BV SCORE'S PERFORMANCE WHEN APPLIED ACCORDING TO INDICATIONS FOR USE AS PART OF ROUTINE CARE FOR CHILDREN PRESENTING TO THE ED WITH FEVER WITHOUT SOURCE (SPIRIT STUDY SUB ANALYSIS)

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Conflict of Interest

	No, Nothing to disclose
V	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
MeMed diagnostics			V					

Partner in clinical studies of Me-Med Diagnostics,
I did not receive any financial grant from the company
No other conflicts of interests

Background – Fever Without a Source

≤ 20%

- Up to 20% of febrile pediatric patients presenting to the ED will not have a source identified by history or PE.

FWS

- Fever without a source is generally defined in patients between 3 and 36 months of age.

SBI

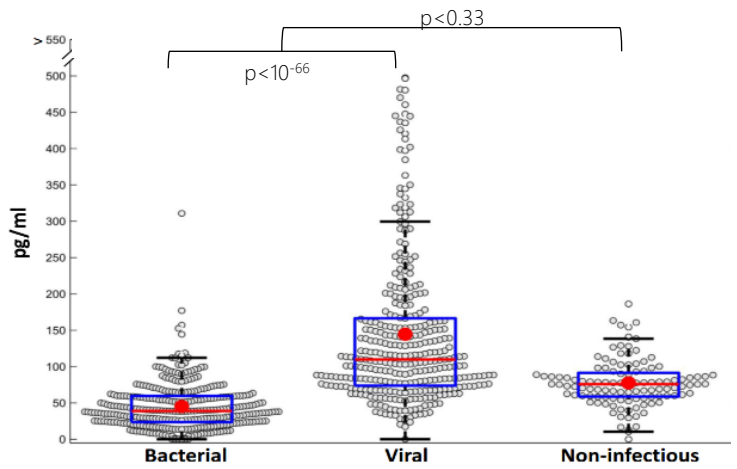
- Most of these patients have a self-limiting viral illnesses, but ~10% could be bacterially infected.
- Bacterial infections in this population include mainly UTI, pneumonia, meningitis, bacteremia

1.Wing R, Dor MR, McQuilkin PA. Fever in the Pediatric Patient. Emergency Medicine Clinics of North America 2013;31(4):1073–96
2. Galetto-Lacour A, Gervaix A. Identifying severe bacterial infection in children with fever without source. Expert Review of Anti-infective Therapy 2010;8(11):1231–7.
3. Colvin JM, Muenzer JT, Jaffe DM, et al. Detection of Viruses in Young Children With Fever Without an Apparent Source. Pediatrics 2012;130(6):e1455–62.
4. Bandyopadhyay S, Bergholte J, Blackwell CD, Friedlander JR, Hennes H. Risk of Serious Bacterial Infection in Children With Fever Without a Source in the Post–Haemophilus influenzae Era When Antibiotics Are Reserved for Culture-Proven Bacteremia. Arch Pediatr Adolesc Med 2002;156(5):512.

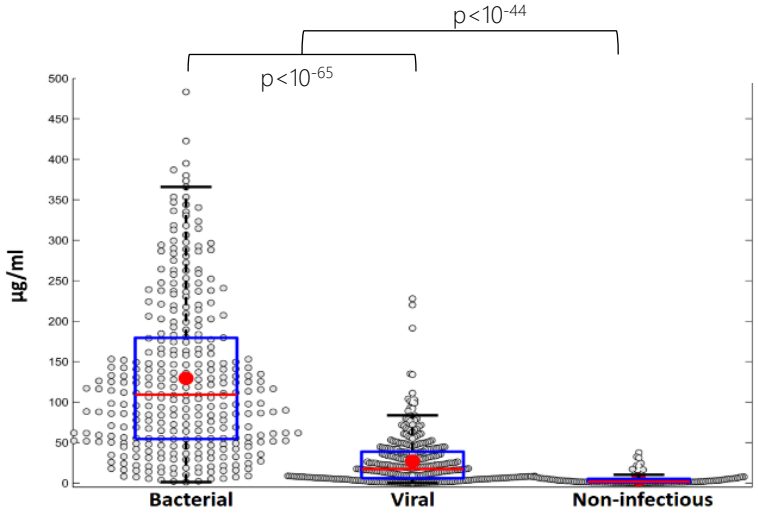
Background – BV Score

Three Biomarkers + Algorithm = Host-Protein Assay (MeMed BV®)

