From 20/20 to “2 x 2”:
Ophthalmology and Epidemiology for the Pediatrician

G. Waldon Garriss, III, MD, MS, FAAP, MACP
The speaker has no conflicts of interest to disclose.
- No commercial support
- No discussion of off-label usage of drugs or devices/equipment

CS = Content specification
Most pediatricians (and other primary care specialists) do not receive an intensive training in ophthalmology.

Eye complaints are common, and some are very serious.

Medical knowledge is changing rapidly, reportedly doubling every two years.

It is essential for physicians to be able to read the medical literature and accurately interpret new data to be able to practice evidence-based medicine.
Objectives

- Appraise common ophthalmologic issues encountered in caring for children
- Review the differential diagnosis of the red eye
- Compare and contrast septal and preseptal cellulitis and discuss the treatment for each

THEN . . .

- Review basic tenets of epidemiology
- Calculate the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios from data entered into a 2 x 2 table
Ophthalmologic Issues
For General Pediatrics
10 day old newborn girl presents with bilateral “pink eye” and purulent drainage
Pregnancy complicated by no prenatal care
Did receive silver nitrate* in the nursery
Discharge sent for culture
Child otherwise looks well
No fever
No respiratory symptoms

*Silver nitrate and Tetracycline – no longer available in the U.S. National Guideline Clearinghouse, 2011
Ophthalmia neonatorum

- Conjunctivitis in infants < 4 weeks old
- Most common eye disease of the newborn
- *Chlamydia trachomatis* – most common
  - 5-14 days after birth
- *Neisseria gonorrhoeae* – 1880 (10%) v. 1881 (0.3%)
  - 2-5 days
- *Staph aureus*
- *Pseudomonas aeruginosa* (rare) 5-18 days
- Silver nitrate – chemical irritation – but risks are outweighed by benefits; onset in 6-12 h; resolved in 24-48 hours
- Role of hand washing
**Chlamydia trachomatis**
- 5-14 days after birth; Rx = oral erythromycin

**Neisseria gonorrhoeae**
- 2-5 days; Rx = Ceftriaxone (IV or IM) and irrigation

**Pseudomonas aeruginosa (rare)**
- 5-18 days; Rx = systemic antibiotics including aminoglycoside

**Staph aureus**
- Parenteral Methicillin and irrigation

**Silver nitrate**
- Onset in 6-12 h; resolved in 24-48 hours
Conjunctivitis in Older Children

- Allergic - clear discharge; ocular itching
- Infectious
  - Viral (association w/ pharyngitis)
    - Adenovirus
    - ECHO virus
    - Coxsackievirus
  - Bacterial (association with otitis media)
    - *H. flu*
    - *Haemophilus aegyptius*
    - *Streptococcus pneumoniae*
    - *Neisseria gonorrhoeae*
# Causes of Red Eye

<table>
<thead>
<tr>
<th><strong>Traumatic</strong></th>
<th><strong>Non-traumatic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal abrasion –</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>may present as the</td>
<td>• Allergic</td>
</tr>
<tr>
<td>persistently</td>
<td>• Viral</td>
</tr>
<tr>
<td>fussy neonate</td>
<td>• Bacterial</td>
</tr>
<tr>
<td>Foreign body</td>
<td></td>
</tr>
<tr>
<td>▪ Corneal foreign</td>
<td>• Blepharitis</td>
</tr>
<tr>
<td>body</td>
<td>• Subconjunctival hemorrhage</td>
</tr>
<tr>
<td>▪ Foreign body</td>
<td>• Anterior uveitis (A.K.A. iritis, iridocyclitis)</td>
</tr>
<tr>
<td>under eye lid</td>
<td>• Orbital (septal) or periorbital (preseptal)</td>
</tr>
<tr>
<td>▪ Intraocular foreign body</td>
<td>• cellulitis</td>
</tr>
<tr>
<td>Hyphema</td>
<td>• Keratitis</td>
</tr>
<tr>
<td>▪ UV keratitis</td>
<td>• Acute glaucoma</td>
</tr>
<tr>
<td>▪ Chemical injury</td>
<td>• Episcleritis and Scleritis</td>
</tr>
<tr>
<td>▪ Blow out fracture</td>
<td>• Pterygium (crosses the limbus and encroaches on</td>
</tr>
<tr>
<td>▪ Corneal laceration</td>
<td>the cornea) and Pingueculum (does not)</td>
</tr>
</tbody>
</table>

CS: Critical Sign(s)
Severe ocular pain
Photophobia
Persistent blurred vision
Proptosis
Reduced ocular movements
Ciliary flush
Irregular corneal light reflection
Corneal epithelial defect or opacity
Pupil unreactive to direct light
Worsening signs after 3 days of Rx
Compromised host: neonate, immunosuppressed, contact lens wearer
Anterior uveitis, A.K.A. Iritis, Iridocyclitis
(can be associated with RA, rubella, mumps)
11 year old girl presents with 1 day of diplopia and right eye pain and swelling
- Normal visual acuity
- Appears ill, but is non-toxic
- T = 38.9 °C
- Mild proptosis
- Some chemosis
- Difficult to ascertain if EOM are intact or not because of pain
Differential Diagnosis for Swelling of or Around the Eye

- Trauma
- Tumor
  - Hemangiomas of lid
  - Ocular tumors
    - Retinoblastoma
    - Choroidal melanoma
    - Neuroblastoma
    - Rhabdomyosarcoma
- Local Edema
- Allergy (pruritus)

- Systemic causes of edema
  - CHF
  - Nephrosis
  - Cirrhosis
  - Malnutrition

- Infection (pain, fever)
  - Preseptal cellulitis
  - Orbital cellulitis
—11-year-old girl with acute right maxillary and ethmoidal sinusitis complicated by right orbital subperiosteal abscess.

