Online Meeting

ESPID
ONLINE MEETING, 24-29 MAY 2021

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GENEVA
24-29 MAY
2021

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

	No, Nothing to disclose
x	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

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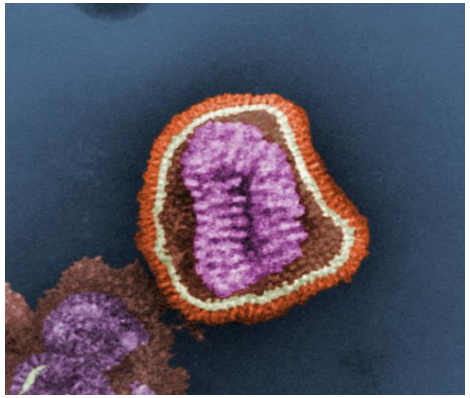
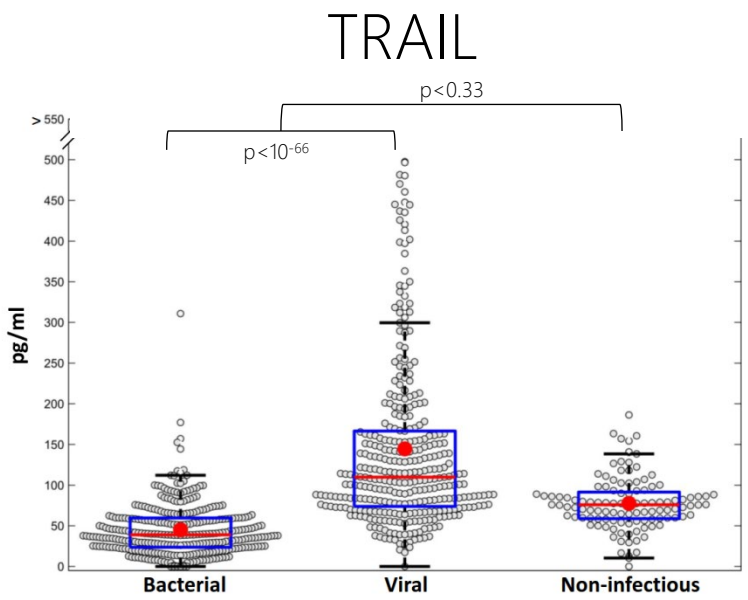
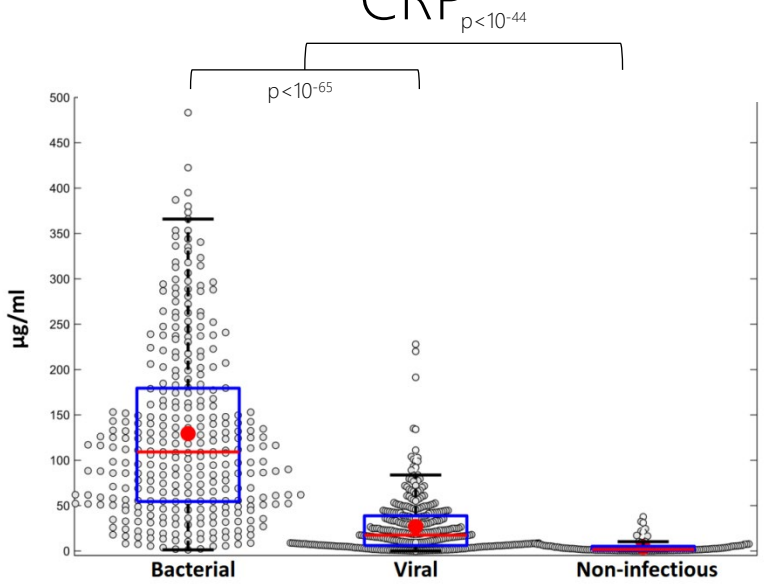


