Preparing European Nephrology for the next pandemic: lessons from the ERACODA collaboration

Priya Vart [1,2], Raphaël Duivenvoorden[3], Casper F.M. Franssen[1], Marc H. Hemmelder[4], Kitty J. Jager[5], Luuk B. Hilbrands [3], Marlies Noordzij[1], Daniel Abramowicz[6,7], Carlo Basile[8], Adrian Covic[9], Marta Crespo[10], Ziad A. Massy[11,12], Alberto Ortiz [13], J. Emilio Sanchez [14], Emily Petridou[15], Colin White[16] and Ron T. Gansevoort [1]

[1]Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Department of Clinical Pharmacy & Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [3]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands, [4]Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands, [5]ERA Registry, Amsterdam UMC location University of Amsterdam, Medical Informatics, Meibergdreef 9; Amsterdam Public Health Research Institute, Quality of Care, Amsterdam, The Netherlands, [6]Department of Nephrology, Antwerp University Hospital, Edegem, Belgium, [7]Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium, [8]Division of Nephrology, Miulli General Hospital, Acquaviva delle Fonti, Italy, [9]Grigore T. Popa University of Medicine and Pharmacy, Dr C.I. Parhon Hospital, Iasi, Romania, [10]Department of Nephrology, Hospital del Mar, Mar Institute for Medical Research, Red de Investigación Renal (RICORS2040) (RD16/0009/0013), Barcelona, Spain, [11]Department of Nephrology, Centre Hospitalier Universitaire (CHU) Ambroise Paré, Assistance Publique-Hôpitaux de Paris (AP-HP), Boulogne-Billancourt, France, [12]Centre for Research in Epidemiology and Population Health (CESP), Institut National de la Santé et de la Recherche Médicale (INSERM) UMRS 1018, Team 5, University Versailles-Saint Quentin, University of Paris Saclay, Villejuif, France, [13]Instituto de Investigación Sanitaria (IIS)-Fundación Jiménez Díaz, Autonomous University of Madrid (UAM), Red de Investigación Renal (REDINREN), Madrid, Spain, [14]Department of Nephrology, University Hospital of Cabuenes, Asturias, Spain, [15]Representative of the European Kidney Patients' Federation, Nicosia, Cyprus and [16]Representative of the European Kidney Patients' Federation, Dublin, Ireland

Correspondence to: Priya Vart; E-mail: p.vart@umcg.nl

ABSTRACT

Owing to the vulnerability of patients with chronic kidney disease to infectious diseases, the coronavirus disease 2019 (COVID-19) pandemic has been particularly devastating for the nephrology community. Unfortunately, the possibility of future COVID-19 waves or outbreaks of other infectious diseases with pandemic potential cannot be ruled out. The nephrology community made tremendous efforts to contain the consequences of the COVID-19 pandemic. Despite this, the COVID-19 pandemic has highlighted several shortcomings in our response to the pandemic and has taught us important lessons that can be utilized to improve our preparedness for any future health crises of a similar nature. In this article we draw lessons from the European Renal Association COVID-19 Database (ERACODA) project, a pan-European collaboration initiated in March 2020 to understand the prognosis of COVID-19 in patients on kidney function replacement therapy. We discuss the challenges faced in generating timely and robust evidence for informed management of patients with kidney disease and give recommendations for our prepared-ness for the next pandemic in Europe. Limited collaboration, the absence of common data architecture and the sub-optimal quality of available data posed challenges in our response to COVID-19. Aligning different research initiatives, strengthen-ing electronic health records, and involving experts in study design and data analysis will be important in our response to the next pandemic. The European Renal Association may take a leading role in aligning research initiatives via its engagement with other scientific societies, national registries, administrators and researchers.

Keywords: European nephrology, kidney, pandemic, pre-paredness, recommendation

INTRODUCTION

In 2020, the coronavirus disease 2019 (COVID-19) pandemic hit the nephrology community hard. Initially, mortality rates were extremely high, especially among patients on kidney function replacement therapy (KFRT). With the serial muta-tions towards a less virulent strain and the ongoing deployment

Table 1: List of challenges in obtaining high-quality data, its consequences, and recommendations for improvement.

