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A host-based assay comprising TRAIL, IP10, and CRP can improve antibiotic treatment decisions for viral PCR positive children by accurately ruling out co-infection

Cihan Papan et al.

39TH ANNUAL MEETING OF THE

**EUROPEAN SOCIETY FOR
PAEDIATRIC INFECTIOUS DISEASES**

Organised jointly by ESPID and the ESPID Foundation

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Conflict of Interest

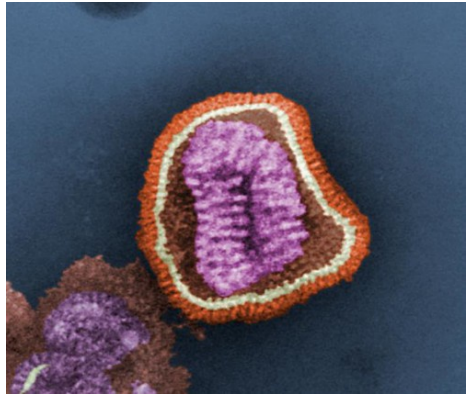


<input type="checkbox"/>	No, Nothing to disclose
<input checked="" type="checkbox"/>	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
MeMed								Coordinator of consortium that received EU award funding this study (grant #701088)

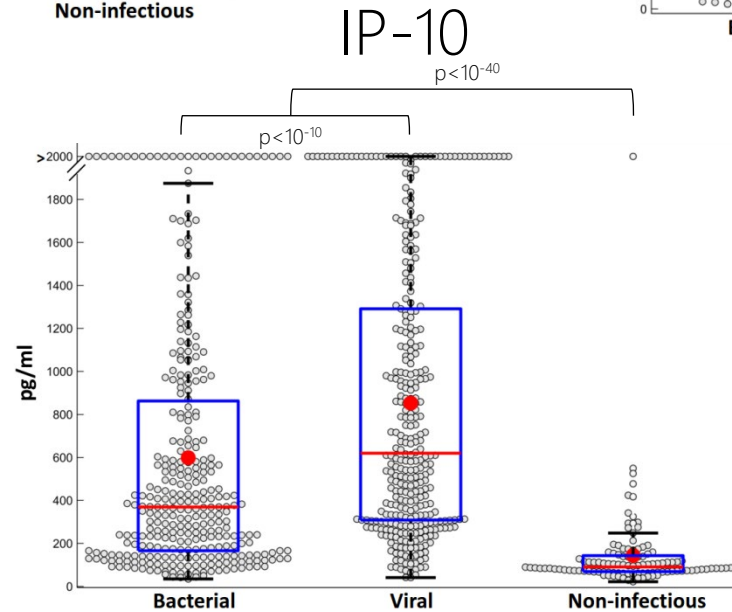
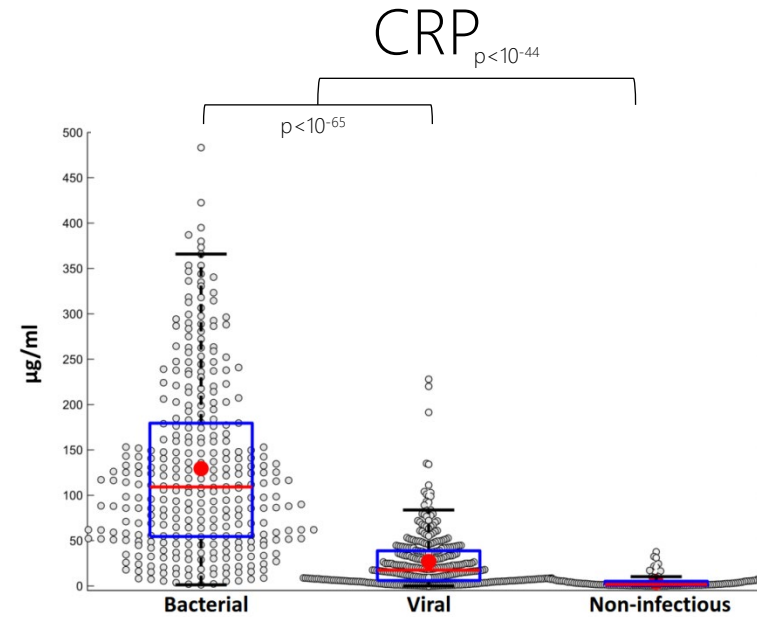
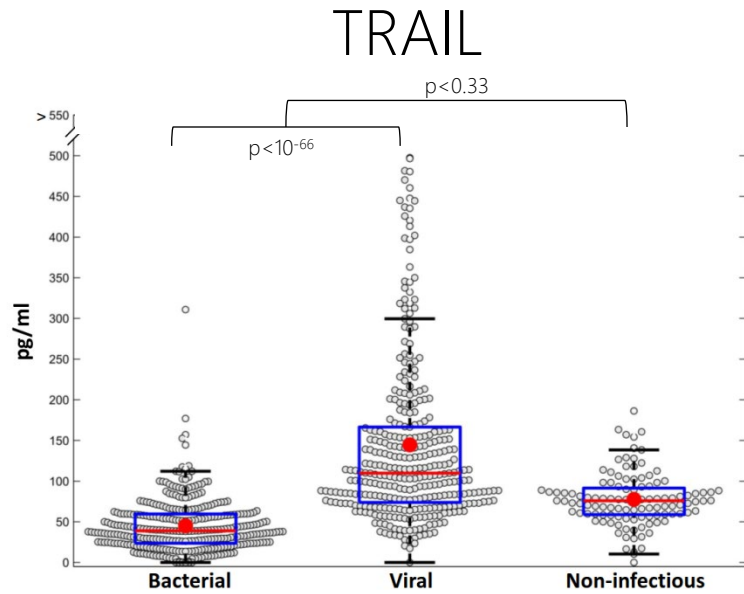
Background

