What neo semeiology brings to the care of patient with COVID-19.

Philippe Brouqui MD, PhD*, Carole Eldin MD, PhD, Sophia Boudjema RN PhD & Didier Raoult MD PhD

Aix Marseille Université, IRD, MEPHI, IHU-Méditerranée Infection, Marseille, France

AP-HM, IHU-Méditerranée Infection, Marseille, France

Financial support

This study was funded by ANR-15-CE36-0004-01 and by ANR "Investissements d'avenir", Mediterranée infection 10-IAHU-03.

Conflict of Interest: No author has any conflict of interest. All authors have submitted to the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

English edition of the manuscript: This manuscript has been edited by a native English speaker.

Text Words 2787

Abstract words :51

Figure: 1, table 1 and panel 1

Keywords: COVID-19, Happy, asymptomatic, hypoxemia, anosmia, semeiology, emerging

Abstract: By definition, semiology of a new emerging infection is unknown. Early case definition is usually based upon the most resembling disease. Testing asymptomatic and symptomatic persons irrespective of their clinical presentation allowed describing new semiology features such as anosmia and happy hypoxemia in COVID-19, leading to a more appropriate care of patient.

Introduction

Medical semiology is a part of medicine dedicated to the study of signs and symptoms based upon interview on patient's medical history, underlying disease, complaints, physical examination, and paramedical information obtained throughout objective features reported by imaging, echography and many other technical approaches. Medical semiology has evolved since Hippocrates. Chest auscultation has long been considered a useful part of the physical examination until the invention of the stethoscope by René Laennec in 1816 [1]. Then, the technological advances in ultrasonography, radiographic computed tomography , magnetic resonance imaging, and PET have helped clinicians in their diagnostic investigations[2]. Nevertheless, the most impressive advance in infectious diseases was germ identification and isolation, evidencing the microbial etiology of the disease. Until then, signs and symptoms were the main tools to describe a disease and pneumococcal pneumonia was precisely described in 1836 as the "Pneumonie aux yeux d'or " reflecting jaundice and hepatorenal failure in late pneumococcal pneumonia [3]. Modern description of an infectious disease relies on the frequency of sign during the whole disease, as an infection is a dynamic phenomenon which begins at the onset of the disease and hopefully finishes when the disease is cured. During this time, signs and symptoms are not present all time long. One-point observation gives only a short vision of the disease. To describe this new disease there is a need to observe patient from the onset to the recovery. Neo semiology is describing new signs and symptoms observed during a new disease.

The current description of an infectious disease, most of time, starts by identification of the pathogen by molecular testing in patient with a very simple clinical description mainly based on few signs called "case definition" usually borrowed to the closest disease. The most recent example is the discovery of COVID-19 caused by SARS-Cov2 in the end of 2019 in mainland China [4] [5].

Initially this disease was named severe acute respiratory syndrome as it presented itself similarly to SARS-CoV-1 that was described previously in Hanoi and spread in Europe and the Americas in 2004 [6]. SARS-CoV-1 presented with fever in all cases 751/752 (99.9%) , cough in 460/702 cases (65.5%) dyspnea in 12- 92% of cases, and lymphopenia (66%) [7]. Initial abnormal CT scanner was recorded in most patients (80-100%). Anosmia, ageusia, happy hypoxemia were not recorded in this disease and

neither were eosinopenia, elevated D. Dimers and thrombosis. In a review published years after, the clinical presentation was reported as a two-phase illness. The first phase of one week duration in which fever is present in 100% of the cases, and is associated with chills, myalgia , malaise and headaches sometimes with diarrhea [8]. In this prodromic phase, respiratory symptoms were typically absent although a mild cough might occur. However, half of patients at this stage had radiographic abnormalities on the Chest X-ray. Ground glass opacities were observed earlier with CT scanner suggesting that lung imaging abnormalities were present in most cases. The respiratory phase begins late in the first week in between 8-10 days. At this time, fever might improve or resolve while respiratory symptoms get worse. This description is very similar to COVID-19 except for fever. Asymptomatic persons were rarely reported in SARS-Cov1 disease. SARS was uncommon in children and appeared milder than in adults [8]. It is important to notice here that SARS clinical description was frequently based upon unproven diagnostic and that WHO case definition given for SARS-CoV-1 screening had a positive predictive value ranging from 96% in a specialized SARS clinic in Hong Kong to 4% in the USA [8]. Moreover, the patients observed during SARS-CoV-1 epidemic were those severely ill who needed care. The fact that asymptomatic cases were reported as rare is likely linked to the weak extent of systematic testing suggesting an incomplete investigation of the signs and symptoms of this disease leaving SARS-CoV-1 largely undiscovered.

