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Open Forum Infectious Diseases

REVIEW ARTICLE

Misdiagnoses in the Context of Suspected Pandemic Influenza or Coronavirus Disease 2019: A Systematic Review

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There have been numerous reports of patients initially misdiagnosed in the 2009 H1N1 influenza and coronavirus disease 2019 (COVID-19) pandemics within the literature. A systematic review was undertaken to collate misdiagnoses during the H1N1 and COVID-19 pandemics and identify which cognitive biases may contribute to this. MEDLINE, Embase, Cochrane and MedRxiv databases were searched for misdiagnoses or cognitive biases resulting in misdiagnosis, occurring during the H1N1 or COVID-19 virus pandemics. Eligible studies were assessed for quality using JBI criteria; primary outcome was the final diagnosis. Sixty-nine studies involving 2551 participants were included. We identified 686 cases of misdiagnosis, categorized as viral respiratory infection, other respiratory infection, non-respiratory infection, and non-infective. Misdiagnoses are listed and relevant investigations are offered. No article described prospective assessment of decision making in the pandemic setting or debiasing diagnostic thinking. Further research is required to understand why misdiagnoses occur and harm arises and how clinicians can be assisted in their decision making in a pandemic context.

Keywords. cognitive bias; coronavirus; influenza; misdiagnosis; respiratory virus pandemic.

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, many countries have adopted a syndromic approach to clinical assessment, similar to during the H1N1 influenza pandemic in 2009–2010 [1–4]. However, presentations of other diseases may be similar to these viral infections [5]. In other settings, syndromic approaches risk incorrect diagnosis, particularly in the context of changing disease epidemiology [6]. This might be exacerbated by cognitive biases impairing the decision making of healthcare workers in a pandemic context [7, 8]. Such instances of misdiagnosis may have contributed to excess mortality during the COVID-19 pandemic not directly attributable to infection with the virus [9, 10].

The existing literature offers published reports of missed or delayed diagnoses during both pandemics, although the investigators are not aware of any systematic review of these. This systematic review aims to establish which conditions may be misdiagnosed in the assessment and management of acute febrile illness in adults and children during a respiratory virus pandemic, and it aims to identify which cognitive biases may contribute to cases of misdiagnosis during a respiratory virus pandemic. We have summarized the published literature regarding cases of misdiagnosis, and contributing cognitive biases, in the context of the COVID-19 and 2009 H1N1 influenza respiratory virus pandemics, including assessment of harm where possible. This work aims to inform the response to the current and future pandemics, by highlighting common and important diagnoses to be considered in patients presenting with suspected acute viral respiratory illness and outlining what is known about the impacts of cognitive biases on the diagnostic process in the pandemic context.

METHODS

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1) [11]. A protocol was prepared and registered with PROSPERO (CRD42021202820).

Search terms are shown in Supplementary Methods. Two separate searches were conducted in Medline, Embase,

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Cochrane, and MedRxiv databases, from inception to the end of June 2021. Search terms for H1N1 influenza/COVID-19 were combined with terms for delayed or missed diagnosis forming Search 1. Search terms for H1N1 influenza/COVID-19 were combined with terms for cognitive bias/diagnostic error, based on a previously described search strategy, forming Search 2 [8]. The search strategy was devised in collaboration with an information specialist.

Search results were imported into Microsoft Excel v14 spreadsheets, and duplicates were removed. All unique results underwent title, abstract, and subsequently full-text screening by two independent reviewers based on the inclusion criteria. Disagreements were resolved through discussion, with the involvement of a third reviewer if consensus could not be reached.

Eligibility Criteria

Studies describing adults or children, initially diagnosed with 2009 H1N1 influenza or COVID-19, but subsequently demonstrated to have an alternative diagnosis, were eligible. Studies were not restricted by study design, but the case(s) of misdiagnosis must have occurred during the 2009 H1N1 influenza or COVID-19 pandemics. Date restrictions corresponding to the pandemics were not applied due to the possibility of delays in publication, although authors must have identified that the cases occurred within the context of the 2009 H1N1 influenza or COVID-19 pandemics. Studies published in a non-English language, describing cases where 2009 H1N1 influenza (during that pandemic) or COVID-19 was eventually diagnosed, or presenting no clinical data were excluded. Letters, preprints, and conference abstracts were eligible provided other eligibility criteria were met.

