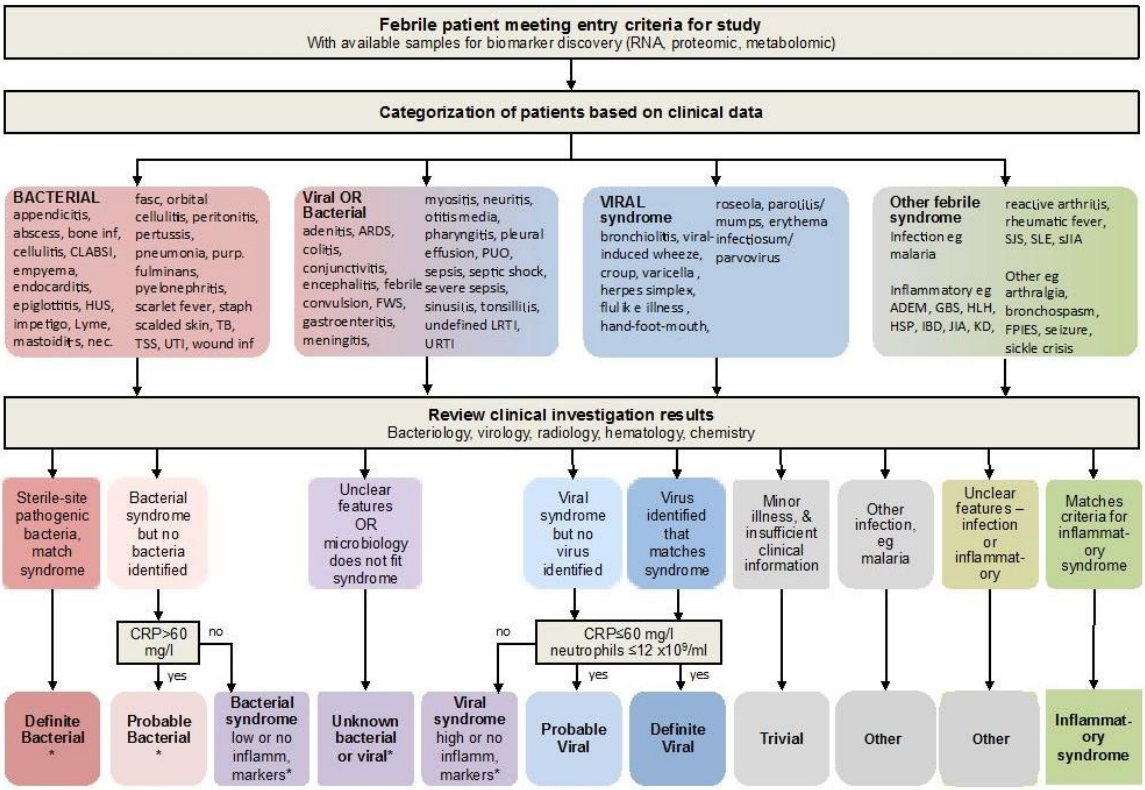
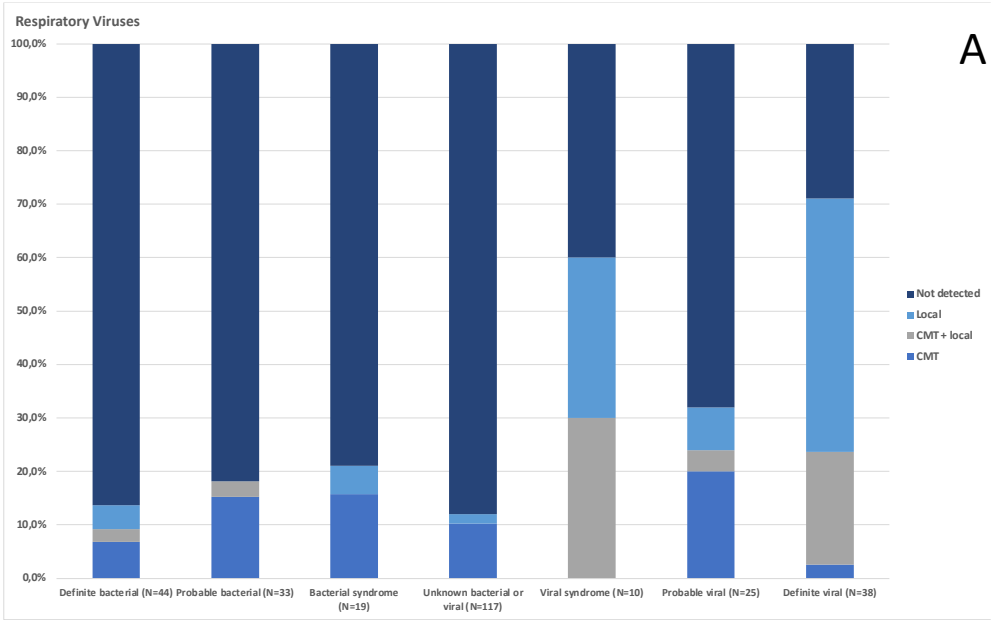
Supplementary Material

