INFECTIOUS DISEASES

LIAISON® MeMed BV®
Clinical publications overview

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The LIAISON® MeMed BV® is the new fully-automated and high-throughput solution which enables physicians to accurately differentiate between bacterial and viral infections, thus supporting early and more-informed treatment and patients management decisions.

MeMed and DiaSorin have jointly collaborated to make the MeMed BV® assay available on DiaSorin's chemiluminescent LIAISON® platforms. The clinical characteristics of the MeMed BV® and LIAISON® MeMed BV® assays are completely identical. They both use the same antibodies and antigens, the same mathematical algorithm and coefficients to calculate the SCORE value

The clinical performances for the MeMed BV® assay, as reported in this summary, can thus be applied to the new LIAISON® MeMed BV® assay.

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BV Signature Discovery: ***Curiosity Study***

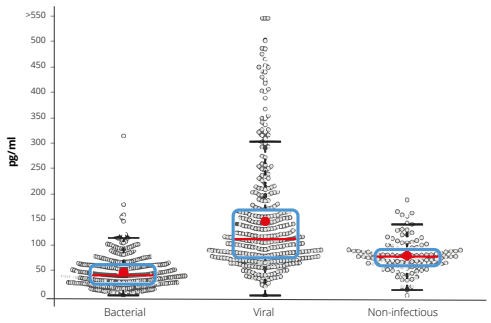
Oved K et al.
PLoS One. 2015
A novel host-proteome signature for distinguishing between acute bacterial and viral infections

An algorithm combining the host proteins TRAIL, IP-10 and CRP (called 'BV signature') differentiates bacterial from viral infection across a broad population

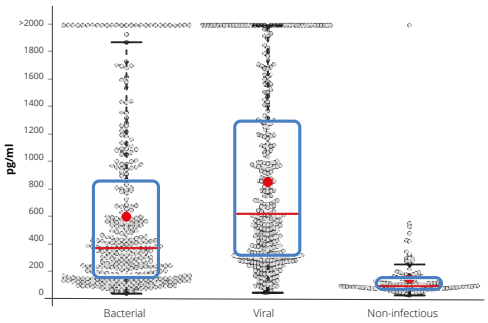
STUDY CHARACTERISTICS: 1002 pediatric and adult patients with suspiction of acute infection, recruited prospectively from emergency department. Final diagnosis was attained in 765 patients

KEY MESSAGES:

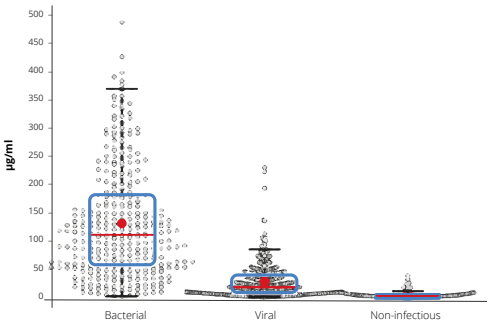
- In extensive screening process, **TRAIL** (TNF-related apoptosis-inducing ligand), **IP-10** (Interferon gamma-induced protein-10) and **CRP** (C-reactive protein) **were identified as differentially expressed in bacterial versus viral infections**



TRAIL $p<10^{-66}$ (bacterial vs viral) $p<0.33$ (infectious vs non-infectious)

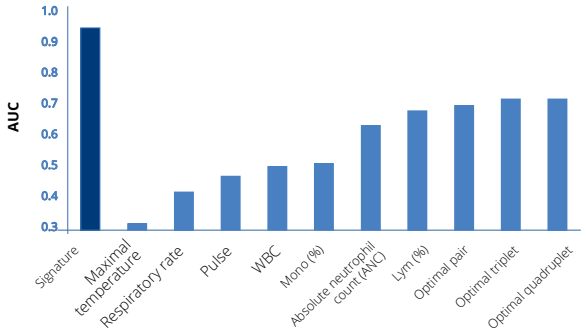


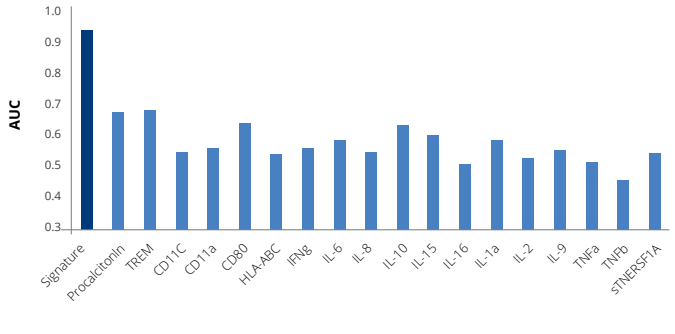
IP-10 $p<10^{-10}$ (bacterial vs viral) $p<10^{-40}$ (infectious vs non-infectious)



CRP $p<10^{-65}$ (bacterial vs viral) $p<10^{-44}$ (infectious vs non-infectious)

- **BV signature** was derived based on a broad population with suspicion of acute infection and **is robust** to children and adults, more than 50 pathogens and multiple clinical syndromes, including upper and lower respiratory tract infection, urinary tract infection and fever without source
- **BV signature compares favorably to laboratory parameters and protein biomarkers**





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BV Signature Clinical Validation in Children: ***Opportunity Study***

van Houten CB et al.
Lancet Infect Dis. 2017
A host-protein based assay to differentiate between bacterial and viral infections in preschool children (OPPORTUNITY): a double-blind, multicentre, validation study

High performance of BV validated in preschool children with lower respiratory tract infection symptoms and fever without source

STUDY CHARACTERISTICS: 777 pediatric patients with symptoms of lower respiratory tract infection or fever without source, recruited prospectively from emergency department. The assay was run on 577 patients

KEY MESSAGES:

- **High performance** validated across cohorts defined by reference standards **with increasing levels of diagnostic certainty**:
  - Suspected bacterial/viral etiology (at least two experts give same adjudication label; majority)
  - Bacterial/viral etiology (all three experts give same adjudication label; unanimous)
  - Microbiologically confirmed etiology (unanimous plus microbiological identification)

