Infectious diseases and the role of needle biopsy post-mortem

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Post-mortem examinations continue to play a crucial role in understanding the epidemiology and pathogenesis of infectious diseases. However, the perceived infection risk can preclude traditional, invasive, complete diagnostic autopsy. Post-mortem examination is especially important in emerging infectious diseases with potentially unknown infection risks, but rapid acquisition of good quality tissue samples is needed as part of the scientific and public health response. Needle biopsy post-mortem is a minimally invasive, rapid, closed-body autopsy technique that was originally developed to minimise the infection risk to practitioners. Since its inception, needle biopsy post-mortem has also been used as a technique to support complete diagnostic autopsy provision in poorly resourced regions and to facilitate post-mortem examinations in communities that might have religious or cultural objections to an invasive autopsy. This Review analyses the evolution and applicability of needle biopsy post-mortem in investigating endemic and emerging infectious diseases.

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Introduction

Infectious diseases remain a persistent leading cause of global mortality, with a multinational study from 2017 suggesting that infectious diseases caused approximately 15% of all deaths globally that year.[1] WHO reported that lower respiratory tract infections were the fourth most common cause of death globally in 2019, with higher rates of infectious disease mortality in low-income countries than in other countries.[2] Since then, the risk to global health by infections such as COVID-19, which appears to have affected middle-income and high-income countries more severely, has increased.[3,4] Infectious disease will remain a major risk to global health security because of the potential for future emerging pandemics[5] and the rising rates of antimicrobial resistance.[6]

Central to the global health response to infectious disease is understanding the biology and pathogenesis of the causative organism, for which post-mortem examinations have had and continue to play an essential role, as seen with HIV and AIDS in the 1980s[7] and COVID-19 in the 2020s.[8,9] Post-mortem tissue can be used to isolate pathogens, understand the pathogenesis of a disease, investigate therapy effectiveness, and identify defining disease features and the extent of associated complications.

The invasive complete diagnostic autopsy, which involves evisceration of a cadaver and whole-organ dissection, is still considered the gold standard for death investigation.[10–13] Nevertheless, autopsy rates worldwide have been decreasing substantially over the past few decades[14,15] for numerous reasons, including real and perceived difficulties in obtaining consent from bereaved families for religious or cultural reasons. For instance, a study of Ugandan hospital deaths in 2011 found that the most common reason relatives gave for declining an autopsy was "not wanting to delay the burial".[16] Other reasons include a decrease in autopsy requests from clinicians due to the potential stigma surrounding autopsies, a preconception that consent would be declined, or a belief that the cause of death is already known.[16,17]

Specific to the context of deaths involving an infectious disease, case reports suggest infection transmissions linked to autopsies.[18,19] A study from 2022 also showed that after complete autopsies in cases of COVID-19, personal protective equipment was contaminated with SARS-CoV-2 RNA or even the active virus.[20] Thus, the actual or perceived risk and the fear of infection can preclude or limit complete diagnostic autopsies, which aligns with our experience and several published autopsy guidelines.[8,21,22]

To address these issues, a closed-body autopsy technique has been developed, which is known as needle biopsy post-mortem or minimally invasive autopsy.[23] This technique involves using a biopsy needle to percutaneously sample organs or tissues of the deceased without the need for large incisions, whole-organ removal, or dissection.

Many studies have investigated needle biopsy post-mortems as a possible substitute for traditional complete diagnostic autopsies.[23–28] Compared with complete diagnostic autopsies, needle biopsy post-mortem has a reduced risk of infection. Other advantages include a higher likelihood of consent, the possibility of performing the needle biopsy post-mortem at the bedside right after death, and that it is a quicker procedure than complete autopsy.[23,25,28–30] Limitations of the needle biopsy technique have also been identified. This technique might have no or only limited suitability for some organs (eg, the brain, small organs such as the parathyroid glands, and hollow organs such as the bowel), and if performed without imaging guidance, obtained specimens might not be representative.[24]

This Review examines the use of needle biopsy post-mortems in infectious diseases. The primary objective was to evaluate whether needle biopsy post-mortem can serve as a valid alternative to a complete diagnostic autopsy in the context of emerging and endemic infectious diseases.