?

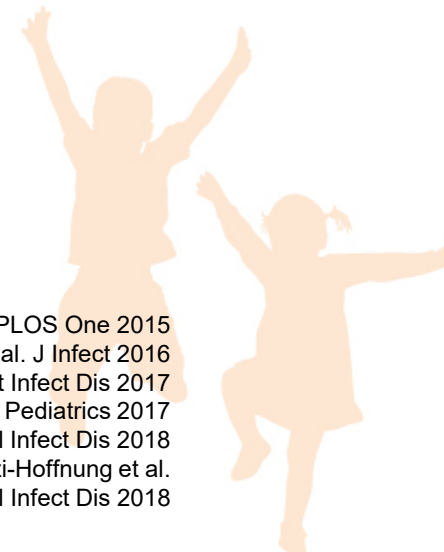


- Diagnosing infection etiology is a huge clinical challenge
- Available markers of inflammation have imperfections, leading to antibiotic overuse
- Antibiotic overuse is a main driver of antimicrobial resistance

Background



TNF-related apoptosis-inducing ligand (TRAIL)
 Interferon-gamma induced protein 10 (IP-10)
 C-reactive protein (CRP)



Methods – AutoPilot-Dx Study (NCT03052088)



- Study design: Prospective, external validation and diagnostic accuracy study
- Study population: children with respiratory tract infection or FWS \geq 90 days of age
- Inclusion criteria:
 - Body temperature $\geq 38^{\circ}\text{C}$
 - History of illness ≤ 7 days
- Exclusion criteria:
 - Previous febrile episode within past 2 weeks
 - Antibiotic treatment $> 48\text{h}$
 - HIV, Hep.B/C, immunodeficiency / immunosuppression
- Study procedure: standard of care + serum sample (signature) + nasopharyngeal multiplex PCR
- Primary objectives:
 - Diagnostic performance of the signature with pre-determined cutoffs [< 35 (viral), > 65 (bacterial)] vs. reference standard (= Expert panel adjudication)
 - potential clinical utility regarding antibiotic prescribing

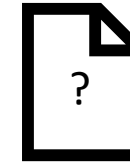
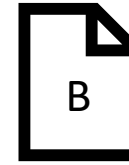


→ What is the clinical value in children with a positive virus PCR?

