Multi-centre EuRopean study of MAjor Infectious Disease Syndromes

FIRST WEBINAR: A MERMAIDS TALE

PREPARE is funded by the European Commission under grant number 602525

Programme

1. Introduction to PREPARE (Menno de Jong)
2. MERMAIDS ARI Background (Peter Horby)
3. MERMAIDS ARI Sites, set-up and inclusions (James Lee)
4. MERMAIDS ARI Cohort characteristics (Louise Sigfrid)
5. MERMAIDS for COVID-19 (James Lee)
6. Transcriptomic results, *Myth of Truth* (Cosimo Cristella)
7. PED-MERMAIDS *More than a children's story* (Malte Kohns)

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Platform for European Preparedness Against (Re-)emerging Epidemics

PREPARE: EU funded network for harmonised large-scale clinical research studies on infectious diseases:

- prepared to rapidly respond to any severe infectious disease outbreak
- providing evidence for clinical management of patients and for informing public health responses

- Start date: 1 February 2014
- End date: 31 January 2021

> 800 laboraties
> 800 hospitals
> 600 primary care practicies

This project is funded by the European Commission's FP7 Programme under grant agreement No. 602525

Multi-centre EuRopean study of MAjor Infectious Disease Syndromes - Acute Respiratory Infections (MERMAIDS-ARI)

Preliminary results

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MERMAIDS-ARI Background

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Three MERMAIDS studies

ARI

- Determinants of severity of acute respiratory infections
- 500 primary care patients
- 1,500 hospitalised patients.
- Eight countries
- 1st Oct - 30th April

ARBO

- Burden, clinical management and impact of arbovirus illnesses in South East Europe
- 1500 adult patients
- Seven countries
- 1st May – 31st Oct

PED

- Aetiology of sepsis-like syndrome
- Aetiology of ARI
- Case-control
- 300 SLS cases and 52 controls
- 320 ARI cases and 320 controls
- Ten countries
- Continuous

ARI Design

Primary objective

To identify host- and pathogen- related determinants of severity of community acquired ARI in adults.

Secondary objectives

To describe the aetiology, clinical management and outcomes of adult patients with ARI

To develop and validate prognostic and diagnostic algorithms for ARI

Prospective observational study

2000 adults primary (500 adults) and secondary care (1500 adults) across Europe.

Setting

8 countries, 29 hospital sites, 9 primary care sites

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Differentially expressed genes as assessed by RNA transcriptome

Mild group

	Inf.	HRV	RSV	S.pneu
No comorbidity	*n*	*n*	*n*	*n*
Chronic pulmonary disease	*n*	*n*	*n*	*n*
Chronic cardiovascular disease	*n*	*n*	*n*	*n*
Chronic metabolic disease	*n*	*n*	*n*	*n*

Severe group

	Inf.	HRV	RSV	S.pneu
No comorbidity	*n*	*n*	*n*	*n*
Chronic pulmonary disease	*n*	*n*	*n*	*n*
Chronic cardiovascular disease	*n*	*n*	*n*	*n*
Chronic metabolic disease	*n*	*n*	*n*	*n*

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Analysis

- **Differentially expressed host genes** in hospitalised and primary care managed participants, **stratified by pathogens and comorbidities**

- **Pathogens:**
  - Influenza virus
  - Human Rhinovirus (HRV)
  - Respiratory Syncytial Virus (RSV)
  - Streptococcus pneumoniae

- **Comorbidities** (Charleson comorbidity index)
  - No comorbidity
  - Chronic pulmonary disease
  - Chronic cardiovascular disease
  - Diabetes

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Sites, set-up and inclusions

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Inclusion criteria

Primary Care	Hospital
Patient is self-attending to primary care	Patient is admitted to hospital
Age ≥ 18 years Clinical suspicion of a new episode of acute respiratory tract infection Onset of the following symptoms, within the last 7 days: Sudden onset self-reported history of fever AND/OR temperature of ≥38°C at presentation AND At least one respiratory symptom (cough, sore throat, runny or congested nose) AND At least one systemic symptom (headache, muscle ache, sweats or chills or tiredness)	

MERMAIDS Study Procedures

Procedures	Day0	Day 2	Hospital cohort: Discharge	Day 28
Screening/Consent	X			
Baseline data	X			
Nasopharyngeal swab	X		X	X
Nasopharyngeal RNA	X		X	X
Physical examination	X			
EDTA blood	X	X	X	
RNA blood	X	X	X	X
SST blood (serum)	X			X
Clinical observations	X		X	X
Concomitant meds	X		X	X
Clinical management	X	X	X	
Follow up outcome				X

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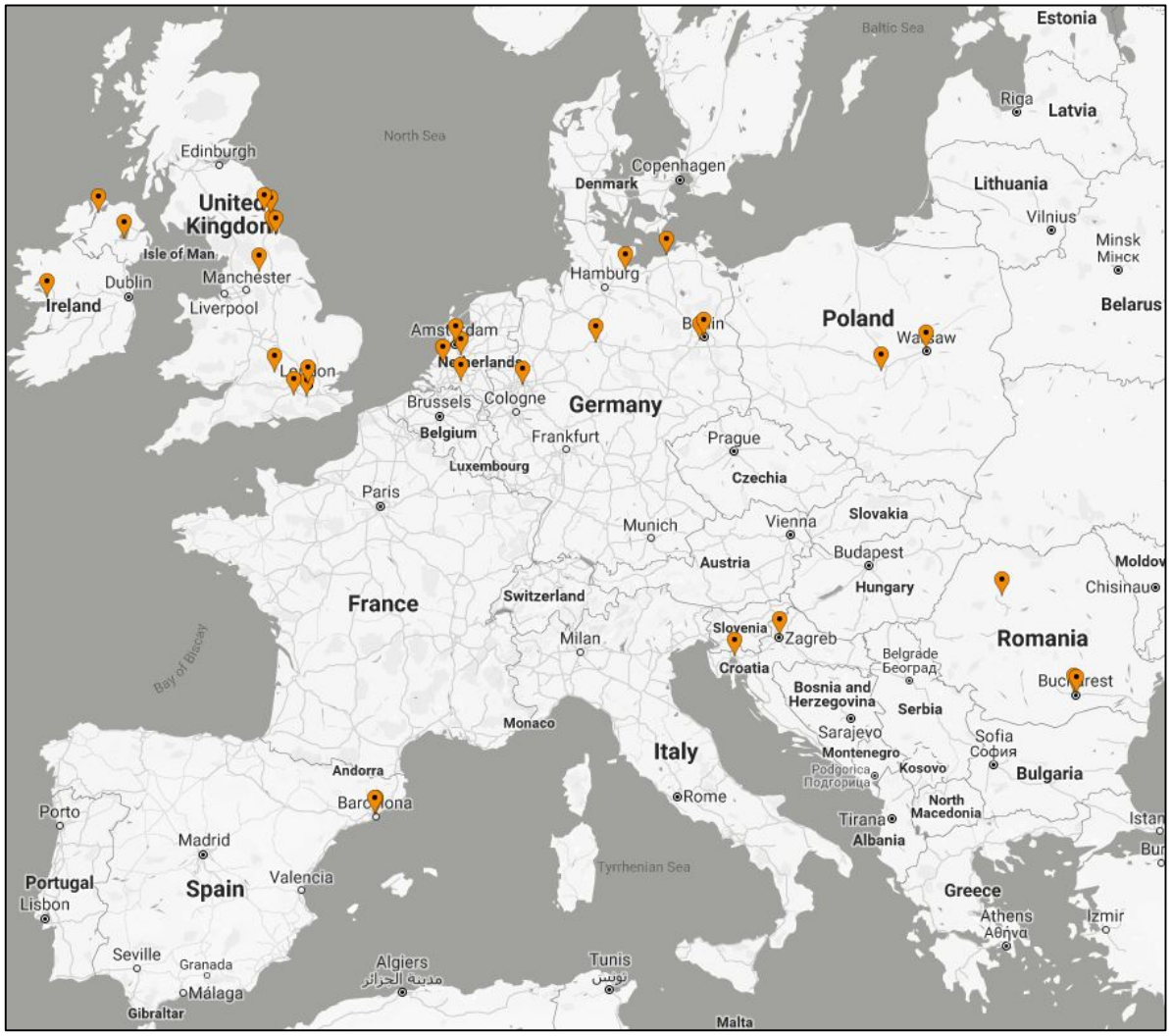
MERMAIDS Recruiting Sites



Eight countries
38 sites
- 9 primary cares
- 29 secondary care

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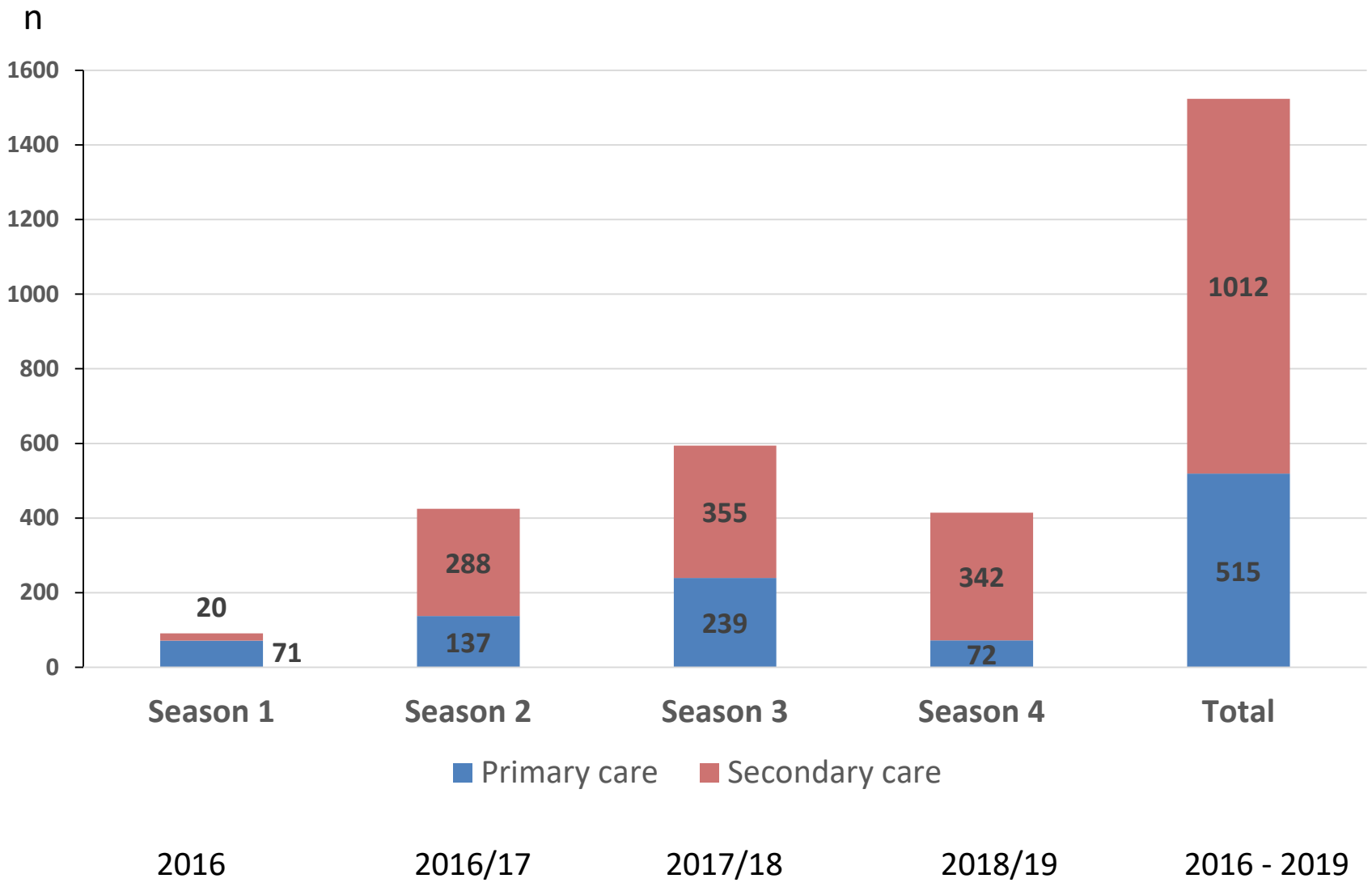
MERMAIDS Recruitment by season



