FDA 'Experience' with Clinical Trials for Immune Biomarkers of Infection and Sepsis

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What Is the Context for this Workshop

- Microbial-based and non-microbial devices that can discriminate viral, bacterial, and non-infectious etiologies (or in the context of sepsis, 'SIRS') are essential for antibiotic stewardship, with all the benefits thereof ...
- Non-microbial markers that can increase the probability of bacterial infection or are prognostic for disease progression are also valuable for clinicians, however…
- **In both instances, performance estimates *may* be inaccurate due to the absence of well-defined comparator methods…**

What is Not the Subject of this Workshop…

- FDA clearance of [fill-in-the-blank] and the evidence for/or against that specific analyte.
- **The Workshop goal is to be forward looking, i.e., to generate discussion regarding two specific issues, and through this start conversations regarding how to best enable sponsors to move forward with non-microbial markers of infection and prognosis.**

We, and Others, Agree that this is an Important Issue that Must be Addressed…

National Strategy for Combating Antibiotic Resistant Bacteria, 2014:

3.1 Develop and approve new diagnostics, including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic resistance that can be implemented in a wide range of settings.

- In the future, widespread availability of point-of-need tests that rapidly distinguish between viral and bacterial infections will significantly reduce unnecessary antibiotic use.

Distinguishing the Etiology of Infection (*when* Infectious) May be Challenging…

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Is it a bacterial infection or virus?

October 01, 2013

Bacterial infections are caused by bacteria, while viral infections are caused by viruses. That's the easy part. Differentiating between the two requires medical intervention since both may cause fever and irritability. And the treatments vary significantly.

https://www.dukemedicine.org/blog/it-bacterial-infection-or-virus

FDA-cleared *In Vitro* Diagnostic Devices

CRP Indication For Use:

- CRP Test is an *in vitro* diagnostic device for the quantification of C-reactive protein (CRP) in human serum, plasma, and whole blood by a solid phase, sandwich-format, immunometric assay. **The measurement of CRP aids in evaluation of the acute inflammatory process induced by infectious microbial agents or by noninfectious inflammatory stimuli**.

NICE guidelines [CG191] Pneumonia: Diagnosis and Management of Community- and Hospital-acquired Pneumonia in Adults (2014)

1.1 Presentation with lower respiratory tract infection

1.1.1 For people presenting with symptoms of lower respiratory tract infection in primary care, *consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed*. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows:

- Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre.
- Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre.
- Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre

FDA-cleared *In Vitro* Diagnostic Devices

Procalcitonin Indication For Use:

- Immunoassay for the quantitative determination of PCT (procalcitonin) in human serum and Li-heparin, K2-EDTA and K3-EDTA plasma. **It is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock**.

Comparative Effectiveness Review Number 78: Procalcitonin-Guided Antibiotic Therapy (AHRQ, 2012)

- **Procalcitonin guidance reduces antibiotic use when used to discontinue antibiotics in adult ICU patients and to initiate or discontinue antibiotics in patients with respiratory tract infections. Populations for future research include immunocompromised patients, patients with other conditions (e.g., pregnancy, cystic fibrosis), and pediatric patients**. Future research should compare procalcitonin guidance with antibiotic stewardship programs and to implementation of guidelines. Outcomes of high interest for future research are the consequences of reduction in antibiotic use for antibiotic resistance and for adverse events of antibiotic therapy.

Biomarkers as Point-of-Care Tests to Guide Prescription of Antibiotics in Patients with Acute Respiratory Infections in Primary Care (Review). *R Aabenhus et al. Cochrane Review, 2014*

- "Overall a reduction in the use of antibiotic treatments was found in the C-reactive protein group (631/1685) versus standard of care (785/1599)…"
- "The observed heterogeneity disappeared in our preplanned subgroup analysis based on study design: RR 0.90, 95% CI 0.80 to 1.02; I^2 statistic = 5% for RCTs and RR 0.68, 95% CI 0.61 to 0.75; I^2 statistic = 0% for cluster-RCTs, suggesting that this was the cause of the observed heterogeneity…"

R Aabenhus et al., Cochrane Review, 2014 (continued)

- "A point-of-care biomarker (e.g. C-reactive protein) to guide antibiotic treatment of ARIs in primary care can reduce antibiotic use, although the degree of reduction remains uncertain. Used as an adjunct to a doctor's clinical examination this reduction in antibiotic use did not affect patient-reported outcomes, including recovery from and duration of illness. However, a possible increase in hospitalisations is of concern. A more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point-of-care biomarker to other antibiotic-saving strategies."

Context Redux

- FDA's role is to confirm that the sponsor has demonstrated reasonable safety and effectiveness for a new device
  - Having well-defined performance estimates is essential for adoption and use
  - Appropriate clinical trial design and conduct is essential for comparing performance and assuring study comparability
  - The wrong precedent can be a problem compounded for a long time
    - Think rapid tests for influenza

Questions…

1. Please discuss appropriate comparator methods for studies of upper and lower respiratory infections – specifically address microbiological, clinical, radiological, and other components that should be included as part of a comparator method.

LRTI Comparators

"Among 2259 patients who had radiographic evidence of pneumonia and specimens available for both bacterial and viral testing, a pathogen was detected in 853 (38%): one or more viruses in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and a fungal or mycobacterial pathogen in 17 (1%). The most common pathogens were human rhinovirus (in 9% of patients), influenza virus (in 6%), and *Streptococcus pneumoniae* (in 5%)."

