

APPLYING MOLECULAR SYNDROMIC TESTING ALONGSIDE BIOMARKERS: THE PROGRESS PARADIGM



Εθνικόν και
Καποδιστριακόν
Πανεπιστήμιον
Αθηνών

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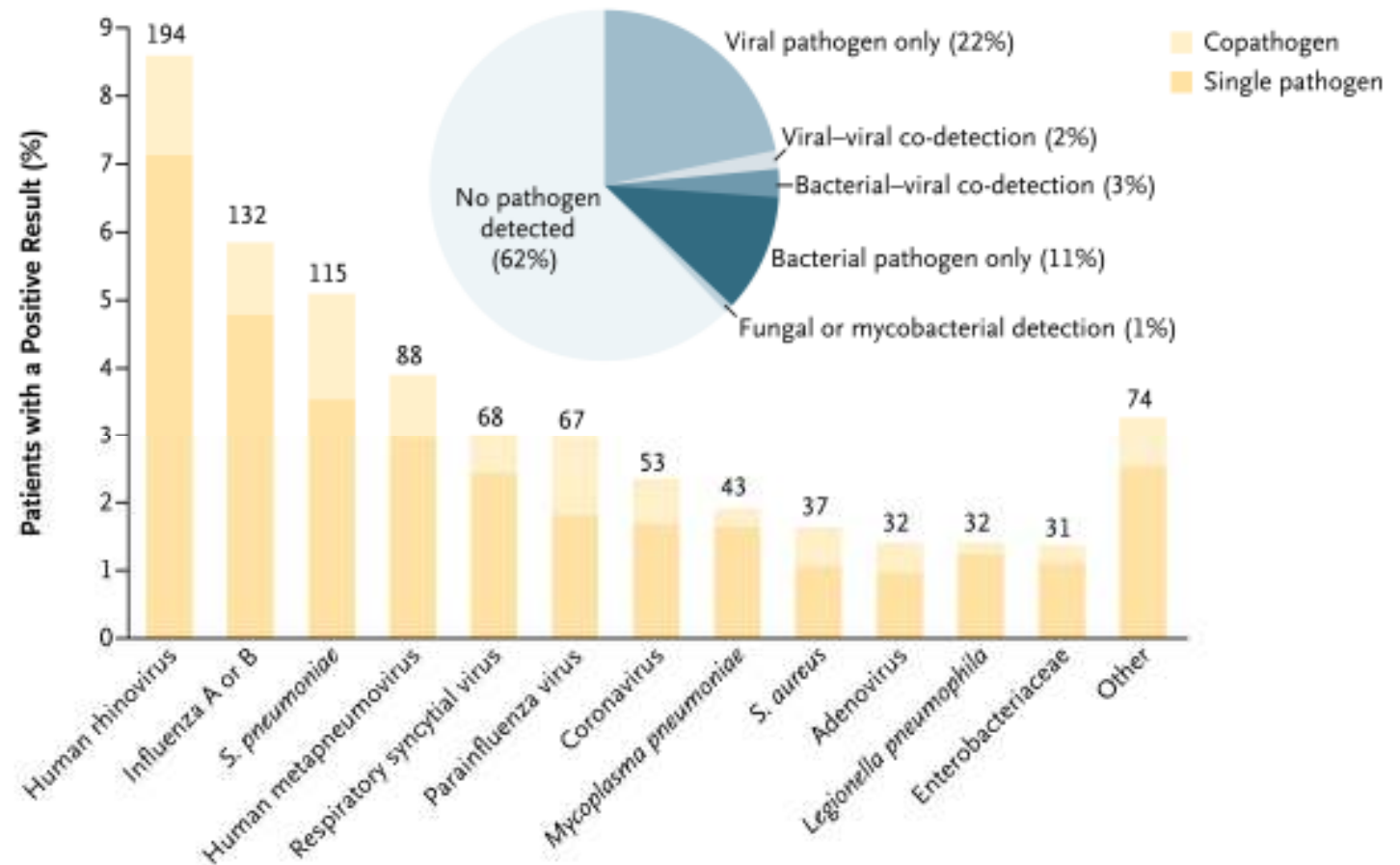
CONFLICT OF INTEREST DISCLOSURE

- Honoraria (paid to the University of Athens) from bioMérieux, Greece, Biotest AG Germany, MSD Hellas, Pfizer Hellas
- Consultant for InflaRx GmbH, Xbiotech Inc
- Independent educational grants (paid to the University of Athens) from AbbVie USA, AxisShield UK, Astellas Pharma Europe, Biotest AG Germany, BioMérieux France, InflaRx GmbH, the Medicines Company, ThermoFisher Brahms GmbH, Xbiotech Inc
- Funding by the FrameWork 7 program HemoSpec (granted to the University of Athens) and by the Horizon 2020 ITN European Sepsis Academy

EPIDEMIOLOGY OF CAP IN USA: EPIC STUDY

(Jain S, et al. *N Engl J Med* 2015; 373: 415)

- January 2010-June 2012: 2,259 patients
- 3 Chicago hospitals, 2 Nashville hospitals

