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Biobanking in times of crisis – The COVID-19 Autopsy and Biosample Registry Baden-Wuerttemberg

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A B S T R A C T

Biobanking plays a critical role in diagnostics, biomarker research and development of novel treatment approaches for various diseases. In urgent need of understanding, preventing and treating coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the importance of biobanking including data sharing and management further increased. To provide high quality tissue biomaterials and data for research and public health, the COVID-19 Autopsy and Biosample Registry was established in the state of Baden-Wuerttemberg (BW) in Germany, combining expertise and technologies of the Institutes of Pathology of the five university hospitals in BW (Heidelberg, Tübingen, Ulm, Freiburg, Mannheim). The COVID-19 Autopsy and Biosample Registry BW comprises tissue samples from autopsies and associated data of deceased patients in the context of SARS-CoV-2 infection and/or vaccination against SARS-CoV-2. The aim is to collect autopsy biospecimens, associated clinical and diagnostic data in a timely manner, register them, make them accessible for research projects and thus to support especially tissue-related research addressing COVID-19. By now, the BW network holds multiple collaborations and supported numerous publications to increase the understanding of COVID-19 disease. The achievements of the BW network as a landmark biobanking model project represent a potential blueprint for future disease-related biobanking and registry effort.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by an outbreak of severe respiratory infections in 2019 in Wuhan, China, created a global crisis of extraordinary proportions [1]. The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern on 30th January 2020, and a pandemic on 11th March 2020 [2,3].

From March 2020, standardized autopsies of deceased patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-
CoV-2) were performed at the Institutes of Pathology of the university hospitals in Baden-Wuerttemberg (BW) to contribute to the elucidation of the pathogenesis of fatal COVID-19. Supported by the Ministry of Science, Research and Arts of Baden-Wuerttemberg (MWK), the COVID-19 Autopsy and Biosample Registry BW was established to support COVID-19 research by standardized biobanking with focus on collection, processing and storing of COVID-19 tissue samples in urgent need of understanding the disease, including therapy strategies as well as the understanding of the efficacy and adverse effects of anti-SARS-CoV-2 vaccination. Here, we describe structure, potential and achievements of the COVID-19 Autopsy and Biosample Registry BW as a blueprint for infectious disease-oriented tissue biobanking.

2. Material and methods

2.1. COVID-19 autopsies and biobanking

Standardized autopsies of COVID-19-related deaths were performed regularly at the Institutes of Pathology at the university hospitals in Heidelberg, Tübingen, Freiburg, Ulm and Mannheim under strict adherence to safety precautions and according to consented standard operating procedures (SOPs) as previously described [4]. In brief, autopsies were performed with limited number of personnel in autopsy rooms with precautionary signs and restricted access. The personnel were protected by appropriate personal protections equipment (PPE) including overall, surgical hood, FFP3 mask, safety goggles, two pairs of gloves, clogs with covers, apron and protective sleeves. If not necessary, the cranium was not opened to minimize aerosol and dust formation. A logbook with involved personnel was kept. After autopsy, all surfaces and equipment were decontaminated and infectious waste was collected in specific containers.

The following inclusion criteria for autopsies were applied: 1) Deceased persons having been tested positive for SARS-CoV-2 infection and/or vaccinated against SARS-CoV-2. 2) Informed consent for autopsies was either given by relatives or autopsies were ordered under §25 (4) German Infection Protection Act for epidemic control or by the public prosecutor’s office. 3) Deceased persons were ≥ 18 years old. The registry and biobanking as well as scientific use of biomaterials stored was authorized by an ethics committee of each involved site, respectively (Heidelberg, No. S-242/2020; Ulm, No. 276/13; Tübingen, No. 236/2021B02; Mannheim, 2020–653 N; Freiburg EK 316/20). All procedures were conducted in accordance with the Declaration of Helsinki. The project, supported by the Ministry of Science, Research and Arts of Baden-Wuerttemberg (MWK), is coordinated under the roof of the Tissue Bank of the German Center for Infection Research (DZIF) located in Heidelberg.

For biobanking, both formalin-fixed, paraffin-embedded (FFPE) as well as cryo-preserved tissue samples minimally of the heart, lung, stomach, intestine, kidney, liver, spleen, pharyngeal tonsils and thymus were obtained, registered and stored in a decentralized manner and under harmonized conditions at the five participating university hospitals in BW, also supported by the funds of the MWK. As cryo-preserved tissues from SARS-CoV-2 infected patients are potentially infectious, specific biosafety measures were applied. Thus, samples were stored in a separate lockable − 80 °C freezer and sample procession was performed under biosafety level 2 conditions using PPE (FFP3 protective masks, goggles/visor, surgical hood, nitrile gloves, disposable gowns). To support the biobank logistics in managing and tracking of FFPE and cryo-preserved tissue samples, at the central Heidelberg site the platform STARLIMS (Abbott Laboratories) was used.

