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RESEARCH ARTICLE

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Clinical diagnosis of SARS-CoV-2 infection: An observational study of respiratory tract infection in primary care in the early phase of the pandemic

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KEY MESSAGES

- Early in the pandemic, without POC-testing, GPs over-diagnosed SARS-CoV-2 on clinical grounds in RTI-suspected patients.
- The true-positive patient group was more intensively managed (follow-up, antiviral prescribing and advice) than the true negative group.
- Large-scale, coordinated research in primary care early in the pandemic could have aided GPs in decision-making.

ABSTRACT

Background: Early in the COVID-19 pandemic, GPs had to distinguish SARS-CoV-2 from other aetiologies in patients presenting with respiratory tract infection (RTI) symptoms on clinical grounds and adapt management accordingly.

Objectives: To test the diagnostic accuracy of GPs' clinical diagnosis of a SARS-CoV-2 infection in a period when COVID-19 was a new disease. To describe GPs' management of patients presenting with RTI for whom no confirmed diagnosis was available. To investigate associations between patient and clinical features with a SARS-CoV-2 infection.

Methods: In April 2020–March 2021, 876 patients (9 countries) were recruited when they contacted their GP with symptoms of an RTI of unknown aetiology. A swab was taken at baseline for later analysis. Aetiology (PCR), diagnostic accuracy of GPs' clinical SARS-CoV-2 diagnosis, and patient management were explored. Factors related to SARS-CoV-2 infection were determined by logistic regression modelling.

Results: GPs suspected SARS-CoV-2 in 53% of patients whereas 27% of patients tested positive for SARS-CoV-2. True-positive patients (23%) were more intensively managed for follow-up, antiviral prescribing and advice than true-negatives (42%). False negatives (5%) were under-advised, particularly for social distancing and isolation. Older age (OR: 1.02 (1.01–1.03)), male sex (OR: 1.68 (1.16–2.41)), loss of taste/smell (OR: 5.8 (3.7–9)), fever (OR: 1.9 (1.3–2.8)), muscle aches (OR: 2.1 (1.5–3)), and a known risk factor for COVID-19 (travel, health care worker, contact with proven case; OR: 2.7 (1.8–4)) were predictive of SARS-CoV-2 infection. Absence of loss of taste/smell, fever, muscle aches

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and a known risk factor for COVID-19 correctly excluded SARS-CoV-2 in 92.3% of patients, whereas presence of 3, or 4 of these variables correctly classified SARS-CoV-2 in 57.7% and 87.1%.
Conclusion: Correct clinical diagnosis of SARS-CoV-2 infection, without POC-testing available, appeared to be complicated.

Introduction

The COVID-19 pandemic brought dramatic changes in primary health care delivery, especially for patients with respiratory tract infections (RTI) [1–4]. Early in the pandemic, without testing for SARS-CoV-2 in place, general practitioners (GPs) faced many uncertainties [2]. First, descriptive data from hospitalised patients were readily available, but the clinical presentation of those attending primary care was largely unknown [5]. Second, without evidence-based guidelines, there was uncertainty about management of patients presenting with milder symptoms. Third, most consultations were by telephone, reducing physical examination opportunities [4]. Given the required advice about isolation and therapeutic implications of the diagnosis, it was highly relevant to distinguish between SARS-CoV-2 and other aetiologies when routine testing, incidence data and a complete description of this new illness were lacking [6].

Initially, pandemic research focused on hospitalised patients [7], whereas most patients were managed in the community. Primary care has a crucial role in any emergency response, usually being the first point of patient contact and its function as gatekeeper for secondary care [1, 3]. Prediction of SARS-CoV-2 infection, based on signs and symptoms, would have helped guiding initial evaluation, follow-up and monitoring [8].

Our study aimed to investigate from the initial stage of the pandemic: (1) the aetiology of circulating RTI; (2) how accurately GPs were able to predict a subsequent microbiological diagnosis of SARS-CoV-2 infection; (3) patient management for follow-up, medication prescribing, advice and referral; and 4) which particular signs, symptoms and patient characteristics were associated with proven SARS-CoV-2 infection.

Methods

SOS-COVID was a prospective, observational study in nine European countries. The study was approved by Ethics Committees in each participating country, registered in the Dutch trial registry (https://www.onderzoekmetmensen.nl/en/trial/29166), and funded by the EU's Horizon 2020 programme (RECOVER, 101003589).