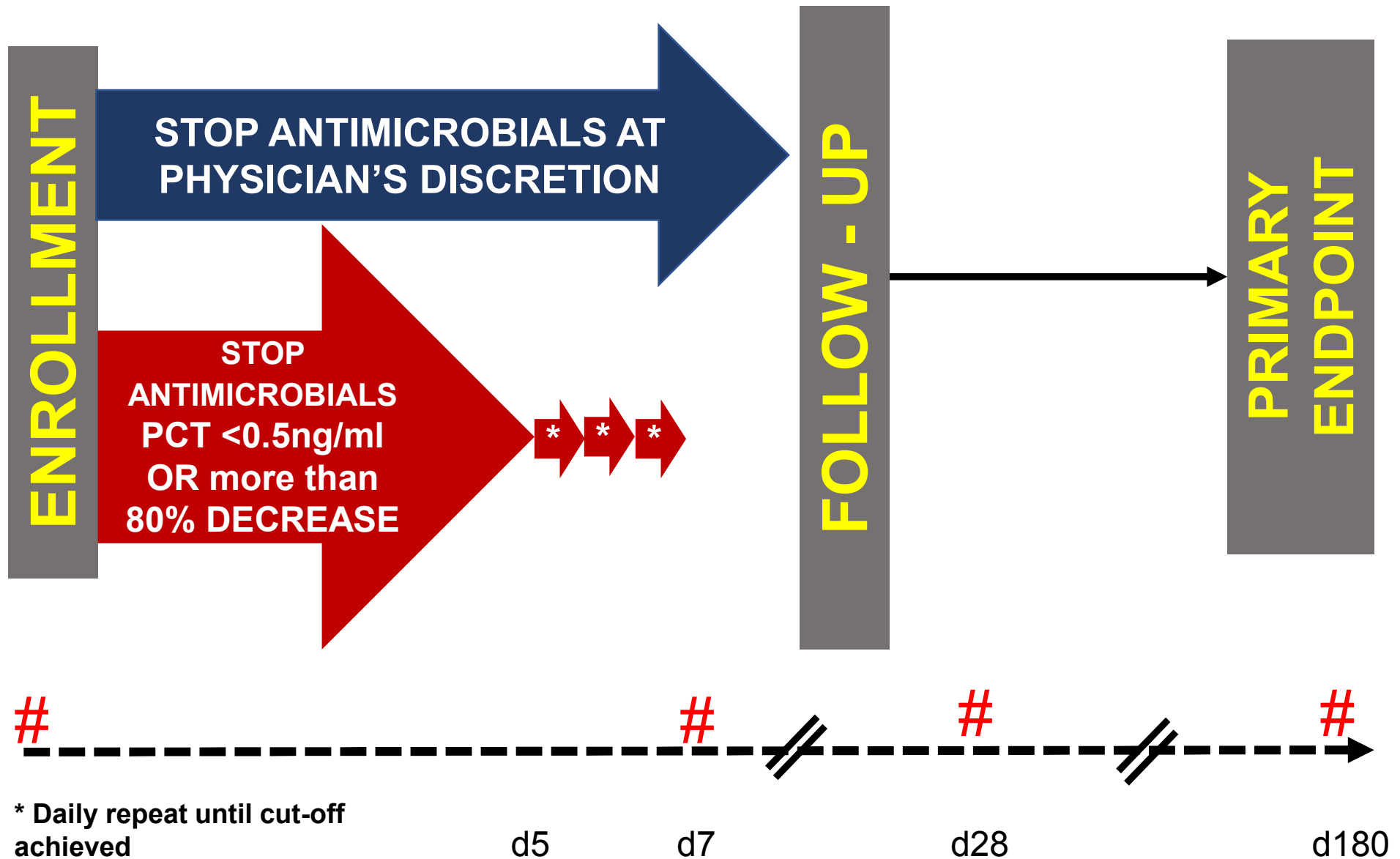


AIM OF THE STUDY

- Can epidemiology be affected by the co-presence of sepsis?
- No available study with the new Sepsis-3 definitions
- Can microbiology detection impact on inflammatory burden?
- Sub-analysis of the PROGRESS trial (A randomized prospective clinical trial to assess the role of procalcitonin-guided antimicrobial therapy to reduce long-term infections sequelae)

PROGRESS STUDY DESIGN

(ClinicalTrials.gov: NCT03333304; EudraCT number: 2017-002011-33)



Inclusion Criteria:

- Male or Female
- Age \geq 18 years
- Sepsis by Sepsis-3 definitions (SOFA \geq 2 outpatients/ SOFA increase \geq 2 in patients)
- Lung infection (Community-acquired pneumonia / hospital-acquired pneumonia, ventilator-associated pneumonia) OR Acute Pyelonephritis OR Primary bacteremia

Exclusion Criteria:

- Deny to consent
- Pregnancy-lactation
- Infections requiring prolonged antibiotic treatment
- Virus or parasite Infections
- Tuberculosis
- Cystic Fibrosis
- Severely Immunocompromised patients

MICROBIOLOGY METHODS

- ✓ Blood cultures
- ✓ Sputum cultures
- ✓ Pleural fluid cultures
- ✓ Antigen detection of *Legionella* and *S. pneumoniae* in urine (BINAX)
- ✓ BIOFIRE® FILMARRAY® in sputum

All samples obtained within 24 hours of admission prior to administration of antibiotics