Jain et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults, NEJM, 2015

URI Comparator Methods

Must be easier…

- "Thirty-eight percent (78/205) of febrile patients had a confirmed infection, 26% (53/205) viral and 12% (25/205) bacterial, while 62% (127/205) had a microbiologically unconfirmed respiratory illness (MURI)."
  - *A Prospective Multicenter Clinical Evaluation of a Rapid Diagnostic Test to Detect Clinically Significant Immune Responses to Viral And Bacterial Acute Respiratory Infections (Shapiro et al. ID Week 2015)*

EPIC* Study Workup

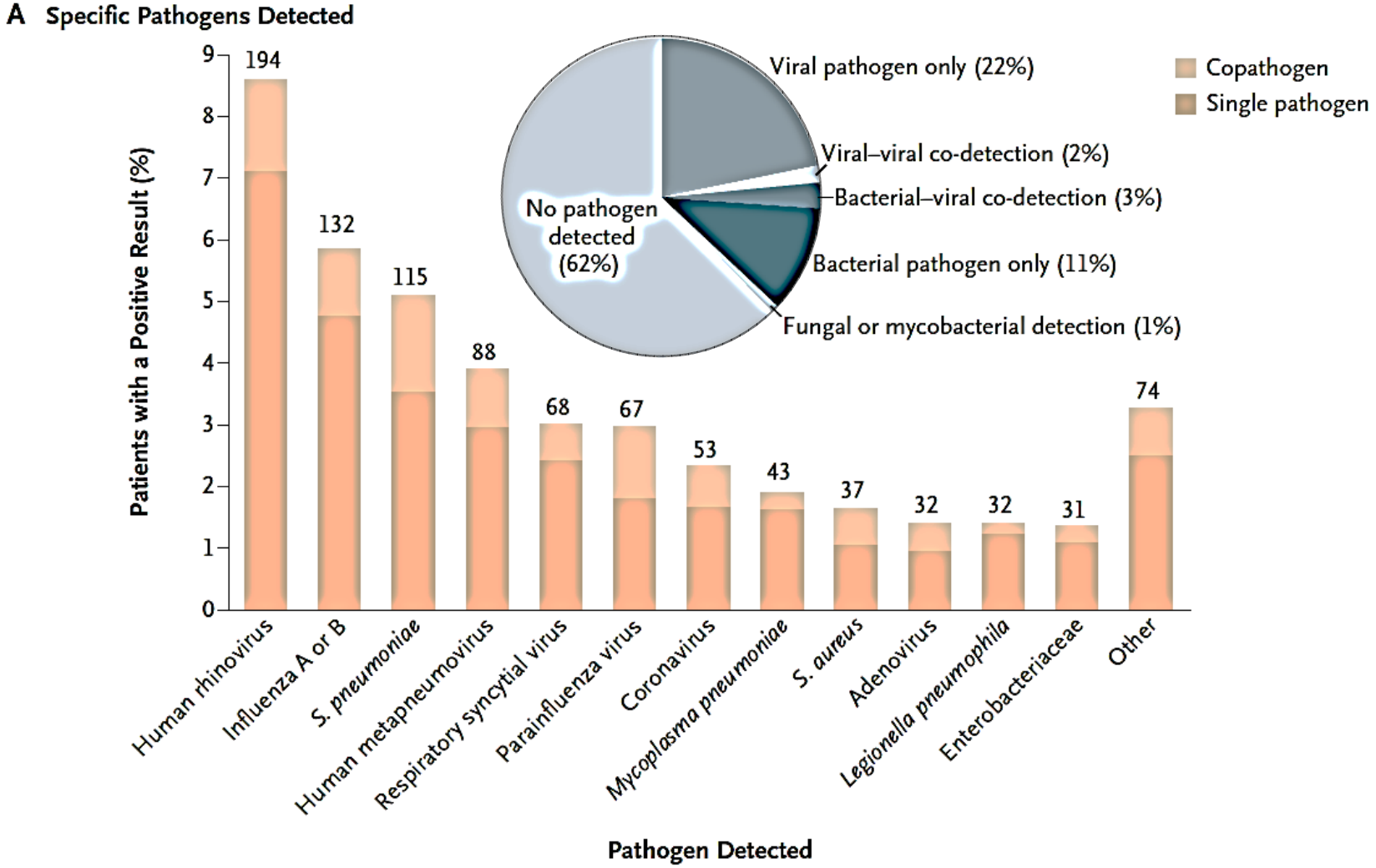
- Standard bacterial cultures: Blood, pleural fluid, high-quality sputum samples, endotracheal aspirates, and quantified BAL specimens
- Sputum *Legionella* PCR
- Pleural fluid: PCR assays for Enterobacteriaceae, *Haemophilus influenzae*, Pseudomonas, *Staphylococcus aureus*, *Streptococcus anginosus*, *S. mitis*, *S. pneumoniae*, and *S. pyogenes*
- Urinary antigen: *Legionella pneumophila, S. pneumoniae*
- Nasopharyngeal and oropharyngeal swabs: Adenovirus; *Chlamydophila pneumoniae*; Coronaviruses 229E, HKU1, NL63, and OC43; Human Metapneumovirus; Human Rhinovirus; Influenza A and B; *Mycoplasma pneumoniae*; Parainfluenza virus types 1, 2, and 3, Respiratory Syncytial Virus (RSV)

* Etiology of Pneumonia in the Community

Workup (continued)

- Serologic testing: Adenovirus, HMPV, Influenza A and B, Parainfluenza viruses, and RSV "was performed on available paired acute-phase and convalescent-phase serum specimens."
- Other microbiologic testing conducted for clinical care, including testing for fungi or mycobacteria.