TRAIL



CRP



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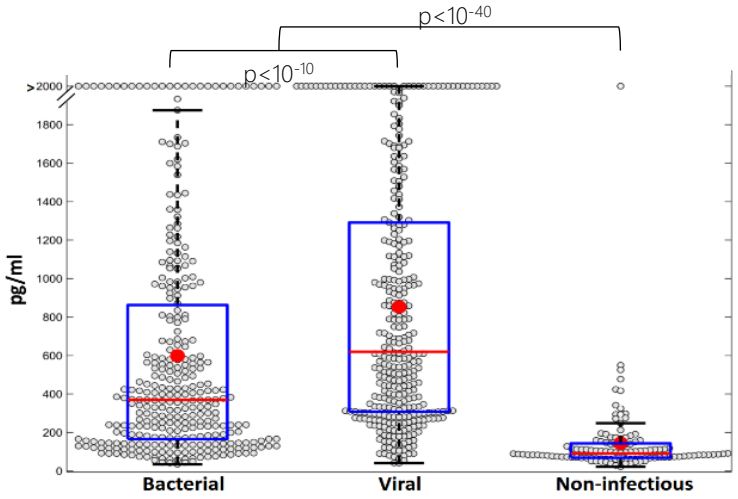
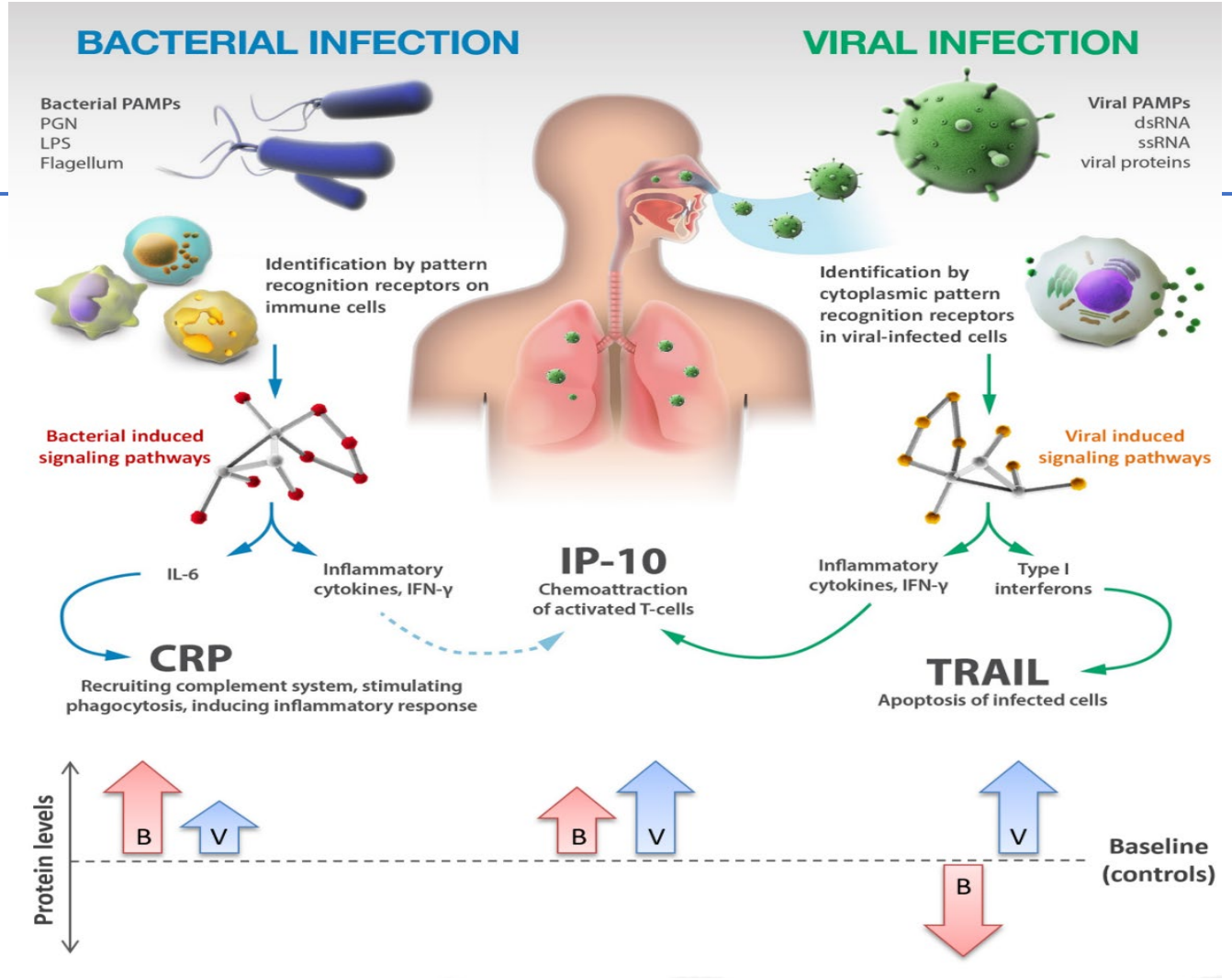


Oved et al. PloS One 2015



Synthesized by the liver peaking 36-48 hrs. after infection onset
Stimulated by IL-6
Recruits the complement pathway, stimulates phagocytosis, induces inflammatory response

IFN-γ-induced cytokine
Secreted by several cell types in individuals with "infection" and autoimmune diseases

TNF cytokine
Induces apoptosis of virally-infected cells (in-vitro)
The most informative biomarker in the signature
TRAIL is elevated in virally-Infected patients

MeMed BV – Results & Interpretation

High likelihood of viral infection (or other non-bacterial etiology)

Moderate likelihood of viral infection (or other non-bacterial etiology)

Equivocal

(~8-12% of cases)

Moderate likelihood of bacterial infection (or co-infection)

High likelihood of bacterial infection (or co-infection)

Background – BV Score

PLOS ONE

RESEARCH ARTICLE

A Novel Host-Proteome Signature for Distinguishing between Acute Bacterial and Viral Infections