Setting

We invited coordinating teams in another EU-funded consortium (www.value-dx.eu) to set-up SOS-COVID in their country. General practices in Belgium ($n = 6$), Germany (1 testing hub, recruiting patients from about 40 GPs), Spain ($n = 5$), Georgia ($n = 5$), Hungary ($n = 3$), Ireland ($n = 5$), Moldova ($n = 5$), the Netherlands ($n = 1$ centre where patients with RTI from 6 practices were seen), and Poland ($n = 5$) participated.

Patients were included between 14 April 2020 and 26 March 2021; routine testing became available mid 2020.

Participants and eligibility

GPs were instructed to check eligibility of consecutively contacting patients: aged one year or older with cough, sore throat and/or coryza, or otherwise suspected of COVID-19 (without RTI symptoms, where GPs for other reasons suspected COVID-19), with symptoms less than 14 days, of unknown aetiology. Patients or guardians willing to provide informed consent and comply with study requirements were included. Patients who were terminally ill or tested for SARS-CoV-2 were ineligible. Patients could be included during a face-to-face (F2F) consultation (practice, home visit), by telephone, or video. After a remote consultation, a delegate of the GP visits the patient on the same or next day to take the swab or deliver swabbing material for the patient to self-swab.

Study procedures and data collection

Upon inclusion, a baseline Case Report Form (Supplementary CRF) was completed by the GP covering patient characteristics, known risk factors for COVID-19 at that time (travel to high-risk country, contact with proven case, healthcare worker), signs and symptoms, physical examination (for F2F consultations only), GPs' overall rating of illness severity, how GPs managed their patients (prescribing, advice, follow-up,

referral), precautions taken by the patient, information regarding working environment and social life. A combined oropharyngeal and nasal swab (both nostrils) was collected using one flocked swab, stored in universal transport media, frozen between −20 and −80 °C and shipped in batches to the central laboratory in Antwerp, where they were stored at −80 °C until analysis. CRF data were entered into an online data capture system, Research Online, using a patient ID, GDPR compliant.

Microbiological analysis

Samples were extracted with the NucliSens EasyMag (bioMérieux, France). After pre-amplifying the nucleic acid extracts, real-time PCR was done using Custom TaqMan® Array Cards and the Fast Advance Master Mix according to the manufacturer's instructions (ThermoFisher Scientific). Influenza A, B, A-H1, and A-H3, human coronaviruses NL63, 229E, OC43, HKU1, MERS, SARS-Co-V 1 and 2, parainfluenza viruses 1-4, human metapneumovirus, rhinovirus, RSV A and B, adenovirus, enterovirus, enterovirus D68, parechovirus, and bocavirus were detected in a Quantstudio 7 flex instrument.

Outcomes

- The proportion of patients with SARS-CoV-2 and other viral aetiology of illness. If participants declined to be swabbed twice (one for direct local analysis when testing became implemented and one for the study), we allowed a PCR-based SARS-CoV-2 result from a local laboratory. When two swabs were taken, a patient was considered positive if one was positive.
- Diagnostic accuracy of GPs' clinically-based SARS-CoV-2 diagnosis for a positive PCR test, by calculating sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and overall accuracy (the summed percentages of correctly suspected SARS-CoV-2 positive and negative patients) using crosstabs. This analysis was split for participants recruited before and after 14 October 2020 (1st and 2nd half of included patients) and by consultation type (F2F or remote).
- GPs' management (scheduled follow-up visit, medication prescribing, provided advice and hospital referral), split for true-positive, true-negative, false positive and false negative SARS-CoV-2 patients. Statistical differences between the groups was determined using Chi-square testing. Adjusted residuals (>1.96 or <1.96) were used to determine which particular group(s) significantly differed from others.

Missing data, which was less than 1%, was not corrected. Analyses were performed using SPSS version 26.0.

Prediction SARS-CoV-2 infection

Variables possibly related to SARS-CoV-2 infection are shown in Table 4. Multilevel logistic regression modelling, with country included as random effect, was used to analyse variables' association with SARS-CoV-2 infection. Subsequently, a backwards stepwise selection procedure was used to determine which variables to retain in the model. Variables were sequentially rejected in order of p-value until no variables remained with p-values ≥ 0.05. Results are presented as unadjusted and adjusted Odds Ratios (OR) with 95% confidence intervals (CI) and associated p-values (likelihood ratio test). Analyses were performed using STATA SE version 16.1. Using the four strongest predictors, it was determined to what extent these, individually and in combination, correctly identified and excluded SARS-CoV-2 infection.