EPIC Pathogens



URI Comparator Methods

- Definition of a URI for a Clinical Trial
  - Is fever (by history or at presentation) appropriate as an inclusion criteria to enrich enrollment of patients with bacterial infections?
- Viral etiology via PCR multiplex
  - Should all viral detections be considered the etiology of illness in symptomatic individuals in the absence of a 'bacterial infection' for calculating PPA and NPA?
    - How to address asymptomatic infection, particularly rhinovirus or (perhaps) bocavirus
    - Is a concurrent comparator group necessary to document the occurrence of asymptomatic infection in the same population

URI Comparator Methods (2)

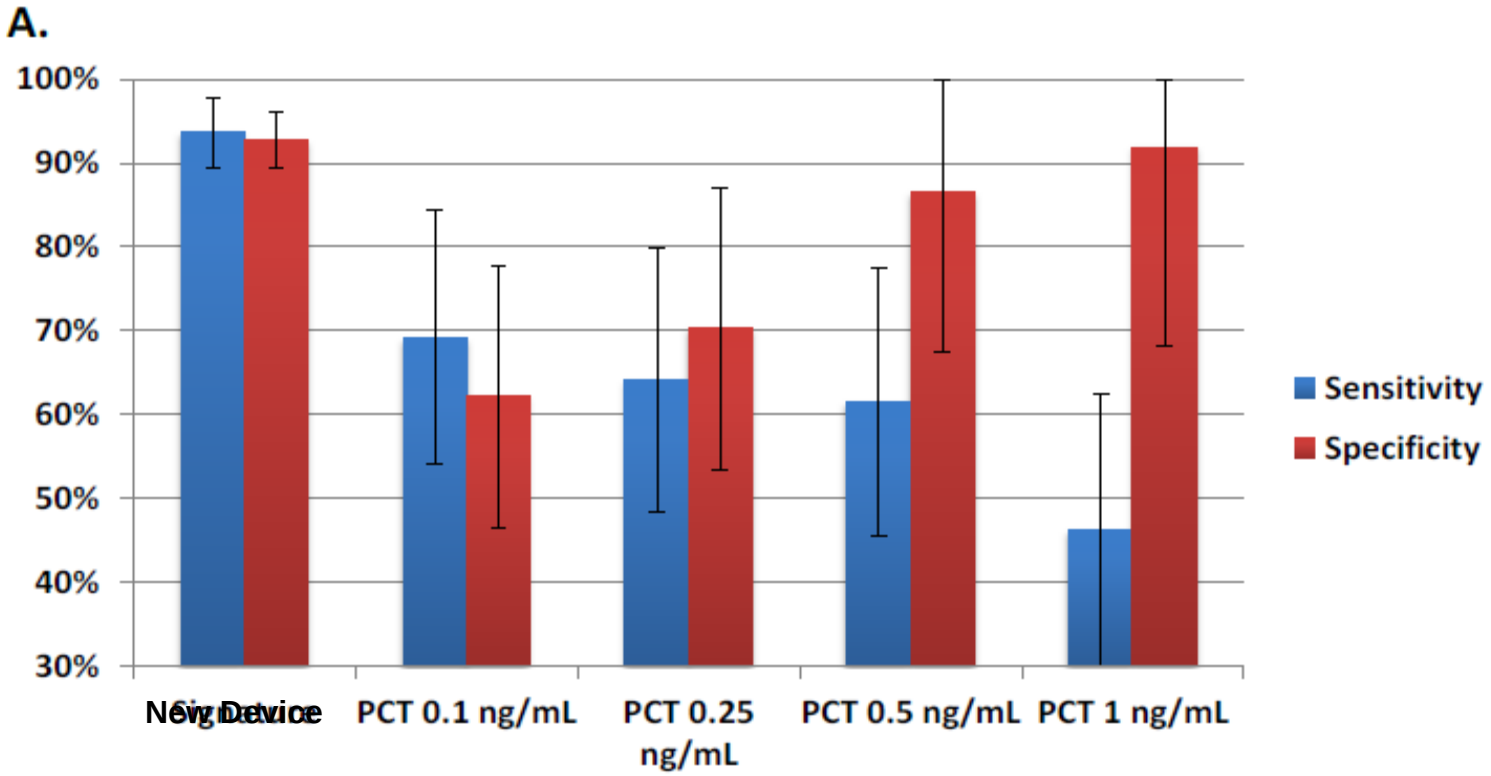
- Bacterial etiologies
  - Should all Group A Streptococcus detections be considered the etiology of illness in symptomatic individuals
    - How can bacterial colonization be addressed
  - Is there a 'bacterial' subset, as well as a viral subset, that can be defined analogous to a 'Microbiological intent to treat'
  - What other methods could be used for determining a bacterial etiology
    - Is there a role for serology? (This is a substantial concern)
    - PCR/culture for *Fusobacterium*? PCR/Culture for other bacteria?

URI Comparator Methods (3)

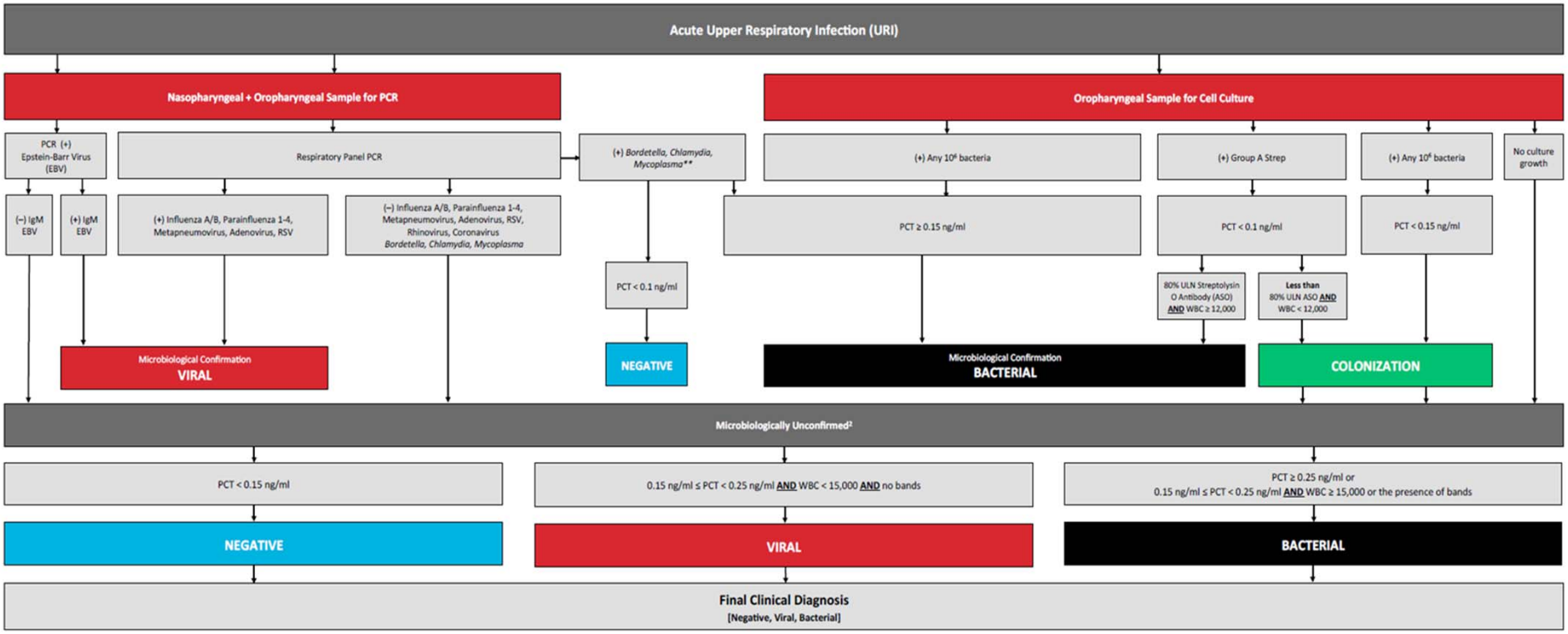
- When *neither* a viral or bacterial pathogen is identified
  - What is the role for other biomarkers, e.g., WBC, PCT, etc.
  - Should this be a predetermined algorithm (example to follow)
- In general, what is the role for clinical assessment as part of the study design for assigning results
  - If so, what *specific* measurements should be captured, both clinical and laboratory to enable 'clinical assessment'
- Should studies *always* include other biomarker comparators for assessing performance

