High Throughput Respiratory Panel Testing on an Open Array

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Objectives

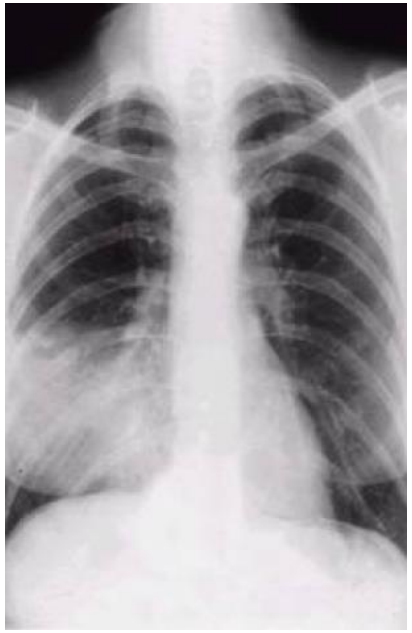
- The Diagnostic Challenge
- Syndromic Panels (respiratory)
- Open Array Concept
- Respiratory Array Comparisons
- Automation
- Future applications

A Routine Diagnostic Challenge

Presentation and Initial Testing

- Abrupt onset of fever, cough, and chest pain
- Examination: shallow respirations, “splinting”, rales, bronchial breath sounds
- Chest x-ray: Right middle lobe infiltrate
- Laboratory: white blood cell count 22,000 with 78% PMNs, 12% bands, 8% lymphocytes, 2% monocytes
- Sputum gram stain: respiratory epithelial cells, mixed bacterial flora

Acute Pneumonia in an Infant



Possible Pathogens

- Streptococcus pneumoniae
- Mycoplasma pneumoniae
- Legionella pneumoniae
- Chlamydophilapneumoniae
- Haemophilusinfluenzae
- Moraxella catarrhalis
- Staphylococcus aureus
- Streptococcus pyogenes
- Klebsiellapneumoniae
- Pseudomonas aeruginosa
- Francisellatularensis
- Mycobacterium tuberculosis
- Coxiellaburnetii
- Chlamydia psittaci
- **Respiratory viruses**
- Pneumocystis jirovecii
- Endemic fungi
- Non-infectious, eg. Granulomatosis with polyangiitis

Classic Microbiology Testing

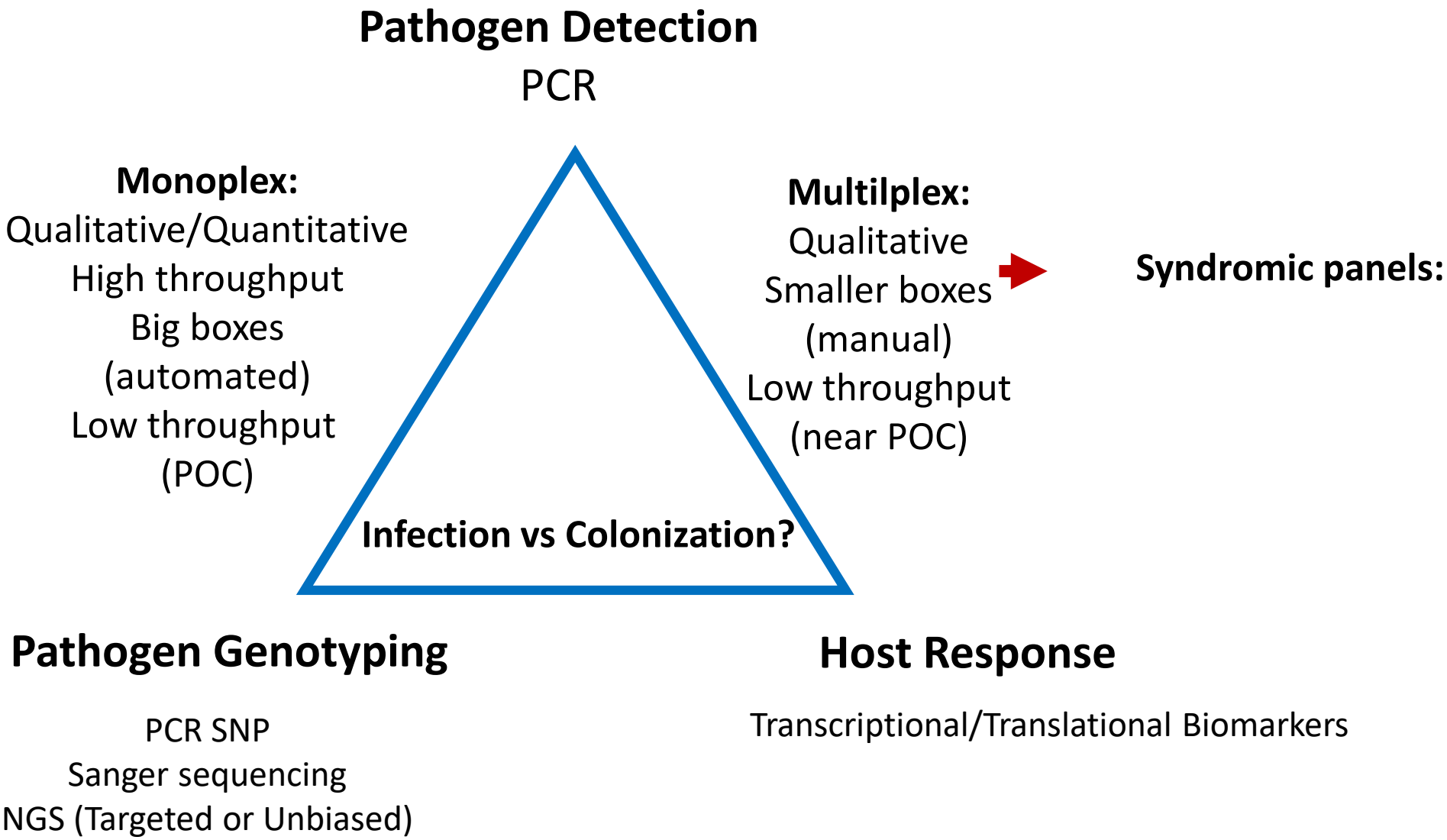
Slow
Insensitive
Labor intensive
Expensive

Molecular Microbiology Testing

Rapid
Sensitive
Less labor intensive
expensive

Courtesy Greg Storch

Landscape Molecular Infectious Disease Testing



Multiplex Test Options and Issues

- Conventional single/multi-well PCR (3-5 targets)
- Array based PCR (closed or open)
- Tagged beads
- Electronic arrays
- Gold nanoparticles

Rapid Panel Technologies (10-25 targets)

- Turn around time
- Large or small platform (POC)
- Ease of use/automation
- Throughput
- Integration into “routine” testing

Not integrated into routine testing

Limited Scalability

Expensive

Syndromic Panels

- Respiratory (upper and lower)
- Encephalitis/meningitis
- Blood sepsis
- Gastrointestinal

time sensitive

Greatest value:
Testing & communication of results are rapid
&
Infrastructure in place to act on the data!

- Transplantation
- Tick borne disease

less time sensitive

Review Accuracy and Clinical Impact Multiplex Viral Tests

Vos et. al Clin Infect Dis. 2019 Jan 28

- Trending toward decreased turn around times
- Trending toward reduced length of stay
- Increased appropriate use of oseltamivir (Influenza positive patients)
- No effect antibiotic prescriptions or duration
- No effect in-hospital isolation or number of hospital admissions
- Training and education of physicians critical for good outcomes
- Combination rapid testing and result-based guidelines effect clinical outcomes

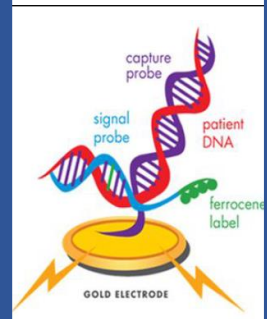
Respiratory Panel Issues

- Scope of Menu
- Performance (Sensitivity-Specificity)
- Speed and Scalability of testing
- Utilization of Results
- Impact Results
- Cost

At many institutions, cost drives degree of utilization of Syndromic Panel testing despite advantages over classic tests

Pinsky and Hayden J. Clin Microbiol May 29 2019

- Appropriate panel size depends on Pre-test probability of pathogen's presence
  - Healthy adult in Flu season (Flu AB)
  - Healthy infant (Flu AB, RSV, Adeno)
  - Lower respiratory, compromised patient (many viruses and bacteria)
- Additional targets
  - New viral variants
  - Resistance genes
  - "Rare" pathogens (metagenomic discoveries)?
  - Host response genes to determine infection /disease vs colonization?

Platform	NxTAG	FilmArray†	Verigene‡	ePlex	XT-8	Open Array RTM	Fusion
	Influenza A	Influenza A	Influenza A	Influenza A	Influenza A	Influenza A	Influneza A
	Influenza A H1	Influenza A H1	Influenza A H1	Influenza A H1	Influenza A H1		
	Influenza A H3	Influenza A H3	Influenza A H3	Influenza A H3	Influenza A H3	Influenza A/H3	
	-	Influenza A 2009 H1 N1	-	Influenza A 2009 H1N1	Influenza A 2009 H1N1	Influenza A 2009 H1	
Viral Targets	Influenza B	Influenza B	Influenza B	Influenza B	Influenza B	Influenza B	Influenza B
	Respiratory syncytial virus A	Respiratory syncytial virus	Respiratory syncytial virus A	Respiratory syncytial virus A	Respiratory syncytial Virus A	Respiratory syncytial Virus A	**Respiratory syncytial Virus** AB
	Respiratory syncytial virus B		Respiratory syncytial virus B	Respiratory syncytial virus B	Respiratory syncytial virus B	Respiratory syncytial virus B	
	Parainfluenza virus 1	Parainfluenza virus 1	Parainfluenza virus 1	Parainfluenza virus 1	Parainfluenza virus 1	Parainfluenza Virus 1	Parainfluenza Virua 1234
	Parainfluenza virus 2	Parainfluenza virus 2	Parainfluenza virus 2	Parainfluenza virus 2	Parainfluenza virus 2	Parainfluenza Virus 2	
	Parainfluenza virus 3	Parainfluenza virus 3	Parainfluenza virus 3	Parainfluenza virus 3	Parainfluenza virus 3	Parainfluenza virus 3	
	Parainfluenza virus 4	Parainfluenza virus 4	Parainfluenza virus 4	Parainfluenza virus 4	-	Parainfluenza virus 4	
	Meta-pneumovirus	Meta-pneumovirus	Meta-neumovirus	Meta-pneumovirus	Meta-pneumovirus	Meta-pneumovirus	**Meta-pneumovirus**
	Rhino/Enterovirus	Rhino/Enterovirus	Rhinovirus	Rhino/Enterovirus	Rhinovirus	Rhinovirus 1/2 Rhinovirus 2/2 Enterovirus	Rhinovirus
	Adenovirus	Adenovirus	-	Adenovirus	Adenovirus B/E	Adenovirus 2	Adenovirus species
					Adenovirus C		
	Bocavirus	-	-	-		Bocavirus	
	Coronavirus 229E	Coronavirus 229E		Coronavirus		Coronavirus 229 E	
	Coronavirus HKU1	Coronavirus NL63	-			Coronavirus HKU1	
	Coronavirus NL63	Coronavirus OC43				Coronavirus NL63	
						Coronavirus 043 Herpes virus 3/4/5/6	
Bacterial Targets	*M. Pneumoniae*	*M. pneumoniae*	-	*M. pneumoniae*		*M. Pneumoniae*	
	C. Pneumoniae	*C. Pneumoniae*	-	C. pneumoniae	-	*C. Pneumoniae* *Klebsiella pneumonia* *Staphylococcus aureus*	
	-	B. Pertussis	*B. pertussis*	-	-	B. Pertussis	
	-	B. parapertussis	B. parapertussis/bronchaspetica	-	-	B. parapertussis/bronchiseptica	
	-		*B. holmesil*	-	-		
						Legionella pneumophila	
						Streptococcus pneumonia *Haemophilus influenzae*	