Yellow fever

Although data are limited, reports suggest that the first recorded needle biopsy post-mortem dates to 1930 during a yellow fever epidemic in Brazil.[31,32] Décio Parreiras and Werneck Genofre, doctors in Rio de Janeiro at the time, created a device that could collect liver samples without disfiguring the body. The instrument was known as the Parreiras-Genofre spindle, which was later improved and named the viscerotome by Elsmere Rickard, an American

working in Brazil with the Rockefeller Foundation. Notably, the needle biopsy post-mortem was pioneered for an infectious disease necessitating a minimised risk of transmission to the pathologist.

Needle biopsy post-mortems were also performed during a 2018 yellow fever epidemic in São Paolo, Brazil.[33] A study of 20 patients by Duarte-Neto and colleagues used ultrasonography to assist in collecting biopsy samples from the liver, kidneys, heart, lungs, and spleen. They reported 100% concordance between ultrasound-guided biopsy and complete diagnostic autopsy in these cases. The main pathological finding was panlobular hepatitis with hepatic failure, and the infectious agent was identified in 85% of the post-mortem cases.

HIV

The first study that used needle biopsy post-mortem in cases of HIV infections was performed in 1994 by Baumgart and colleagues in Australia.[34] In their study, 12 (75%) of 16 major diagnoses were found to have been missed ante mortem, including tuberculosis, cytomegalovirus pneumonitis, and cytomegalovirus hepatitis, and the cause of death was changed after needle biopsy post-mortem was performed in seven (43·7%) of the 16 cases.

In 2001, 150 Spanish patients with HIV underwent needle biopsy post-mortem, obtaining a 40·6% agreement with the presumed ante-mortem diagnosis.[35] The needle biopsy post-mortem confirmed at least one diagnosis not previously suspected, including AIDS-related conditions such as cytomegalovirus pneumonitis and atypical mycobacterial infections, and also other conditions such as liver cirrhosis due to hepatitis C in 41 (27·3%) of 150 individuals.

Using ultrasound-guided needle biopsy post-mortem, Wong and colleagues investigated the cause of death of patients who received antiretroviral therapy in South Africa and showed that tuberculosis caused the majority of deaths.[36]

The first study to evaluate the concordance between needle biopsy post-mortems and complete autopsies in HIV was conducted in 2014 in a cohort of 96 adults in Uganda.[37,38] The causes of death varied, but infections accounted for 72% of the major diagnoses. Diagnostic concordance rates with complete autopsy were 52% for ultrasound-guided biopsies and 50% for biopsies without imaging guidance. Concordance was higher with infectious diagnoses, up to 57%, and specifically showed a much higher concordance of 79% for the diagnosis of tuberculosis, which also caused the most deaths in this cohort. The most important reasons for discordance were sampling error, which was most likely because too few samples per organ were collected and variation in sampling location was low, and organs such as the meninges, gastrointestinal tract, and lymph nodes were not sampled.

In Brazil and Mozambique, complete autopsy and needle biopsy post-mortem were performed on 164 (18 children, 36 maternal deaths, and 110 adults) people with HIV. The leading causes of death in adults were tuberculosis (22·7% in adults, 13·9% in maternal deaths), toxoplasmosis (13·6% in adults), bacterial infections (13·6% in adults, 13·9% in maternal deaths), and cryptococcosis (10·9% in adults, 11·1% in maternal deaths). The overall concordance between needle biopsy post-mortem and complete autopsy was 78% (100% in children, 91% in adults, and 78% in maternal deaths).[39]

Malaria

Malaria is one of the leading causes of death in low-income and middle-income countries (619 000 estimated deaths in 2021), and children younger than 5 years remain the most at-risk group for infection.[40] Post-mortem needle biopsy of the frontal lobe via a supraorbital approach can be a useful technique to detect the *Plasmodium* parasite. This approach has been used in Thailand, Viet Nam, Malawi, and Papua New Guinea.[41–45] A study conducted on 41 children in Malawi reported a diagnostic concordance of 87% between needle biopsy post-mortem and complete autopsy.[42] As part of a larger study in Mozambique, needle biopsy post-mortems were performed in 264 cases. Malaria infection was deemed the cause of death in six (2·3%). The needle biopsy post-mortem technique had a 100% concordance with complete autopsy in identifying malaria-specific deaths.[46]

Rabies

Although biopsy post-mortems in human infectious disease are the focus of this Review, rabies is a zoonotic disease with a mammalian transmission vector (such as bats and dogs). Every year, rabies results in tens of thousands of fatalities, mostly in Asia and Africa, with 40% of the victims being younger than 15 years.[47]