Methods – potential clinical utility

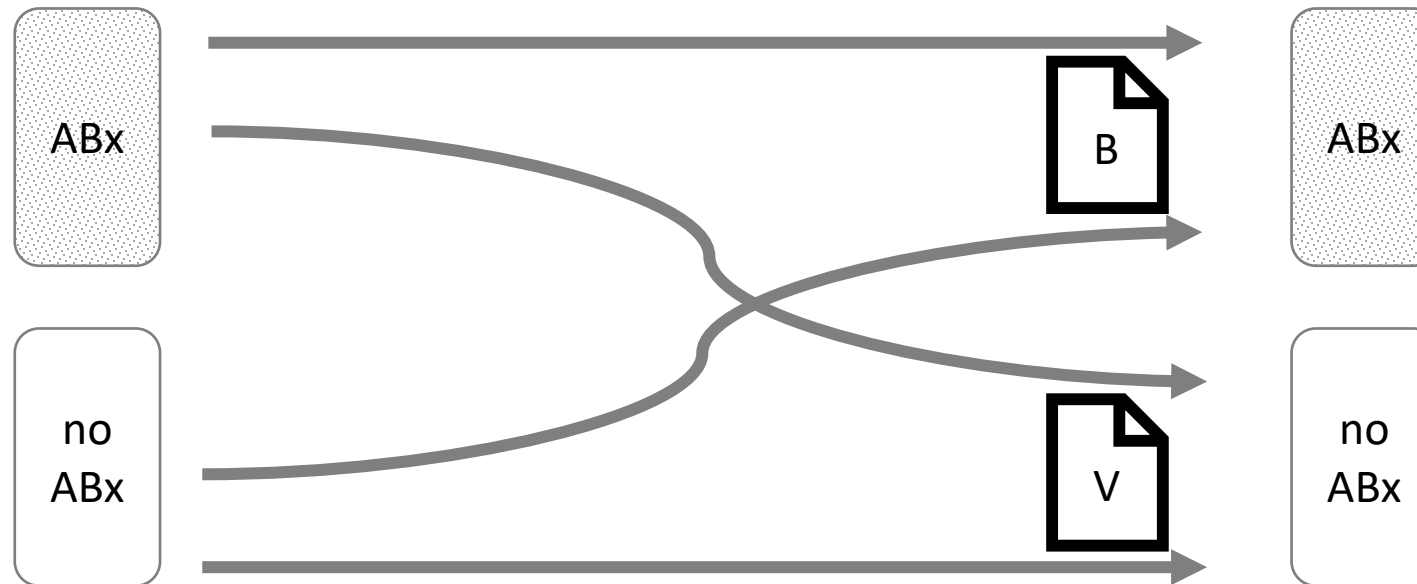


- Signature results were not available to the treating physicians throughout the study
- Assumptions to assess the potential impact:
 - Bacterial signature result (>65) → starting antibiotics
 - Viral signature result (<35) → withholding antibiotics
 - Equivocal signature result (35-65) → no change in practice