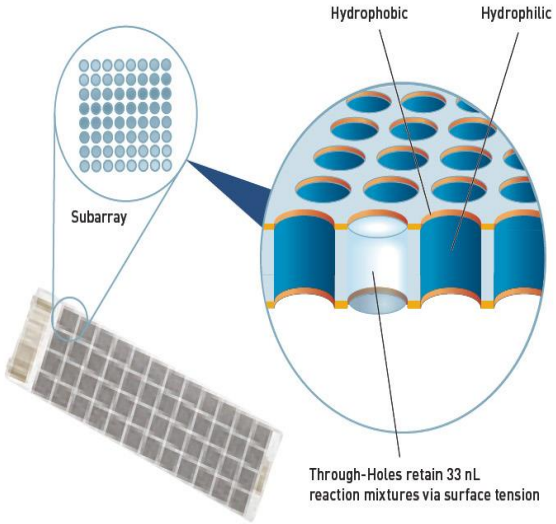
adapted from Schmitz & Tang Future Microbiol. 2018 13(16)

64 subarray wells

48 subarrays/chip

3,072 amplification wells /chip

33 nL PCR Rx mix



two sub-arrays per assay (triplicate targeting)

24 Samples per run

A 1	1	2	3	4	5	6	7	8
a	hMPV	hMPV	hMPV	HHV6	RV_1of2	RV_1of2	RV_1of2	RSVA
b	CoV_HKU1	CoV_229E	CoV_229E	HHV6	HHV3	HBoV	HBoV	RSVA
c	CoV_HKU1	CoV_NL63	CoV_229E	HHV6	HHV3	HHV3	HBoV	RSVA
d	CoV_HKU1	CoV_NL63	hPIV2	hPIV1	AdV_1of2	HHV4	Flu_A_H1	Flu_A_pan
e	CoV_OC43	CoV_NL63	hPIV2	hPIV1	AdV_1of2	HHV4	Flu_A_H1	Flu_A_pan
f	CoV_OC43	CoV_OC43	hPIV2	hPIV1	AdV_1of2	HHV4	Flu_A_H1	Flu_A_pan
g			hRNase P	B.atrophaeus	HHV5	HHV5		
h			hRNase P	Xeno RNA Control	Xeno RNA Control	HHV5		

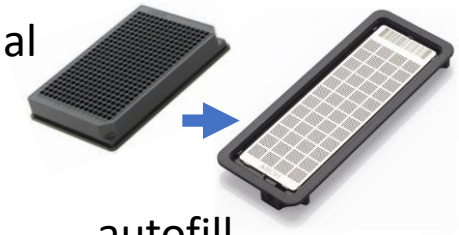
B1	1	2	3	4	5	6	7	8
a	L.pneumophila	L.pneumophila	K.pneumoniae	K.pneumoniae	RV_2of2	RV_2of2	RV_2of2	RSVB
b	L.pneumophila	EV_pan	K.pneumoniae	H.influenzae	S.aureus	M.pneumoniae	M.pneumoniae	RSVB
c	EV_D68	EV_pan	hPIV4	H.influenzae	S.aureus	S.aureus	M.pneumoniae	RSVB
d	EV_D68	EV_pan	hPIV4	H.influenzae	AdV_2of2	Bordetella	Flu_B_pan	Flu_A_H3
e	EV_D68	S.pneumoniae	hPIV4	C.pneumoniae	AdV_2of2	Bordetella	Flu_B_pan	Flu_A_H3
f	S.pneumoniae	S.pneumoniae	hPIV3	C.pneumoniae	AdV_2of2	Bordetella	Flu_B_pan	Flu_A_H3
g			hPIV3	C.pneumoniae	B.pertussis	B.pertussis		
h			hPIV3	B.atrophaeus	Xeno RNA Control	B.pertussis		

Workflow

NP swab specimen

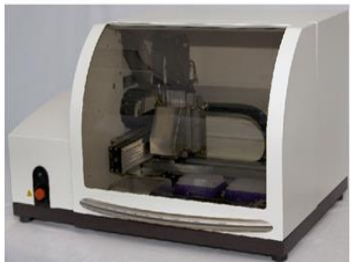
Chemagic Nucleic acid Extraction: 200 µL of sample eluates in 80 µL

manual

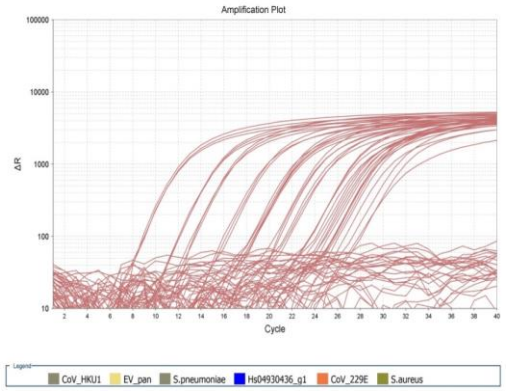


autofill

Reverse transcription and pre-amplification



Open Array plate loading using the AccuFill system



Real-time PCR and Data analysis

Description of Study and Testing

- 245 frozen archived nasopharyngeal (NP) swab specimens previously tested Genmark RVP
- 5 µL of each sample was reverse-transcribed/pre-amplified, diluted, added to Master Mix in 384-well plate, loaded to array with AccuFill
- Samples amplified on QuantStudio 12K Flex RT-PCR instrument
- Crossing threshold and amplification curve QC metrics were calculated by the instrument software
- Data filtration and resulting resulting

Results:

Analyte	Positive Percent Agreement (PPA)			Negative Percent Agreement (NPA)		
	TP/(TP + FN)	%	95% CI	TN/(TN + FP)	%	95% CI
Adenovirus (Adv)	17/18	94.4	72.7-99.8	232/232	100	98.4-100
Human Metapneumovirus	27/27	100	87.2-100	222/223	99.5	97.5-99.9
Influenza A	21/21	100	83.9-100	229/229	100	98.4-100
Influenza A H1-2009	3/3	100	29.3-100	247/247	100	98.5-100
Influenza A H3	18/18	100	81.4-100	232/232	100	98.4-100
Influenza B	13/14	92.9	66.2-99.82	235/236	99.6	97.7-99.9
Human Parainfluenza Virus 1	24/26	92.3	74.9-99.1	224/224	100	98.4-100
Human Parainfluenza Virus 2	1/1	100	2.5-100	250/250	100	98.6-100
Human Parainfluenza Virus 3	13/13	100	75.3-100	236/237	99.6	97.7-99.9
Rhinovirus (RV)	98/125	78.5	70.2-85.6	125/125	100	97.1-100
Respiratory Syncytial Virus A	6/6	100	54-100	242/243	99.6	97.7-99.9
Respiratory Syncytial Virus B	18/18	100	81.5-100	231/232	99.6	97.6-99.9

Version 2 of the panel improved the detection of RV significantly

Analyte	Positive Percent Agreement (PPA)			Negative Percent Agreement (NPA)		
	TP/(TP + FN)	%	95% CI	TN/(TN + FP)	%	95% CI
Rhinovirus	119/125	95.2	89.9-98.22	125/125	100	97.1-100

Dual Infections

Open Array RTM	GenMark RVP	No. of multiple positive samples
Flu A/H3+RV	Flu A/H3+RV	1
Flu B+RSVB	FluB+RSVB	1
FluB+ Enterovirus Pan	FluB+RV	1
AdV+ RV	AdV B-E +RV	1
AdV+ RV	AdV C+ RV	5
AdV+hPIV3	AdV+hPIV3	2
AdV+RSVB	AdV+RSVB	2
AdV+hMPV	AdV+hMPV	1
hPIV1+RV	hPIV1+RV	4
hPIV1+CoV_HKU1	hPIV1	1
hPIV1+RSVB	hPIV1	1
hPIV3+RV	hPIV3+RV	4
RV+CoV_NL63	RV	2
RV+CoV_OC43	RV	2
RV+CoV_HKU1	RV	1
RV+HBoV	RV	3
AdV+RV+RSVB	AdV+RV+RSVB	1

Detected in 33 (13.2 %) specimens

27 cases found in both methods

Open Array RTM co-detected coronavirus and bocavirus not available in the GenMark RVP panel

1 case had triple detection by both methods.