A post-mortem brain biopsy technique similar to that used in malaria has been adopted for suspected rabies cases. A study from 1996 in Senegal used an occipital biopsy technique on 23 clinically diagnosed cases of rabies, demonstrating rabies virus positivity in 22 (95·6%) of the cases via direct immunofluorescence.[48] Compared with a complete diagnostic autopsy, the biopsy post-mortem approach might decrease the need for rabies postexposure prophylaxis, as the exposure of practitioners to rabies-infected tissue is lower with needle biopsies because of a decreased risk of splash and sharps injuries.[49]

A 2012 study from India[50] showed that rabies virus can be confirmed via RT-PCR with post-mortem skin biopsies from animals. This technique could act as a potential tool for surveillance of animal populations in rabies-endemic resource-limited areas.

The studies reporting needle biopsy post-mortems in yellow fever, HIV, malaria, and rabies are summarised in table 1.

Emerging infectious disease: COVID-19

Emerging infectious diseases remain a risk to the global population, typified by the COVID-19 pandemic caused by SARS-CoV-2. Since the start of the pandemic, many studies

	Country	Population	Imaging guidance	Sample size	Disease	Concordance with complete autopsy
Benchimol (2001)[31]*	Brazil	..	..	..	Yellow fever	..
Franco (1969)[32]*	Brazil	..	..	..	Yellow fever	..
Baumgart et al (1994)[34]	Australia	Adults	..	16	HIV	..
Sow et al (1996)[48]	Senegal	Adults and children	..	23	Rabies	..
Tong et al (1999)[49]	Philippines	Adults	..	1	Rabies	..
Guerra et al (2001)[35]	Spain	Adults	..	150	HIV	..
Pongponratn et al (2003)[41]	Thailand and Viet Nam	Adults	..	..	Malaria	..
Milner et al (2005)[42]	Malawi	Children	..	41	Malaria	87%
Wong et al (2012)[36]	South Africa	Adults	Ultrasonography	39	HIV	..
Manning et al (2012)[45]	Papua New Guinea	Children	..	3	Malaria	..
Milner et al (2012)[43]	Malawi	Children	..	71	Malaria	..
Cox et al (2014)[38]	Uganda	Adults	Ultrasonography	99	HIV	50% (without ultrasonography) and 52% (with ultrasonography)
Laman et al (2014)[44]	Papua New Guinea	Children	..	1	Malaria	..
Karat et al (2017)[51]	South Africa	Adults	Ultrasonography	34	HIV	..
Duarte-Neto et al (2019)[33]	Brazil	Adults	Ultrasonography	20	Yellow fever	100%
Letang et al (2021)[39]	Brazil and Mozambique	Adults and children	..	164	HIV	78%
Rakislova et al (2021)[46]	Mozambique	Adults and children	..	264	Malaria	100% (for the six included malaria cases)

*Source for first recorded needle biopsy post-mortem in 1930 by Parreiras and colleagues.

Table 1: **Summary of studies that used the needle biopsy post-mortem technique in yellow fever, HIV infection, malaria, and rabies**

used needle biopsy post-mortem as a biohazard precaution to elucidate the disease pathogenesis[8,9,21,52–69] (table 2). Accordingly, the COVID-19 pandemic represents a model to examine the utility of the needle biopsy post-mortem in understanding emerging infectious diseases.

Studies using needle biopsy post-mortem for COVID-19 have been conducted in Asia, Europe, Africa, and Latin America. In a systematic review across 16 studies and 216 needle biopsy post-mortems in COVID-19, diffuse alveolar damage in different stages was the most common pathological finding in all but one study.[62] This finding agrees with those of most studies based on complete diagnostic autopsies. Notably, the single study not showing diffuse alveolar damage identified myocarditis in a child, which is thus a proposed alternative cause of death in paediatric COVID-19.[52]

Needle biopsy post-mortem can be used to detect diffuse alveolar damage, as it is less likely to be missed due to sampling error. Rare regional heterogeneity, such as focal alveolar damage in only one lung region, could be overcome by multiregional biopsies (eg, sampling from all lung lobes).[8] Notably, thrombotic lesions, mainly in the lungs or kidneys and occasionally across multiple sites, were also reported in approximately half of the COVID-19 studies reporting the results of needle biopsy post-mortems.[62] Biopsies might miss singular thromboses in larger vessels; however, diffuse thrombotic microangiopathy seen in systemic infections or inflammatory disorders such as COVID-19 might be readily identified. The risk of missing singular, non-systemic lesions (eg, a large thrombus or an abscess) can be reduced by combining needle biopsy post-mortem with imaging techniques to localise the lesion.[71,72]