URI Comparator Methods (4)

- Should studies include other non-microbial biomarkers as comparators?

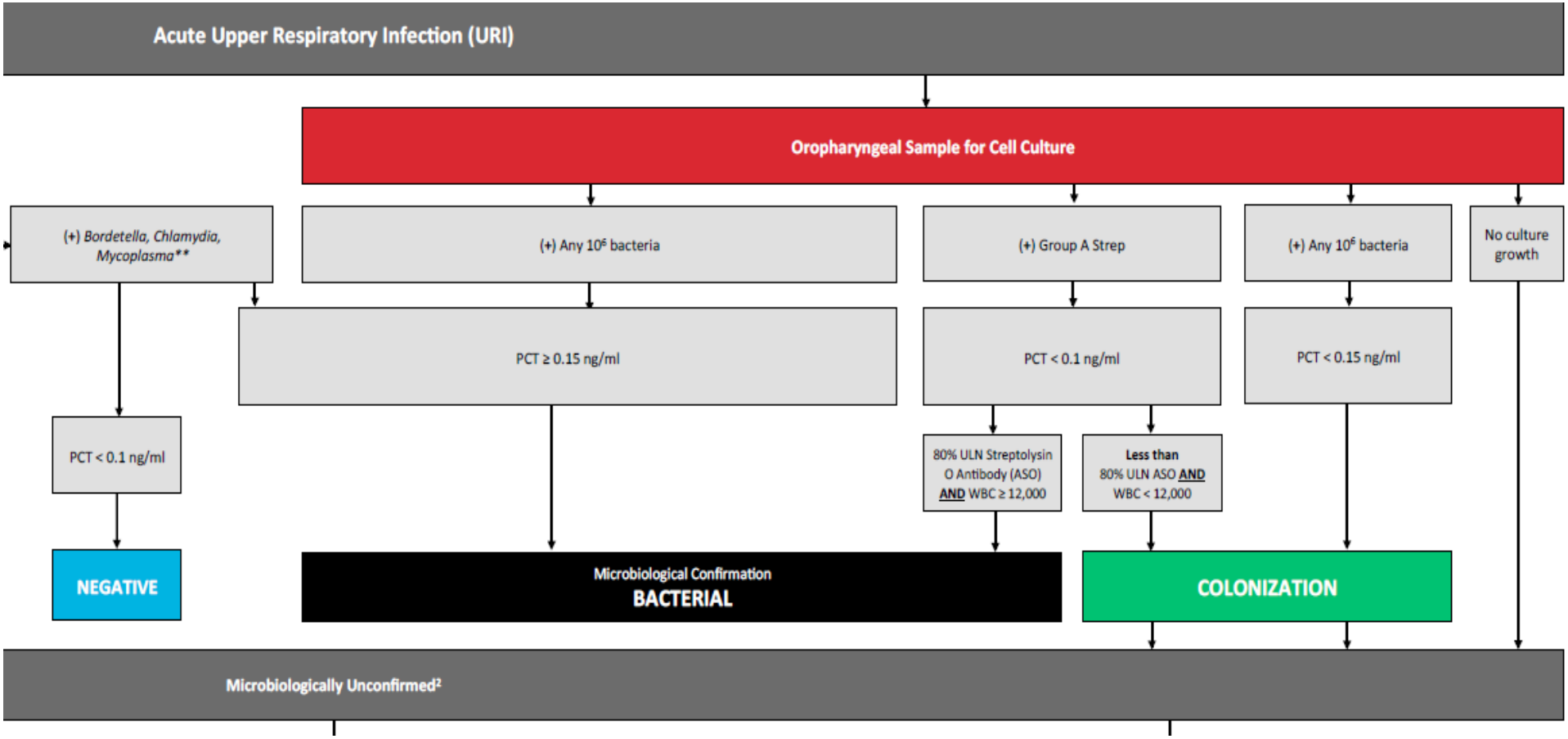


An Actual (Somewhat) Example…

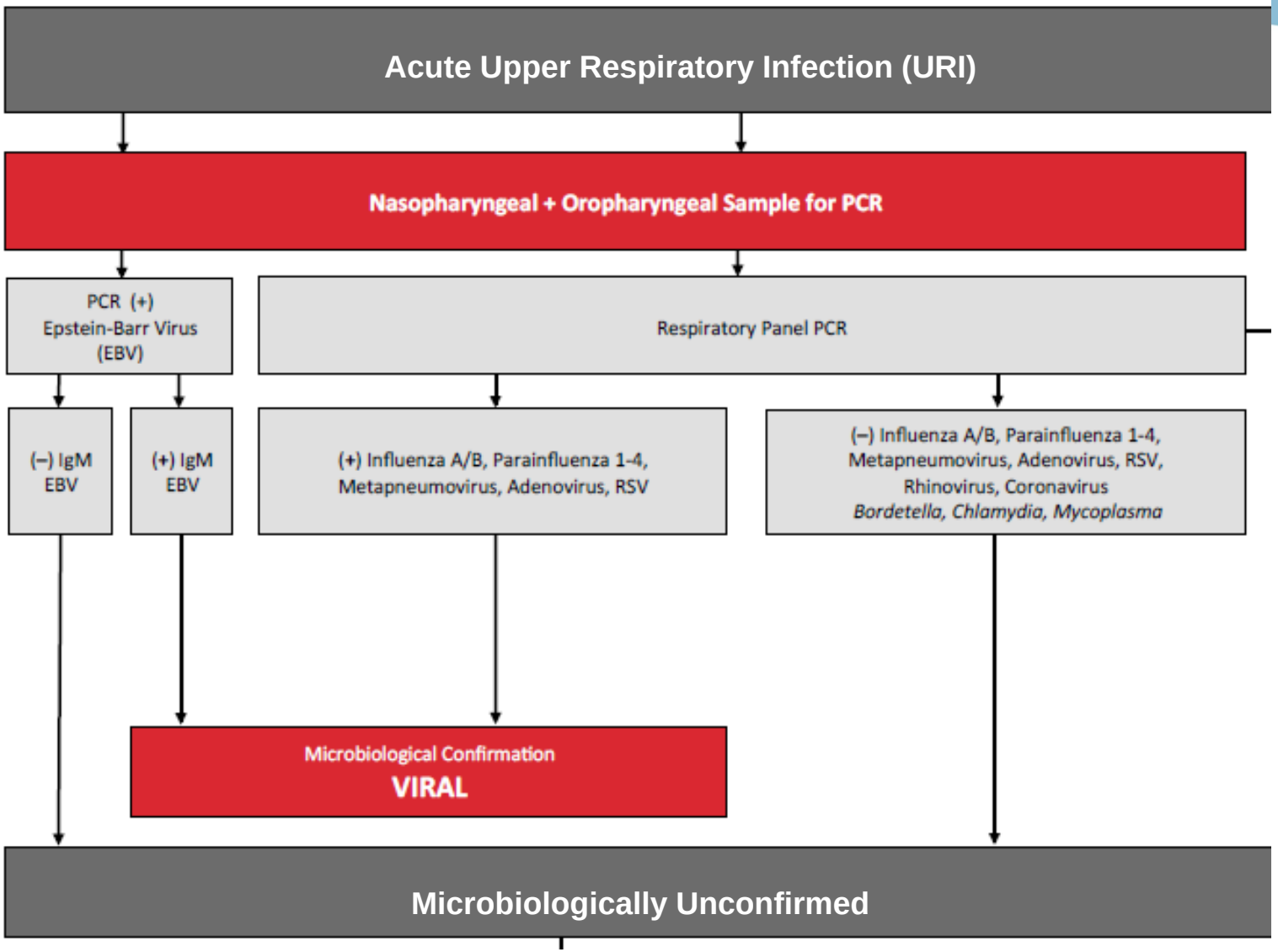


[1] Due to the high likelihood of rhinovirus and coronavirus stimulating a non-systemic host response, all rhinovirus and coronavirus positive results will be treated as non-systemic host response.
[2] Since PCR is highly sensitive, it is unlikely that a viral or atypical bacteria will not be detected; thus any elevated PCT ≥ 0.1 ng/ml is more likely bacterial.
***Typical bacteria**: Group A and C beta-hemolytic streptococcus, Neisseria gonorrhea, Corynebacterium diphtheria, Arcanobacterium