	Majority cohort	Unanimous cohort	Microbiologically confirmed cohort
CE-IVD cutoff			
Number of patients in subgroup	443	354	295
Sensitivity	86·7 (75·8–93·1)	87·8 (74·5–94·7)	88·9 (67·2–96·9)
Specificity	91·1 (87·9–93·6)	93·0 (89·6–95·3)	92·8 (89.1-95.3)
Positive predictive value	60·5 (49·9–70·1)	62·1 (49·2–73·4)	44·4 (29·5–60·4)
Negative predictive value	97·8 (95·6–98·9)	98·3 (96·1–99·3)·	99·2 (97·2–99·8)
Positive likelihood ratio	9·8 (7·0–13·7)	12·5 (8·2–19·0)	12·3 (7·8–19·4)
Negative likelihood ratio	0·1 (0·1–0·3)	0·1 (0·1–0·3)	0·1 (0·0–0·4)
Diagnostic odds ratio	66·7 (29·3–152·0)	95·2 (34·0–267·0)	102·8 (22·1–478·9)

- **The assay significantly improved diagnosis of bacterial infection** in children aged 2 to 60 months presenting with lower respiratory tract infection or fever without source at the hospital **compared with CRP and procalcitonin**

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BV Signature Clinical Validation in Children: ***Pathfinder Study***

Srugo I et al.
Pediatrics. 2017
Validation of a Novel Assay to Distinguish Bacterial and Viral Infections

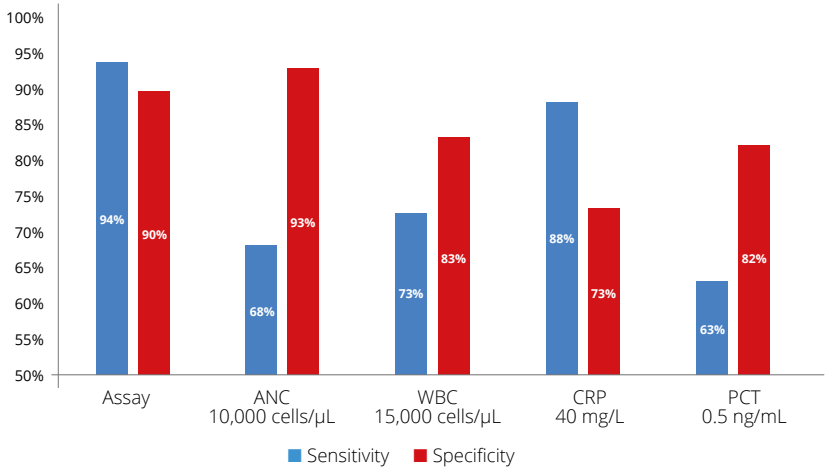
High performance of BV validated in children aged 3 months to 18 years with suspicion of acute infection

STUDY CHARACTERISTICS: 597 pediatric patients, recruited retrospectively from emergency department. The assay was run on 307 patients

KEY MESSAGES:

- The **assay significantly outperformed to routine laboratory parameters** and **other biomarkers**. In particular, it demonstrated **comparable sensitivity and significantly improved specificity compared with CRP and significantly improved sensitivity and specificity compared with PCT**
- The **host-signature assay yielded robust sensitivity and specificity across a wide range of patient subgroups**, including age and clinical syndrome. It performed comparably irrespective of time from symptom onset

Subgroup	No. of Patients (Ref. Bacterial, Ref. Viral)	Equivocal (%)	Sensitivity (95% CI)	Specificity (95% CI)
Age				
3 mo ≤ age < 3 y	184 (30, 154)	10.3	93.1 (83.2–100)	91.9 (87.3–96.6)
3 y ≤ age ≤ 5 y	41 (12, 29)	12.2	100 (100–100)	83.3 (67.3–99.4)
5 y ≤ age ≤ 18 y	82 (26, 56)	14.6	91.7 (79.7–100)	87.0 (76.8–97.1)
Time from symptom onset				
0 ≤ day < 2	68 (17, 51)	5.9	93.3 (79.0–100)	87.8 (78.2–97.3)
2 ≤ day < 4	80 (17, 63)	10.0	100 (100–100)	92.9 (85.9–99.8)
4 ≤ day < 6	94 (18, 76)	17.0	88.9 (72.8–100)	86.7 (77.8–95.5)
6 ≤ day ≤ 7	63 (16, 47)	11.1	93.8 (80.4–100)	92.5 (84.0–100)
Clinical syndrome				
CNS infection	3 (0, 3)	33.3	N/A	100 (100–100)
FWS	111 (8, 103)	11.7	87.5 (57.9–100)	87.8 (80.9–94.7)
GE	11 (1, 10)	9.1	100 (100–100)	100 (100–100)
LRTI	47 (20, 27)	8.5	95.0 (84.5–100)	100 (100–100)
URTI	92 (17, 75)	15.2	92.9 (77.4–100)	84.4 (75.2–93.5)
UTI	16 (16, 0)	0	93.8 (80.4–100)	N/A
Other	21 (6, 15)	4.8	100 (100–100)	100 (100–10
Country				
Israel	212 (32, 180)	16	93 (84–100)	86 (80–92)
Switzerland	95 (36, 59)	3	94 (86–100)	100 (100–100)



- The **assay is highly accurate**, significantly reducing both false negatives **(potentially reducing missed bacterial infections)** and false-positives **(potentially reducing antibiotic overuse**), with an equivocal assay outcome in under 12% of cases

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Performance of BV compares favorably to other candidate tools for differentiating between bacterial and viral infection in children and adults with respiratory tract infection and fever without source

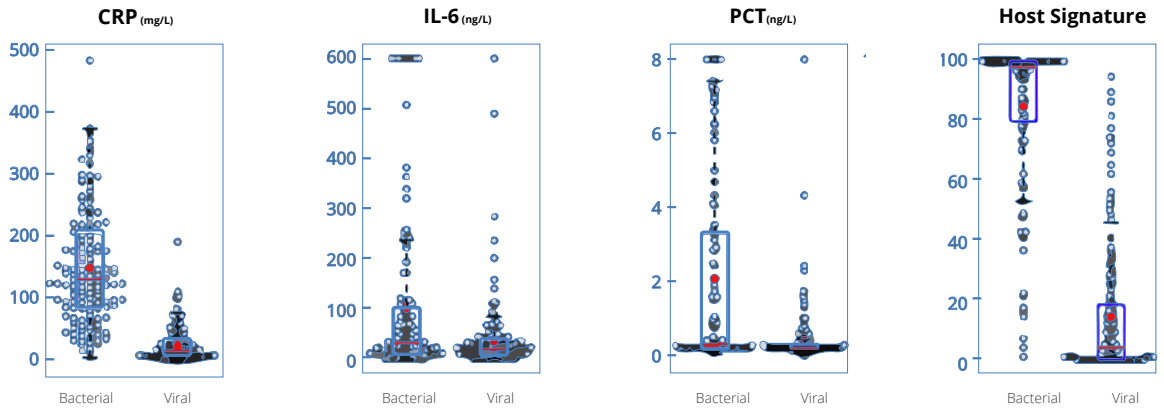
BV Signature Comparison to Other Biomarkers: ***Curiosity Sub-Study***