During the COVID-19 pandemic, needle biopsy post-mortem studies provided important epidemiological information. For example, in South Africa, Sabet and colleagues completed biopsy post-mortems on 66 people who had died at home. These authors found previously undiagnosed COVID-19 in 14 (21.2%) of 66 cases.[21] Needle biopsy post-mortem studies also revealed information about disease progression. In China, researchers showed that diffuse alveolar damage in COVID-19 can progress to pulmonary fibrosis.[69]

Haemophagocytosis of the bone marrow has also been observed in most COVID-19 deaths in a study analysing post-mortem trephine biopsies of the posterior superior iliac spine. The study concluded that needle biopsy post-mortem can be an alternative to complete diagnostic autopsy for investigating systemic bone marrow haematopathology.[57]

The only study that directly compared needle biopsy post-mortems with complete diagnostic autopsies in COVID-19 was conducted in Spain.[56] Needle biopsy post-mortem was able to differentiate COVID-19 as the primary cause of death in four cases and confirmed COVID-19 as a contributing factor to the cause of death in cases of aspiration pneumonia and myocardial infarction, showing 100% concordance with complete autopsy. Importantly, this study also followed up with the pathologists and mortuary staff, none of whom tested positive for COVID-19 afterwards, despite the biopsies being performed in a basic autopsy suite without negative pressure air flow, suggesting the safety of the needle biopsy technique.

Molecular correlations with histopathological findings are increasingly relevant in infectious disease autopsies. In COVID-19, molecular investigations might include

	Country	Population	Imaging guidance	Sample size	Concordance with complete autopsy
Hanley et al (2020)[8,9]	UK	Adults	Ultrasonography	1	..
Sabet et al (2023)[21]	South Africa	Adults	..	66	..
Wu et al (2020)[70]	China	Adults	Ultrasonography	1	..
Dolhnikoff et al (2020)[52]	Brazil	Children	Ultrasonography	1	..
de Almeida Monteiro et al (2021)[53]	Brazil	Adults and children	Ultrasonography	28	..
Yang et al (2020)[54]	China	Adults	Ultrasonography	12	..
D'Onofrio et al (2020)[55]	Belgium	Adults	CT	18	..
Rakislova et al (2021)[56]	Spain	Adults	..	6	100%
Prieto-Peréz et al (2020)[57]	Spain	Adults	..	33	..
Bhandari et al (2021)[58]	India	Adults and children	..	12	..
Takahashi et al (2021)[59]	Japan	Adults	..	1	..
Mauad et al (2021)[60]	Brazil	Adults	Ultrasonography	41	..
Brook et al (2021)[61]	USA	Adults	Ultrasonography	5	..
Beigmohammadi et al (2021)[62]	Iran	Adults	Ultrasonography	7	..
Duarte-Neto et al (2020)[63]	Brazil	Adults	Ultrasonography	10	..
Zhang et al (2020)[64]	China	Adults	..	1	..
Bruce-Brand et al (2020)[65]	South Africa	Adults	..	4	..
Flikweert et al (2020)[66]	Netherlands	Adults	Ultrasonography and CT	7	..
Monteiro et al (2020)[67]	Brazil	..	Ultrasonography	31	..
Li et al (2021)[69]	China	Adults	Ultrasonography	30	..

Table 2: **Summary of studies that used the needle biopsy post-mortem technique in COVID-19**

both establishing SARS-CoV-2 as the cause of infection and defining the variant type. In future pandemics, correlations among molecular, genetic, or proteomic analyses can be used to infer therapeutic effectiveness (eg, antimicrobial sensitivity or resistance). A considerable advantage of needle biopsy post-mortem is that it can be performed earlier in the post-mortem period and, potentially, at the decedent's bedside.[30,68] A shorter post-mortem interval has been associated with improvements in RNA quality, and this observation might also apply to other biomolecular and ultrastructural analyses.[73] Thus, techniques such as RT-PCR, immunohistochemistry, and electron microscopy have been used to detect SARS-CoV-2 in a wide range of organs in COVID-19 needle biopsy post-mortems. Beyond the demonstrable applications of improved biomolecule quality in current practice, the advantages for future pandemics and research are considerable.

