RECOVER Closing Conference

Observational studies in Primary Care: PPAS-COVID and SOS-COVID

Alike van der Velden
Christopher Butler

6-7 June 2023

Esplanade Hotel, Zagreb, Croatia

Primary care team

Chris Butler, Emily Bongard: Oxford University, UK
Alike van der Velden, Theo Verheij, Rianne Jahja: UMCU, the Netherlands

Collaboration with other WPs, others

Social Science team: Sarah Tonkin-Crine, Sibyl Anthierens, Marta Wanat, Melanie Hoste
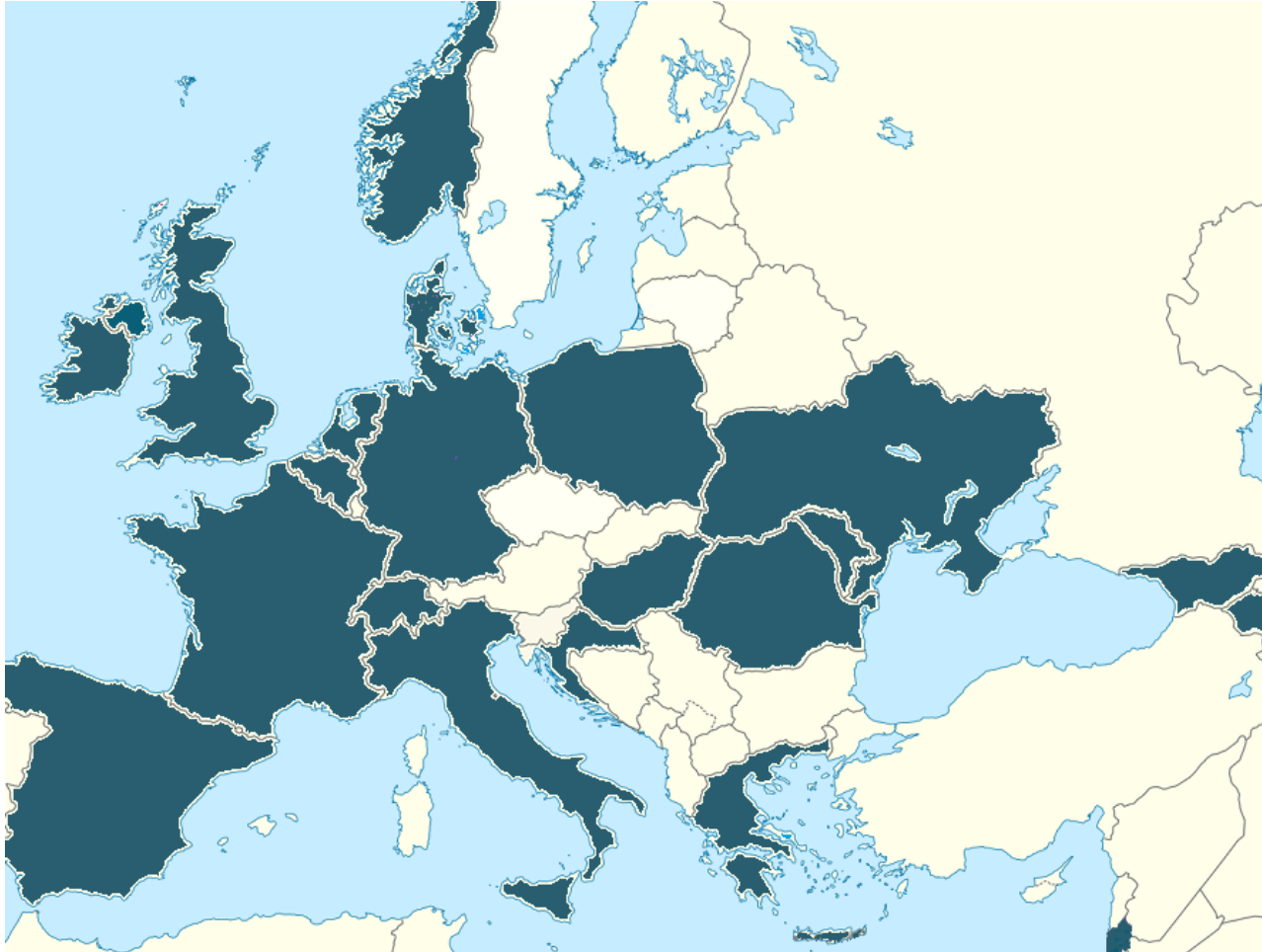
LAB WP: Greet Ieven, Katherine Loens, Christine Lammens
DM WP: Roxanne Schaakxs, Frank Leus

Statistics: Milensu Shanyinde, Ly-Mee Yu, René Eijkemans, Roderick Venekamp

National coordinating teams in 9 countries, with their GP practices

Primary Care Network

3-20 GP practices per country

Primary Care
Norway
Denmark
UK
Ireland
Netherlands
Belgium
Germany
Poland
Ukraine
Hungary
Romania
Moldova
Armenia
Georgia
Greece
Spain
France
Croatia

Point Prevalence Audit Survey (PPAS)