Data Extraction

The variables for data extraction are available in Supplementary Methods. Data from each eligible study were extracted by one reviewer and audited for accuracy by a second reviewer. Discrepancies were resolved through discussion, with the input of a third reviewer if agreement could not be reached. Where articles presented cohorts with and without a diagnosis of pandemic virus infection (COVID-19 or 2009 H1N1 influenza), these were eligible if the patients without the pandemic virus were initially assessed for suspected pandemic virus infection. In this case, only clinical data regarding the cohort without the pandemic virus was extracted. For quality assessment purposes, this was then considered as a case series.

Outcomes

The outcomes of this systematic review and their prioritization were:

Primary Outcomes

Primary outcomes of the review were: (1) final diagnosis after initial respiratory viral diagnosis revised; and (2) cognitive features/human factors associated with diagnostic delay.

Secondary Outcomes

Secondary outcomes of the review were: (1) length of diagnostic delay (time); (2) severity of diagnostic delay (clinical markers of severity); (3) mortality including mortality attributable to diagnostic delay; (4) length of stay including excess length of stay attributable to diagnostic delay; and (5) cognitive features/human factors associated with overturning incorrect diagnosis.

Quality Assessment

Each included study underwent critical appraisal of its quality. We used the JBI Manual for Evidence Synthesis Critical Appraisal Checklists for both case reports and case series [12]. Quality assessments were completed independently by two reviewers. Any discrepancies between the assessments were discussed to reach a consensus, with the involvement of a third reviewer if necessary. No studies were excluded from the systematic review on the basis of quality.

Data Synthesis

Due to the diversity of methodology and data found after the searches, no formal meta-analysis was undertaken. Eligible studies were grouped by methodology and size. To facilitate a narrative review, final diagnoses were grouped by etiology. Studies with over 20 cases were considered likely to be more representative of the misdiagnosis population and used to group diagnoses by frequency. Reporting biases were assessed qualitatively by comparing studies of differing designs. Qualitative certainty assessment was undertaken, informed by GRADE domains [13]. There was no funding source for this study and no ethical approval was required.

RESULTS

Identification and Selection of Studies

In Search 1, a total of 2267 unique articles were identified, 143 underwent full-text screening, 69 were eligible for inclusion (Supplementary References). In Search 2, 1921 unique articles were identified, and 113 underwent full-text screening. Zero articles contained primary data regarding cognitive biases resulting in misdiagnosis in the context of 2009 H1N1 influenza or COVID-19 pandemics. Seventeen articles described misdiagnoses and were transferred to Search 1 for eligibility assessment against those criteria. PRISMA diagrams are shown in Supplementary Figures 1 and 2.

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Characteristics of the Included Articles

Table 1 presents the characteristics of the 69 included studies, totaling 2551 participants. Sixteen of 69 (23%) of the studies, comprising 1441 participants, relate to the 2009 H1N1 influenza pandemic, whereas 53/69 (77%) studies, with 1110 participants, are from the COVID-19 pandemic. Study designs were predominantly case reports (44/69) or short case series (17/69). Eight large studies, including 20 or more participants, were identified: four case series and four cohort studies. The most common country settings were the United Kingdom (13/69) and United States (11/69), with the remaining studies dispersed across Europe, Asia, North America, South America, and Africa. Articles primarily reported adult cases (56/69); 6/69 reported children only and 6/69 described both adults and children. One study did not report age. Participants ranged from 0 to 84 years of age. Across seven of the larger studies, female participants ranged from 33% to 57%, and one study did not report gender. Among the case reports and short case series, a total of 40 male and 33 female cases were described. The healthcare settings were predominantly secondary care (61/69), with remaining studies situated in tertiary care (5), primary/secondary care (2), and primary care (1). The method of assessment resulting in a presumptive diagnosis of H1N1/COVID-19 was reported in 62/69 articles (54 in-person, 4 telephone, 3 combined telephone and in-person, and 1 online assessment).

Quality Assessment

The individual quality assessments of all included studies are outlined in Supplementary Tables 2 and 3. The case reports were generally of good quality, with 31 out of 45 studies satisfying at least six of the eight quality criteria (median 7, range 3–8) (Supplementary Figure 3). Studies commonly gave a good account of the clinical presentation and diagnostic methods. Detail regarding the clinical condition of patients by the time of the correct diagnosis was frequently poorly described.