Other emerging infectious diseases

The experience with COVID-19 has reaffirmed that respiratory infections have the potential to trigger a global pandemic.[74] Influenza, for instance, poses a constant global health threat, leading to recurring outbreaks, with four pandemics having occurred within the past century, at least three major outbreaks during the 18th and three in the 19th century.[75] In 1997, one of the first outbreaks of avian influenza A (H5N1) in humans occurred in Hong Kong. Of the six individuals who had died, post-mortem biopsies of the lungs and kidneys were performed on one of the individuals, demonstrating lung tissue positive for the H5 antigen.[76] Influenza A (H1N1) developed into a pandemic in 2009, originating in Mexico and then spreading to the USA and other countries. A retrospective study from 2012 evaluated biopsy post-mortems of 46 patients, showing evidence of diffuse alveolar damage in the lungs, consistent with previous complete autopsy studies.[77] These findings suggest that needle biopsy post-mortem is a valid technique for influenza.

Roberts and colleagues used needle biopsy followed by a complete autopsy to study a mixture of bacterial and viral pneumonias in a population of 64 infants in Kenya.[78] They reported a 66% concordance in histological diagnosis between needle biopsy post-mortem and complete diagnostic autopsy. The concordance was higher (80%) for the molecular diagnosis of the causative organism. However, the needle biopsy post-mortems identified a larger number of bacterial agents, including upper respiratory tract flora, which the researchers thought represented contamination (table 3).

The Pneumonia Etiology Research for Child Health (PERCH) group, a multinational group of clinicians and scientists investigating childhood pneumonia in low-income countries, proposes using needle biopsy post-mortems in children who have died from respiratory infection. The PERCH group plans further studies using multimodal post-mortem lung biopsies to minimise sampling error. They identified numerous benefits of this technique including increased acceptance by relatives of the deceased, better preservation of pathogens, and decreased post-mortem bacterial contamination due to the shorter post-mortem interval.[81]

WHO lists several types of viral haemorrhagic fever as priority diseases of interest[5] because of their potential to

	Country or region	Population	Imaging guidance	Sample size	Disease	Concordance with complete autopsy
Chan et al (2002)[76]	Hong Kong	Adults	..	1	Influenza A (H5N1)	..
Shelke et al (2012)[77]	India	Adults	..	46	Influenza A (H1N1)	..
Marchiori et al (2012)[79]	Brazil	Adults	..	4	Influenza A (H1N1)	..
Roberts et al (2012)[78]	Kenya	Children	..	64	Respiratory infections	66% (histological diagnosis) and 80% (molecular testing)
Yu et al (2013)[80]	China	Adults	..	3	Influenza A (H7N9)	..

Table 3: **Summary of studies that used the needle biopsy post-mortem technique in other respiratory infections**

cause pandemics. Complete diagnostic autopsies have historically revealed important pathological information about these diseases,[82] such as massive liver necrosis and gastrointestinal haemorrhage. However, as these infections are generally categorised as Hazard Group 4,[83] some countries such as the UK now advise against performing autopsies altogether.[22] To the best of our knowledge, no studies have used needle biopsy post-mortem in cases of fatal viral haemorrhagic fever up to 2024. Nevertheless, were a viral haemorrhagic fever to develop into a global pandemic, the public health benefits of extracting tissue for research might outweigh the purported individual infection risks. To that end, the experiences with other infectious diseases highlighted by this Review suggest that in eventuality, needle biopsy post-mortem would be the safest and best way to proceed.

WHO also prioritises and addresses the risk of a hypothetical future pandemic caused by a hitherto unknown pathogen, defined as Disease X.[5] Rapid assimilation and acquisition of knowledge from across the world about the disease's pathophysiology, tropism, and treatment options would be important, and needle biopsy post-mortem could provide an effective and safer approach to tissue sampling and biobanking.