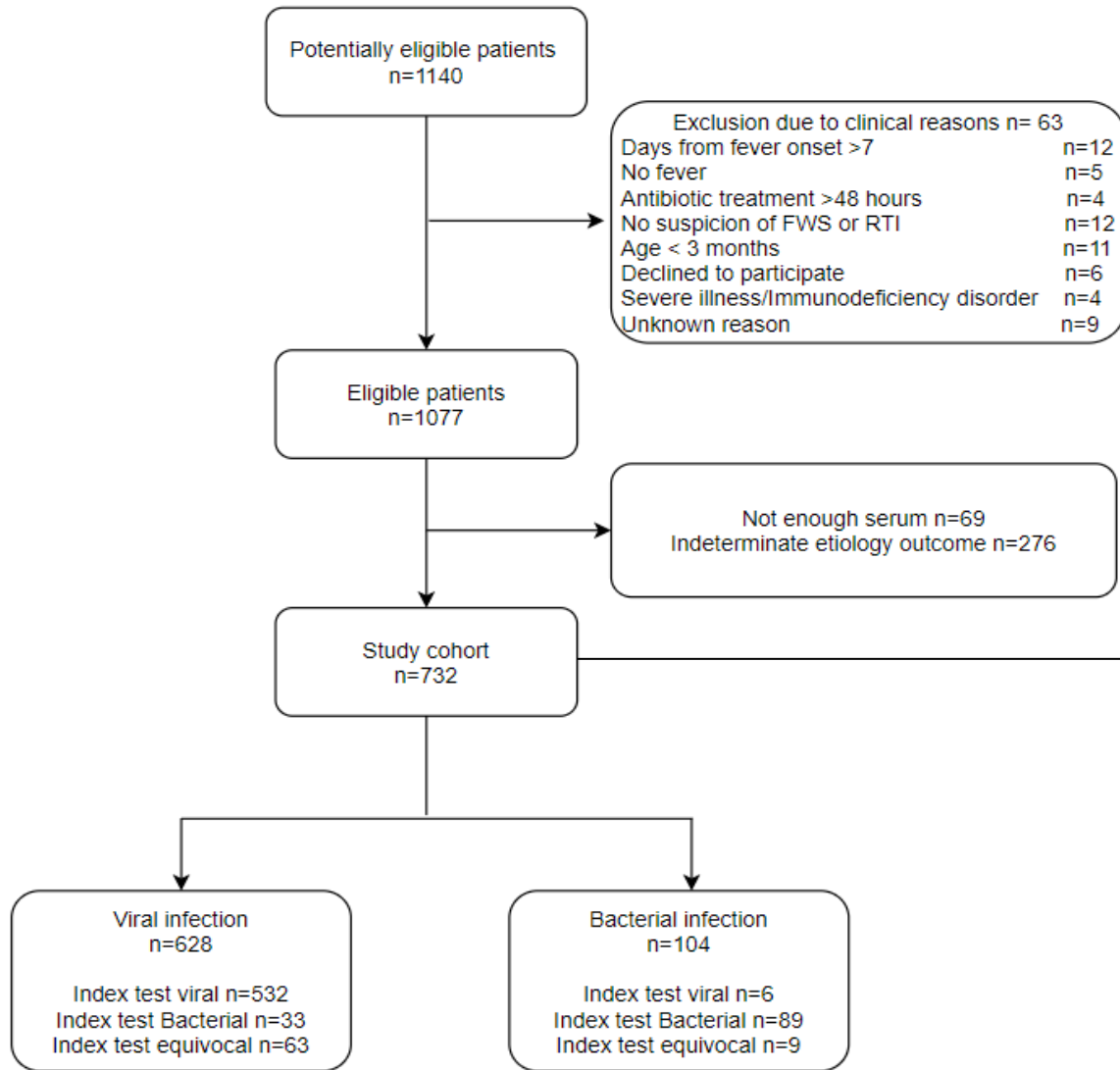
Current practice

Current practice + signature

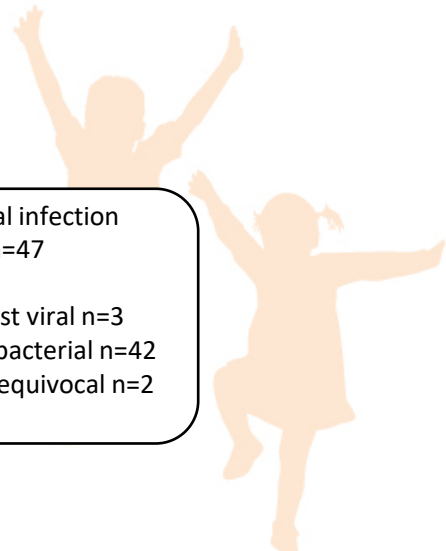
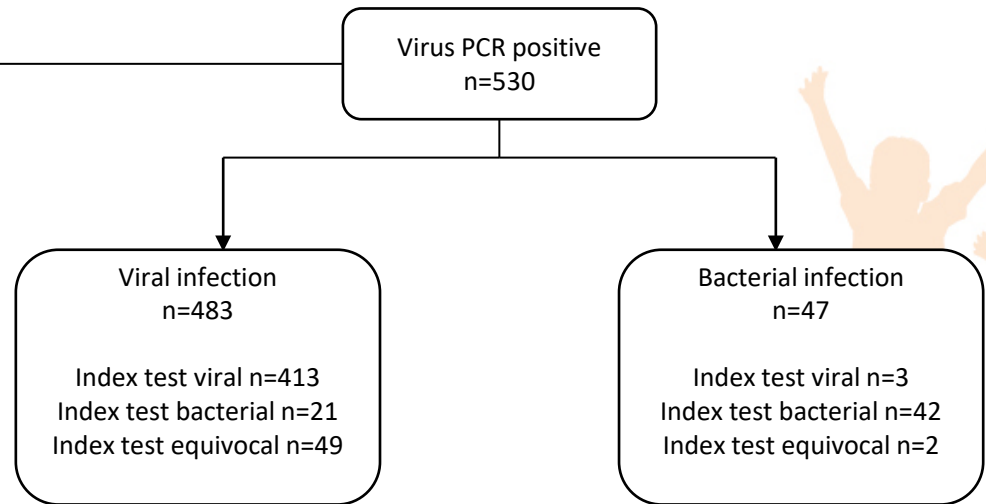


Results

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Subgroup analysis



Results

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In all virus PCR positive children, those with a bacterial reference standard diagnosis were older, had higher temperatures, were more often hospitalized and treated with antibiotics.