The largest anticipated pandemic until now was influenza and all state preparedness plans were based upon this hypothesis. Consequently, case definition of an emerging respiratory infection was based upon influenza-like illness (ILI) or severe acute respiratory infection (SARI) definition. In their guidelines on pandemic influenza threat, it was suggested that “Any suspected case of human infection with a novel influenza virus must first meet the criteria for influenza-like illness (ILI), defined as temperature of >38°C plus either sore throat or cough. Since lower respiratory tract involvement might result in dyspnea (shortness of breath), dyspnea should be considered as an additional criterion. Therefore, the full clinical criteria are: fever plus one of the following: sore throat, cough, or dyspnea”[9].

Finally, this case definition was used for screening SARS-CoV-2-infected patients [10]. In their COVID-19 surveillance webinar on May 22, 2020, the CDC still argued that ILI and SARI surveillance is applicable to COVID-19 because the most frequent signs and symptoms (fever, cough and fatigue) are similar [11]. Exhaustive epidemiological investigation in Iceland reveals that 14% and 22% of patients at diagnostic did not meet the case definitions of the CDC and WHO respectively [12]. A recent paper comparing main clinical characteristics of patients with COVID-19 with those with influenza showed that COVID-19 patients presented less frequently with fever and persistent fever [13], and that COVID-19 presented itself neither as ILI nor as SARI [14].

The testing strategy set up by our institution very early in the outbreak associated with careful clinical description of this disease in all positive patients allowed revealing many different clinical presentations and improved the semiology knowledge and the clinical spectrum of this new disease [15]. During the first phase of the pandemic, we observed 3,737 positive patients who were diagnosed and cared for in our institution some as outpatients in the day hospital, others in hospitalization. Clinical data registered in the hospital information system was analyzed with multiple correspondence analysis which allowed to highlight the association between clinical presentation, risk factor, ICU and death [15]. A first cluster of patients was very early isolated with upper respiratory presentation (anosmia, ageusia and chest pain) in young people with good outcome, and a second cluster characterized by lower respiratory infection with dyspnea, cough and fever in older patients who presented with an onset-treatment time longer than 5 days, with intermediate pulmonary lesion at CT Scanner and more severe outcome. We linked D-Dimers with thromboses, and pulmonary emboly to poor outcome and described the impact of asymptomatic hypoxemia on ICU and death. We will focus on these new signs that better describe the disease and help establishing the clinical diagnosis, predict the outcome, and finally guide and optimize the care of our patient.

Role of testing.

In our institution, we tested 151,830 peoples who presented themselves at the screening center during the whole epidemic and we diagnosed 19,055 patients among whom we cared for # 16,000 as of today (11 000 as outpatients and 5000 in beds). Among confirmed positive patients, asymptomatic ones represent 30.2% which suggests that the virus is largely circulating unnoticed in the population. Only a large testing allows appreciating the weight of asymptomatic presentation and its possible role played in the epidemic. Testing people whatever their clinical presentation, is also mandatory to describe any unexpected clinical form. Ageusia and anosmia would have never been described if tests had only been performed in selected patients with ILI or SARI as defined in the WHO case definition. Finally, to describe a new respiratory infectious disease testing should not be restricted to symptomatic patients with ILI / SARI but largely applied to every symptomatic or asymptomatic person willing to be tested.

Role of Clinical observation

Once tested and diagnosed, meticulous clinical observation of signs and symptoms is crucial in the description of a new emerging disease and justifies that clinicians' first observation shall be published quickly in case reports, small series, and larger cohort studies shall be led to release important features that will help in improving the care along the epidemic.