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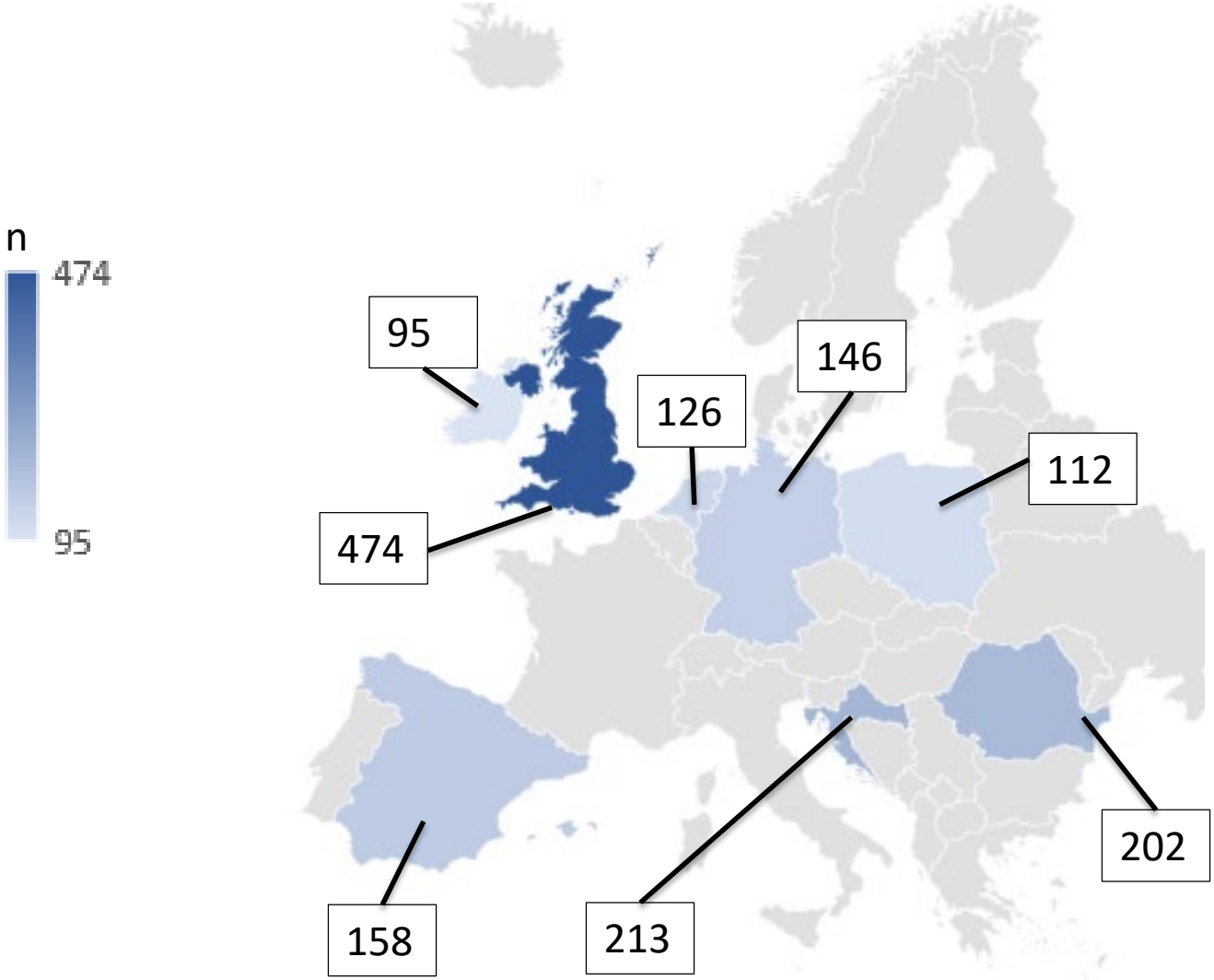
Recruitment by Country



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Cohort characteristics

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Baseline characteristics

PREPAR MERMAIDS-ARI recruitment 2016 - 2019

Characteristics	Primary Care (n=515)	Secondary Care (n=1012)
Age, median (IQR)	44 (33-57)	60 (45-71)
Female, n (%)	317 (61.6)	473 (46.7)
Ethnicity, white n (%)	489 (95.0)	933 (92.2)
Pregnant, n (%)	1 (0.2)	12 (1.2)
Days onset to inclusion, median (IQR)	3 (2– 4)	4 (2 – 5)
Never smoked regularly, n (%)	282 (54.8)	389 (37.8)
Influenza vaccine (≤ 6 m), n (%)	399 (77.5)	601 (59.4)
No comorbidity, n (%)	246 (47.8)	234 (23.1)
One comorbidity, n (%)	164 (31.8)	274 (27.1)
Two or more comorbidities, n (%)	99 (19.2)	497 (49.1)

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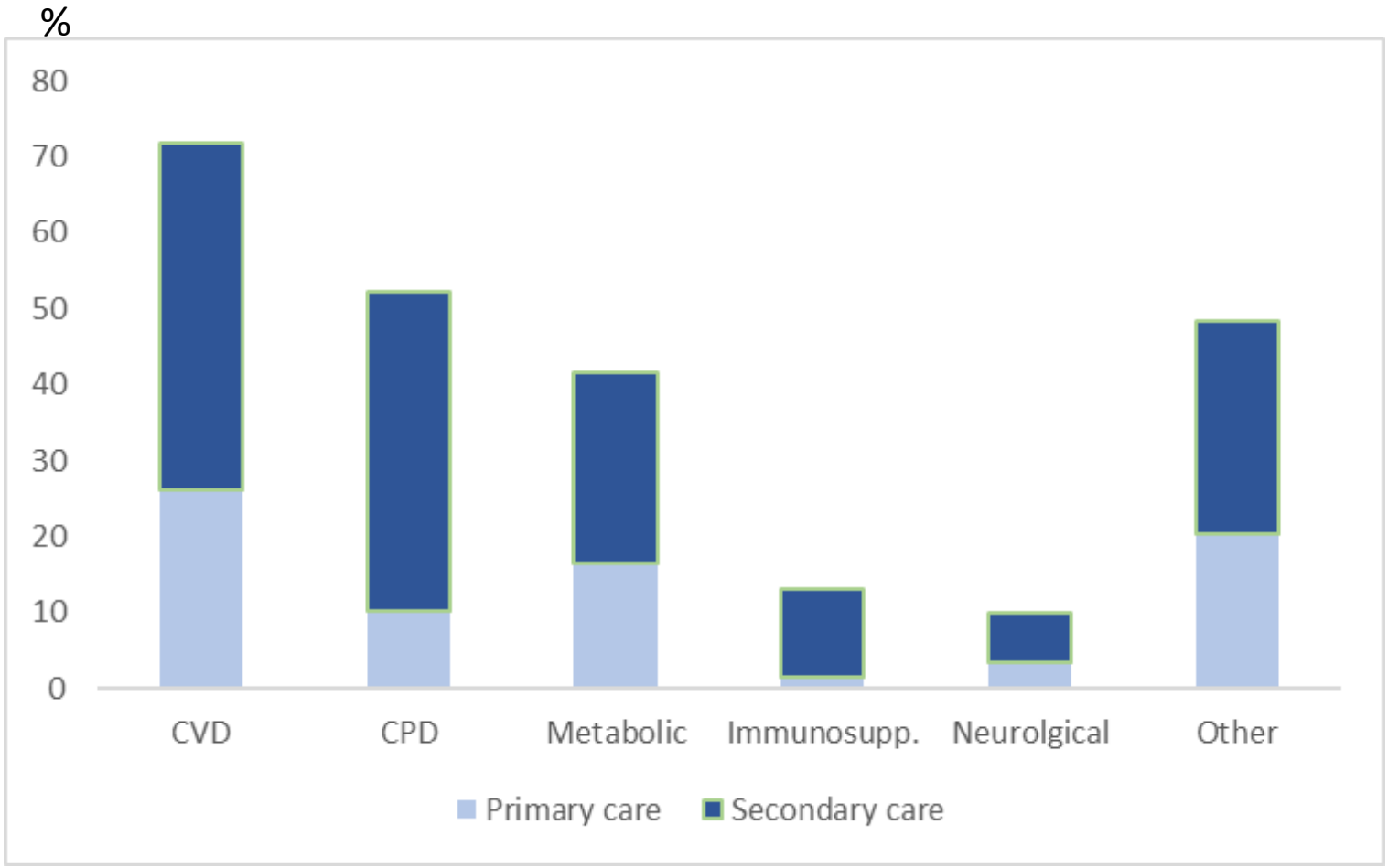
Comorbidities



CVD: Chronic cardiovascular disease, CPD =Chronic pulmonary disease
Missing values < 2

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Symptoms on inclusion		Primary care	Secondary care
Cough	**Yes, n (%)**	**457 (88.7)**	**914 (90.3)**
	No, n (%)	58 (11.3)	98 (9.7)
	Missing, n (%)	-	-
Sore throat	**Yes, n (%)**	**395 (76.7)**	**419 (41.4)**
	No, n (%)	120 (23.3)	590 (58.3)
	Missing, n (%)	-	3 (0.3)
Runny, congested nose	**Yes, n (%)**	**378 (73.4)**	**476 (47.0)**
	No, n (%)	137 (26.6)	532 (52.6)
	Missing, n (%)	-	4 (0.4)
Dyspnoea	**Yes, n (%)**	**122 (23.7)**	**730 (72.1)**
	No, n (%)	322 (62.5)	262 (25.9)
	Missing, n (%)	71 (13.8)	20 (2.0)
Headache	**Yes, n (%)**	**381 (74.0)**	**614 (60.7)**
	No, n (%)	134 (26.0)	397 (39.2)
	Missing, n (%)	-	1 (0.1)
Muscle ache	**Yes, n (%)**	**377 (73.2)**	**609 (60.2)**
	No, n (%)	138 (26.8)	400 (39.5)
	Missing, n (%)	-	3 (0.3)
Sweat/chills	**Yes, n (%)**	**374 (72.6)**	**758 (74.9)**
	No, n (%)	141 (27.4)	253 (25.0)
	Missing, n (%)	-	1 (0.1)
Tiredness	**Yes, n (%)**	**412 (80.0)**	**862 (85.2)**
	No, n (%)	103 (20.0)	149 (14.7)
	Missing, n (%)	-	1 (0.1)

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Assessments on enrolment

Assessment	Primary Care	Secondary Care
CRB-65, mean (SD)	0.2 (0.4)	0.7 (0.8)
PSI score, median (IQR)	38.3 (26 - 51)	65.1 (45 – 86)
Respiratory rate ≥24/min, n (%)	15/506 (3.0)	224/998 (22.4)
Pulse ≥100/min, n (%)	50/511 (9.8)	423/1008 (42.0)
Oxygen saturation <95% on room air, n (%)	33/383 (8.6)	404/954 (44.3)
SBP ≤90 mmHg or DBP ≤60 mmHg, n (%)	55/509 (10.8)	201/1009 (19.9)
CRP >10 mg/dl(>100mg/L), n (%)	9/66 ^(13.6)	439/949 (46.3)

*Only 18 % (93/515) of primary care patients had at least one biochemical test result documented vs. 94% (949/1012) in secondary care

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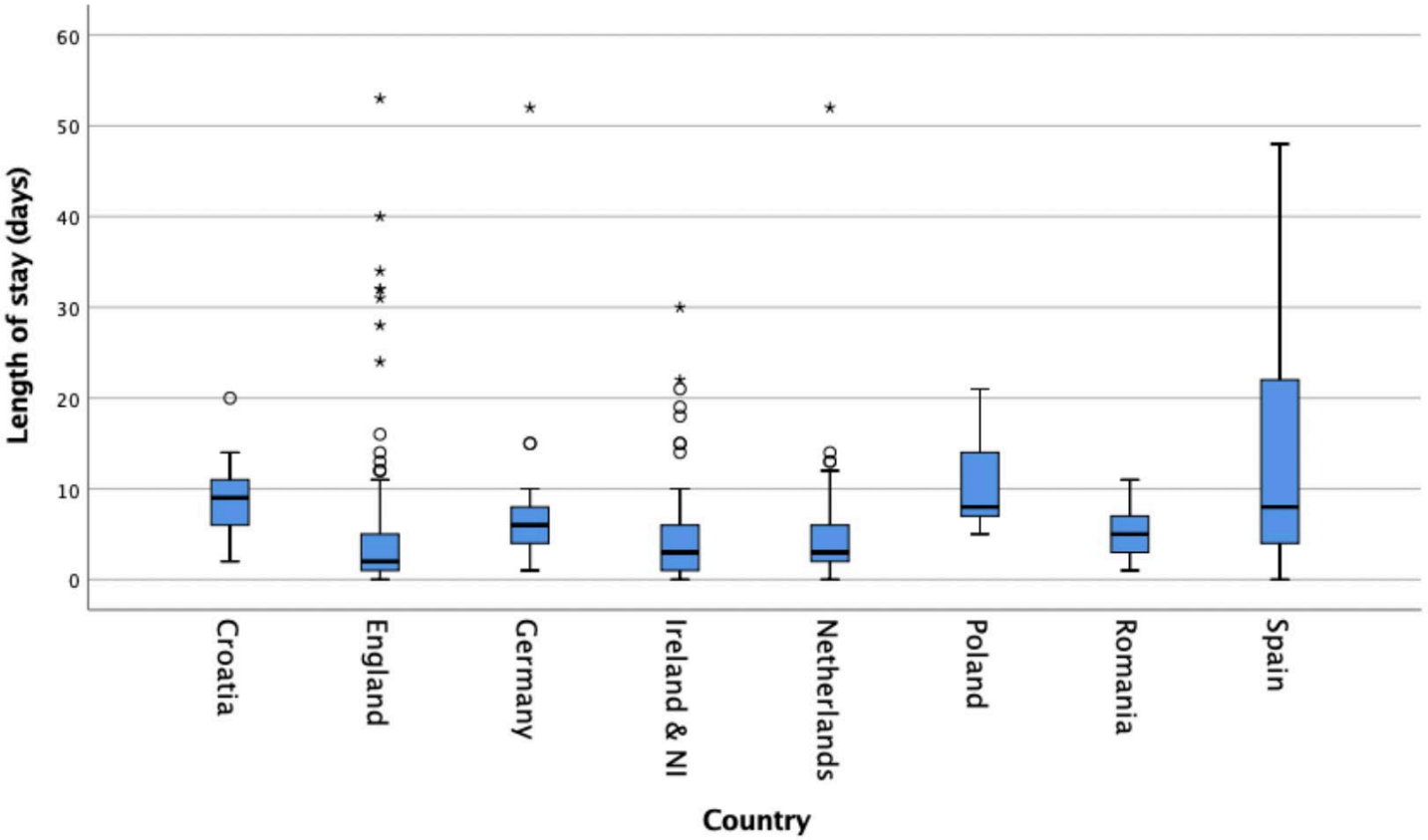
Length of stay by country



Median length of hospital stay: 5 days (IQR: 3 – 9)