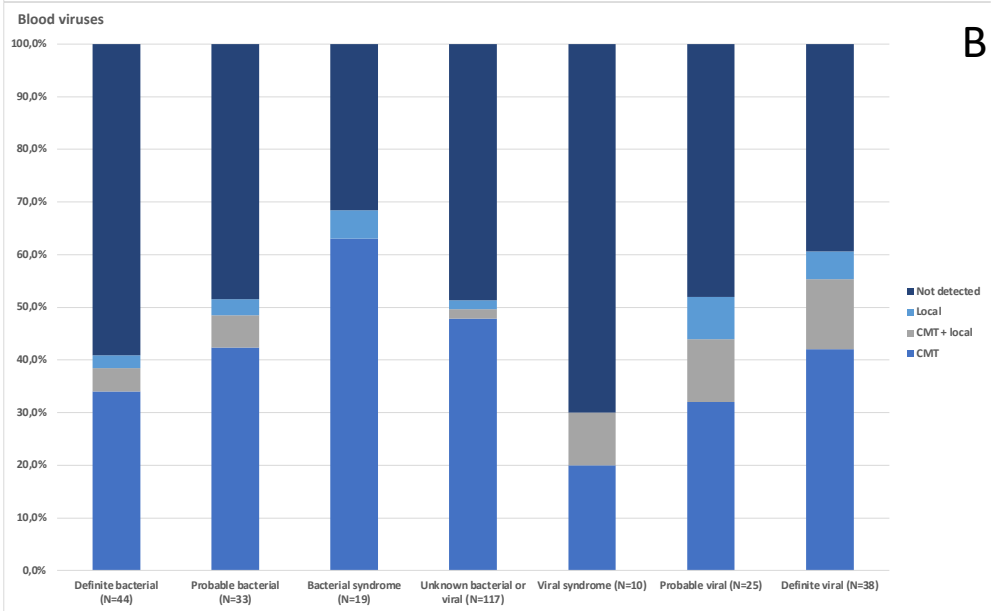
Supplementary Figure 1: Validated phenotyping algorithm as used in the PERFORM study (Nijman et al. 2021[38])