PPAS 1 – VALUE-Dx

- Anonymous registration of patients presenting to their GP with CA-ARTI
  - Patient characteristics, clinical presentation
  - Management: POC/lab testing, antibiotic/other prescribing, provided advice
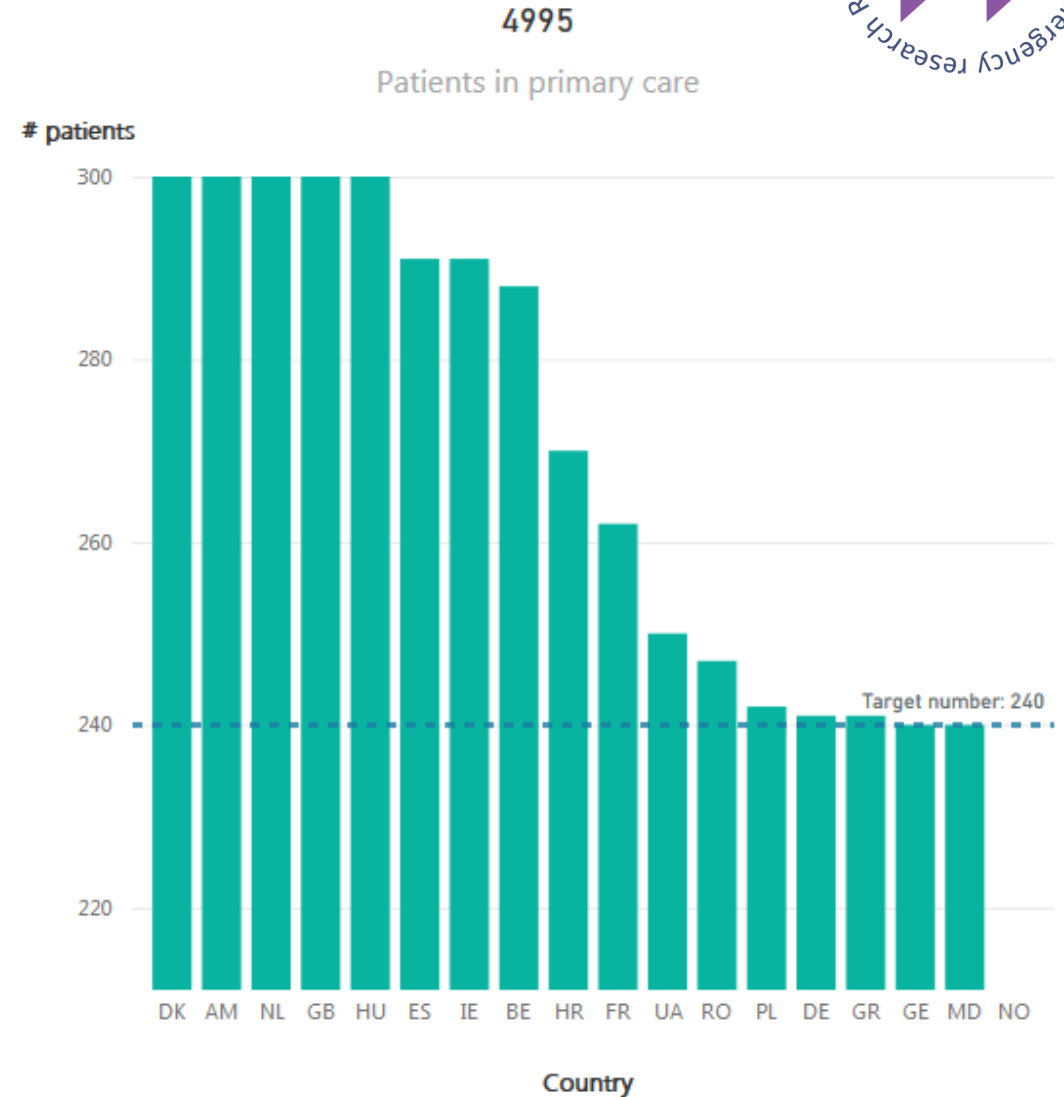
- 18 countries

- Dec 2019 - Jan 2020

4995
Patients in primary care

patients

300
280
260
240 — Target number: 240
220

DK AM NL GB HU ES IE BE HR FR UA RO PL DE GR GE MD NO

Country

BJGP Open

RESEARCH

Point-of-care testing, antibiotic prescribing, and prescribing confidence for respiratory tract infections in primary care: a prospective audit in 18 European countries

Alike W van der Velden[1]*, Alma C van de Pol[1], Emily Bongard[2], Daniela Cianci[1], Rune Aabenhus[3], Anca Balan[4], Femke Böhmer[5], Valerija Bralić Lang[6], Pascale Bruno[7], Slawomir Chlabicz[8], Samuel Coenen[9], Annelies Colliers[9]

WP2 Objectives

- To establish the prevalence, disease spectrum, severity and predictors of SARS-CoV-2 infection and its complications in selected European countries*

- To explore primary care patients' en primary care healthcare professionals' perspectives on the coronavirus pandemic in selected European countries*

- To explore the opportunity of testing POC diagnostics for SARS-CoV-2 in the PRUDENCE trial (as part of VALUE-Dx, IMI)