BIOFIRE® FILMARRAY® Pneumonia Panel *plus*



Bacteria (semi quantitative)	Antibiotic Resistance Genes
<i>Acinetobacter calcoaceticus-baumannii</i> complex	ESBL
<i>Enterobacter cloacae</i>	CTX-M
<i>Escherichia coli</i>	
<i>Haemophilus influenzae</i>	Carbapenemases
<i>Klebsiella aerogenes</i>	KPC
<i>Klebsiella oxytoca</i>	NDM
<i>Klebsiella pneumoniae</i> group	Oxa48-like
<i>Moraxella catarrhalis</i>	VIM
<i>Proteus</i> spp.	IMP
<i>Pseudomonas aeruginosa</i>	
<i>Serratia marcescens</i>	Methicilin Resistance
<i>Staphylococcus aureus</i>	mecA/mecC and MREJ
<i>Streptococcus agalactiae</i>	
<i>Streptococcus pneumoniae</i>	
<i>Streptococcus pyogenes</i>	

Atypical Bacteria (Qualitative)	Viruses
<i>Legionella pneumophila</i>	Influenza A
<i>Mycoplasma pneumoniae</i>	Influenza B
<i>Chlamydia pneumoniae</i>	Adenovirus
	Coronavirus
	Parainfluenza virus
	Respiratory Syncytial virus
	Human Rhinovirus/Enterovirus
	Human Metapneumovirus
	Middle East Respiratory Syndrome Coronavirus (MERS-CoV)*
	* MERS-CoV will only be available on the Pneumonia Panel <i>plus</i>



STUDY ENDPOINTS

Primary endpoint

- Ability of respiratory FilmArray® panel to detect severe pneumonia pathogens compared to conventional microbiology
(# epidemiology of severe pneumonia admitted to hospital)

Secondary endpoints

- Association of pneumonia FilmArray® panel with PCT
- Association of pneumonia FilmArray® panel with the inflammatory host response

Exploratory endpoint

- Detection of resistance by pneumonia FilmArray® panel

POWER OF THE STUDY

Hypothesis elements

- Pathogen detection by conventional microbiology 30%
- Pathogen detection of respiratory FilmArray®: 55%
- Alpha: 5%
- Power 90%

Sample size

- 88 patients

Power and sample size (version 3.1.2)

266 ENROLLED SEPSIS PATIENTS

10 consent withdrawal and
request for removal of all data

256 INTENTION-TO-TREAT POPULATION

101 other infection (acute
pyelonephritis, primary
bloodstream infection)

155 PATIENTS WITH LOWER RESPIRATORY TRACT INFECTIONS

Community-acquired pneumonia: No contact with healthcare setting ≥ 90 days

Healthcare-associated pneumonia: Chronic hemodialysis or residency in long-term care facilities or hospitalization ≤ 3 months

+ ALL

- New chest X-ray infiltrate
- ≥ 2 of: cough, dyspnea, auscultatory findings consistent with consolidation
- ≥ 1 of: PCT ≥ 0.25 $\mu\text{g/l}$, $\text{pO}_2 \leq 60\text{mmHg}$, $\text{SaO}_2 \leq 90\%$, RR ≥ 20 breaths/min

90 PATIENTS WITH AVAILABLE SPUTUM SAMPLES

PATIENTS DEMOGRAPHICS (1)

		EPIC*
Gender male, no. (%)	56 (62.2)	NA
Age (years, mean \pm SD)	75.8 \pm 12.3	NA
APACHE II (mean \pm SD)	3.0 \pm 4.6	NA
SOFA (mean \pm SD)	4.3 \pm 2.4	NA
Charlson's comorbidity index, mean \pm SD	5.2 \pm 2.0	NA
Diabetes mellitus 2, no. (%)	30 (33.3)	597 (26.0)
Chronic heart failure, no. (%)	17 (18.9)	810 (35.0)
Chronic obstructive pulmonary disease, no. (%)	20 (22.2)	968 (42.0)
Procalcitonin (μ g/l), median (IQR)	0.46 (2.53)	NA
C-reactive protein (mg/l), median (IQR)	99.6 (165.8)	NA
White blood cells (/mm ³), mean \pm SD	11,088 (4,910)	NA

IQR: inter-quartile range

NA: non-available

*Jain S, et al. *N Engl J Med* 2015; 373: 415

PATIENTS DEMOGRAPHICS (2)

	PROGRESS	EPIC*	p**
Community-acquired pneumonia, no. (%)	56 (62.2)	2320 (100)	<0.001
Healthcare-associated pneumonia, no. (%)	31 (34.4)	0 (0)	<0.001
Pneumonia severity index median (IQR)	113 (88-135)	76 (52-103)	NA
Class 1-3, no.(%)	23 (25.6)	1510 (65.0)	<0.001
Class 4, no.(%)	35 (38.9)	606 (26.0)	0.007
Class 5, no.(%)	32 (35.6)	204 (9.0)	<0.001
In-hospital mortality, no. (%)	22 (24.4)	52 (2.0)	<0.001
28-day mortality, no. (%)	23 (25.6)	NA	NA