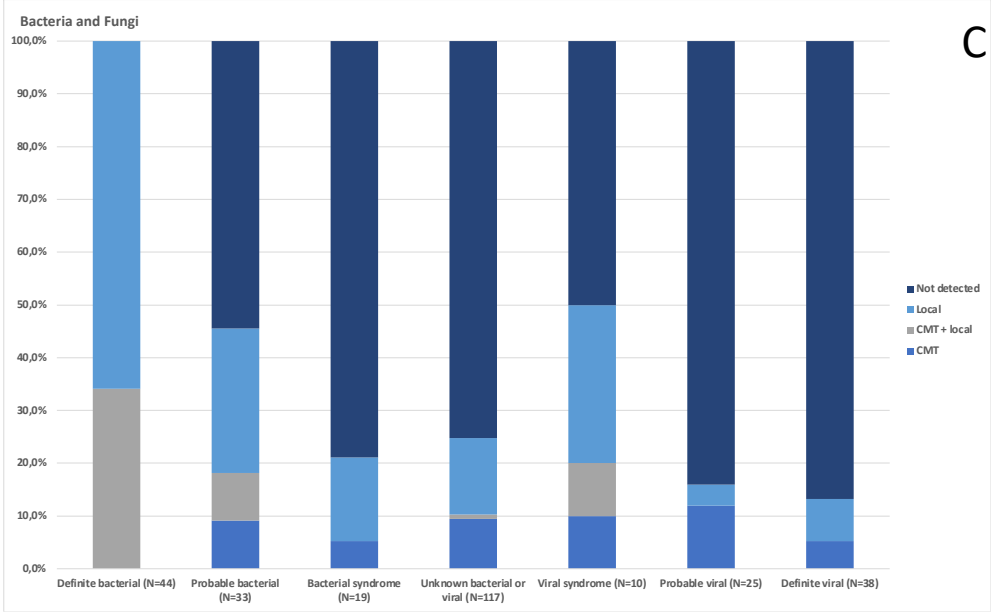


*DB/PB/unknown bacterial or viral: patients CAN have identified viral co-infection

Supplementary Figure 2: Pathogen detection rates by phenotype and by local investigations, CMT or both local investigations and CMT. A: respiratory viruses, B: blood viruses, C: blood bacteria and fungi







Supplementary Table 1: Overview of respiratory and blood pathogen targets for centralized molecular testing

Blood bacteria	**Blood viruses**	**Blood fungi**	**Respiratory bacteria**	**Respiratory viruses**
A. baumanii	Adenovirus	*Aspergillus* 1,2	*C. pneumoniae*	Adenovirus
E. aerogenes	CMV	*Aspergillus* 3	*L. pneumoniae*	Bocavirus
E. cloacae	EBV	*Candida* 1,2,3	*M. pneumoniae*	Coronavirus 229E
E. coli	Enterovirus			Coronavirus HKU1
E. faecalis	HHV6a			Coronavirus NL63
E. faecium	HHV6b			Coronavirus OC43
Enterobacterales 16S	HHV7			Enterovirus
Enterobacterales rpoB	Parechovirus			Influenza A
Group A *Streptococcus*	Parvovirus			Influenza A.H1
Group AB *Streptococcus*				Influenza A.H3
Group B *Streptococcus*				Metapneumovirus
H. influenzae				Parainfluenza 1
K. kingae				Parainfluenza 2
K. pneumoniae				Parainfluenza 3
N. meningitidis				Parainfluenza 4
P. aeruginosa				Rhinovirus
Pan Bacterial				RSV A
Pan *Staphylococcus*				RSV B
Pan *Streptococcus*				
S. aureus				
S. marcescens				
S. pneumoniae				
Streptococcus 16S				

Supplementary Table 2: Detection rates of pathogens identified by local, best practice microbiological diagnostics. (N=episodes)