    * interim findings fed back to decision makers

Methods: Point Prevalence Audit Survey - COVID

AIM

To describe patient presentation and management during the hectic period of the first wave of the COVID pandemic
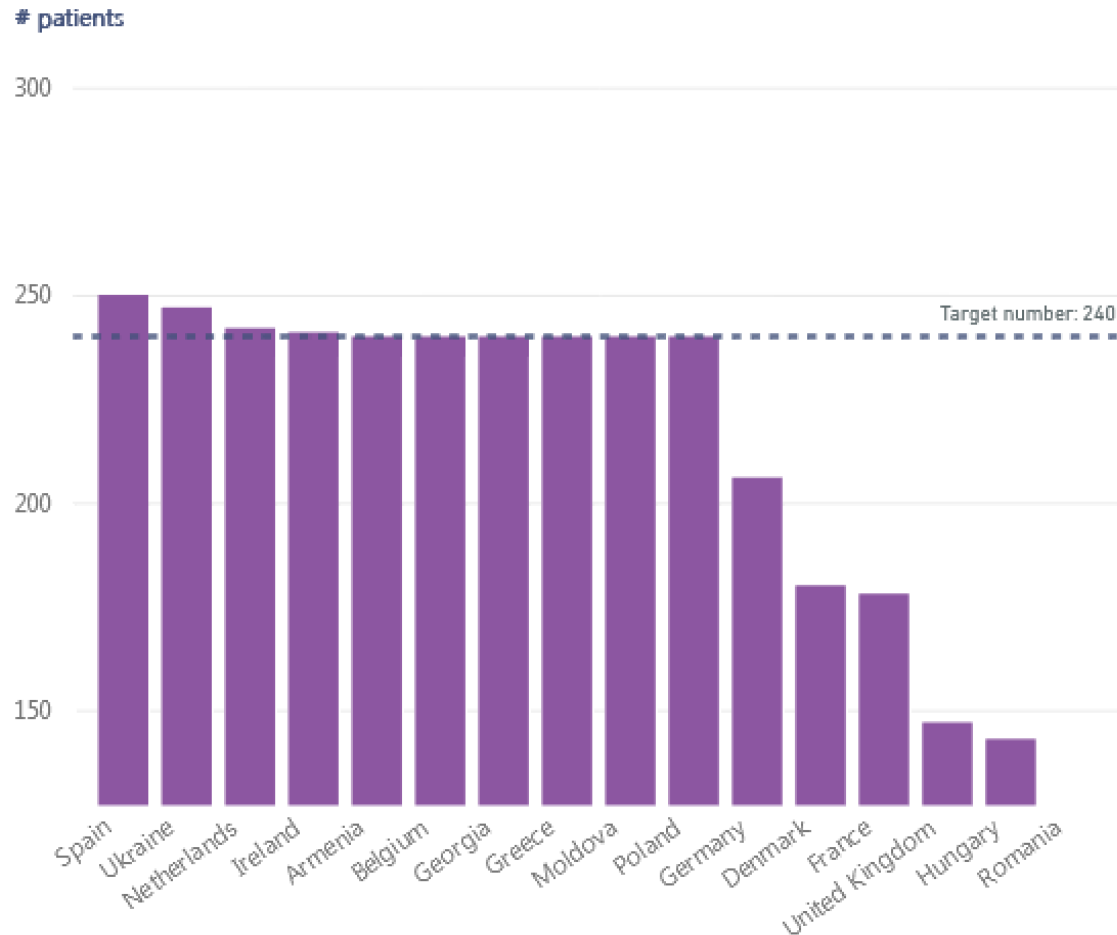
STUDY SET-UP

- anonymous registration of patient and management data, adding items relevant to the pandemic: type of consultation, risk-factors, use of PPE, suspicion SARS-CoV-2
- 16 countries
- initiated in March 2021
- 3301 registrations
- nearly real-time data reporting and analysis
- data could be compared to PPAS1 from just before the pandemic

Results PPAS-COVID: registrations

Number of patients included per country

patients

Target number: 240

Spain, Ukraine, Netherlands, Ireland, Armenia, Belgium, Georgia, Greece, Moldova, Poland, Germany, Denmark, France, United Kingdom, Hungary, Romania

Open access   **Original research**

BMJ Open   **Primary care for patients with respiratory tract infection before and early on in the COVID-19 pandemic: an observational study in 16 European countries**

Alike W van der Velden [1], Eva A Bax,[1] Emily Bongard [2], Rune Munck Aabenhus,[3] Marilena Anastasaki,[4] Sibyl Anthierens,[5] Anca Balan,[6] Femke Böhmer,[7] Pascale Bruno,[8] Slawomir Chlabicz,[9] Samuel Coenen [5], Annelies Colliers [5], Susanne Emmerich,[10] Ana Garcia-Sangenis [11], Hrachuhi Ghazaryan,[12] Sanne R van der Linde,[1] Lile Malania,[13] József Pauer,[14] Angela Tomacinschii,[15] Sarah Tonkin-Crine [2], Akke Vellinga [16], Ihor Zastavnyy,[17] Theo Verheij,[1] Herman Goossens,[18] Christopher C Butler [2]

Results PPAS-COVID: patient management

	Mean (%)	Range (%)
Phone, video/skype	59	10 - 91
PPE during F2F consultations	98	55 - 100
- apron	52	1 - 100
- face, nose/mouth	96	46 - 100
- safety glasses	57	0 - 98
- gloves	67	2 - 100
Hospital referral	8	1 - 17
Suspicion SARS-CoV-2 infection	43	4 - 84