2.2. COVID-19 Autopsy and Biosample Registry BW

A web-based solution was established in the DZIF Tissue Bank in Heidelberg to allow pseudonymized collection of clinico-pathological data from all participating sites using Microsoft.NET 5/Blazor and Radzen embedded in an agile software development process. The standardized and harmonized data collection includes all relevant patient-related data: autopsy data, histopathological and radiological findings, immunisation status, as well as clinical and virological data (Supplementary Table S1). Pseudonymized data (autopsy data and correlative clinical and/or diagnostic data) are saved in a web-based registry under an officially reviewed data privacy concept and in accordance with the ethical vote. Since samples and data are exclusively collected from deceased patients, general German Data Protection Regulations are not applicable.

The sample collection was partly integrated in the online search tools of the German Biobank Node (GBN; Sample Locator), the Central Biosample Register (ZBR) of the DZIF, and the National COVID-19 Registry (DeRegCOVID) of the national academic research network for COVID-19-related research requests. Tissue samples and data can also directly be requested for research purposes via the COVID-19 sample request form available at all participating sites (see, e.g., request form of the DZIF Tissue Bank in Heidelberg and further information on the website) [5,6]. After project review and approval, samples will be processed and transferred. Transfer of samples and data is project specific and pseudonymized according to SOPs and documented by material transfer agreement.

3. Results

The project has established an autopsy and biosample registry and network to support COVID-19-related research. The network rapidly realigned projects with focus on COVID-19 in collecting, processing, and storing of COVID-19 autopsy tissue samples and data in order to investigate the pathophysiology of the disease, to evaluate therapy- and vaccination-related findings and to characterize adverse events following anti-SARS-CoV-2 vaccination. For the COVID-19 Autopsy and Biosample Registry BW laboratory biosafety conditions were set up and existing autopsy and biobank infrastructures were used under the roof of the DZIF Tissue Bank.

3.1. Collective of the COVID-19 Autopsy and Biosample Registry BW

Until the end of the first funding period (December 2021), a total of 250 autopsies were registered in the COVID-19 Autopsy and Biosample Registry BW including the collection of tissue samples from 174 patients deceased having been tested positive for SARS-CoV-2, 64 patients deceased in close context of an anti-SARS-CoV-2 vaccination, and 12 patients deceased after having a COVID-19 breakthrough infection after complete vaccination (see Table 1; including all registered cases with a SARS-CoV-2 infection and/or anti-SARS-CoV-2 vaccination as cause of death or severe comorbidity/co-acting cause of death).

Exemplarily, regarding the distribution of COVID-19 autopsies from March 2020 to December 2021 in relation to COVID-19 deaths at the Heidelberg site (UKHD), a high rate of autopsies was yielded (Fig. 1). Overall, the temporal pattern of COVID-19 deaths and autopsies at UKHD resembled the pattern in Germany. While the number of autopsies for deceased COVID-19 patients decreased from April 2021 on, an increasing number of autopsies from persons deceased in close correlation with anti-SARS-CoV-2 vaccination was performed.

Considering the age distribution of the collective, the median age accounted for 71 years when patients deceased after SARS-CoV-2 infection, while it accounted for 63 years for deaths occurring in close temporal correlation with anti-SARS-CoV-2 vaccination (Table 1). In both groups (SARS-CoV-2-infected and anti-SARS-CoV-2 vaccinated) there was a higher prevalence of deaths in males compared to females. Within all five university hospitals, in total 4383 FFPE tissue samples and 7766 cryo-preserved samples were collected for COVID-19-related research projects. The distribution of FFPE- and cryo-preserved tissue samples among autopsies after SARS-CoV-2 infection, anti-SARS-CoV-2 vaccination, and breakthrough infection after completed vaccination is
listed in Table 2. Number of autopsies and collected samples varied between the participating centres, depending on different sizes of the centres and region size served by the university hospitals as well as differences in pre-existing infrastructures which needed to be aligned and harmonized.

