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Systematic Review of Safety and Efficacy of COVID-19 Vaccines in Patients With Kidney Disease

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Chronic kidney disease (CKD) affects 37 million or 15% of the U.S. population and 2 in every 1000 Americans are on dialysis or living with a kidney transplant.[1] In 2020, coronavirus disease 2019 (COVID-19) infection became the third leading cause of death for persons 45 through 84 years of age, and individuals with kidney disease are recognized as being at higher risk for severe complications from COVID-19 infection.[2,S1] While vaccination is a powerful and cost-effective method to reduce infection-related morbidity and mortality, vaccine efficacy has historically not been rigorously studied in individuals with CKD, and COVID-19 vaccine immunogenicity is largely unknown in this high-risk population. Numerous clinical trials of candidate COVID-19 vaccines have been undertaken; however, it is unknown whether results are generalizable to individuals living with kidney disease, in particular those on dialysis or receiving chronic immunosuppression for treatment of glomerulonephritis or kidney transplantation. We sought to systematically review registered COVID-19 vaccine clinical trials for inclusion of criteria relevant to individuals with kidney disease (Supplementary Methods).

RESULTS

As of December 6, 2020, we screened 342 registered COVID-19 vaccine clinical trials (142 from ClinicalTrials.gov[S2] and 200 from the WHO Clinical Trial database[S3]). Excluded trials included: 118 duplicate trials, 52 trials repurposing non–COVID-19 vaccines (e.g., Bacillus Calmette-Guerin vaccine), and four trials studying vaccination for nonprimary prevention of COVID-19 (Figure 1). Trial characteristics of the resulting 123 unique COVID-19 vaccine trials are displayed in Table 1.

Any CKD was explicitly excluded from 16% of trials, "serious renal disease" from 33% of trials, and left to "investigator discretion" in an additional 46% of trials. Few studies used a specific estimated glomerular filtration rate threshold of ≥60 ml/min/1.73 m^2 to determine eligibility (6%). In phase 3 trials specifically, 39.4% included patients with any or mild/moderate CKD, with the remaining 60.6% of trials leaving the window open for their exclusion. Individuals receiving immunosuppression for maintenance of a kidney transplant or treatment of an underlying glomerular disease were excluded from 78% of non–live attenuated trials and all live-attenuated trials (n = 3). Exclusion was not explicit in the remaining trials. Similarly, individuals with an immunocompromising disease were excluded from 86% of trials, with the remaining trials having unclear or absent criteria for those with immunocompromising health conditions. In phase 3 trials, 93.5% excluded patients with immunocompromising conditions and 64.5% excluded those on any immunosuppression, and an additional 32.3% excluding any immunosuppression other than low-dose (10 to 20 mg/day) prednisone. Two recently published phase 3 trials of severe acute respiratory syndrome coronavirus 2 vaccines now in clinical use are illustrative of the lack of clarity and inclusion of patients with kidney disease. Pfizer's trial of BNT162b2 included participants with stable chronic medical conditions; however, only 0.7% of randomized subjects (n = 256) had "renal disease"; a proportion well below the 15% CKD prevalence in the general population.[3] Moderna's trial of the mRNA-1273 vaccine also included participants with stable chronic medical

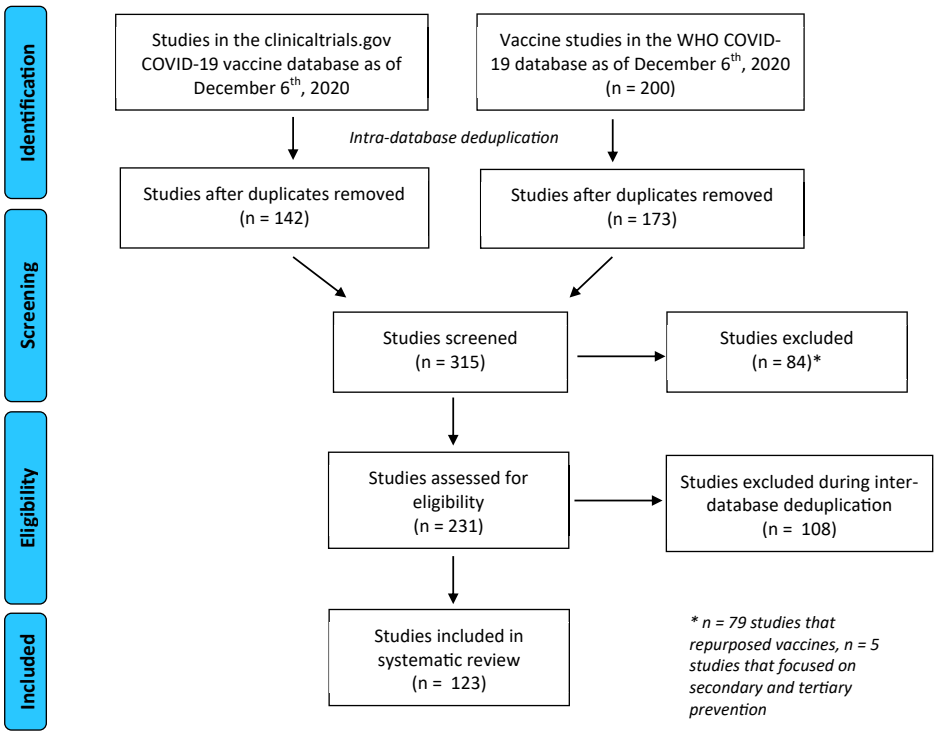

Figure 1. Summary of vaccine trial search and selection. CT, clinical trials; COVID-19, coronavirus disease 2019.