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Diagnostic results

Pathogen*	Primary care (n = 515) n (%)	Hospital care (n = 1012) n (%)
Any Influenza (reference lab.)	133 (25.8)	261 (25.8)
Rhinovirus	80 (15.5)	103 (10.2)
Coronavirus (non SARS-CoV-2)	47 (9.1)	33 (3.3)
RSV	17 (3.3)	34 (3.4)
Metapneumovirus	6 (1.2)	35 (3.5)
Parainfluenza virus 1-4	10 (1.9)	23 (2.3)
Influenza cases detected by type (reference lab)	**Primary care (n=133)**	**Secondary care (n=261)**
Influenza B	72 (54.1)	78 (29.9)
Influenza A (non H1N1)	41 (30.8)	89 (34.1)
Influenza A H1N1	20 (15.0)	95 (36.4)
Bacterial (Local diagnostics)	**Primary care**	**Secondary care**
A bacterial pathogen detected	139	155
Streptococcus pneumoniae	-	59 /155 (38.0)
Legionella pneumophila	-	8 /155 (5.2)
Staphylococcus aureus	-	3/155 (2.6)
Mycoplasma pneumoniae	-	4 /155(2.6)

- 63% administered antibiotic on inclusion in secondary care

Viral diagnostics: Reference laboratory at University of Antwerp (NPH RT PCR).
Bacterial diagnostics: local diagnostic outcomes

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Outcomes

Parameter	Primary care N (%)	Secondary care N (%)
ICU/HDU admission	n/a	39/1011 (3.9)
Supplemental oxygen	n/a	491 /1006 (48.8)
Non-invasive ventilation	n/a	36/1006 (3.6)
Invasive ventilation	n/a	6 /1006 (0.6)
Prone invasive ventilation	n/a	5/1006 (0.5)
ARI infection on outcome	480 / 503 (95.4)	943/1006 (93.7)
Alive, discharged to home	503/512 (98.2)	895/1011 (88.54)
Day 28 mortality	0 (0.0)	14/1011 (1.4)

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MERMAIDS for COVID-19

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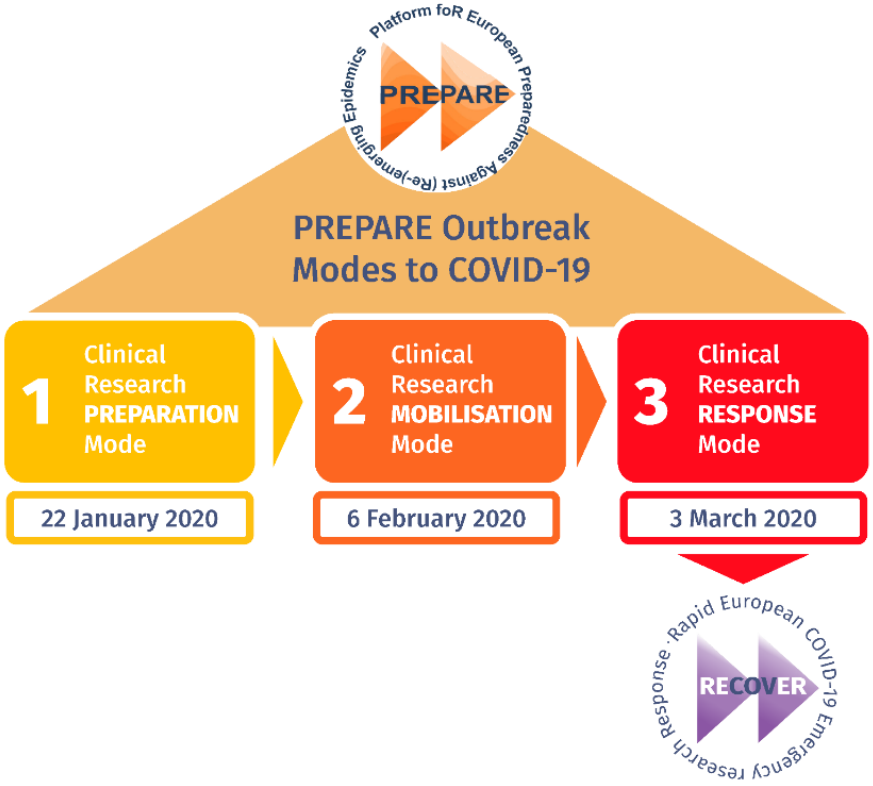
PREPARE's outbreak response action to the COVID-19 epidemic



RECOVER emerges from an EU-initiative called PREPARE that was first set-up in 2014.

PREPARE is designed to ensure that clinical research is set in motion to study the many uncertainties of a new disease, which has the potential to threaten the health and security of European citizens.

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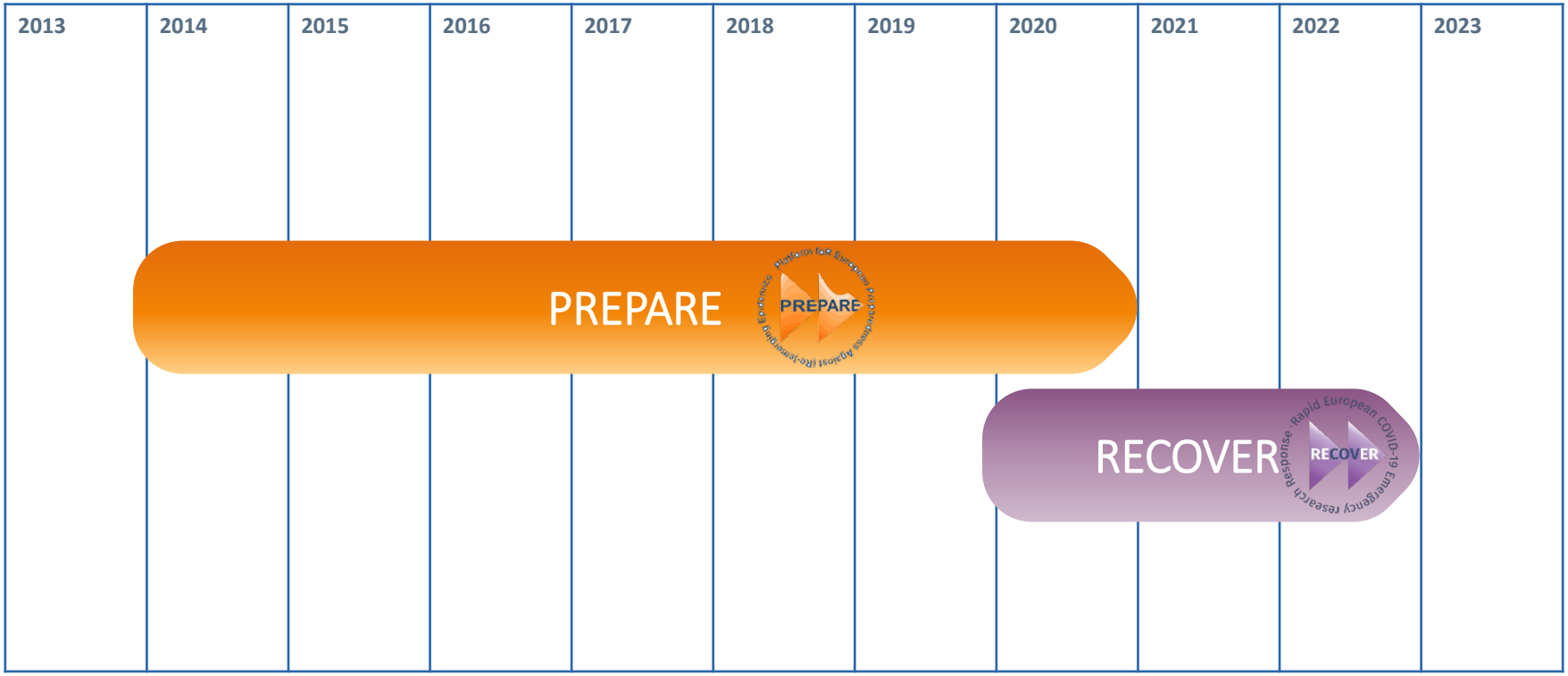
Funding Timeline



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MERMAIDS for COVID-19

- Increased the target to 3000 and extended duration to February 2022
- Can compare **mild and severe** COVID-19 cases, and compare SARS-CoV-2 with **other respiratory viruses**
- Can compare **mild and severe** COVID-19 cases, **stratified by comorbidities**
- Can determine **host responses** and **pathophysiology** in COVID-19
- Can determine pathogen and host **mechanisms underlying disease severity** of COVID-19

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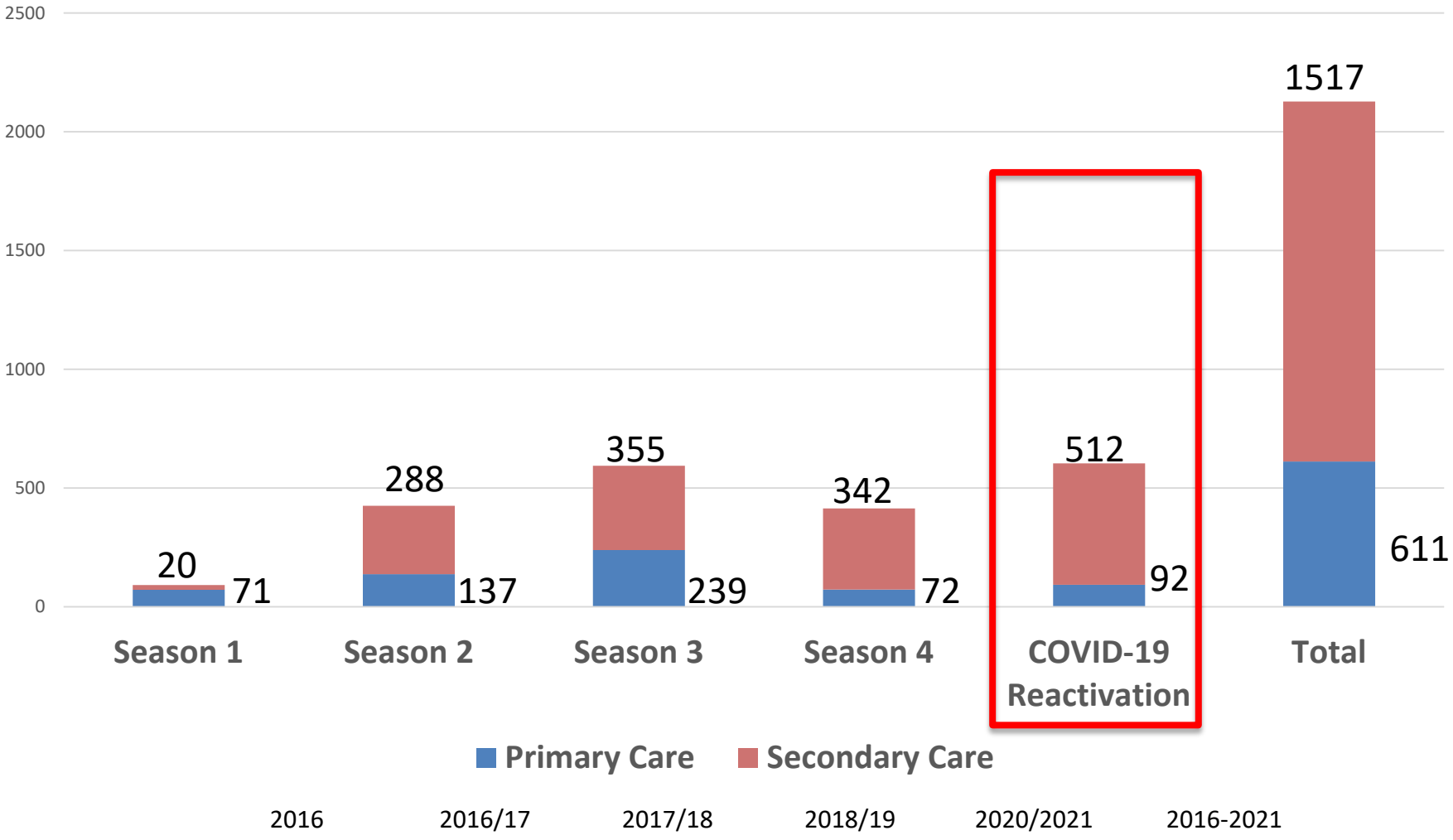
MERMAIDS

Recruitment per season + COVID-19 Reactivation



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Acknowledgements

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MERMAIDS

Platform foR European Preparedness Against (Re-)emerging Epidemics
PREPARE

Belgium

Universiteit Antwerpen

Ireland

Galway University Hospitals
Ospidéil na h-Ollscoile Gaillimh
UNIVERSITY HOSPITAL GALWAY
MERLIN PARK UNIVERSITY HOSPITAL

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Vivantes

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UNIVERSITÄTS KLINIKUM FREIBURG

CAPNETZ STIFTUNG
KOMPETENZNETZ CAPNETZ
Community Acquired Pneumonia
AMBULANT ERWORBENE PNEUMONIE

Poland

MEDICAL UNIVERSITY OF LODZ

RUB

Instytut Gruźlicy i Chorób Płuc

Myth of truth?