Results

RTI aetiology early in the pandemic

Of 885 included patients, nine were excluded as no SARS-CoV-2 result was available; their swab was lost, not properly stored, nor available from local testing. Participants (855) had a swab analysed for the full respiratory panel and 21 had a swab analysed locally only for SARS-CoV-2. Table 1 shows the results of the microbiological analyses; 27% (238/876) were SARS-CoV-2 positive, with a large between-country variation.

Table 1. Microbiological analyses of patients included in the SOS-COVID study ($n = 876$).

	All ($N = 876$)	BE (104)	DE (94)	ES (88)	GE (150)	HU (100)	IE (42)	MD (100)	NL (103)	PL (95)
SARS-CoV-2, %	27.2	11	12	36	17	42	7	61	16	38
Rhinovirus, %	15.7	13	17	14	7	27	21	22	9	17
Coronaviruses, %	3.3	0	5	1	5	0	0	9	0	7
Metapneumovirus, %	3.0	0	0	0	0	0	0	0	0	28

Numbers of patients are shown, overall and per country, with percentages of patients positive for the viruses indicated; swabs from 855 patients were analysed using the full respiratory panel, SARS-CoV-2 outcomes for an additional 21 patients were from a local lab.

Other coronaviruses were most prevalent in Moldova and Poland, rhinovirus in Hungary, and human metapneumovirus in Poland. No influenza A/B, parainfluenza 1–4, enterovirus D68, or RSV A/B were found, and low levels of adenovirus, bocavirus, and enterovirus (<1%).

Diagnostic accuracy of GPs' clinically-based diagnosis for a PCR-confirmed SARS-CoV-2 infection

Suspected SARS-CoV-2 aetiology was correct for 22.7% (199/876) of patients and SARS-CoV-2 suspicion was incorrect for 30.4% (266/876, false-positives). Non-SARS-CoV-2 suspicion was correct in 42.5% (372/876) of patients and a SARS-CoV-2 infection was missed in 4.5% (39/876, false-negatives). Table 2 shows the diagnostic accuracy measures. Overall accuracy seemed slightly higher for F2F consultations (67%) than for virtual consultations (61%), due to a higher number of false positives from virtual consultations, reflected by a lower specificity. Sensitivity, however, was higher during virtual consultations, by a lower number of false negatives. Overall accuracy did not improve during the second stage of patient inclusion.

GPs' patient management by diagnostic group

Management appeared to be dependent on the diagnostic group (Table 3). The true positive patients were managed more intensively, with more scheduled follow-up visits, more antiviral prescribing and more advice for themselves and family members than the true negatives. Antivirals (umifenovir, ergoferon, inosine pranobex, kagocel and oseltamivir) were prescribed in Moldova and Poland, where these were also prescribed for influenza(-like-illness) before the pandemic [9]. Less antibiotics were prescribed for true positive patients. Notwithstanding, true negative patients still received ample advice for quarantine and social distancing.

False negative patients generally presented with mild illness, non-affected taste/smell, and absence of a risk factor for COVID-19. They were less often scheduled for follow-up visits and received less advice than the true positives. They could have benefitted from more intensive treatment and more preventive advice could have limited viral spread.

Predicting SARS-CoV-2 aetiology

Table 4 shows baseline characteristics for patients with and without confirmed SARS-CoV-2 infection.

Table 2. Diagnostic accuracy measures of GPs' clinical SARS-CoV-2 diagnosis of patients in the SOS-COVID study.

	All patients ($n = 876$)	Type of contact		Inclusion period	
		F2F ($n = 632$)	Phone/video ($n = 244$)	1st half ($n = 438$)	2nd half ($n = 438$)
Overall accuracy, %	65 (62–68)	67 (63–71)	61 (54–67)	66 (61–70)	65 (60–69)
Sensitivity, %	84 (78–88)	77 (69–83)	98 (91–100)	74 (64–83)	89 (83–93)
Specificity, %	58 (54–62)	64 (59–68)	43 (35–51)	63 (58–68)	52 (46–58)
PPV, %	43 (40–45)	41 (38–45)	45 (42–49)	33 (29–37)	50 (46–53)
NPV, %	91 (88–93)	89 (86–92)	97 (90–99)	91 (88–94)	90 (85–93)

Accuracy measures, with confidence intervals between brackets, are reported of a GPs' clinically-based diagnosis for a PCR-confirmed SARS-CoV-2 infection, for all included patients, per type of contact, and before and after mid-October 2020. The clinical diagnosis was made before the swabs were analysed. F2F: face-2-face; PPV and NPV: positive and negative predictive values.