conditions, but has not released data about the prevalence of participants with kidney disease.[4]

Immunocompromised subjects were excluded from both trials. A recently announced phase 3 trial investigating Novavax's candidate vaccine, NVX-CoV2373, will not exclude prospective participants with stable CKD (NCT04611802), although those receiving chronic immunosuppressants are excluded.

DISCUSSION

Our findings suggest that inclusion of patients with kidney disease in completed and ongoing COVID-19 vaccine studies remains low, with the majority of trials explicitly excluding individuals with "severe" or "chronic" kidney disease and those receiving immunosuppression. Few trials specify an estimated glomerular filtration rate cutoff or CKD stage below which individuals were excluded, leaving room for investigator discretion and lack of clarity for providers to counsel their patients. Our findings have several important implications. First, the low inclusion rates of patients with kidney disease continue to perpetuate the dearth of data on vaccine immunogenicity, efficacy, and safety in the kidney disease population. The Centers for Disease Control and Prevention recommends that individuals with high-risk medical conditions, including those with CKD and those immunocompromised from solid organ transplants, be prioritized for vaccination, without any data on COVID-19 vaccine efficacy in these populations.[5] Currently, trials are underway to study COVID-19 vaccine response in children who were excluded from the original studies and the same should occur for patients with CKD and/or immunosuppressed status. Second, the low rates of CKD inclusion in trials may further exacerbate disparities already pervasive in the pandemic. In the United States, African-Americans and Latinos bear a disproportionate burden of both CKD and of mortality due to COVID-19.[6] Without the evidence base to guide vaccination programs in patients with kidney disease, this population could potentially experience lower vaccine effectiveness and hence perpetuate racial and ethnic disparities in COVID-19 disease burden.

Existing observational cohorts of patients receiving immunosuppression should strongly consider evaluating vaccine immunogenicity, as large-scale vaccination may make future placebo-controlled studies challenging. Moreover, vaccine immunogenicity and effectiveness at standard vaccine doses and dosing regimens may not yield protective or sustained immune responses in immunosuppressed individuals.[7,8,S4] Likewise, test characteristics of assays to evaluate COVID-19 vaccine immunogenicity have been shown to differ between immunosuppressed transplant recipients and the general population, suggesting that neutralizing titers and/or T-cell–based techniques may need to be used to fully understand vaccine immunogenicity in this population.[9]

Table 1. Trial Characteristics of 123 COVID-19 Vaccine Studies Included in the Analysis

	All Trials	Phase 1	Phase 2	Phase 3
N (%)	123 (100)[a]	78 (63.4)	59 (48.0)	33 (26.8)
Continent of participants				
Africa	2 (1.6)	2 (2.6)	1 (1.7)	0 (0)
Asia	55 (44.7)	37 (47.4)	31 (52.5)	10 (30.3)
Australia	6 (4.9)	6 (7.7)	2 (3.4)	0 (0)
Europe	23 (18.7)	13 (16.7)	10 (16.9)	8 (24.2)
North America	29 (23.6)	20 (25.6)	14 (23.7)	8 (24.2)
South America	8 (6.5)	0 (0)	1 (1.7)	7 (21.2)
Type of vaccine				
Live attenuated	3 (2.4)	1 (1.3)	1 (1.7)	2 (6.1)
Inactivated	18 (14.6)	8 (10.2)	9 (15.3)	9 (27.3)
mRNA	18 (14.6)	11 (14.1)	10 (16.9)	4 (12.1)
DNA	12 (9.8)	10 (12.8)	7 (11.9)	2 (6.1)
Replicating viral vector	8 (6.5)	7 (9.0)	4 (6.8)	0 (0)
Nonreplicating viral vector	34 (27.6)	18 (23.1)	14 (23.7)	12 (36.3)
Protein subunit	28 (22.8)	22 (28.2)	13 (22.0)	3 (9.1)
Virus-like particles	2 (1.6)	1 (1.3)	1 (1.7)	1 (3.0)
CKD exclusion				
Patients with GFR <60 ml/min/1.73 m^2	7 (5.7)	5 (6.4)	3 (5.0)	2 (6.1)
All patients with CKD	17 (13.8)	14 (17.9)	8 (13.6)	1 (3.0)
Patients with serious kidney disease	41 (33.3)	27 (34.6)	21 (35.6)	11 (33.3)
Per investigator discretion based on chronic condition	56 (45.5)	32 (41.0)	27 (45.8)	17 (51.5)
Patients with CKD not excluded	2 (1.6)	0 (0)	0 (0)	2 (6.1)
Exclusion from non–live attenuated studies				
Patients with immunosuppressive conditions	103 (85.8)	65 (84.4)	48 (82.8)	29 (93.5)
Patients with immunosuppressive conditions not excluded	6 (5.0)	3 (3.9)	3 (5.2)	1 (3.2)
Unclear if patients with immunosuppressive conditions are excluded	11 (9.2)	9 (11.7)	7 (12.0)	1 (3.2)
Patients on any immunosuppressive medications	94 (78.3)	63 (81.8)	49 (84.5)	20 (64.5)
Patients on immunosuppressive medications other than low-dose steroids	21 (17.5)	10 (13.0)	7 (12.1)	10 (32.3)
Patients on immunosuppressive medications not excluded	3 (2.5)	2 (2.6)	1 (1.7)	1 (3.2)
Unclear if patients on immunosuppressive medications are excluded	2 (1.7)	2 (2.6)	1 (1.7)	0 (0)