Hoang J K et al. AJR 2010;194:W527-W536

©2010 by American Roentgen Ray Society
Preseptal (Periorbital) Cellulitis

- Inflammation of the lids and periorbital tissues w/o signs of true orbital involvement
  - No proptosis, normal EOM function, normal pupillary response
- Most often unilateral
- Mostly in children < 5 y.o.
- No sex predilection
- 3 x more common than orbital cellulitis
Inflammation to the tissues of the orbit
- Proptosis, limited eye movement, potential decrease in visual acuity, chemosis
- More common in children
  1 week – 16 years old (mean age = 6.8 yrs)
- 2:1 male predominance
- More common in winter months
  - Ethmoiditis – most common predisposing factor
- Mostly unilateral
- Acute complications: cavernous sinus thrombosis, vision loss, CNS infection
**PRESEPTAL CELLULITIS**
- Consider CT
  - If you cannot adequately assess EOM, etc.
  - CNS involvement
  - Clinical deterioration
  - Not better after 24-48 hours
- Blood culture (7% +) if signs of systemic illness
- Ocular discharge culture
- CBC*
- CRP/ESR*

**ORBITAL CELLULITIS**
- CT – to determine extent/involvement of orbit
  - Subperiosteal abscess
  - Orbital abscess
  - Orbital cellulitis
- Ocular discharge or sinus fluid culture
- Blood culture
- CBC

(*If normal – not sufficient to r/o orbital cellulitis)

## Pathogenesis

<table>
<thead>
<tr>
<th>PRESEPTAL CELLULITIS</th>
<th>ORBITAL CELLULITIS</th>
</tr>
</thead>
</table>
| ▪ Localized infection of eyelid or adjacent structure  
  ▪ Conjunctivitis  
  ▪ Hordeolum  
  ▪ Chalazion  
  ▪ Dacroadenitis  
  ▪ Dacrocystitis  
  ▪ Bacterial cellulitis (trauma)  
  ▪ Hematogenous dissemination  
  ▪ Acute sinusitis  
  ▪ Inflammatory edema | ▪ Acute sinusitis (ethmoid*, frontal, and maxillary)  
  ▪ Subperiosteal abscess  
  ▪ Orbital abscess  
  ▪ Orbital cellulitis  
  ▪ Cavernous sinus thrombosis  
  ▪ Hematogenous dissemination  
  ▪ Endophthalmitis  
  ▪ Traumatic inoculation  
  ▪ Endophthalmitis |
PRESEPTAL CELLULITIS

- Staph
- Strep
- H influenzae (nontypeable)
- Strep pneumoniae*
- M catarrhalis

ORBITAL CELLULITIS

- Staph aureus (including MRSA)
- Staph epidermidis
- Strep pyogenes
- Strep pneumoniae*
- Haemophilus influenzae type b*

* On the decline secondary to vaccination practices
**PRESEPTAL CELLULITIS**

- Oral antibiotics if:
  - Eyelid swelling is modest
  - Non-toxic
  - Reliable parents
- Otherwise, admit
- Oral = parenteral
- Typically 10-14 days (until resolution)
- Consider parenteral antibiotics (especially if not better in 24-48 h)

**ORBITAL CELLULITIS**

- Admit
- Parenteral antibiotics to cover *S. aureus*, *S. pyogenes* and anaerobes
- 3 week course of treatment
- May need to involve others:
  - ID
  - Ophthalmology
  - ENT
  - Neurosurgery

Eyelid and Nasolacrimal Duct

- Chalazion and Hordeolum ("Stye")
- Nasolacrimal Duct Obstruction
- Ptosis
**HORDEOLUM (STYE)**
- Infection of
  - Meibomian gland (internal)
  - Zeis (external)
- *Staph aureus*
- Usually self-limited (5-7 days)
- Warm compress*
- May use topical antibiotics

**CHALAZION**
- Lipogranuloma develops around meibomian gland
- Foreign body reaction to lipid materials
- May resemble cellulitis – but no significant pain, fever, or leukocytosis
- May resolve spontaneously
- Warm compress*
- Topical antibiotics
- If still there in a month – consult ophthalmology

---

*4-5 time /day, for 10-15 minutes; advise w/ caution because increased risk of burns

Acute, purulent inflammation of eyelid
  ▫ If bacteria present, typically S. aureus
May evolve to chalazion

**Treatment:**
  ▫ Frequent warm compresses
  ▫ Ophthalmology if fails to improve after 2-4 weeks
    • Little evidence for topical antibiotics or steroids
Chalazion

- Chronic inflammation due to obstruction of oil gland at eyelid
- Painless, rubbery, nodular
  - (May initially be red or edematous)

**Treatment:**
- Small = observe
- Large = frequent warm compresses for 2-4 weeks
  - Option for ophthalmology for curettage
Clinical findings:
- Persistent or chronic intermittent tearing
- Larger tear meniscus
- Debris on eyelashes
- Occasional redness of the conjunctiva

Treatment:
- Spontaneous resolution by 6 months in 90%
  - Observation is reasonable
  - Lacrimal sac massage several times daily also reasonable
- After 12 months, < 1% of remaining will resolve spontaneously
  - Lacrimal Duct Probe by ophthalmology
Ptosis

“Differentiate clinical findings associated with congenital ptosis from those of acquired ptosis”

- Congenital ptosis
  - Typically because of a deficiency in levator palpebrae muscle fibers
    - usually unilateral
    - neurologically isolated
    - non-progressive
    - lid-creases absent
    - amblyopia in 20-30%

- Acquired ptosis:
  - tendon, muscle, neuromuscular junction or nerve can be source
Strabismus