Challenges in obtaining high-quality data	Problematic consequences	Recommendations
Limited availability of diagnostic equipment	Incomplete overview of kidney patients infected with the disease Differential sampling by type of kidney function replacement therapy Increased risk of obtaining inaccurate answers about prognosis in kidney patients relative to the general population or when comparing patients with different kidney function replacement therapy	Patient and professional kidney societies develop a common front and engage with national and European authorities to ensure adequate and equitable distribution of diagnostic equipment
Lack of established pathways for collaboration among ongoing disease surveillance networks, government entities, health bodies, patient and professional kidney societies, kidney registries and researchers	Disjointed efforts fostering inefficient use of available resources, inadequate data and expertise Discordance between research agenda and immediate patient needs	ERA leading the efforts in developing a framework for collaboration among relevant agencies within and between countries Additionally, facilitating research initiatives by developing a standardized research protocol and offering methodological advice
Lack of a common data architecture	Limited information on important clinical aspects of the disease	Patient and professional kidney societies together highlight the importance of data linkage especially in case of a pandemic and for the high-risk population of patients with kidney disease
Inadequate linkage of electronic health records, kidney disease registries and other relevant data sources (e.g. pharmacy) within and between countries	Limited statistical power	Patient and professional kidney societies work with European and national counterparts to overcome administrative barriers in data linkage
Suboptimal quality of existing data sources including electronic health records and kidney disease registries	Incomplete understanding of the disease consequences and prognostic factors Questionable generalizability and validity of drawn conclusions	Strengthen existing data sources including supplementing existing kidney disease registries with early-stage chronic kidney disease and routine quality control of collected data Involving experts in study design and data analysis

of several effective COVID-19 vaccines and treatments in many countries, there is an expectation that the COVID-19 pandemic will be controlled to a manageable level. Unfortunately, the possibility of future COVID-19 waves or outbreaks of other infectious diseases with pandemic potential cannot be ruled out. The health and economic devastation resulting from COVID-19 has highlighted several shortcomings in our response to the COVID-19 pandemic and has taught us important lessons that can be utilized to improve our preparedness for any future health crises of a similar nature.

In this article, we aim to outline the lessons we learned from our response to the COVID-19 pandemic specifically concerning patients with chronic kidney disease. These patients typically have an impaired immune response and, as a consequence, have a high risk of severe complications from COVID-19, respond sub-optimally to vaccines, and are vulnerable to any future COVID-19 waves or another pandemic. This article in particular focuses on the issues related to the timely generation of robust evidence and draws lessons from the European Renal Association COVID-19 Database (ERACODA) collaboration. This project was initiated and in part funded by the European Renal Association (ERA) in March 2020 to understand the prognosis of COVID-19 in patients on KFRT. ERACODA became a collaborative project of 225 nephrologists from 33 mostly European countries, who entered granular data on patients and disease characteristics and several outcomes of more than 4500 patients on KFRT with

COVID-19. Details can be found at https://www.eracoda.org. Since its inception two and a half years ago the results of ERA-CODA have been reported in more than 15 manuscripts. This article discusses the challenges in obtaining high-quality data in the early phase of the pandemic, and its consequences for the analysis and interpretation of these data. In addition, it makes recommendations for improvement to ensure preparedness for future pandemics.

CHALLENGES IN OBTAINING HIGH-QUALITY DATA

Owing to the infectious nature of the disease and early reports of potentially high risk of severe complications from COVID-19 in patients with chronic kidney disease [1–3], there was unprecedented urgency in understanding the vulnerability of kidney patients to getting infected with COVID-19 and its consequences. The nephrology community made tremendous efforts in responding to this urgency which led to multiple well-intentioned initiatives [4–6]. However, a detailed and robust understanding of the implications of COVID-19 required high-quality data that should typically represent a sample of a well-defined target population of individuals with and without kidney disease with detailed information on COVID-19 diagnosis, symptoms, treatment and consequences collected systematically over time. Unfortunately, this proved challenging for several reasons (Table 1).

P. Vart *et al.*

First, it took a long time before data became available that originated from a robust population-wide screening and systematic collection of data on the diagnosis of COVID-19, disease symptoms, treatment and patient outcomes in any of the European countries [7]. This was in part due to the limited availability of diagnostic tests at the start of the pandemic [8], but also to the lack of a clear health data architecture. Even within a single country, it occurs that different agencies collect and store different data in different formats with different regulations for data protection and patient privacy. The European Union (EU) General Data Protection Regulation, which is interpreted in different ways across EU countries, makes it often difficult to link multiple data sources. Besides, there are no established pathways for collaboration among ongoing disease surveillance networks, government entities, health bodies, nephrological societies, kidney registries and researchers within and between different countries [9–11]. While all kinds of data may be needed to prevent, detect, alert and respond to COVID-19, the lack of common data architecture and required collaboration hindered our response to COVID-19.

Second, although existing kidney registries and electronic health records proved instrumental in our response to COVID-19, they were often limited in their completeness and accuracy. For instance, national kidney disease registries, like other disease registries, were limited in data on treatment, disease severity and clinical characteristics of patients (e.g. data on hospitalization for COVID-19 were available but data on rehabilitation or recovery were not), and thus were not ideal resources for studying the disease course of COVID-19. Importantly, kidney disease registries comprise mainly patients on KFRT and have limited to no data on patients with earlier stages of chronic kidney disease. Similarly, electronic health records such as those originating from primary care were incomplete on some key risk factors, such as body mass index and Clinical Frailty Score, which were identified as one of the main risk factors for poor outcomes from COVID-19 in the general population [12, 13]. Inaccuracy in the recording of comorbidities and COVID-19-related deaths in electronic health records has also been well documented [14, 15], and limited the quality of the data.