Upper respiratory *Staphylococcus aureus*, *Streptococcus pneumonia and Haemophilus influenzae* also detected by RTM

Open Array Automation for Pharmacogenomic, Cystic Fibrosis and AJ Genetic Panel Testing

(no pre-amplification but requires DNA normalization)

PCR setup:

***2 vertical subarrays to accommodate 120 PGx assays/sample.**

***46 samples run in duplicate/run, two controls, AMP NTC, Ext NTC.**

PGX v4.0 Standard Low Volume Runs

96-Well DNA Plate

	1	2	3	4	5	6	7	8	9	10	11	12
A	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
B	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	S24
C	S25	S26	S27	S28	S29	S30	S31	S32	S33	S34	S35	S36
D	S37	S38	S39	S40	S41	S42	S43	S44	S45	S46		
E												
F												
G												
H										NTC1		

Tube Rack

1	POS1	Control 1: Normalized DNA
2	POS2	Control 2: Normalized DNA
3	NTC2	Amp NTC: MBG Water
4		EMPTY
25	MMX	OpenArray Taqman Master Mix
26	MMX	
27	MMX	
28	MMX	
29	MMX	
30	MMX	

384 Open Array plate

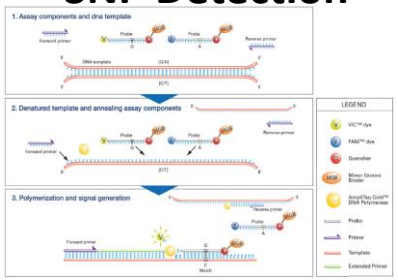
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S25	S26	S27	S28	S29	S30	S31	S32	S33	S34	S35	S36
B	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S25	S26	S27	S28	S29	S30	S31	S32	S33	S34	S35	S36
C	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	POS1	S37	S38	S39	S40	S41	S42	S43	S44	S45	S46	S24	NTC1
D	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	POS1	S37	S38	S39	S40	S41	S42	S43	S44	S45	S46	S24	NTC1
E	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S25	S26	S27	S28	S29	S30	S31	S32	S33	S34	S35	S36
F	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S25	S26	S27	S28	S29	S30	S31	S32	S33	S34	S35	S36
G	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	POS2	S37	S38	S39	S40	S41	S42	S43	S44	S45	S46	S24	NTC2
H	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	POS2	S37	S38	S39	S40	S41	S42	S43	S44	S45	S46	S24	NTC2

Courtesy Whitney Donahue and Gwen McMillian (ARUP)

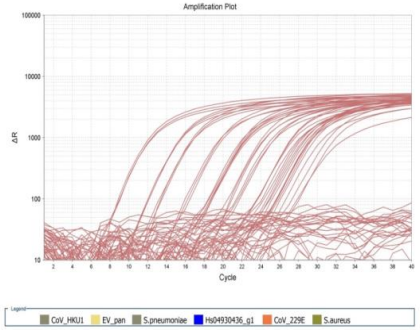
Potential New Open Array Applications

- Adaptive platform for new targets and evolving panel needs
- High complexity resistance testing
- Quantitative analysis of infectious disease host transcriptional and epigenetic response
- Broad targeted pathogen detection assay for critically ill patients with negative classic and molecular syndromic panel results

SNP Detection



Detection & Quantitation



Massive Array

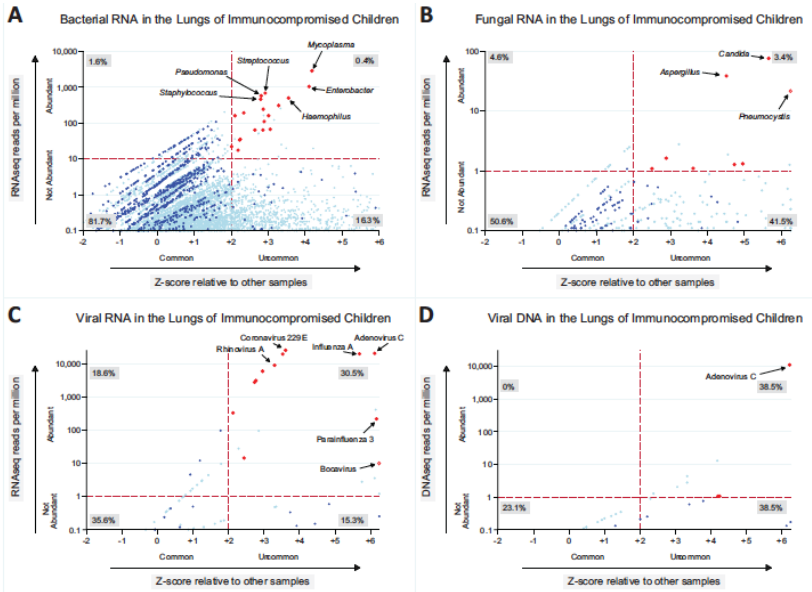
NGS: The ultimate Pan-syndromic Panel?

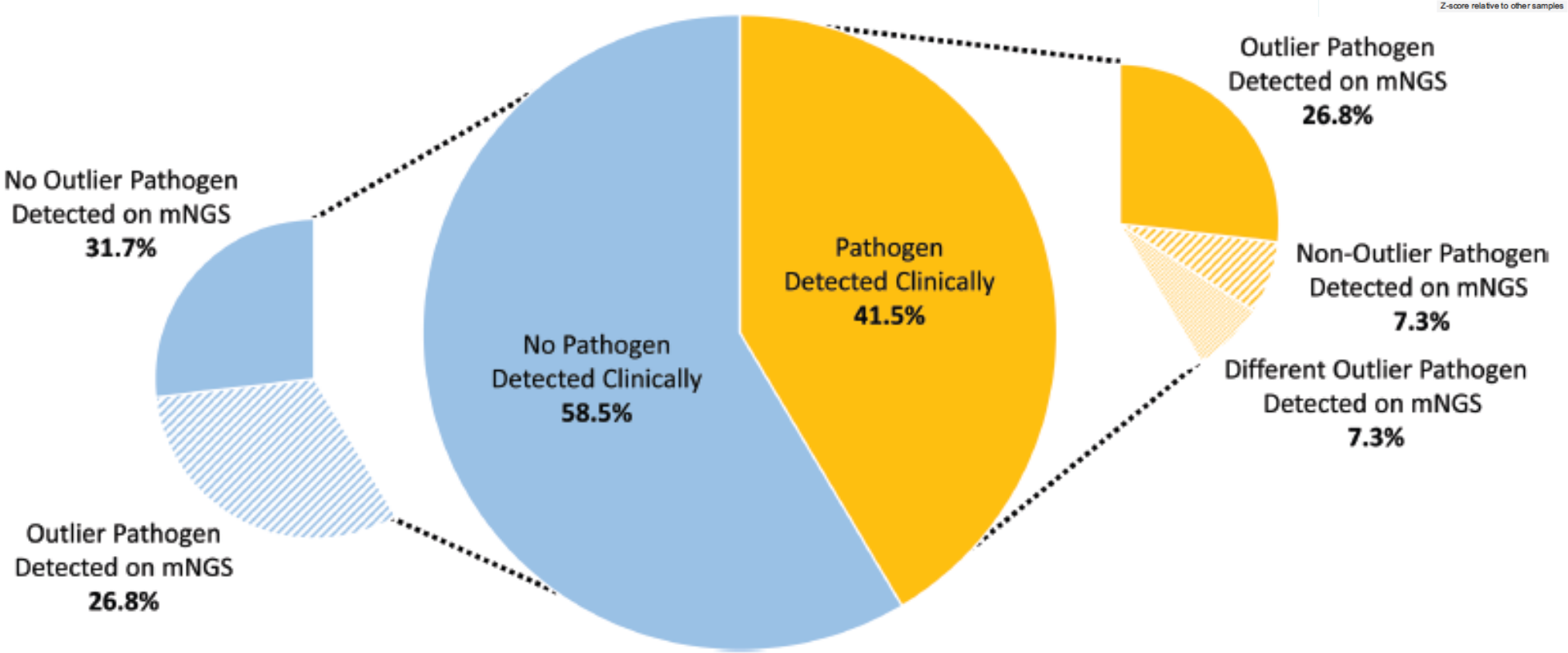
- Detection of any virus, bacteria, fungi or parasite from patient sample or culture
- Pathogen typing, resistance assessment, and host response in a single test
- Allows for new pathogen discovery and rapid response to outbreaks
- Decreased sensitivity with high backgrounds (host or microbiome)
- Complex laboratory workflow with contamination risk
- Challenging bioinformatics
- 1-2 day turn around time
- Expensive except with large runs

Pulmonary Metagenomic Sequencing Suggests Missed Infections in Immunocompromised Children

Matt S. Zinter,[1] Christopher C. Dvorak,[2] Madeline Y. Mayday,[1] Kensho Iwanaga,[3] Ngoc P. Ly,[3] Meghan E. McGarry,[3] Gwynne D. Church,[3] Lauren E. Faricy,[4] Courtney M. Rowan,[5] Janet R. Hume,[6] Marie E. Steiner,[6,7] Emily D. Crawford,[8,9] Charles Langelier,[10] Katrina Kalantar,[9] Eric D. Chow,[9] Steve Miller,[11] Kristen Shimano,[2] Alexis Melton,[2] Gregory A. Yanik,[12] Anil Sapru,[1,13] and Joseph L. DeRisi[8,9]

Zinter et al. CID 2019:68 (1 June) • 1847

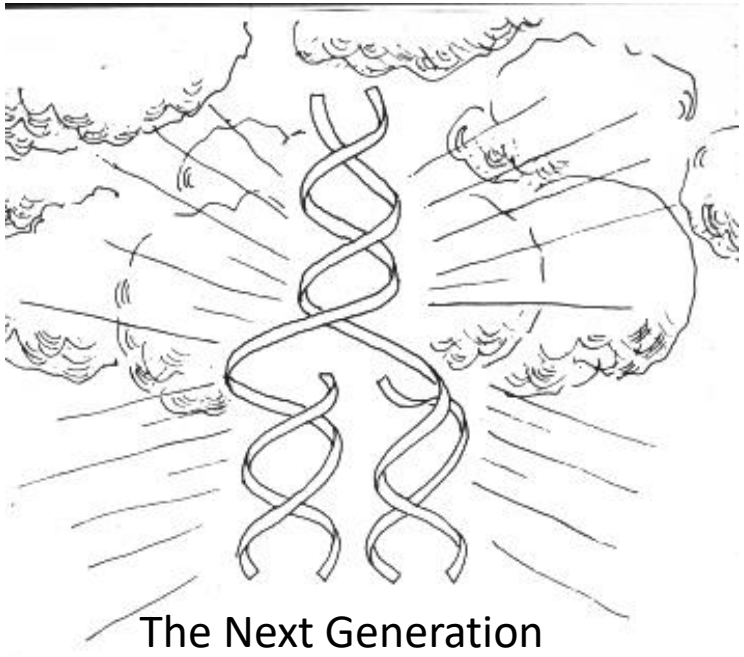




Open Array Summary

- Sensitive and Specific high multiplex assay
- Cost effective
- Quantitative capability
- Rapid and flexible design and modification
- Good contamination control
- Amenable to automation and high throughput
- Very high content panels possible

Salika Shakir
Susan Slechta
Elizabeth Hays



The Next Generation

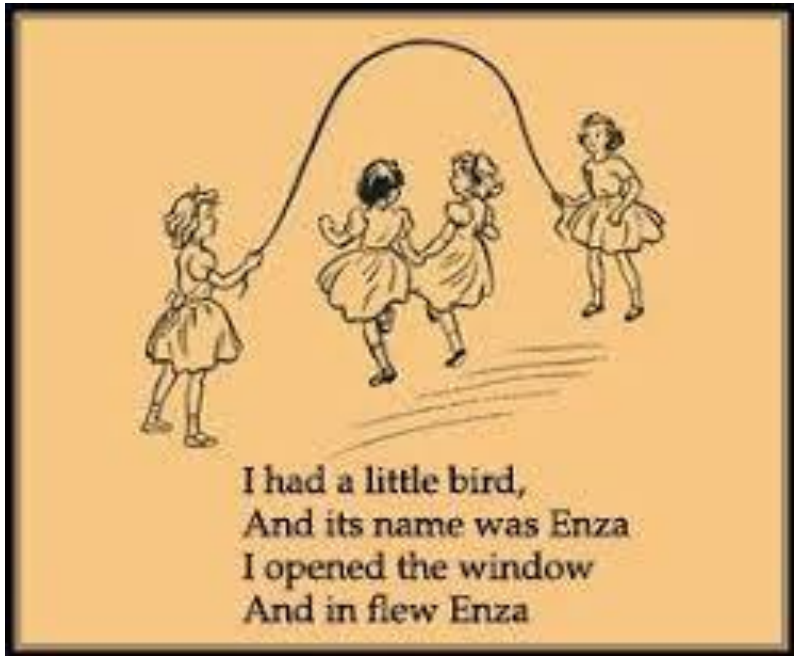
What you’re missing in your Respiratory Pathogen detection