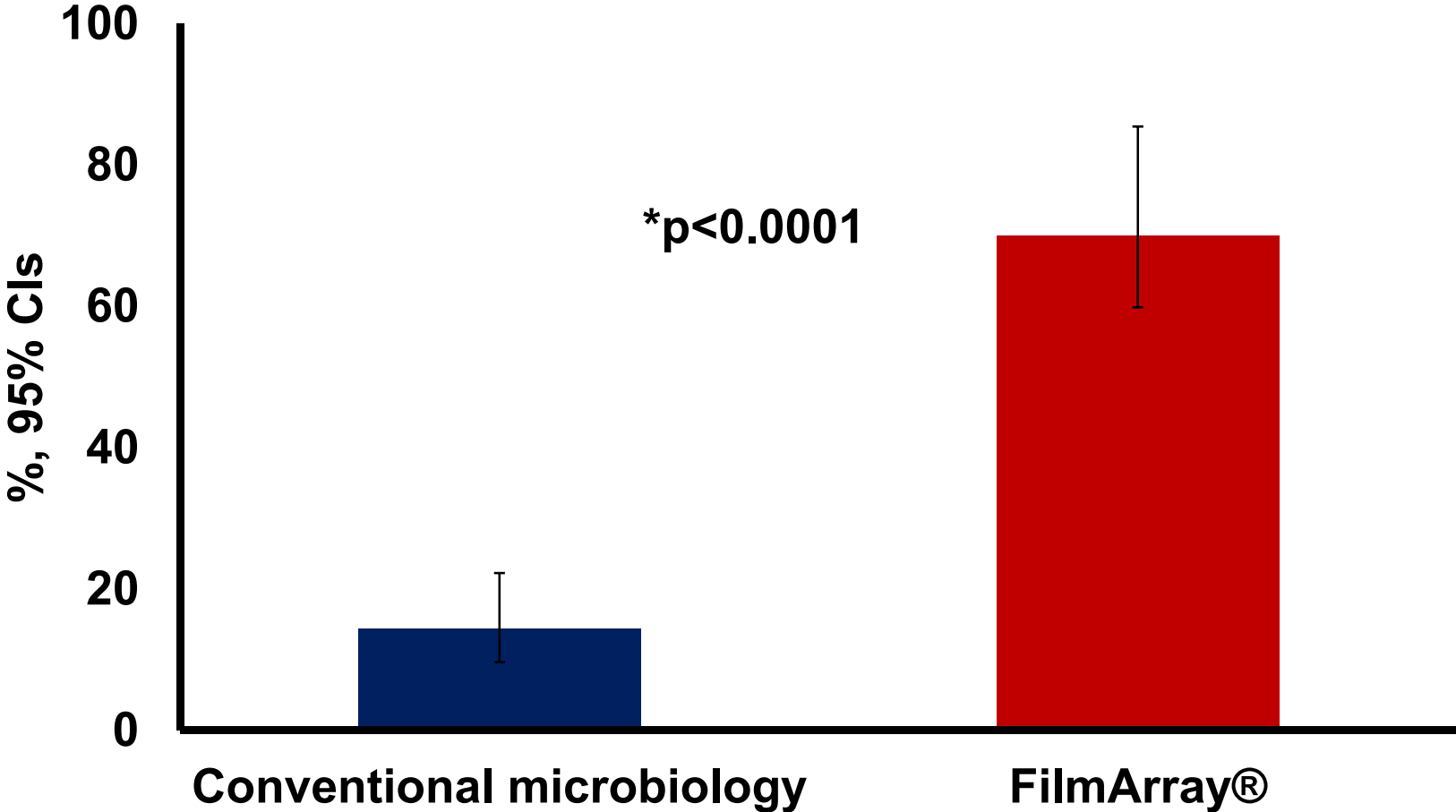
*Jain S, et al. *N Engl J Med* 2015; 373: 415