Ultimately, the urgency of the situation, lack of clear and complete data architecture, and inadequate collaboration led to the initiation of multiple well-intentioned but poorly resourced, uncoordinated and sometimes poor-quality efforts to collect data or use existing data. This contributed to a significant waste of manpower and expertise in study design, data collection and analysis.

LIMITATIONS OF USED DATA

The aforementioned challenges impacted several aspects of the quality of collected and used data. First, the limited availability of diagnostic tests (e.g. polymerase chain reaction test) at the start of the pandemic impacted the generalizability of findings from early studies and our ability to assess the true burden of the disease, including the total number of kidney patients with COVID-19 at a given time and the actual rate of poor outcomes. At the start of the COVID-19 pandemic, diagnostic tests were only available for patients with severe symptoms who were tested for COVID-19 upon a visit to a healthcare facility. As a result, the early studies investigating prognosis in patients with COVID-19 were only able to include such patients and consequently overestimated the risk of complications from COVID-19. This was evident when patient outcomes were compared with the period when diagnostic tests were more widely available. For instance, in ERACODA and other comparable datasets [16–18], mortality rates were compared between the first and second waves of the pandemic, both dominated by the original virulent COVID-19, Alpha and Delta variants. It appeared that in dialysis patients and kidney transplant recipients, the rate of mortality was significantly lower in the second wave compared with the first wave. ERACODA had the advantage of collecting information on the reason for COVID-19 testing. When this was compared between the first two waves, the percentage of patients identified through routine screening was found to be greater in the second wave compared with the first wave. Importantly, when patients with similar disease severity were compared between the first two waves, the mortality rate between the first and second waves was comparable. This suggests that it was the increased identification of patients with the milder disease during the second wave that largely explained the differences in the risk of complications between the two waves [16].

Second, initial single-center studies were characterized by a small sample size and varying study design [18–26], which did not allow a detailed assessment of a clinical question. For example, to determine whether patients on KFRT were at higher risk of complications from COVID-19 compared with those not on KFRT, matching of KFRT and non-KFRT subjects on key factors including age, sex and several comorbidities was needed and, thus, required a larger sample size compared with what can typically be collected in a single-center study. Such studies often were also not powered to identify any subgroup of KFRT patients (e.g. by type/duration of KFRT or use of specific medication) that may be at a particularly higher or lower risk of complications compared with non-KFRT patients. Moreover, because there was no well-defined or even ill-defined common strategy on how to collect data, studies differed, among others, in the case definition of COVID-19, hospitalization thresholds, definitions and availability of relevant comorbidities and complications, and data format [27, 28]. Importantly, studies also differed in the period of data collection, which is especially relevant for infectious diseases due to the continuous emergence of new viral strains with varying degrees of infectivity and fatality rate [29]. Therefore, combining such studies from different centers in meta-analyses and systematic reviews was challenging.

Third, the urgency of the situation, limited resources and limited clinical information in available data sources forced most investigators to obtain convenience samples and include patients for whom data were easily accessible, for example, patients visiting hospitals. In such studies comparison of different patient groups, such as dialysis patients and kidney transplant recipients, becomes difficult because these groups

visit hospitals for different reasons and with different frequencies and as a result differ in their likelihood of being included in a study. For instance, most hemodialysis patients visit a hospital three times a week, and COVID-19 testing was done once every week or sometimes on every visit to the dialysis ward. In contrast, many transplant recipients visit their institution only once every 3 months, and testing is then done only in case of complaints. The chances of dialysis patients being diagnosed with COVID-19 are therefore inherently higher, although in many cases it can be mild or even asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This contributed to challenges in answering some of the most pertinent clinical questions at that time, namely whether the risk of a poor outcome of COVID-19 differed between patients treated with dialysis versus kidney transplant recipients. Additionally, in such studies differences in the testing for COVID-19 in dialysis patients and kidney transplant recipients made it difficult to determine whether patients who recently received kidney transplantation were at higher risk of complications from COVID-19 compared with dialysis patients on a waiting list for transplantation. Consequently, the evidence necessary to decide whether transplant programs should continue or discontinue during the height of the pandemic was rather suboptimal. In the same vein, studies relying on existing electronic health records reported limited to no information on patients with early stages of chronic kidney disease, largely due to inadequate and inaccurate flagging of patients with early-stage kidney disease in these records. As a result, this group of patients remained largely underserved throughout the pandemic.

Fourth, in ERACODA and similar other multi-center and/or multi-national initiatives [30, 31], treating physicians and nurses were requested to voluntarily record data of patients with COVID-19. At the start of the pandemic when the burden of healthcare was at its peak, it was not always possible to collect detailed information on patients and disease characteristics. To limit the burden on participating physicians and nurses, ERACODA shortened its questionnaire on multiple occasions and often at the expense of leaving out relevant questions related to treatment and patient prognosis (e.g. questions related to the use of immunosuppressants and reasons for change, change in KFRT during hospital admission, course of kidney function after a diagnosis of COVID-19 and cause of death). Furthermore, as the pandemic progressed and more clinical questions emerged, such as the potential risk of thrombosis and acute kidney injury from COVID-19, it was not possible to collect such information without risking the loss of participation because of an increased burden on already strained healthcare professionals.