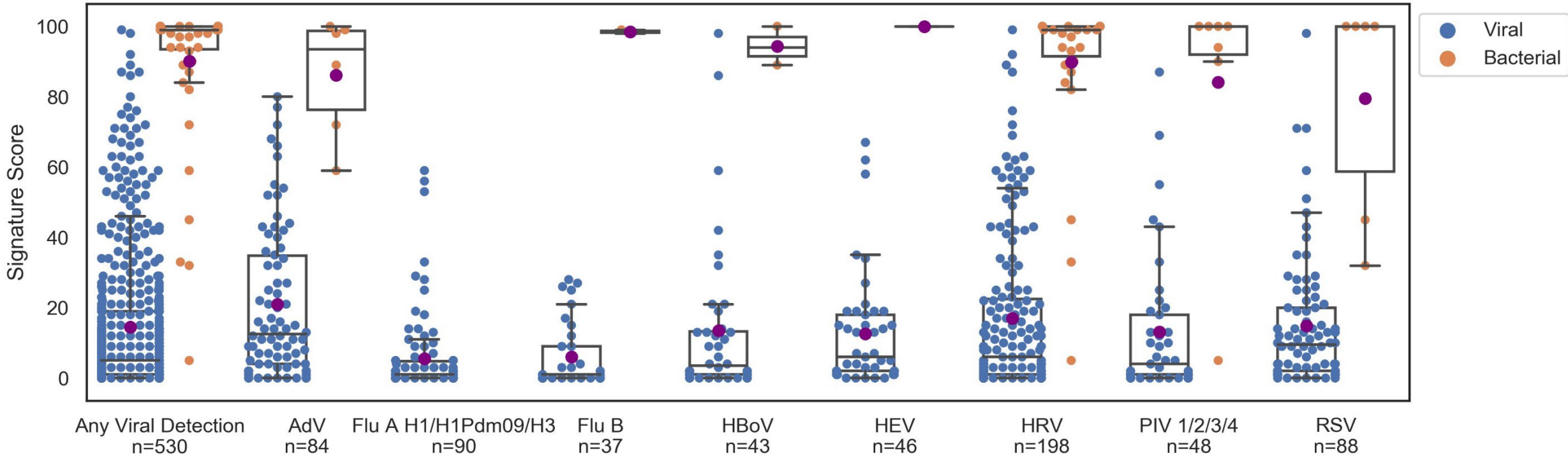
	Viral per reference standard	Bacterial per reference standard	p-value
n (%)	483/530 (91.1%)	47/530 (8.9%)	
Age, mean (SD)	2.9 (3.0)	3.9 (2.3)	p<0.001
Max. temperature, °C, mean (SD)	39.2 (0.8)	39.6 (0.7)	p=0.001
Hospital admission, n (%)	339/483 (70.2%)	44/47 (93.6%)	p<0.001
Antibiotics initiated, n (%)	143/483 (29.6%)	43/47 (91.4%)	p<0.001

Results

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In all virus PCR positive children, those with a viral reference standard diagnosis had lower signature scores than those with a bacterial reference standard diagnosis
14.5 vs. 90 ($p < 0.001$)