Anosmia and ageusia

Our first SARS-CoV-2 patient complained shortly after admission of anosmia. The patient assumed that this was related to the treatment (hydroxychloroquine and azithromycin). This singular complaint was seriously considered. Before COVID-19 era, although reported in type 3 parainfluenza virus [16], anosmia and ageusia were no usual complaints from patients with acute upper respiratory syndrome, and were not investigated in medical interview. In fact, loss of smell and taste has been shown common in COVID-19 [17] and olfactory dysfunction was reported in 52.73% (95% CI, 29.64%-75.23%) among patients with COVID-19 [18]. In our experience, among COVID-19 patients 41.6% (4.8% in control) reported anosmia and ageusia, (6.1%) reported anosmia only, and 5.2% reported ageusia only. Overall, the prevalence of anosmia and/or ageusia in COVID-19-patients was 356/673 (53%) which is similar to what was reported in the literature [18] [19]. Loss of smell and taste is more frequent in young people (< 65 y-o). The calculated predictive positive value of the loss of both smell and taste was 57.59 % and 66,67% in people older than 65 y-o and younger than 64 y-o respectively suggesting that along with other signs both of these would be of help in establishing a clinical diagnostic score for COVID-19. Consequently, these two signs, ignored until now, will likely become a new important sign in clinical investigation of respiratory infection.

Silent pneumonia

In the early phase, to have an evaluation of lung abnormalities in the disease we decided to perform low dose CT scanner (LDCT) to all COVID-19-positive patients who were treated in our institute whatever clinical presentation age and comorbidity [20] . Among the first 3737 patients diagnosed with SARS-Cov-2, we selected 2012 with available information for dyspnea and LDCT scanner within the first 48-72 hours of admission. Among them 1370/2012 (68.1%) presented with no dyspnea, 642/2012 (31.9%) presented with dyspnea. The LDCT scanner showed signs compatible with pneumonia in 937/1370 (68.4%) of patients with no-dyspnea suggesting that silent pneumonia was very frequent in COVID-19. Of them 648/937 (69.2%) were of minimal grade 1, 236/937 (25.2 %) of intermediate grade 2, and 53/937 (5.7%) of severe grade 3 [21].

Happy (asymptomatic) Hypoxemia

We and others have experienced these COVID-19 elderly patients who presented with no symptoms, wellbeing and for whom national and international guidelines suggested to be isolated at home and who came back to hospital on day 9 or 10 with a so serious acute respiratory distress that they are cared for directly in ICU [22]. In our hands, more than two thirds of patients hospitalized in intensive care units (ICUs) came directly from home or were admitted to the ICU after less than three days of

standard ward hospitalization. Many patients who then developed respiratory failure experienced hypoxemia and hypocapnia without signs of respiratory distress, especially elderly patients. Hypoxemia without dyspnea has been named “happy hypoxemia” or asymptomatic hypoxemia and has been reported to be associated with the outcomes of patients with COVID-19 [23]. In our cohort of patients diagnosed with COVID-19, 65% do not complain of shortness of breath. Among patients without dyspnea at admission, 28% had a hypoxemia /hypocapnia syndrome. Asymptomatic hypoxemia was associated with a very poor outcome (33% were transferred to ICU and 26% died) [23]. Consequently, it was suggested that pulse oxymetry monitoring at home would be an important mean to predict the outcome along with NEWS score and LDCT scanner [23].

Hypokalemia

Hypokalemia (< 3.5mmol/l) is found in 404/3315 (12.2 %) patients with COVID 19 at initial presentation. Hypokalemia is induced by kaliuresis due to an increased secretion of aldosterone in relation with SARS-Cov 2 induced elevations of angiotensin II concentrations [24]. Consequently, hypokalemia being a favorizing factor for cardiac arrhythmia, we systematically tested for hypokalemia before HCQ/AZ treatment initiation and if K<3.6 mmol/l we delayed HCQ until serum level of potassium returned to normal.