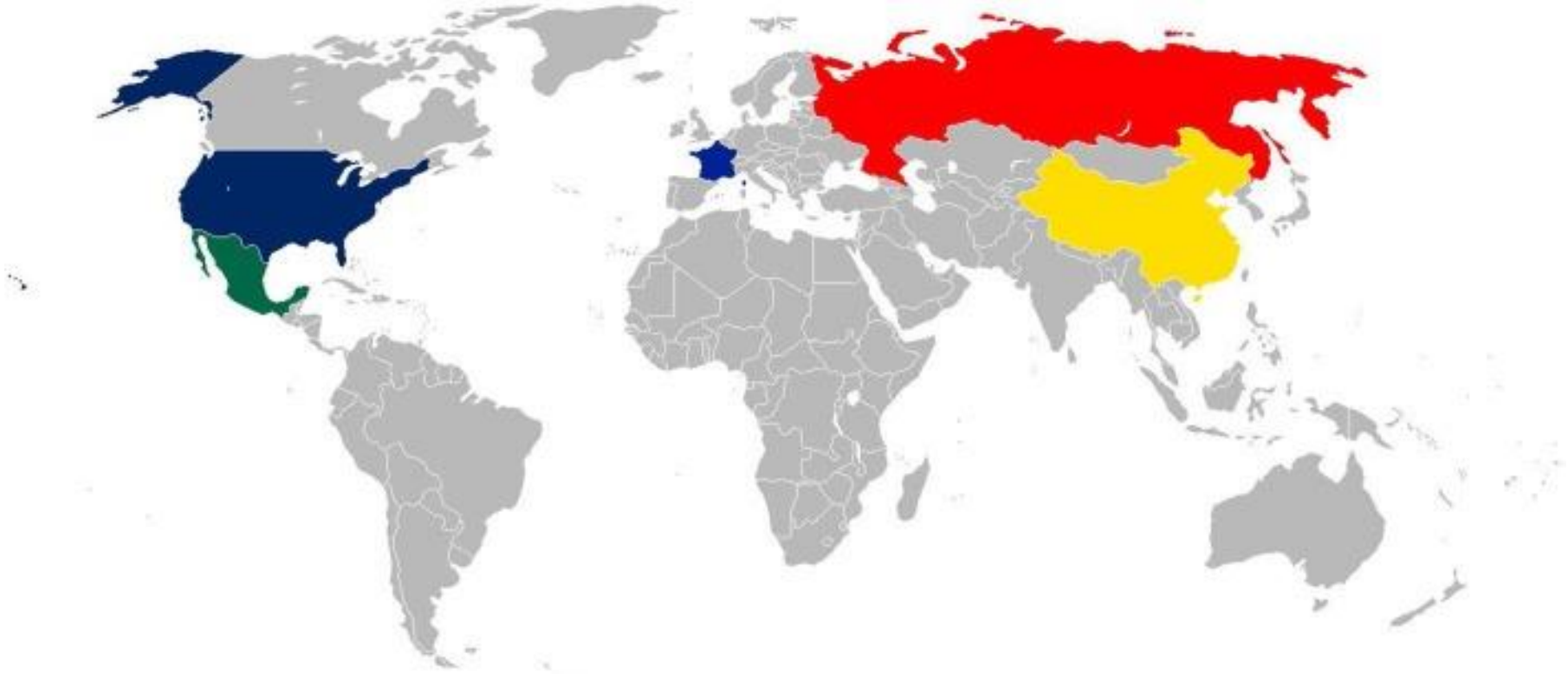
(A survey of viral-bacterial co-infections in respiratory samples using Real Time-PCR)


Health
TrackRx®

edvardmunch.com

Health TrackRx®





World Map showing countries confirmed and suspected of being the origin of influenza pandemics. Blue – The origin of the 1918 Spanish is still unclear, although various papers suggest the United States (New York) or France as the origin; yellow – China the origin of the 1957 Asian flu pandemic; Hong Kong, the origin of the 1968 Hong Kong pandemic; red – Russia, the origin of the 1889 and 1977 Russian flu pandemics; green – Mexico, the origin of the 2009 Swine flu pandemic.

(Morris et al., 2017)

Introduction

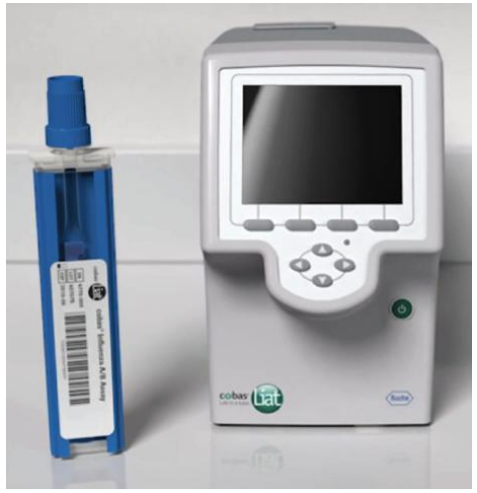
- Respiratory infections due to Influenza and non-Influenza respiratory viruses are responsible for direct and indirect medical costs worth $50 billion annually in the United States (Fendrick et al., 2003, Putri et al., 2018).
- Pneumonia is one of the leading causes of mortality in children under 5 years of age (WHO, 2016).
- Patient morbidity and mortality associated with respiratory viral infections is exacerbated by concurrent or secondary bacterial co-infections (Brealey et al., 2015).
- The leading cause of mortality in the Influenza pandemics of the last century was bacterial co-infection (Joseph et al., 2013).
- Viral infections of the respiratory tract can predispose to bacterial infections and vice-versa (Nguyen et al., 2015)

Introduction

- Respiratory infectious diseases usually present as a collection of symptoms (Influenza-like Illness - ILI).
- Empirical therapy till the results come in (best guess and possibly bad antibiotic stewardship).
- Similar symptoms necessitate the correct diagnosis of the causal organism

Introduction

- Most commercially available popular point of care tests have an extremely limited menu (Influenza A&B, RSV and Group A Strep.).



Introduction

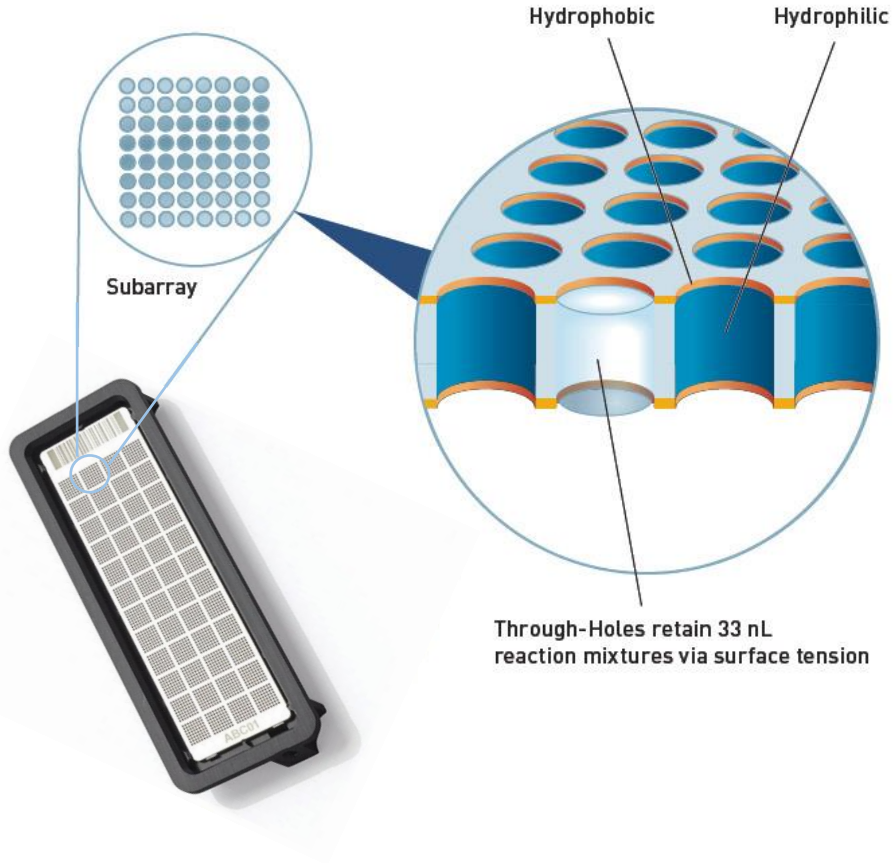
A testing strategy that incorporates a syndromic, multiplexed panel with Real Time-PCR saves both time and money and can result in better decisions

Detecting Respiratory pathogens using a syndromic panel on a nanofluidics platform