- Misaligned eyes
  - Always present = “TROPIA”
  - Intermittent = “PHORIA”
    - Typically when fixation interrupted

- Deviated inward (adducted) = “ESO”
- Deviated outward (abducted) = “EXO”
- Specify right or left
Penlight Test for Strabismus

- Normal
- Light from patient's right (Normal)
- Left Esotropia
- Left Exotropia
- Pseudostrabismus
Use the Cover/Uncover Test to Detect Tropias and Phorias

- **Child fixes on an object in front of them**
  - Toy, face, other

- **Cover 1 eye, and observe the uncovered eye**
  - Did it have to move to stay fixed on the object?
  - If so, suggests it was not initially aligned on the object

- **Uncover the eye, and observe it as you remove the cover**
  - Did it have to move to refocus on the object?
  - If so, suggests it drifted while it was covered

SUGGESTS TROPIA

SUGGESTS PHORIA
Expect normal alignment by 4 months of age

Refer patients with strabismus to Ophthalmologist after 4 months

Treatment options:
- Correct Refraction Errors if present
- Occlusion therapy (Patching or Blurring using atropine)
- Surgical realignment

NOTE: Constant esotropia—unlikely to spontaneously resolve, warrants evaluation at any age (even < 4 months of age)

Long-term consequence = Amblyopia
- Cosmetic / Psychosocial consequences, as well
Reduced visual acuity from disuse (or misuse) during visual development
- Within the first decade of life (typically < 5 years of age)
- May be unilateral or bilateral
- Types:
  - Strabismic amblyopia
  - Anisometropic amblyopia
  - Ametropic amblyopia
  - Deprivation amblyopia
Amblyopia - Causes

- Anything that distorts images from an eye or limits binocular vision:
  - Strabismus with constant deviation
  - Cataracts
  - Severe refractive errors
  - Hemangiomas
  - Ptosis
  - Tumors
Nystagmus

- Rhythmic, oscillating, to-and-fro eye movement
  - Horizontal
  - Vertical
  - Rotatory
- Peripheral (i.e. vestibular) vs central (i.e. brain)
- Treatment focused on symptoms (vertigo)
  - occasional prism lenses, botulism toxin, ocular surgery
- Anyone with nystagmus needs ophthalmologic evaluation
  - Pure vertical nystagmus concerning for central causes
50% idiopathic
50% due to:
- Congenital infections
- Genetic / Metabolic disease
- Teratogens
- Ocular disorders

Clue = Bilateral
Any of the TORCH infections
- Toxoplasmosis
- Rubella (#1)
- CMV
- HSV, VZV
- Syphilis
Numerous conditions associated, including:
- Trisomies
- WAGR (Wilms, aniridia, GU anomalies, retardation)
- CHARGE
- NF-2
- Sturge-Weber
- Alport
- Galactosemia
- Copper metabolism disorders
Congenital Cataracts - Teratogens

- Alcohol
- Corticosteroids
Goal to prevent amblyopia
Identify the underlying cause
Surgery (ASAP) within 2 months of birth
Cataracts at Other Ages

- Systemic Diseases (e.g. JIA, IBD with uveitis)
  - Includes genetic/metabolic syndromes for which cataracts may develop later
- Treatments and Medications
  - Corticosteroids
  - Radiation
- Trauma
Trauma
Clinical Findings:
- PAINFUL – cornea lined with numerous sensory nerves of 1st branch of trigeminal
- Photophobia
- Blepharospasm
- Conjunctival injection
- Lid swelling

Abrasions identified by: fluorescein exam with blue light
Corneal Abrasion – Treatment

- Eliminate any foreign bodies
- Antibiotic ointment or drop 2-4 times daily until healed (and symptoms resolve)
  - This is prophylaxis (ointment lubrication probably superior to drops)
- Pain control (consider topical NSAID). Oral opioids can be needed briefly
- ? patching → somewhat controversial; no consensus
- Follow-up in 1-2 days with re-exam
  - Should be healed
  - If not, consider foreign body, ulcer, different process (e.g. herpes keratitis)
  - Refer to ophthalmology if large or persistent lesion, or if symptoms > 3 days
Corneal abrasions in contact lens wearer
- If any white opacities, ulcerations or corneal infiltrates
  - NEED TO SEE OPHTHALMOLOGY THAT DAY
- Otherwise, need anti-pseudomonal antibiotics and
  - See ophthalmologist or optometrist within 24 hours
- In all cases – do not wear contact lenses
Foreign Body

- Need to examine all conjunctival surfaces
- To remove: irrigate or use a cotton tip to remove gently – use of a drop of topical anesthetic may help
- Approach as with corneal abrasion:
  - Evaluate for corneal damage with fluorescein
  - Topical antibiotics as prophylaxis
Retinopathy of prematurity

“Plan the appropriate screening and clinical evaluation of retinopathy of prematurity”

- More preterm at birth = longer time to develop serious ROP
- Screening: dilated indirect ophthalmoscopy
Retinopathy of prematurity

- All infants BW < 1500 g or < 30 weeks GA screened
  - or unstable infants > 1500 g or > 30 wks
- Exams continue until fully vascularized
- Timing of subsequent exams based on retinal findings

<table>
<thead>
<tr>
<th>Gestation Age at Birth</th>
<th>Age 1st Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 weeks</td>
<td>7 weeks</td>
</tr>
<tr>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>27-30</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 30 + risk factors</td>
<td>4</td>
</tr>
</tbody>
</table>
Papilledema

“Recognize the clinical findings associated with papilledema”

- Increased ICP:
  - Headache, N/V – worse in AM, worse recumbent
  - VI\textsuperscript{th} nerve palsy, diplopia due to lateral rectus palsy
  - Late – Cushing triad (loss of vision also a late finding)