**Chi-square test

IQR: inter-quartile range

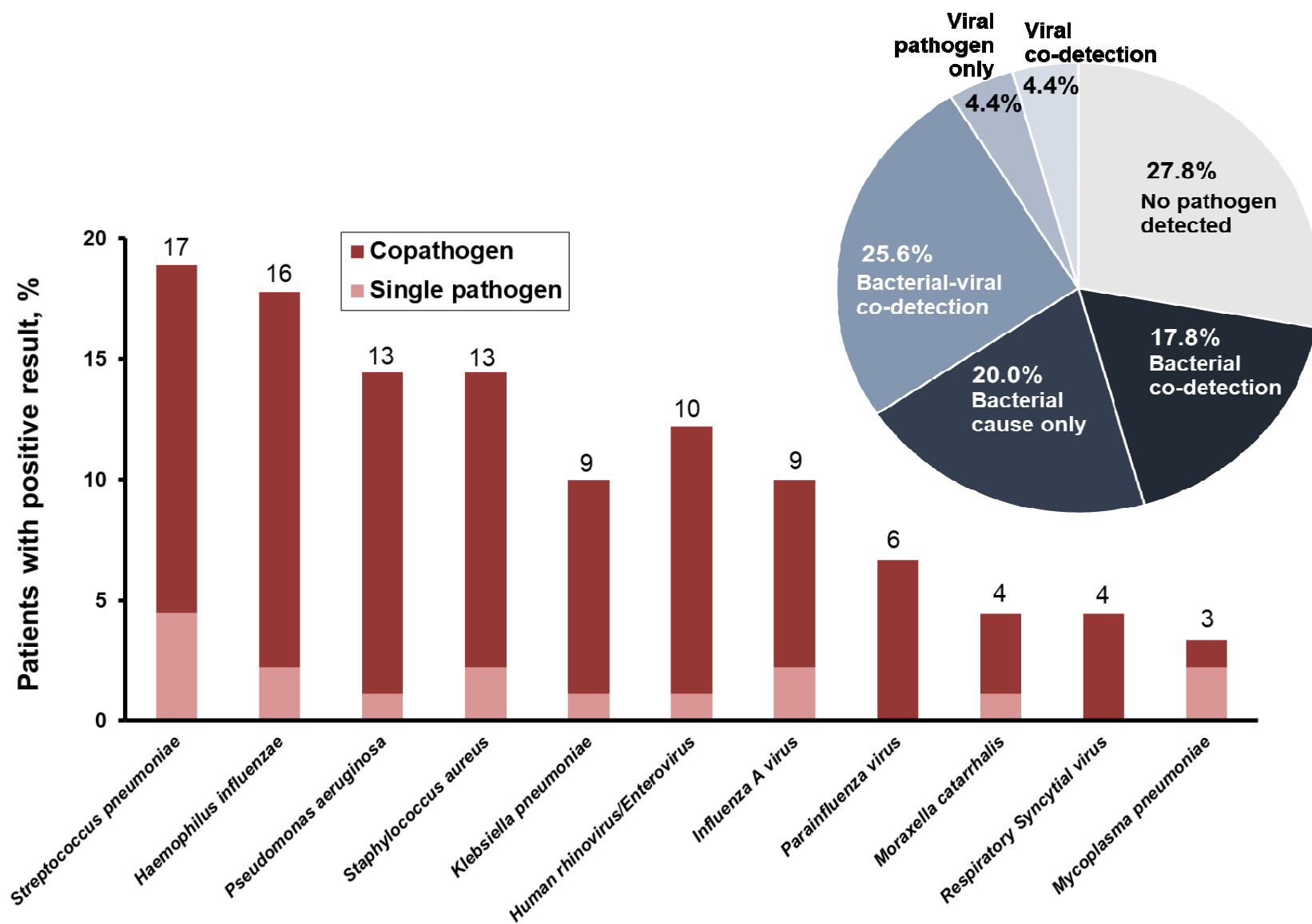
NA: non-available

PRIMARY ENDPOINT COMPARATIVE DETECTION OF PATHOGENS



*by the Fisher exact test
CI: confidence interval

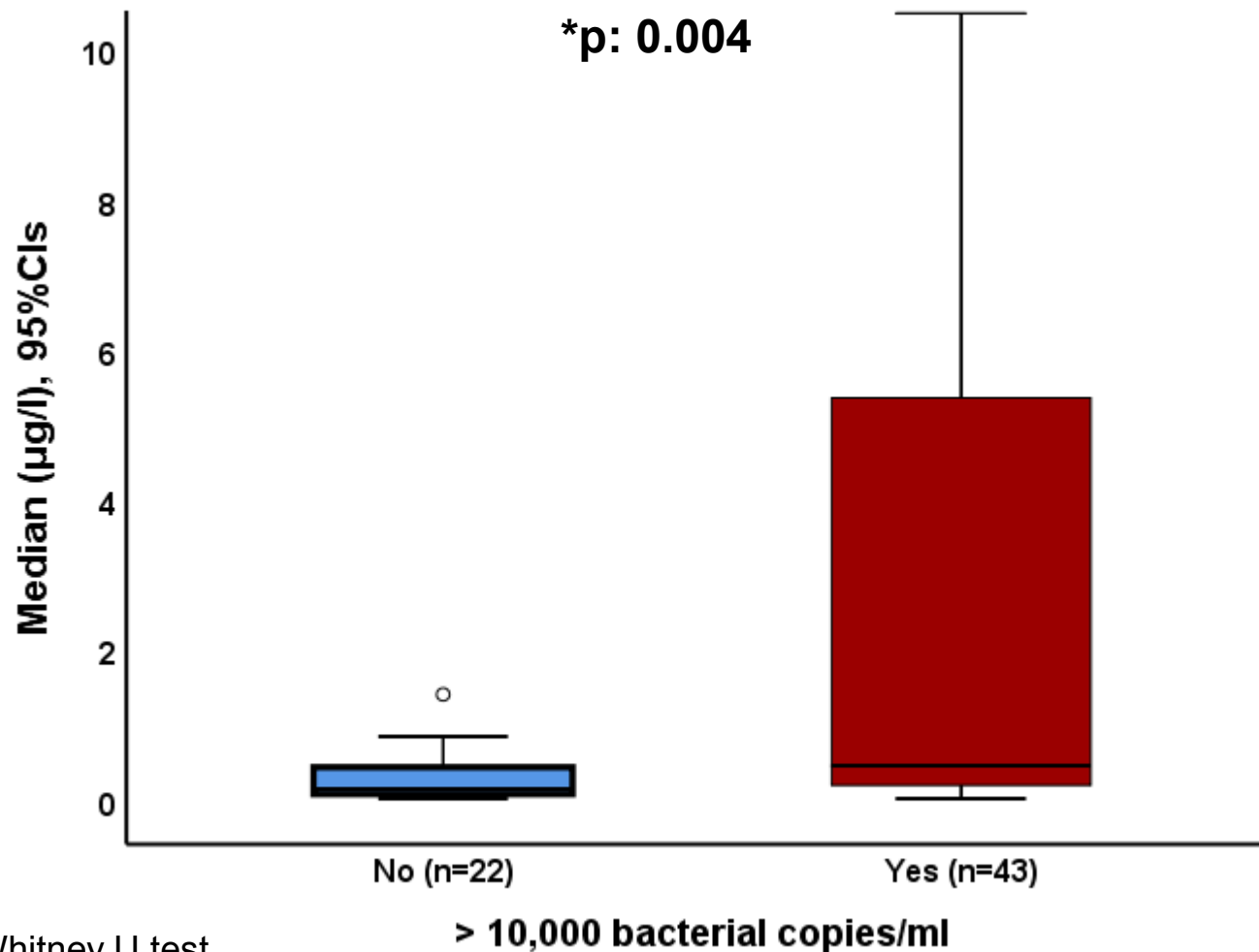
PRIMARY ENDPOINT: EPIDEMIOLOGY