Profiling host gene expression during acute respiratory infections

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Outline

- Study design and objectives
- Introduction to transcriptome analysis
- Host gene expression in Covid-19
- Placing Covid-19 in the context of other ARI
- Final remarks

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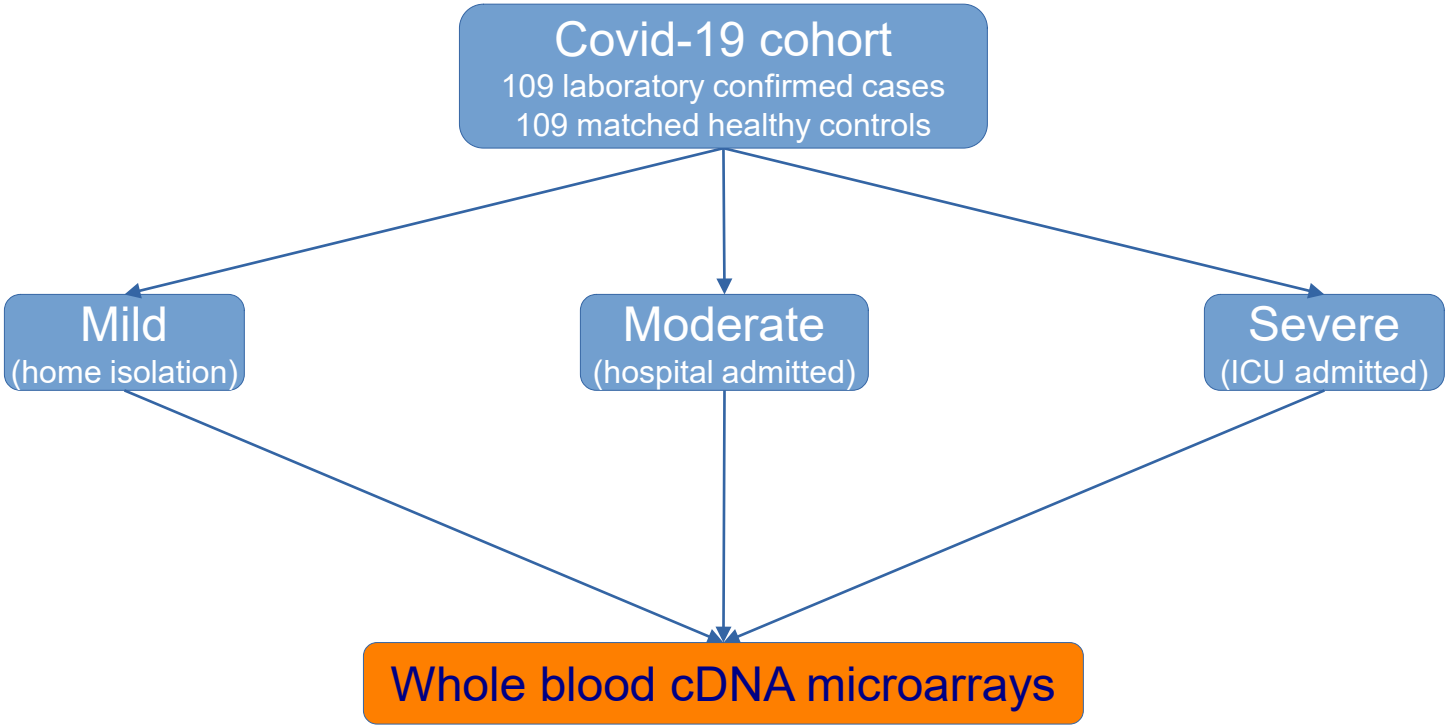
Design and objectives



- Gain insights into Covid-19 pathophysiology
- Identify molecular determinants of progression to severe disease
- Dysregulated pathways
- Predictors of outcome
- Drug targets

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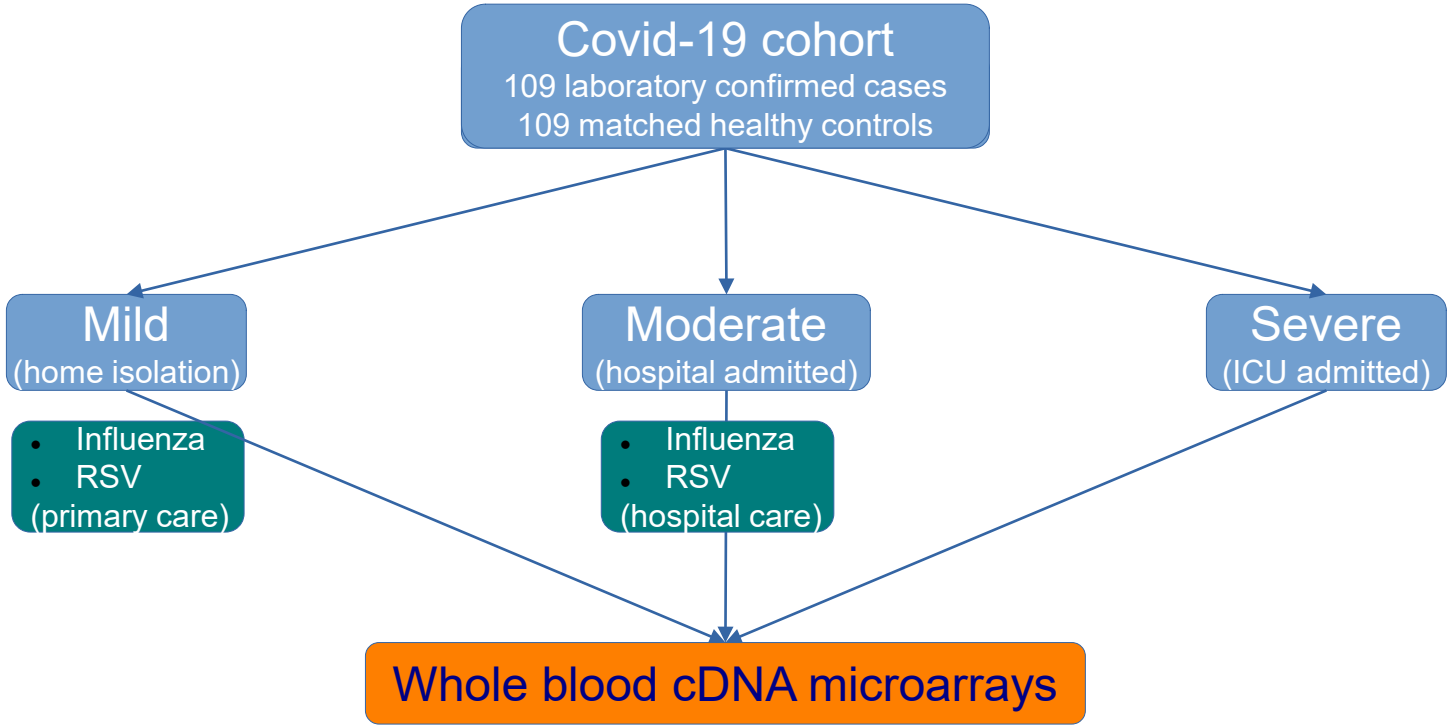
Design and objectives



Phase 1

- Gain insights into Covid-19 pathophysiology
- Identify molecular determinants of progression to severe disease
- Dys-regulated pathways
- Predictors of outcome
- Drug targets

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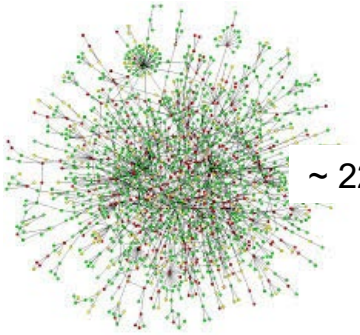
Patients characteristics

	Control (N = 103)	Mild (N = 29)	Moderate (N = 22)	Severe (N = 57)
Age				
Median	62	49	63.5	65
Gender				
Male (%)	74 (72%)	19 (66%)	11 (50%)	49 (86%)
Comorbidity				
Any	69 (67%)	9 (31%)	13 (59%)	40 (70%)
Days of illness				
Median	0	7	7	16
Death				
n	0 (0%)	0 (0%)	2 (9%)	15 (26%)

Untangling complex systems



~ 22,333 genes

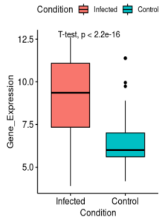
Complexity

DATA ANALYSIS

- Global variation/perturbation of gene expression (PCA)
- Transcriptome decomposition (modules)

  - Groups of biologically and functionally related genes

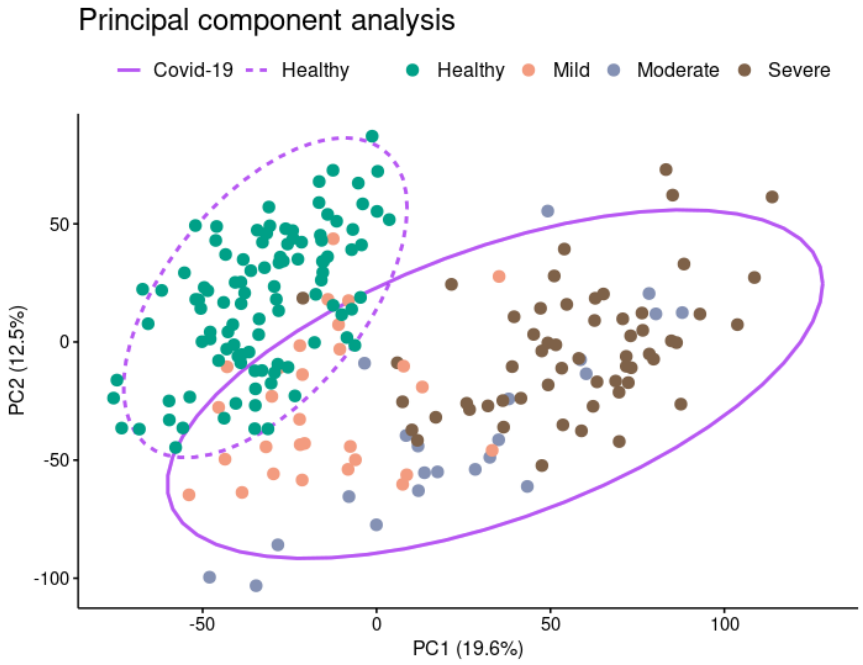
- Differentially expressed genes (DEGs)



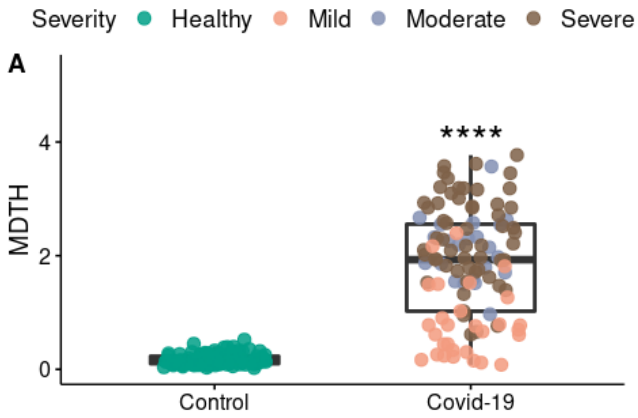
  - Fold-Change = Magnitude of difference
  - P-value = Significance of difference

- Genes prioritization

Global variation of expression profiles



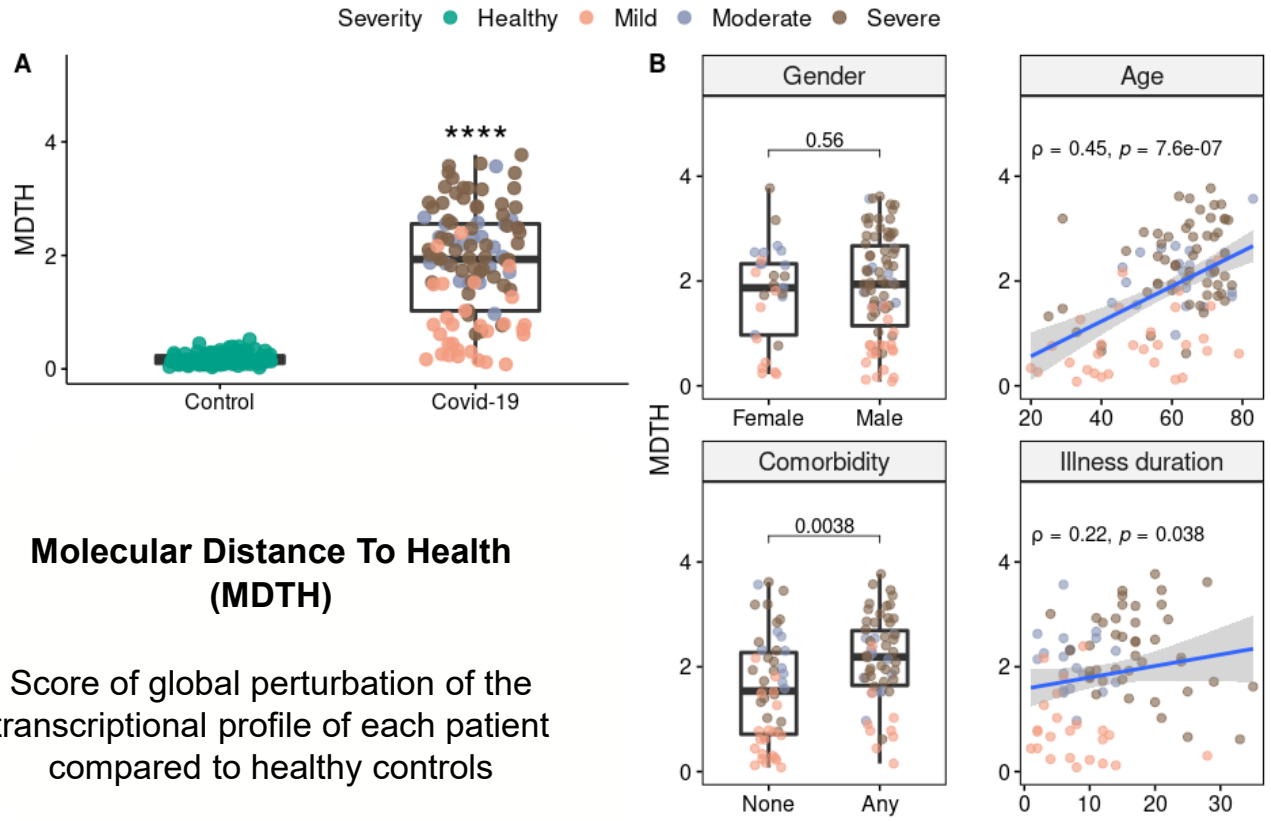
Global perturbation of expression profiles