- Fundus:
  - Loss of venous pulsations (sensitive, not specific)
  - Optic disc elevated, cup obliterated, disc margins obscured
Ruptured Globe

- Blunt or penetrating trauma
- Clues:
  - Vision loss, retinal detachment, optic disc edema
  - Irregular pupil
  - Conjunctival chemosis or subconjunctival hemorrhage
  - Lid or conjunctival laceration,
  - Sclera lac with uveal prolapse, Corneal lac with iris prolapse
  - Cataract
- Urgent Ophthalmology Evaluation
  - Consider U/S or CT to evaluate for intraocular foreign body
  - Shield eye, anti-emetics, bed-rest
Blood in the anterior chamber
  - Often due to blunt trauma

VISION THREATENING INJURY – URGENT OPTHTHO REFERRAL

Protective shield over eye and limit activity until seen by ophthalmology
  - Goal to avoid further injury
Orbital Floor Fracture
(aka a “Blow-out” Fracture)

- Common mechanism = baseball or small round object to eye

  Clues and clinical findings:
  - Decreased visual acuity
  - Diplopia
  - Prolapse of orbital fat into maxillary sinus → enophthalmos (eye receded into orbit)
  - Vertical restrictive strabismus due to prolapse of inferior rectus into floor defect with entrapment of the muscle
  - Increased IOP
  - Worry about retrobulbar or optic nerve hemorrhage, globe rupture, hyphema
  - Initial Management: Head CT and urgent ophthalmology evaluation
Epidemiology
(Basics for the Boards)
Also known as “I can’t stand it” (or I feel like self-induced ocular trauma)
Basic Epidemiologic Definitions

**Prevalence** – total number of cases of the disease in a population at a given time
(e.g. according to the CDC, 18,000/100,000 or 18% of the adolescents in the US were obese in 2012)

**Incidence** – number of *new cases* during a given time period
(e.g. incidence for ALL in children < 14 y.o. is 3.7-4.9/100,000/yr.)
Cases Non-Cases
<table>
<thead>
<tr>
<th>Exposed</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Exposed</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

A + C  B + D
A + B  C + D

Case-Control Study yields an:

Odds Ratio = \( \frac{A/C}{B/D} = \frac{AD}{BC} \)

Cohort Study yields a:

Relative Risk = \( \frac{A/(A+B)}{C/(C+D)} \)

Ratio of odds of an exposure in one group compared with another.

Risk of an event, relative to exposure.
Applies to randomized controlled trials

“Analyze what you randomize”

Look to make sure that this is included

There may also be “per protocol” analysis, but an intention-to-treat is essential!

Without intention-to-treat analysis the benefits of randomization are lost (undone)
Absolute Risk Reduction (ARR) - Absolute difference in the event rate between two groups

- Example: For patients treated w/ drug “X,” the incidence of developing the disease = 0.30; for patients treated w/ drug “Y,” the incidence of developing the disease is 0.10

- \( \text{ARR} = |0.30 - 0.10| = 0.2 \)

- \( \text{NNT} = 1/\text{ARR} \)
  - \( 1/0.2 = 5 \)
  - \( \text{NNT} < 50 \) is generally considered “good”
  - NNH calculated the same way but here, the event rate is for an adverse outcome
1880 (prior to silver nitrate) incidence was 0.10/year
1881 (after introduction of silver nitrate) incidence fell to 0.003
ARR = |0.10 – 0.003| = 0.097
NNT = 1/ARR = 1/0.097 = 10.3
(remember to round up to the nearest whole number because there is no such thing as a “part” of a patient)
Therefore the NNT = 11
The Big Four

- **Sensitivity** – proportion of actual positive correctly identified as such
  - Sens = TP/TP + FN

- **Specificity** – proportion of actual negatives correctly identified as such
  - Specificity = TN/TN + FP

- **Positive predictive value** – proportion of patients with a (+) test who have the disease
  - PPV = TP/TP + FP

- **Negative predictive value** – proportion of patients with a negative test who do not have the disease
  - NPV = TN/TN + FN
## Putting it Together

"Those Pesky Little 2x2 Tables"

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Putting it Together

---

**“Those Pesky Little 2x2 Tables”**

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Condition (determined by the Gold Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease (+)</td>
</tr>
<tr>
<td>Test (+)</td>
<td>True (+)</td>
</tr>
<tr>
<td>Test (-)</td>
<td>False (-)</td>
</tr>
</tbody>
</table>
Putting it Together
“Those Pesky Little 2x2 Tables”

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Working example:
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep. Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST. Of the 100 that were (-) for Strep, 10 had a (+) RST and 90 had a (-) RST.
### Putting it Together
“Those Pesky Little 2x2 Tables”

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Condition (determined by the Gold Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease (+)</td>
</tr>
<tr>
<td>Test (+)</td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
</tr>
</tbody>
</table>

**Working example:**
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep.
## Putting it Together

"Those Pesky Little 2x2 Tables"

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

100 100 = 200

Working example:
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep.
Putting it Together
“Those Pesky Little 2x2 Tables”

Working example:
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep. Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST.
### Working example:

Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep. Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST.
### Putting it Together

**“Those Pesky Little 2x2 Tables”**

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Of the 100 that were (-) for Strep, 10 had a (+) RST and 90 had a (-) RST.

#### Working example:
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep.

Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST.