SECONDARY ENDPOINT 1

ASSOCIATION OF PCT WITH PNEUMONIA

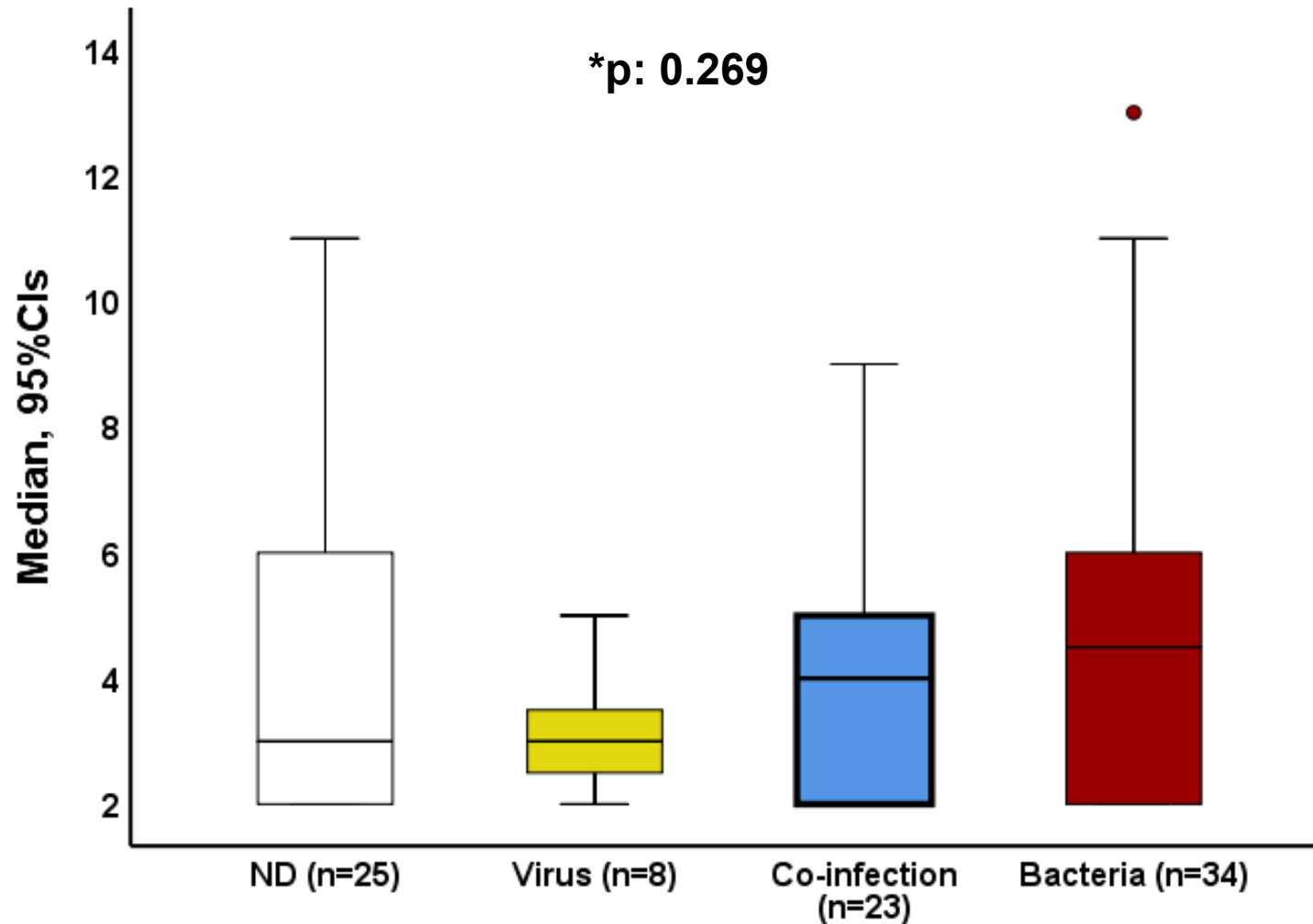
FILMARRAY® LOAD



*by the Mann-Whitney U test
CI: confidence interval

SECONDARY ENDPOINT 2

ASSOCIATION OF SOFA SCORE WITH FILMARRAY® RESULTS



*by ANOVA

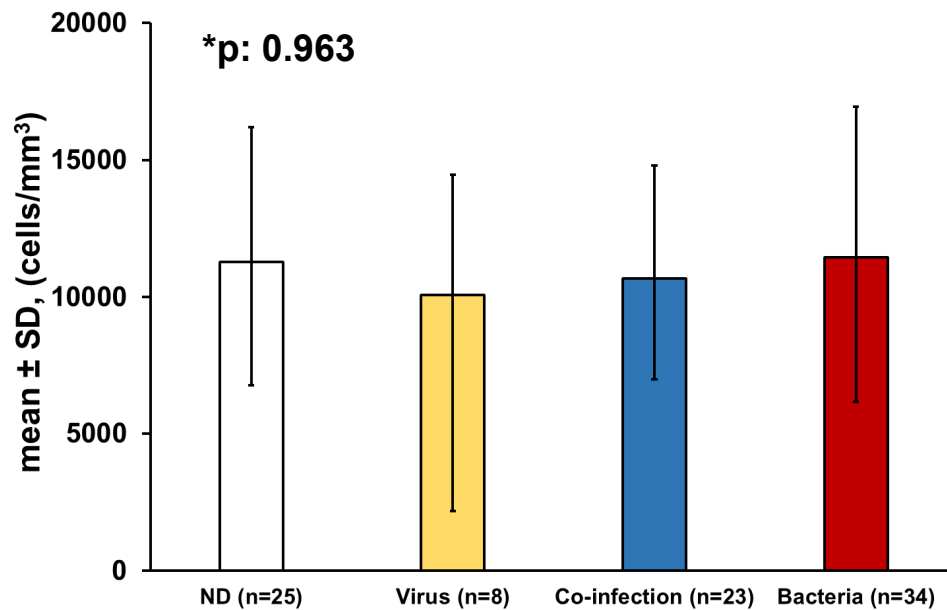