Finally, even well-resourced efforts aimed at developing vaccines or finding treatments for COVID-19 included only small numbers of patients with kidney disease and could therefore not demonstrate efficacy by kidney disease status [32, 33]. Moreover, these trials often did not include patients on immunosuppressive therapy. This was a major concern for patients and treating physicians alike, because many patients on KFRT, especially kidney transplant recipients,

are on long-term immunosuppressive therapy. Consequently, despite suboptimal evidence of vaccine efficacy, the same vaccination regime was followed for kidney patients as for the general population [34]. Later studies demonstrated lower seroresponse rates to COVID-19 vaccination in these patients compared with individuals from the general population and prompted policy changes to extend the routine vaccination series to include three primary doses in these patients. Unfortunately, these studies also suffered from the consequences of uncoordinated efforts. For instance, multiple studies started in Europe to investigate the efficacy of COVID-19 vaccination in patients with kidney disease [35]. Although there is value in having multiple studies with diverse approaches, multiple studies with similar conditions and often with suboptimal study design (e.g. lack of a control group) were also conducted when the efficacy of the vaccine in kidney patients was already known. At the same time, there were fewer empirical studies examining interventions of immediate clinical relevance, e.g. improving the effectiveness of vaccinations, and assessing the efficacy of dexamethasone and tocilizumab as treatments for COVID-19 in patients with impaired kidney function or using immunosuppressants [36].

SHORTCOMINGS OF USED STUDY DESIGNS AND ANALYTIC APPROACHES

Intervention studies and observational studies are two main modes of generating evidence-based information for clinical practice. Intervention studies conducted with traditional approaches to identify effective prevention and treatment strategies generally take many months if not years to complete. This is in part due to the challenge to integrate trial procedures with usual patient care, which requires efforts from healthcare staff at a participating center. In case of a health emergency of the nature of COVID-19, the need for a vaccine and treatment is urgent while the healthcare staff is already tremendously burdened with the surge of patients needing immediate care. Furthermore, traditionally the exposure of the nephrology community to pragmatic clinical trials has been limited compared with other disciplines [37]. As a consequence, at the start of the pandemic, it was mainly the observational studies that informed clinical practice. The challenges in obtaining robust data and the inherent limitations of observational studies increased the risk of biased findings and ultimately compromised the investigation of several critical clinical questions that could inform patient management (Table 1).

Clinicians faced a dilemma in deciding whether or not to modulate immunosuppressant use in kidney transplant patients with COVID-19 because of the potential risk of graft rejection when tapering immunosuppression and the risk of severe COVID-19 complications when not tapering this medication. To this end, several studies compared prognosis in patients with and without modulation of immunosuppressants using traditional analytic approaches. Because the decision to taper immunosuppressant use was often related to the severity of the disease (i.e. confounding by indication), it is difficult to judge whether it was the change in immunosuppressant use or the change in the underlying health condition of a
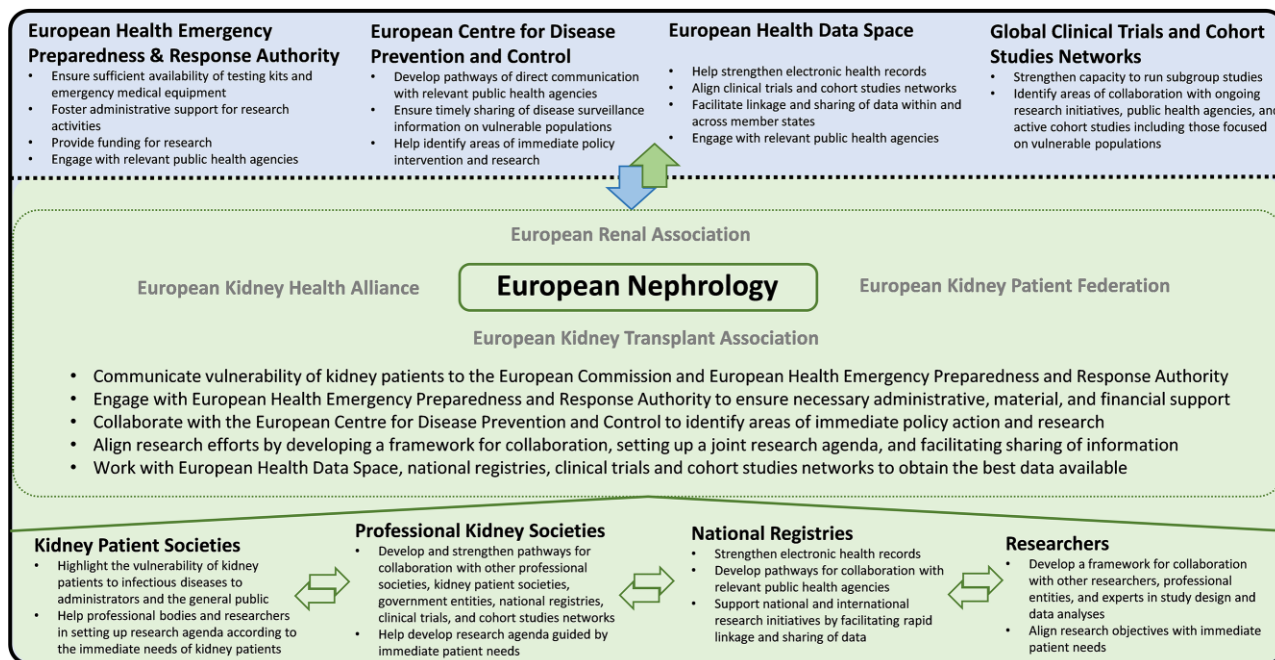
Figure 1: Key stakeholders and their suggested roles in ensuring timely and robust evidence for clinical management of kidney patients during a pandemic.