Table 3. GPs' management of patients included in the SOS-COVID study, split for correctly and non-correctly classified SARS-CoV-2 and non-SARS-CoV-2 aetiology ($n = 876$).

	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 (Chi-square testing, with adjusted residuals).

Table 4. Patient characteristics, signs and symptoms of patients included in the SOS-COVID-study stratified by PCR-confirmed SARS-CoV-2 status.

	Overall ($n = 876$)	SARS-CoV-2 POS ($n = 238$)	SARS-CoV-2 NEG ($n = 638$)	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age, mean (SD)	38.8 (16.1)	40.9 (14.1)	38.0 (16.7)	1.02 (1.01 to 1.03)	0.002	1.02 (1.01 to 1.03)*	0.004
Male sex, %	44.6	49.6	42.8	1.51 (1.09 to 2.10)	0.014	1.68 (1.16 to 2.41)	0.005
Risk factor for COVID-19, %	31.7	49.2	25.4	2.43 (1.70 to 3.47)	< 0.001	2.67 (1.80 to 3.97)	< 0.001
Smoking, %	30.0	26.9	31.2	0.95 (0.66 to 1.36)	0.775		
Overweight/obesity, %	34.0	35.7	33.4	1.01 (0.72 to 1.42)	0.965		
Any comorbidity, %	28.0	29.0	27.6	1.07 (0.75 to 1.54)	0.698		
Fever, %	52.0	67.2	46.6	2.18 (1.51 to 3.13)	< 0.001	1.88 (1.26 to 2.81)	0.002
Cough, %	65.9	67.6	65.2	1.47 (1.03 to 2.12)	0.036		
Dyspnoea, %	17.4	17.2	17.4	1.48 (0.92 to 2.38)	0.106		
Increased/purulent sputum, %	11.3	7.1	12.9	0.65 (0.36 to 1.16)	0.146		
Abnormal auscultation, %	4.3	2.1	5.2	0.49 (0.18 to 1.34)	0.165		
Chest pain, %	7.3	5.9	7.8	1.22 (0.63 to 2.37)	0.554		
Tachypnoea, %	2.5	3.8	2.0	1.91 (0.74 to 4.92)	0.179		
Headache, %	50.5	58.0	47.6	1.11 (0.80 to 1.56)	0.524		
Muscle ache, %	37.2	56.7	30.3	2.59 (1.84 to 3.62)	< 0.001	2.11 (1.46 to 3.06)	< 0.001
Fatigue, %	53.4	64.3	49.4	1.66 (1.17 to 2.37)	0.005		
Loss of taste/smell, %	17.4	41.2	8.6	5.55 (3.68 to 8.39)	< 0.001	5.79 (3.72 to 9.02)	< 0.001
Moderate/severe illness, %	30.4	34.5	28.8	1.62 (1.14 to 2.32)	0.007		
Taken specific precautions, %	96.9	97.5	96.7	1.75 (0.67 to 4.58)	0.252		
Working outdoors/school/day-care, %	51.6	58.8	48.9	1.36 (0.96 to 1.91)	0.080		
For adults: working >10 others, %	24.2	28.2	22.7	1.40 (0.95 to 2.05)	0.085		
Moderate/many social contacts, %	36.6	49.2	32.0	0.95 (0.64 to 1.40)	0.788		

Per item, percentages of patients are reported overall and for SARS-CoV-2 positive and negative patients. Except for age, all variables are dichotomous. Multilevel logistic regression models for SARS-CoV-2 infection include country fitted as random effect; *age per one year older. Unadjusted odds ratios (OR) and adjusted ORs retained from the backward stepwise selection procedure with p-values are shown (Likelihood ratio test).

Table 5. Prediction of SARS-CoV-2 infection based on four variables from the multilevel logistic regression model.