CI: confidence interval

ND: not detected

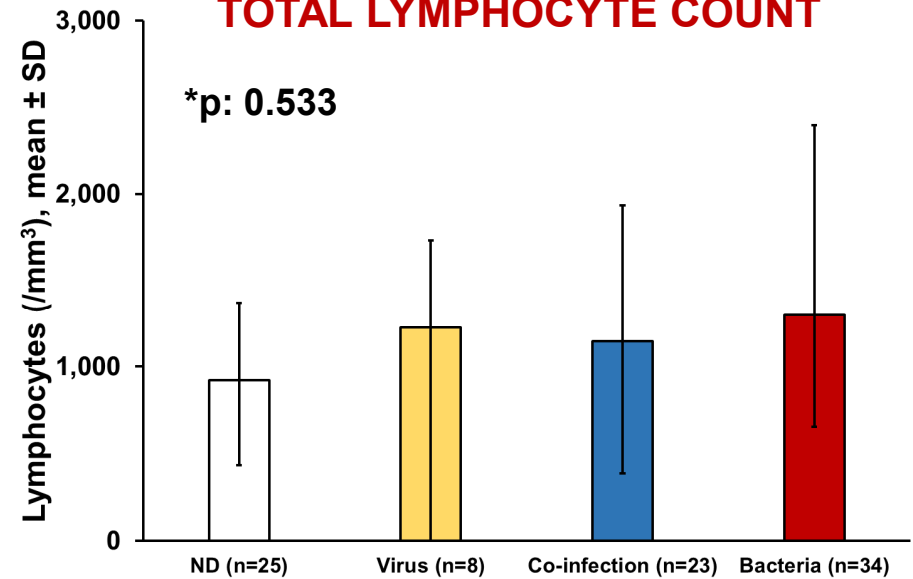
SECONDARY ENDPOINT 2

ASSOCIATION OF BLOOD CELL COUNTS WITH FILMARRAY® RESULTS

TOTAL WHITE BLOOD CELL COUNT



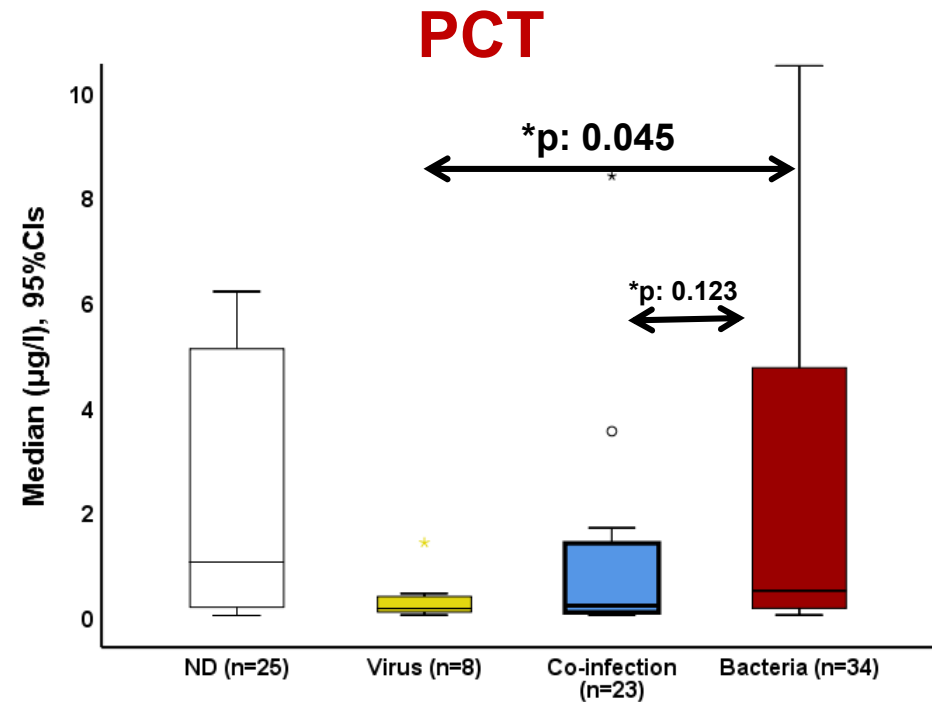
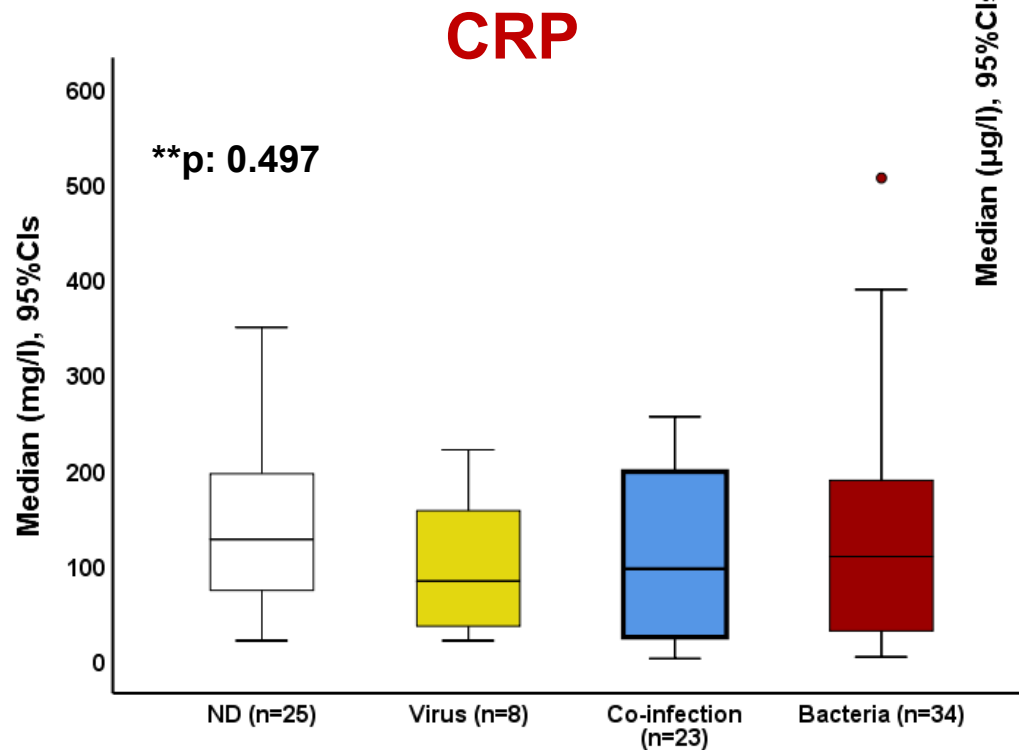
TOTAL LYMPHOCYTE COUNT