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Validation of a Novel Assay to Distinguish Bacterial and Viral Infections

THE LANCET Infectious Diseases

Articles

A host-protein based assay to differentiate between bacterial and viral infections in preschool children (OPPORTUNITY): a double-blind, multicentre, validation study

Assessing the Febrile Child for Serious Infection: A Step Closer to Meaningful Rapid Results

David W. Kimberlin, MD, Claudette L. Poole, MD

BMJ Paediatrics Open

Update of a clinical prediction model for serious bacterial infections in preschool children by adding a host-protein-based assay: a diagnostic study

Chantal van Houten,[1] Josephine Sophia van de Maat,[1 2] Christiana Naaktgeboren,[3] Louis Bont,[1] R Oostenbrink[1 2]

Springer Link

Original Article | Open Access | Published: 26 April 2018

A host-protein signature is superior to other biomarkers for differentiating between bacterial and viral disease in patients with respiratory infection and fever without source: a prospective observational study

Liat Ashkenazi-Hoffnung, Kfir Oved, Roy Navon, Tom Friedman, Olga Boico, Meital Paz, Gali Kronenfeld, Liat Etshtein, Asi Cohen, Tanya M. Gottlieb, Eran Eden, Irina Chistyakov, Isaac Srugo, Adi Klein, Shai Ashkenazi & Oded Scheuerman

European Journal of Clinical Microbiology & Infectious Diseases 37, 1361–1371(2018) | Cite this article

3708 Accesses | 15 Citations | 53 Altmetric | Metrics

ELSEVIER

Diagnostic Microbiology and Infectious Disease

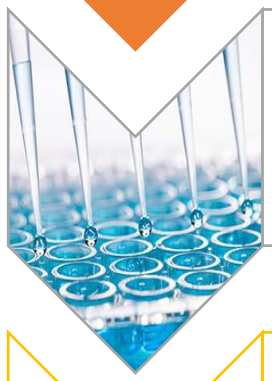
journal homepage: www.elsevier.com/locate/diagmicrobio

A novel host-protein assay outperforms routine parameters for distinguishing between bacterial and viral lower respiratory tract infections☆

Methods – Spirit Study

Spirit study, NCT03075111

- A retrospective analysis of patients from two medical centers in Israel for whom the BV score was taken **as part of routine care**
- October 2014 > October 2017.



- BV score was calculated using an Elisa kit;
- Hence the results were available to physicians within hours to days from blood draw.

- For each patient, the physician filled a questionnaire at the time of blood draw, listing the suspected clinical syndrome and degree of confidence in infection etiology.
- For the purpose of current analysis – all patients <u>regarded as FWS according to the physician form</u> were evaluated.

Methods – Spirit Study

- Microbiological
- Radiological

- lab
- Clinical information & follow up

Each independent expert presumptive etiology			
Bacterial	Viral	Non-infectious	indeterminate

Methods – Spirit Study

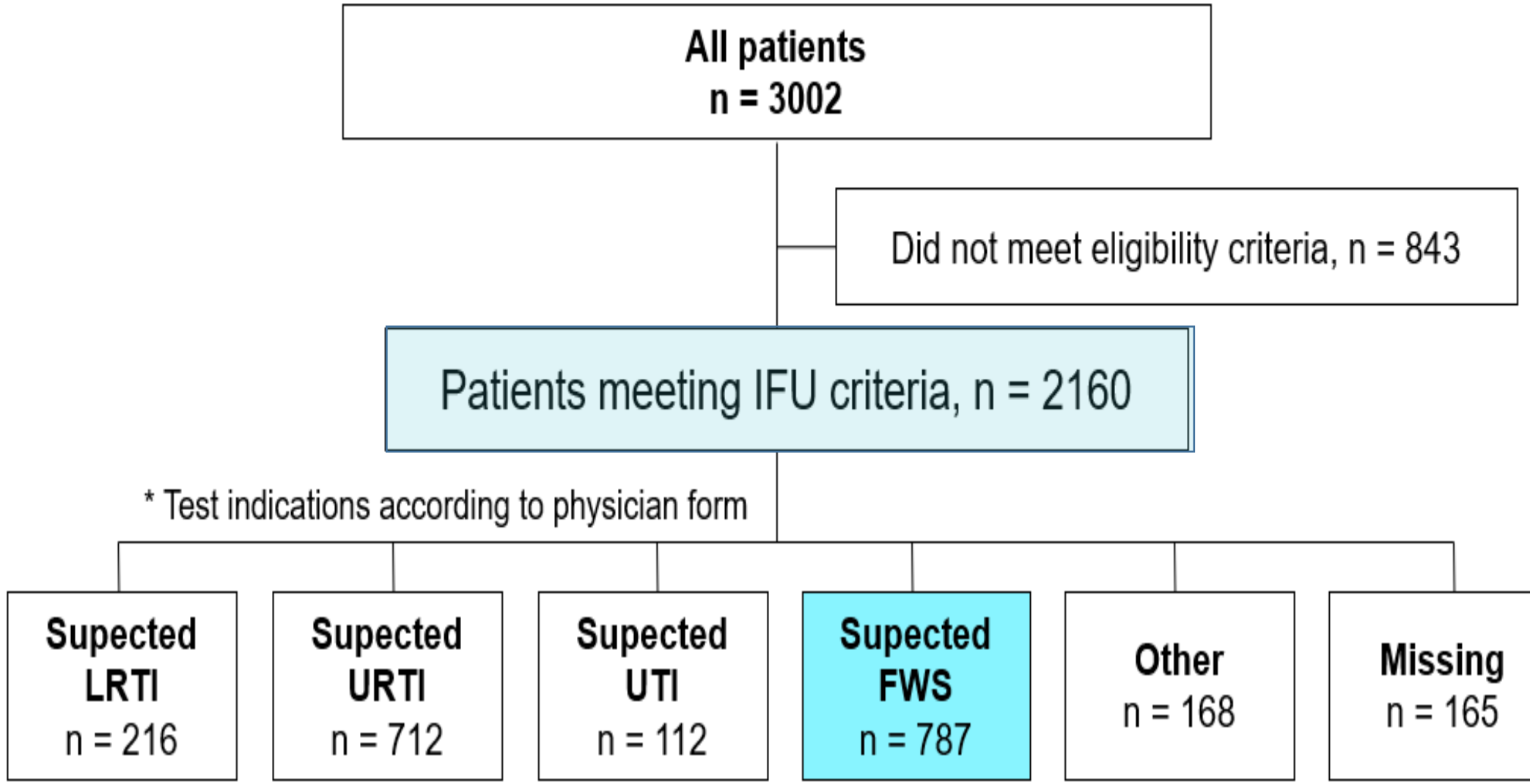
INCLUSION:

- Test was taken by physician as part of routine workup for febrile illness
- aged 3 month to 18 years of age
- Peak temperature ≥ 38°C within the last 7 days
- Symptom duration ≤ 7 days

EXCLUSION:

- Suspicion of infectious gastroenteritis according to physician questionnaire
- Congenital or acquired Immunodeficiency
- Active inflammatory/malignant disease
- Known infection with HBV/HCV/HIV/TB
- Significant trauma or burns in the past 7 days
- Unrelated febrile episode within 2 weeks

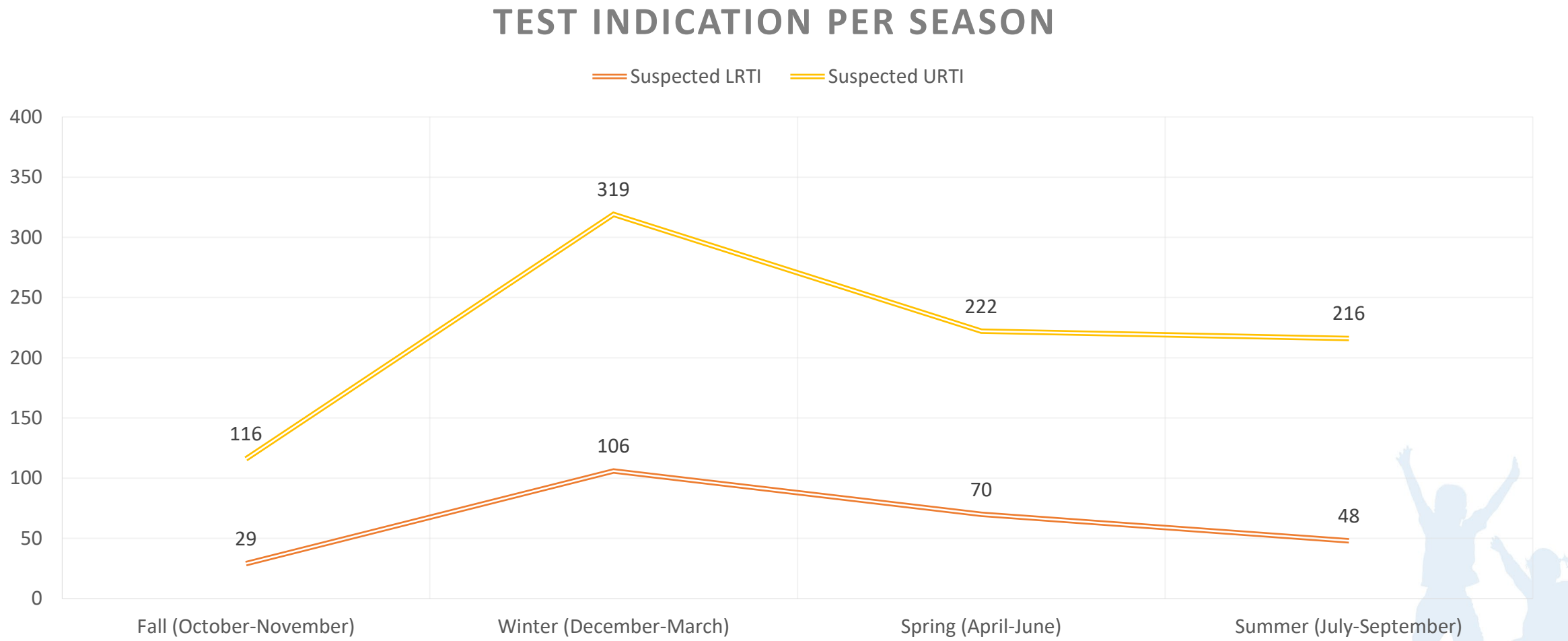
Results – Study Population



Results – Patient Characteristics

Statistic Category	Fever Without Source (n=787)
Age (years) - median (IQR)	2 (4.1)
Gender, male - n (%)	416 (52.8%)
Time from symptoms onset in days - median (IQR)	2 (3)
Maximal temperature in C - median (IQR)	39.5 (1.1)
Hospitalized - n (%)	340 (43.2%)
Hospitalization duration in days - median (IQR)	0 (3)

