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REVIEW ARTICLE

Autopsies in pandemics – a perspective on barriers and benefits. Is it time for a revival?

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Influenza virus and coronavirus pandemics regularly sweep the globe, at great cost of health and economy. Our aim was to conduct a PubMed search for autopsy studies on influenza and coronavirus to investigate the contribution of autopsies during pandemics, focussing on autopsy methods and procedures and the role of autopsy findings in pandemics. The retrieved autopsy studies generally relied on microscopy, polymerase chain reaction (PCR), immunostaining and electron microscopy. Most were small and reported on lung effects, including diffuse alveolar damage (DAD), pneumonia and tracheobronchitis. Antibiotic therapy has diminished a role for bacterial pneumonia, whereas obesity is an emerging risk factor. Autopsy studies have provided new insights into coronavirus disease 2019 (COVID-19) treatments like anticoagulative therapy. Unfortunately, autopsies during pandemics are hampered by lack of guidelines, facilities and expertise for handling potentially infectious corpses and by widely varying recommendations for personal protective equipment and procedures. The Department of Forensic Pathology, at the Forensic Institute, at the University of Copenhagen in Denmark has, in collaboration with the Department of Pathology, Rigshospitalet, Copenhagen, initiated a prospective observational study on COVID-19-related deaths encompassing postmortem imaging, standardized autopsy procedures/reporting and extensive tissue sampling for histological, chemical, microbiological and genetic analysis. The study involves a diverse array of research groups at the University of Copenhagen, and the clinical field.

Key words: Autopsy; pandemic; influenza; COVID-19; infectious disease.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic currently wreaks global havoc on both lives and finances. The World Health Organization (WHO) utilizes a system of 'phases' to describe viral transmission, where 'Phase 6' is a pandemic and applies when a transmittable disease occurs in two WHO regions at the same time (1). Influenza pandemics have struck in the 19th, 20th and 21st centuries. The first beta-coronavirus pandemic, severe acute respiratory syndrome (SARS), appeared in 2002, with cases on all continents but the Antarctic, although the number of cases was small outside Asia and Canada. In 2012, Middle East Respiratory Syndrome (MERS) appeared in the Middle East and spread from there to Europe, North America, Africa and Asia, although deaths occurred only in Asia and Europe. In 2019, SARS-coronavirus-2 (SARS-CoV-2) was detected in sewage samples as early as March in Europe (2) and November in South America (3), but the index case is generally attributed to China in December 2019 (4). Cases and deaths followed in the rest of Asia, North America, Europe, Australia, Africa and South America.

The first autopsy of a presumably viral, pandemic death was performed in 1729 (5). Autopsy

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techniques vary considerably (6), but the overall autopsy approach has changed little since the publication of 'De abditis nonnullis ac mirandis morborum et sanatorium causis' in 1507. During the 18th and 19th century, Morgagni, Rokitansky and Virchow pioneered autopsy practice considerably by correlating clinical symptoms with autopsy findings (7). Autopsies today are generally performed in two separate settings: the clinical and the forensic. The nature of pandemics results in deaths occurring in both settings. The clinical autopsy is performed at the request of the physician or the family, whereas a forensic autopsy is performed at the request of the authorities, depending on the legislation. The clinical autopsy includes external examination of the body and a thorough gross and microscopic examination of organs (8). The gold standard for a forensic autopsy is similar, but also includes sampling of tissue and fluids for ancillary examinations, such as toxicology, chemistry, microbiology and genetic testing. Postmortem computed tomography (PMCT) is increasingly considered part of the gold standard forensic autopsy, but it is not available at all institutions (9). In some forensic settings, alternative 'autopsies' using postmortem radiology (e.g. Virtopsy) are proposed as alternatives or supplements to the standard autopsy (9).

Autopsy rates have declined globally since the 1960s (7), and systematic autopsies are generally scarce during pandemics. The reason for this scarcity during pandemics is correlated with the fear of transmission of the disease, a lack of proper facilities and procedures, and stringent regulations imposed by governments and scientific communities.

The guidelines for safe autopsy are based on either national or international systems that group infectious diseases depending on factors that include severity, transmission rate and treatment options. In the English Hazard Group system (10), SARS-CoV-2 is a group 3 pathogen (of 4 groups), meaning that it may lead to severe human disease, may pose a significant risk to employees and may be capable of human-to-human transmission. SARS-CoV-1 and MERS-CoV are also group 3 pathogens, whereas influenza A is a group 2 pathogen. In the United Kingdom, autopsies in which hazard group 4 pathogens are suspected are only allowed in select mortuaries and should generally be avoided (11). Hazard classifications differ between countries. In Denmark, influenza A and SARS-CoV-2 are classified as group 2 (12). Only autopsies involving group 3 pathogens are performed in a separate suite, but the personal protection equipment (PPE) remains identical to that used in a standard autopsy.

In order to maintain safe work conditions and at the same time balance the need for clinical information, governments or professional organizations may issue guidelines concerning safety and PPE use, as well as physical safety measures regarding separate suites, air flow and specific equipment (13, 14). In China, the 2002 SARS pandemic prompted the construction of a biosafety level 3 facility (15), which was only used for three autopsies. These types of facilities are rare, and approximately 81% of U.S. medical examiners/coroners have no access to biosafety level 3 facilities (16). Consequently, some institutions refrain from doing autopsies altogether or perform less thorough autopsies (10, 17). To diminish the risk of infection, various measures have been recommended regarding PPE (rubber boots, facemask, visor, hair net, waterproof gown, double gloving, Kevlar gloves, etc.), prevention (vaccination, pre-autopsy testing of deceased, PMCT, down-draft tables) and procedures (no high pressure water, no power tools) (11, 18, 19).

The need for systematic autopsies during pandemics is crucial in order to learn as much as possible about novel infectious diseases for the purpose of prevention and treatment. This was clearly demonstrated during the human immunodeficiency virus (HIV) pandemic, where autopsies served to document the connection between pathogen and pathology and ultimately formed the basis for treatment (20).

Inspired by the current SARS-CoV-2 pandemic, we examine the role of the autopsy in understanding the pathogenesis of viral pandemics for the purpose of prevention and treatment. Our focus is on the execution of autopsies in pandemics and on the results of studies in earlier pandemics.

METHODS

This is a narrative review of autopsy practice and its impact in viral pandemics. As such, we did not perform a systematic literature search. We searched MEDLINE (PubMed) for literature on our chosen topics. A detailed description of the search methods and strings is provided in Appendix 1.

RESULTS

Execution of autopsies during pandemics

The majority of the autopsy studies are case reports (21, 22) or case series (23, 24). Larger observational studies are limited and mostly report only gross and microscopic changes (25). Most of the studies utilize biopsies rather than full body autopsy (26, 27).