*by ANOVA
ND: not detected
SD: standard deviation

SECONDARY ENDPOINT 2

ASSOCIATION OF INFLAMMATORY MARKERS WITH FILMARRAY® RESULTS

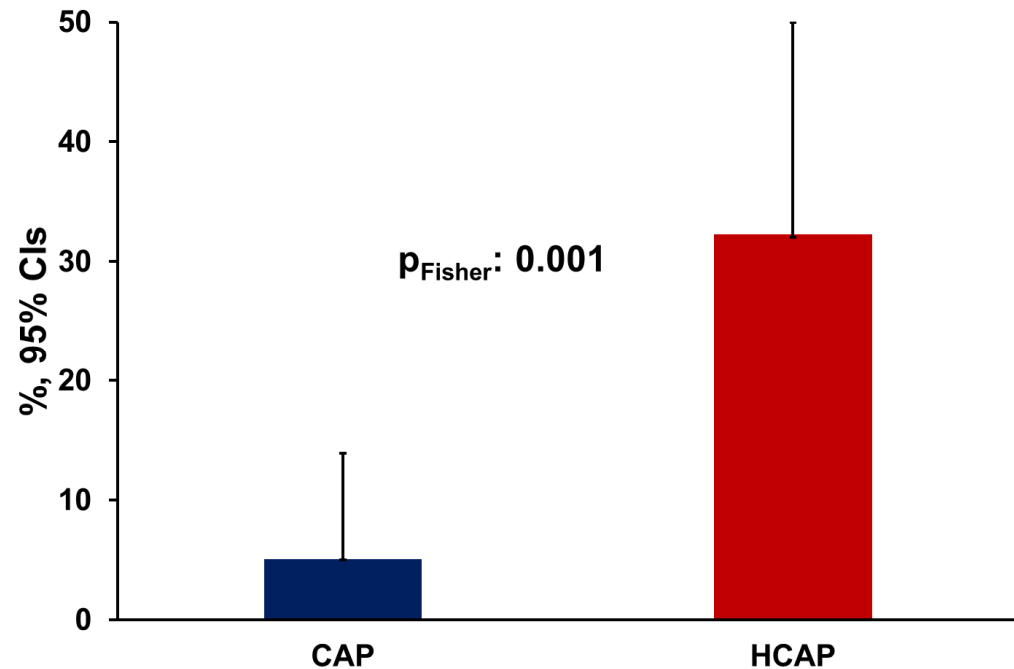


*by the Mann-Whitney U test
**by the Kruskal Wallis test
CI: confidence interval
ND: not detected

EXPLORATORY ENDPOINT: RESISTANCE DETECTION

None	77 (85.6%)
KPC	4 (4.4%)
CTX-M	6 (6.6%)
VIM	2 (2.2%)
NDM	2 (2.2%)
mecA/C	5 (5.5%)

ASSOCIATION BETWEEN RESISTANCE DETECTION AND EPIDEMIOLOGY RISK FACTORS



CAP: community-acquired pneumonia
HCAP: healthcare-associated pneumonia

CONCLUSIONS

BIOFIRE® FilmArray® Pneumonia Panel plus

- Detects severe pneumonia pathogens at significantly greater rate than conventional microbiology
- Viral pathogens often co-exist (pave the way to bacteria?)

Association with inflammation

- $>10^5$ bacterial copies/ml signify higher PCT (true pathogens)
- Lack of differences between type of detected pathogens and degree of inflammation

Resistance detection

- Significantly greater in HCAP (reflection of epidemiology risk)



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