Molecular Distance To Health (MDTH)

Score of global perturbation of the transcriptional profile of each patient compared to healthy controls

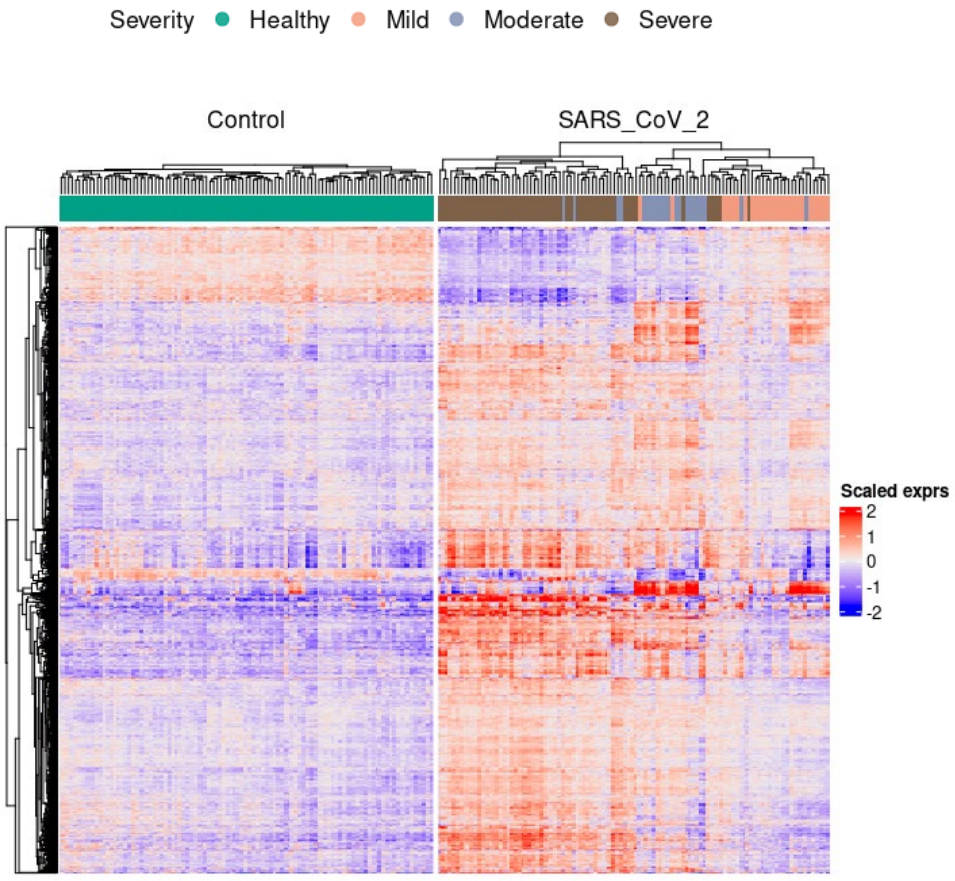
Global perturbation of expression profiles



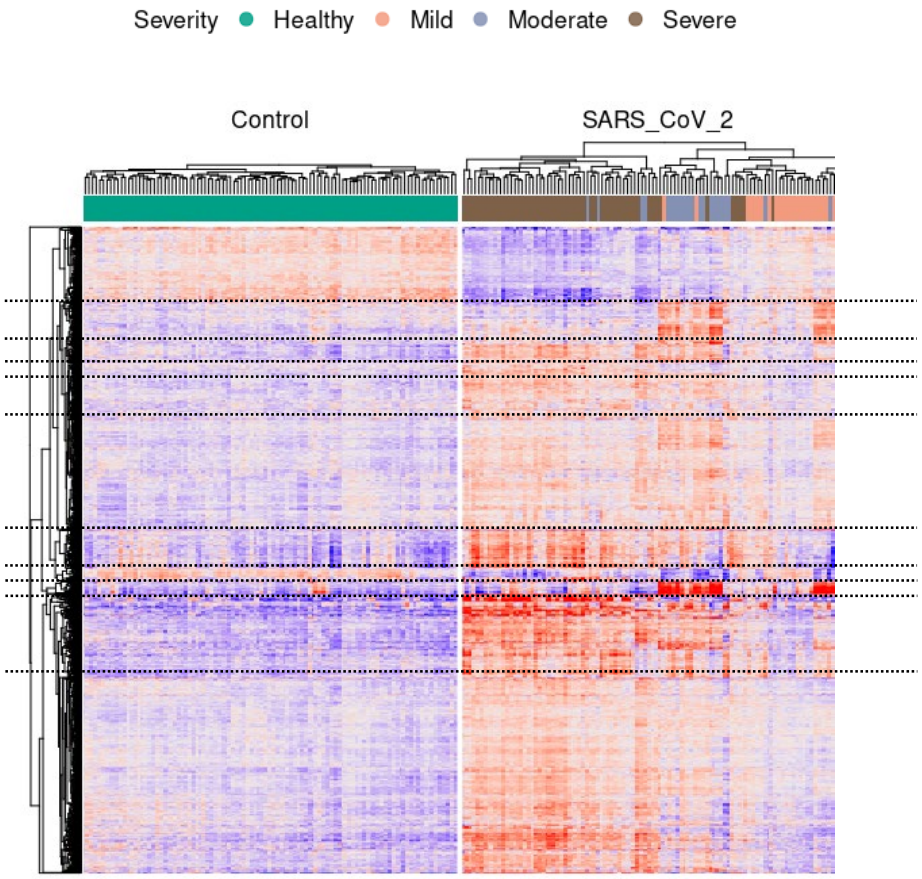
Molecular Distance To Health (MDTH)

Score of global perturbation of the transcriptional profile of each patient compared to healthy controls

Unveiling the modular architecture of GEP

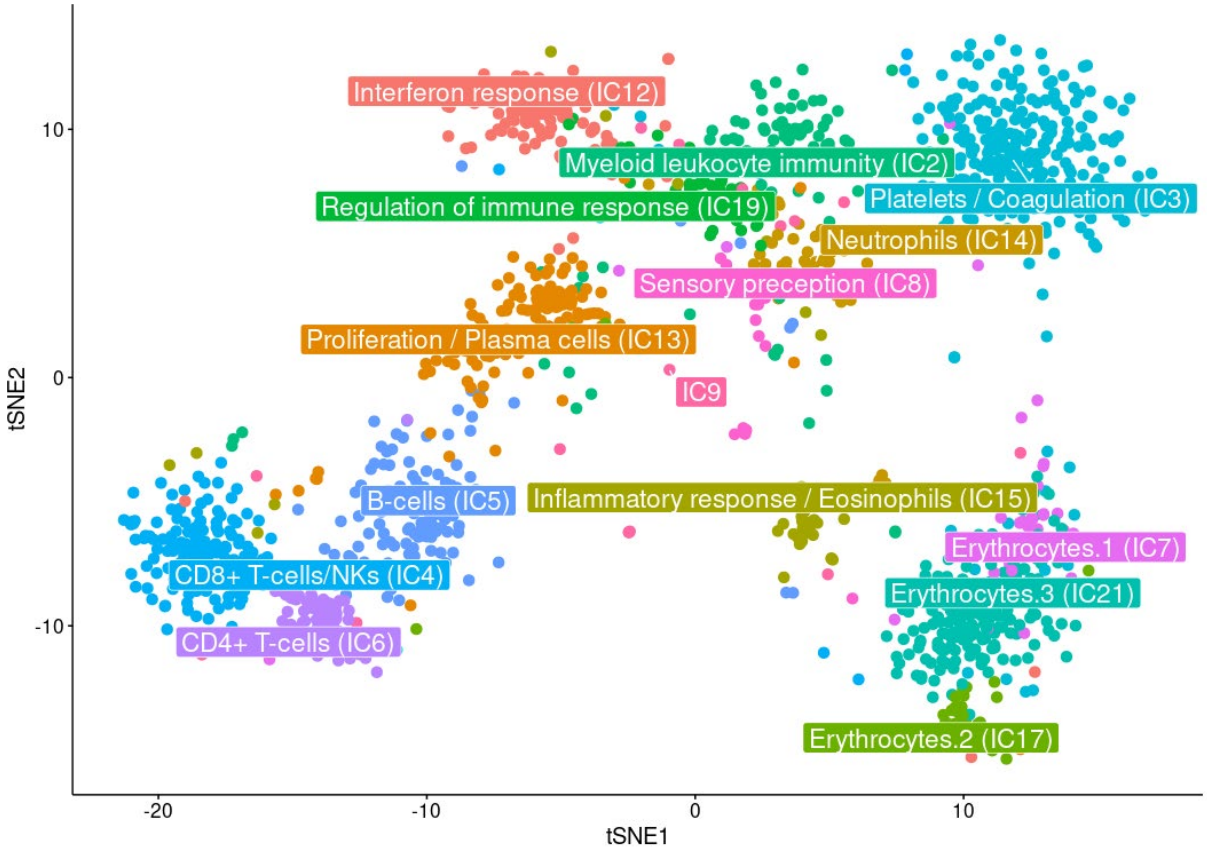


Unveiling the modular architecture of GEP



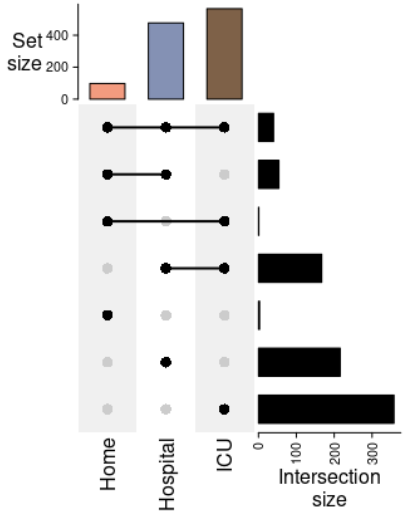
Unveiling the modular architecture of GEP