	Risk ($n = 278$)	Fever ($n = 455$)	MA ($n = 326$)	T/S ($n = 152$)	0 ($n = 196$)	1 ($n = 316$)	2 ($n = 219$)	3 ($n = 111$)	4 ($n = 31$)
Patients, %	31.7%	52%	37.2%	17.4%	22.4%	36.1%	25%	12.7%	3.5%
SARS-CoV-2, *n*, %	117	160	135	98	15	54	78	64	27
	42.1%	35.2%	41.4%	64.5%	7.7%	17.1%	35.6%	57.7%	87.1%
Correctly identified, *n*, %	105	136	121	92	11	37	63	61	27
	89.7%	85%	89.6%	93.9%	73.3%	68.5%	80.8%	95.3%	100%

The first row shows the percentages of patients with the variable of interest present. Risk: any risk factor for COVID-19 (at that time, as specified in Methods), MA: muscle aches, T/S: loss/impaired taste/smell, 0-4: 0, 1, 2, 3, 4 variables out of four present. The second and third rows show the numbers of patients with the variable of interest present in SARS-CoV-2 positive, and in correctly-identified SARS-CoV-2 positive patients, together with the percentages of the number in the cell above.

Commonly reported symptoms were fever, cough, headache and fatigue.

Regression modelling showed that SARS-CoV-2 positive patients were more likely to be older, male, presenting with fever, cough, muscle ache, fatigue, and loss of taste/smell, and presenting with moderate or severe illness. Dyspnoea, tachpnoea, abnormal auscultation, chest pain and behavioural aspects were not associated with SARS-CoV-2 infection. Variables that remained independently associated with increased probability of SARS-CoV-2 infection were higher age, male sex, loss of taste/smell, fever, muscle aches, and any known risk factor for COVID-19 at that time.

Role of predictors in GPs' suspicion

Table 5 shows that of SARS-CoV-2 positive patients with loss of taste/smell, a known risk factor for COVID-19, muscle aches or fever over 85% were correctly classified by GPs. Combining these four variables highlights that their absence correctly excluded a SARS-CoV-2 infection in 92.3%. Presence of three or all four correctly classified SARS-CoV-2 infection in 57.7% and 87.1% of patients, respectively; GPs accurately classified these patients.

Discussion

Main findings

Early in the pandemic, GPs were challenged to identify patients with SARS-CoV-2 infection. The SOS-COVID study included patients contacting their GP with RTI symptoms of unknown aetiology and asked the recruiting GP about the aetiology they suspected. Despite high incidence of SARS-CoV-2 (27% in our study, with absence of influenza and RSV) the suspicion of the presence or absence of SARS-CoV-2 was correct for only 65% of patients. There was a tendency for over-calling SARS-CoV-2, which might have resulted in unnecessary concern and/or anxiety. On the other hand, of SARS-CoV-2 infected patients, 16%

were missed; they received less preventive advice, which might have resulted in greater spread of the virus. GPs' diagnostic accuracy did not improve over time, suggesting a similar presentation to other RTIs. Overall, GPs advised preventive measures to a high degree, even in the non-SARS-CoV-2 suspected group. Loss of taste/smell was identified as a discriminating factor for SARS-CoV-2 infection, together with fever and muscle aches.

Strengths and limitations

The main strengths of our study were its multicentre, prospective design, with structured data capture and enrolment of symptomatic patients seeking primary healthcare for RTI symptoms. The study was implemented when testing was not yet available or limited, so patients and GPs were unaware of aetiology of illness. Patients were recruited from diverse countries; during the pandemic, primary care in these countries was involved in initial contact, patients' medical care and follow-up [4, 10].

Results are relevant to a non-vaccinated cohort and before newer variants emerged, which limits generalisability and practical applicability of outcomes. The between-country variation in SARS-CoV-2 positivity rates might have complicated analyses; this was corrected by adding 'country' as a random effect in the regression analysis. Due to widespread implementation of low-cost SARS-CoV-2 testing a clinical prediction rule has become less relevant. Finally, the limited sample size and false positive/negative SARS-CoV-2 PCR laboratory results might have influenced results.

Comparison with existing literature

Particularly in the early phase of the pandemic, accurate identification of SARS-CoV-2 infection would have helped GPs make appropriate management decisions. It appeared difficult to formulate an accurate clinical prediction model for SARS-CoV-2 infection [11–13]. COVID-19 often presents as an RTI with a broad spectrum of clinical symptoms and therefore diagnostic accuracy of individual signs and symptoms is low [11, 13]. Anosmia, considered diagnostic by many, can be present after some other viral infections [14]. Anosmia alone cannot discriminate COVID-19 from non-COVID-19, but in combination with other symptoms may be able to do so in outpatients [11, 15]. A Japanese study identified anosmia, headache and sputum production associated with SARS-CoV-2, whereas fever and dysgeusia were not [16]. A Swiss study reported associations for anosmia, fever, myalgia and cough [13], and an Italian study found older age, fever, and anosmia/ageusia [17]. The association of older age with SARS-CoV-2 infection was found in more studies [18]. Considering that age groups were affected differently during various stages of the pandemic, the age association depends on the timing of patient inclusion.