haemolyticum, Fusobacterium necrophorum*
****Atypical bacteria:** Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae*

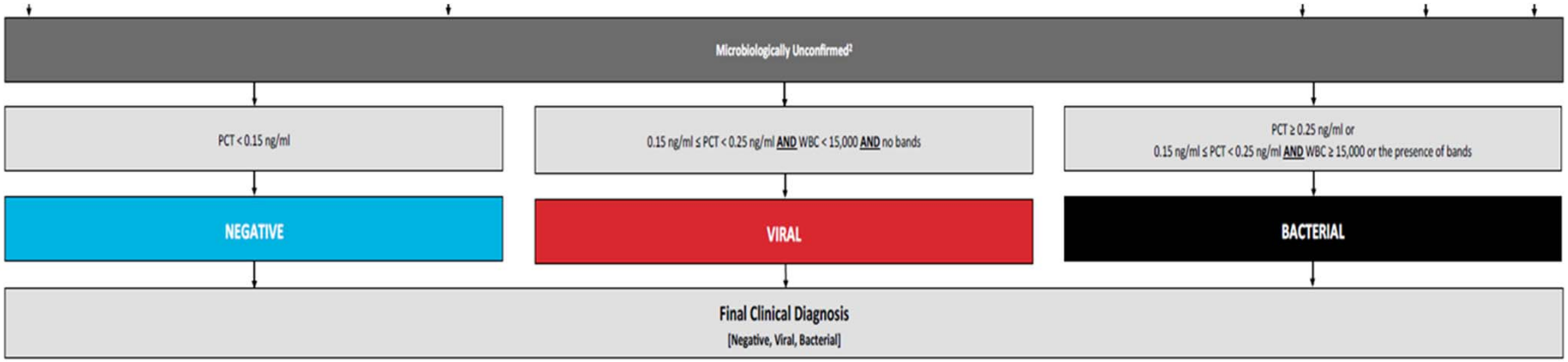
Bacterial Pathway



Viral Pathway



Microbiologically Unconfirmed



- PCT < 0.15 ng/ml: **NEGATIVE**
- 0.15 ng/ml ≤ PCT < 0.25 ng/ml <u>and</u> WBC < 15,000 <u>and</u> no bands: **VIRAL**
- PCT≥ 0.25 ng/ml or 0.15 ng/ml ≤ PCT < 0.25 ng/ml **AND** WBC ≥ 15,000 or the presence of bands: **BACTERIAL**

Procalcitonin Concentrations among Children Hospitalized with Pneumonia: Associations with Etiology and Prognosis (Stockman et al., IDSA 2015)

TABLE 2. Procalcitonin concentrations for selected pathogen detections among children hospitalized with CAP.