Armenia
Denmark

Denmark
ES, UK, HU

Georgia
Spain

Results PPAS-COVID: antibiotic prescribing
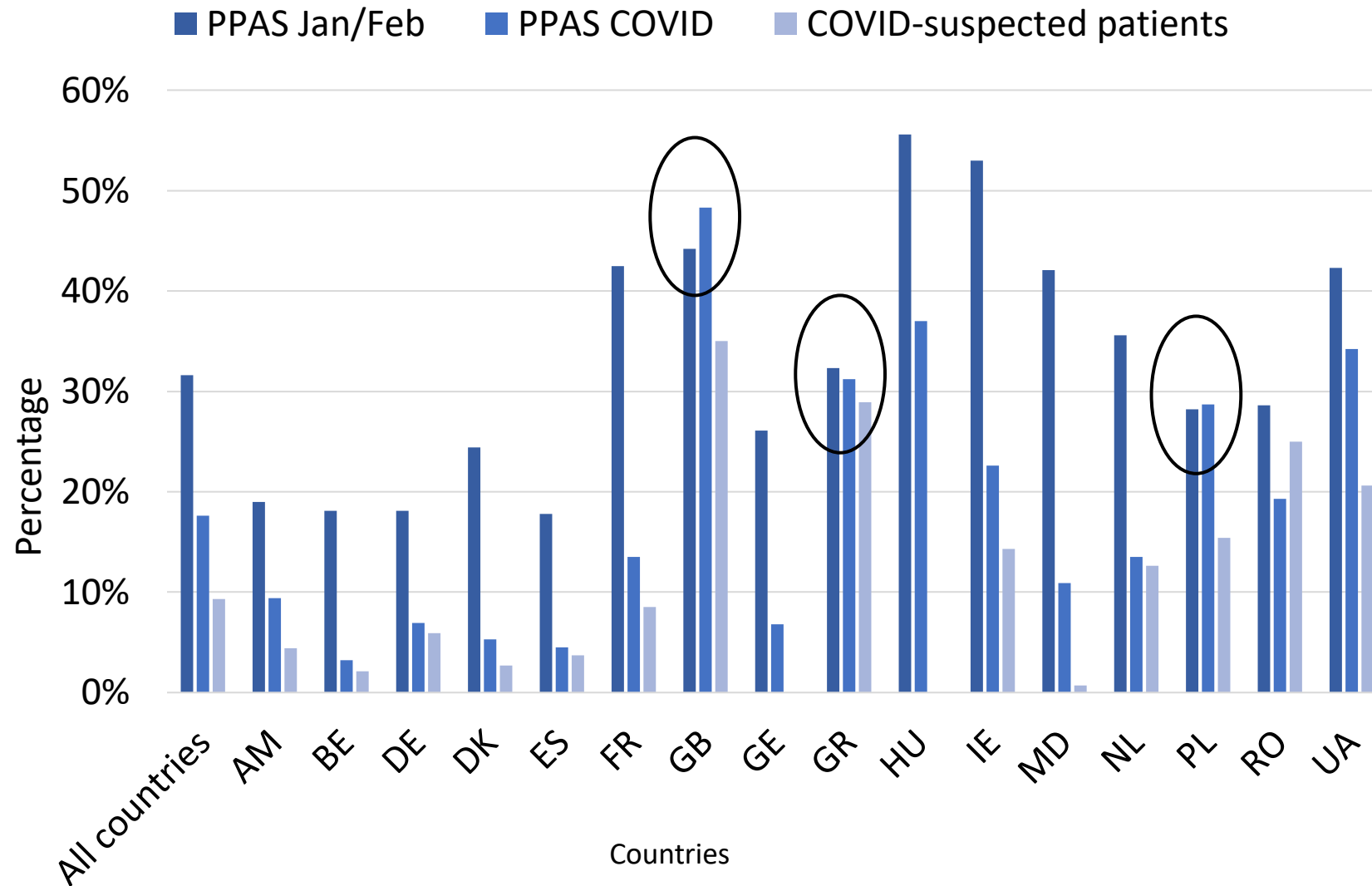
PPAS-COVID: dissemination via online reports

12|06|2020

RECOVER Work Package 2 and the national coordinating team

Extended Point Prevalence Audit Survey (PPAS)

Results for the Netherlands

Country Information
- Country: THE NETHERLANDS
- Registration period: 23 March 2020 to 28 April 2020
- Total number of patient consultations: 242

Additional remarks from interview study with GPs and patients:
- Clinicians report that initially there were a lot of telephone consultations but they still did some face to face visits, they are slowly setting up video consultations. They have not been overburdened with work and practice has been quieter than usual.
- Initially there was a shortness of protective equipment
- Clinicians have rapidly needed to learn new ways of working, dealing with, new case definitions and new daily guidance and new evidence, which has sometimes been conflicting.
- The regional crisis team collected information and made it available to practices, however in the initial phase of the pandemic the information was too technical and not practical.
- There has been a lot of flexibility from practice staff and colleagues within and across practices sharing tips, providing informal training and information to keep each other updated
- Patients are very understanding and grateful for care given by GPs but some still do not feel comfortable consulting because of the risk of catching COVID. Clinicians are concerned about managing those with chronic conditions who have postponed consulting.

Additional remarks on data below:
- Only 17% of patients were actually seen at the practice, the others were contacted by telephone
- Half of the patients had a chronic condition
- 60% of patients had mild symptoms

Consultation at	Protective measures: yes	88.5%	apron/body protection	94.4%*
			face, nose/mouth protection	98.1%
			safety glasses	96.3%
			gloves	100%
	Telephone	71.9%		
	Video/skype	2.1%		
Has patient already been tested for COVID?	Yes	7.0%	Result:	
			Positive	47.1%*
			Negative	41.2%
			Unknown	11.8%
	No	93.0%		

The aim of the survey is to provide information of how patients with respiratory tract infection are managed during the pandemic, what medicines are prescribed and advice provided, and will reveal marked differences between countries with respect to **patient management**.

