactions

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Oculorespiratory syndrome

- In 2000-2001 season: Health Canada received 960 out of 2,450 (39.2%) AEFI reports that described a constellation of respiratory symptoms, accompanied by complaints of "red eyes."³
- Majority of cases that year involved a single manufacturer's product that contained higher proportions of micro-aggregates of unsplit virions.⁴


In subsequent seasons, the indicated vaccine was reformulated to reduce the proportion of unsplit virion. However, adverse events reports that met definition of ORS were still reported in association with all influenza vaccines available in Canada.⁵
ORS may occur in association with any influenza vaccine.⁵,⁶


Risk of ORS

- First-time influenza vaccine recipients (n=122) developed ORS more often (5.0% attributable risk vs 2.2%, p=0.094) than those previously vaccinated (n=499) ¹¹
- Canadian AEFI reports from 2000-2004 (3264 cases met definition for ORS)
  - Majority of subjects age 45-64 (44%)
  - Mean and median age: 49 yo (Range 6mo-97 yo)
  - Female predominance (75%) across all age groups (except children <15 yo, 1:1 ratio)

Risk of Recurrence of ORS

- Multicenter, randomized, DBPC crossover; 61 participants (34 revaccinated, 27 placebo)
- Results of multivariate analysis of vaccinated persons showed that age of 65 years remained a significant predictor of ORS recurrence (p=0.02) independent of underlying chronic condition or sex.
- Age 20-39 (1/5) = 20% recurrence rate
- Age 40-59 (8/21) = 38% recurrence rate
- Age 60-64 (3/5) = 60% recurrence rate
- Age >65 (3 of 3) = 100% recurrence rate


Ocular, respiratory, and facial symptoms associated with onset of oculorespiratory syndrome (ORS), as defined according to the ORS2001 definition, within 24 h after injection.

- Most patients (56% of participants) described recurrence as “mild” compared to original episode:
  - 25% “Similar”
  - 19% “Worse”
- Cough and red eyes most commonly reported (20% vs 0% for placebo)

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Development of the varicella vaccine

- 1970s: First live attenuated vaccine was developed and tested in Japan by Takahashi et al
  - Designated Oka strain
  - Isolated from vesicular fluid of healthy 3 yo boy infected with VZV
  - Attenuated through serial passaging through human embryonic lung cells, embryonic guinea-pig cells, and human diploid cells (Arvin 1996).
  - 51 healthy children were inoculated. 92% experienced VZV antibody formation (Takahashi 1975)


Varicella

- Aka “chickenpox”
- Caused by human alpha herpesvirus varicella-zoster (VZV)
- Transmitted through direct contact with or inhalation of infectious fluid
- Highly contagious, infects ~ 90% of susceptible household contacts and 10–35% of individuals with limited exposure (Ross 1962)
- Incubation period: 10–21 days


Varicella infection

- 50% of cases experience general malaise, fever, headache, or abdominal pain w/ 1–2 d prior to rash onset
- Rash is pruritic, erythematous papules which develop into small, fluid-filled vesicles
  - Usually begins on scalp/face/torso before spreading to proximal limbs and mucosal areas
- Possible complications: pneumonia, secondary bacterial infxn (Staph aureus and Strep), transient hepatitis, thrombocytopenia and various neurologic complications including meningitis
**Q2:**

Which of the following is true?

A. Immunocompromised patients often experience less severe varicella infection
B. Immunocompromised patients are at less risk of fatal varicella infection
C. Treatment with IV acyclovir does not lessen illness severity and fatality in immunocompromised individuals
D. Treatment with IV acyclovir is most effective when used within 24 hours of presentation

**Epidemiologic evidence**

- The committee reviewed 5 studies to evaluate the risk of pneumonia after the administration of varicella vaccine.
- Four studies were NOT considered because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.
- One controlled study (Black 1999) contributed to the weight of epidemiologic evidence

**Varicella infection in the immunocompromised**

- Patients undergoing cancer treatment or those with congenital defects in cellular immunity
- Often experience more severe varicella infection and are at greater risk of fatal infection (Whitley 2010)
- One of the risk factors for developing shingles
  - Others: aging, VZV infx prior to 18 months of age
  - Tx in immunocompromised → Acyclovir (since 1980s)
  - IV acyclovir effectively lessens illness severity and fatality in immunocompromised individuals if used w/i 24 h of presentation (Balfour 1990)

**Epidemiologic evidence**

- Retrospective cohort study in 89,753 patients (12 to 8 months, older children, and adults) enrolled at the Northern California KPMCP from April 1995-Dec 1996
- Eligible patients were identified in the clinical database, and received at least 1 dose of varicella vaccine during the study period.
- Potential AEs were obtained from the database.
- Diagnoses from hospitalizations, ER, and outpatient clinic visits were included in the analysis

Epidemiologic evidence

- Events following routine pediatric vaccinations within the equivalent 30- or 60-day risk period were recorded for the historical cohort.
- Prevaccination and postvaccination control periods were included in the analysis.
  - Prevaccination periods defined as 31-60 days before outpatient clinic visits or ER visits, and 31-90 days before hospitalizations.
  - Postvaccination periods defined as 91-120 days after outpatient clinic visits or ER visits, and 91-150 days after hospitalizations.


Weight of epidemiologic evidence

- The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision to assess an association between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in pneumonia

Kathleen Stratton et al. Committee to Review Adverse Effects of Vaccines: Evidence and Causality; Institute of Medicine, 2012.

Mechanistic Evidence

- The are 11 publications reporting disseminated VZV with pneumonia after administration of a varicella vaccine
  - Only 5 cases (reported in 6 publications) contributed to the weight of mechanistic evidence.

Weight of mechanistic evidence

- All of the cases report patients with either a genetic or acquired immunodeficiency
  - NK cell defect, HIV, DiGeorge syndrome, steroid immunosuppression
  - One exception: Down syndrome patient
  - Vaccine-strain varicella virus was demonstrated in the vesicular fluid, endotracheal fluid, tracheal aspirates, lung biopsy, and BAL

Kathleen Stratton et al. Committee to Review Adverse Effects of Vaccines: Evidence and Causality; Institute of Medicine, 2012.
Causality Conclusion 5.2

- "The evidence convincingly supports a causal relationship between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in pneumonia in individuals with demonstrated immunodeficiencies."

Kathleen Stratton et al. Committee to Review Adverse Effects of Vaccines: Evidence and Causality; Institute of Medicine, 2012.