Heart rhythm disturbance

Very early in the epidemic we published about the efficacy of hydroxychloroquine 600mg/d for 10 days in a small comparative study on SARS-Cov2 viral load [25] . We then decided to propose to our patients a treatment with HCQ and AZ to which we have later associated Zinc [15]. In order to secure the treatment, we perform with our cardiologist colleague, systematic evaluation of heart rhythm disturbance by EKG on all patients followed in our center. We performed 7,800 EKG on the first 3737 patients entered in the cohort. Among them, 88 were contraindicated for HCQ/AZ treatment including 24 for prolonged QTc [15]. Since then, EKG was performed to all patient volunteers before being treated by HCQ-AZ and no serious cardiac complication was observed in the 16,000 patients treated in our institute. These results indicate that the risks of severe arrhythmia induced by combined HCQ-AZ therapy for COVID-19 can be minimized by the institution of simple clinical management (*Maille B, et al. in this issue of CID).*

Risk management of thrombosis

Pulmonary embolism is causing death in COVID-19 in 20-30% of cases in severe patients [26]. Elevated D-Dimers are linked to bad outcome [15]. However, in our experience, we were surprised to diagnose pulmonary embolism in patients with no severe infection. Consequently, preventive

anticoagulation should be systematically prescribed in outpatients >70 y-o, those with risk factor for thrombosis, and if D-Dimers are between 0.5-1µg/ml. When D-Dimers are found up to 2µg/ml, angiography CT scanner to rule out pulmonary embolism is mandatory in our opinion. Interestingly, such parameter eventually differs in prevalence depending on viral genotype and virulence [27]. Other recent data has shown that arterial thrombosis is also prevalent in COVID-19 infection , as part of a hypercoagulable state [28].

Influence on knowledge and care (Table)

As we tested all patients who presented themselves to us, we can precisely describe signs and symptoms of COVID-19 from the onset of symptoms and in mild, moderate and severe clinical forms. Systematic testing allows determining the prevalence of asymptomatic persons. We reported that children are infrequently susceptible to infection [29], that samples with PCR ct >34 are culture negative and can be used to manage the discharge of hospitalized patient which was very useful to improve patient rotation in wards [30]. The Ct is in our hands a very useful criterion for corticosteroid therapy indication, as in an infectious disease, it is usually admitted that corticosteroid therapy during acute infection is deleterious [31]. Large systematic testing of islander peoples reveals that at diagnosis (14%) and (22%) of people did not meet the case definition of the Centers for Disease Control and Prevention and the World Health Organization, respectively [12] . This is also findings reported by Lechien et al. in 1420 European patients positive for SARS COV2 [32]. The earliest symptoms in COVID-19 are headaches and anosmia with nasal obstruction, more frequently observed in younger >60 y-o , and are expression of an upper respiratory tract infection [32]. Cough, dyspnea and fever appear later on, in between 8 and 10 days after the onset, reflecting the lower respiratory tract infection in moderate-severe form in hospitalized patient [15] (Figure). Moreover, detection of anosmia/ageusia is important as rehabilitation therapy is usually efficient if started early [33]. As in two thirds of patients without dyspnea at presentation LDCT scanner shows pneumonia, sometimes severe, in our opinion LDCT Scanner is recommended in aged patients with comorbidity especially if oxygen saturation is below 95%. In these patients with comorbidities, including age, the lack of dyspnea is not a sign of wellbeing. We suggest a regular monitoring of older patients, especially those with diabetes [34], by pulse oximetry, and if Sat O2 measured <95% twice at 15-minute intervals to immediately inform the physician in charge of the patient for complementary investigation at a hospital. If treatment with HCQ/AZ is proposed to the patient, we suggest controlling the potassium level and performing ECG, and systematically controlling D. Dimers to allow thrombosis prevention. In our opinion this strategy allows a very low case fatality ratio of COVID-19 (Ref paper CID).

As by definition, a new disease semiology is unknown, case definition should be actualized in real time. Dyspnea was included in the case definition of all three guidelines but is reported in fact in between 30-50% of cases, as was fever reported in only 15-98% of cases depending on how late the patients were seen. Signs are changing as the disease is progressing from upper respiratory to pulmonary expression. Headaches, nasal obstruction, anosmia and ageusia should be added in case definition of suspected COVID-19 because they are the most frequent signs in the early phase of the disease and allow an early diagnostic and treatment (Panel).