Modules: groups of biologically and functionally related genes

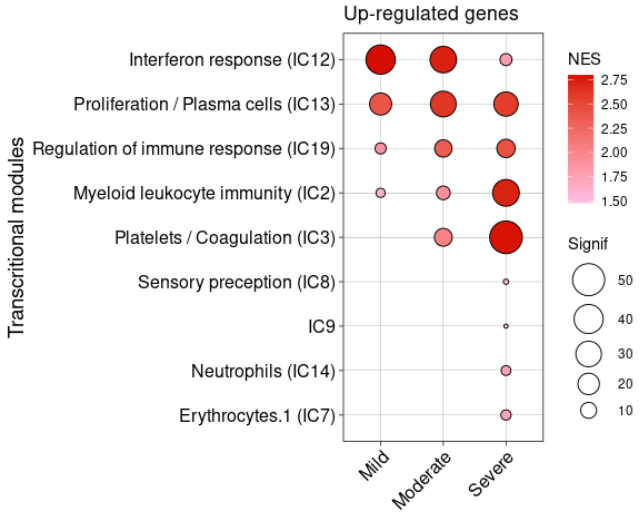


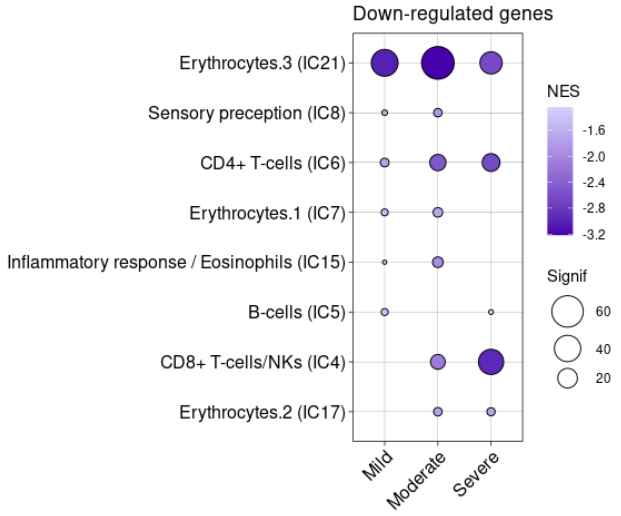
Differential gene expression

Shared genes across severity

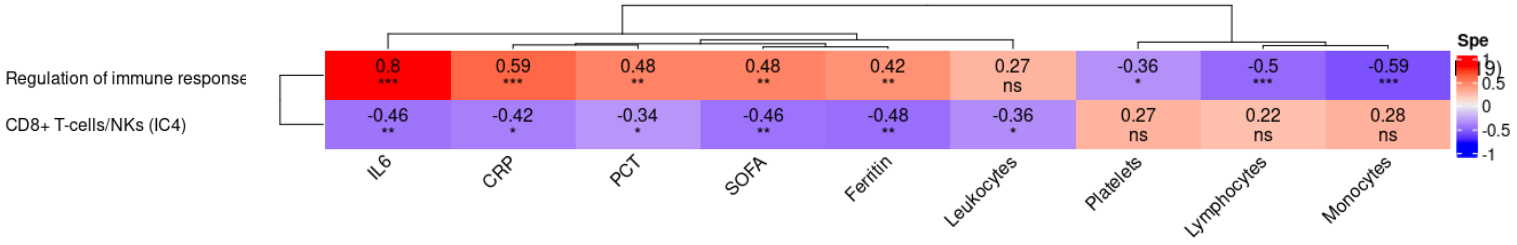


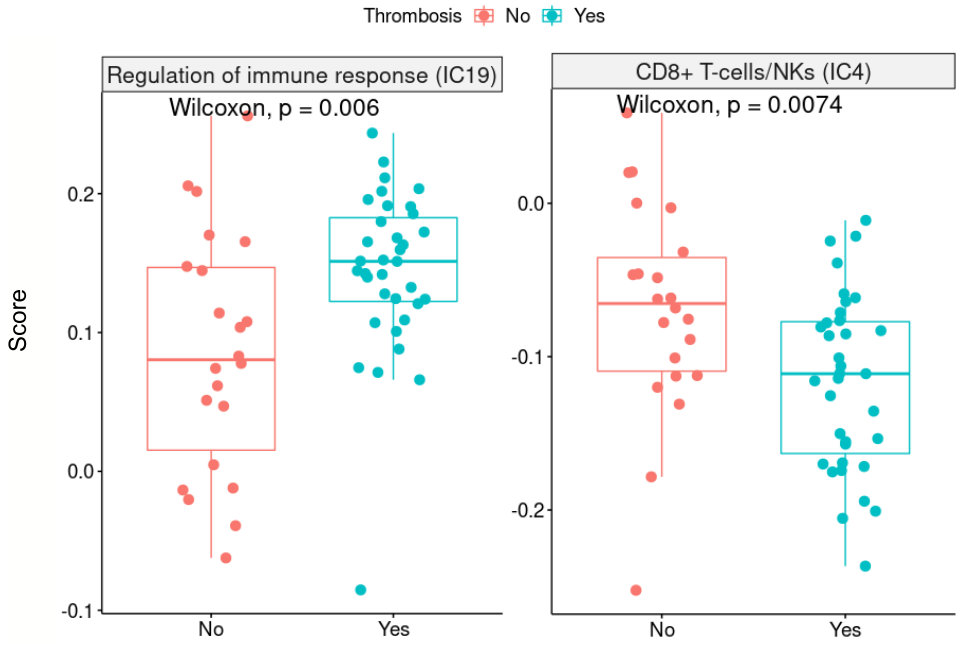
Transcriptional modules enrichment



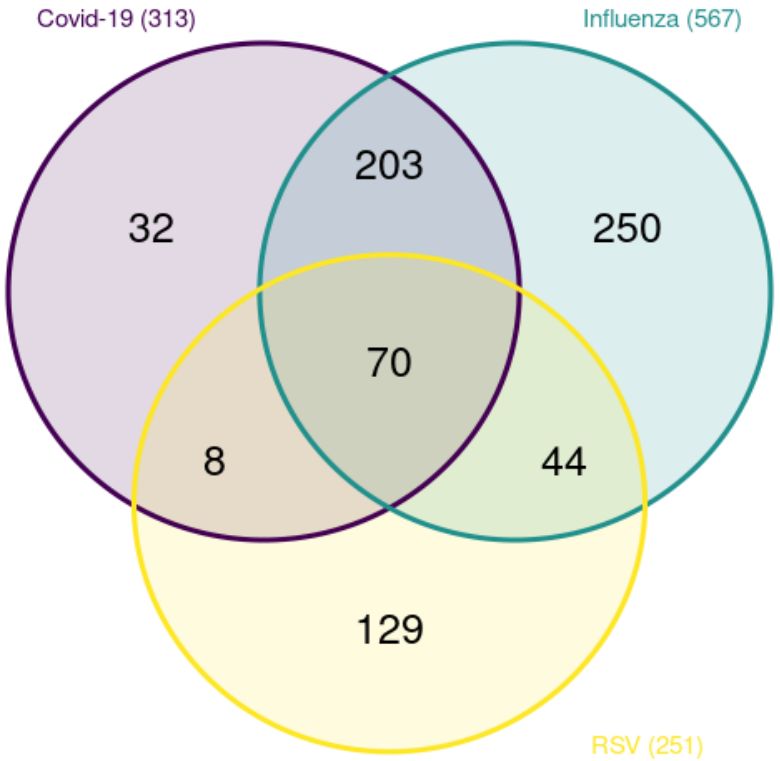


Modules validation with clinical traits

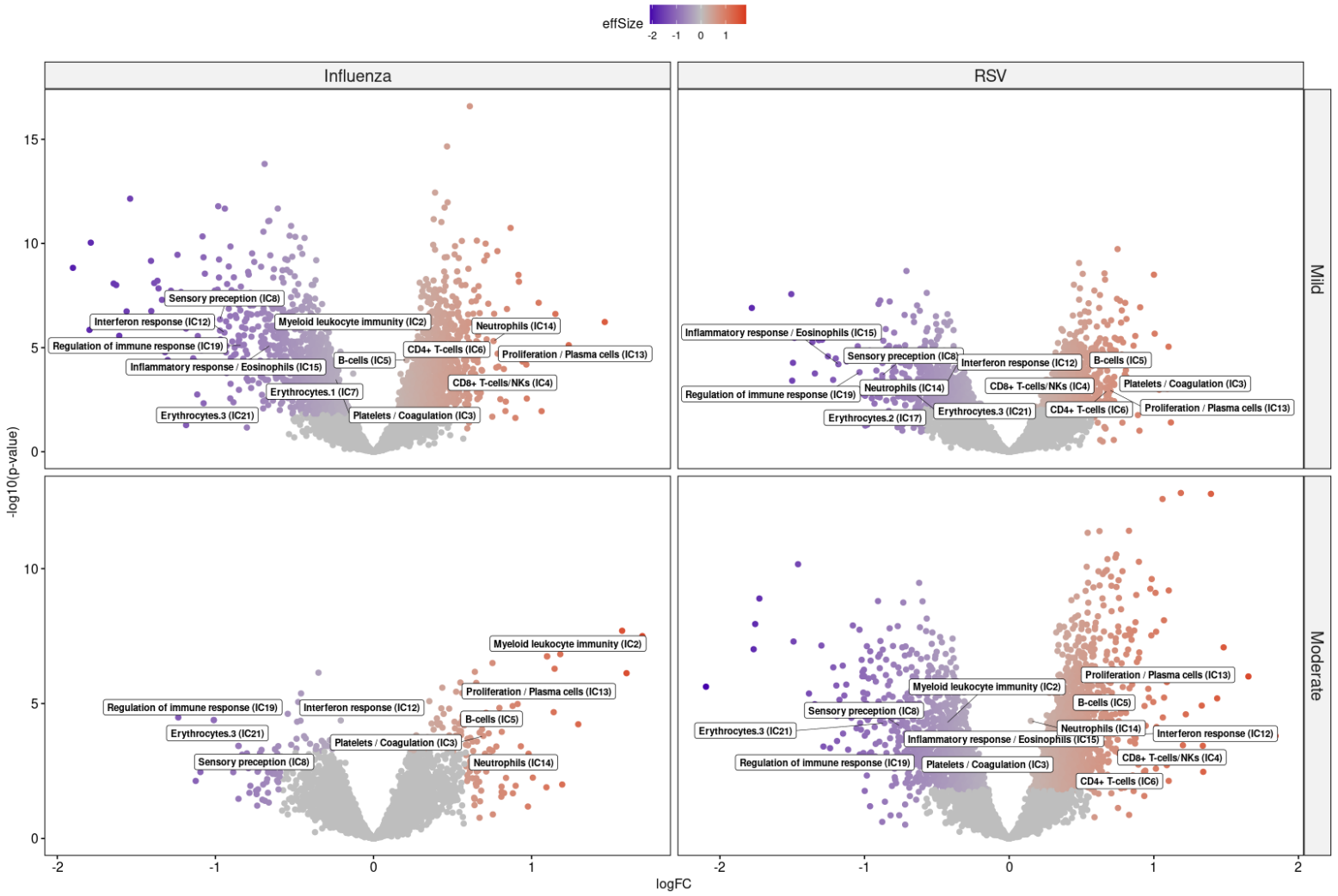




Covid-19 compared to other respiratory infections



Covid-19 compared to other respiratory infections



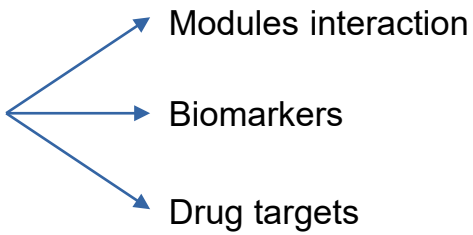
Higher in influenza ⟷ Higher in covid19 Higher in RSV ⟷ Higher in covid19

Final remarks

- Severe covid-19 is characterized by dysregulation in:
  - Inflammatory pathways
  - Myeloid cells activation
  - Adaptive immunity
  - Coagulation / platelets activation
  - Sensory perception

- Covid-19 exhibit a considerable number of commonalities and few but relevant differences with other respiratory pathogens

- Ongoing work:
  - Network analysis



- Future work:
  - Gain insights into differences and commonalities in other relevant respiratory pathogens

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Platform foR European Preparedness Against (Re-)emerging Epidemics
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AMBULANT ERWORBENE PNEUMONIE

Poland

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Instytut Gruźlicy i Chorób Płuc

Multi-centre EuRopean study of MAjor Infectious Disease Syndromes –
Community-acquired acute respiratory tract infection in childhood (PED-MERMAIDS)

More than a children's tale: Aetiology and management of paediatric ARI hospitalisations

PREPARE Webinar Series – 17/03/2021

Malte Kohns Vasconcelos, St George's, University of London

PREPARE is funded by the European Commission under grant number 602525

Objectives

Primary objective: To estimate the proportions of children aged 0-6 years old with acute respiratory infection (ARI) which is attributable to Respiratory Syncytial Virus (RSV), Influenza virus, Human Rhinovirus or *S. pneumoniae*.

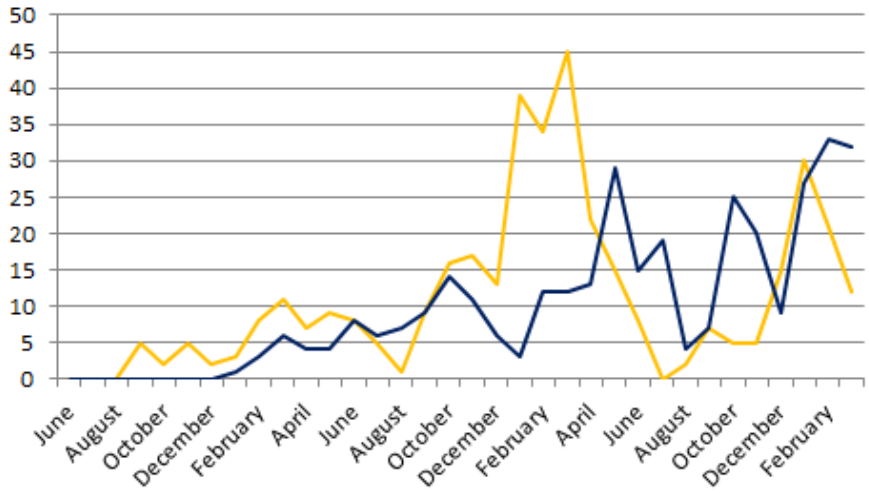
Objectives

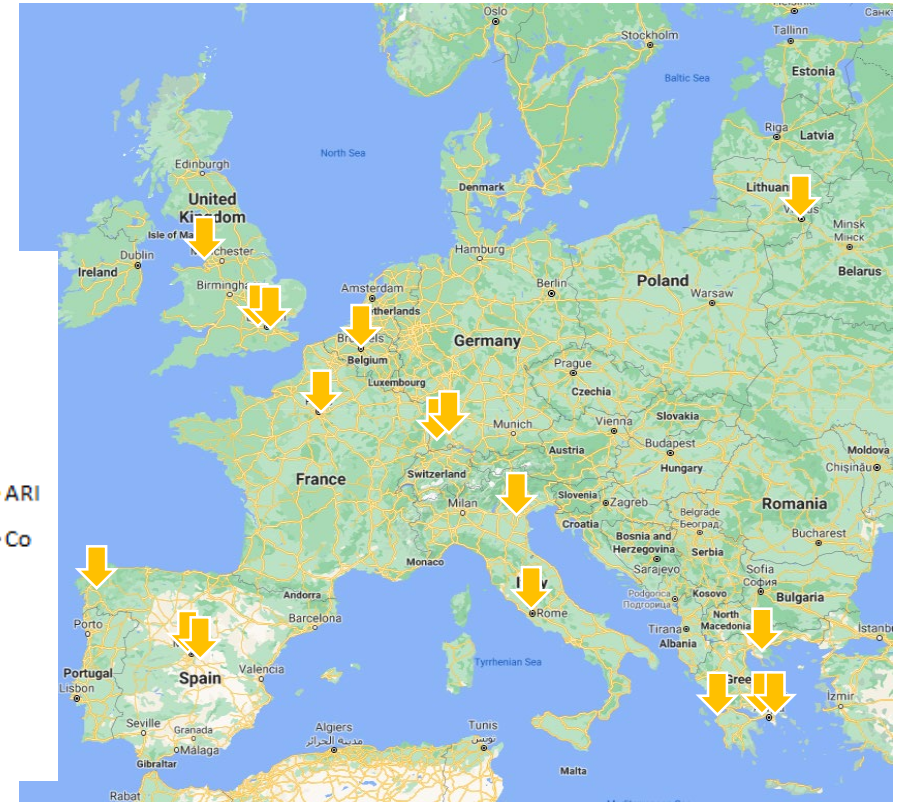
Secondary objectives:

- To assess if viral load is associated with disease severity in children (aged <6 years) with ARI and RSV, FLU and/or HRV detectable in NP swabs
- To assess if bacterial load is associated with disease severity in children (aged <6 years) with ARI and S. pneumoniae detectable in NP swabs
- **To assess association between viral-viral and viral-bacterial co-detection and disease severity in children aged <6 years with ARI and RSV, influenza virus, HRV or S. pneumoniae detectable in NP swabs**
- **Describe the clinical management of ARI in hospitalised children (< 6 years old) across Europe**
- To establish whether common pathways exist that may explain the development of severe ARI in both adults and young children