The quality of the case series was variable (Supplementary Figure 4). Studies were assessed using ten criteria, although statistical analysis was often not applicable. Of the remaining nine criteria, no study satisfied all nine. Eleven of 24 satisfied at least five criteria (median 4, range 1–8). Some did not give details on consecutive or complete inclusion of patients. Quality of the eight larger studies was higher, with 7/8 satisfying five or more quality criteria, compared with 4/16 for smaller case series (Figure 1).

Primary Outcomes

In total, 686 misdiagnoses are described with 97 different final diagnoses (Table 2 and Supplementary Table 4). There were more articles from the COVID-19 pandemic than for the 2009 H1N1 influenza pandemic, although more cases overall were identified from the 2009 H1N1 pandemic. There was considerable overlap in the diagnoses identified, so misdiagnoses from both pandemics were analyzed together. The most common diagnoses among the described cases were community-acquired pneumonia/lower respiratory tract infection (225), respiratory syncytial virus (RSV) (84), and other seasonal respiratory viruses (rhinovirus, adenovirus, human metapneumovirus, parainfluenza, and seasonal coronaviruses (82)). Other major final diagnoses included the following: exacerbation of chronic pulmonary disease (24), influenza (16), tonsillitis/streptococcal pharyngitis (14), cardiac failure/pulmonary oedema (14), gastroenteritis (13), and bacteremia (12). Diseases misdiagnosed as 2009 H1N1 influenza or COVID-19 can be grouped as viral respiratory infection, other respiratory infection, non-respiratory infection, and non-infective. The final diagnoses described in many case reports were not identified in case series with consecutive inclusion.

Prevalence of misdiagnoses or delayed diagnoses was inferred using the eight larger studies, several of which reported consecutive inclusion of participants, totaling 600 cases (Table 3). Diagnoses were grouped by frequency: high prevalence was defined as 5% of cases or more, and medium prevalence was defined as 1%–5% of cases. Low prevalence diagnoses comprised less than 1% of cases in the larger studies, but they were reported more than once in more than one article overall. Diagnoses reported by a single article were considered rare and are not shown. Rogier et al [14] grouped some diagnoses (eg, neurological disease) without reporting the individual diagnoses separately, and we have preserved these groupings. We have grouped other diagnoses, such as malignancy, vasculitis/autoimmune disease, and iatrogenic pneumonitis where individual diagnoses were rare but collectively they made a meaningful contribution.

Among high prevalence misdiagnoses, all were seen in studies from both the 2009 H1N1 influenza and COVID-19 pandemics. Among the medium prevalence misdiagnoses, influenza, mycoplasma pneumonia, and neurological disease were only reported from the COVID-19 pandemic. In contrast, tonsillitis/streptococcal pharyngitis was only reported during the 2009 H1N1 influenza pandemic.

Secondary Outcomes

Thirty-nine studies specified the length of diagnostic delay for a total of 50 patients. This ranged from 8 hours to 61 days, with a mean delay of 8.9 days. Eighteen studies presented an impact of delay, describing severity of symptoms, complications, or admission to intensive care. Twenty-two studies reported the total length of hospital stay for 177 patients, which ranged from 2-64 days, with a mean of 18 days. Nine studies described a patient death, whereas the remaining studies either reported 0% mortality (52/69) or made no comment on patient survival (8/69). One study alluded to diagnostic delay contributing to patient death [15]. The most common reasons cited for misdiagnosis

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Table 1. Characteristics of Included Studies