Tables 1 and 2 present an overview of methods applied in the studies discussed in this review. H&E staining and light microscopy of human tissue (most commonly lung tissue), either sampled at autopsy (17, 28) or obtained from either postmortem or antemortem biopsies (26, 29), are the most common method of examination. Other histopathological methods include special staining for fungi (30, 31), immunostaining (22, 24) and electron microscopy (32, 33) of tissues sampled at autopsy. More advanced methods include PCR analysis of ante- or postmortem swabs taken, for example, from the upper airways or of tissue sampled at autopsy to detect and classify viruses (28, 34). Other methods are virus cultures of human tissue sampled at autopsy (35), lung tissue bacterial cultures (36), PMCT of the deceased (37), genome analysis of virus (22, 33), microCT of sampled lung tissues (38), in situ hybridization of tissue sampled at autopsy (39) and enzyme-linked immunosorbent assay (ELISA) of sera sampled at autopsy (31).

Influenza virus: Spanish Flu, Hong Kong Flu, Asian Flu and Swine Flu

Influenza A viruses are RNA viruses and part of the Orthomyxoviridae family. Influenza strains with affinity for upper airways generally spread easily but cause mild disease, whereas strains with affinity for the lower airways cause more severe disease but spread less easily (40, 41). The symptoms of the influenza A viruses are fever, cough, sore throat, headache, myalgia and fatigue. In children, gastrointestinal symptoms are common. The incubation period for influenza viruses is 1–4 days. The prevalence is greatest in school-age children, and the disease is more severe in infants, the older population and those with comorbidities, such as chronic heart and lung disease or diabetes. Complications include exacerbation of chronic obstructive pulmonary disease (COPD) and bacterial pneumonia (42). For the clinical diagnosis, swabs and PCR testing are utilized but the accuracy is suboptimal (28). Table 3 provides an overview of prior influenza pandemics.

Influenza A generally spreads by animal-to-human or human-to-human routes via direct contact, aerosols and droplets – the virus can be spread either directly onto mucosal membranes or via surfaces such as door handles (43). In vitro studies have demonstrated how influenza viruses bind through their surface glycoprotein haemagglutinin (HA) onto sialic acid-containing receptors on the surfaces of epithelial cells, typically those in the respiratory tract (29, 43).

Autopsy studies on influenza concern either seasonal flu (i.e. epidemic influenza) or novel pandemic influenza (e.g. swine flu). Macroscopic features in influenza-related deaths are oedematous lungs with hyperaemia and tracheobronchitis (26, 28, 30, 31). Microscopic features are tracheobronchitis, diffuse alveolar damage (DAD) in both exudative and

Table 1. Methods in influenza autopsies

Study, author	Sample	Autopsy	Auxiliary methods	Histopathology	Tissue for microscopy
Influenza virus					
Edler et al. (28)	2	Full	RT-PCR for virus		H, Lu, *'all other'*
Fujita et al. (24)	4	Autopsy/AM biopsy	RT-PCR for virus	Special stains Immunostaining	NR
Harms et al. (30)	8	NR	PCR for virus Lung tissue cultures	Special stains Immunostaining	*'Major organs'*
Bal et al. (26)	9	Autopsy/AM biopsy	RT-PCR for virus	Special stains E.M. Immunostaining	H, Lu, T, Li, S, P, K, *'G-I tract'*, BM, LN, Sk, V, AG, SM
Voltersvik et al. (33)	19	NR	RT-PCR for virus Viral genome sequencing	Immunostaining	Lu
Tamme et al. (44)	21	NR	Lung tissue cultures		H, Lu, S, P, Li, B, K
Sheng et al. (34)	68	Archival material	PCR of tissue Lung tissue cultures		Lu
Drescher et al. (31)	84	Full	ELISA of sera Virus isolation	Special stains	H, B, *'respiratory tract'*
Hers et al. (36)	148	NR	Virus isolation Lung tissue cultures		Lu

Abbreviations: AG, Adrenal glands; AM, Antemortem; B, Brain; BM, Bone marrow; CSF, Cerebrospinal fluid; E.M., Electron Microscopy; GB, Gall bladder; G-I tract, Gastrointestinal tract; H, Heart; I, Intestines; K, Kidneys; Li, Liver; LN, Lymph nodes; Lu, Lungs; NR, Not reported; P, Pancreas; PE, Pleural effusion; R, Reproductive organs; S, Spleen; SG, Submandibular gland; Sk, Skin; SM, Skeletal muscle; T, Trachea; TG, Thyroid gland; V, Vessels.

Table 2. Methods in corona autopsies

Study, author	Sample	Autopsy	Auxiliary methods	Histopathology	Tissue for microscopy
COVID-19					
Menter et al. (76)	21	Full/Partial	RT-PCR for virus	Special stains E.M. Immunostaining	Lu, T, H, K, Li, AG, LN, S, BM, B
Wichmann et al. (37)	12	Full	RT-PCR for virus Virology PMCT	Immunostaining	Lu, H, K, Li, S, P, B, R, I, SM, V, Ph
Lax et al. (75)	11	Full/Partial	RT-PCR for virus	Immunostaining	Lu, H, K, Li, P, S, TG, AG, GB, SG, I
Ackermann et al. (38)	7	Only lungs	Corrosion casting Genome analysis of virus microCT of lung tissue	E.M. Immunostaining	Lu
Schaller et al. (94)	10	Full	RT-PCR for virus		Lu, H, Li, S, K, B, PE, CSF
Fox et al. (72)	10	NR	RNA labelling	E.M. Immunostaining	Lu, H
Youd et al. (95)	9	Full	RT-PCR for virus Microbiology		Lu, H
Carsana et al. (71)	38	Full		E.M. Immunostaining Special stains	Lu
Bradley et al. (81)	14	Full/Partial	PCR for virus	E.M. Immunostaining	Lu, T, H, K, Li, P, S, TG, AG, PG, I, B, LN
MERS					
Ng et al. (22)	1	Full	Viral genome sequencing	E.M. Immunostaining	H, Lu, T, S, LN, BM, K, B, I
SARS					
Lang et al. (67)	3	Full	RT-PCR for virus	E.M.	Lu, LN, S, Li
Gu et al. (39)	18	Full	RT-PCR for virus In situ hybridization of tissue	E.M. Immunostaining	Lu, T, S, LN, K, B, Li, R, H, P, AG, SM, *'G-I tract'*, TG
Chong et al. (68)	14	Full	PCR for virus In situ hybridization of tissue Microbiology Virology	Immunostaining	Lu, H, K, Li, LN, S
Ding et al. (69)	3	Full		E.M. Immunostaining Special stains	Lu, H, S, LN, Li, K, AG, B, SM, BM
Nicholls et al. (29)	6	Full/PM lung samples	Virology RT-PCR for virus Microbiology	E.M. Immunostaining F.M.	Lu, S
Hwang et al. (32)	20	Only lungs	RT-PCR for virus	Special stains E.M. Immunostaining	Lu
Franks et al. (96)	8	Only lungs	RT-PCR for virus	Special stains Immunostaining	Lu
Tse et al. (70)	7	Full/Partial	RT-PCR for virus	Special stains E.M. Immunostaining	Lu, S, *'other organs'*