Bacteria	**Causative**	**Detected**	**Virus**	**Causative**	**Detected**
Acinetobacter baumannii	1	1	Adenovirus	5	7
Burkholderia cepacia complex	1	1	BK-virus	1	1
Campylobacter jejuni	1	1	CMV	3	10
Coagulase negative Staphylococcus	13	20	Coronavirus	1	2
Corynebacterium spp.	1	1	EBV	2	3
Delftia acidovorans	1	1	Enterovirus	2	8
Enterobacter cloacae	3	4	HHV6	0	1
Enterococcus faecalis	1	1	HIV	0	1
Enterococcus faecium	0	1	HSV-1	2	4
Enterococcus spp.	1	1	Influenza A	6	6
Escherichia coli	16	16	Influenza B	8	9
Fusobacterium spp.	1	1	Metapneumovirus	0	2
Group A Streptococcus	1	1	Norovirus	2	6
Klebsiella pneumoniae	3	3	Parainfluenza 2	1	4
Lactobacillus rhamnosus	1	1	Parvovirus	2	4
Micrococcus spp.	0	2	Rhinovirus	4	15
Mycobacterium bovis	0	1	Rotavirus	0	2
Mycoplasma pneumoniae	1	1	RSV	9	10
Neisseria meningitidis	1	1	VZV	1	1
Pseudomonas aeruginosa	8	9	**Other pathogens**	**Causative**	**Detected**
Rothia mucilaginosa	1	1	*Candida spp.*	2	11
Serratia marcescens	1	1	*Cryptosporidium spp.*	0	1
Staphylococcus aureus	7	7	*Pneumocystis jirovecii*	1	1
Streptococcus pneumoniae	1	1			
Streptococcus viridans group	4	4			

Supplementary Table 3: Detection rates of individual pathogens with centralized molecular testing by phenotype

	All cases (N=336)	Definite Bacterial (N=45)	Proven/presumed bacterial (N=96)	Definite Viral (N=37)	Proven/presumed viral (N=72)	Unknown bacterial or viral (N=118)	Controls (N=54)
Respiratory viruses							
Influenza A	5 (1.5%)	0	2 (2.1%)	2 (5.4%)	3 (4.2%)	0	0
Influenza A.H1	0	0	0	0	0	0	0
Influenza A.H3	5 (1.5%)	0	2 (2.1%)	2 (5.4%)	3 (4.2%)	0	0
Influenza B	4 (1.2%)	0	0	1 (2.7%)	3 (4.2%)	0	0
RSV A	2 (0.6%)	0	0	1 (2.7%)	1 (1.4%)	1 (0.8%)	0
RSV B	4 (1.2%)	0	0	1 (2.7%)	2 (2.8%)	0	0
Parainfluenza 1	0	0	0	0	0	0	0
Parainfluenza 2	2 (0.6%)	0	0	0	0	1 (0.8%)	0
Parainfluenza 3	1 (0.3%)	0	1 (1.0%)	0	0	0	0
Parainfluenza 4	1 (0.3%)	0	1 (1.0%)	0	0	0	0
Coronavirus 229E	3 (0.9%)	0	0	1 (2.7%)	2 (2.8%)	0	0
Coronavirus NL63	3 (0.9%)	0	1 (1.0%)	1 (2.7%)	1 (1.4%)	1 (0.8%)	0
Coronavirus OC43	3 (0.9%)	0	0	1 (2.7%)	2 (2.8%)	1 (0.8%)	0
Coronavirus HKU1	0	0	0	0	0	0	0
Metapneumovirus	1 (0.3%)	0	0	0	0	1 (0.8%)	0
Adenovirus	3 (0.9%)	0	1 (1.0%)	1 (2.7%)	1 (1.4%)	0	0