Infectious disease monitoring in general populations

In some low-income communities with poor civil registration systems and limited access to health care, verbal autopsy, often based on set questionnaires, is still used to estimate the cause of death.[84] In a verbal autopsy, a cause of death is determined on the basis of information gleaned from interviewing people known to the deceased but without a physical examination of the deceased. These low-income areas have the highest infectious disease burden and mortality,[2] and accurate diagnosis and disease monitoring for the sake of local and global public health remains a priority. A study from 2016 assessed the accuracy of 147 verbal autopsies in HIV-infected individuals against the reference standard of 34 needle biopsy post-mortems.[51] Verbal autopsy underestimated mortality caused by tuberculosis and other infectious diseases. The 2021 study on malaria by Rakislova and colleagues found a low concordance between verbal autopsy and complete diagnostic autopsy, with malaria being overreported in verbal autopsies, whereas the sensitivity and specificity of needle biopsy post-mortem was 100%.[46]

The Cause of Death through Minimally Invasive Autopsy (CaDMIA) and CaDMIA-plus projects were developed to expand access to post-mortems in low-income and middle-income countries.[85] These projects later evolved into the Minimally Invasive Tissue Sampling (MITS) Alliance, and some projects were included as part of the Child Health and Mortality Prevention Surveillance (CHAMPS) project. These projects aim to test the validity of needle biopsy post-mortems as a routine technique in general populations in seven different countries in sub-Saharan Africa and south-east Asia where traditional complete diagnostic autopsies might not be accepted for cultural reasons or not be feasible due to scarcity and in some cases an absence of resources, leaving a verbal autopsy or no autopsy at all as the only alternatives. A standard protocol for needle biopsy post-mortem has been developed as part of the CHAMPS project[85] (table 4).

As part of a project in Mozambique, for example, 264 ultrasound-guided needle biopsy post-mortems were performed, followed by complete diagnostic autopsies[92,93] (112 adults,[86-88] 59 neonates,[87] 54 children,[95] and 57 maternal deaths[90]). Moreover, 61 paired needle biopsy post-mortems and complete autopsies were conducted in Manaus, in the Brazilian Amazon (59 adults, 2 children).[94] Although infectious disease was not the focus of these studies, 71% of the adults in the Mozambique group and 72% of those in the Brazil group died due to infection, highlighting the importance of infectious diseases in these countries.

Based on a study in Mozambique, Garcia-Basteiro and colleagues reported good concordance between needle biopsy and complete autopsy diagnoses (78·8% for infectious diseases, 75·9% overall).[93] Gastrointestinal infections were among the conditions most undetected by biopsy, probably caused by sampling error. In that study, 56·6% of the non-neonatal deaths were HIV-positive, and 35·9% had evidence of tuberculosis.[93] Martínez and colleagues[87] investigated infectious diseases in 30 adult deaths and identified the pathogen in 89·5% of cases using needle biopsy specimens, but the biopsy did not detect one case of pneumonia and one case of meningoencephalitis. In another study, 54 children underwent both needle biopsy and complete post-mortem,[89] showing good diagnostic concordance (93% for infectious diseases, 89% overall).

	Country	Population	Sample size	Concordance with complete autopsy
Castillo et al (2015)[86]	Mozambique	Adults	30*	..
Martinez et al (2016)[87]	Mozambique	Adults	30*	..
Castillo et al (2016)[88]	Mozambique	Adults	112†	76%
Bassat et al (2017)[89]	Mozambique	Children	54†	93%
Castillo et al (2017)[90]	Mozambique	Maternal deaths	57†	89%
Menendez et al (2017)[91]	Mozambique	Stillbirths and neonates	59†	78%
Fernandes et al (2019)[92]	Mozambique	Adults and children	264	89%
Garcia-Basteiro et al (2019)[93]	Brazil	Adults and children	61	90%
Palhares et al (2019)[94]	Mozambique	Adults and children	223†	..
Letang et al (2021)[39]	Brazil and Mozambique	Adults and children	164	78%
Rakislova et al (2021)[46]	Mozambique	Adults and children	264	..

CaDMIA=cause of death through minimally invasive autopsy. MITS=minimally invasive tissue sampling. *Same population of 112 adults. †Same population of 264 adults and children.

Table 4: **Summary of studies that used the needle biopsy post-mortem technique as part of the CaDMIA project or MITS Alliance**

	Country	Population	Type of imaging	Sample size	Concordance with complete autopsy
Fariña et al (2004)[96]	Spain	Adults and children	Ultrasonography	100	83%
Aghayev et al (2007)[97]	Switzerland	Adults	CT	3	..
Aghayev et al (2008)[98]	Switzerland	Adults	CT	2	..
Breeze et al (2008)[99]	UK	Stillbirths	MRI and ultrasonography	30	..
Weustink et al (2009)[100]	Netherlands	Adults	CT, MRI, and ultrasonography	30	77%
Filograna et al (2010)[101]	Switzerland	Adults	CT	1	..
Bolliger et al (2010)[71]	Switzerland	Adults	CT and angiography	20	90%
Flach et al (2012)[72]	Switzerland	Adults	CT	1	100%
van der Linden et al (2014)[73]	Netherlands	Adults	CT	24	..
Blokker et al (2018)[102]	Netherlands	Adults	CT	295	92%
Wagensveld et al (2019)[103]	Netherlands	Adults	CT and MRI	46	..
Wagensveld et al (2018)[104]	Netherlands	Adults	CT and MRI	100	..
Votino et al (2018)[105]	Belgium	Stillbirths	Ultrasonography	88	..
Latten et al (2019)[106]	Netherlands	Adults	CT	60	45%