Abbreviations: AG, Adrenal glands; B, Brain; BM, Bone marrow; CSF, Cerebrospinal fluid; E.M., Electron Microscopy; F.M., Fluorescent Microscopy; GB, Gall bladder; G-I tract, Gastrointestinal tract; H, Heart; I, Intestines; K, Kidneys; Li, Liver; LN, Lymph nodes; Lu, Lungs; NR, Not reported; P, Pancreas; PE, Pleural effusion; PG, pituitary gland; Ph, Pharynx; PM, Postmortem; R, Reproductive organs; S, Spleen; SG, Submandibular gland; Sk, Skin; SM, Skeletal muscle; T, Trachea; TG, Thyroid gland; V, Vessels.

proliferative stages, pneumonia and thrombus formation in small vessels (24, 26, 28, 30, 31, 34, 36, 44). Bacterial pneumonia was present in pulmonary tissue from all cases from the 1918 pandemic (34) and in 80% of cases during the 1958 pandemic (36). Interestingly, Hers et al. found no lung lesions

Table 3. Influenza virus pandemics

Point of time	Disease	Mortality (mio) (97)
1874	Influenza pandemics	Unknown
1889	Influenza pandemics	Unknown
1918	'Spanish flu', H1N1	50–100
1957	'Asian flu', H2N2	1–4
1968	'Hong Kong Flu', H3N2	1–4
2009	'Swine Flu', H1N1	0.02–0.5

in 17 confirmed influenza deaths in 1958 (36). An overview of pulmonary findings regarding influenza autopsy studies is provided in Table 4.

Extrapulmonary manifestations of influenza infection have received sparse comments in autopsy studies. Some studies have reported that up to 50% of autopsied influenza-related deaths have histopathological signs of myocarditis, although the importance of bacterial co-infection in this manifestation is undetermined (45, 46). Acute tubular necrosis (ATIN) (47, 48), influenza-associated encephalitis (IAE) (49, 50) and liver damage (26, 51) have coincided with influenza infection. Evidence regarding thromboembolic disease related to influenza is inconclusive (52). Nevertheless, most of these manifestations are believed to be a result of systemic inflammation rather than direct viral action (52). Generally, it is difficult to assert whether extrapulmonary complications of influenza infection are direct consequences of influenza, systemic illness or exacerbation of prior underlying disease.

Coronavirus: SARS-CoV, MERS-CoV and SARS-CoV-2

SARS-CoV, MERS-CoV and SARS-CoV-2 are all zoonotic viruses and part of the family of beta-coronaviridae. Although they belong to the same family of virus, SARS-CoV-2 seems to cause milder infections than the other two coronaviruses (53). The most common symptoms for all three viruses are fever, cough and myalgia, followed by respiratory symptoms (dyspnoea) and gastrointestinal symptoms (diarrhoea). However, gastrointestinal symptoms are apparently less common in SARS-CoV-2-infected patients (53–55). The incubation periods for SARS-CoV, MERS-CoV and SARS-CoV-2 are approximately 4 days (with a range of 2–10 days) (56), 5 days (with a range of 2–14 days) (57) and 5 days (with a range of 1–14 days) (58), respectively. These viruses affect all age groups, but older age and comorbidities, such as diabetes and cardiovascular disease, are associated with the development of more severe disease forms (59, 60). Table 5 provides an overview of the year of emergence and the mortality of these coronaviruses.

All three coronaviruses spread via droplets from human to human and likely also from animal to human (22, 55, 61). In addition, SARS-CoV and SARS-CoV-2 likely spread through contact transmission (55, 62) and SARS-CoV via a faecal–oral route as well (55). SARS-CoV-2 is more widely transmitted in the community than are SARS-CoV and MERS-CoV. The explanation for this seems to be that SARS-CoV-2 is both more contagious and

Table 4. Pulmonary findings in influenza autopsies (microscopic findings constituting DAD = DAD)

Study	Lung oedema	Microth-rombus	Medium and large vessel thrombus	Tracheobronchitis	Lymphadeno-pathy	Superimposed pneumonia	DAD
Edler et al. (28)	+	–	–	+	+	+	–
Fujita et al. (24)	–	–	–	+	–	+	+
Harms et al. (30)	+	+	+	+	+	+	+
Bal et al. (26)	+	–	–	+	–	–	–
Voltersvik et al. (33)	–	–	–	–	–	+	+
Tamme et al. (44)	+	–	–	+	–	+	+
Sheng et al. (34)	+	+	–	+	–	+	+
Drescher et al. (31)	–	–	–	–	–	+	+
Hers et al. (36)	–	+	–	+	–	–	–

Table 5. Beta-coronavirus pandemics

Point of time	Disease	Mortality (22,55,98)
2002	Severe acute respiratory syndrome, SARS, SARS-CoV	9.6% of 8096 infected
2012	Middle Eastern Respiratory Syndrome, MERS, MERS-CoV	35.6% of 1368 infected
2019	Coronavirus disease 2019, COVID-19, SARS-CoV-2	3.16% of 29.7 mio infected

has a longer incubation period than SARS-CoV and MERS-CoV (53).

SARS-CoV and SARS-CoV-2 use the same receptor, the angiotensin-converting enzyme 2 (ACE-2), to enter human cells, while MERS-CoV enters human cells through the dipeptidyl peptidase 4 receptor (DPP4). Immunohistochemistry on biopsies from living patients has demonstrated that ACE-2 receptors are expressed in the epithelial cells of the respiratory tract and small intestines, as well as in endothelial and smooth muscle cells of several organs (63). Immunohistochemistry on biopsies from living patients, organ donors and animals has revealed that DPP4 receptors are primarily located on cells in the lower respiratory tract and on epithelial cells in the kidney, small intestine, liver and prostate (22, 64–66).

Relatively few autopsy studies exist on patients with COVID-19, but when compared to SARS and MERS, they are numerous. Quite a few studies involving postmortem findings of SARS patients exist, but only a few are based on whole-body autopsy (29, 39, 67–70) and only Ng et al. have published autopsy findings on MERS-related deaths (22). Many of the findings in COVID-19 autopsies are similar to those reported for SARS and, in part, for MERS. In all three infections, the respiratory tract is believed to be the main target of the virus; therefore, most research is focused on the respiratory system and, in particular, on the lungs (22, 60) (see Table 6). On macroscopic gross examination, the lungs infected with SARS, MERS and COVID-19 are typically described as oedematous and consolidated (22, 70, 71), with regions of haemorrhage (29, 69, 72). Pulmonary thromboembolism originating from deep venous thrombosis (37, 72–74), a tendency for thrombus formation in branches of pulmonary arteries (23, 75) and signs of superimposed bronchopneumonia are also seen in several of the COVID-19 deceased patients (37, 75, 76). Microscopically, DAD is the most reported acute histopathological finding in the lungs for all three coronaviruses (22, 39, 67). Different stages of DAD have been found, typically correlating with the duration of illness. Other microscopic findings reported for SARS and COVID-19 are microvessel thrombi (32, 38, 68, 72) and vascular injury, such as endotheliitis and vasculitis (39, 69, 76, 77). An overview of pulmonary findings regarding corona autopsy studies is shown in Table 6.