Bocavirus	1 (0.3%)	1 (2.2%)	1 (1.0%)	0	0	0	0
Rhinovirus	22 (6.5%)	3 (6.7%)	7 (7.3%)	3 (8.1%)	5 (6.9%)	7 (5.9%)	3 (18.8%)
Enterovirus	1 (0.3%)	0	1 (1.0%)	0	0	0	0
Blood viruses							
Adenovirus	9 (2.7%)	0	2 (2.1%)	1 (2.7%)	2 (2.8%)	3 (2.5%)	1 (1.9%)
CMV	7 (2.1%)	1 (2.2%)	2 (2.1%)	1 (2.7%)	2 (2.8%)	2 (1.7%)	2 (3.7%)
EBV	37 (11.0%)	6 (13.3%)	13 (13.5%)	4 (10.8%)	7 (9.7%)	8 (6.8%)	6 (11.1%)
HHV6a	2 (0.6%)	0	1 (1.0%)	0	0	1 (0.8%)	0
HHV6b	42 (12.5%)	7 (15.6%)	15 (15.6%)	4 (10.8%)	4 (5.6%)	16 (13.6%)	13 (24.1%)
HHV7	113 (33.6%)	10 (22.2%)	30 (31.3%)	12 (32.4%)	23 (31.9%)	43 (36.4%)	20 (37.0%)
Parvovirus	18 (5.4%)	2 (4.4)	5 (5.2%)	4 (10.8%)	5 (6.9%)	8 (6.8%)	1 (1.9%)
Enterovirus	2 (0.6%)	0	1 (1.0%)	1 (2.7%)	1 (1.4%)	0	0
Parechovirus	1 (0.3%)	0	0	0	0	1 (0.8%)	0
Respiratory bacteria							
Chlamydophila pneumoniae	0	0	0	0	0	0	0
Legionella pneumoniae	0	0	0	0	0	0	0
Mycoplasma pneumoniae	2 (0.6%)	0	0	0	1 (1.4%)	1 (0.8%)	0
Blood bacteria							
Neisseria meningitidis	1 (0.3%)	0	0	0	1 (1.4%)	0	0
Streptococcus pneumoniae	1 (0.3%)	0	0	0	0	1 (0.8%)	1 (1.9%)
Haemophilus influenzae	0	0	0	0	0	0	0

Staphylococcus aureus	4 (1.2%)	1 (2.2%)	2 (2.1%)	1 (2.7%)	1 (1.4%)	1 (0.8%)	1 (1.9%)
Pan Staphylococcus	8 (2.4%)	4 (8.9%)	5 (5.2%)	1 (2.7%)	1 (1.4%)	2 (1.7%)	0
Pan bacterial	15 (4.5%)	7 (15.6%)	9 (9.4%)	1 (2.7%)	1 (1.4%)	5 (4.2%)	0
Group A Streptococcus	0	0	0	0	0	0	0
Group B Streptococcus	1 (0.3%)	0	1 (1.0%)	0	0	0	0
Acinetobacter baumanii	2 (0.6%)	0	0	1 (2.7%)	1 (1.4%)	0	0
Pseudomonas aeruginosa	1 (0.3%)	0	0	0	0	0	0
Serratia marcescens	3 (0.9%)	1 (2.2%)	1 (1.0%)	1 (2.7%)	2 (2.8%)	0	0
Escherichia coli	2 (0.6%)	2 (4.4%)	2 (2.1%)	0	0	0	0
Kingella kingae	1 (0.3%)	1 (2.2%)	1 (1.0%)	0	0	0	0
Enterobacter aerogens	2 (0.6%)	1 (2.2%)	1 (1.0%)	0	0	1 (0.8%)	0
Pan Streptococcus	0	0	0	0	0	0	0
Streptococcus 16S	2 (0.6%)	1 (2.2%)	1 (1.0%)	0	0	1 (0.8%)	0
Enterococcus faecalis	1 (0.3%)	1 (2.2%)	1 (1.0%)	0	0	0	0
Enterococcus faecium	2 (0.6%)	1 (2.2%)	2 (2.1%)	0	0	0	0
Enterobacter cloacae	4 (1.2%)	3 (6.7%)	4 (4.2%)	0	0	0	1 (1.9%)
Group AB Streptococcus	1 (0.3%)	0	0	0	1 (1.4%)	0	0
Klebsiella pneumoniae	3 (0.9%)	2 (4.4%)	2 (2.1%)	0	0	1 (0.8%)	1 (1.9%)
Enterobacterales rpoB	7 (2.1%)	4 (8.9%)	4 (4.2%)	0	0	2 (1.7%)	0
Enterobacterales 16S	6 (1.8%)	4 (8.9%)	4 (4.2%)	0	0	2 (1.7%)	0

Fungi							
Aspergillus 3	0	0	0	0	0	0	0
Candida 1,2,3	1 (0.3%)	1 (2.2%)	1 (1.0%)	0	0	0	0
Aspergillus 1,2	1 (0.3%)	0	0	0	1 (1.4%)	0	0

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