patient that was related to the prognosis in these patients [38]. Instrumental variable analysis [39] or a comparison of data from centers where immunosuppressant use was not changed with centers where immunosuppressant use was modulated in all patients irrespective of underlying disease severity could be more informative. However, answering such clinical questions was further complicated by the fact that patients were on multiple immunosuppressants and different immunosuppressants were modulated for different patients for different reasons. Unfortunately, an instrumental variable analysis by different patient subgroups in small studies does not allow a valid inference, and descriptive statistics in these studies are prone to bias. Centers modulating immunosuppressants independent of disease severity were also not commonplace.

The risk of COVID-19 complications was anticipated to be greater in kidney transplant recipients compared with dialysis patients because of the possible inability of mounting a satisfactory immune response owing to the use of immunosuppressants. However, due to more frequent testing of COVID-19 in hemodialysis patients (especially in-center hemodialysis patients), these patients were not only more likely to be identified with a mild disease as described above, but they were also more likely to be identified earlier in their disease course. Most studies that compared kidney transplant recipients and dialysis patients in their time-to-event analysis started patient follow-up from the date of diagnosis. In such studies, the analysis was likely influenced by lead-time bias [40] towards the lower risk of poor outcomes in dialysis patients compared with kidney transplant recipients.

Identifying risk factors for getting infected with COVID-19, or identifying prognostic factors in those infected with COVID-19, was particularly problematic in studies including only hospitalized patients. In such studies chances of findings

associations that do not exist in the target population are generally high (i.e. collider bias) [41]. For instance, the observed association between smoking and COVID-19 infection in hospitalized patients may not be an accurate impression of their true association in the general population. To make this clear, suppose that patients are admitted to the hospital for one of two reasons: smoking-related illness or COVID-19. Performing COVID-19 tests on these hospitalized individuals will likely show lower infection rates among smokers than among non-smokers because the former group can also be hospitalized for a smoking-related illness and not necessarily COVID-19.

RECOMMENDATIONS

Now, almost 3 years since the start of the COVID-19 pandemic, can we say that we are optimally prepared to obtain the right numbers and information to respond in a timely manner to the next pandemic? Nothing could be less true. Additional steps are needed to generate a timely and well-informed response that can aid in the protection of kidney patients from the next pandemic (Table 1, Fig. 1).

First, it is critical to ensure that our efforts in tackling any future health crisis for patients with kidney disease are aligned. In Europe, the ERA may take a central role in engaging with the EU task force for pandemic response, the newly created European Health Emergency Preparedness and Response Authority [42], and other European initiatives. Furthermore, it could engage with the various national health bodies, nephrological societies and kidney registries, but also with researchers and patients. In this role, the ERA together with other representative bodies, such as the European Kidney Health Alliance and European Kidney Patients' Federation, can

help in communicating issues specifically related to patients with kidney disease to the European Commission and can help generate necessary support (administrative, material and financial). The ERA could work with the European Center for Disease Prevention and Control to directly obtain emerging information on infectious diseases in patients with kidney disease, which can be relayed to the wider nephrology community to identify areas of immediate policy intervention and research. The ERA could also engage with research initiatives within and outside Europe and with the International and American Societies of Nephrology (ISN and ASN) and other professional bodies (e.g. European Kidney Transplant Association) to help align efforts via the development of standardized research protocols and to facilitate sharing of information. The ERA may already initiate a dialogue among stakeholders, identify resources (infrastructure and personnel), and help define roles and responsibilities for organizations and individuals so that the pitfalls of small localized efforts can be avoided and a roadmap of response to any next public health emergency of international concern is in place.