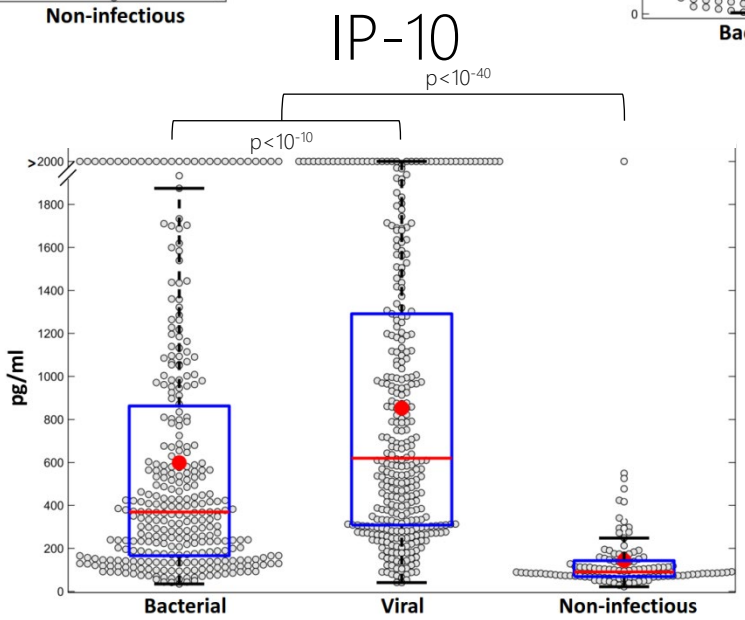
- Diagnosing infection etiology is a huge clinical challenge
- Available markers of inflammation have imperfections, leading to antibiotic overuse
- Antibiotic overuse is a main driver of antimicrobial resistance

Courtesy of
Ami Vitale / World Bank
NIAID
Kat Masback

Background







TNF-related apoptosis-inducing ligand (TRAIL)

Interferon-gamma induced protein 10 (IP-10)

C-reactive protein (CRP)

Oved et al. PLOS One 2015
Eden et al. J Infect 2016
Van Houten et al. Lancet Infect Dis 2017
Srugo et al. Pediatrics 2017
Stein et al. Diagn Microbiol Infect Dis 2018
Ashkenazi-Hoffnung et al.
Eur J Clin Microbiol Infect Dis 2018

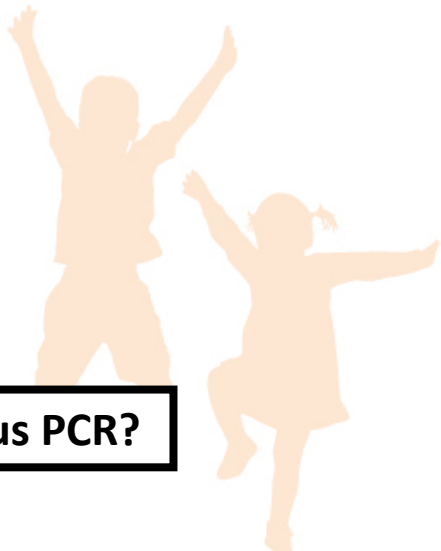
Methods – AutoPilot-Dx Study (NCT03052088)

- Study design: Prospective, external validation and diagnostic accuracy study
- Study population: children with respiratory tract infection or FWS ≥ 90 days of age

- Inclusion criteria:
  - Body temperature ≥38°C
  - History of illness ≤7 days
- Exclusion criteria:
  - Previous febrile episode within past 2 weeks
  - Antibiotic treatment >48h
  - HIV, Hep.B/C, immunodeficiency / immunosuppression

- Study procedure: standard of care + serum sample (signature) + nasopharyngeal multiplex PCR

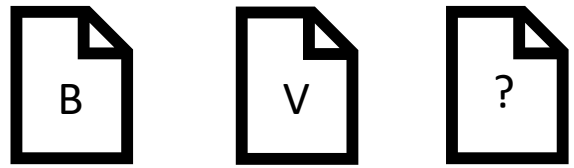
- Primary objectives:
  - Diagnostic performance of the signature with pre-determined cutoffs [<35 (viral), >65 (bacterial)] vs. reference standard (= Expert panel adjudication)
  - potential clinical utility regarding antibiotic prescribing