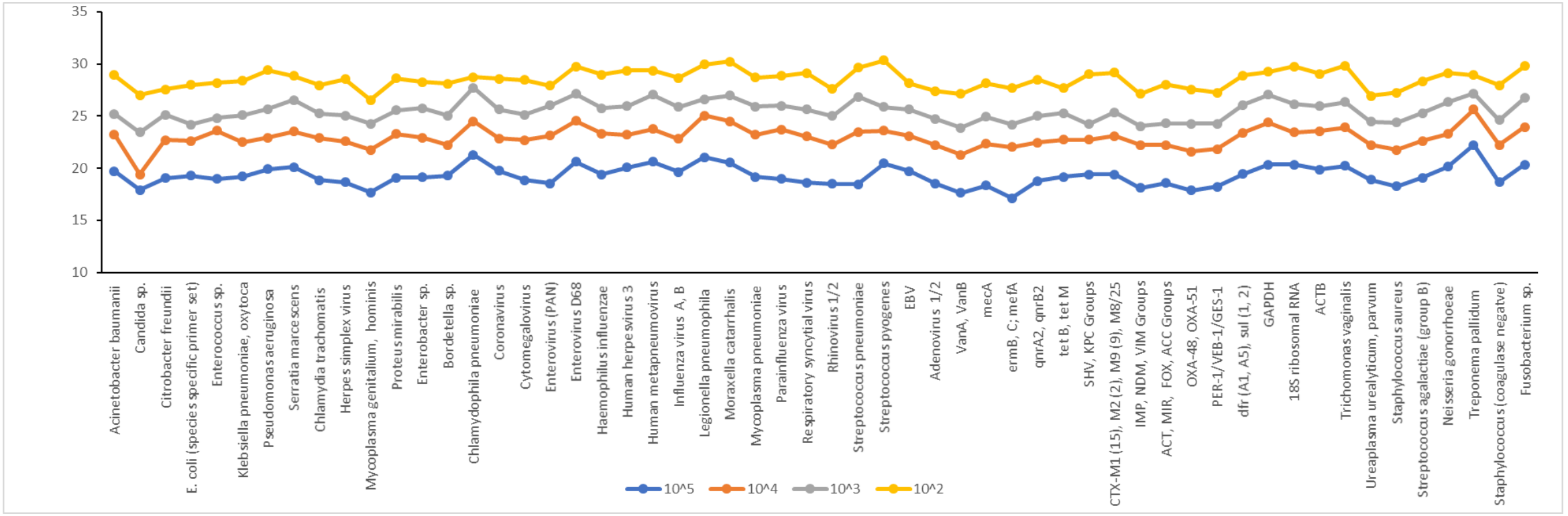
Health TrackRx®

Adenovirus	RhinoVirus	Van A, Van B
Coronavirus (229E, HKU1, NL63, OC43)	Parainfluenza virus 1, 2, 3, 4	erm B, erm C
Enterovirus (pan)	Respiratory Syncytial Virus	SHV, KPC
Varicella zoster Virus	Bordetella	mef A
Epstein-Barr Virus	Chlamydophila pneumoniae	mec A
Human Metapneumovirus	Haemophilus influenzae	tet B, tet M
Influenza A	Klebsiella pneumoniae	dfrA1, dfrA5
Influenza B	Legionella pneumophila	sul1, sul2
Moraxella catarrhalis	Mycoplasma pneumoniae	A. baumanii
Streptococcus pneumoniae	Staphylococcus aureus	C. trachomatis
Candida	E. aerogenes	E. cloacae
F. necrophorum	F. nucleatum	HSV
P. aeruginosa	S. agalactiae	S. pyogenes

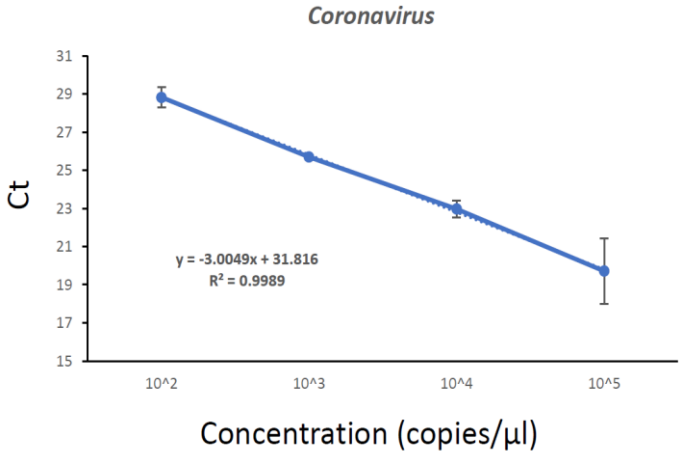
	Core Respiratory		Supplementary		Antibiotic Resistance

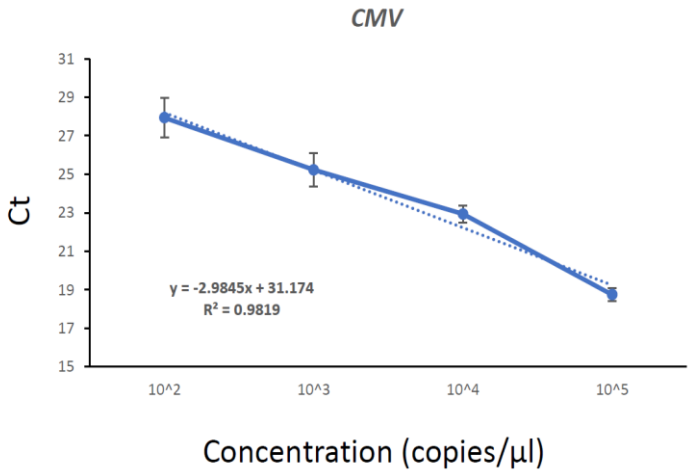


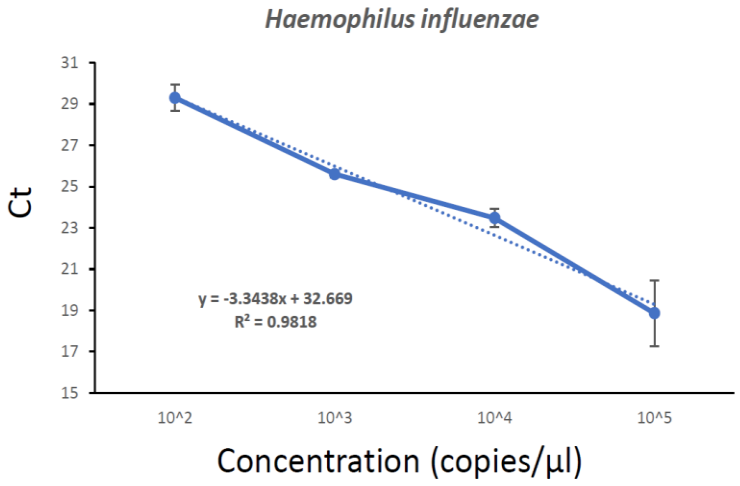
Analytical sensitivity of the assays

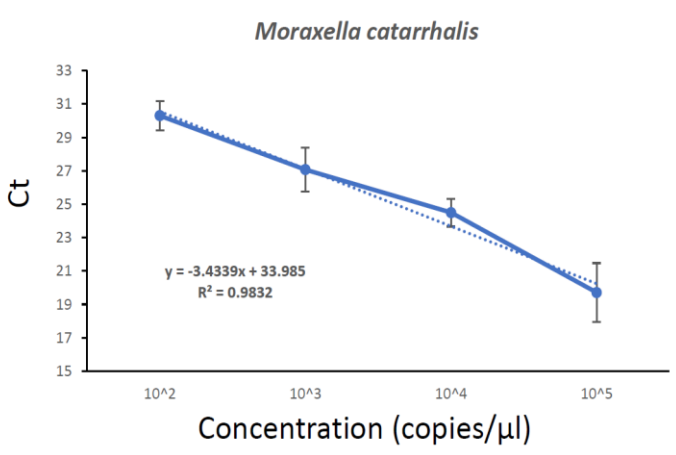


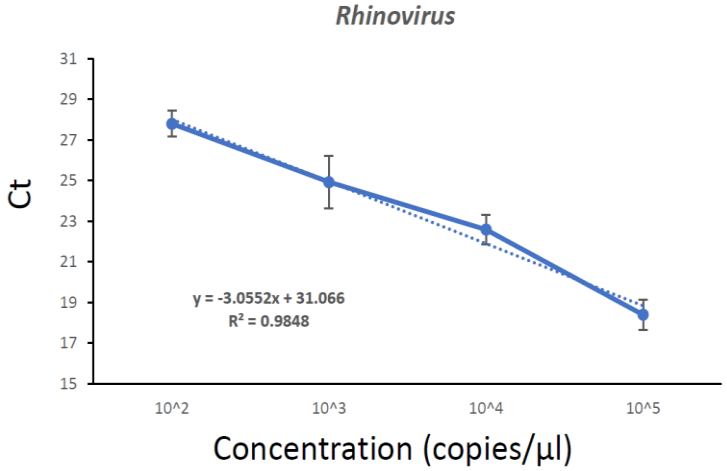
Analytical sensitivity of the assays

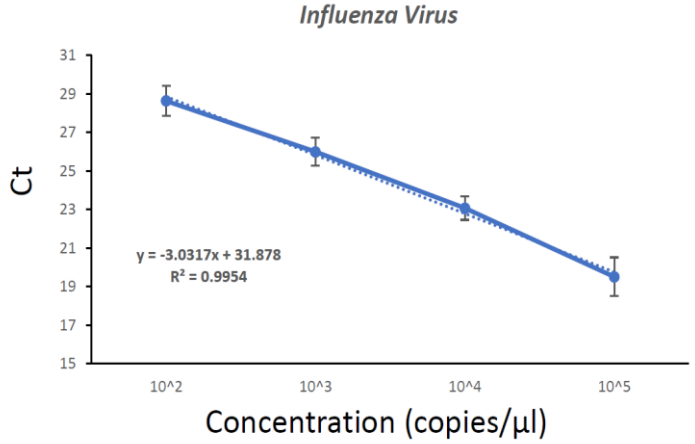












Workflow

Sample

Nucleic Acid Extraction

Reverse Transcription & Pre-Amplification

RT-PCR

Report

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Research Open Access

A Survey of Viral-bacterial Co-infection in Respiratory Samples Using Multiplex Real Time-PCR