Ashkenazi-Hoffnung L et al. Eur J Clin Microbiol Infect Dis. 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

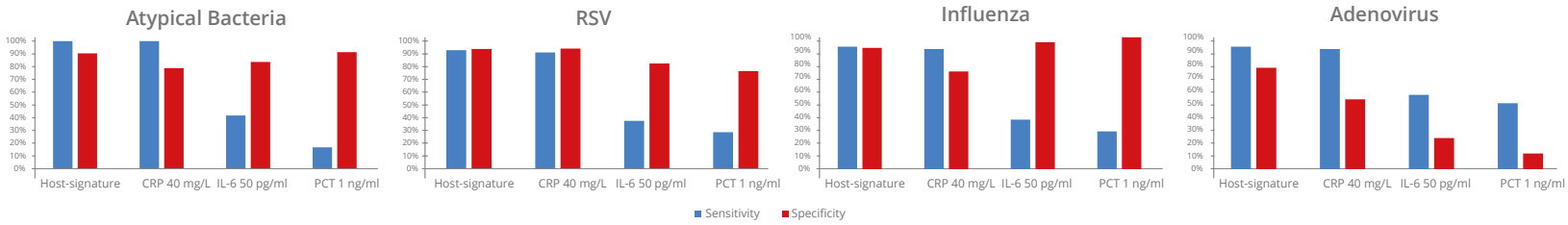
STUDY CHARACTERISTICS: 1002 children and adults patients with diverse clinical syndromes and a spectrum of pathogens, recruited from hospitalized population or emergency. Final diagnosis was attained in 314 patients

KEY MESSAGES:

- CRP, IL-6, and PCT exhibited higher mean (standard deviation) levels in bacterial as compared to viral infections. The **host-protein signature** demonstrated **the most pronounced differential in bacterial versus viral infections**



- The host-protein signature yielded significantly **higher total accuracy** for differentiating between viral and bacterial infections in patients with respiratory diseases due to **different pathogens**



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Performance of BV compares favorably to standard laboratory and clinical parameters that are routinely used in clinical practice to facilitate diagnosis of lower respiratory tract infection (LRTI)

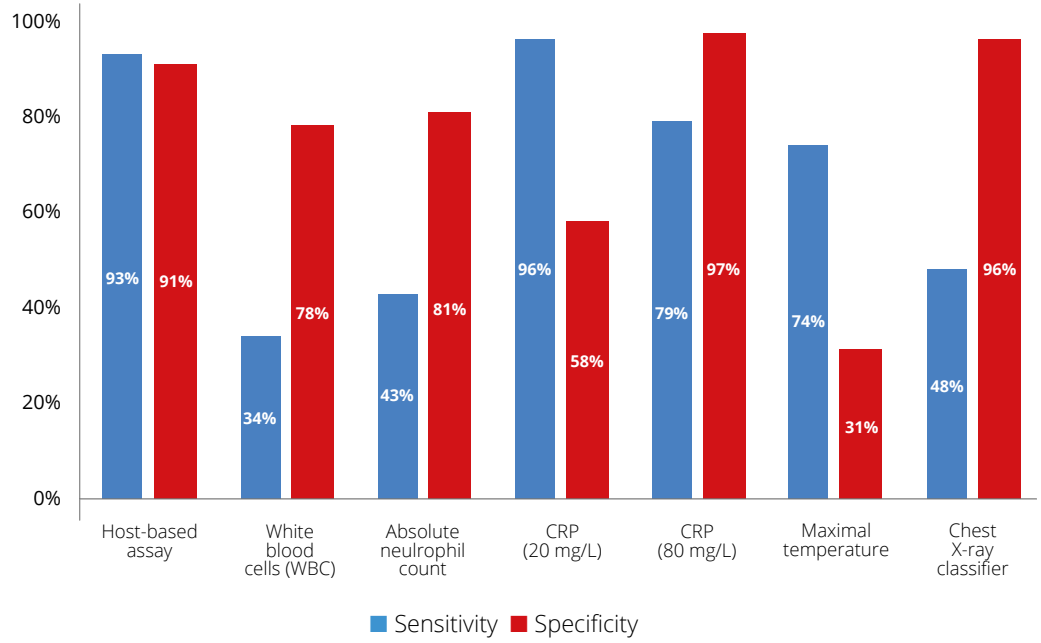
BV Signature Performances:
Curiosity Sub-Study

Stein M. et al.
Diagn Microbiol Infect Dis. 2018
A novel host-protein assay outperforms routine parameters for distinguishing between bacterial and viral lower respiratory tract infections

STUDY CHARACTERISTICS: 1002 pediatric and adults patients with clinical suspicion of lower respiratory tract infection, recruited from emergency department, pediatric and internal medicine wards. Performance evaluation was performed on 124 patients

KEY MESSAGES:

- The **BV signature has significantly higher performance compared to standard laboratory and clinical parameters** that are routinely used in clinical practice to facilitate diagnosis of low respiratory tract infections
- The **assay**'s high sensitivity and specificity in distinguishing between bacterial and viral low respiratory tract infections highlights its **potential to aid clinicians avoid missing bacterial infections**
- In the evaluated cohort, the assay assigned a viral score to 91% of the viral patients that were treated with antibiotics, suggesting that **this assay may assist in reducing antibiotic overuse**



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BV signature accurately differentiate between bacterial and viral infections and complements viral detection to support appropriate antibiotic use