### 3.2. Research support

Starting from April 2020, within the BW network 35 research projects have been supported by tissue samples of the COVID-19 Autopsy and Biosample Registry BW (Table 2). These projects included histopathological, immuno-phenotypical, molecular, and (micro-) radiographic investigations providing valuable prognostic and pathophysiologic characterization of COVID-19. Moreover, the pathophysiology of serious adverse events after anti-SARS-CoV-2 vaccination has been addressed.

### 3.3. Network of the COVID-19 Autopsy and Biosample Registry BW

In order to optimize autopsy frequency and data acquisition, close collaboration with public prosecutor’s offices, governmental and local offices as well as the Institute of Forensic Medicine Heidelberg was established. On national level, the COVID-19 Autopsy and Biosample Registry BW is involved in biobanking networks such as the German Biobank Alliance (GBA) and the German Biobank Node (GBN), and cooperates with several other research networks such as the DZIF, the German Center for Lung Research (DZL), and the national academic research network (Network of University Medicine, NUM; DEFEAT PANDEMics) (Fig. 2). Moreover, a cooperation with the Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut, PEI) exists including detailed reporting of vaccination-related serious adverse events and breakthrough infections. On international level, the COVID-19 Autopsy and Biosample Registry BW is involved in the Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium (BBMRI-ERIC).

### Table 1
Number and characteristics of registered autopsy cases (December 2021).

|                      | SARS-CoV-2 positive deceased | Anti-SARS-CoV-2 vaccinated deceased | Anti-SARS-CoV-2 vaccinated and SARS-CoV-2 positive deceased |
|----------------------|------------------------------|------------------------------------|----------------------------------------------------------|
|                      | Age-median (min/max)         | Female/ Male (n)                   | Age-median (min/max)          | Female/ Male (n)                   | Age-median (min/max)          | Female/ Male (n) |
| Heidelberg           | 72 (31/95)                   | 30/65                              | 61.5 (21/95)                  | 14/28                              | 80 (50/103)                  | 4/7 |
| Tübingen             | 62 (18/89)                   | 10/22                              | 74 (24/90)                   | 2/7                                | 64                           | 0/1 |
| Ulm                  | 57 (21/82)                   | 3/10                               | 65 (28/79)                   | 3/8                                | –                            | – |
| Freiburg             | 73 (43/95)                   | 16/13                              | –                            | –                                  | –                            | – |
| Mannheim             | 44 (36/79)                   | 3/2                                | 73 (69/77)                   | 0/2                                | –                            | – |
| Total                | 71 (18/95)                   | 62/112                             | 63 (21/95)                   | 19/45                              | 79 (50/103)                  | 4/8 |

* deceased ≥ 14 days after second vaccination

### Table 2
Biobanking of samples (December 2021).

|                      | Number of preserved tissue samples (n) in total (SARS-CoV-2 infection/Anti-SARS-CoV-2 vaccination/breakthrough infections) | Number of local biosample-related projects (n) |
|----------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| FFPE                 | FFPE                                                        | Cryo-preserved                              |
| Heidelberg           | 1048 (659/302/87)                                             | 6254 (4019/1740/495)                        | 18                                         |
| Tübingen             | 1552 (1106/413/33)                                           | 124 (124/0/0)                               | 8                                          |
| Ulm                  | 941 (597/344/0)                                              | 1180 (681/499/0)                            | 3                                          |
| Freiburg             | 540 (540/0/0)                                                | 0 (0/0/0)                                   | 3                                          |
| Mannheim             | 302 (195/107/0)                                              | 208 (208/0/0)                               | 3                                          |
| Total                | 4383 (3097/1166/120)                                         | 7766 (5032/2239/495)                        | 35                                         |

* formalin-fixed, paraffin-embedded
3.4. Registry publications and public relations activities

With the support of the COVID-19 Autopsy and Biosample Registry BW, important COVID-19-related research results have been achieved and published by the participating sites. Such as those, the network contributed to the understanding of COVID-19 pathophysiology investigating pulmonary pathology [4,7] and microvascular changes [8], provided insights into anti-SARS-CoV-2-vaccination-induced adverse effects [9], and supported the understanding of COVID-19 infections in basic research [10,11]. All publications of the network are listed in the Supplementary Table S2.

In addition, awareness in public relations improved public knowledge on COVID-19 and autopsies in general (for a list of public relations activities see Supplementary Table S3). These public relations activities included presentations at conferences, lectures, articles in scientific journals and newspapers (online and print), newsletter, TV reports and podcasts.