Pandemic	Author Name (Year)[a]	Quality of Evidence and Study Design	Setting	Country	Participants (n)
2009 H1N1 Pandemic	Ho et al (2009)	3 - Retrospective case-note review	Tertiary care	United Kingdom	110
	Payne et al (2009)	4 - Case series	Secondary care	United Kingdom	3
	Houlihan et al (2010)	4 - Case series	Secondary care	United Kingdom	8
	Knight and Glennie (2010)	5 - Case report	Primary care	United Kingdom	1
	Schofield and Trent (2010)	5 - Case report	Secondary care	United Kingdom	1
	Dosekun et al (2010)	4 - Case series	Primary and secondary care	United Kingdom	2
	Al-Shakerchi et al (2011)	3 - Retrospective case-note review	Secondary care	United Kingdom	71
	Cunha et al (2011)	5 - Case report	Secondary care	USA	1
	Loudon et al (2011)	4 - Case series	Secondary care	United Kingdom	3
	Rashid A et al (2011)	5 - Case report	Secondary care	United Kingdom	1
	Harris et al (2011)	5 - Case report	Secondary care	United Kingdom	1
	Metan et al (2011)	5 - Case report	Secondary care	Turkey	1
	Lo et al (2011)	4 - Case series	Secondary care	USA	3
	Moody et al (2011)	5 - Case report	Secondary care	United Kingdom	1
	Rumoro et al (2012)	3 - Retrospective assessment of case-definition performance	Tertiary care	USA	1233
	Lam et al (2012)	5 - Case report	Secondary care	USA	1
COVID-19 Pandemic	Fang et al (2020)	5 - Case report	Secondary care	China	1
	Coleman et al (2020)	5 - Case report	Secondary care	United Kingdom	1
	Tzouvelekis et al (2020)	5 - Case report	Secondary care	Greece	1
	Sahu et al (2020)	4 - Case series	Secondary care	USA	3
	Pisapia et al (2020)	3 - Retrospective observational study	Secondary care	Italy	37
	Yousefzai and Bhimaraj (2020)	5 - Case report	Secondary care	USA	1
	Khalid and Zaheer (2020)	4 - Case series	Secondary care	Pakistan	6
	Rigamonti et al (2020)	5 - Case report	Secondary care	Switzerland	1
	Cherubini et al (2020)	4 - Case series	Secondary care	USA	3
	Ramalingam et al (2020)	5 - Case report	Secondary care	India	1
	Danziger et al (2020)	4 - Case series	Secondary care	Israel	7
	Easom et al (2020)	4 - Case series	Tertiary care	United Kingdom	68
	Bernardes et al (2020)	5 - Case report	Secondary care	Portugal	1
	Budhram et al (2020)	5 - Case report	Secondary care	Canada	1
	Carbone et al (2020)	5 - Case report	Secondary care	Italy	1
	Chi et al (2020)	3 - Retrospective case-note review	Secondary care	China	68
	Delledonne et al (2020)	3 - Retrospective case-note review	Secondary care	Italy	490
	Guo et al (2020)	4 - Case series	Secondary care	China	2
	Harada et al (2020)	5 - Case report	Primary and Secondary Care	Japan	1
	Turan et al (2020)	5 - Case report	Secondary care	Turkey	1
	Urbanek et al (2020)	4 - Case series	Secondary care	Germany	2
	Zhao et al (2020)	4 - Case series	Secondary care	China	2
	Tang et al (2020)	5 - Case report	Secondary care	Philippines	1
	Theodorou et al (2020)	5 - Case report	Secondary care	Greece	1
	Sarinoglu et al (2020)	5 - Case report	Secondary care	Turkey	1
	Schizas et al (2020)	5 - Case report	Secondary care	Greece	1
	Scopelliti et al (2020)	5 - Case report	Secondary care	Italy	1
	Kichloo et al (2020)	5 - Case report	Secondary care	USA	1
	Momenzadeh et al (2020)	5 - Case report	Secondary care	Iran	1
	Serrano et al (2020)	4 - Case series	Secondary care	Spain	2
	Pitoyo et al (2020)	4 - Case series	Secondary care	Indonesia	3
	Asker et al (2021)	5 - Case report	Secondary care	Turkey	1
	Barben et al (2021)	5 - Case report	Secondary care	France	1
	Beddok et al (2021)	5 - Case report	Secondary care	France	1
	Cardoso et al (2021)	5 - Case report	Secondary care	Portugal	1

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Table 1. Continued

Pandemic	Author Name (Year)[a]	Quality of Evidence and Study Design	Setting	Country	Participants (n)
	Chaudry et al (2021)	5 - Case report	Secondary care	India	1
	Endara et al (2021)	5 - Case report	Secondary care	Ecuador	1
	Terzi et al (2021)	4 - Case series	Secondary care	Turkey	3
	Tendulkar et al (2021)	5 - Case report	Secondary care	India	1
	Ro et al (2021)	4 - Case series	Secondary care	Japan	2
	Strelow et al (2021)	5 - Case report	Tertiary care	USA	1
	Rogier et al (2021)	3 - Retrospective cohort study	Secondary care	France	374
	Salmi et al (2021)	5 - Case report	Secondary care	Finland	1
	Schindler et al (2021)	5 - Case report	Secondary care	Austria	1
	Schiuma et al (2021)	5 - Case report	Secondary care	Italy	1
	Hayes et al (2021)	4 - Case series	Secondary care	USA	2
	Hussain et al (2021)	5 - Case report	Secondary care	India	1
	Koksal and Gunes (2021)	5 - Case report	Secondary care	Turkey	1
	Meenakshisundaram et al (2021)	5 - Case report	Secondary care	India	1
	Mindaye et al (2021)	5 - Case report	Tertiary care	Ethiopia	1
	Naik et al (2021)	5 - Case report	Secondary care	India	1
	Novak et al (2021)	5 - Case report	Secondary care	USA	1
	Paramo-Zunzunegui et al (2021)	5 - Case report	Secondary care	Spain	1