Although SARS-CoV has been detected in most extrapulmonary organs, no definite consensus exists regarding the pathological findings because of the small number of autopsy studies and cases included in each study (39, 67–69). Nevertheless, a similarity seems evident in the findings reported by those few studies concerning the effects of SARS. In lymph nodes and spleen, typical findings have been haemorrhagic necrosis, atrophy and lymphoid depletion (39, 67–69). In the liver, fatty degeneration and centrilobular necrosis has been reported (39, 67–69). In some SARS autopsies, the kidneys show focal haemorrhage and various degrees of acute tubular necrosis (39, 68, 69). Other findings worth mentioning are mild diffuse inflammation and atrophy of the submucosal lymphoid tissues of the digestive tract (39, 78), haemorrhage and necrosis in the adrenal glands (67, 69), and oedema and neuronal degeneration in the brain (39, 69). In other organs like the heart and pancreas, the findings have been nonspecific. Generally, it is not clear whether the extrapulmonary organ manifestations are due to direct or indirect effects of the virus.

According to autopsy studies, the SARS-CoV-2 virus has been detected in various extrapulmonary tissues, including the upper airways, heart, intestines, kidneys, lymph node, brain, liver and spleen (79–81). While some studies suggest that some of the extrapulmonary manifestations (e.g. acute kidney failure, myocarditis and endotheliitis) (77, 81, 82) may be related to SARS-CoV-2 infection, little evidence exists for acute pathological changes caused by the virus itself other than in the respiratory system (60).

No MERS-CoV was detected outside the lungs at autopsy, despite MERS-CoV RNA being a common finding in urine and acute renal failure being a common complication of MERS-CoV (22)

Autopsy-confirmed knowledge changing clinical approaches

From the beginning of its era, the autopsy has provided the health system with new knowledge on different aspects of the human body and diseases. Autopsies on patients with influenza viruses or coronaviruses are no exception.

A study of autopsies from the influenza pandemic in 1918, the Spanish Flu, revealed that the pandemic started four months earlier than assumed and that the high mortality appeared to be caused not only by viral virulence but also by bacterial superinfection and factors related to host immunity (34).

An autopsy study on the seasonal flu (H3N2), Hong Kong flu, showed that 81% of sudden unexplained deaths (SUD) had elevated IgM compared to 2.5% of the controls. The study researchers concluded that testing for viral infection in cases of unknown causes of death could be helpful (31).

An autopsy study on the influenza pandemic in 2009, the Swine Flu, showed that a specific

Table 6. Pulmonary findings in corona autopsies (microscopic findings constituting DAD = DAD)

Study (disease)	Lung oedema	Microthrombus	Medium and large vessel thrombus	Tracheobronchitis	Superimposed pneumonia	DAD
Menter et al. (76)	+	+	+	+	+	+
Wichmann et al. (37)	+	+	+	–	+	+
Lax et al. (75)	+	+	+	–	+	+
Ackermann et al. (38)	+	+	+	–	–	+
Schaller et al. (94)	–	–	–	–	+	+
Fox et al. (72)	+	+	–	–	–	+
Youd et al. (95)	+	–	–	–	+	+
Carsana et al. (71)	+	–	–	–	+	+
Bradley et al. (81)	+	+	–	+	+	+
Ng et al. (22)	+	–	NR	+	–	+
Lang et al. (67)	+	+	–	–	NR	+
Gu et al. (39)	+	–	NR	–	–	+
Chong et al. (68)	+	–	+	–	+	–
Ding et al. (69)	+	+	–	+	–	+
Nicholls et al. (29)	+	–	–	–	–	+
Hwang et al. (32)	–	+	–	–	+	+
Franks et al. (96)	–	+	–	–	+	+
Tse et al. (70)	+	–	+	–	+	+

NR, not reported.

mutation in the virus made it more lethal than the original virus. The study concluded that disease severity correlated with the specific mutation, obesity and underlying disease (33). A retrospective autopsy study on the Swine Flu in Estonia showed that influenza or influenza complications were the primary cause of death in 1/3 of all fatal cases during the 2009–2010 pandemic. The researchers concluded that a high autopsy rate, together with recommendations for testing with reverse transcription polymerase chain reaction (RT-PCR) for influenza viruses, had enabled the identification of cases that had no clinical suspicion of influenza. Furthermore, they found that none of the deceased had been immunized; therefore, they also emphasized the importance of vaccination (44).

The few full autopsy studies on SARS have shown that the virus affects multiple organs and causes damage to the immune system. Some authors have proposed a pathogenic mechanism for SARS that consists of SARS-CoV entry into the body by invasion of epithelial cells of the respiratory tract and alveoli and subsequent damage to these cells and tissues. At the same time, the virus infects both resident and circulating immune cells, thereby leading to a weakening of the immune defence and causing a rapid progression of the disease (39, 55).

Even a single autopsy can sometimes contribute to the discovery of important knowledge. The one autopsy performed during the MERS pandemic showed that MERS-CoV does not affect the kidneys directly, as was otherwise thought. No extrapulmonary virus was detected, despite clinical findings of virus in the urine (22).

A German autopsy study on SARS-CoV-2 has shown how important autopsies can be while the pandemic is still present. The study showed deep venous thrombosis and pulmonary embolism in 40% of deceased individuals infected with SARS-CoV-2 (25) compared to a prevalence of 16% among medical intensive care patients (83). This finding led to a change in anti-coagulation treatment in Germany.

DISCUSSION

In this review, we have examined the role of the autopsy in understanding the pathogenesis of pandemics and epidemics for the purpose of prevention and treatment. We have focused on the execution of autopsies in pandemics and the results of autopsy studies in prior relatively comparable pandemics that were caused by influenza virus and coronavirus.

Overall, our search has shown that autopsy studies are sparse during influenza and coronavirus pandemics and often exist only in the form of case reports or case series, thereby limiting a systematic overview of the pathology of diseases. We found no large observational studies on epidemic disease employing algorithm-based, standardized sampling or investigations such as those done in 'The Survive Study' (84). Most studies are done on biopsies, rather than as full body autopsies, raising the

possibility of potentially overlooking changes in organs not a priori suspected and therefore not sampled (26, 27). As Kuiken and Taubenberger state, our understanding of pathology in novel viral infections in humans is critically hampered by the few autopsies performed (40). The quality of the studies also varies and might further diminish the role of pathology in modern medicine. Sample sizes are generally small, investigative methods have remained virtually unchanged for 60 years, and scientific reporting is inconsistent.

The autopsy methods utilized in influenza virus and coronavirus pandemics are primarily light microscopy and, in some cases, electron microscopy and immunohistochemical staining. Some studies rely on antemortem PCR analysis of swabs, while others perform PCR analysis on postmortem swabs and/or tissue to confirm the diagnosis, and expand the understanding of the presence and of virus in tissues and of the direct and indirect effects of the virus in organs. Some studies use further advanced methods, thereby contributing to the understanding of these virus diseases and their consequences (see Tables 1 and 2).