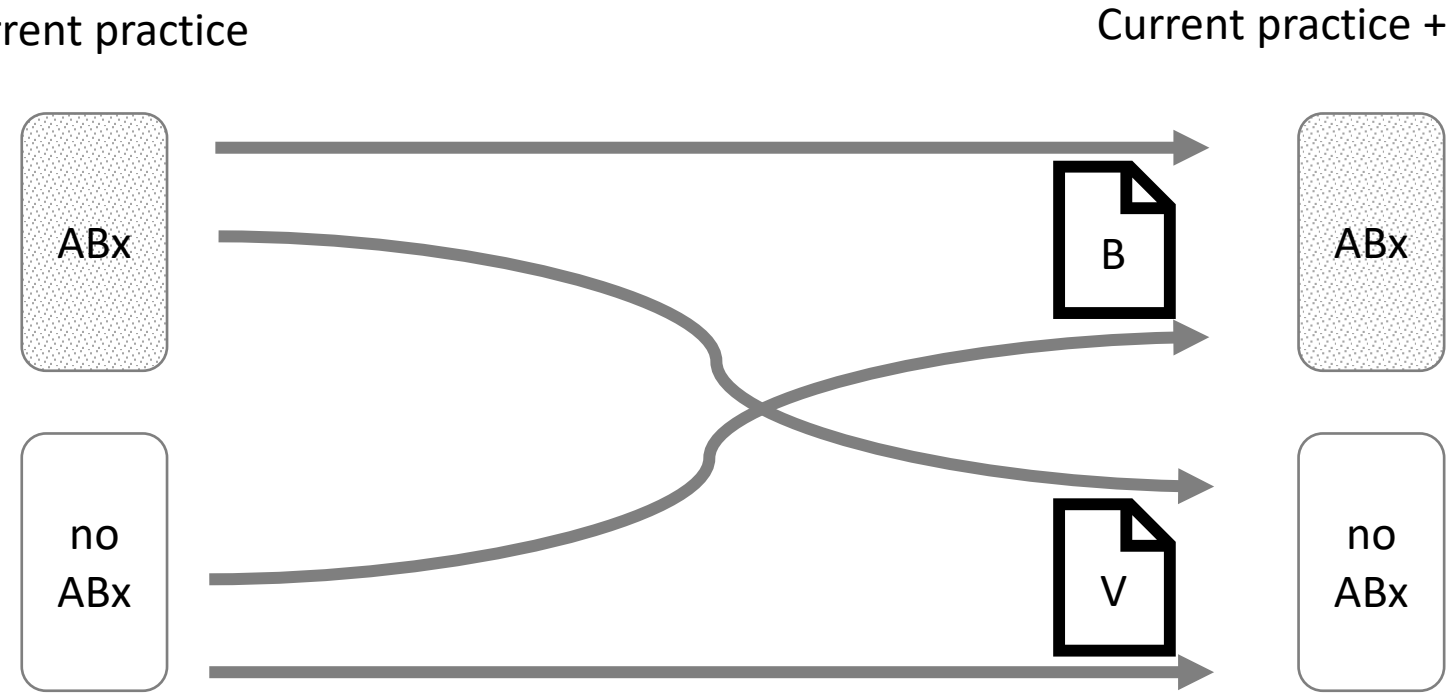


→ What is the clinical value in children with a positive virus PCR?