Of the 100 that were (-) for Strep, 10 had a (+) RST and 90 had a (-) RST.
### Condition (determined by the Gold Standard)

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

100 100 = 200

Working example:
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep.
Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST.
Of the 100 that were (-) for Strep, 10 had a (+) RST and 90 had a (-) RST.
### Putting it Together “Those Pesky Little 2x2 Tables”

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test (+)</strong></td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td><strong>Test (-)</strong></td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

= 90 = 110 = 200

Working example: Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep. Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST. Of the 100 that were (-) for Strep, 10 had a (+) RST and 90 had a (-) RST.
### Disease (+) Disease (-)

<table>
<thead>
<tr>
<th>Test (+)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
<td>110</td>
</tr>
</tbody>
</table>

Total Count = 200

What is the sensitivity of the RST?

What is the specificity of the RST?

What is the PPV?

What is the NPV?

What is the LR (+)?

What is the LR (-)?
### Disease (+) Disease (-)

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

\[ \text{Test (+)} = 90 \]
\[ \text{Test (-)} = 110 \]
\[ \text{Total} = 200 \]

**What is the sensitivity of the RST?**

Sensitivity = \( \frac{\text{TP}}{\text{TP} + \text{FN}} \) = \( \frac{80}{100} \) = 80%

**What is the specificity of the RST?**

What is the PPV?

What is the NPV?

**What is the LR (+)?**

**What is the LR (-)?**
### Disease (+) Disease (-)

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
<td>110</td>
</tr>
</tbody>
</table>

Total = 200

What is the sensitivity of the RST?

Sensitivity = TP/(TP + FN) = 80/100 = 80%

What is the specificity of the RST?

Specificity = TN/(TN + FP) = 90/100 = 90%

What is the PPV?

What is the NPV?

What is the LR (+)?

What is the LR (-)?
Putting it Together
“Those Pesky Little 2x2 Tables”

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

\[
\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{80}{100} = 80\%
\]

\[
\text{Specificity} = \frac{TN}{TN + FP} = \frac{90}{100} = 90\%
\]

\[
\text{PPV} = \frac{TP}{TP + FP} = \frac{80}{90} = 89\%
\]

What is the NPV?

What is the LR (+)?

What is the LR (-)?
### Disease (+) Disease (-)

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td></td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>= 90</strong></td>
<td><strong>= 110</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>= 100</strong></td>
<td><strong>= 100</strong></td>
</tr>
</tbody>
</table>

What is the sensitivity of the RST?
Sensitivity = TP/(TP + FN) = 80/100 = 80%

What is the specificity of the RST?
Specificity = TN/(TN + FP) = 90/100 = 90%

What is the PPV?
PPV = TP/(TP + FP) = 80/90 = 89%

What is the NPV?
NPV = TN/(TN + FN) = 90/110 = 82%

What is the LR (+)?

What is the LR (-)?
### Putting it Together

**“Those Pesky Little 2x2 Tables”**

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

= 90 = 110 = 200

What is the sensitivity of the RST?
Sensitivity = TP/(TP + FN) = 80/100 = 80%

What is the specificity of the RST?
Specificity = TN/(TN + FP) = 90/100 = 90%

What is the PPV?
PPV = TP/(TP + FP) = 80/90 = 89%

What is the NPV?
NPV = TN/(TN + FN) = 90/110 = 82%

What is the LR (+)? Sensitivity/(1 – Specificity) = 0.80/0.1 = 8

What is the LR (-)?
What is the sensitivity of the RST?
Sensitivity = TP/(TP + FN) = 80/100 = 80%

What is the specificity of the RST?
Specificity = TN/(TN + FP) = 90/100 = 90%

What is the PPV?
PPV = TP/(TP + FP) = 80/90 = 89%

What is the NPV?
NPV = TN/(TN + FN) = 90/110 = 82%

What is the LR (+)?  Sensitivity/(1 – Specificity) = 0.80/0.1 = 8

What is the LR (-)?  (1 – Sensitivity)/Specificity = 0.2/0.9 = 0.22
Likelihood Ratios Pearls

- LR of a positive test that “rules in” a diagnosis is calculated by: \( \text{Sensitivity}/(1 - \text{Specificity}) \)

- Positive LRs of 2, 5, and 10 increase the probability of disease by 15%, 30%, and 45% respectively

- LR of a negative test or a test that “rules out” a diagnosis is calculated by: \( (1 - \text{Sensitivity})/\text{Specificity} \)

- Negative LRs of 0.5, 0.2, and 0.1 decrease the probability of disease by 15%, 30%, and 45% respectively
Pretest and Posttest Probabilities

- Pretest Probability – your best estimation of the likelihood of a disease/condition before the test
- Posttest Probability – how your best estimation of the likelihood of a disease/condition is altered after taking into account the results of a test
  - Altered by LR’s
Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%\(^1\).

How does a (+) RST alter the probability (i.e., what is the posttest probability)?

Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%.

How does a (+) RST alter the probability (i.e., what is the posttest probability)?

Moving from Pretest Probability to Posttest Probability

- Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%.
- How does a (+) RST alter the probability (i.e., what is the posttest probability)?
- What about a (-) RST?

---

Summary

- Not all conjunctivitis is bacterial; timing matters
- Red eye – it’s more than conjunctivitis
- Very important to differentiate septal from preseptal cellulitis
- Any pathology that interferes with vision at an early age can have long-term complications if untreated – including problems with alignment, cataracts
- 2 x 2 tables can be used to calculate sensitivity, specificity, PPV, NPV, LR(+) and LR (-)
Practice Changes You May Wish to Make

- Consider inviting a local pediatric eye specialist to help augment your staff’s training in the recognition and management of common eye problems.

- Consider organizing (or participating in – if one already exists) a journal club in your area to help facilitate lifelong learning amongst your pediatric colleagues and to enhance your professional satisfaction.
“We are what we repeatedly do. Excellence, then, is not an act, but a habit.”
- Aristotle
waldon.garriss@wellstar.org
The speaker has no conflicts of interest to disclose.