The explanation for the lack of systematic autopsy studies during influenza virus and coronavirus pandemics is multifaceted. One major reason is anxiety among autopsy personnel about becoming infected. In a 2019 survey of U.S. medical examiners and coroners, 51% and 78%, respectively, answered that they would not perform autopsies in cases of suspected or confirmed highly infectious disease (16). The survey further demonstrated that only 56% had received training in how to use PPE and that only 44% had been involved in handling suspected or confirmed highly infectious cases, whereas 62% indicated a lack of proper training for staff. Lack of proper facilities and procedures may deter the pathologist from performing certain, if not all, procedures. The precautions at autopsy for SARS, COVID-19 and MERS are similar and are more extensive than for influenza-suspected deaths. The use of PPE may be hampered by low compliance (85), thereby exposing the pathologist to health risks (15, 23). Yaacoub et al. performed a systematic review on the safe management of bodies with suspected or confirmed SARS-CoV-2, but they found no evidence for any proposed guidelines (86).

The lack of systematic autopsy studies during pandemics is clearly also the result of regulations by governments and scientific communities. The Danish law on epidemics entails a provision for autopsy at the request of the epidemic committees (87). So far, this provision has not been enacted during the COVID-19 pandemic, resulting in a low autopsy rate. In Hamburg, Germany, autopsies were performed during the first wave of the COVID-19 pandemic, despite an opposite recommendation by the German Robert Koch Institute (25). In Italy, autopsies were performed at the discretion of the pathologist, with core biopsies and PMCT recommended as alternatives (88, 89). The Danish Society of Pathology presented algorithms for safe handling and execution of autopsies at the beginning of the COVID-19 pandemic, but these essentially left all but one department in eastern Denmark unable – or unwilling – to perform autopsies (no publicly available reference).

Despite the small sample sizes and the variability in quality of the autopsy studies during influenza virus and coronavirus pandemics, autopsy studies have contributed to the understanding of the pathology of these viruses. The pathological findings are generally identical and include oedematous lungs and DAD. Secondary bacterial infection at autopsy ranges from 100% of cases in 1918 (34), through 80% of cases in 1958 (36) to 40% in 2009 (44). The lowering frequency is presumably due to better antibacterial treatments. The extrapulmonary findings are generally attributed to the immune response or organ dysfunction secondary to infection, rather than to a direct viral cytopathic effect (26). One autopsy case report described the pathological findings in a MERS-related death (22), and the benefits of that study were widely heralded (90) for contributing significantly to the understanding of MERS effects in the kidneys. In the COVID-19 pandemic, autopsy findings have guided anti-thrombotic treatment in Germany and Denmark (37).

Overall, an acute need exists for systematic autopsies during pandemics. Autopsies are very important for identifying emerging infectious diseases and describing the pathological consequences of both novel and established diseases (91). The importance of autopsies in understanding disease pathogenesis was demonstrated in the HIV pandemic, where autopsies contributed significantly, for example, to the understanding of the AIDS-related disorder, Kaposi's sarcoma. Furthermore, a study on 101 deceased patients with AIDS documented that 74% had AIDS-related disorders that had not been suspected or diagnosed clinically (20). Even during inter-epidemic periods, autopsy studies have helped reduce the number of exclusion diagnoses, such as SUD, by demonstrating that influenza virus was present in a disproportionate amount of cases (31).

Autopsy studies make the establishment of tissue biobanks possible, thereby enabling future research

(43, 83). This was demonstrated with the breakthrough in understanding the Spanish Flu, as de novo analysis of autopsy material from the biobank – the National Tissue Repository – of samples from 1918 demonstrated, that the Spanish flu had caused deaths at least four months prior to recognition of the pandemic. Similarly, PCR analysis identified the strain (34).

Another important aspect in pandemics is to classify the cause of death correctly. The question of whether the patient died *with* the disease versus *from* the disease is better answered by autopsy than clinically (92). The poor accuracy of swabs or 'quick tests' (28) may result in misclassification of cause of death, so these tests are not reliable substitutes for autopsy. An example of the impact of correct classification of cases and non-cases is the case fatality rate in New York City, USA, during the 2009 Swine Flu pandemic, which ranged from 0.0008% to 0.2% depending on whether clinical information, swabs or autopsies were used to establish cause of death (93).

A collaborative autopsy study between The Forensic Institute at University of Copenhagen and the Department of Pathology, Rigshospitalet, Copenhagen, has initiated the establishment of a biobank and databank of confirmed and suspected COVID-19-related deaths to help in clarifying the pathogenesis of SARS-CoV-2 infection and its long-term complications. The study utilizes standardized sampling and reporting. An autopsy algorithm is available upon request, should any institution wish to mirror our data and thus facilitate in obtaining a larger cohort and international comparison of COVID-19 deaths. Likewise, the data collected will be available for future research upon request, on the condition that the proposed project is scientifically solid and complies with legislation on data and ethics. Data for the biobank are gathered at standardized, accredited autopsies that encompass PMCT, postmortem magnetic resonance imaging (if deemed necessary), external examination, opening of all three body cavities, standardized sampling from all organs for microscopy, standardized tissue and fluid sampling for toxicological, genetic and microbiological analysis, and standardized reporting. We will be publishing a protocol article with more details. This approach is similar to our prior 'SURVIVE' study that marked the beginning of a national, prospective, comprehensive collection and analysis of data from autopsies of the mentally ill, with collaboration from chemists, geneticists, cardiologists, epidemiologists, radiologists and pathologists (84).

CONCLUSION

Autopsies enable the detection of novel disease, help to monitor the spread of infectious disease, enable the reliable registration of deaths related to epidemics, correct clinical misdiagnoses, serve as quality control, identify prognostic and risk factors, and aid in treatment through identification of target sites for infection and complications of infection. Biobanks provide the possibility of using new methods on old samples.

If autopsies are to provide meaningful insight into novel diseases such as COVID-19, then ancillary and interdisciplinary methods, as well as standardized algorithms utilizing full body autopsies, should be employed. Looking solely to confirm suspected findings can lead to erroneous conclusions and might also limit the knowledge that can be gained from autopsies in both hospital and forensic settings.

If autopsies are to be performed systematically, then governmental and scientific society support is needed that stresses how knowledge is lost when autopsies are not performed and that stresses the importance of maintaining autopsy competencies and facilities.

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REFERENCES

1. Fukuda K, Organization WH, Programme WHOGI. Pandemic Influenza Preparedness and Response: A WHO Guidance Document. World Health Organization; 2009.
2. Chavarria-Miró G, Anfruns-Estrada E, Guix S, Paraira M, Galofré B, Sáanchez G, et al. Sentinel surveillance of SARS-CoV-2 in wastewater anticipates the occurrence of COVID-19 cases. medRxiv 2020:2020.06.13.20129627.
3. Fongaro G, Hermes Stoco P, Sobral Marques Souza D, Grisard EC, Magri ME, Rogovski P, et al.SARS-CoV-2 in human sewage in Santa Catalina, Brazil, November 2019. medRxiv. 2020:2020.06.26.20140731
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;383:1199–1207.
5. Morens DM, Taubenberger JK. Pandemic influenza: certain uncertainties. Rev Med Virol. 2011;21(5): 262–84.
6. Davis GG, Winters GL, Fyfe BS, Hooper JE, Iezzoni JC, Johnson RL, et al. Report and recommendations of the association of pathology chairs' Autopsy Working Group. Acad Pathol. 2018;5:2374289518793988.