Country information:
- ▸▸ Country: THE NETHERLANDS
- ▸▸ Registration period: 23 March 2020 to 28 April 2020
- ▸▸ Total number of patient consultations: 242

- ▸▸ **~60%** of patients presented **mild symptoms**
- ▸▸ **69.8%** of patients received advice to isolate at home for **14 days**
- ▸▸ **5.4%** of the patients were referred to **hospital**
- ▸▸ **95%** of GPs were very to moderately confident in advice and treatment they provided

www.recover-europe.eu @recover_europe #CORONAVIRUS #COVID-19

PPAS3 and PPAS4

Journal of
Antimicrobial
Chemotherapy

Point prevalence audit surveys of respiratory tract infection consultations and antibiotic prescribing in primary care before and during the COVID-19 pandemic in Ireland

M. Shah [1,2]*, A. Fleming [3], T. M. Barbosa[3], A. W. van der Velden [4], S. Parveen[5] and A. Vellinga [5]

antibiotics

MDPI

Article

Disease-Specific Quality Indicators for Outpatient Antibiotic Prescribing for Respiratory Infections (ESAC Quality Indicators) Applied to Point Prevalence Audit Surveys in General Practices in 13 European Countries

Akke Vellinga [1,*], Addiena Luke-Currier [1], Nathaly Garzón-Orjuela [1], Rune Aabenhus [2], Marilena Anastasaki [3], Anca Balan [4], Femke Böhmer [5], Valerija Bralić Lang [6], Slawomir Chlabicz [7], Samuel Coenen [8,9], Ana García-Sangenís [10,11], Anna Kowalczyk [12], Lile Malania [13], Angela Tomacinschii [14], Sanne R. van der Linde [15], Emily Bongard [16], Christopher C. Butler [16], Herman Goossens [9] and Alike W. van der Velden [15]

Methods: SARS-CoV-2 Observational Study (SOS-COVID)

AIM

To establish the prevalence, disease spectrum, severity and predictors of SARS-CoV-2 infection and its complications in European primary care

STUDY SET-UP

- Inclusion during GP contact (F2F or virtual) for CA-ARTI, during COVID-19 pandemic
- Baseline patient characteristics, S&S, risk-factors, measurements, GPs' management
- Swab (combined nasal and pharynx)
- Follow-up for 28 days, D7 and D28 phone calls
- Netherlands, Belgium, Georgia, Hungary, Moldova, Spain, Germany, Poland, Ireland

Methods: aetiology of illness (I)

- Samples frozen on site
- Sent to Antwerp for analysis

RNA extraction	PCR set-up	Custom made Taqman card
NucliSENS easyMag (BioMérieux)		**Quantstudio 7flex**
• max 23 samples • ± 2 hours	• max 40 samples • ± 1.5 hours	• max 8 samples • 1.0 hour

Methods: aetiology of illness (II)

- Custom-made respiratory panel

Viruses:
- influenza A virus (pan, duplo)
- Influenza A virus/H1-2009
- Influenza A virus/H3
- influenza B virus (pan, duplo)
- human rhinovirus (2 targets, duplo)
- human coronavirus (229E, NL63, HKU1, OC43)
- MERS-CoV
- SARS-CoV
- SARS-CoV-2 (3 targets)
- human parainfluenza (1-4)
- human bocavirus
- human respiratory syncytial virus A (2 assays, duplo)
- human respiratory syncytial virus B (2 assays, duplo)
- human metapneumovirus A&B

Viruses:
- human parechovirus
- Enterovirus (pan)
- Enterovirus D68
- human adenovirus (2 assays, duplo)

Bacteria:
- *Mycoplasma pneumoniae*
- *Staphylococcus aureus*
- *Chlamydia pneumoniae*
- *Haemophilus influenzae*
- *Streptococcus pneumoniae*
- *C. psittaci*
- *B. pertussis*
- *B. holmesii*
- *M. catarrhalis*
- *L. pneumophila*

Results SOS-COVID: inclusions

Number of patients included per country
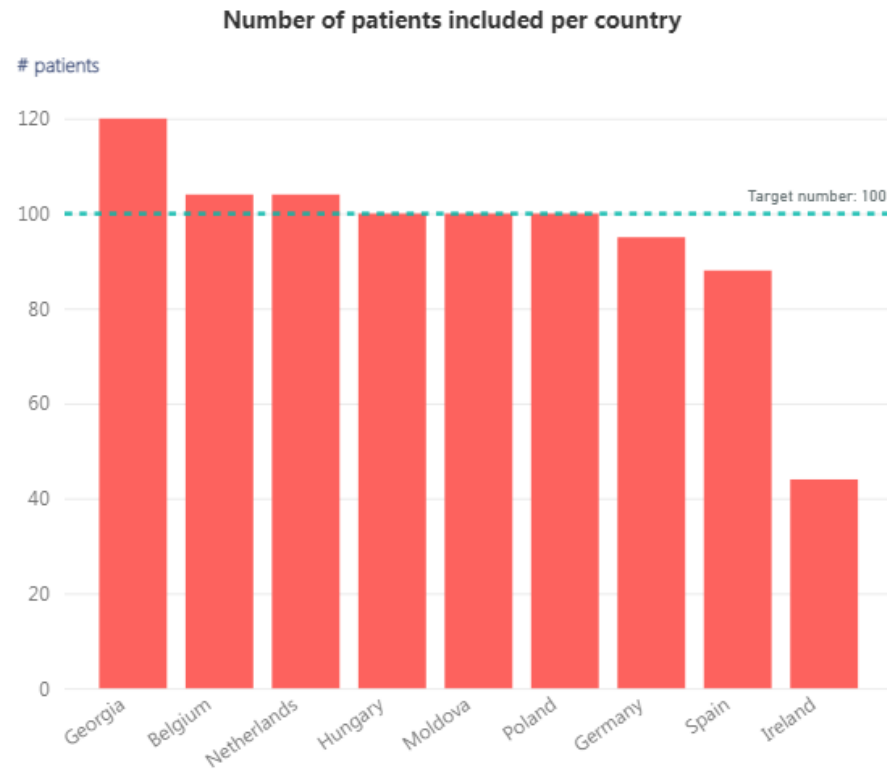
Total number of patients included