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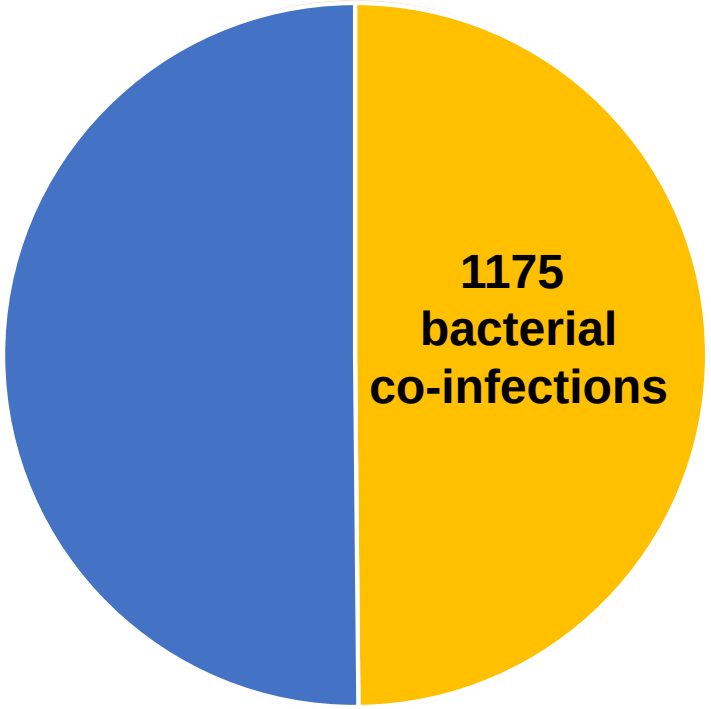
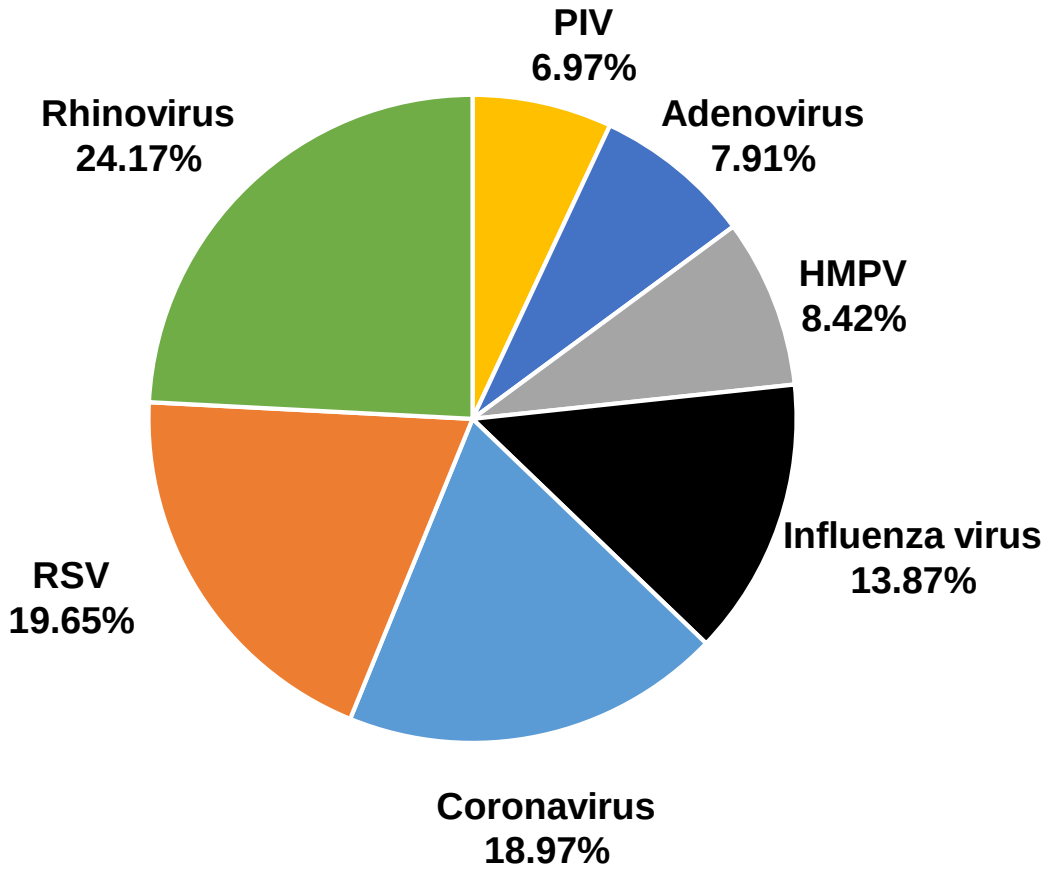
Overview

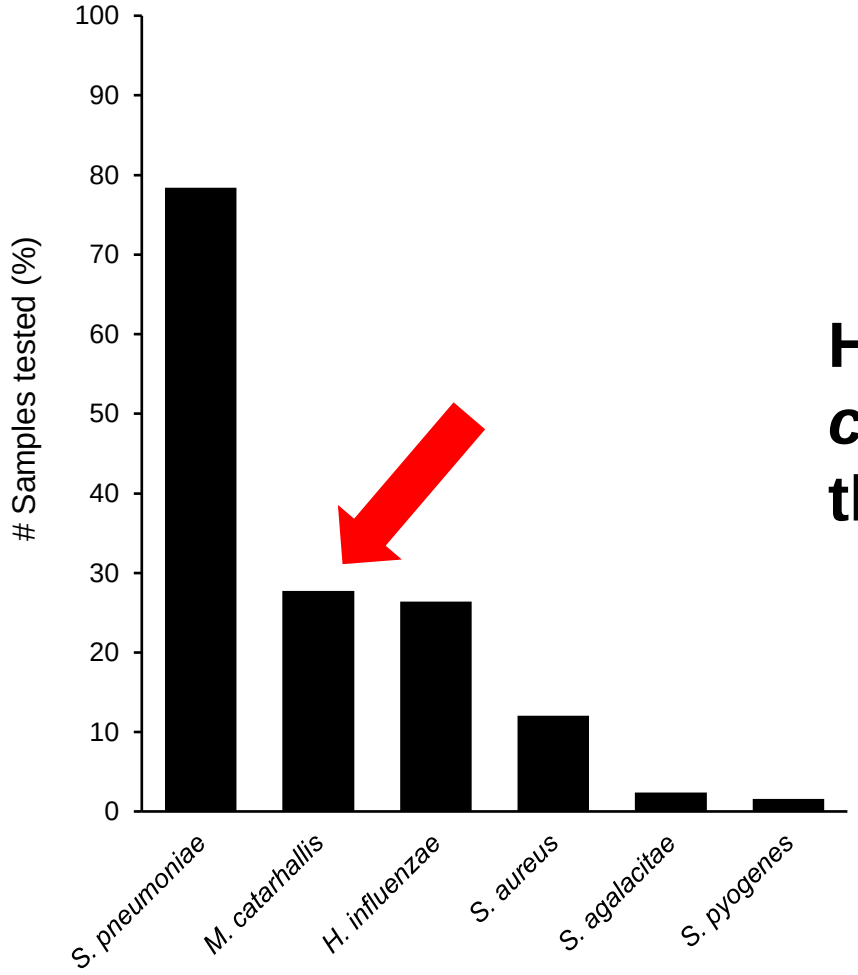


Approximately 50% of samples positive for respiratory viral infections tested positive for bacterial co-infections