Results – Seasonal Distribution



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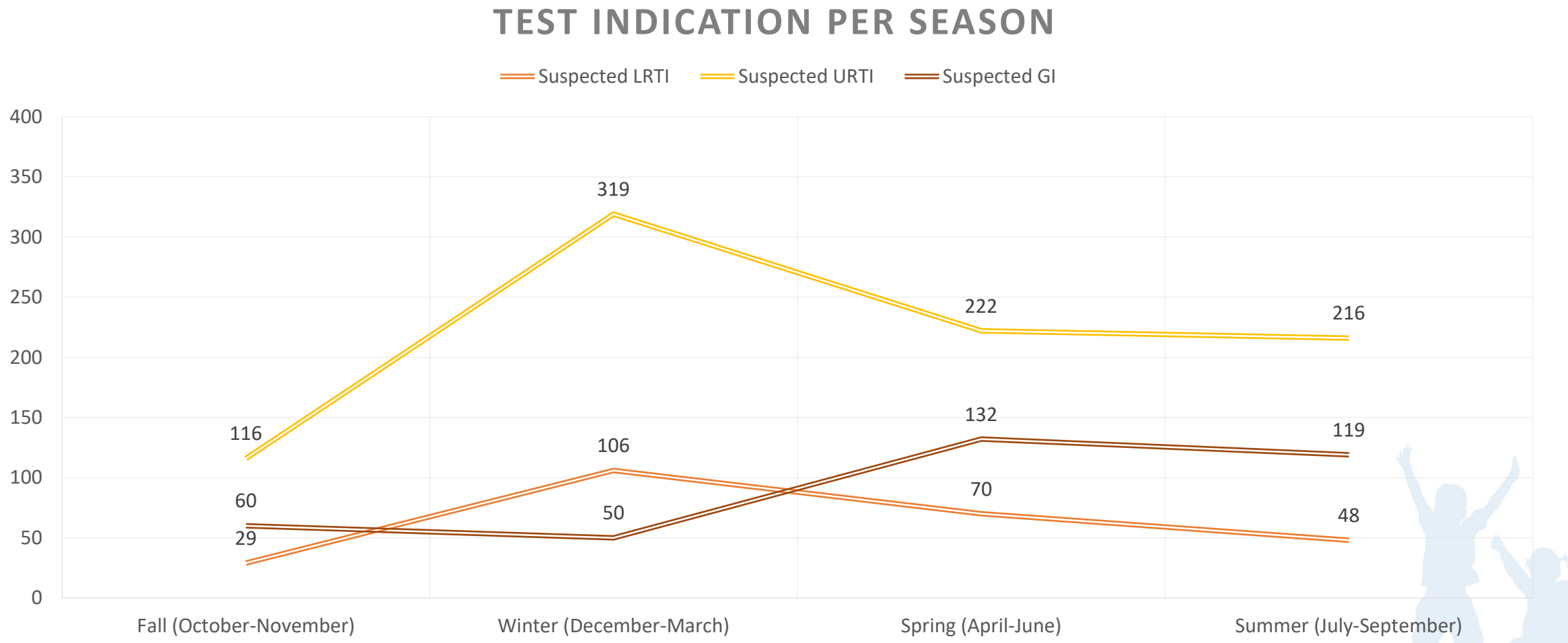