7. van den Tweel JG, Wittekind C. The medical autopsy as quality assurance tool in clinical medicine: dreams and realities. Virchows Arch. 2016;468(1):75–81.
8. Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch. 2017;471(6):691–705.
9. Bolliger SA, Thali MJ. Imaging and virtual autopsy: looking back and forward. Philos Trans R Soc Lond B Biol Sci. 2015;370(1674):20140253.
10. Hanley B, Lucas SB, Youd E, Swift B, Osborn M. Autopsy in suspected COVID-19 cases. J Clin Pathol. 2020;73:239–242.
11. Burton JL. Health and safety at necropsy. J Clin Pathol. 2003;56(4):254–60.
12. Arbejdstilsynet. Biologiske agenser og arbejdsmiljø – 8 – Klassifikation af biologiske agenser i risikogruppe 2, 3 og 4; 2011 (Available from: https://at.dk/regler/bekendtgoerelser/biologiske-agenser-arbejdsmiljoe-57-sam/bilag-8/
13. Lacy JM, Brooks EG, Akers J, Armstrong D, Decker L, Gonzalez A, et al. Covid-19: postmortem diagnostic and biosafety considerations. Am J Forensic Med Pathol. 2020;41:143–151.
14. Ramsthaler F, Verhoff MA, Gehl A, Kettner M. The novel H1N1/swine-origin influenza virus and its implications for autopsy practice. Int J Legal Med. 2010;124(2):171–3.
15. Li L, Gu J, Shi X, Gong E, Li X, Shao H, et al. Biosafety level 3 laboratory for autopsies of patients with severe acute respiratory syndrome: principles, practices, and prospects. Clin Infect Dis. 2005;41(6):815–21.
16. Le AB, Brooks EG, McNulty LA, Gill JR, Herstein JJ, Rios J, et al. U.S. Medical Examiner/Coroner capability to handle highly infectious decedents. Forensic Sci Med Pathol. 2019;15(1):31–40.
17. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. Histopathology. 2020;77:198–209.
18. McLaughlin S, Kind K, Thomson L, Bouhaidar R. Unexpected active tuberculosis on Post Mortem CT: A case report and review of the literature. Forensic Sci Int. 2016;266:e64–e67.
19. Douceron H, Deforges L, Gherardi R, Sobel A, Chariot P. Long-lasting postmortem viability of human immunodeficiency virus: a potential risk in forensic medicine practice. Forensic Sci Int. 1993;60(1–2):61–6.
20. Geller SA. The autopsy in acquired immunodeficiency syndrome. How and why. Arch Pathol Lab Med. 1990;114(3):324–49.
21. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;22(5):911–5.
22. Ng DL, Al Hosani F, Keating MK, Gerber SI, Jones TL, Metcalfe MG, et al. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of middle east respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Am J Pathol. 2016;186(3):652–8.
23. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. Am J Clin Pathol. 2020;153(6):725–33.
24. Fujita J, Ohtsuki Y, Higa H, Azuma M, Yoshinouchi T, Haranaga S, et al. Clinicopathological findings of four cases of pure influenza virus A pneumonia. Intern Med. 2014;53(12):1333–42.
25. Edler C, Schroder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med. 2020;134(4):1275–84.
26. Bal A, Suri V, Mishra B, Bhalla A, Agarwal R, Abrol A, et al. Pathology and virology findings in cases of fatal influenza A H1N1 virus infection in 2009–2010. Histopathology. 2012;60(2):326–35.
27. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respiratory Med. 2020;8(4):420–2.
28. Edler C, Klein A, Gehl A, Ilchmann C, Scherpe S, Schrot M. The new influenza A (H1N1/09): symptoms, diagnostics, and autopsy results. Int J Legal Med. 2011;125(2):157–61.
29. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, et al. Lung pathology of fatal severe acute respiratory syndrome. Lancet. 2003;361(9371):1773–8.
30. Harms PW, Schmidt LA, Smith LB, Newton DW, Pletneva MA, Walters LL, et al. Autopsy findings in eight patients with fatal H1N1 influenza. Am J Clin Pathol. 2010;134(1):27–35.
31. Drescher J, Zink P, Verhagen W, Flik J, Milbradt H. Recent influenza virus A infections in forensic cases of sudden unexplained death. Arch Virol. 1987;92(1–2):63–76.
32. Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. Pulmonary pathology of severe acute respiratory syndrome in Toronto. Modern Pathol. 2005;18(1):1–10.
33. Voltersvik P, Aqrawi LA, Dudman S, Hungnes O, Bostad L, Brokstad KA, et al. Pulmonary changes in Norwegian fatal cases of pandemic influenza H1N1 (2009) infection: a morphologic and molecular genetic study. Influenza Other Respir Viruses. 2016;10(6):525–31.
34. Sheng ZM, Chertow DS, Ambroggio X, McCall S, Przygodzki RM, Cunningham RE, et al. Autopsy series of 68 cases dying before and during the 1918 influenza pandemic peak. Proc Natl Acad Sci USA. 2011;108(39):16416–21.
35. Hers JF, Mulder J. Broad aspects of the pathology and pathogenesis of human influenza. Am Rev Respir Dis. 1961;83(2 Pt 2):84–97.
36. Hers JF, Masurel N, Mulder J. Bacteriology and histopathology of the respiratory tract and lungs in fatal Asian influenza. Lancet. 1958;2(7057):1141–3.
37. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med. 2020;173(4):268–277.
38. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N Engl J Med. 2020;383(2):120–8.

39. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med. 2005;202(3):415–24.
40. Kuiken T, Taubenberger JK. Pathology of human influenza revisited. Vaccine. 2008;26(Suppl 4):D59–66.
41. Ibricevic A, Pekosz A, Walter MJ, Newby C, Battaile JT, Brown EG, et al. Influenza virus receptor specificity and cell tropism in mouse and human airway epithelial cells. J Virol. 2006;80(15):7469–80.
42. Taubenberger JK, Morens DM. The pathology of influenza virus infections. Annu Rev Pathol. 2008;3:499–522.
43. Neumann G, Kawaoka Y. Transmission of influenza A viruses. Virology. 2015;480:234–46.
44. Tamme K, Minajeva A, Adamson V, Ristmägi K, Põder J, Lutsar I. Clinical and pathological findings of fatal 2009–2010 pandemic influenza A (H1N1) infection in Estonia. Medicina (Kaunas). 2012;48 (1):48–56.
45. Paddock CD, Liu L, Denison AM, Bartlett JH, Holman RC, Deleon-Carnes M, et al. Myocardial injury and bacterial pneumonia contribute to the pathogenesis of fatal influenza B virus infection. J Infect Dis. 2012;205(6):895–905.
46. Oseasohn R, Adelson L, Kaji M. Clinicopathologic study of thirty-three fatal cases of Asian influenza. N Engl J Med. 1959;260(11):509–18.
47. Carmona F, Carlotti AP, Ramalho LN, Costa RS, Ramalho FS. Evidence of renal infection in fatal cases of 2009 pandemic influenza A (H1N1). Am J Clin Pathol. 2011;136(3):416–23.
48. Mauad T, Hajjar LA, Callegari GD, da Silva LF, Schout D, Galas FR, et al. Lung pathology in fatal novel human influenza A (H1N1) infection. Am J Respir Crit Care Med. 2010;181(1):72–9.
49. Simon M, Hernu R, Cour M, Casalegno JS, Lina B, Argaud L. Fatal influenza A(H1N1)pdm09 encephalopathy in immunocompetent man. Emerg Infect Dis. 2013;19(6):1005–7.
50. Ishigami A, Kubo S, Ikematsu K, Kitamura O, Tokunaga I, Gotohda T, et al. An adult autopsy case of acute encephalopathy associated with influenza A virus. Leg Med (Tokyo). 2004;6(4):252–5.
51. Yuen KY, Chan PK, Peiris M, Tsang DN, Que TL, Shortridge KF, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet. 1998;351(9101):467–71.
52. Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. Influenza Other Respir Viruses. 2017;11(5):372–93.
53. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol. 2020;26(6):729–34.
54. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497.
55. Guo Y, Korteweg C, McNutt MA, Gu J. Pathogenetic mechanisms of severe acute respiratory syndrome. Virus Res. 2008;133(1):4–17.
56. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009;9(5):291–300.
57. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013;369(5):407–16.
58. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172(9):577–82.
59. Choi WS, Kang CI, Kim Y, Choi JP, Joh JS, Shin HS, et al. Clinical presentation and outcomes of middle east respiratory syndrome in the Republic of Korea. Infect Chemother. 2016;48(2):118–26.
60. Calabrese F, Pezzuto F, Fortarezza F, Hofman P, Kern I, Panizo A, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. Virchows Arch. 2020;477(3):359–72.
61. Wilson N, Corbett S, Tovey E. Airborne transmission of covid-19. BMJ. 2020;370:m3206.
62. Konopka KE, Nguyen T, Jentzen JM, Rayes O, Schmidt CJ, Wilson AM, et al. Diffuse Alveolar Damage (DAD) from Coronavirus Disease 2019 infection is morphologically indistinguishable from other causes of DAD. Histopathology. 2020;77:570–578.
63. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–7.
64. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495(7440):251–4.
65. Darmoul D, Voisin T, Couvineau A, Rouyer-Fessard C, Salomon R, Wang Y, et al. Regional expression of epithelial dipeptidyl peptidase IV in the human intestines. Biochem Biophys Res Comm. 1994;203(2): 1224–9.
66. Fukasawa KM, Fukasawa K, Sahara N, Harada M, Kondo Y, Nagatsu I. Immunohistochemical localization of dipeptidyl aminopeptidase IV in rat kidney, liver, and salivary glands. J Histochem Cytochem. 1981;29(3):337–43.
67. Lang ZW, Zhang LJ, Zhang SJ, Meng X, Li JQ, Song CZ, et al. A clinicopathological study of three cases of severe acute respiratory syndrome (SARS). Pathology. 2003;35(6):526–31.
68. Chong PY, Chui P, Ling AE, Franks TJ, Tai DY, Leo YS, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. Arch Pathol Lab Med. 2004;128(2):195–204.
69. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol. 2003;200(3):282–9.
70. Tse GM, To KF, Chan PK, Lo AW, Ng KC, Wu A, et al. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). J Clin Pathol. 2004;57(3):260–5.
71. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern

Italy: a two-centre descriptive study. Lancet Infect Dis. 2020;20:1135–1140.
72. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respirat Med. 2020;8(7):681–686.
73. Buja LM, Wolf DA, Zhao B, Akkanti B, McDonald M, Lelenwa L, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovascular Pathol. 2020;48:107233.
74. Grimes Z, Bryce C, Sordillo EM, Gordon RE, Reidy J, Paniz Mondolfi AE, et al. Fatal Pulmonary thromboembolism in SARS-CoV-2-infection. Cardiovascular Pathol. 2020;48:107227.
75. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020;173:350–361.
76. Menter T, Haslbauer JD, Nienhold R, Savic S, Deigendesch H, Frank S, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology. 2020;77(2):198–209.
77. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417–8.
78. Shi X, Gong E, Gao D, Zhang B, Zheng J, Gao Z, et al. Severe acute respiratory syndrome associated coronavirus is detected in intestinal tissues of fatal cases. Am J Gastroenterol. 2005;100(1):169–76.
79. Sekulic M, Harper H, Nezami BG, Shen DL, Sekulic SP, Koeth AT, et al. Molecular detection of SARS-CoV-2 infection in FFPE samples and histopathologic findings in fatal SARS-CoV-2 cases. Am J Clin Pathol. 2020;154(2):190–200.
80. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med. 2020;383(6):590–2.
81. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet. 2020;396(10247):320–32.
82. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219–27.
83. Gibson CD, Colvin MO, Park MJ, Lai Q, Lin J, Negassa A, et al. Prevalence and predictors of deep vein thrombosis in critically ill medical patients who underwent diagnostic duplex ultrasonography. J Intensive Care Med. 2020;35(10):1062–6.
84. Banner JH, Christensen M, Gheorghe A, Bugge A, Ottesen G, Boel L, Thomsen J, et al. LSURVIVE: Let the dead help the living – an autopsy-based cohort study for mapping risk markers of death among those with severe mental illnesses. Scandinavian. J Forensic Sci. 2019;24(1):7–17.
85. Fritzsche FR, Ramach C, Soldini D, Caduff R, Tinguely M, Cassoly E, et al. Occupational health risks of pathologists–results from a nationwide online questionnaire in Switzerland. BMC Public Health. 2012;12:1054.
86. Yaacoub S, Schünemann HJ, Khabsa J, El-Harakeh A, Khamis AM, Chamseddine F, et al. Safe management of bodies of deceased persons with suspected or confirmed COVID-19: a rapid systematic review. BMJ Glob Health. 2020;5(5).
87. Bekendtgørelse af lov om foranstaltninger mod smitsomme og andre overførbare sygdomme, 9 (2019).
88. Fineschi V, Aprile A, Aquila I, Arcangeli M, Asmundo A, Bacci M, et al. Management of the corpse with suspect, probable or confirmed COVID-19 respiratory infection - Italian interim recommendations for personnel potentially exposed to material from corpses, including body fluids, in morgue structures and during autopsy practice. Pathologica. 2020;112:64–77.
89. Sapino A, Facchetti F, Bonoldi E, Gianatti A, Barbareschi M. Societa Italiana di Anatomia Patologica e Citologia S. The autopsy debate during the COVID-19 emergency: the Italian experience. Virchows Arch. 2020;476(6):821–3.
90. Walker DH. Value of autopsy emphasized in the case report of a single patient with middle east respiratory syndrome. Am J Pathol. 2016;186(3):507–10.
91. Schwartz DA. Emerging and reemerging infections. Progress and challenges in the subspecialty of infectious disease pathology. Arch Pathol Lab Med. 1997;121(8):776–84.
92. Ermenc B. Comparison of the clinical and post mortem diagnoses of the causes of death. Forensic Sci Int. 2000;114(2):117–9.
93. Vaillant L, La Ruche G, Tarantola A, Barboza P. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. Euro Surveill. 2009;14(33).
94. Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem Examination of Patients With COVID-19. JAMA. 2020;323 (24):2518–20.
95. Youd E, Moore L. COVID-19 autopsy in people who died in community settings: the first series. J Clin Pathol. 2020;73:840–844.
96. Franks TJ, Chong PY, Chui P, Galvin JR, Lourens RM, Reid AH, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Hum Pathol. 2003;34 (8):743–8.
97. Paget J, Spreeuwenberg P, Charu V, Taylor RJ, Iuliano AD, Bresee J, et al. Global mortality associated with seasonal influenza epidemics: New burden estimates and predictors from the GLaMOR Project. J Glob Health. 2019;9(2):020421.
98. World Health Organisation. Coronavirus disease (COVID-19) pandemic 2020 updated 17 September. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