4. Discussion

SARS-CoV-2 infection causing COVID-19 has continued to spread across the world and represents a severe clinical, diagnostic and epidemiological challenge. It is important to react to this challenge and support disease-related research by standardized high quality biobanking and acquisition of related data by an established network and infrastructure. The pandemic showed the need and demand for information sharing and research. This includes rapid and safe collection as well as sharing of subsequent analysis of high-quality biosamples and associated data to globally support research. Consequently, COVID-19-related biospecimens were collected worldwide, mostly focusing on the collection of liquid samples such as blood, sputum and urine [12–14]. However, especially tissue samples are essential for improving the understanding of the pathophysiology of COVID-19 for clinical management and vaccine application. For this, under the roof of the DZIF Tissue Bank existing approaches, tools and software were used to establish a new and rapidly applicable integrated autopsy network, registry and biosample platform in BW as an immediate respond in the beginning of the pandemic in 2020. Consented SOPs and regular communication between the partner sites, as well as performance-associated support and standardized web-based acquisition of consented datasets were used to minimize the heterogeneity of the sites and allowing decentralized storage of biosamples.

The COVID-19 autopsy and biobanking network is a successful example and blueprint not only for focussed infectious diseases-related biobanking and registry, but also for the efficiency of this effort demonstrating impressively that autopsies and associated biobanking and registry are of central importance for the systematic assessment of new diseases such as COVID-19. Histopathological examination of tissues in settings of clinical autopsies as supported by our biobanking efforts were an essential tool in the COVID-19 pandemic to reveal impact of pulmonary (micro-) vascular thromboembolism, systemic viral spread, and the complex synergy of immune system and viral effects in severe COVID-19 (Supplementary Table S2). The close match of overall and local COVID-19-deaths with autopsy numbers based on a high autopsy rate further supports the disease representativity of the registry.

The COVID-19 Autopsy and Biosample Registry BW established a local network which enables fast and direct communication, i.e., with hospital and resident physicians on-site as well as local public prosecutor’s and public health offices. Without these intense collaborations on local level and the support of the MWK the high rate of autopsies in BW would not have been achievable from the early beginning of the pandemic. Quantitative information of autopsy cases is, i.a., included in the national COVID-19 registry DeRegCOVID resulting in a national cross-border network and collaborations supporting multicentre collection analyses of COVID-19 death on national level [15,16]. Furthermore, given the huge impact of the COVID-19 pandemics on all aspects of public life, another important aspect of our autopsy and biobanking network in BW and the DEFEAT PANDEMics network on the national level is their role in shaping public opinion since the beginning of the pandemics. After initial reservations aired by various medical agencies about the use of clinical autopsies in fatal COVID-19 because of the perceived risks, the rapid roll-out of clinical autopsies and the associated registries not only provided crucial knowledge about disease pathophysiology but stimulated extensive reporting and lively
discussions in public media, garnering broad acceptance and high publicity for our work.

5. Conclusions

So far, despite the short time span and considering the time needed to build up research-relevant collectives, significant progress has been made in understanding of the novel disease as demonstrated by the significant number of publications from various topics as well as numerous cooperation with research and biobanking networks. Thus, the BW network represents a landmark biobanking model project and a potential blueprint for future disease-related biobanking and registry effort.

Informed consent and patient details

Informed consent for autopsies was either given by relatives or autopsies were ordered under §25 (4) German Infection Protection Act for epidemic control or by the public prosecutor’s office. The registry and biobanking as well as scientific use of biomaterials stored was authorized by an ethics committee of each involved site, respectively (Heidelberg, No. S-242/2020; Ulm, No. 276/13; Tübingen, No. 236/2021BO2; Mannheim, 2020–653N; Freiburg EK 316/20). All procedures were conducted in accordance with the Declaration of Helsinki.

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CRediT authorship contribution statement

LMD, IMK, and PS contributed to conceptualization of the study, CS, AM, MW, FM, FF, HB, and PS provided support for obtaining samples and data as well as expertise as pathologists. LMD, IMK and LH coordinated the activity of all participants. LMD drafted the initial manuscript. IMK, LH, FF, and PS revised the manuscript. All authors read and approved the final manuscript.

Declaration of interest

None.

Availability of data and materials

All datasets on which the conclusions of the manuscript rely are included in the published article and its supplementary information files. Further data are not publicly available due to ethical restrictions. Pseudonymized information is potentially available from the corresponding authors on reasonable request.

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The DZIF Tissue Bank is part of the BioMaterialBank Heidelberg (BMBH) and a partner of the German Biobank Alliance (GBA).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2022.154011.

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