- No commercial support
- No discussion of off-label usage of drugs or devices/equipment

\[\text{CS} = \text{Content specification}\]
Please Note

- This material covers some of the basics of epidemiology that are covered on the ABP certification/recertification examinations.
- The material was once a part of the “live” course, but has now been moved to a supplement for self-study.
- A small portion of the material was presented in the “live” 2017 presentation, but the material is kept as part of the supplement to facilitate your review.
Objectives

- Summarize the strengths and limitations of cross-sectional, case-control, cohort, RCTs, and meta-analysis studies
- Calculate the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios from data entered into a 2 x 2 table
- Convert pretest probability to a posttest probability using a likelihood ratio and a nomogram
Validity – the degree to which a measurement corresponds to the true state of the phenomenon being measured (synonym = accuracy)
- Content validity
- Construct validity
- Criterion validity
- Threats to validity: chance, bias, and confounding

Reliability – the extent to which repeated measurements of a relatively stable phenomenon fall close together
- Reproducible
- Precision

May be valid (clustered around the truth), but not reliable
Validity – the degree to which a measurement corresponds to the true state of the phenomenon being measured (synonym = accuracy)
- Content validity
- Construct validity
- Criterion validity
- Threats to validity: chance, bias, and confounding

Reliability – the extent to which repeated measurements of a relatively stable phenomenon fall close together
- Reproducible
- Precision

Reliable (i.e., reproducible and precise) but not valid
Validity – the degree to which a measurement corresponds to the true state of the phenomenon being measured (synonym = accuracy)
- Content validity
- Construct validity
- Criterion validity
- Threats to validity: chance, bias, and confounding

Reliability – the extent to which repeated measurements of a relatively stable phenomenon fall close together
- Reproducible
- Precision
Target Practice Illustration: Validity and Reliability

A: Somewhat Valid (i.e., around the truth) but not Reliable

B: Neither Valid nor Reliable

C: Not Valid, but Reliable

D: Both Valid and Reliable
Bias – error related to the ways the targeted and sampled populations differ

Bias is a threat to validity (as is chance and confounding)

2 major categories of bias

- Selection bias – error when one or more sampled groups does not accurately represent the population it is intended to represent
- Information/misclassification bias – error induced by non-comparable information sources

Depending on the type of bias, the results can be distorted in either direction (towards or away from the “null”)

CS
Confounding – a special type of bias (error), where a factor associated with both the exposure of interest and the outcome of interest

Confounding is a threat to validity (as are chance and bias)
Type I – conclusion that “there is a difference” when, in fact, there is no difference

Type II – conclusion that “there is no difference” when, in fact, there is a difference

- It is generally considered more egregious to make a Type I error (e.g., you don’t want to claim a treatment works if it doesn’t)
- $\alpha$ is the probability of making a type I error
- $\beta$ is the probability of making a type II error
More About $\alpha$ and $\beta$

- $\alpha$ has to do with the P value
- By convention $\alpha$ should be 0.05 or less
- Investigator gets to choose the $\beta$ (most typically either 0.2 or 0.1)
- Power = 1 - $\beta$
  - If $\beta = 0.2$, the study has a “power” of 0.8
  - If $\beta = 0.1$, the study has a “power” of 0.9
- $\alpha$ and $\beta$ are part of the information used to calculate sample size
Validity

Internal validity – degree to which results of an observation are correct for the patients studied (must deal w/ chance, bias, and confounding)

External validity (generalizability) – degree to which results of an observation hold true in other settings
Validity and the Impact of Bias, Confounding, and Chance

All patients with condition of interest

External Validity

Internal Validity

Sample

Selection Bias

Measurement Bias

Confounding

Chance

Conclusions

Study

Adapted from Fletcher, Fletcher, and Wagner EH. Clinical Epidemiology: the Essentials, 1996 Williams & Wilkins
Refer back to the cartoon on the last slide as you review the next 5 slides.

Bias and confounding (a specific type of bias) are errors that can lead an investigator to a wrong conclusion.

Chance events (due to random events) can also lead an investigator to a wrong conclusion.

To feel good about the conclusion, you need to make certain that chance, bias and confounding were all evaluated and minimized as much as possible.
Selection Bias: Think of it this way . . . .

- Since we don’t have data for all persons with a condition, we do some sort of trial (or experiment) on a “sample” of all affected persons.
- Depending on how the sample is “chosen” or selected and then how the sample is “assigned” to various treatment groups – there may be a “selection bias.”
Between groups, there should be a uniform way to detect a treatment response.

If you “look harder” for an effect, side effect, etc. in one group than you do in the other, you can introduce a “measurement bias.”
Confounding is another type of bias that can lead you to an incorrect conclusion. With confounding, some factor (associated with both the exposure of interest and the outcome of interest) causes a difference – but makes it appear that the difference was due to the exposure of interest.
“Chance” is something that can always happen – and we use statistics to help determine how likely we believe that an outcome happened by chance.

Generally speaking, a p value $\leq 0.05$ is considered statistically significant.