COVID-19 brought an incredible new knowledge in a very short time. New signs and symptoms should be now evaluated in other acute respiratory infection and ageusia, anosmia (described in para influenzae 3) should be systematically added in the interview of these patients. General practitioners should be aware of the occurrence of silent pneumonia and happy hypoxemia and prescribe LDCT scanner and oxygen saturation surveillance. Prevention of thrombosis should lie on D dimer measurement.

Acknowledgments

This manuscript has been edited by a native English speaker.

Figure and table legend

Figure : COVID-19 disease and key semeiological elements over time. The figure shows that asymptomatic peoples represent 30-50% of cases, the first clinical signs at onset are upper respiratory signs such as headaches, anosmia and nasal obstruction most often observed in young people followed by lower respiratory symptoms including cough dyspnea and fever most often seen in the elderly. In the last population, Happy hypoxemia (30% mortality) is observed in one third of patients. In patients without dyspnea, 70% have an abnormal CT Scanner showing pneumonia. Antiviral treatment should be provided in the early viral phase whereas corticosteroids, being deleterious and not indicated and should only be prescribed in the inflammatory phase in severe disease.

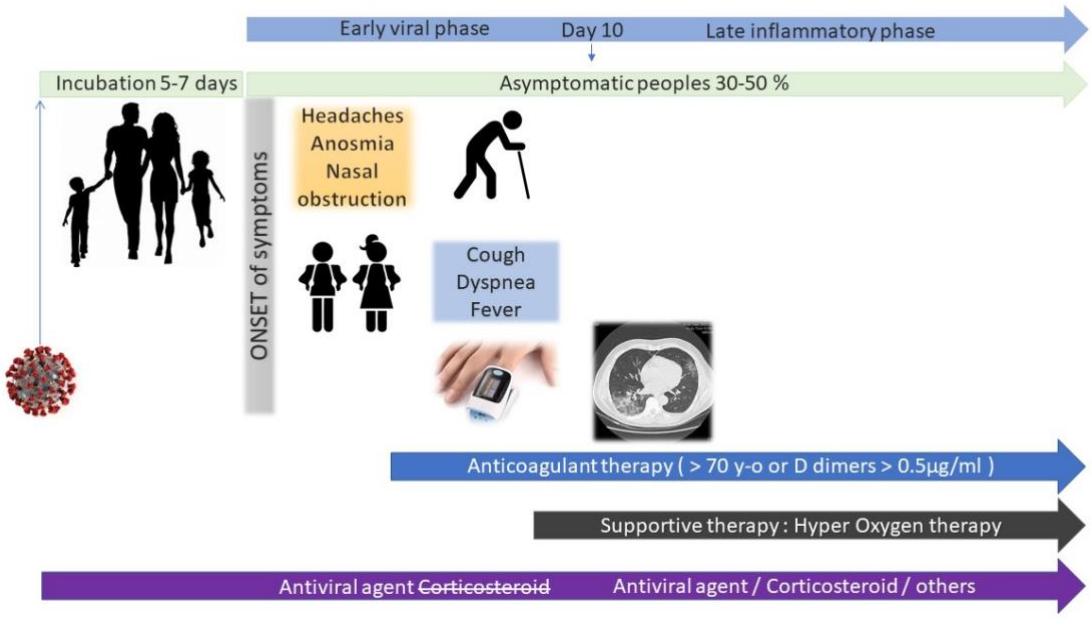

Table: Neosemiology of COVID-19. What we learnt at IHU MI and implication on the care.