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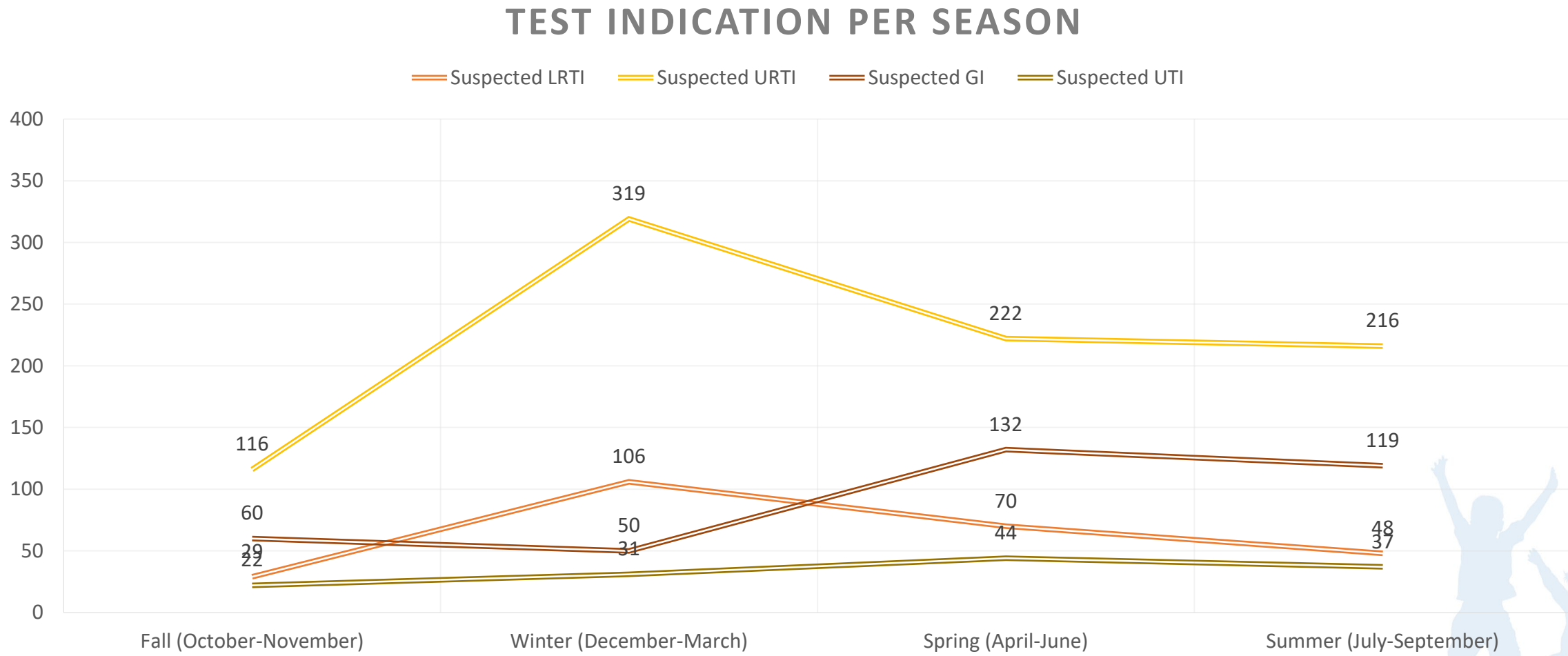