This means that $\leq 1/20$ times would you expect that event to occur by random chance.
Validity

- Only when chance (through statistics), bias (through careful study design, patient allocation, etc.), and confounding (through careful study design) are evaluated and felt to be of minimal or no impact can a study be considered valid.
- When a study has “internal validity,” that means you are comfortable that the findings are due to the treatment/exposure and not due to chance, bias, or confounding.
- If the study can be generalized to other settings, it is said to have “external validity.”
Bradford-Hill Criteria for Establishing Causality

- Strength of association
- Consistency of findings across research sites and methodologies
- Specificity – causation is likely if a very specific population at a specific site has a disease with no other likely explanation
- Temporality – “effect” has to follow the “cause”
- Biological gradient (dose response)
- Plausibility – is there a plausible explanation?
- Coherence with what we already know
- Experiment (reversibility)
- Analogy – similar factors on other analogous conditions

Prevalence – total number of cases of the disease in a population at a given time (e.g. according to the CDC, 18,000/100,000 or 18% of the adolescents in the US were obese in 2008)

Incidence – number of new cases during a given time period (e.g. incidence for ALL in children < 14 y.o. is 3.7-4.9/100,000/yr.)
Odds Ratios and Relative Risk

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Non-Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Not Exposed</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>A + C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B + D</td>
<td>A + B</td>
<td>C + D</td>
</tr>
</tbody>
</table>

Case-Control Study yields an:

\[
\text{Odds Ratio} = \frac{A/C}{B/D} = \frac{AD}{BC}
\]

Cohort Study yields a:

\[
\text{Relative Risk} = \frac{A/(A+B)}{C/(C+D)}
\]

Ratio of odds of an exposure in one group compared with another.

Risk of an event, relative to exposure.
Levels of Evidence and Hierarchy of Study Design

1 A - Systematic Reviews, Meta-analysis
1 B - Randomized Controlled Trials
   2 A - Clinical Trials
   2B - Cohort Studies
   3A – Case Control Studies
   3B – Case Series
   4 – Case Study/Case Report
   5 – Animal Studies, in vitro Studies
   6 – Expert Opinions, Editorials, Ideas

Adapted from Garriss GW, Green JK, and Roumie, CL. Vanderbilt Resident Journal Club Guide: Primer of Epidemiology and Biostatistics; 2009
Case Reports and Case Series (A Type of Descriptive Study)

**Description/Strengths**
- Case reports – detailed report of signs, sx, dx, Rx, and f/u from a single patient
- Primary means by which novel or rare clinical events are presented
  - Toxic shock syndrome
  - Lyme disease
  - HANTA virus infection
- Case series (group of patients) – allows some rudimentary quantitative analyses
  - AIDS

**Weaknesses**
- No comparison group
- Purely descriptive
- Cannot be used to make inferences about the general population of patients with that disease
Cross-sectional (Prevalence) Studies
(A Type of Descriptive Study)  

**Description/Strengths**

- “Snapshot” at a single point in time
- Answers “How common is this disease/condition?”
  - Inexpensive for common diseases
  - Usually able to get a better response rate than other study designs
- Relatively short study duration
  - Can be addressed to specific populations of interest

**Weaknesses**

- Unsuitable for rare or short duration diseases (prevalence = incidence x duration)
- No data on temporal relationship between risk factors and disease development
- High refusal rate may make accurate prevalence estimates impossible
- Disease process may alter exposure
# Case-Control Studies

(A Type of Observational Study)

<table>
<thead>
<tr>
<th>Description/Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>★ Non-experimental (natural experiment)</td>
<td>★ Cannot control for unrecognized confounders</td>
</tr>
<tr>
<td>★ Retrospective design</td>
<td>★ Not designed to evaluate rare exposures (unless attributable risk is high)</td>
</tr>
<tr>
<td>★ Cases and controls selected by investigator</td>
<td>★ Cannot compute incidence rates</td>
</tr>
<tr>
<td>★ Relatively quick and inexpensive</td>
<td>★ More difficult to establish a clear temporal relationship</td>
</tr>
<tr>
<td>★ Well-suited for rare outcomes</td>
<td>★ Prone to bias (especially selection bias, misclassification [recall bias])</td>
</tr>
<tr>
<td>- Good to evaluate diseases with long latent periods</td>
<td></td>
</tr>
<tr>
<td>- Examine multiple etiologic factors for a single outcome</td>
<td></td>
</tr>
<tr>
<td>- Typically yields an OR and answers “What risk factors are associated with this disease?”</td>
<td></td>
</tr>
</tbody>
</table>
Cohort Studies (A Type of Observational Study)

**Description/Strengths**
- Longitudinal observation with repeated measurements over time
- Types of cohort studies:
  - Prospective
  - Retrospective
  - Nested
- Strongest of observational study designs
- Typically yields a RR

**Weaknesses**
- Loss to follow up is the single biggest problem with all types of cohort studies
- Needs “blinding” when deciding outcome status
- Subject to confounding
- Expensive
- Not feasible for rare outcomes
## Controlled Clinical Trials (A Type of Experimental Study)

<table>
<thead>
<tr>
<th>Description/Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>★ Subjects are assigned to groups – but not truly by randomization</td>
<td>★ Without randomization, cannot control for unrecognized confounders</td>
</tr>
<tr>
<td>★ Study strengthened by “blinding”, especially double blinding</td>
<td></td>
</tr>
<tr>
<td>★ Clearly established temporal relationship b/t exposure and outcome</td>
<td></td>
</tr>
</tbody>
</table>
Randomized Controlled Trials (A Type of Experimental Study)

**Description/Strengths**
- Subjects are randomly assigned to groups
- Study strengthened by “blinding”, especially double blinding
- Clearly established temporal relationship b/t exposure and outcome
- Most powerful study to protect against bias and confounding
- ONLY way to control for unrecognized confounders

**Weaknesses**
- Expensive and time consuming
- Non-adherence with protocol and loss to follow up may present huge problems
- Must do (include) an “intention to treat” analysis to maintain benefits of randomization
- Because of strict enrollment criteria, very likely less generalizable
Intention-to-Treat Analysis

- Applies to randomized controlled trials
- “Analyze what you randomize”
- Look to make sure that this is included
- There may also be “per protocol” analysis, but an intention-to-treat is essential!
- Without intention-to-treat analysis the benefits of randomization are lost (undone)
Systematic Reviews and Meta-analyses