	Influence on knowledge and Care
Systematic PCR testing	-Prevalence of asymptomatic persons -Children are not infected -False positive test if ct >34 -Discharge of hospitalized patient when CT>34 enhances patient rotation in wards - allows criteria for corticosteroid therapy
Anosmia	-Enhances clinical diagnostic probability -Allows early detection -Allows early rehabilitation and treatment -Anticipated post-covid complaint and follow-up
Ageusia	-Enhances clinical diagnostic probability, anticipated post-covid complaint
LDCT Scanner	- Asymptomatic or silent pneumonia - Criteria for hospitalization - Complementary antibiotic therapy if associated with fever
Oxygen saturation < 95%	- Alerts on happy hypoxemia in patient without shortness of breath - Criterion for hospitalization and oxygen supplementation - Indication for Hyper oxygen therapy
Rash	
Point of care serum potassium level (5 minutes)	-Frequent hypokalemia in Covid related to virus-induced hyper aldosteronism -Used as HCQ/AZT treatment eligibility criterion
ECG	-Allows establishing the absence of risk for HCQ/AZT combination -QTc< 460 ms used as treatment eligibility criterion
D Dimers	- Prophylactic anti-coagulation if up to 0.5µg/ml - Angio CT Scanner to rule out pulmonary embolism if up to 2µg/ml

Panel: Signs and symptoms at presentation (4-8 days after onset) described in COVID and CDC, WHO, and French (HCSP) original case definitions. Depending on time of presentation and severity of disease signs, symptoms changed reflecting the dynamic of infection.

	CDC[1]	WHO[2]	HCSP[3]	[12]	[15]	[32]	[5]
	April 5-2020	April 23-2020	March 5-2020	Iceland (Nb 1564)	Marseille (Nb 3737)	Europe (Nb 1420)	Wuhan (Nb 138 p)
Physicians in charge				Int. Med.	Infect. Dis. Microbiol.	Otorhinolaryngologists	Intensivist, Pneum. Infect. Dis.
Date admission / Onset				day 7	day 4-8	unknown	day 4-8
Disease presentation				Mixt Panel*	All people**	Mild-Moderate symptomatic***	Hospitalized/Severe
Asymptomatic					30.0		
Headaches				35.1		70.3	6.5
Anosmia				27.3	39.2	70.2	
Ageusia				29.7	37.8	54.2	
Nasal obstruction				21.0	32.7	67.8	
Dyspnea				27.0	28.2	49.1	31.2
Sore throat				18.0		52.9	
Thoracic pain					22.1		
Fatigue				35.7		63.3	69.6
fever				65.3	15.6	45.4	98.6
Myalgia				26.9		62.5	34.8
Cough				37.1	50.2	63.2	59.4
Nausea				9.6		19.2	10.1
Vomiting				1.7		19.2	3.6
Diarrhea				10.1		38.1	10.1
Abdominal pain				6.3			2.2
Prevalence	>60%	60-50	50-40	40-30	30-20	<20	Unknown

1- CDC April 5-2020 https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/
2- WHO April 7-2020. Coronavirus disease 2019 (COVID-19) Situation Report – 94. 20200423-sitrep-94-covid-19.pdf (who.int)
3- HCSP March 5-2020 http://www.cphg.org/wp-content/uploads/2020/03/AVIS-HCSP-2020-03-05.pdf

References

[1] Dr. Forbes's New Translation of the Second Edition of Laennec on Auscultation. *Medico-Chir Rev* 1828; 8: 103–116.

[2] Bohadana A, Izbicki G, Kraman SS. Fundamentals of lung auscultation. *N Engl J Med* 2014; 370: 2053.

[3] Vermillion SE, Gregg JA, Baggenstoss AH, et al. Jaundice associated with bacteremia. *Arch Intern Med* 1969; 124: 611–618.

[4] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382: 1708–1720.

[5] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061–1069.

[6] Cherry JD. The chronology of the 2002-2003 SARS mini pandemic. *Paediatr Respir Rev* 2004; 5: 262–269.

[7] Peiris JSM, Yuen KY, Osterhaus ADME, et al. The Severe Acute Respiratory Syndrome. *N Engl J Med* 2003; 349: 2431–2441.

[8] Muller M, McGeer A. Severe Acute Respiratory Syndrome (SARS) Coronavirus. *Semin Respir Crit Care Med* 2007; 28: 201–212.

[9] National Pandemic Influenza Plans | Pandemic Influenza (Flu) | CDC, https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/national-strategy-planning.html (2018, accessed 25 November 2020).