Pathogen	Median procalcitonin concentration (IQR)
Classic bacterial pathogen detected (n = 54)	4.98 (0.76-19.97)
Bacterial pathogen alone (*n* = 17)	2.98 (0.93 – 12.48)
Bacterial/viral co-infection (*n* = 37)	6.74 (0.91 – 27.18)
Atypical bacterial pathogen detected (n = 82)	0.10 (0.06 – 0.31)
Atypical pathogen detected alone (*n* = 58)	0.09 (0.06 – 0.21)
Atypical pathogen/viral co-infection* (*n* = 24)	0.05 (0.05 – 0.05)
Viral pathogen detected alone (n = 349)	0.33 (1.12 – 1.34)
Respiratory syncytial virus only (*n* = 102)	0.30 (0.11 – 0.95)
Influenza only (*n* = 23)	0.62 (0.13 – 2.51)
No pathogen identified (n = 47)	0.44 (0.10 – 1.83)

Questions:

2. Please discuss what performance parameters (e.g., positive and negative agreements) should be considered appropriate for upper respiratory and lower tract infections.
   - Is there a minimum performance standard for Group A Streptococcus
   - How should viruses that are commonly asymptomatic be addressed
     - If these are excluded, do we need to substantially increase sample size
   - Should performance against 'known' pathogens be the benchmark for performance, and if so, what should these standards be
     - For example, in symptomatic patients with influenza should performance be similar to that of the microbiological assay

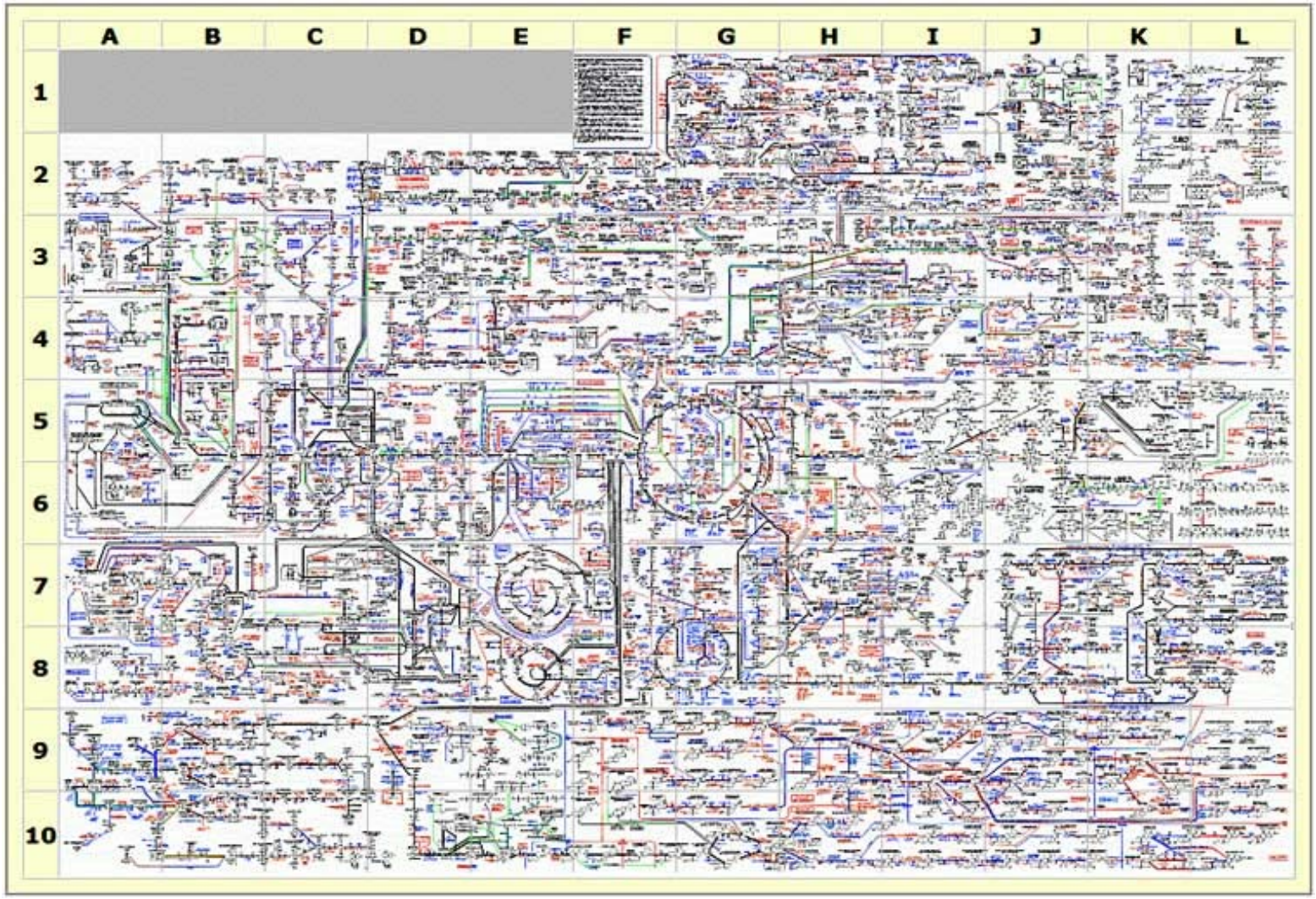
Questions:

3. Please address if results can be combined across all ages, or if performance should be confirmed independently in different age subgroups.
4. Please discuss if immunocompromised hosts or targeted subgroups (e.g., COPD, asthma), where consequences of inaccurate results may be greater, need to be studied in clinical trials or it is acceptable to include these as device limitations.
   – Is this an essential aspect of clinical use?