Table 5: **Summary of studies that used the needle biopsy post-mortem technique with imaging guidance**

Despite the overall high concordance in infectious disease, two cases of rabies and a case of tetanus were undetected by the needle biopsy.[89]

In the study conducted in Brazil by Palhares and colleagues, needle biopsy post-mortem diagnoses agreed with complete autopsy diagnoses in 90% of cases, with a slightly higher concordance (93%) for infectious disease deaths.[94] The authors identified the causative pathogen in 80% of needle biopsy post-mortems and 91% of the complete diagnostic autopsies, with the main difference in diagnosis due to the decreased ability of the needle biopsy technique to identify CNS infections such as toxoplasmosis or cryptococcal meningoencephalitis.

Most studies in the CaDMIA project used ultrasound guidance as part of their protocol for needle biopsy post-mortems. Numerous studies[71–73,96–106] (table 5) have shown that imaging guidance can overcome many of the limitations of needle biopsies, including the ability to reliably and accurately sample specific organs or lesions and the macroscopic visualisation of pathology to some degree.

Many studies[71–73,97–104,106] have investigated the use of CT and MRI as alternative imaging techniques to assist needle biopsy post-mortems. As most of these studies were performed in high-income countries and did not specifically investigate the number of deaths caused by infectious diseases, these studies are not within the scope of this Review. Nevertheless, CT and MRI have been validated as adjunctive techniques in needle biopsy post-mortems and remain options to investigate infectious disease in the future, assuming that the facilities and resources are available to accommodate these imaging modalities.

Conclusion

This Review analysed needle biopsy post-mortem studies performed between 1930 and 2021, focusing on the use of this technique in diagnosing, monitoring, and researching infectious diseases. The history of the needle biopsy technique has been detailed, with specific mention of its use in yellow fever, HIV, rabies, and malaria. These diseases were selected to highlight the evolution of needle biopsy post-mortems because the volume of research related to these

conditions is larger. The focus on these diseases is likely to be caused by a combination of historical factors, the increased biohazard risk of these diseases (all are classed as Hazard Group 3),[83] the fact that these diseases tend to be endemic in areas where post-mortem resources are sparse, and the potentially increased local or cultural aversion to complete diagnostic autopsies in these same areas. Thus, the needle biopsy post-mortem technique gained popularity in the 2010s in low-income and middle-income countries, particularly in Africa and South America, where death investigation systems might not be as robust as in high-income nations. Needle biopsy post-mortem can be used for emerging infectious diseases such as COVID-19. These sampling techniques can probably be extrapolated for usage in deaths from other infectious disease.

19 of the 64 reviewed studies performed a complete diagnostic autopsy after needle biopsy post-mortem and reported diagnostic concordance of pathological findings. The concordance ranged from 45% to 100%, with an overall weighted mean concordance of 80%. Imaging does not appear to substantially change needle biopsy post-mortem accuracy, with a weighted mean concordance of 79·2% compared with 79·9% when performed without imaging guidance. Although the overall mean concordance appears acceptable, the values had a wide range. In the majority of reviewed studies, one of the most common causes for discordance with complete invasive autopsy appeared to be the risk of sampling error and the difficulty in reliably sampling particular organs (eg, the brain, bowel, vessels, and small organs). Sampling error can be partially remedied using imaging guidance[71,72] and collecting more biopsy samples from individual organs.[81]

Nine of the studies that evaluated concordance between needle biopsy post-mortem and complete diagnostic autopsy specifically investigated deaths caused directly by infectious disease, some of which include sub-analyses of CaDMIA project and MITS Alliance studies. When these nine studies were combined with those that reported the accuracy of identifying the infectious agent with needle biopsies (via culture or molecular tests), the weighted mean diagnostic accuracy to establish the diagnosis or identify the pathogen in needle biopsy post-mortems was approximately 87%.