[10] WHO COVID-19 Case definition, https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1 (accessed 25 November 2020).

[11] McCarron M, Henao O, Davis T, et al. COVID-19 Surveillance Webinar. 40.

[12] Eythorsson E, Helgason D, Ingvarsson RF, et al. Clinical spectrum of coronavirus disease 2019 in Iceland: population based cohort study. *BMJ* 2020; 371: m4529.

[13] Qu J, Chang LK, Tang X, et al. Clinical characteristics of COVID-19 and its comparison with influenza pneumonia. *Acta Clin Belg* 2020; 75: 348–356.

[14] Surveillance and monitoring, https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/maternal-health/about/global-influenza-programme (accessed 25 November 2020).

[15] Lagier J-C, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. *Travel Med Infect Dis* 2020; 36: 101791.

[16] Sugiura M, Aiba T, Mori J, et al. An epidemiological study of postviral olfactory disorder. *Acta Oto-Laryngol Suppl* 1998; 538: 191–196.

[17] Ollarves-Carrero MF, Rodriguez-Morales AG, Bonilla-Aldana DK, et al. Anosmia in a healthcare worker with COVID-19 in Madrid, Spain. *Travel Med Infect Dis* 2020; 35: 101666.

[18] Tong JY, Wong A, Zhu D, et al. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. *Otolaryngol Neck Surg* 2020; 163: 3–11.

[19] Boudjema S, Finance J, Coulibaly F, et al. Olfactory and gustative disorders for the diagnosis of COVID-19. *Travel Med Infect Dis* 2020; 37: 101875.

[20] Castelli M, Maurin A, Bartoli A, et al. Prevalence and risk factors for lung involvement on low-dose chest CT (LDCT) in a paucisymptomatic population of 247 patients affected by COVID-19. *Insights Imaging* 2020; 11: 117.

[21] Leger T, Jacquier A, Barral P-A, et al. Low-dose chest CT for diagnosing and assessing the extent of lung involvement of SARS-CoV-2 pneumonia using a semi quantitative score. *PloS One* 2020; 15: e0241407.

[22] Ottestad W, Seim M, Mæhlen JO. COVID-19 with silent hypoxemia. *Tidsskr Den Nor Legeforening*. Epub ahead of print 21 April 2020. DOI: 10.4045/tidsskr.20.0299.

[23] Brouqui P, Amrane S, Million M, et al. Asymptomatic hypoxia in COVID-19 is associated with poor outcome. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. Epub ahead of print 29 October 2020. DOI: 10.1016/j.ijid.2020.10.067.

[24] Silhol F, Sarlon G, Deharo J-C, et al. Downregulation of ACE2 induces overstimulation of the renin-angiotensin system in COVID-19: should we block the renin-angiotensin system? *Hypertens Res Off J Jpn Soc Hypertens* 2020; 43: 854–856.

[25] Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; 56: 105949.

[26] Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020; 191: 148–150.

[27] Gautret P. Different pattern of the second outbreak of COVID-19 in Marseille, France. *Int J Infect Dis* 2021; 3.

[28] Kashi M, Jacquin A, Dakhil B, et al. Severe arterial thrombosis associated with Covid-19 infection. *Thromb Res* 2020; 192: 75–77.

[29] Colson P, Tissot-Dupont H, Morand A, et al. Children account for a small proportion of diagnoses of SARS-CoV-2 infection and do not exhibit greater viral loads than adults. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2020; 39: 1983–1987.

[30] La Scola B, Le Bideau M, Andreani J, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2020; 39: 1059–1061.

[31] Youssef J, Novosad S, Winthrop K. Infection Risk and Safety of Corticosteroid Use. *Rheum Dis Clin North Am* 2016; 42: 157–176.

[32] Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020; 288: 335–344.

[33] Hura N, Xie DX, Choby GW, et al. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2020; 10: 1065–1086.

[34] O'Donnell CR, Friedman LS, Russomanno JH, et al. Diminished perception of inspiratory-resistive loads in insulin-dependent diabetics. *N Engl J Med* 1988; 319: 1369–1373.