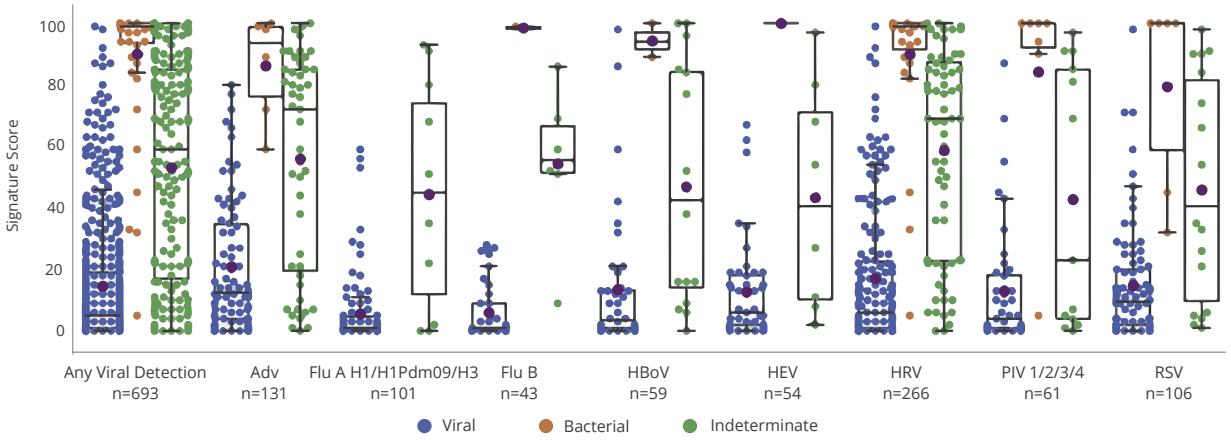
STUDY CHARACTERISTICS: 1140 pediatric patients with clinical suspicion of lower respiratory tract infection or fewer without source, recruited from emergency department. Performance evaluation was performed on 732 patients

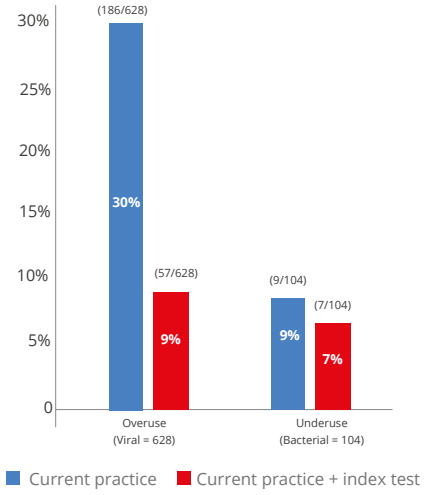
BV Signature Performances:
Autopilot study

Papan C et al.
Clin Microbiol Infect. 2021
A host signature based on TRAIL, IP-10, and CRP for reducing antibiotic overuse in children by differentiating bacterial from viral infections: A prospective, multicentre cohort study

KEY MESSAGES:

- The BV signature performed consistently across different patient subgroups. It yielded high sensitivity and specificity irrespective of time from symptom onset, demonstrating a clearer discrimination between bacterial and viral cases over illness duration as compared to CRP or PCT
- The **BV signature detected bacterial immune responses in viral PCR-positive patients**
- The test can support appropriate antibiotic use. If antibiotics were prescribed according to the results of the signature, only 57.6% of children would have been prescribed antibiotics and 42.4% would not, representing **a 1.4-fold reduction**





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Potential Impact of the BV Score on Decision Making And Antibiotic Stewardship in Pediatric Patients:
Rosetta Study

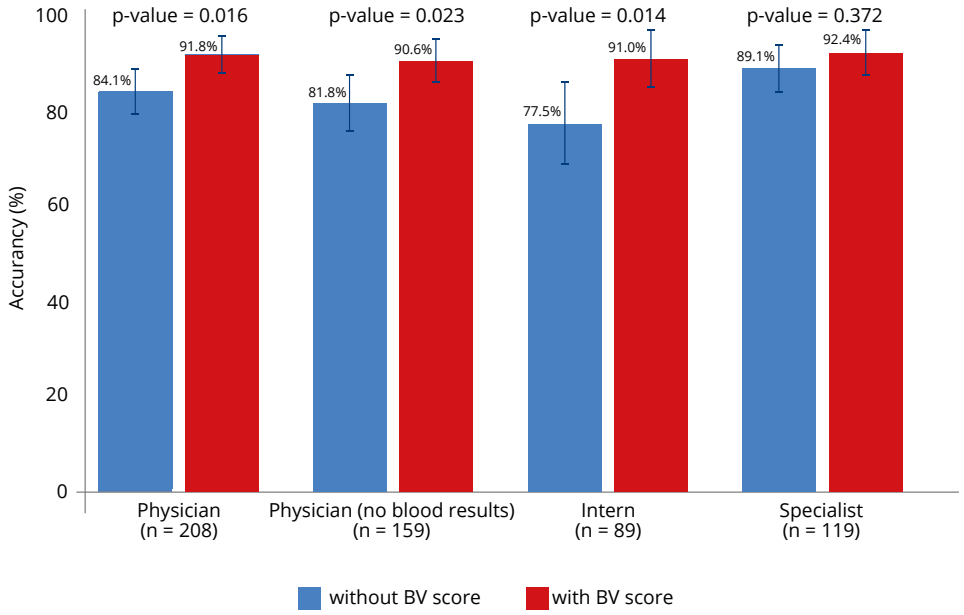
Mor M et al.
PLos One 2023
Bacterial vs viral etiology of fever: A prospective study of a host score for supporting etiologic accuracy of emergency department physicians

The BV test potentially reduce the diagnostic uncertainty in febrile child in the emergency department

STUDY CHARACTERISTICS: 465 pediatric patients with respiratory tract infections (RTIs) or fever without source (FWS) recruited at ED.
298 patients enrolled

KEY MESSAGES:

- BV score **accurately differentiated BV infections** (sensitivity 88.9%, specificity 92.1%, PPV 53.3%, NPV 98.8%)
- BV results matched the physician's suspicion and the reference standard diagnosis in 72% of the cases; of these, **52%** were labeled by the physician with low confidence meaning that the **BV result could reinforce the physician's etiological suspicion**
- In **12% of the cases the BV test** aligned with the reference standard diagnosis but not with the physician's suspicion, and therefore **could correct the physician's etiologic diagnosis and the treatment decisions**
- The information provided by the BV score could potentially reduce diagnosis error by **~ 2-fold (from 15.9% to 8.2%)**. The impact is estimated to be greater **(2.5-folds, from 22.5% to 9%)** when the physician is more junior (Intern)