Recruitment

Continuous (year-round) recruitment between September 2016 and March 2019
Parallel recruitment of cases and controls
Patients were recruited as they presented to participating EDs, mainly during day-time hours





Eligibility criteria (ARI group)

- Clinical suspicion of a new episode of acute respiratory tract illness within the last 7 days
- The attending physician has decided that the child requires hospitalisation
- Primary reason for hospital admission is clinical suspicion of a new episode of ARI
- Temperature >38°C measured by any method
- Age < 6 years old on the day of admission (day 0) into the study

AND at least TWO of the below with at least ONE of either 1 or 2 (At least 2 YES mandatory):

- Signs of reduced general state: Poor feeding, vomiting, lethargy drowsiness.
- Signs of respiratory dysfunction: Age related tachypnoea or brady/apnoea or decreased oxygen saturation (<92% in room air)
- Signs of upper respiratory tract infection
- Signs of lower respiratory tract infection

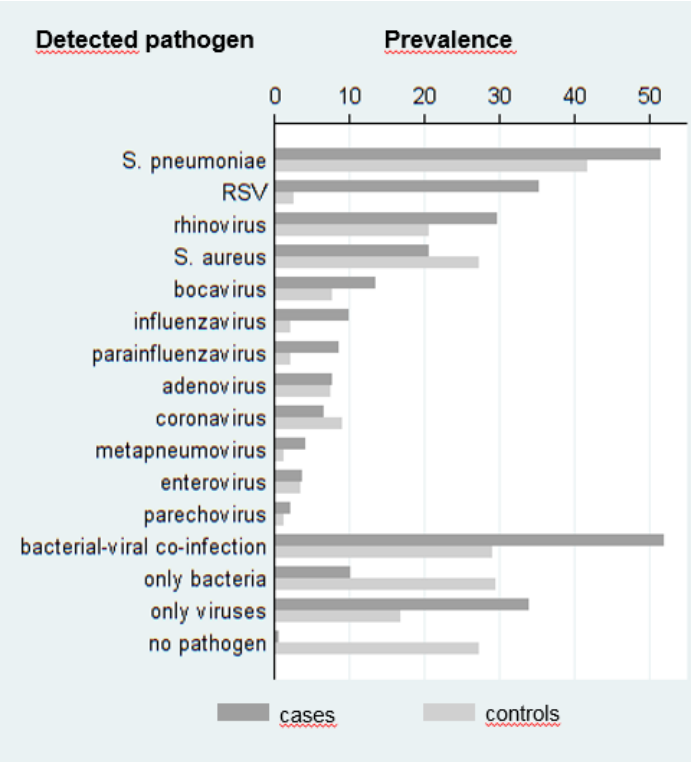
Exclusion for: complex comorbidities or immunosuppression, non-infectious aetiology or non-ARI focus

Controls: hospital outpatients or attending for elective procedure – not necessarily asymptomatic

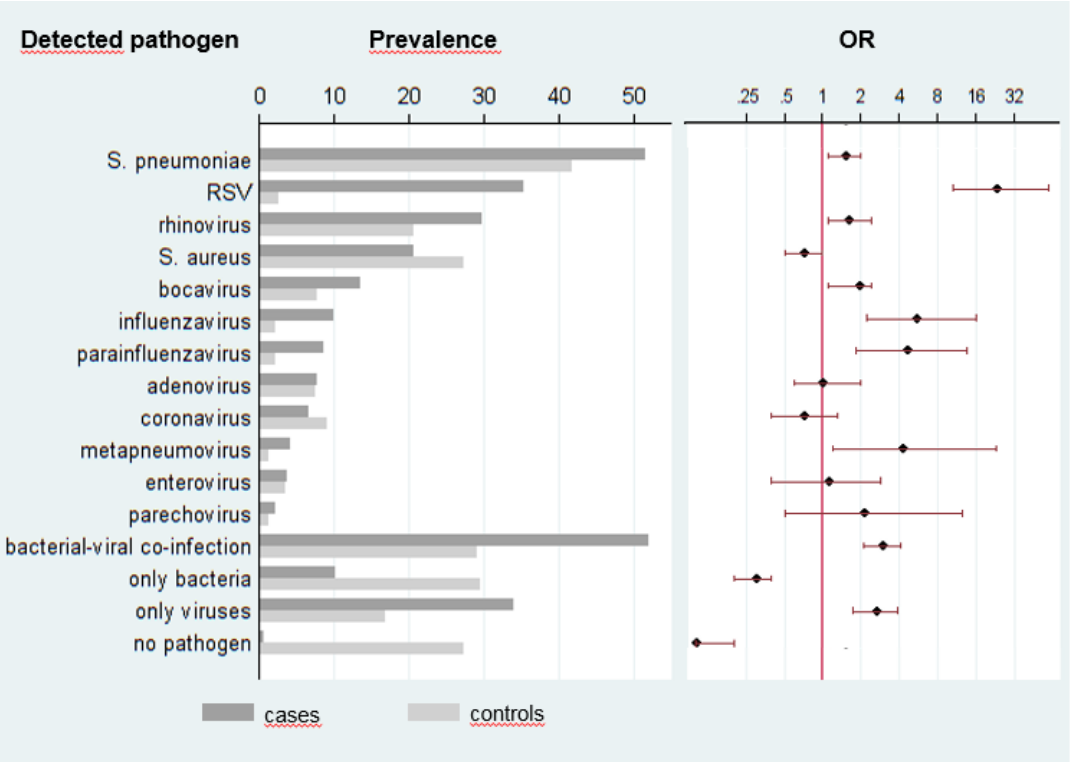
Case-control study population

Groups:		ARI	Control	p-value
Total inclusions (n)		349	306	-
Sex (male, n, %)		202 (57.9)	200 (65.4)	<0.001
Age in years (median, IQR)		1.09 [0.42, 2.49]	1.80 [0.93, 3.65]	<0.001
Age range (n, %)	<12 months	160 (45.9)	83 (27.1)	
	12 - <36 months	120 (34.4)	114 (37.3)	
	>= 36 months	69 (19.8)	109 (35.6)	<0.001
Inclusion by season (n, %)	Oct – Dec	76 (21.8)	85 (27.8)	
	Jan – Mar	182 (52.2)	115 (37.6)	
	Apr – Sep	91 (26.1)	106 (34.6)	<0.001
Inclusion by country (n, %)	Greece	144 (41.3)	50 (16.3)	
	Italy	85 (24.4)	46 (15.0)	
	Spain	45 (12.9)	45 (14.7)	
	UK	55 (15.8)	94 (30.7)	
	other	20 (5.7)	71 (23.2)	<0.001

Pathogen detection in cases and controls



Pathogen detecion in cases and controls



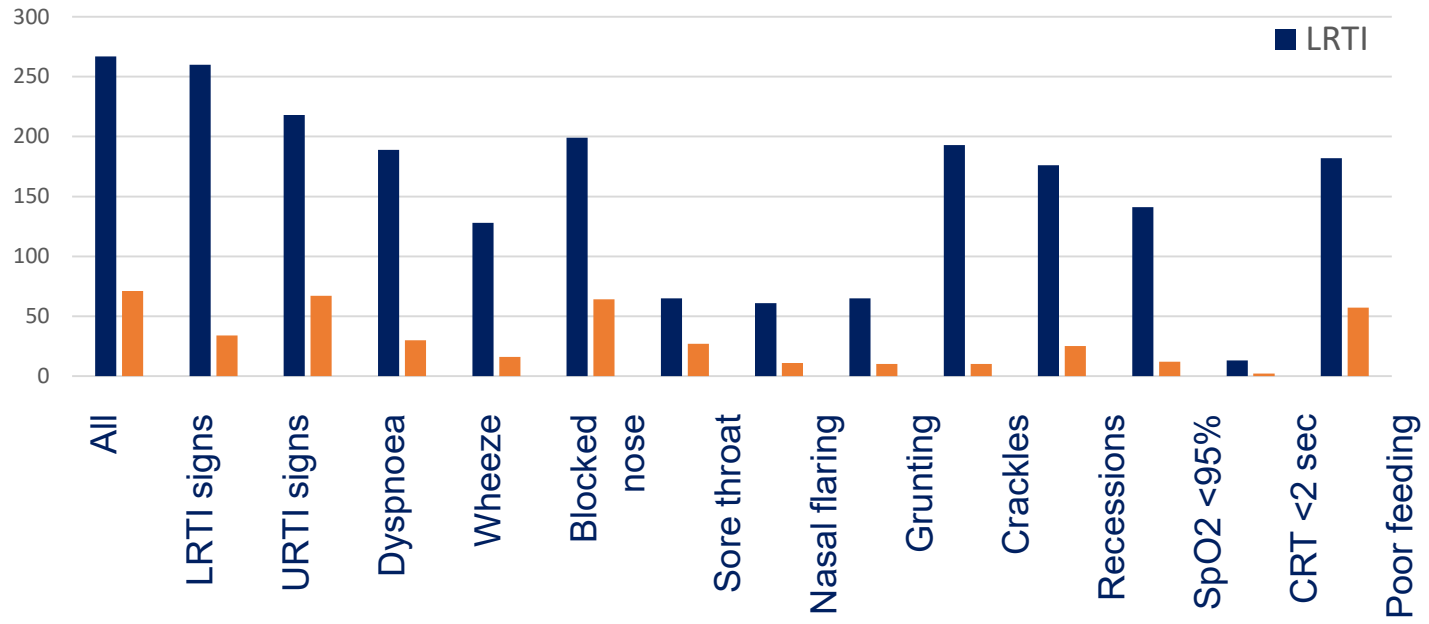
Odds ratio of detection in cases compared to controls by multiplex PCR in nasopharyngeal swabs, by pathogen, adjusted for age and season (logistic regression)

Pathogen	Adjusted OR	95%-CI	p-value
S. pneumoniae	1.7	1.2-2.3	0.002
RSV	20.6	9.4-45.3	<0.001
Influenza virus	6.1	2.5-14.9	<0.001
No pathogen detected	0.1	<0.1-0.2	<0.001

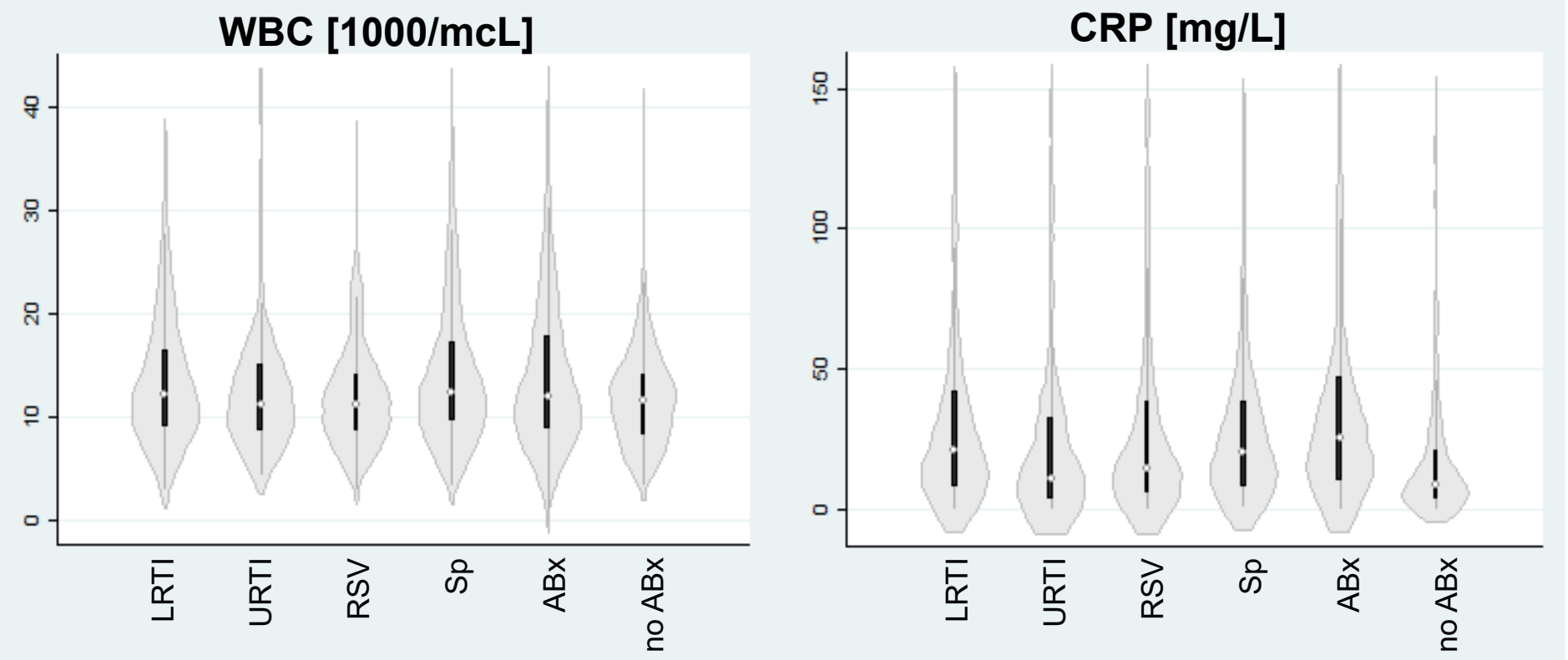
Aetiological fractions by age and season