**Description/Strengths**
- Systematic Review – focuses on single question and tries to identify, appraise, and synthesize relevant evidence
- Meta-analysis combines results from similar studies to answer a defined question from existing data

**Weaknesses**
- Both are subject to publication bias
- Results of meta-analysis highly depend on results of included trials
- May give false sense of certainty
- Prone to bias (bias from each individual study combined)
- May over emphasize statistical significance at expense of clinical significance
Basic Stats

- Measures of central tendencies
  - Mean – the “average”
  - Median – the “half way” point
  - Mode – most frequently occurring value
- Range = lowest value to highest value
- Standard deviation = absolute value of the average difference of individual values from the mean
  - If there is a Gaussian distribution, 1 SD = 68%, 2 SDs = 95%; 3 SDs = 99.7% (Empirical Rule)
- Standard error – similar to standard deviation but is an estimate of the standard deviation of a statistic
  - SE is used to calculate confidence intervals
  - Confidence interval – expression of stability of the estimate
  - Confidence intervals – another way to express statistical significance
Absolute Risk Reduction (ARR) - Absolute difference in the event rate between two groups

- Example: For patients treated w/ drug “X,” the incidence of developing the disease = 0.30; for patients treated w/ drug “Y,” the incidence of developing the disease is 0.10
  - $\text{ARR} = |0.30 - 0.10| = 0.2$

- $\text{NNT} = \frac{1}{\text{ARR}}$
  - $1/0.2 = 5$

- $\text{NNT} < 50$ is generally considered “good”
- $\text{NNH}$ calculated the same way but here, the event rate is for an adverse outcome
The Big Four

- **Sensitivity** – proportion of actual positive correctly identified as such
  - Sens = TP/TP + FN

- **Specificity** – proportion of actual negatives correctly identified as such
  - Specificity = TN/TN + FP

- **Positive predictive value** – proportion of patients with a (+) test who have the disease
  - PPV = TP/TP + FP

- **Negative predictive value** – proportion of patients with a negative test who do not have the disease
  - NPV = TN/TN + FN
### Putting it Together

“Those Pesky Little 2x2 Tables”

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Putting it Together

**“Those Pesky Little 2x2 Tables”**

<table>
<thead>
<tr>
<th>Outcome of test</th>
<th>Condition (determined by the Gold Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease (+)</td>
</tr>
<tr>
<td>Test (+)</td>
<td>True (+)</td>
</tr>
<tr>
<td>Test (-)</td>
<td>False (-)</td>
</tr>
</tbody>
</table>
### Putting it Together

“Those Pesky Little 2x2 Tables”

<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Test (-)</td>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

|                | 100         | 100         | = 200       |

What is the sensitivity of the RST?

\[
\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{80}{100} = 80\%
\]

What is the specificity of the RST?

\[
\text{Specificity} = \frac{TN}{TN + FP} = \frac{90}{100} = 90\%
\]

What is the PPV?

\[
\text{PPV} = \frac{TP}{TP + FP} = \frac{80}{90} = 89\%
\]

What is the NPV?

\[
\text{NPV} = \frac{TN}{TN + FN} = \frac{90}{110} = 82\%
\]

What is the LR (+)?

\[
\text{LR (+)} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{0.80}{0.1} = 8
\]

What is the LR (-)?

\[
\text{LR (-)} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{0.2}{0.9} = 0.22
\]
• LR of a positive test that “rules in” a diagnosis is calculated by: \( \text{Sensitivity}/(1 – \text{Specificity}) \)

• Positive LRs of 2, 5, and 10 increase the probability of disease by 15%, 30%, and 45% respectively

• LR of a negative test or a test that “rules out” a diagnosis is calculated by: \((1 – \text{Sensitivity})/\text{Specificity}\)

• Negative LRs of 0.5, 0.2, and 0.1 decrease the probability of disease by 15%, 30%, and 45% respectively
Pretest and Posttest Probabilities

- **Pretest Probability** – your best estimation of the likelihood of a disease/condition before the test
- **Posttest Probability** – how your best estimation of the likelihood of a disease/condition is altered after taking into account the results of a test
  - Altered by LR’s
Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%\(^1\).

How does a (+) RST alter the probability (i.e., what is the posttest probability)?

Moving from Pretest Probability to Posttest Probability

- Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25% \(^1\)

- How does a (+) RST alter the probability (i.e., what is the posttest probability)?

Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%\(^1\).

How does a (+) RST alter the probability (i.e., what is the posttest probability)?

What about a (-) RST?

Each “study type” has different strengths/weaknesses; each has an important role in the advancement of medical knowledge.

- Chance, bias, and confounding are the major threats to a study’s internal validity.
- 2 x 2 tables can be used to calculate sensitivity, specificity, PPV, NPV, LR(+), and LR (-)
Questions?

“We are what we repeatedly do. Excellence, then, is not an act, but a habit.”
- Aristotle
waldon.garriss@wellstar.org
<table>
<thead>
<tr>
<th>Condition (determined by the Gold Standard)</th>
<th>Disease (+)</th>
<th>Disease (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Working example:
Using throat culture as the “gold standard,” evaluate a new rapid Strep test. Test is used in 200 patients – 100 with culture positive Strep and 100 with culture negative Strep. Of the 100 that were (+) for Strep, 80 had a (+) RST and 20 had a (-) RST. Of the 100 that were (-) for Strep, 10 had a (+) RST and 90 had a (-) RST.
Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%.

How does a (+) RST alter the probability (i.e., what is the posttest probability)?

Reasonable pretest probability that a sore throat is due to Strep in an unselected office-based pediatric population is 20-25%.

How does a (+) RST alter the probability (i.e., what is the posttest probability)?

What about a (-) RST?