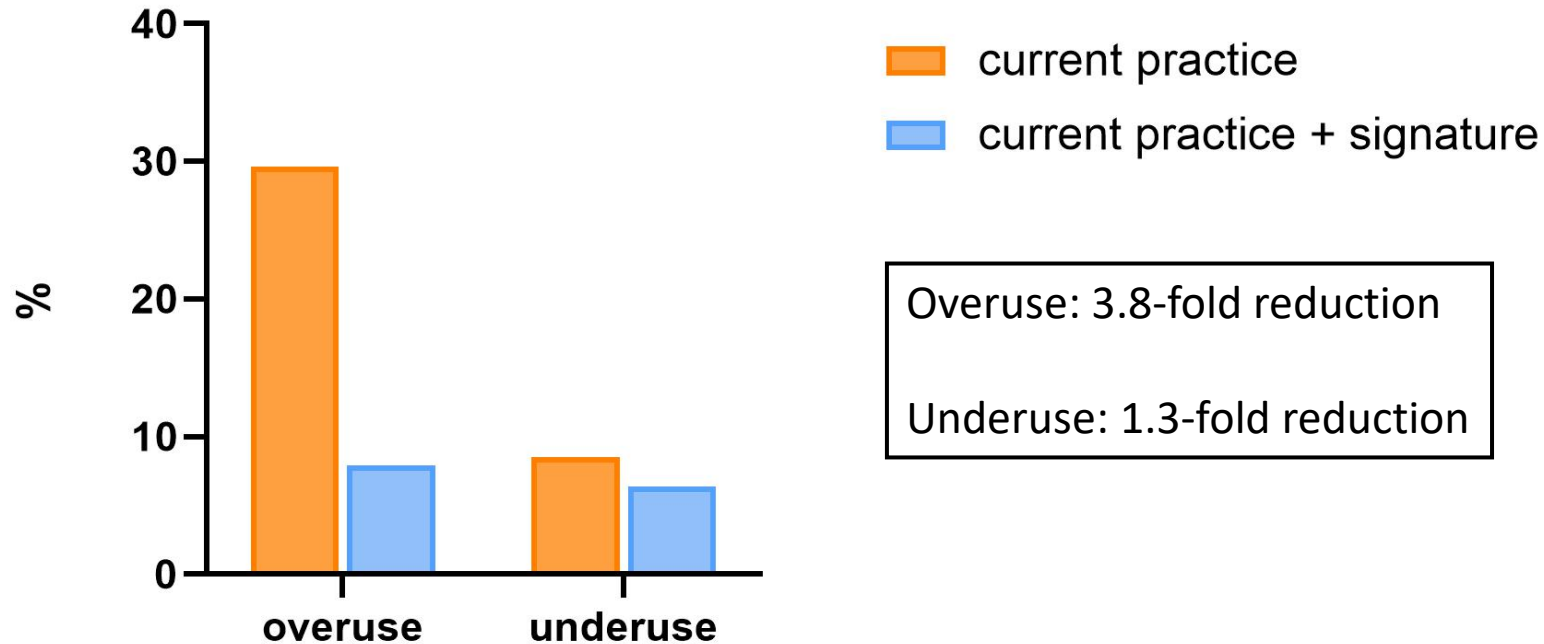
Results

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The signature has the potential in virus PCR positive children to

- reduce antibiotic overuse **from 143/483 cases (29.6%) to 38/483 cases (7.9%)** ($p < 0.001$)
- reduce antibiotic underuse from 4/47 (8.5%) to 3/47 (6.4%) (n.s.)



Discussion & Summary

- **Strengths:**

- Largest validation study to date in children aged up to 18 years of age
- Blinded expert panel to ensure unbiased evaluation
- Rigorous reference standard, i.e. PCR analysis, follow-up call, unanimous expert panel adjudication

- **Limitations:**

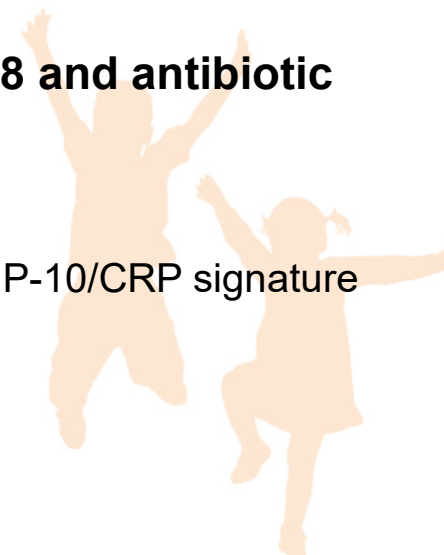
- Imperfect reference standard
- Unblinded for CRP, potential incorporation bias
- No real-life measurement of clinical utility

- **Take-away messages:**

- **The TRAIL/IP-10/CRP signature helps to distinguish bacterial (co-)infection from viral infection in presence of positive virus PCR**
- **The discriminatory accuracy is irrespective of a specific virus**
- **Potential to reduce antibiotic overuse in children with a positive virus PCR by factor 3.8 and antibiotic underuse by factor 1.3**

- **Outlook:**

- Prospective evaluation as an antibiotic stewardship tool using point-of-need platform that delivers TRAIL/IP-10/CRP signature result in 15 minutes from serum



Many thanks to...



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AND

- All patients and their parents
- All physicians and nurses

Questions? Comments?
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Tecan

Quantify Research

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