Despite the lower overall accuracy and reliability of needle biopsy post-mortems than those of complete diagnostic autopsies (panel), the information provided is still considered valuable, especially in cases of infectious disease because needle biopsy technique results in better quality of the tissue for pathogen identification, histological processing, and biobanking.[73,81] Ultimately, in low-income countries, given the constraints imposed by limited resources and a degree of cultural hesitancy towards invasive autopsy, needle biopsy post-mortem can still be an effective death investigation technique and is better than no autopsy at all.

One of the most important advantages of the needle biopsy post-mortem in infection is, as a closed-body autopsy, the reduced risk of pathogen transmission by aerosol or inoculation, which is invaluable during infectious disease outbreaks and epidemics.[63] The advantage of needle biopsy post-mortem was highlighted by its effective and safe use during the COVID-19 pandemic.[56] In the setting of an emerging infectious disease, the actual or perceived risk of post-mortem transmission might be a barrier to death investigation or research, especially in resource-limited settings associated with a lack of personal protective equipment or modern facilities.

Needle biopsy post-mortems are, therefore, particularly valuable in low-income countries that often have a high infectious disease burden. Limitations of the biopsy technique such as the lower overall accuracy of this approach compared with that of a complete diagnostic autopsy can be less important in these countries, as the only alternatives might either be a verbal autopsy or no autopsy at all.[38,92]

***Panel:* Comparison of advantages and disadvantages between needle biopsy post-mortem and complete diagnostic autopsy**

Needle biopsy post-mortem

Advantages

- Cheaper than a complete diagnostic autopsy with all ancillary tests performed
- Rapid procedure; thus, fewer delays in funeral arrangements
- Reduced disfigurement of the deceased
- Higher likelihood of consent
- Easy to perform; can be performed at the bedside in hospitals
- Closed-body autopsy, associated with a decreased infection risk
- High-quality tissue for RNA and molecular analyses

Disadvantages

- No appreciation of macroscopic pathology
- Might require imaging guidance
- Risk of sampling error and bias
- Difficulty in sampling some organs (eg, the brain, bowels, parathyroid glands)
- Necessitates tissue retention in every case
- Cannot be used for suspicious and forensic cases

Complete diagnostic autopsy

Advantages

- The gold standard for investigating a death
- Educational tool
- Acts as an audit and quality control mechanism in the practice of medicine
- Cases do not always necessitate tissue retention and processing (eg, ruptured aneurysms)

Disadvantages

- Lower likelihood of consent
- Increased infection risk
- Time-consuming and physically strenuous
- Needs a dedicated mortuary facility
- Requires more training for adequate performance

Search strategy and selection criteria

We searched PubMed for articles published between July, 1955, and April, 2023, using the following terms: "needle biopsy post-mortem" plus "needle biopsy autopsy", "tissue sampling", "minimally invasive post-mortem" plus "minimally invasive autopsy", and "minimally invasive tissue sampling" individually and in combination with "infectious diseases", "COVID-19", "yellow fever", "HIV", "AIDS", "malaria", "influenza", "rabies", "Ebola", and "viral haemorrhagic fever". A total of 209 articles were retrieved, and relevant articles were also identified through searches in the authors' personal files, in Google Scholar, Springer Online Archives Collection, and Science Direct. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English and Spanish were included.

Drawing on the authors' personal experiences of performing autopsies and devising national post-mortem guidelines during the COVID-19 pandemic,[8] even in settings with adequate personal protective equipment and resources, the fear of infection can exceed the objective risk to practitioners and the wider public; a viewpoint supported by literature showing that health-care workers had higher levels of anxiety and fear than the general population during the COVID-19 pandemic.[107–109] This apprehension was also present in those with organisational responsibility for the facilities in which post-mortems were performed. Therefore, needle biopsy post-mortem could act as a bridge to continuing autopsy practice in such scenarios while allaying fears and improving staff morale. In particular, needle biopsy post-mortems could facilitate safer and more accepted research and investigation into a novel or unknown pathogen, such as WHO's hypothetical Disease X, before its infection risk or hazard group is properly characterised.

Contributors

RG and MO contributed to the project administration, supervision, study design, manuscript review, and revision of the original draft. LM contributed to the study design, literature search, writing of the original draft, and data interpretation. MO contributed to the funding acquisition. BH and TES contributed to the literature search, writing of the original draft, and data interpretation.

Declaration of interests

We declare no competing interests.

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