- **The availability of the BV test when evaluating a febrile child in the ED has potential to reduce diagnostic uncertainty and support physician's decision-making process**

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BV impacts patient management in real-world settings, supporting appropriate antibiotic use

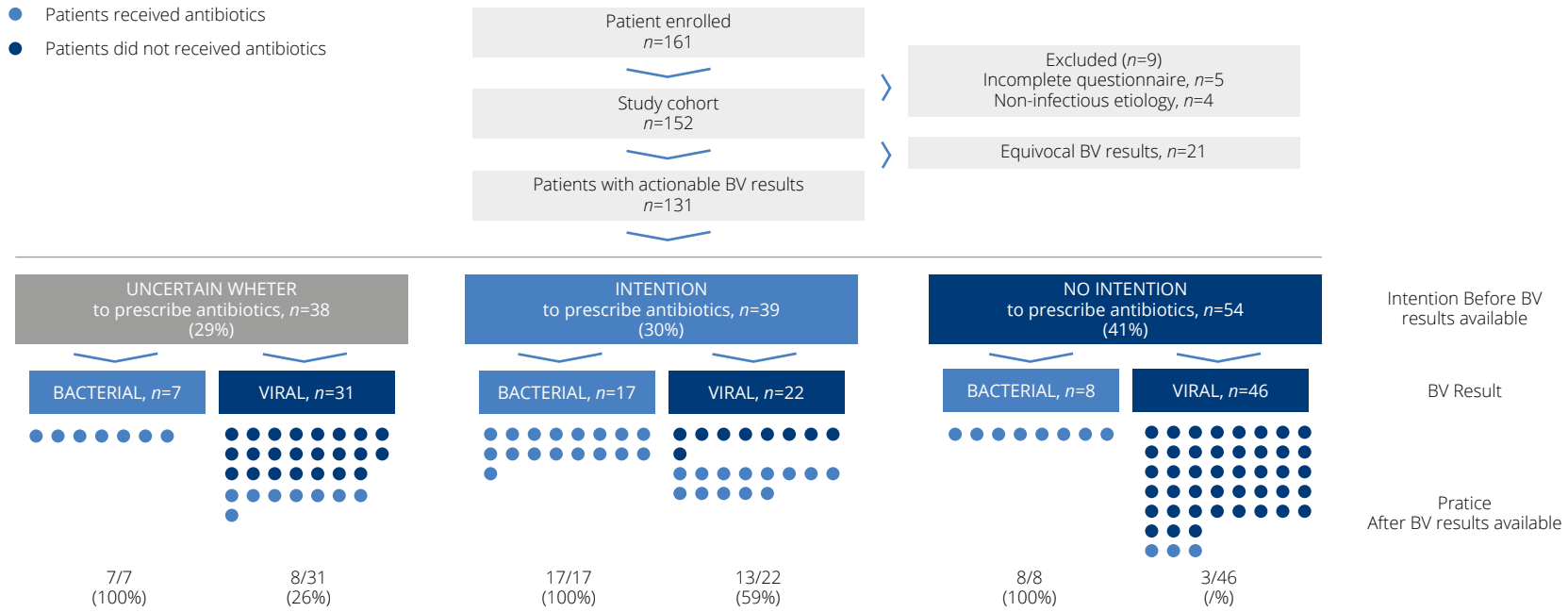
STUDY CHARACTERISTICS: 152 pediatric and adults (elderly includes) patients with suspected bacterial or viral infections LRTI presenting at Emergency Department and Urgent Care Centers.
The impact of MeMed BV was evaluated in 131 patients with actionable results

Real World Evidences For Urgent Care Setting-adults and Pediatric Patients

Kalmovich B et al. Biomedicines. 2023 Impact on Patient Management of a Novel Host Response Test for Distinguishing Bacterial and Viral Infections: Real World Evidence from the Urgent Care Setting

KEY MESSAGES:
The impact of BV on patient management was evaluated comparing the physician's intention to treat with antibiotics prior to receiving the BV results and the treatment prescription after the receipt of BV results. Overall **clinicians prescribed antibiotic in accordance with BV results in 81.7% (107/31) of all cases. In particular**:

- Treatment uncertainty (29.0%, 38 patients): prescription in accordance with BV in 78.9% of cases
- Treatment intention (29.8%, 39 patients): **BV aided in reducing unwarranted use of antibiotics in 41%** (9/22) of cases where physicians changed their patient management and acted in accordance with BV results
- No treatment intention (41.2%, 54 patients): **14.8%** (8/54) of patients had bacterial BV result and subsequently **treated with antibiotics representing potentially missed bacterial infections**



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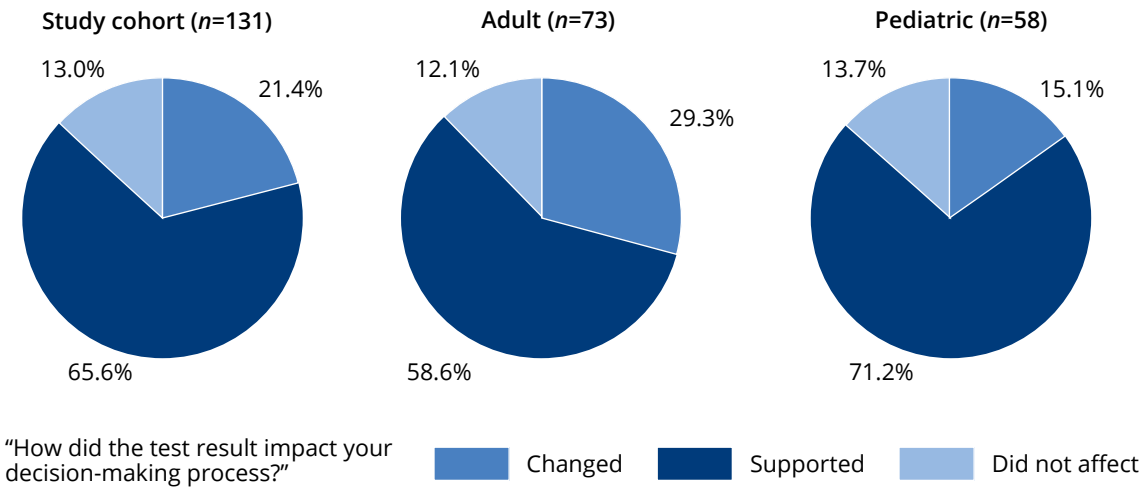
- **BV had a positive impact of patient management in 87.0% of cases** (100% in elderly patients). In particular, the MeMed BV test:
  - **Supported** the clinical decision making in **65.6%** (86/131) of all cases
  - **Changed** the physician's decisions regarding antibiotic treatment for **21.4%** (28/131) of all patients