APPENDIX 1

Methods

We searched the MEDLINE (PubMed) databases with the terms (autopsy OR necropsy OR necrotomy OR post mortem) AND (mers OR mers-cov OR Middle Eastern respiratory OR influenza OR flu OR swine flu OR bird flu OR avian flu OR h1n1 OR h2n1 OR h3n2 OR h5n1 OR hong kong virus OR asian virus OR spanish flu). We performed a separate search on SARS-CoV-2 with the string ('SARS Virus'[Mesh]) AND (Pathology OR autopsy OR post-mortem), and COVID-19 with the string (((wuhan[All Fields] AND ('coronavirus'[MeSH Terms] OR 'coronavirus'[All Fields])) AND 2019/12[PDAT]: 2030[PDAT]) OR 2019-nCoV[All Fields] OR 2019nCoV[All Fields] OR COVID-19[All Fields] OR SARS-CoV-2[All Fields]) AND (Pathology OR post-mortem OR autopsy). We performed the searches in mid-2020 and retrieved 1046 publications on influenza and MERS and, respectively, 402 and 2032 publications on SARS and COVID-19. We primarily selected autopsy studies as our focus. The publications were screened for relevance, focusing on these terms. The retrieved publications consisted of case reports, case series, observational studies and reviews. We screened the references of the included articles to capture additional relevant studies. An overview of the studies can be found in Appendix 2 – overview of studies mentioned in article.

APPENDIX 2

Overview of studies mentioned in article

Authors	Title	Year	Article	N	Disease
Ackermann et al. (38)	Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19	2020	Case series	7/7	COVID-19
Barton et al. (23)	COVID-19 Autopsies, Oklahoma, USA	2020	Case series	2	COVID-19
Bradley et al. (81)	Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series	2020	Case series	14	COVID-19
Buja et al. (73)	The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities.	2020	Case series	3	COVID-19
Calabrese et al. (60)	Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists	2020	Review	-	COVID-19

(continued)

Authors	Title	Year	Article	N	Disease
Carsana et al. (71)	Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study	2020	Case series	38	COVID-19
Fox et al. (72)	Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans	2020	Case series	10	COVID-19
Grimes et al. (74)	Fatal Pulmonary Thromboembolism in SARS-CoV-2-Infection. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology	2020	Case series	2	COVID-19
Konopka et al. (62)	Diffuse Alveolar Damage (DAD) from Coronavirus Disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD	2020	Case series	8	COVID-19
Lax et al. (75)	Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-Center, Clinicopathologic Case Series	2020	Case series	11	COVID-19
Menter et al. (76)	Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction	2020	Case series	21	COVID-19
Puelles et al. (80)	Multiorgan and Renal Tropism of SARS-CoV-2	2020	Case series	22	COVID-19
Schaller et al. (94)	Postmortem Examination of Patients With COVID-19	2020	Case series	10	COVID-19
Sekulic et al. (79)	Molecular Detection of SARS-CoV-2 Infection in FFPE Samples and Histopathologic Findings in Fatal SARS-CoV-2 Cases	2020	Case series	2	COVID-19
Su et al. (82)	Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China	2020	Case series	26	COVID-19

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Authors	Title	Year	Article	N	Disease
Varga et al. (77)	Endothelial cell infection and endotheliitis in COVID-19	2020	Case series	3	COVID-19
Wichmann et al. (37)	Autopsy Findings and Venous Thromboembolism in Patients With COVID-19	2020	Case series	12	COVID-19
Youd et al. (95)	COVID-19 autopsy in people who died in community settings: the first series	2020	Case series	9	COVID-19
Ng et al. (22)	Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014	2016	Case report	1	MERS
Ding et al. (69)	The clinical pathology of severe acute respiratory syndrome (SARS): a report from China	2003	Case series	3	SARS
Franks et al. (96)	Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore	2003	Case series	8	SARS
Lang et al. (67)	A clinicopathological study of three cases of severe acute respiratory syndrome (SARS)	2003	Case series	3	SARS
Nicholls et al. (29)	Lung pathology of fatal severe acute respiratory syndrome	2003	Case series	6	SARS
Chong et al. (68)	Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis	2004	Case series	14	SARS
Tse et al. (70)	Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS)	2004	Case series	7	SARS
Gu et al. (39)	Multiple organ infection and the pathogenesis of SARS	2005	Case series	18	SARS
Hwang et al. (32)	Pulmonary pathology of severe acute respiratory syndrome in Toronto. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.	2005	Case series	20	SARS

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Authors	Title	Year	Article	N	Disease
Shi et al. (78)	Severe acute respiratory syndrome associated coronavirus is detected in intestinal tissues of fatal cases	2005	Case series	7	SARS
Guo et al. (55)	Pathogenetic mechanisms of severe acute respiratory syndrome	2008	Review	-	SARS
Harms et al. (30)	Autopsy findings in eight patients with fatal H1N1 influenza	2010	Case series	8	Swine influenza
Edler et al. (28)	The new influenza A (H1N1/09): symptoms, diagnostics, and autopsy results	2011	Case series	2	Swine influenza
Bal et al. (26)	Pathology and virology findings in cases of fatal influenza A H1N1 virus infection in 2009-2010	2012	Case series	9	Swine influenza
Tamme et al. (44)	Clinical and pathological findings of fatal 2009-2010 pandemic influenza A (H1N1) infection in Estonia	2012	Case series	21	Swine influenza
Fujita et al. (24)	Clinicopathological findings of four cases of pure influenza virus A pneumonia	2014	Case series	4	Swine influenza
Voltersvik et al. (33)	Pulmonary changes in Norwegian fatal cases of pandemic influenza H1N1 (2009) infection: a morphologic and molecular genetic study	2016	Case series	19	Swine influenza
Hers et al. (36)	Bacteriology and histopathology of the respiratory tract and lungs in fatal Asian influenza	1958	Case series	148	Asian influenza
Drescher et al. (31)	Recent influenza virus A infections in forensic cases of sudden unexplained death	1987	Case series	84	Hong Kong influenza
Sheng et al. (34)	Autopsy series of 68 cases dying before and during the 1918 influenza pandemic peak	2011	Case series	68	Spanish influenza