[a]Complete reference information for the references cited in column 2 of Table 1 are listed in the Supplementary Material.

were overlapping clinical findings (37), overlapping radiological findings (14), and pandemic as a distracting factor (6). Four studies outlined cognitive biases impairing the decision making process, specifically premature closure bias (3) and anchoring bias (1).

DISCUSSION

This systematic review aimed to establish the most common misdiagnoses and their contributory cognitive biases during the COVID-19 and 2009 H1N1 influenza pandemics. Sixty-nine studies, of 2551 participants, were included. A total of 686 misdiagnoses were identified, consisting of viral respiratory infections (28%), respiratory infections of bacterial or fungal causes (44%), non-respiratory infections (14%), and non-infective (or noncommunicable) diseases (14%). In eight large case series, there was a high prevalence of bacterial pneumonia and viral respiratory infections as well as a range of causes of febrile illness and various causes of breathlessness. Many misdiagnoses noted in case reports, such as leptospirosis, may be rare except in endemic areas and were not seen in consecutive case series. This is suggestive of a degree of publication bias [16]. Within the larger studies and with regards to the primary outcome of the diagnoses most commonly missed or delayed in patients initially assessed for respiratory virus pandemic illness, there is low to moderate risk of bias, moderate to high consistency in findings among the studies, moderate imprecision and directness, and low risk of publication bias. Some diagnoses were reported with high frequency, adding confidence to assessment of real risk of misdiagnosis [13]. With regards to the prevalences of misdiagnoses shown in Table 3, we believe further research is very likely to have an important impact on our confidence in the placing of listed diagnoses and is likely to change the placing of some diagnoses.

This systematic review is limited by the small number of high-quality studies. There were no comparative studies of different approaches to assessment, and only one study reported a comprehensive list of diagnoses from a large number of patients [14]. Quantification of delay to definitive management and attribution of harm was poorly described, and our findings are likely to be subject to bias. Data from different waves of the COVID-19 pandemic are lacking. The symptomatology of variants may be different, which may allow it to mimic different diseases [17]. It is possible that clinician experience with the pandemic illness may improve discrimination, and this may evolve over time. Non-pharmacological interventions such as community-wide "lockdown" measures, social distancing, and mask wearing were part of many countries' responses to COVID-19, more than for 2009 H1N1 influenza, and this has influenced background rates of some diseases including influenza and exacerbations of chronic obstructive pulmonary disease [18–21]. Use of these interventions has varied across time and place during the COVID-19 pandemic, and this may have influenced prevalences and clinician behavior, resulting in delayed diagnoses. Most articles, describing the majority of cases, were from high-income countries, which limits applicability to low- or middle-income settings, where endemic infections may be important. There is little published evidence

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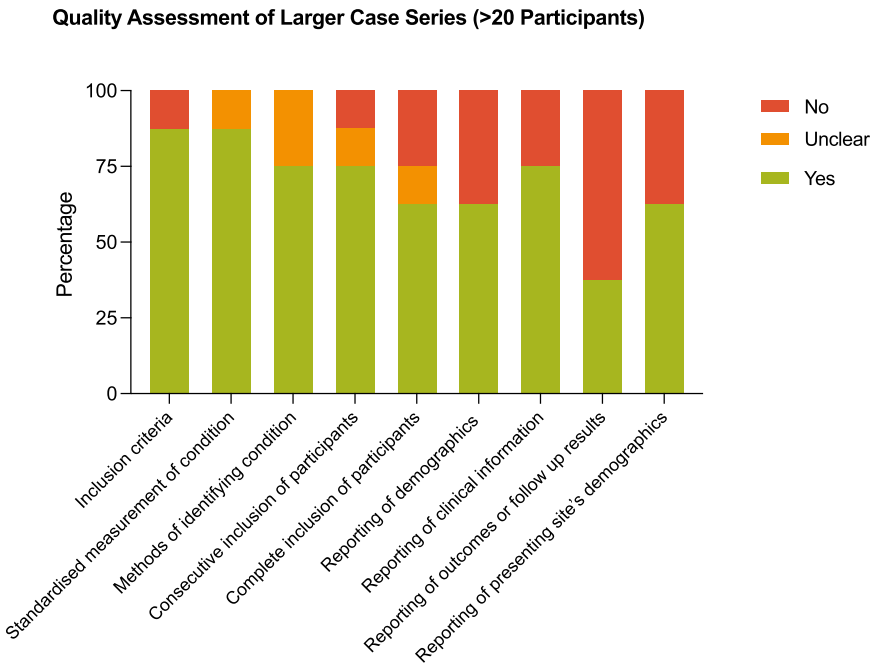