ILI causing viruses detected in co-infected samples

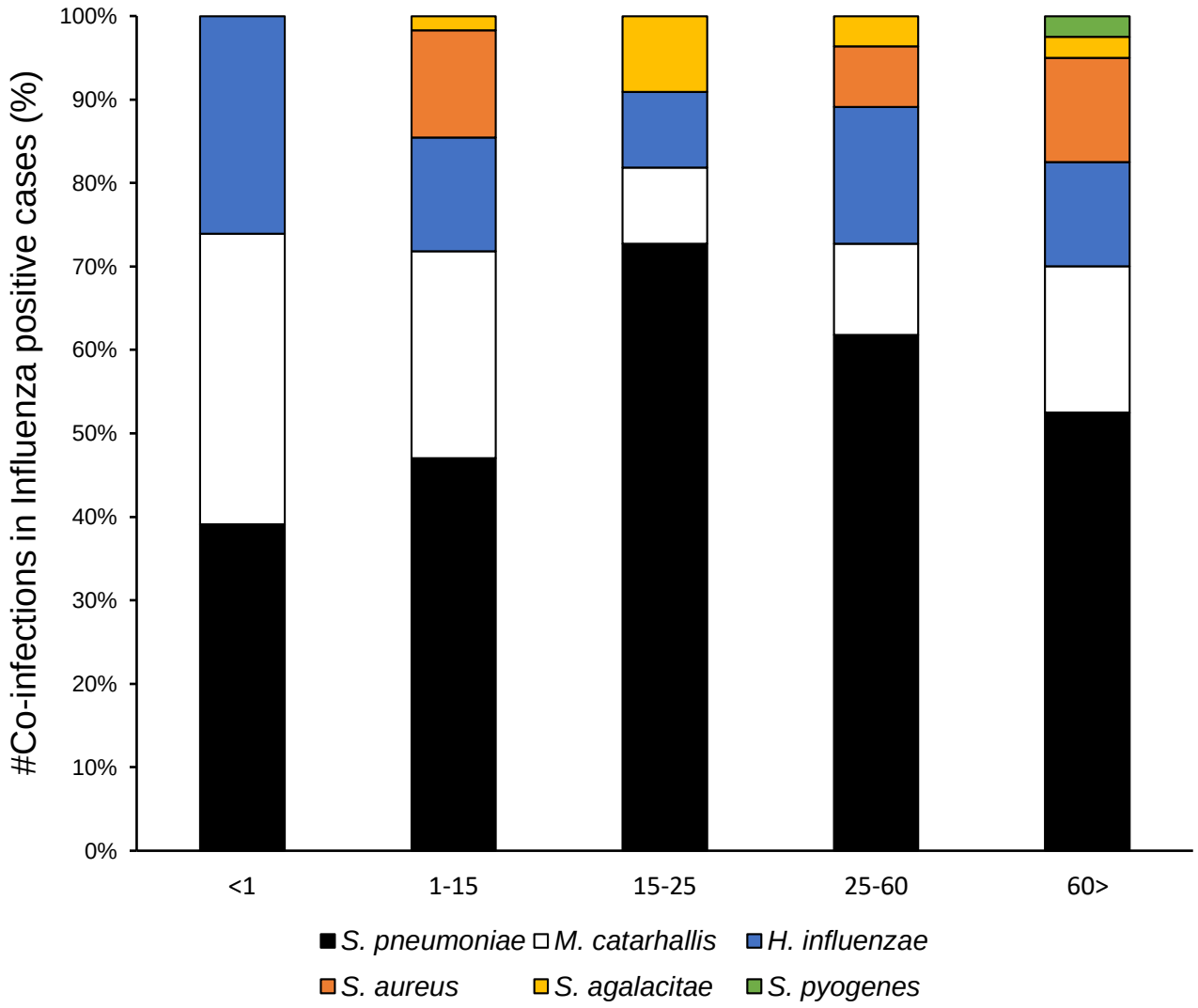


Pneumonia causing bacteria detected in co-infected samples

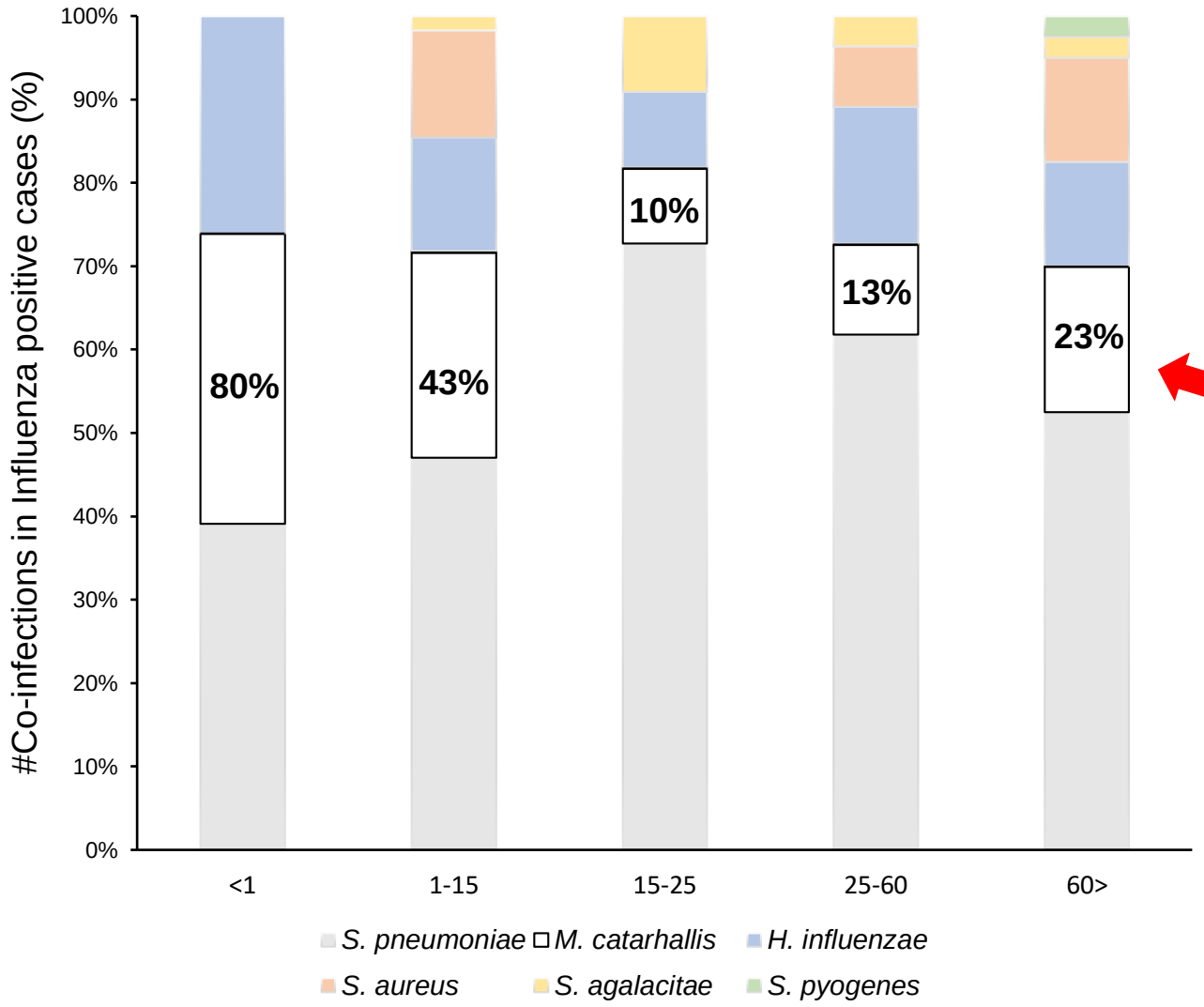


Higher levels of *Moraxella catarrhalis* detected as co-infections than previously reported

Bacterial co-infections in Influenza positive cases

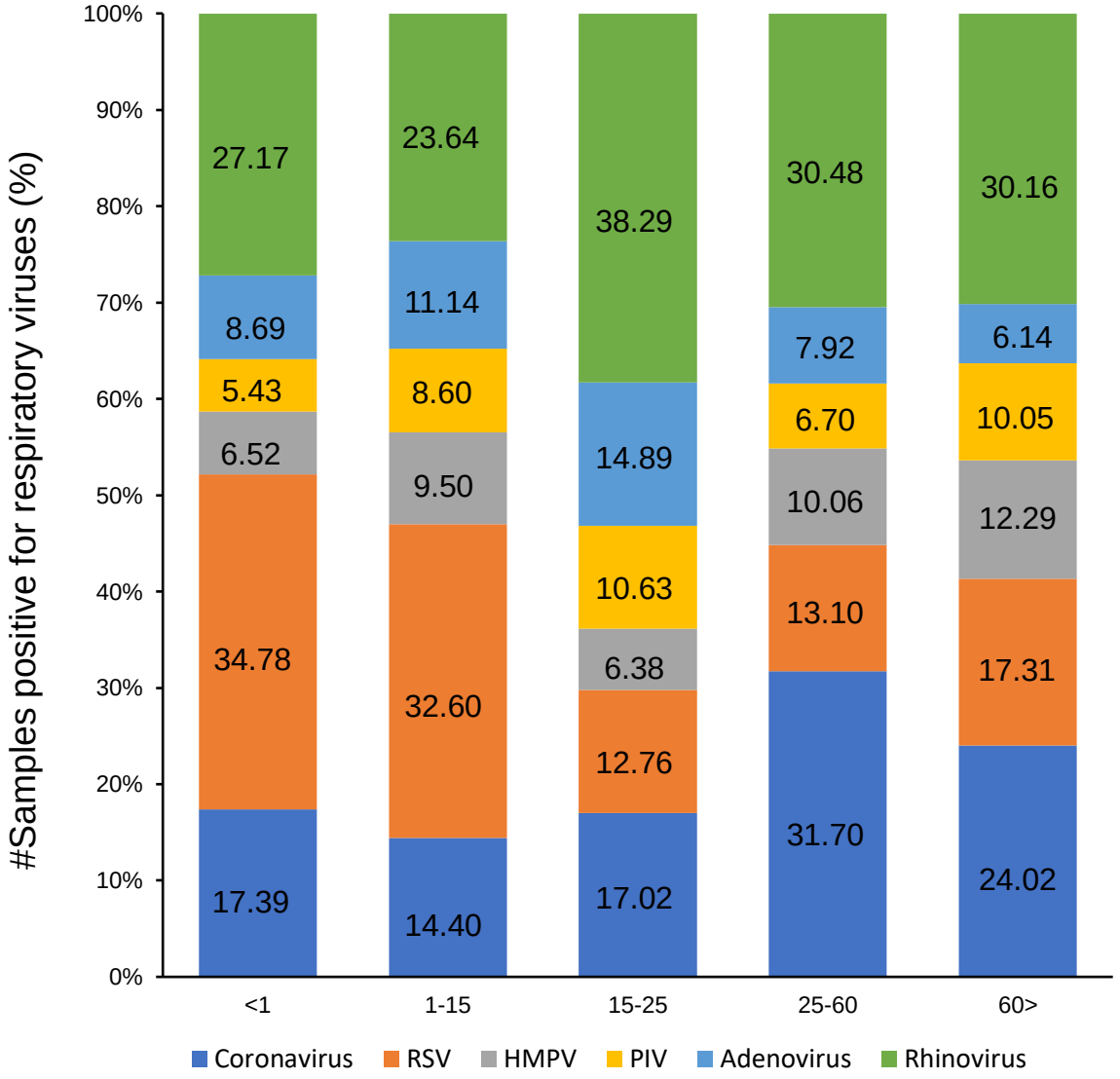


Bacterial co-infections in Influenza positive cases

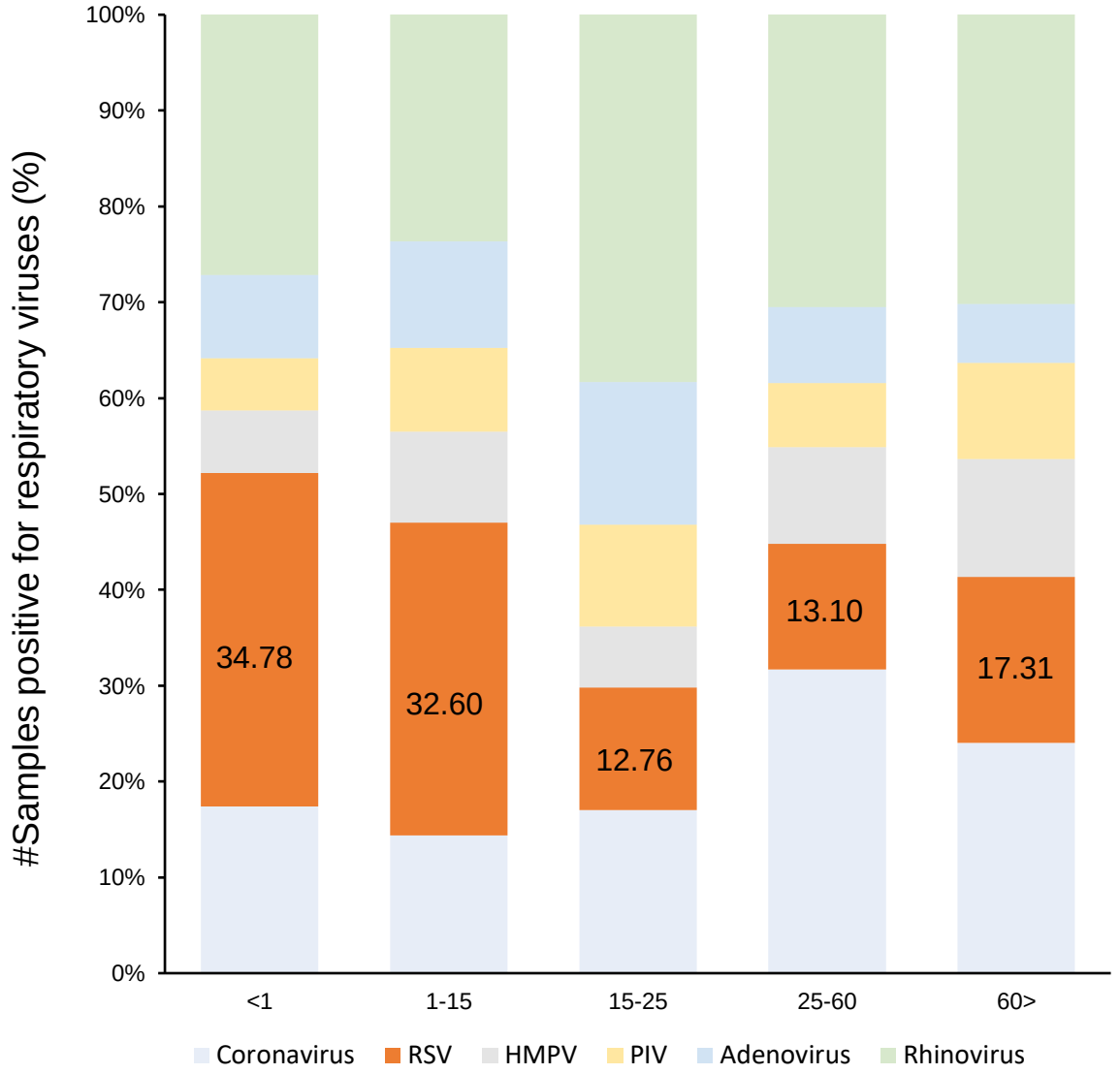


Higher instances of *M. catarrhalis* co-infection in younger (0-15 years) and elderly (>60 years) population