Second, the linkage of relevant data sources is critical and should be facilitated. The National Health Service data structure in the UK, which allowed secure linkage and transparent use of data from registries, primary care, secondary care and other relevant health records across four nations of the UK, has shown the immense importance of combining a rich set of datasets in generating swift and reliable evidence for clinical practice. For the useful linkage of relevant data sources, existing data sources also need to be strengthened for completeness, accuracy and data harmonization. Among others, existing registries need to be supplemented with a systematic recording of patients with early-stage kidney disease. These patients constitute the largest proportion of patients with kidney disease and are also at increased risk of complications from infectious diseases [43, 44]. Periodic quality control exercises and involving patients in the review of their health records can be considered for improving data quality. To execute these tasks, central data governance within a country and at the European level is needed, which can help with issues related to patient privacy, harmonization of collected data across different sources and quality control. The recent establishment of the European Health Data Space is a welcome step in this direction [25].

Third, pre-defined and already consented cohorts of engaged patients together with technological advancements (e.g. web applications for real-time recording of symptoms especially in self-isolating patients) can be utilized for a more detailed assessment of clinical questions. A new pan-European project named Connecting European Cohorts to Increase Common and Effective Response to SARS-CoV-2 Pandemic (ORCHESTRA) has been established on similar principles to rapidly advance the knowledge of the effects and treatment of COVID-19 [45]. Similarly, collaboration with existing platforms specifically designed in anticipation of a pandemic can be established in collecting timely, detailed and well-harmonized data for kidney patients. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [46] is a good example of such a platform. ISARIC is a global network of clinical research in infectious diseases. Its existing infrastructure allows clinical data and biological samples to be collected rapidly in a globally harmonized manner, which was effectively utilized in response to the COVID-19 pandemic in the UK.

Fourth, global trials may collaborate with consenting national kidney disease registries to ensure the inclusion of a sufficient number of patients with kidney disease for the assessment of the efficacy–adverse events ratio of novel vaccines and treatments in the general population. Pragmatic clinical trials can also be implemented in identifying novel treatments for patients with kidney disease. In such trials, a treatment can be added or removed as evidence emerges, or subcategories of patients can be added that were initially not considered. Pragmatic clinical trials are not only suitable for a wide range of settings, e.g. for different types of patients, and differences in care across healthcare facilities and treating physicians, but also minimize the burden on front-line hospital staff working within an overstretched care system during a major pandemic. The RECOVERY trial which started in March 2020 in the UK is now a global trial and has emerged as an example of such a pragmatic trial design that has been immensely successful in providing high-quality evidence for the treatment of COVID-19 in a relatively short time [47].

Fifth, the engagement of experts in study design and analysis can help avoid the pitfalls of complex data [48] and improve efficiency. Such experts should be engaged early at the design stage of a study. The RECOVERY trial also demonstrates the benefits of involving experts in study design and analysis who were able to adapt trial design such that it interfered the least possible amount with routine care during the pandemic while not compromising the methodological robustness of the trial [47].

Finally, evidence that is generated is only useful once it is effectively assessed, communicated and implemented. For evidence assessment in real time, dedicated multiple task forces can be formed, with each working group composed of clinicians specialized in a clinical discipline (e.g. dialysis) and research methodologists. These task forces will be tasked to judiciously assess the clinical evidence, to clearly mark the quality of evidence and to translate this evidence into actionable recommendations in real time. The ERA may take the lead in forming these working groups. For evidence dissemination, there is a need to establish a central resource (e.g. a website) of information for patients with kidney disease and clinicians. Active efforts should be made (e.g. via communication with scientific societies and patients or via advertisements) about the existence of such resources. This resource should be regulated and regularly updated by clinical and methodological experts based on the critical evaluation of emerging evidence to ensure accurate transmission of information to, both, patients and clinicians.

CONCLUSIONS

Patients with kidney disease are particularly vulnerable to any future pandemic of an infectious nature. Our response to

the COVID-19 pandemic has highlighted gaps in generating timely and robust evidence for informed management of patients with kidney disease. To ensure our preparedness for the next pandemic in Europe, there is a need to align different research initiatives, strengthen electronic health records for completeness, accuracy and linkage, and involve experts in efficient study design and appropriate use of data. To achieve these objectives, the ERA may take a central role in communicating the vulnerability of patients with kidney disease to infectious disease to administrators and in aligning research initiatives via its engagement with other scientific societies, national registries and researchers.