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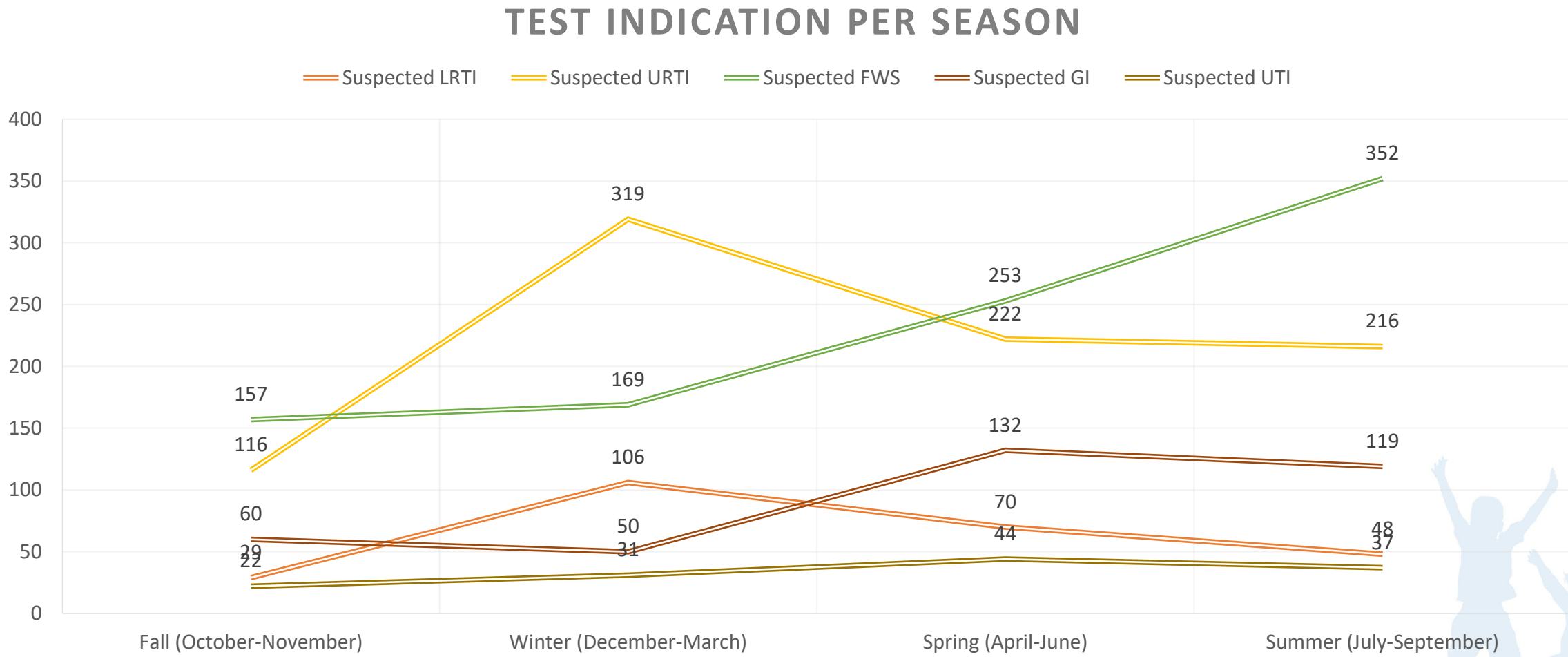
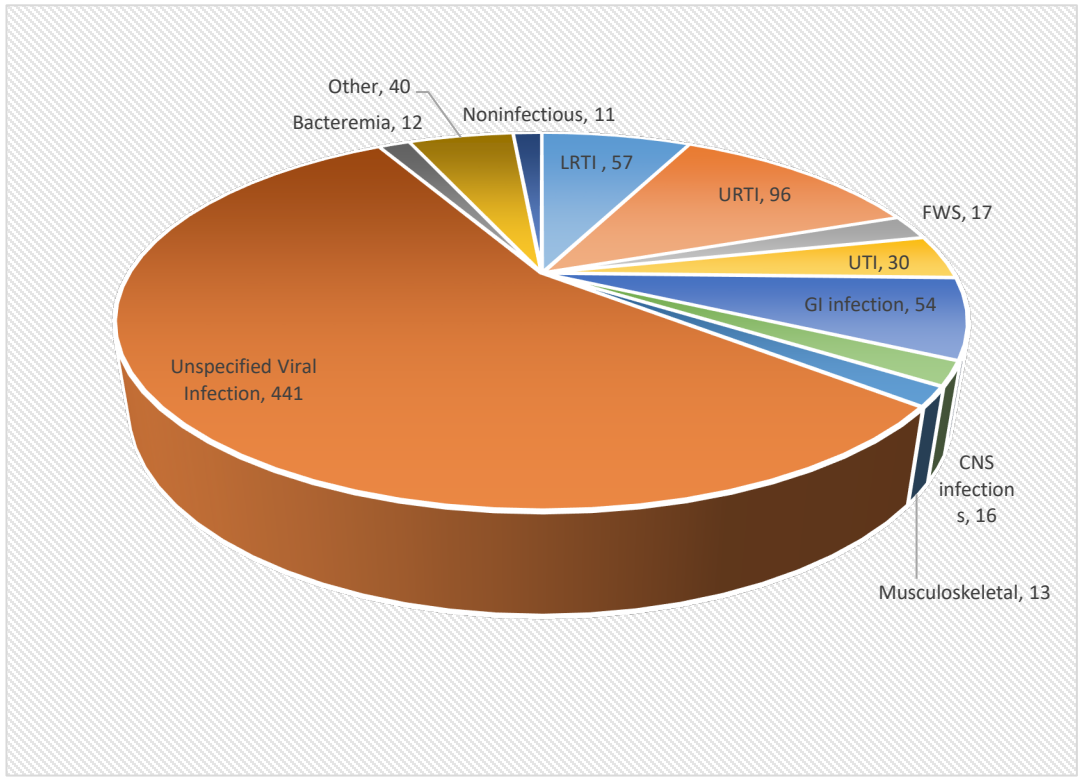
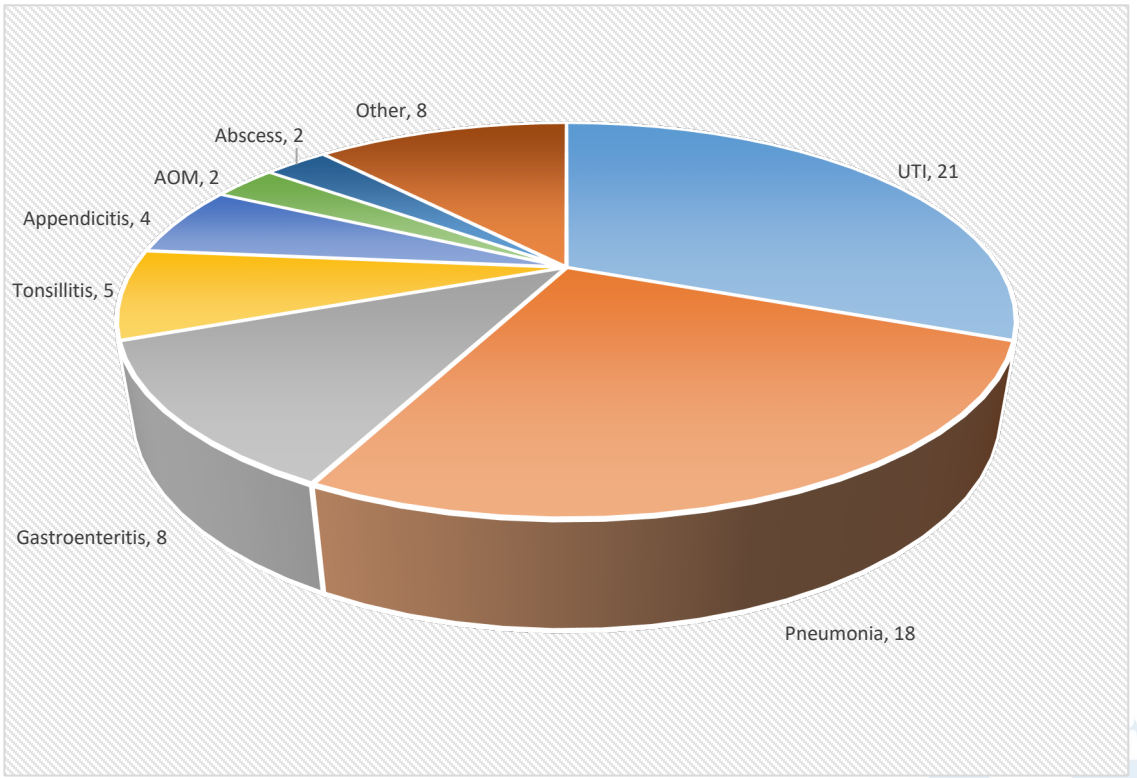