The ability to develop a robust clinical prediction rule is limited by differences between studies over time and in patient populations, due to sampling from different care settings and stage of the pandemic. Moreover, few other respiratory viruses were prevalent due to the implementation of public health measures and predictive power is influenced by prior probability.

Implementing research in a pandemic

Approvals for the study were fast in some countries. A few ethical boards exempted the study from complete evaluation and allowed permission to start within four days, whereas ethical approval delayed the study start in other countries. Initially, GPs were highly dedicated and motivated to participate as they noticed the pressing need to collect scientific data on COVID-19. However, several barriers were encountered during the study. The relevance of the study was affected by data from public health authorities and the implementation of laboratory-based testing. Patient informed consent was needed in our study, whereas public health could sample and report on findings without. Additionally, there was massive pressure on primary care and individual GPs. Demanding circumstances, insecurities, and high workloads interfered with patient inclusion. Finally, it was also challenging for academic researchers, not having personnel readily available to analyse the samples and emerging data.

Our primary care research network has learned from this experience and recognises our responsibility in pandemic preparedness. Therefore, we have initiated a Perpetual Observational Study, continuously enrolling patients with RTI symptoms under a master protocol [19]. This allows a rapid response to emerging research questions.

Implications of findings

This study highlights the importance of primary care research early in a pandemic and calls for resources in future pandemics. If primary care and public health would have had collaborated more extensively,

continuously validated prediction rules, fine-tuned with the rapidly changing dynamics of SARS-CoV-2, could have had rapid clinical impact and a better evidence-base for risk communication about the mainly self-limiting aspect of COVID-19 [20].

The limited value of findings from physical examination and clinical measurements for predicting SARS-CoV-2 raises a relevant question: whether in the early phase of the pandemic, with shortage of PPE and healthcare professionals, the value of a F2F examination outweighed the risk of viral transmission.

COVID-19 and influenza, which manifest with common symptoms [21], are expected to be prevalent simultaneously. Distinguishing these infections may have implications for treatment, highlighting the continued importance of rapid diagnostic testing. For behaviour, we can question the relevance of distinguishing viral aetiologies. Society could benefit from social distancing and mask-wearing irrespective of which respiratory virus is circulating.

Conclusion

Early in the pandemic, correct clinical diagnosis of a SARS-CoV-2 infection appeared difficult; SARS-CoV-2 was mainly over-diagnosed but also under-diagnosed, particularly in patients presenting with mild symptoms. Loss of taste/smell, fever and muscle aches predicted a SARS-CoV-2 infection. When in a new pandemic diagnostic testing is unavailable, focus should be on collaborative research to develop prediction rules continuously adapted to changing circumstances.

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Authors' contributions

This study was designed and conceived by AWV, CCB and HG. TV and EB provided input to design and protocol. MS, L-MY, AWV performed statistical analyses. KL and MI were responsible for sample management and microbiological analyses. AWV, FB, SC, AC, AG-S, LM, JP, AT and AV implemented the study in their countries (approvals/waivers from Ethics Boards, managing practices, patient follow-up, checking and entering data). AWV wrote the first draft of this manuscript and acted as guarantor. AV and CCB critically revised the manuscript. All authors read and approved the final version of the manuscript.

Disclosure statement

The authors alone are responsible for the content and writing of the paper. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical statement

Regulatory approvals or waivers were sought in each country. The following Ethics Boards were consulted: Medical Ethics Committee of the University Medical Centre Utrecht-the Netherlands, Ethics Committee of the Antwerp University Hospital-Belgium, Bioethical Committee of the Medical University of Bialystok-Poland, Institutional Review Board of the National Centre for Disease Control and Public Health-Tbilisi-Georgia, Research Ethics Committee of the Irish College of General Practitioners-Ireland, Medical Research Council Scientific Research Ethics Committee-Hungary, Rostock University Medical Centre Ethics Committee-Germany, Ethics Committee CEI IDIAP Jordi Gol-Barcelona-Spain, National Committee for Ethical Expertise Ministry of Health, Labour and Social Protection of the Republic of Moldova-Moldova. Dates of approval letters and/or numbers available on request.

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Data availability statement

Data are available upon request, explaining research question and methods, from the first author (AWV) who will seek agreement from the core research team.

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