REFERENCES

1. Cheng Y, Luo R, Wang K et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829–38. http://dx.doi.org/10.1016/j.kint.2020.03.005.
2. Alberici F, Delbarba E, Manenti C et al. Brescia Renal COVID Task Force. Management of patients on dialysis and with kidney transplantation during the SARS-CoV-2 (COVID-19) pandemic in Brescia, Italy. Kidney Int Rep 2020;5:580–5. http://dx.doi.org/10.1016/j.ekir.2020.04.001.
3. La Milia V, Bacchini G, Bigi MC et al. COVID-19 outbreak in a large hemodialysis center in Lombardy, Italy. Kidney Int Rep 2020;5:1095–9. http://dx.doi.org/10.1016/j.ekir.2020.05.019.
4. Pascual J, Melilli E, Jiménez-Martín C et al. Spanish Society of Nephrology COVID-19 Group. COVID-19-related mortality during the first 60 days after kidney transplantation. Eur Urol 2020;78:641–3. http://dx.doi.org/10.1016/j.eururo.2020.06.036.
5. Jager KJ, Kramer A, Chesnaye NC et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int 2020;98:1540–8. http://dx.doi.org/10.1016/j.kint.2020.09.006.
6. Hilbrands LB, Duivenvoorden R, Vart P et al. Erratum to: COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant 2021;36:1962. http://dx.doi.org/10.1093/ndt/gfab028.
7. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-population-wide-testing-country-experiences.pdf (18 June 2022, date last accessed).
8. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32020H1595 (18 June 2022, date last accessed).
9. Clemens T, Brand H. Will COVID-19 lead to a major change of the EU Public Health mandate? A renewed approach to EU's role is needed. Eur J Public Health 2020;30:624–5. http://dx.doi.org/10.1093/eurpub/ckaa103.
10. Bump JB, Friberg P, Harper DR. International collaboration and covid-19: what are we doing and where are we going? BMJ 2021;372:n180. http://dx.doi.org/10.1136/bmj.n180.
11. Kickbusch I, Leung GM, Bhutta ZA et al. Covid-19: how a virus is turning the world upside down. BMJ 2020;369:m1336. http://dx.doi.org/10.1136/bmj.m1336.
12. Sablerolles RSG, Lafeber M, van Kempen JAL et al. COMET research team. Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study. Lancet Healthy Longev 2021;2:e163–70. http://dx.doi.org/10.1016/S2666-7568(21)00006-4.
13. Gao M, Piernas C, Astbury NM et al. Associations between body-mass index and COVID-19 severity in 6.9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol 2021;9:350–9. http://dx.doi.org/10.1016/S2213-8587(21)00089-9.
14. Majeed A, Car J, Sheikh A. Accuracy and completeness of electronic patient records in primary care. Fam Pract 2008;25:213–4. http://dx.doi.org/10.1093/fampra/cmn047.
15. Vart P, Jager KJ, Arnol M et al. COVID-19 pandemic waves and mortality among patients on kidney replacement therapy. Kidney Int Rep 2022;7:2091–6. doi: 10.1016/j.ekir.2022.06.007. http://dx.doi.org/10.1016/j.ekir.2022.06.007.
16. Williamson EJ, Walker AJ, Bhaskaran K et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6. http://dx.doi.org/10.1038/s41586-020-2521-4.
17. Heldman MR, Kates OS, Safa K et al. UW COVID-19 SOT Study Team. Changing trends in mortality among solid organ transplant recipients hospitalized for COVID-19 during the course of the pandemic. Am J Transplant 2022;22:279–88. http://dx.doi.org/10.1111/ajt.16840.
18. Villanego F, Mazuecos A, Pérez-Flores IM et al. Spanish Society of Nephrology COVID-19 Group. Predictors of severe COVID-19 in kidney transplant recipients in the different epidemic waves: analysis of the Spanish Registry. Am J Transplant 2021;21:2573–82. http://dx.doi.org/10.1111/ajt.16579.
19. Georgery H, Devresse A, Scohy A et al. The second wave of COVID-19 disease in a kidney transplant recipient cohort: a single-center experience in Belgium. Transplantation 2021;105:e41–2. http://dx.doi.org/10.1097/TP.0000000000003596.
20. Schmidt-Lauber C, Spoden M, Huber TB et al. Increased rejection rates in kidney transplantations during the COVID-19 pandemic. Transpl Int 2021;34:2899–902. http://dx.doi.org/10.1111/tri.14114.
21. Felldin M, Søfteland JM, Magnusson J et al. Initial report from a Swedish High-volume transplant center after the first wave of the COVID-19 pandemic. Transplantation 2021;105:108–14. http://dx.doi.org/10.1097/TP.0000000000003436.
22. Goicoechea M, LA Sánchez Cámara, Macías N et al. COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. Kidney Int 2020;98:27–34. http://dx.doi.org/10.1016/j.kint.2020.04.031.
23. Gameiro J, Fonseca JA, Oliveira J et al. Acute kidney injury in hospitalized patients with COVID-19: a Portuguese cohort. Nefrologia 2021;41:689–98. http://dx.doi.org/10.1016/j.nefro.2021.04.002.
24. Fontana F, Giaroni F, Frisina M et al. SARS-CoV-2 infection in dialysis patients in northern Italy: a single-centre experience. Clin Kidney J 2020;13:334–9.
25. Elec AD, Oltean M, Goldis P et al. COVID-19 after kidney transplantation: early outcomes and renal function following antiviral treatment. Int J Infect Dis 2021;104:426–32. http://dx.doi.org/10.1016/j.ijid.2021.01.023.
26. Ślusarczyk A, Tracz A, Gronkiewicz M et al. Outcomes of COVID-19 in hospitalized kidney and liver transplant recipients: a single-center experience. Pol Arch Intern Med 2021;131:16070.
27. https://www.europarl.europa.eu/RegData/etudes/STUD/2021/690009/EPRS_STU(2021)690009_EN.pdf (7 July 2022, date last accessed).
28. Mahalingasivam V, Su G, Iwagami M et al. COVID-19 and kidney disease: insights from epidemiology to inform clinical practice. Nat Rev Nephrol 2022;18:485–98. http://dx.doi.org/10.1038/s41581-022-00570-3.
29. Noordzij M, Duivenvoorden R, Pena MJ et al. Collaborative ERACODA authors. ERACODA: the European database collecting clinical information of patients on kidney replacement therapy with COVID-19. Nephrol Dial Transplant 2020;35:2023–5. http://dx.doi.org/10.1093/ndt/gfaa179.