Product availability subject to required regulatory approval

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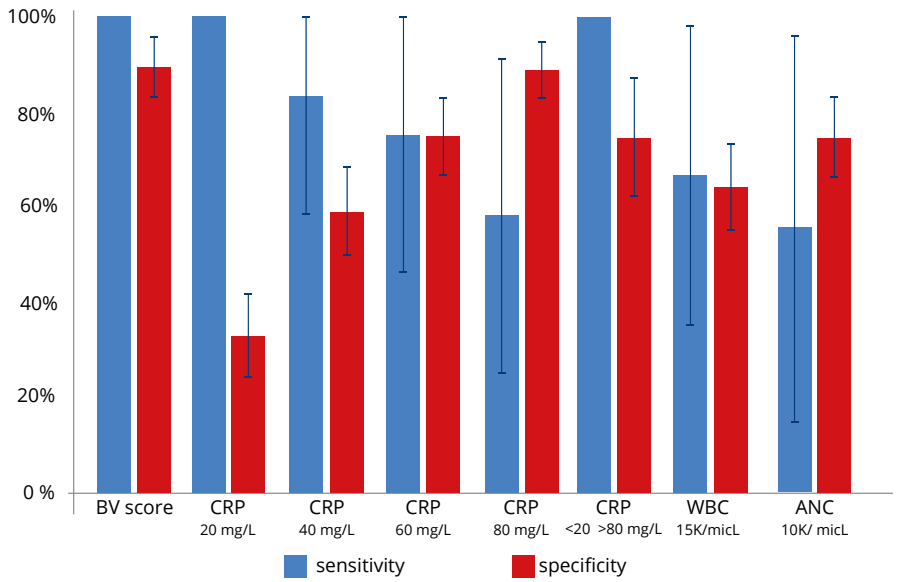
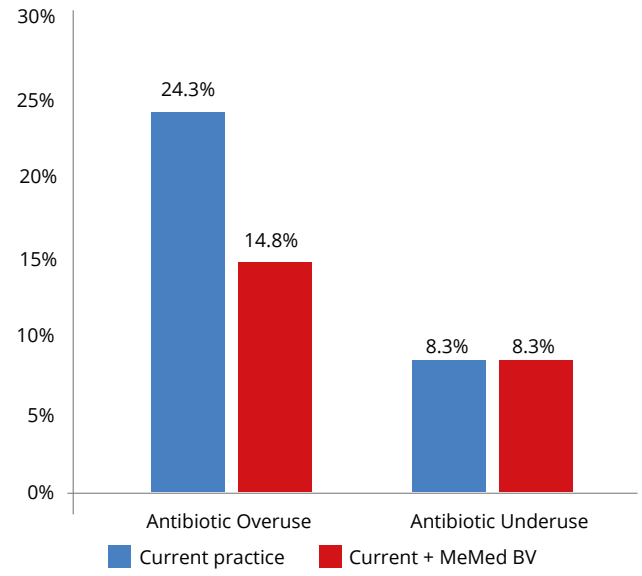
BV accurately differentiates viral from bacterial-viral co-infection in adenovirus PCR positive children

STUDY CHARACTERISTICS: 142 pediatric patients with adenovirus PCR-positive infection recruited at the emergency department and at hospital ward.

KEY MESSAGES:

- Similar to Cytomegalovirus and Epstein Barr Virus, Adenovirus can mimic a bacterial infection. **8-15% of pediatric adenoviral infections are complicated by bacterial co-infections**
- **BV outperformed routine** biomarkers, including **CRP, WBC and ANC** exibiting higher sensitivity and/or specificity and **correctly identifying children with adenoviral infections (without bacterial co-infection)**
- BV could potentially **reduce antibiotic overuse of 1.6-fold** with no significant impact on antibiotic underuse





- There are over 85 different types of human adenoviruses. PCR testing typically detects only common serotypes and in the case of lower RTIs, may not detect the virus. As **a host-based technology that demonstrates robust performance irrespective of viral strain or infection site**, BV addresses these limitations and can aid in management decisions for children with suspected adenoviral infections

BV Signature Accuracy in Pediatrics With Adenovirus Detection: ***Curiosity and Opportunity Sub-analysis***

Stein M et al.
Front Pediatr. 2022
BV score differentiates viral from bacterial-viral co-infection in adenovirus PCR positive children

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BV exhibits high diagnostic performance for febrile adults with suspected LRTI

STUDY CHARACTERISTICS: 490 adults patients with suspected LRTI recruited at emergency department.
Final diagnosis was attained in 415 patients

KEY MESSAGES:

- **BV accurately differentiated between bacterial and viral LRTI regardless of age, comorbidities or presence of a positive PCR for respiratory virus**. In particular, the test performance are manteined among **older patients** (≥65 years), where immunosenescence might be a concern and bacterial infections are more prevalent, and in patients with **COPD**, supporting the improvement of bacterial exacerbation diagnosis and the **antibiotic stewardship** in this population

BV Signature Accuracy in Adults: ***Observer Study***

Halabi S. et al. Clinical Microbiology and Infection 2023 Host test based on tumor necrosis factor-related apoptosis-inducing ligand, interferon gamma-induced protein-10 and C-reactive protein for differentiating bacterial and viral respiratory tract infections in adults: diagnostic accuracy study

	n°	Bacterial prevalence %	Eq %	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Study cohort	314	33.2	9.6	98.1	88.4	82.8	98.8
Ag– (y)							
18–40	92	25.0	12.0	100	91.5	81.5	100
40–65	102	25.5	7.8	96.2	91.2	80.6	98.4
65+	119	46.2	8.4	98.2	81.5	84.4	97.8
Days from symptom onset							
≤2 days	86	33.7	11.6	100	89.6	85.3	100
>2 days	228	32.9	8.8	97.3	88.1	81.8	98.3
Pre-recruitment antibiotics							
Yes	85	55.3	7.1	97.8	84.9	90.0	96.6
No	229	24.9	10.5	98.2	89.2	77.8	99.2
Comorbidity							
COPD	33	57.6	18.2	100	100	100	100

COPD, chronic obstructive pulmonary disease; Eq, equivocal; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval. a Number of patients assigned bacterial or viral reference standard diagnoses.