Results

Discharge Diagnoses (N=787)

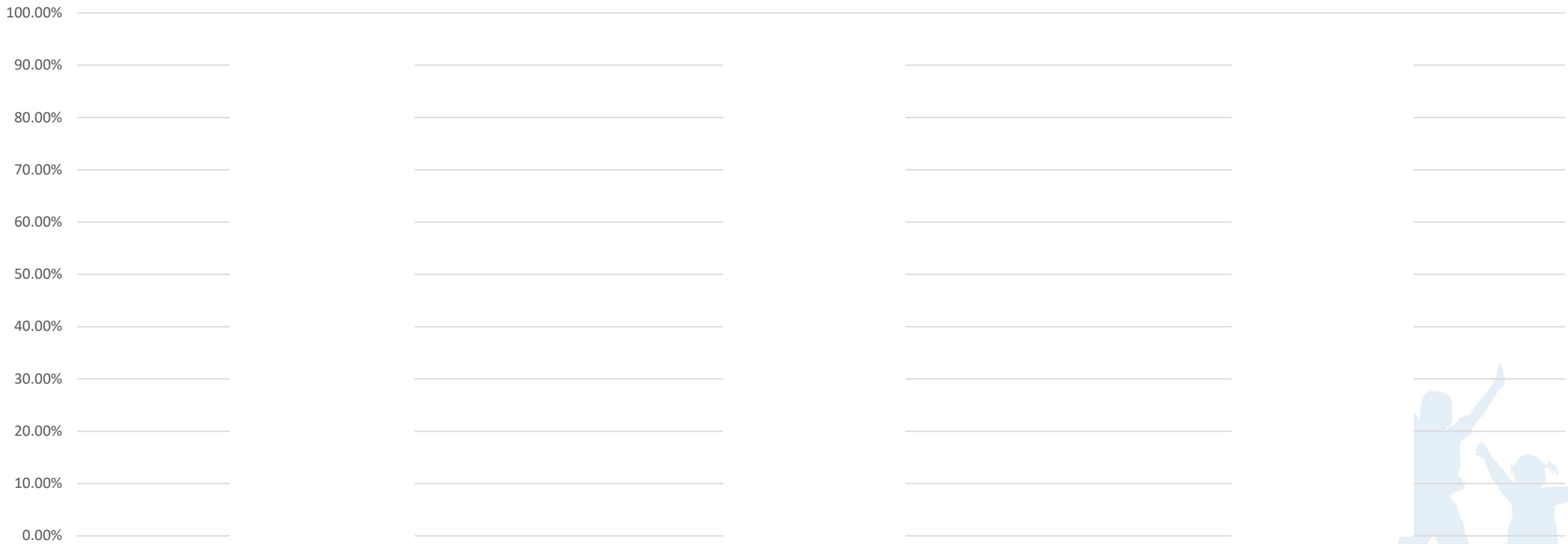


Bacterial Cases Discharge Diagnosis (N=68)



- **Bacterial prevalence for the FWS cohort – 9%, matches known literature.**

Results – BV Score Performance
586 unanimous bacterial\viral adjudication



False Negative Cases (N=6)

BV Score	Experts	Discharge Diagnosis	Sex, Age (y)	Microbiology	CXR	Abx	Hospitalization duration (days)
1	Bacterial	UTI	Female, 1.5	E. coli, urine culture	Not performed	Amoxicillin Clavulanate	0
1	Bacterial	Unspecified viral infection	Female, 1.5	E. coli, urine culture	Not performed	Not given	0
16	Bacterial	UTI	Female, 1	E. coli, urine culture	Normal	Amoxicillin Clavulanate	0
21	Bacterial	Acute tonsillitis	Female, 4	GAS, Nasopharyngeal culture	Not performed	Amoxicillin	4
32	Bacterial	Pneumonia	Female, 9	Negative	RUL consolidation	Ampicillin	2
1	Bacterial	Acute tonsillitis	Male, 6	GAS, Nasopharyngeal culture	Not performed	Amoxicillin	3

Discussion & Limitations

- This is the first study validating the BV score's performance in real-world population.
- During this study BV score was used solely according to physician discretion and as part of routine care
- Some patients listed by physicians as presenting with FWS do not meet current guidelines (for example, patients over 3 years of age).
- The BV score's utility could not be fully evaluated because it was calculated using an old Elisa kit that required prolonged time to produce results and the presence of an experienced lab technician.

Conclusions

High Diagnostic Performance

- The BV score demonstrated high diagnostic performance when applied according to its indication for use as part of routine care for children presenting to the ED with FWS

Utility

- The BV score accurately ruled out bacterial infection in children presenting to the ED with FWS, thus can potentially help minimize antibiotic overuse in this population

Thank you all for listening.