885

- 1st patient in: April 14th 2020
- Study closed: Feb 2021
- Majority of patients unaware of SARS-CoV-2 outcome
- Complete follow-up: 861 patients (97%)

Results SOS-COVID: aetiology of illness (I)

pathogen	Total (%, n = 858)
Influenza A virus	0
Influenza B virus	0
Rhinovirus	15.6
Coronavirus NL63/229E/OC43/HKU1	3.3
RSV A/B	0
Human metapneumovirus A/B	3.0
Parainfluenza virus 1-4	0
Adenovirus	0.8
Bocavirus	0.9
Parechovirus	0
Enterovirus	0.6
Enterovirus D68	0
MERS CoV	0
SARS-CoV	0
SARS-CoV-2	22.7

With results from laboratory-based testing in the country:
27.2% SARS-CoV-2 positive

Results SOS-COVID: aetiology of illness (II)

The Netherlands: **9%**
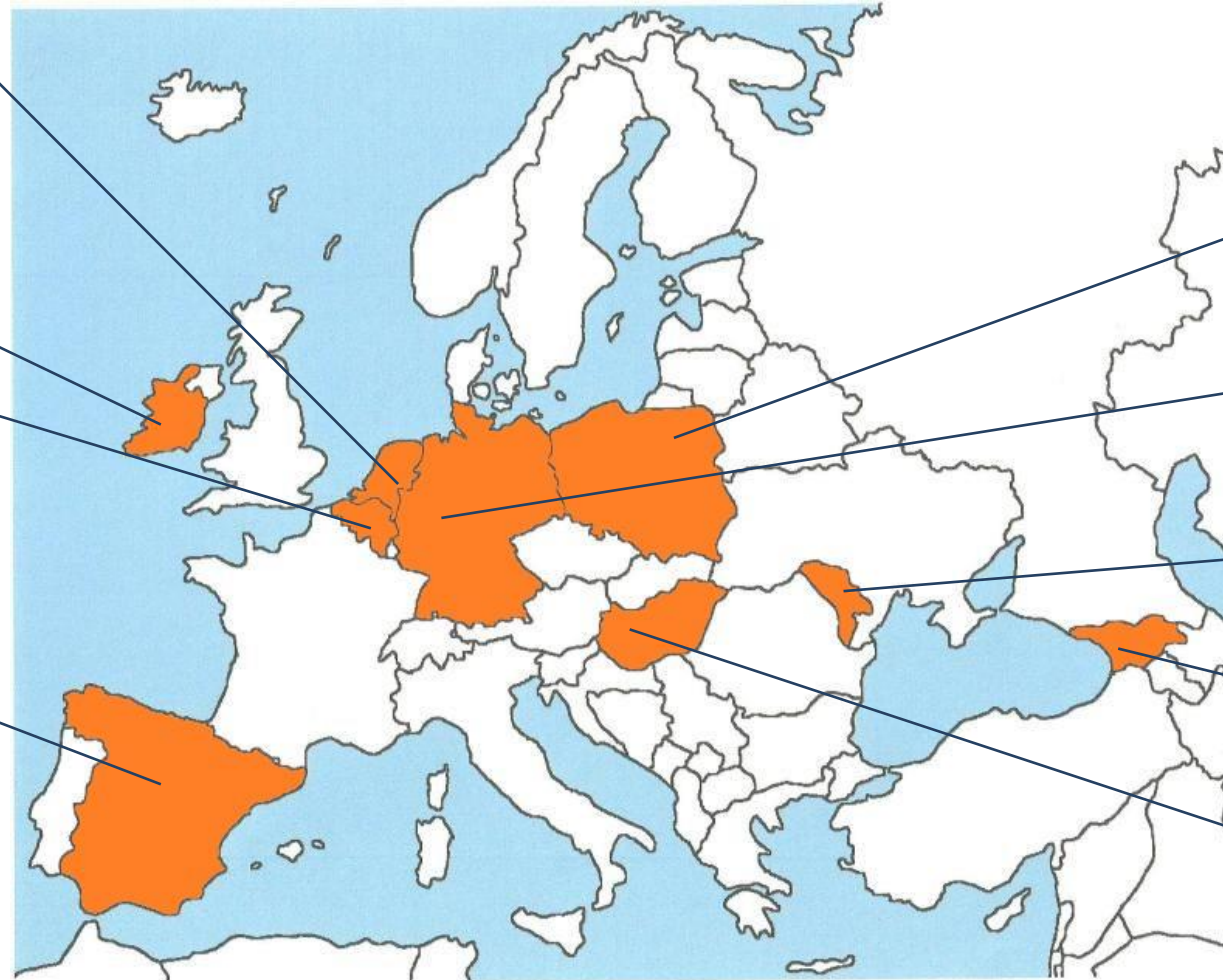
Ireland: **7%**

Belgium: **9%**

Spain: **33%**

Poland: **30%**

Germany: **11%**

Moldova: **52%**

Georgia: **14%**

Hungary: **35%**

Overall: 22.7% (range: 7% - 52%)