Figure 1. Quality assessment of larger case series. Bottom (green), criteria fulfilled; middle (orange), unclear whether criteria fulfilled; top (red), criteria not fulfilled.

from primary care, where alternative diagnoses might be different.

The high prevalence of respiratory virus misdiagnoses reflects the overlapping symptomatology of viral respiratory tract infections and high background prevalence [22]. Of 686 cases of misdiagnoses, more than one quarter were due to another respiratory virus. A range of respiratory pathogens were identified, including RSV, rhinovirus, enterovirus, seasonal coronavirus, and parainfluenza. Diagnoses of viral upper respiratory tract infections were often based on a positive polymerase chain reaction (PCR) test. Multiplex PCR may aid the clinician in isolating the causative organism quickly, in addition to identifying coinfection [23, 24]. Assays to differentiate ribonucleic acid of severe acute respiratory syndrome coronavirus 2, influenza A, and influenza B virus may have reduced cases of influenza being misdiagnosed as COVID-19 [25].

Non-respiratory infections were important misdiagnoses, with gastroenteritis, bacteremia, and urinary tract infection the most common. Gastrointestinal symptoms are seen in approximately 10% of COVID-19 cases and approximately 25% of H1N1 influenza patients [26, 27]. Abnormal liver function tests can be seen in H1N1 influenza and COVID-19 but also in a number of misdiagnoses [28, 29]. Undifferentiated fever has a broad differential diagnosis, and key signs and symptoms may take time to declare themselves [30]. These features may all complicate diagnosis.

It was not possible to quantify the ratio of correct to misdiagnoses during pandemics. This may vary between settings and over time. In Rogier et al [14], 152/402 patients did not have COVID-19, compared with 66/68 in Easom et al [31]. Routinely collected healthcare data could address this question and questions about possible harm. Findings from COVID-19 vaccine trial participants may also be instructive [32].

Our review found a number of life-threatening pathologies. This included (1) noncommunicable diseases such as acute coronary syndrome and diabetic ketoacidosis and (2) infections such as infective endocarditis and meningococcal meningitis. Although few articles reported harms, it is likely that harm could result from diagnostic delay in these cases. Real-world outcomes may be worse than suggested by the literature. Given this potential for harm, investigations to consider to reduce the risk of misdiagnoses during pandemics is offered (Table 4). Investigations are based on the most commonly delayed diagnoses and, where reported, how these were investigated. Clinical utility may depend on the presentation and local disease prevalence. This list should not be considered a recommendation, rather a prompt for diagnosticians.

Multiplex respiratory PCR, in addition to sputum culture and chest x-ray (CXR), should identify many causes of respiratory infection. Intermediate yield investigations may be useful (1) in cases in which the patient is unwell and correct diagnosis is important or (2) in cases in which there are features suggestive of a disease other than a respiratory infection. Full clinical assessment and examination is listed here because it may identify a wide range of diseases seen with medium prevalence, not because clinical examination should not be offered earlier, but rather to remind diagnosticians that this remains a powerful

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Table 2. Misdiagnoses Described in Large Case Series