More Questions (beyond today):

- The most direct comparison is ‘confirmed viral’ versus ‘confirmed bacterial’
  - Can ‘non-confirmed’ subjects be bucketed/graded on a probability of viral versus bacterial infection
- Are risks different in an ER environment relative to more limited outpatient settings such that lower performance may be acceptable in the ER setting

Moving on to Sepsis…



Sepsis…

- Sepsis/septic shock is a phenotype resulting from infection, regardless of the etiology
- Diagnosis: Sepsis/septic shock is a surrogate for the diagnosis of infection in patients with signs, symptoms, and laboratory measurements consistent with this distinction
- Prognosis (may be independent of diagnosis):
  - Progression from ‘infection’ to sepsis/septic shock
  - Mortality
  - Other measures
    - ‘Treatment de-escalation’ (NB: equally applicable to lower respiratory infections or other infections)

Questions:

1. Please comment on the appropriate comparator method for the diagnosis of sepsis.
2. Please discuss acceptable performance for diagnostics for sepsis

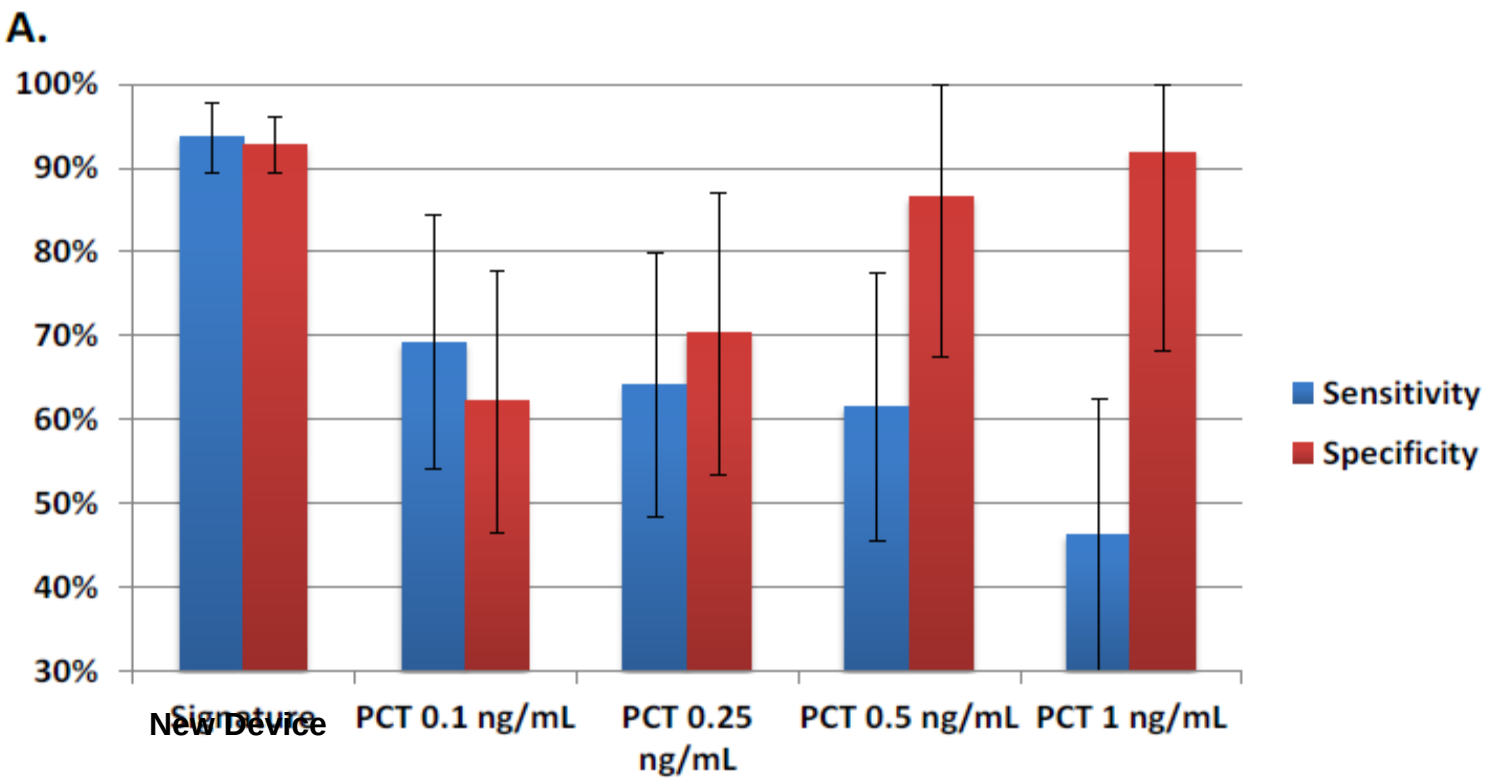
Comparator Methods

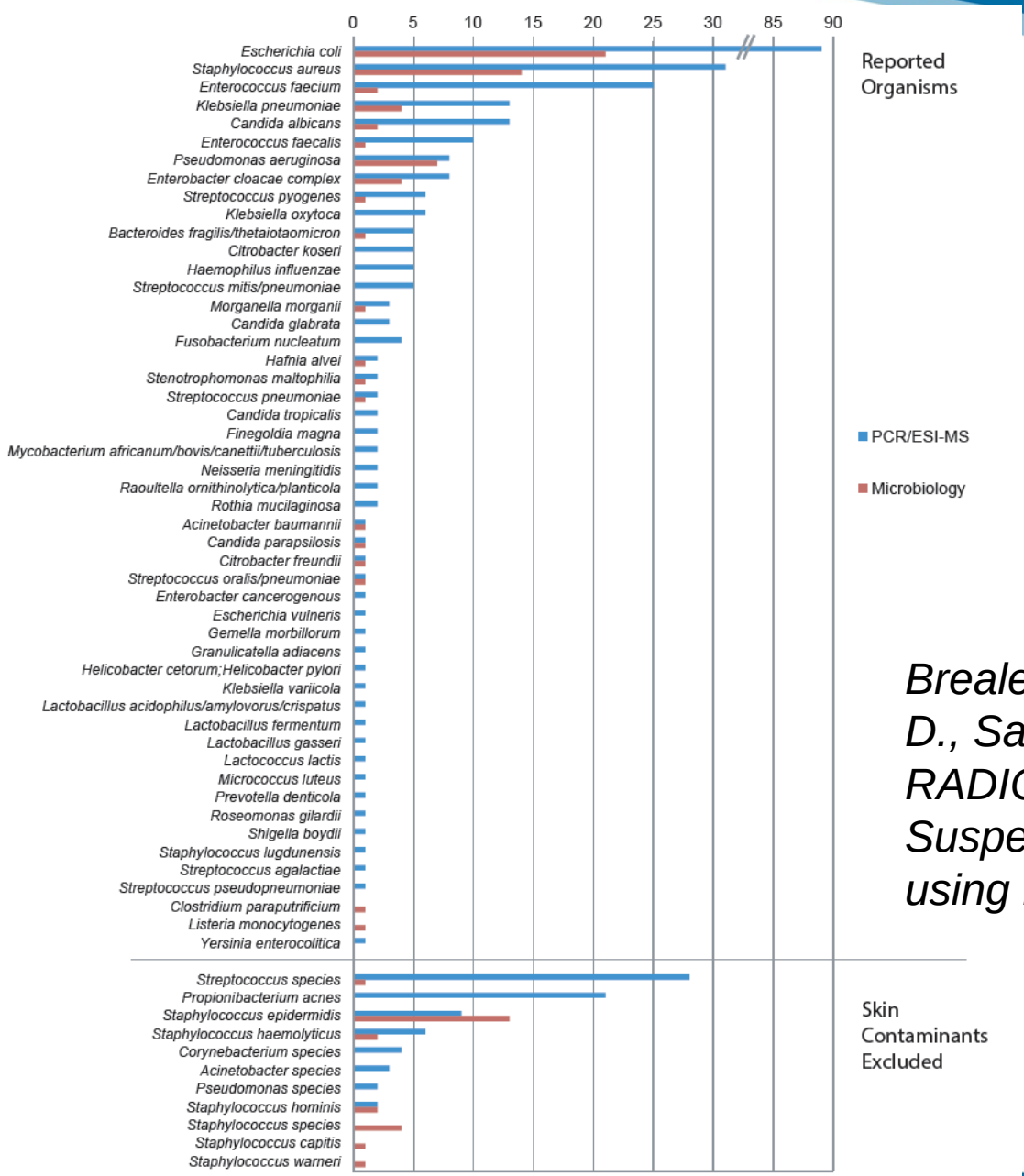
- In the setting of an unknown source, additional workup would be necessary relative to respiratory infections
  - Blood cultures (mandatory)
  - Urinalysis, urine cultures
  - Sputum culture
  - Other cultures as needed
  - CXR (*minimum* imaging)
  - Laboratory measurements
    - WBC
    - Lactate
    - Other biomarkers (may bias ‘clinical assessment’)

Data (?)

- Antibiotics
- Clinical history/risk factors
- Clinical course
  - Signs/mortality
  - Procedures
  - SOFA, APACHE scores
  - Clinical surrogates (e.g., transfer from ICU, extubation)
  - Serial imaging
  - etc.

Comparator Bias (?)





Brealey D., Libert N., Pugin J., Chalfin D., Sampath R., Ecker D. et al. RADICAL Study. Rapid Diagnosis of Suspected Bloodstream Infections using PCR/ESI MS. ICAAC 2014.

European RADICAL Study

Bloodstream Infection Samples (BSI)

BSI

		Culture		
		+	-	Total
PCR/ESI-MS	+	54	169	223
	-	13	380	393
	Total	67	549	616