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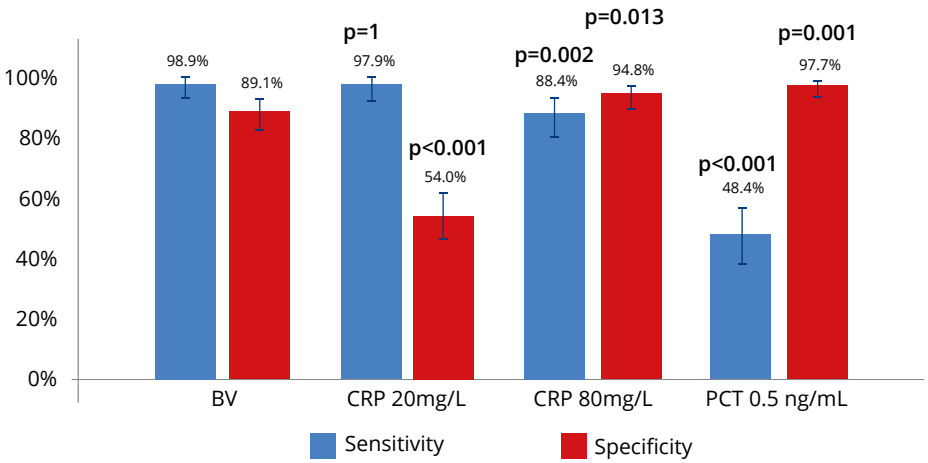
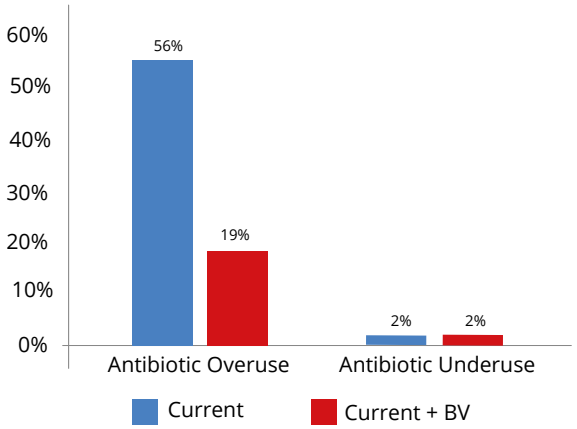
- BV **correctly identify co-bacterial infection in 96%** (24/25) of the patients with bacterial reference standard diagnosis and positive PCR viral detection
- The **higher diagnostic accuracy** of **BV** in comparis**on to CRP and PCT supports the reduction of the diagnostic uncertainty and the potential antibiotic overuse (three-fold decrease, from 56% to 19%)** among patients with suspected LRTI





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Real-world data support the clinical value of the BV test when there is diagnostic uncertainty at the patient's first assessment

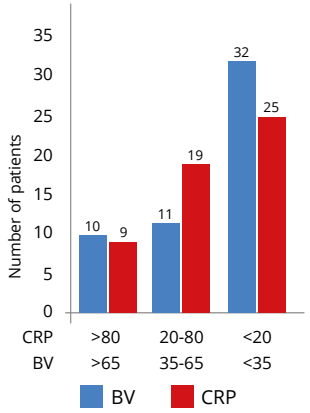
STUDY CHARACTERISTICS: 111 pediatric patients aged > 90 days presenting to the ED or from the Wwrd with symptoms of a respiratory tract infection or fever without an apparent focus compatible with COVID-19

BV signature real-life impact on clinical decision making: DIRECTOR *Sub-Analysis*

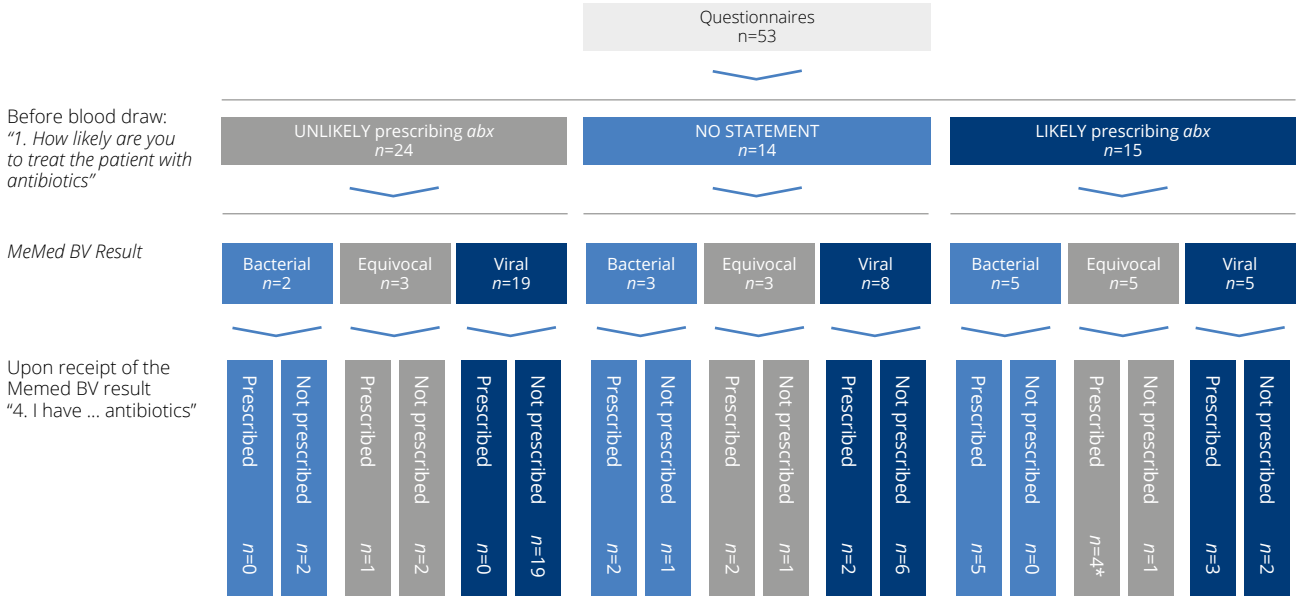
Fröhlich F et al. Infection. 2023 Expression of TRAIL, IP-10, and CRP in children with suspected COVID-19 and real-life impact of a computational signature on clinical decision-making: a prospective cohort study