	Author (Year)[a]	Study Type	Sample Size	Age (As Reported)	Sex (%) M	Sex (%) F	Diagnostic Methodology for H1N1/COVID-19	Revised Diagnoses (n)	Reason for Misdiagnosis
2009 H1N1 influenza	Ho et al (2009)	Retrospective case-note review	110	Median 36	43	57	PCR - Nasopharyngeal swab	Clinically suspected viral respiratory infection (20), community acquired pneumonia (11), bacterial throat infection (9), lower respiratory tract infection (9), infective exacerbation of COPD (7), sepsis of unknown source (7), gastroenteritis (5), urinary tract infection (3), acute coronary syndrome (3), hypersensitivity reaction to drugs (2), Salmonellosis (2), Rhinovirus (2), Viral encephalitis (2), Parainfluenza (1), Metapneumovirus (1), Adenovirus (1), Epstein-Barr virus (1), Dengue (1), Typhoid (1), Herpes Simplex (1), Lemierre's Syndrome (1), neutropenic sepsis (1), *Mycobacterium avium* infection (1), Epididymo-orchitis (1), Hodgkin's lymphoma (1), Crohn's exacerbation (1), metastatic gastric cancer (1), nephrotic syndrome (1), pulmonary oedema (1), torticollis (1), urticaria (1)	Broad case definition
	Al-Shakerchi et al (2011)	Retrospective case-note review	71	Median 49	51	49	Clinical	Reported only for 9 who came to harm: Community acquired pneumonia (2), tonsilitis/lower respiratory tract infection (1), cholecystitis (1), gastroenteritis (1), infective endocarditis (1), urinary tract infection (1), diabetic ketoacidosis (1), acute coronary syndrome (1)	Broad case definition
	Rumoro et al (2012)	Retrospective cross-sectional	1233	NR	47	53	PCR - Nasopharyngeal swab	Reported for the 256 identified diagnoses[a]: Acute bacterial pneumonia (166), respiratory syncytial virus (83), Strep. pharyngitis (4), Infectious mononucleosis (3)	Broad case definition
COVID-19	Pisapia et al (2020)	Retrospective observational	37	Median 37	65	35	PCR - Nasopharyngeal swab	Reported for the 10 identified diagnoses Influenza B (6), Influenza A (1), Parainfluenza (1), *Streptococcus pneumoniae* (1), *Hemophilus influenza* (1)	Not reported
	Easom et al (2020)	Prospective cohort	68	Mean 42.5	47	53	PCR - Nasopharyngeal swab	Upper respiratory tract infection (50), exacerbation of airway disease (5), lower respiratory tract infection (4), gastroenteritis (3), influenza-like illness (2), otitis media (1), well contact (1), inebriation (1), community acquired pneumonia (1)	Broad case definition
	Chi et al (2020)	Retrospective analysis	68	Mean 41.3	67	33	Epidemiological, clinical	Reported for the 16 identified diagnoses: *Mycoplasma pneumoniae* (7), Influenza B (3), Influenza A (2), Adenovirus (2), Chlamydia pneumoniae (2), VTE (1), Dermatomyositis (1)	Overlap of clinical findings
	Delledonne et al (2020)	Retrospective analysis	490	NR	NR	NR	PCR - Nasopharyngeal swab	Reported for the 20 identified diagnoses: Infectious diseases including intracellular pathogens pneumonia, H3 influenza A, tuberculosis, pneumocystosis, campylobacter colitis (11), heart failure (4), Sarcoidosis (1), Wegener's granulomatosis (1), pulmonary fibrosis by amiodarone (1), interstitiopathy by methotrexate (1), idiopathic pulmonary fibrosis (1)	Overlap of clinical findings
	Rogier et al (2021)	Case Control	374	Mean 67.8	47	53	PCR -Nasopharyngeal, CT chest	Reported for the 134 identified diagnoses: Pneumonia (31), heart failure (13), exacerbation chronic pulmonary disease (12), bacteremia (12), neurological disease (10), upper respiratory tract viral infection (7), urinary tract infection (7), cancer or hematologic malignancy discovery or complications (7), other cardiovascular or respiratory disease (5), other infectious disease (5), cirrhosis complication (3), social (3), viral gastroenteritis (3), diverticulitis (3), pulmonary embolism (3), abdominal disease (2), locomotor disease (2), psychiatric disease (2), inflammatory disease (2), urological disease (1), endocrinological disease (1)	Not reported

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computerized tomography; NR, not reported; PCR, polymerase chain reaction; VTE, venous thromboembolism.
[a]Complete reference information for the references cited in column 2 of Table 2 are listed in the Supplementary Material.