Values shown are n (%).
[a]Forty-six discrete database enrollments covered more than one phase.

Glomerular Disease

Individuals with glomerular disease represent 7% to 16% of the ~37 million Americans with CKD.[S5] This population has unique risk factors for infection, including prolonged exposure to immunosuppressive medications, systemic inflammation, altered immune cell function, and urinary loss of immunoglobulin and complement factors. As a result, infections requiring health care use occur at a rate approximately 30 times higher among individuals with glomerular diseases compared to the general U.S. population, with lower respiratory infections comprising ~25% of such infections.[S6] Research priorities for COVID-19 vaccination in this patient population should include an investigation of the effect of systemic inflammation, nephrotic-range proteinuria, and immunosuppression exposure, both at the time of vaccination and during disease relapse, on severe acute respiratory syndrome coronavirus 2 immunity.

Transplant Population

As of 2017, 222,820 people in the United States were living with a kidney transplant.[S7] Considerations in immunization programs for solid organ transplant recipients include increased risk of infectious complications of vaccine preventable illnesses, timing of immunization in relation to transplantation, the potential for waning titers of serologic evidence of immunity, and low completion rates of guideline-recommended immunizations both pre- and post-transplantation.[S8] Given the higher rates of morbidity and mortality in adult solid organ transplant recipients affected by COVID-19, and the high safety and efficacy of available U.S. Food and Drug Administration–approved COVID-19 vaccines, the benefit of vaccination is widely regarded to outweigh any theoretical risks, despite solid organ transplant recipients being largely excluded from clinical trials. Society guidelines and the Centers for Disease Control and Prevention converge in recommending adult solid organ transplant recipients receive prioritized access to immunization against COVID-19.[S9,S10,5]

DIALYSIS POPULATION

In the United States, nearly 470,000 individuals receive maintenance dialysis, with the majority choosing in-

center treatments rather than home therapies.[S7] While there is little doubt that these patients should receive the COVID-19 vaccine, there may be concern about their effectiveness based on data on the durability of the antibody response from influenza vaccines.[S11] Dialysis patients should be explicitly included in future clinical trials of COVID-19 vaccines. Furthermore, large dialysis organizations should work with the Centers for Disease Control and Prevention to develop a monitoring plan for markers of immunogenicity (much like for hepatitis B antibody titers) and for COVID-19–related hospitalizations and mortality. Dialysis organizations already have routine laboratory and clinical evaluations in place, and to not make use of this infrastructure would be a lost opportunity.

In summary, to ensure maximal trust in and uptake of novel COVID-19 vaccines, clinical trials should be designed to explicitly evaluate the immunogenicity of COVID-19 vaccines in patients with kidney disease. A safety label for patients with kidney disease is insufficient. The nephrology community must take rapid action to implement antibody titer monitoring and vaccine immunogenicity studies in CKD patients, particularly those on dialysis, with autoimmune-mediated kidney disease or receiving immunosuppressive medications. Without a timely and coordinated approach, our patients will be left behind the general population in fighting the COVID-19 pandemic.

DISCLOSURES

AM has clinical trial contracts with Boehringer Ingelheim, Calliditas, Duke Clinical Research Institute, and Pfizer, and is a consultant to Bayer. AVK was a consultant for Rockwell Medical in 2020 and received royalties from Up To Date in 2020. RF reports steering committee membership with Vertex Pharmaceuticals. EBW has received funding from Pfizer and Moderna as an investigator for severe acute respiratory syndrome coronavirus 2 vaccine and other vaccine clinical trials. DAG, EK, and AH have nothing to disclose.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary Methods and References

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