KEY MESSAGES:

- **No statistically significant** difference in host-response biomarker expressions and the BV score **for children with SARS-CoV-2 infections as compared to children with other viral or bacterial infections**
- **BV scores were less often equivocal than CRP yielded inconclusive values between 20 and 80mg/L**. This is of particular importance, since the clinical utility of CRP in an early stage of the infection is often hampered by this area of uncertainty in which CRP offers inferior diagnostic accuracy with respect to detecting serious bacterial infections in children
- **BV score in pediatric ED** guides clinical decision-making and **improves the appropriate use of antibiotics**: 64% of pediatricians considered BV helpful in clinical practice, for confirming (52%) as well as changing treatment decision (12%)



Comparison of categorizing disease etiology by BV and CRP (mg/L); BV 0–34: viral etiology, BV 35–65 equivocal etiology, BV 66–100 bacterial etiology; n = 53



Intention to prescribe antibiotics before and after BV result (* already treated with antibiotics, prescribed by family pediatrician); *abx* antibiotics

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BV diagnostic accuracy in febrile pediatric patients: *SPIRIT Study*

Klein A et al. Pediatrics. 2023 Diagnostic Accuracy of a Real-Time Host-Protein Test for Infection

BV delivers clarity in ambiguous febrile pediatric patients

STUDY CHARACTERISTICS: a retrospective, observational study conducted in two medical centers on 3003 children with fevers and symptoms of acute infection that were recruited from emergency department or from the pediatric ward; 1410 of these patients resulted eligible for the analysis

KEY MESSAGES:

- **BV outperformed physician initial assessment in the entire eligible cohort** (1410 patients; sensitivity 84.8% vs. 63.1%, specificity 93.1% vs. 80.9%); **(Tab.1)**
- For 76/1410 patients for whom laboratory tests were available to the physician BV demonstrated significantly higher specificity than the physician's initial etiological suspicion (sensitivity 84.2% vs. 75.0%, specificity 91.5% vs. 75.6%); **(Tab.1)**
- The BV test distinguished bacterial from viral infection with high sensitivity and specificity in cases (736 patients) considered difficult to diagnose after the ED physician's initial assessment (sensitivity 89.7% vs. 66.2%, and specificity 92.6% vs. 72.0%); **(Tab1, Fig.1)**
- **Early availability of the BV test during patient evaluation in the emergency setting adds value to the physician's initial suspicion and can help support medical decision making, thereby potentially expediting triage and reducing additional workup**

		Sensitivity	Specificity	PPV	NPV	Equivocal Rate (%)
Eligible cohort, *n* = 1410	BV	84.8 (79.2-89.0)	93.1 (91.4-94.5)	71.5 (65.6-76.7)	96.8 (95.5-97.7)	12.3
	Physician	63.1 (56.2-69.5)	80.9 (78.3-83.3)	41.7 (36.2-47.3)	91.0 (88.9-92.8)	20.9
Patients for whom laboratory test were available, *n* = 76	BV	84.2 (61.6-95.3)	91.5 (79.5-97.2)	80.0 (57.8-92.5)	93.5 (81.8-98.4)	13.2
	Physician	75.0 (52.8-89.2)	75.6 (61.2-85.9)	57.7 (38.9-74.5)	87.2 (72.8-94.9)	14.5
Low certainty cohort, *n* = 736	BV	89.7 (82.4-94.3)	92.6 (90.0-94.5)	70.6 (62.4-77.6)	97.8 (96.1-98.8)	12.4
	Physician	66.2 (54.8-76.0)	72.0 (67.2-76.4)	32.2 (25.3-40)	91.4 (87.5-94.1)	39.9

Tab. 1: BV diagnostic accuracy compared to the physician's etiological suspicion. PPV, Positive Predictive Value; NPV, Negative Predictive Value

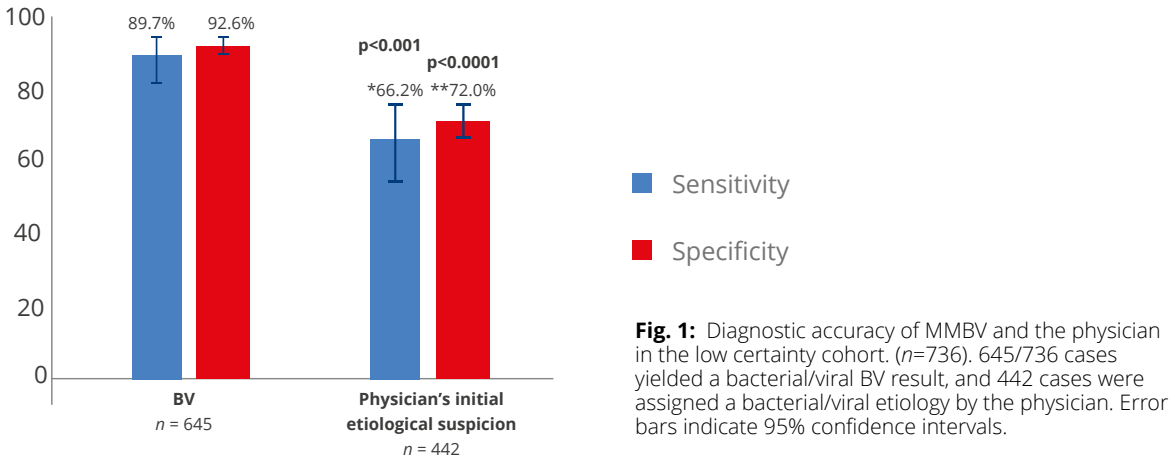

Fig. 1: Diagnostic accuracy of MMBV and the physician in the low certainty cohort. (*n*=736). 645/736 cases yielded a bacterial/viral BV result, and 442 cases were assigned a bacterial/viral etiology by the physician. Error bars indicate 95% confidence intervals.

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