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Table 3. Prevalence of Diagnoses[a]

Aetiology	High Prevalence	Medium Prevalence	Low Prevalence
Viral Respiratory Infection	Respiratory syncytial virus, seasonal respiratory viruses (rhinovirus/enterovirus, seasonal coronavirus, parainfluenza, metapneumovirus, adenovirus, viral URTI unspecified)	Influenza	
Other Respiratory Infection	Bacterial pneumonia	Exacerbation chronic pulmonary disease, tonsillitis/strep throat, mycoplasma pneumonia	Legionella, PCP, TB, Lemierre's disease
Non-respiratory Infection		Gastroenteritis, bacteraemia, urinary tract infection, infection of unknown source/other infection	Infective endocarditis, viral encephalitis, meningococcal meningitis, appendicitis, malaria, skin and soft tissue infection, HIV, EBV, leptospirosis, hydatid disease
Non-infective Illness		Cardiac failure, neurological disease, malignancy or complication of malignancy	Iatrogenic pneumonitis, vasculitis/autoimmune disease, ACS, PE, DKA, sarcoidosis

Abbreviations: ACS, acute coronary syndrome; DKA, diabetic ketoacidosis; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; PCP, *Pneumocystis pneumonia*; PE, pulmonary embolism; TB, tuberculosis; URTI, upper respiratory tract infection.

[a]Criteria for prevalence: high prevalence ≤5% of cases; medium prevalence 1%–5% of cases; low prevalence >1% of cases in larger studies and reported more than once in more than one.

Table 4. Suggested Investigations

Investigation Group	High Yield	Medium Yield	Consider if Indicated
Clinical	Respiratory history and examination	Full clinical history and examination, mouth and throat examination	
Near Patient Tests		Electrocardiogram	Arterial blood gases, urine ketones
Blood Tests		B-natriuretic peptide	Autoimmune screen including ANA and ANCA, malaria film, troponin
Microbiology/ Virology	Multiplex respiratory virus PCR, sputum culture	Bacterial throat swab, blood cultures, stool culture/PCR, urine culture	Blood Meningococcal PCR, CSF examination including PCR, EBV serology, HIV antigen/antibody test, induced sputum/bronchoscopy for cytology/ PCR, leptospira PCR and antibodies, urine legionella antigen
Imaging	Chest radiograph	CT thorax/abdomen/pelvis	CT pulmonary angiography, echocardiogram
Other		Tissue biopsy	Lymph node biopsy

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CSF, cerebrospinal fluid; CT, computerized tomography; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

tool if a patient has an unclear diagnosis after CXR and respiratory PCR. Lower yield investigations may be useful if there are unusual features such as recent travel, or in cases of severe illness in which rapid diagnosis within a broad differential may be lifesaving (eg, antineutrophil cytoplasmic antibody-associated vasculitis).

The second objective of this systematic review was to identify cognitive biases that may be contributing to the misdiagnoses observed during pandemics. Only four articles specifically mentioned biases directly affecting diagnostic processes, with authors tending to appraise the features of the case and not the decision making process [33–36]. This is in keeping with a systematic review by Saposnik et al [8], which identified only 20 studies of cognitive bias in any aspect of clinical medicine. Premature closure bias, whereby the physician ceases to look for further information once establishing the first plausible explanation, was described in three articles [37]. Anchoring bias, in which the physician prioritizes evidence to support the existing hypothesis, was cited in one paper [37]. These labels were ascribed retrospectively by authors. No article described prospective assessment of decision making of clinicians in the pandemic setting or efforts to debias the diagnostic process.

Additional reasons offered for the misdiagnoses reported were that clinical presentations or radiological findings were similar to those of the respiratory virus. In only a small number of cases, the misdiagnosis was attributable to a false-positive test, which suggests that test quality is not a major driver of such misdiagnoses. The overlap between clinical features of pandemic respiratory viruses and a wide range of diseases implies that the diagnosis of acute illness in a pandemic is a difficult clinical problem. There is an unmet need for more research into the diagnostic decision making process to assist clinicians.

CONCLUSIONS

In this systematic review, we have identified common misdiagnoses that have occurred in the 2009 H1N1 influenza and COVID-19 pandemics and suggested corresponding investigations in the attempt to reduce them. More work is required on the interface between clinical presentation and diagnostic

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decision making and the way in which this may be perturbed in a pandemic, such that clinicians may be assisted in making efficient and accurate diagnoses for the benefit of patients. In settings in which a "steady state" of COVID-19 is a goal of public health policy, the challenge of distinguishing COVID-19 from other diseases will persist. We hope that this article itself may contribute to clinician debiasing, but also that an understanding of the particular diagnostic difficulties posed by pandemics may be developed and incorporated into current and future pandemic response plans.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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