Distribution of non-influenza respiratory viruses

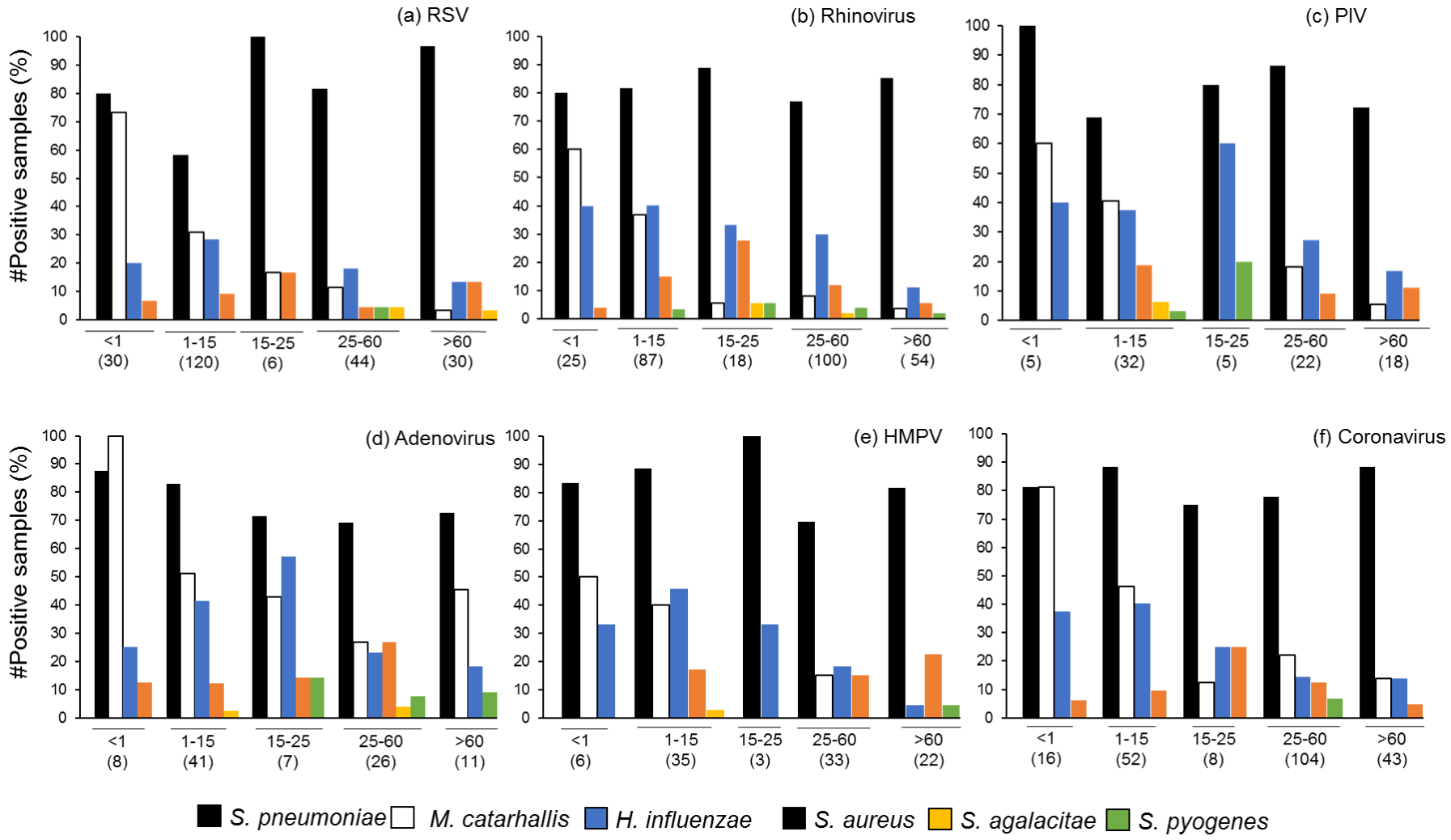


Distribution of non-influenza respiratory viruses

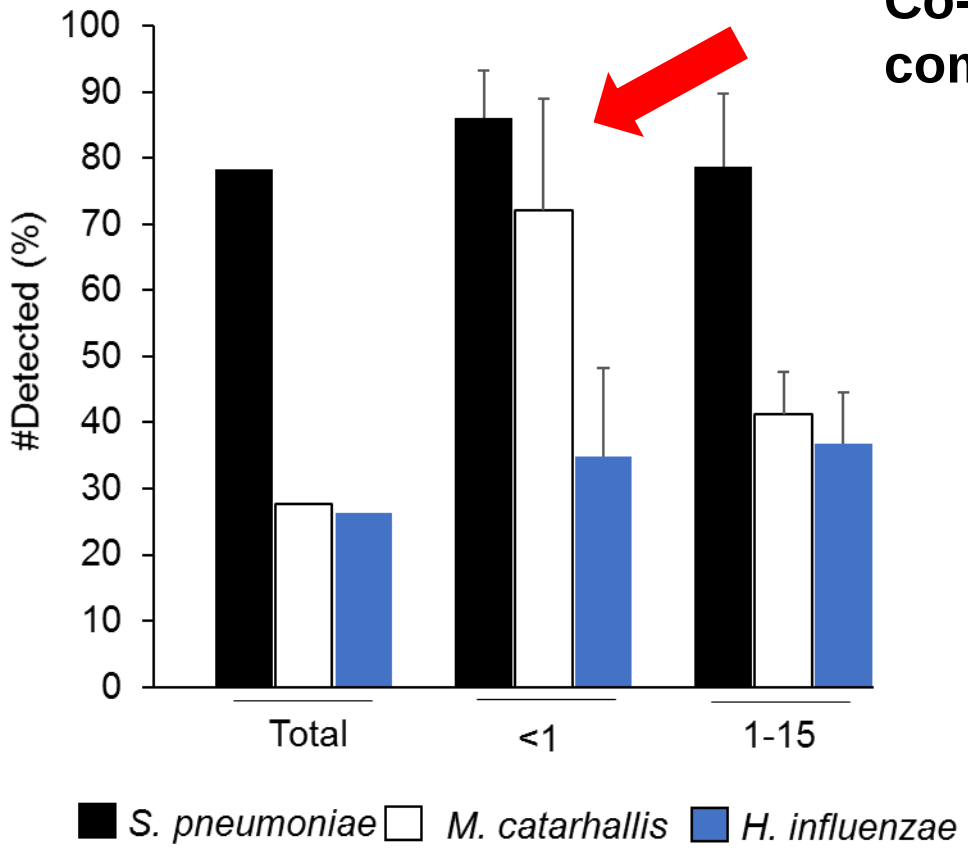


Higher instances of *RSV* infection in younger (0-15 years) and elderly (>60 years) population

Bacterial co-infections in non-Influenza viral positive cases

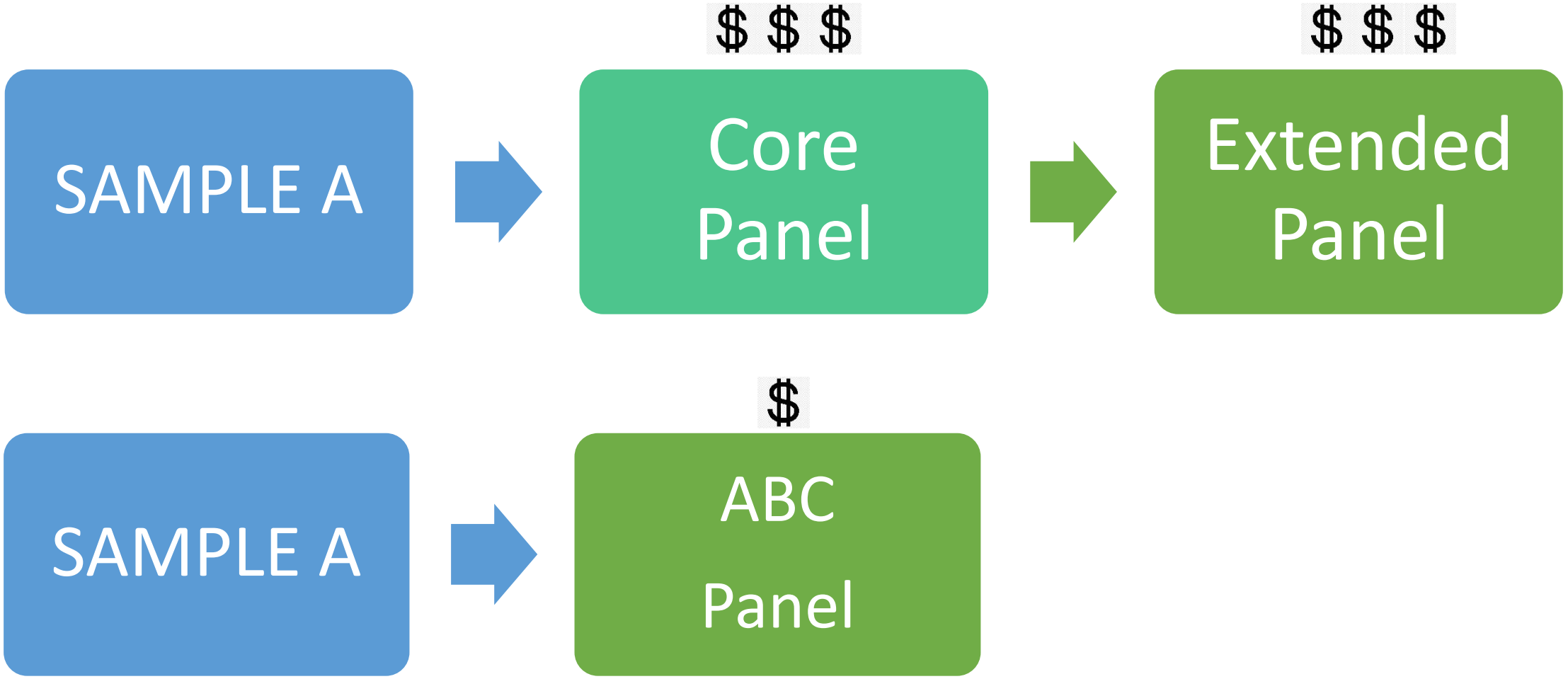


Higher levels of *Moraxella catarrhalis* co-infections detected in younger population



Co-infection levels comparable to *S. pneumoniae*

Economics of Testing



Summary

- Nearly 50% of the viral positive samples detected positive for a pneumonia causing bacterial pathogen.

- Potentially, in one out of every two patients using a viral-only detecting POC test, clinicians would have missed the diagnosis of a concurrent bacterial infection, likely increasing morbidity and mortality, and certainly could increase “time to successful treatment” and infection-associated costs.

- With 27.47% of the co-infection cases testing positive for *M. catarrhalis*, this pathogen was more prevalent than *H. influenzae* and *S. aureus* in our study.

- To our knowledge, this is the first study reporting such high instances of *M. catarrhalis* co-infection rate within the same data set. In the younger population (<1-15 years), *M. catarrhalis* was co-detected, across all viral infections, at significantly higher levels as compared to other age groups

Summary

- A syndromic, multiplexed, comprehensive panel utilizing the latest in nanofluidic Real Time-PCR provides clear insight into the respiratory viral infection and bacterial co-infection patterns.
- The data presented clearly demonstrates the limitations of using a limited menu point of care test for respiratory infections.
- The study presents novel trends for emerging respiratory bacterial pathogens

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Jessica Castaneda, PhD


Questions?

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