Results SOS-COVID: prediction SARS-CoV-2 infection

ANALYSIS

- Multi-level logistic regression, with country as random effect
- Outcome: combined SARS-CoV-2 positivity versus negative ones
- Pre-defined predictors
- O_2 saturation, RR had too many missing values

OUTCOMES

- Performance of risk prediction model
  - discrimination: area under ROC curve: 0.82
  - Well-calibrated
- Age and gender issue, due to country differences, moment in the pandemic?
- Prior to vaccination

	uOR	aOR	p-value
Age (per year)	1.02	1.02	0.001
Male gender	1.5	1.7	0.005
Fever	2.2	2.2	<0.001
Cough	1.5	1.3	0.17
Short of breath	1.5	1.1	0.68
Abnormal auscultation	0.5	0.6	0.34
Loss of taste/smell	5.6	6.3	<0.001
Risk factor for COVID	2.4	2.7	<0.001
Working >10 people	1	1	1
Contacts past 2 weeks	1	1	0.9

Results SOS-COVID: prediction SARS-CoV-2 infection by GP

	GP suspected SARS-CoV-2	GP suspected other aetiology
SARS-CoV-2 positive (PCR)	199	39
SARS-CoV-2 negative (PCR)	266	372

- 65.2% correct
- False-positives: 30.4%
- False-negatives: 4.5%
- ➢ Over-rating was more frequent than under-rating

Results SOS-COVID: management by 'diagnostic group'

Table 3: GPs' management of patients with RTI, split for correctly and non-correctly classified SARS-CoV-2 and non-SARS-CoV-2 aetiology.

|	True Pos (n=199)	True Neg (n=372)	False Pos (n=266)	False Neg (n=39)
Advice symptomatic treatment, %	87.4*	73.7*	77.4	74.4
Scheduled follow-up visit, %	82.4*	42.5*	68*	43.6*
Prescribed: Antibiotic, %	2.5*	9.9*	4.1	7.7
Antiviral, %	13.1*	0.5*	5.6	2.6
Inhaled medication, %	12.6	13.7	8.6	5.1
Antihistamine, %	9	7.3	5.6	2.6
Preventive measures for patient, %	81.9*	62.4*	62	74.4
Home isolation (quarantine), %	95*	71*	90.2*	92.3
Social distancing, %	69.8*	56.5	50.8*	61.5
Staying in separate room, %	61.3*	8.9*	38*	17.9
Advice for family members, %	86.4*	58.6*	61.3	71.8
Home isolation (quarantine), %	56.3*	16.7*	33.8	30.8
Social distancing, %	61.8*	46.2*	48.1	53.8
Hospital referral, %	1.5	0.8	1.5	0

Per item, percentages of patients are shown for True Pos (suspected with confirmed SARS-CoV-2), True Neg (not-suspected, no SARS-CoV-2), False Pos (suspected, no SARS-CoV-2) and False Neg (not-suspected with confirmed SARS-CoV-2) patients. *Significantly different from other groups.

Results SOS-COVID: resolution of illness (I)