30. Jones TC, Biele G, Mühlemann B *et al.* Estimating infectiousness throughout SARS-CoV-2 infection course. *Science* 2021;**373**:eabi5273. http://dx.doi.org/10.1126/science.abi5273.

31. Polack FP, Thomas SJ, Kitchin N *et al.* C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;**383**:2603–15. http://dx.doi.org/10.1056/NEJMoa2034577.

32. Kates OS, Haydel BM, Florman SS *et al.* UW COVID-19 SOT Study Team. Coronavirus disease 2019 in solid organ transplant: a multicenter cohort study. *Clin Infect Dis* 2021;**73**:e4090–9. http://dx.doi.org/10.1093/cid/ciaa1097.

33. Baden LR, El Sahly HM, Essink B *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;**384**:403–16. http://dx.doi.org/10.1056/NEJMoa2035389.

34. Sanders JF, Bemelman FJ, Messchendorp AL *et al.*; RECOVAC Collaborators. The RECOVAC Immune-response study: the immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. *Transplantation* 2022;**106**:821–34. http://dx.doi.org/10.1097/TP.0000000000003983.

35. de Boer IH, Kovesdy CP, Navaneethan SD *et al.* American Society of Nephrology Chronic Kidney Disease Advisory Group. Pragmatic clinical trials in CKD: opportunities and challenges. *J Am Soc Nephrol* 2016;**27**:2948–54. http://dx.doi.org/10.1681/ASN.2015111264.

36. Geetha D, Kronbichler A, Rutter M *et al.* Impact of the COVID-19 pandemic on the kidney community: lessons learned and future directions. *Nat Rev Nephrol* 2022;**18**:724–37.

37. Glenn DA, Hegde A, Kotzen E *et al.* Systematic review of safety and efficacy of COVID-19 vaccines in patients with kidney disease. *Kidney Int Rep* 2021;**6**:1407–10. http://dx.doi.org/10.1016/j.ekir.2021.02.011.

38. Fang G, Brooks JM, Chrischilles EA. Comparison of instrumental variable analysis using a new instrument with risk adjustment methods to reduce confounding by indication. *Am J Epidemiol* 2012;**175**:1142–51. http://dx.doi.org/10.1093/aje/kwr448.

39. Schoot TS, Kerckhoffs APM, Hilbrands LB *et al.* Immunosuppressive drugs and COVID-19: a review. *Front Pharmacol* 2020;**11**:1333. http://dx.doi.org/10.3389/fphar.2020.01333.

40. Morrison AS. The effects of early treatment, lead time and length bias on the mortality experienced by cases detected by screening. *Int J Epidemiol* 1982;**11**:261–7. http://dx.doi.org/10.1093/ije/11.3.261.

41. Griffith GJ, Morris TT, Tudball MJ *et al.* Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 2020;**11**:5749. http://dx.doi.org/10.1038/s41467-020-19478-2.

42. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12870-European-Health-Emergency-Preparedness-and-Response-Authority-HERA-_en (21 July 2022, date last accessed).

43. Naqvi SB, Collins AJ. Infectious complications in chronic kidney disease. *Adv Chronic Kidney Dis* 2006;**13**:199–204. http://dx.doi.org/10.1053/j.ackd.2006.04.004.

44. Appelman B, Oppelaar JJ, Broeders L *et al.* CovidPredict Study Group. Mortality and readmission rates among hospitalized COVID-19 patients with varying stages of chronic kidney disease: a multicenter retrospective cohort. *Sci Rep* 2022;**12**:2258. http://dx.doi.org/10.1038/s41598-022-06276-7.

45. Rinaldi E, Stellmach C, Rajkumar NMR *et al.* Harmonization and standardization of data for a pan-European cohort on SARS-CoV-2 pandemic. *NPJ Digit Med* 2022;**5**:75. http://dx.doi.org/10.1038/s41746-022-00620-x.

46. https://isaric.org/ (21 July 2022, date last accessed).

47. https://www.recoverytrial.net/ (21 July 2022, date last accessed).

48. Noordzij M, Vart P, Duivenvoorden R *et al.* Pitfalls when comparing COVID-19-related outcomes across studies-lessons learnt from the ERACODA collaboration. *Clin Kidney J* 2021;**14**:i14–20. http://dx.doi.org/10.1093/ckj/sfab027.