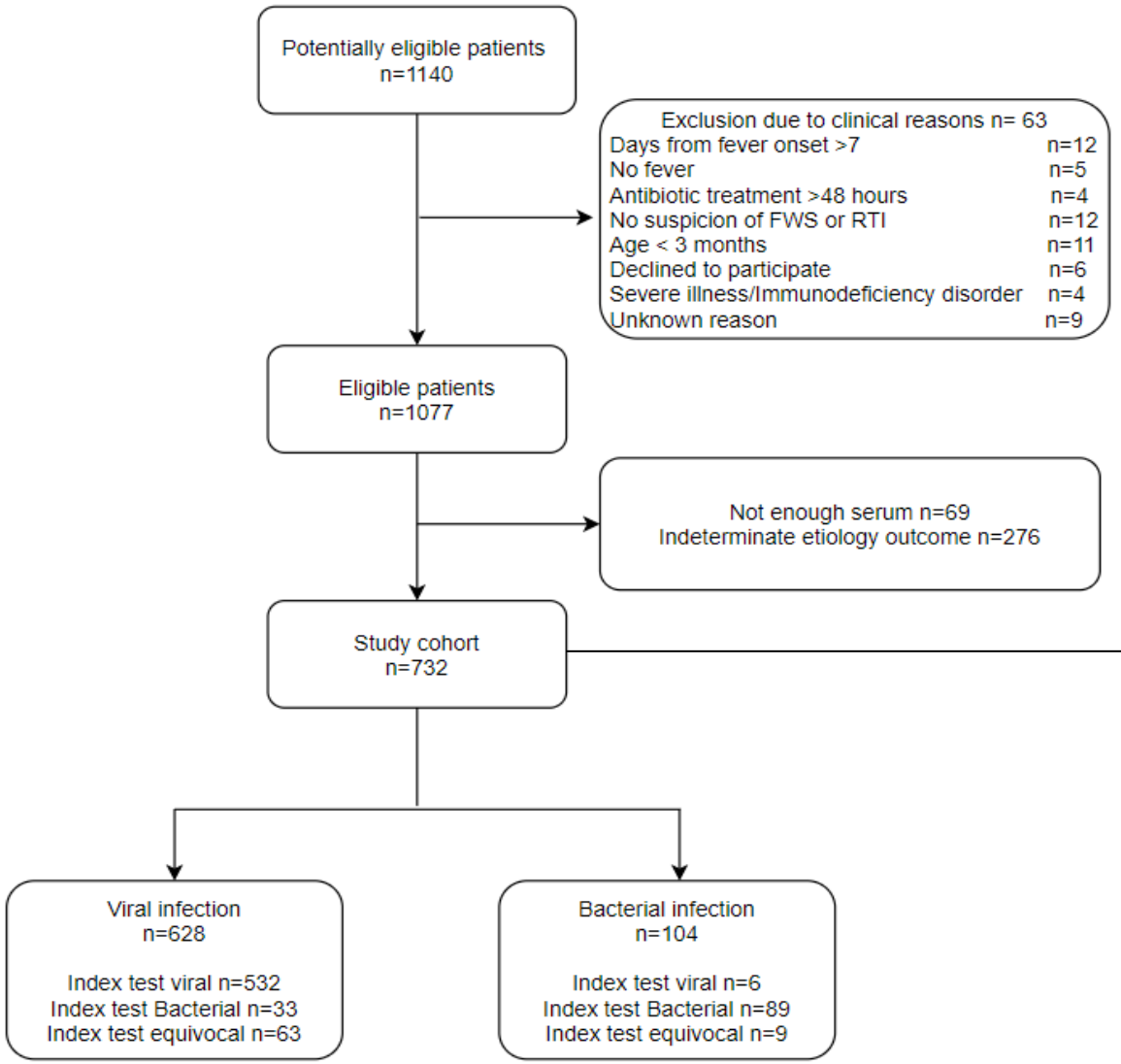
Methods – potential clinical utility

- 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

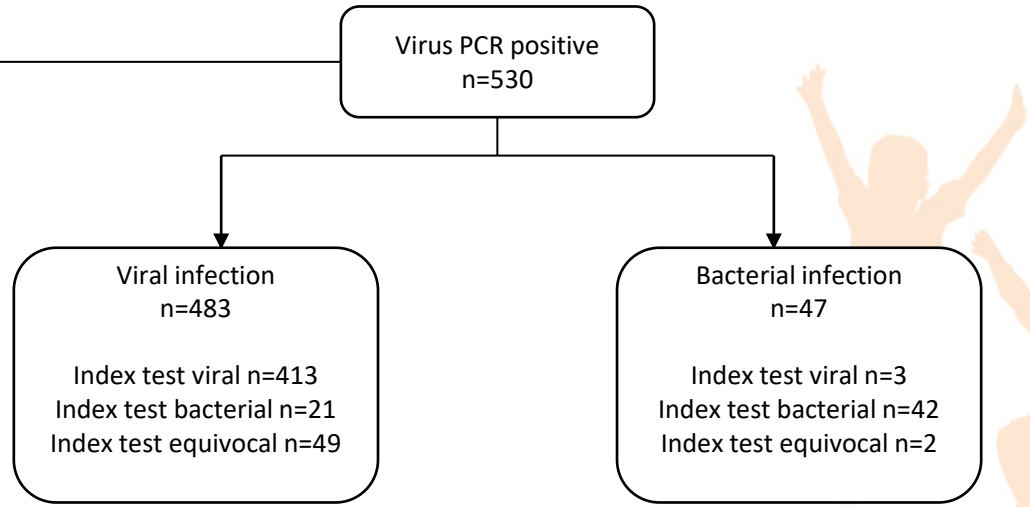




Results



Subgroup analysis



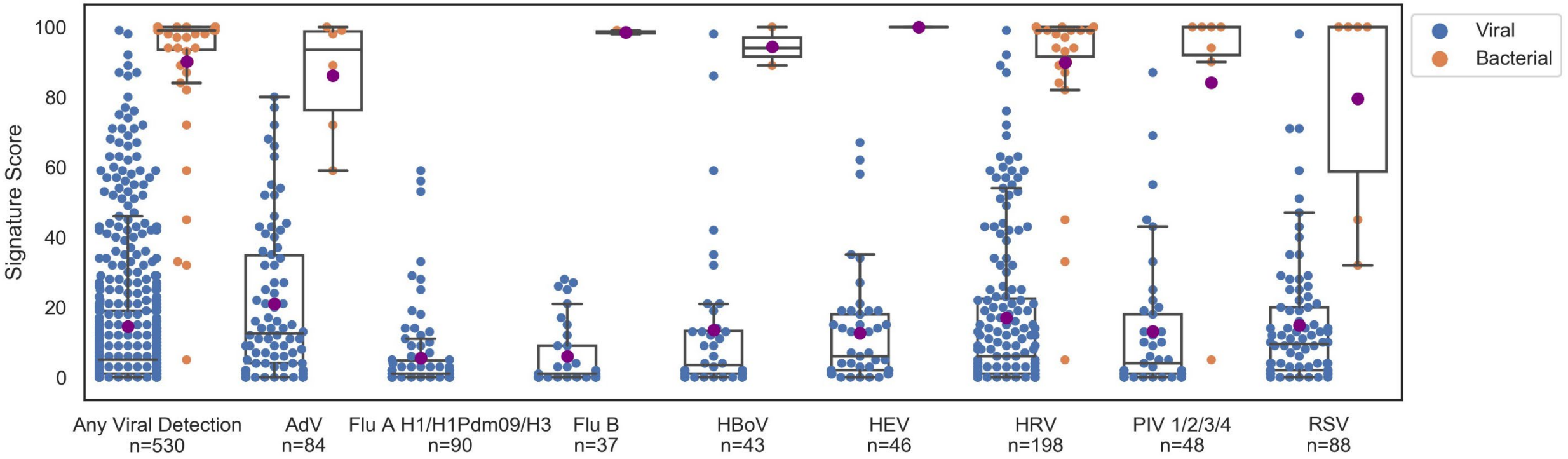
Results

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

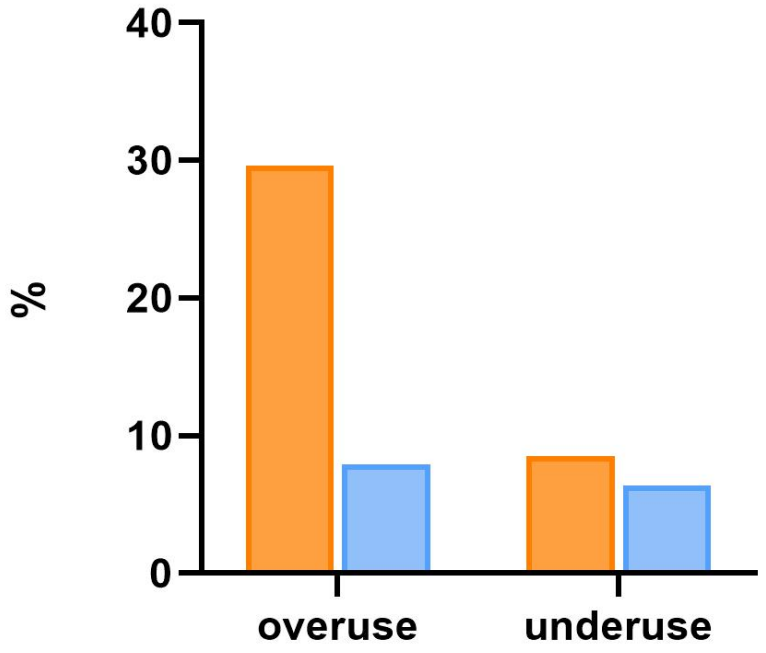
In all virus PCR positive children, those with a viral reference standard diagnosis had lower signature scores than those with a bacterial reference standard diagnosis
14.5 vs. 90 ($p<0.001$)



Results

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.)



current practice

current practice + signature

Overuse: 3.8-fold reduction

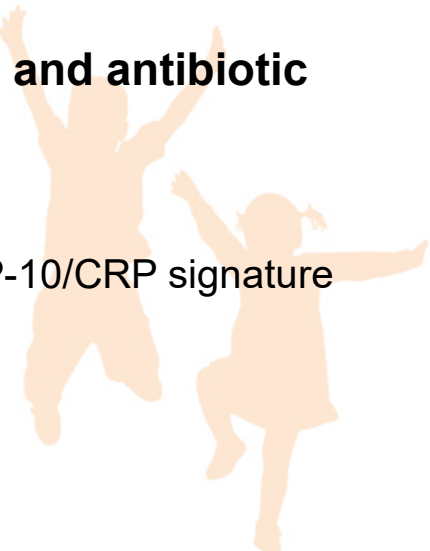
Underuse: 1.3-fold reduction

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

- **<u>Take-away messages:</u>**
  - **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



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- All physicians and nurses

Questions? Comments?
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