ANALYSIS

Kaplan-Meier curves for *time to full recovery* and *time to return to usual daily activities* by SARS-CoV-2 status
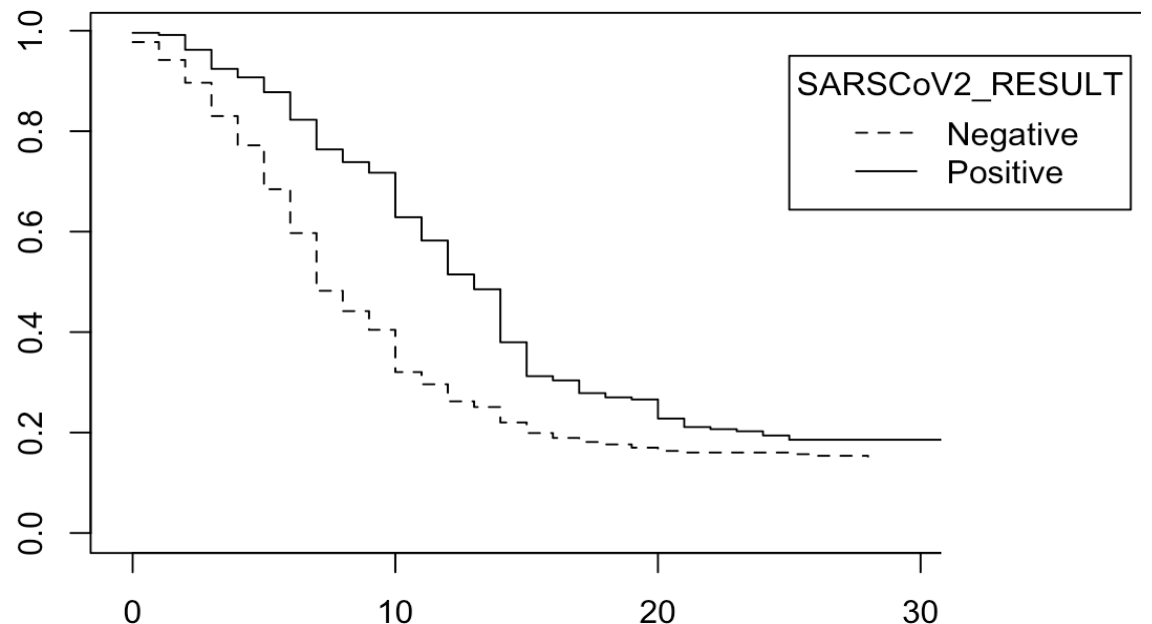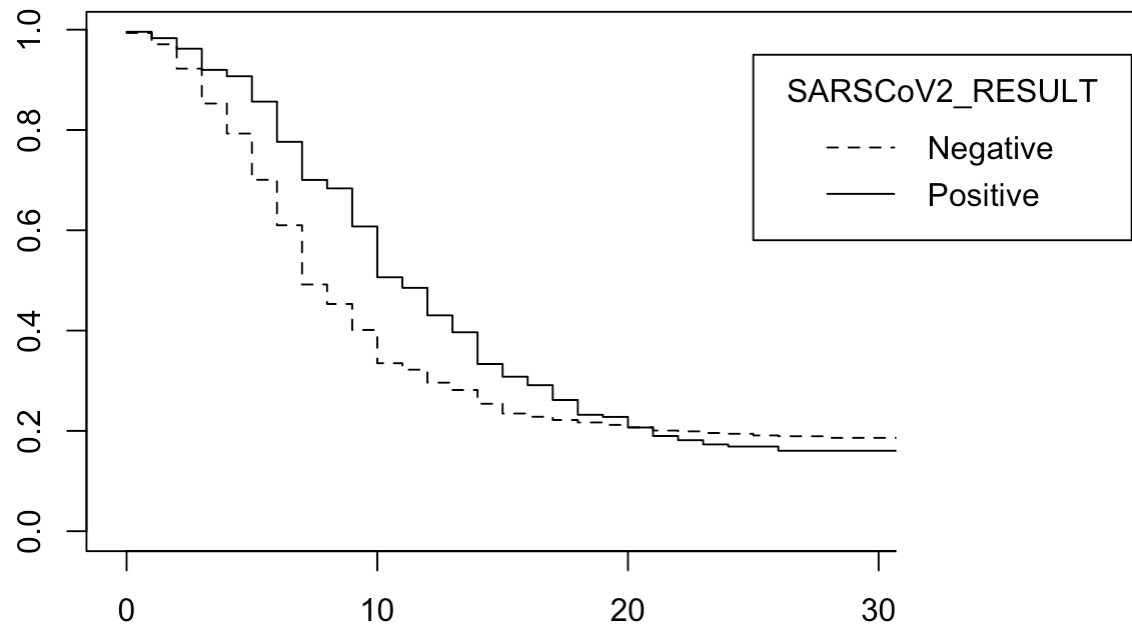
Results SOS-COVID: resolution of illness (II)

	SARS-CoV-2 negative (n=618)	SARS-CoV-2 positive (n=237)	p-value
Fully recovered (mean, day)	7.7	10.6	0.001
Shortness of breath gone (mean, day)	7.1	7.8	0.34
Extreme tiredness gone (mean, day)	7	10.2	<0.001
Back to usual daily activities (mean, day)	7.4	11.5	<0.001

	SARS-CoV-2 negative (n=618)	SARS-CoV-2 positive (n=237)	p-value
Not fully recovered at D28	18.1%	15.6%	0.39
Not recovered from shortness of breath D28	9.5%	4.6%	0.02
Not recovered from tiredness D28	12.8%	9.7%	0.2
Not back to usual daily activities D28	14.4%	18.1%	0.18

Results SOS-COVID: complicated course of illness

	SARS-CoV-2 negative (n=618)	SARS-CoV-2 positive (n=237)	p-value
1 Hospitalisation with o/n stay	1%	10.5%	<0.001
2 Not yet fully recovered D28	18.6%	16%	0.4
3 Short of breath a/o extreme tiredness a/o not to 'usual' D28	21%	21.1%	1

Take home messages

➢ PPAS appeared to be a powerful tool to capture changes in all aspects of primary healthcare delivery for patients with RTI (progress in ECRAID-Base)

➢ Rapid initiation of research was possible in the early phase in the pandemic, due to commitment and trust within the PC Research Network and collaboration with EBs

➢ In (the need for) predicting SARS-CoV-2 infection in patients presenting in PC with symptoms of an RTI we were passed by public health initiatives, implementation of rapid testing, changing circumstances (vaccination, new variants)

➢ Prediction rules for PC would have been helpful in the early phase of the pandemic, as GPs struggled with labelling SARS-CoV-2

➢ Patients with SARS-CoV-2 took longer to recover, however, at day 28, a similar percentage as in the SARS-CoV-2 negative patients experienced residual symptoms

Lessons learned

➢ (Statistical) analysis capacity is needed from the start, particularly for studies where rapid dissemination is required

➢ Pre-approved Network and Site agreements would have facilitated rapid study initiation

➢ Publication of findings appears difficult due to rapidly changing circumstances

Questions for the team?