Sensitivity	81%
Specificity	69%
PPV	24%
NPV	97%

Multi-center RADICAL data are consistent with feasibility data[1].

Brealey D., Libert N., Pugin J., Chalfin D., Sampath R., Ecker D. et al. RADICALStudy. Rapid Diagnosis of Suspected Bloodstream Infections using PCR/ESI MS. ICAAC 2014.

Does it Matter…

- Data essential for assessing *independent* contribution of biomarker
- Assure similar responses across different ages, races, ethnicities, sexes
- However, when the day is done, is clinical assessment the only relevant arbiter
  - Similar to respiratory infections, can ‘non-confirmed’ infections be bucketed and comparison made

Performance

- Benefit/Risk far different from upper respiratory infections
  - Sensitivity far more important than specificity
    - Significant tradeoff, however, reduces clinical value of diagnostic
  - ‘Probability’ or semi-quantitative approaches may be more useful
- Prognostic studies:
  - Benefit/risk significant concern…

Moving Forward

- Is there a comparator method that can be established?
  - If this is uncertain, is there an authoritative group such as FNIH or ARLG that can add to the deliberations of comparators/study design and move these studies forward?
    - NB: More than one approach may be necessary due to bias from using biomarkers that may be part of the candidate device *and* the comparator method, though this may be unavoidable in some exceptional cases.

Moving Forward (2)

- Are there 'structured' datasets/repositories that can be used to directly compare performance across biomarkers
  - Could these be available in an open way, with additions and/or composition that they can be adjusted or revised on an ongoing basis?
    - A repository could be enriched for atypical/rare pathogens
    - A database/repository *could* address combinations of biomarkers or unique subpopulations
- Could this be supplemented by other infections, e.g., enriched for other bacterial diseases
  - Possibly, but this may raise other concerns, including cutoffs, etc.

Thanks….

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