RSV		Age group (PAF%)		
		<12 months	12 - <36 months	≥36 months
Season	Oct – Dec	48.0	38.1	20.0
	Jan – Mar	48.1	35.6	19.2
	Apr – Sep	23.5	16.7	4.8
Influenza virus		**Age group (PAF %)**		
		<12 months	12 - <36 months	≥36 months
Season	Oct – Dec	-	8.0	3.8
	Jan – Mar	11.0	9.5	30.3
	Apr – Sep	3.0	-	4.8

Signs and symptoms at presentation



WBC and CRP


WBC [1000/mcL]
0
10
20
30
40
LRTI
URTI
RSV
Sp
ABx
no ABx
CRP [mg/L]
0
50
100
150
LRTI
URTI
RSV
Sp
ABx
no ABx

Management

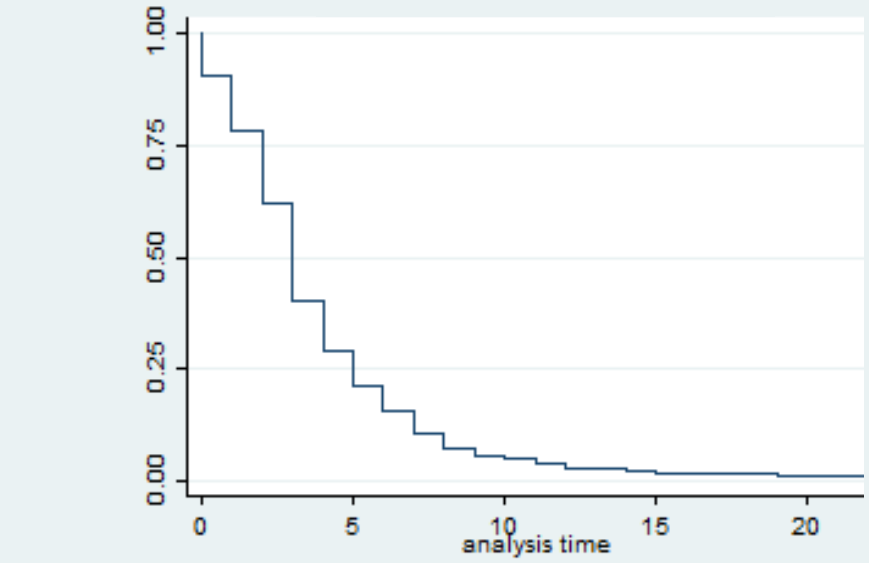
		Type of ARI (discharge diagnosis)		p
		LRTI	URTI	
N		267 (100%)	71 (100%)	
respiratory pathogen testing	any	169 (63.3)	24 (33.8)	<0.001
	culture	37 (13.9)	2 (2.8)	0.008
	RSV	151 (56.6)	22 (31.0)	<0.001
	Influenza	139 (52.1)	21 (29.6)	0.008
chest X-ray		187 (70.0)	23 (32.4)	<0.001
medication	antibiotics	183 (68.5)	25 (35.2)	<0.001
	corticosteroids	100 (37.5)	13 (18.3)	<0.001
	bronchodilators	162 (60.7)	10 (14.1)	<0.001
intravenous fluids		163 (61.1)	24 (33.8)	<0.001
supplementary O_2		152 (56.9)	8 (11.3)	<0.001
ICU admission		12 (4.5)	0 (0.0)	0.169

Antibiotic treatment regimens

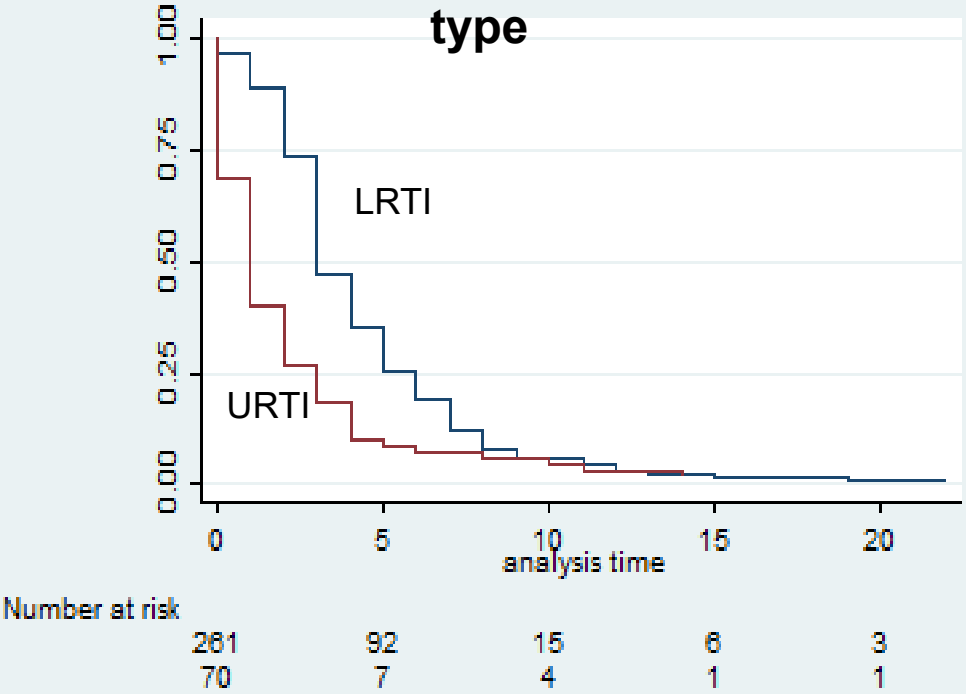
	Spain	Italy	Greece	UK	other
LRTI					
no antibiotic	18 (36.0)	25 (46.3)	61 (56.0)	16 (39.0)	9 (69.2)
combination	3 (6.0)	1 (1.9)	4 (3.7)	2 (4.9)	0 (0.0)
aminopenicillin	16 (32.0)	9 (16.7)	14 (12.8)	7 (17.1)	1 (7.7)
aminopenicillin + BLI	0 (0.0)	7 (13.0)	4 (3.7)	10 (24.4)	0 (0.0)
3rd generation cephalosporin	6 (12.0)	2 (3.7)	8 (7.3)	3 (7.3)	0 (0.0)
other cephalosporin	1 (2.0)	1 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)
macrolide	1 (2.0)	2 (3.7)	0 (0.0)	1 (2.4)	0 (0.0)
other	5 (10.0)	7 (13.0)	17 (15.6)	2 (4.9)	3 (23.1)

Length of hospital stay (days)

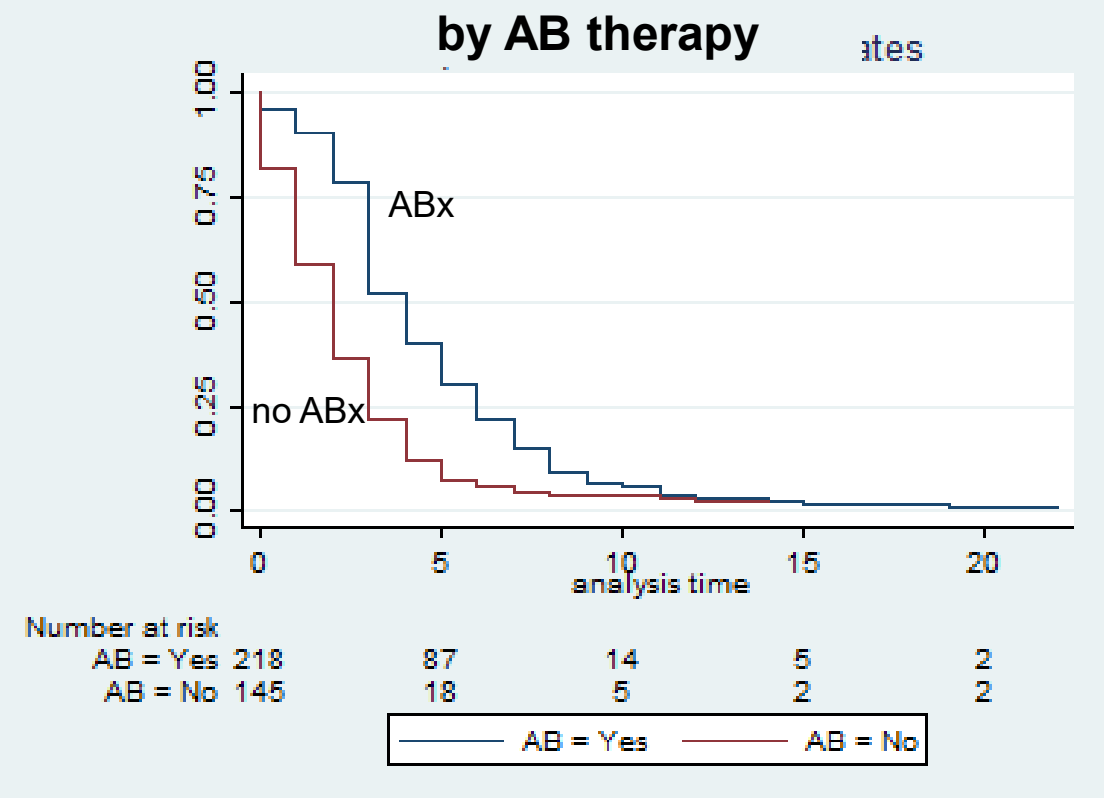
all



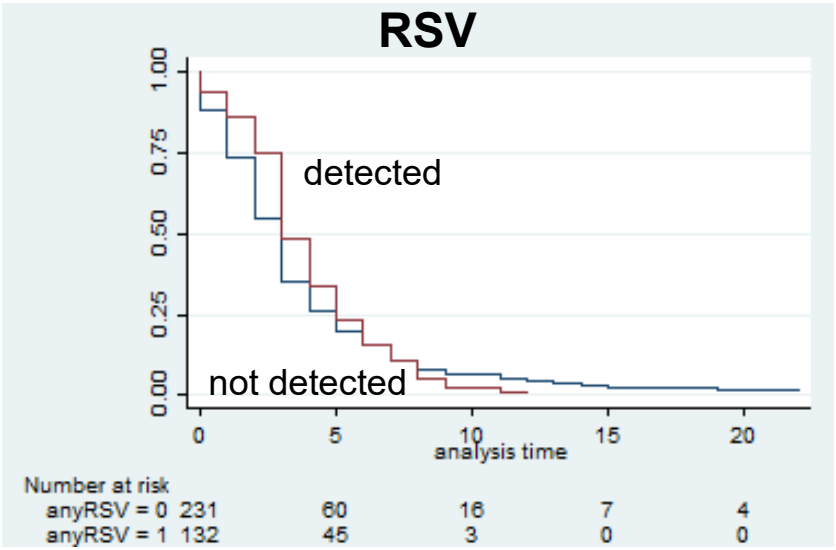
by RTI type

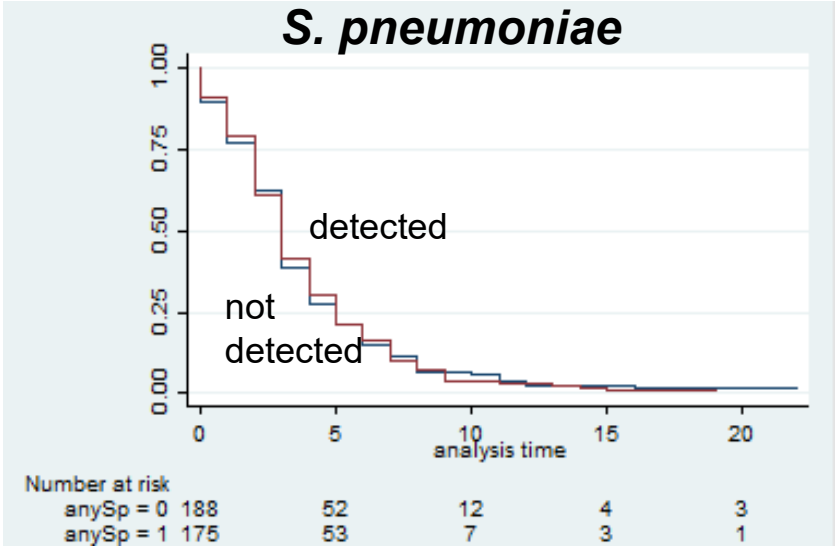


Length of hospital stay by antibiotic therapy



Length of hospital stay by pathogen





	RR	95%-CI	p
RSV	0.80	0.64, 1.01	0.062
influenza	1.08	0.76, 1.53	0.670
S. pneumoniae	1.06	0.86, 1.32	0.570

Adjusted for age, sex and country of inclusion; unspecified RTI type, missing CRP and length of stay imputed by MICE

No interaction for:
- RSV and *S. pneumoniae*
- influenza and *S. pneumoniae*

Strong interaction for influenza and RSV
- 4x lower discharge rate vs single pos
- only 5 double pos cases

Limitations

Selection bias

- convenience sampling
  difficult to compare study sites, representativeness
- requested sampling: URT swabs, bloods
  likely resulting in a sample biased towards sicker children

Residual confounding

- study parameters are causally interlinked, unable to adjust for many

Sample size

- wide confidence intervals for aetiological fraction estimates

Strengths

First European study, geographical representation

Year-round recruitment (capturing seasonality)

Representation of mildly symptomatic children in the control group

Detailed collection of symptom and management data

Biological samples collected

Gene expression samples collected from ARI children and controls (analysis pending)

Conclusions

- Detection of RSV, influenza virus, parainfluenza virus and hMPV on URT samples are strongly associated with ARI hospitalisation; other respiratory pathogens are either rare, or commonly found in well children

- 2/3 of children hospitalised for LRTI receive antibiotic treatment

- LOS is not associated with detected pathogen, but children receiving antibiotics have longer hospital stays than those not receiving antibiotics

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Thank you very much for your attention