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CLINICAL RESEARCH

Systematic Review and Meta-analysis of Herpes Zoster Vaccine in Patients With CKD

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Introduction: Chronic kidney disease (CKD) is a risk factor for herpes zoster (HZ) infection. Few studies have examined HZ vaccine (HZV) in this population. We conducted a systematic review and meta-analysis investigating the efficacy and safety of HZV in patients with renal disease (CKD, dialysis, and transplant).

Methods: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases (up to May 2020) were searched for randomized controlled trials and nonrandomized controlled studies evaluating HZV in patients with CKD for effectiveness and adverse event risks. Studies without a control group (placebo or no vaccine) were excluded. Extraction of prespecified data and risk of bias assessments using the Newcastle-Ottawa scale for cohort studies and the Cochrane Risk of Bias Tool for randomized controlled trials were done by 3 authors. Random-effects meta-analysis was used to generate pooled treatment effects and 95% confidence intervals.

Results: Included were 404,561 individuals from 8 studies (3 randomized controlled trials and 5 nonrandomized). All 8 studies examined HZ as an outcome, with 3 reporting adverse events. Risk of HZ was lower in patients who received HZV compared with controls (hazard ratio, 0.55; 95% confidence interval, 0.37–0.82; $P < 0.01$); however, heterogeneity was high ($I^2 = 88\%$, $P < 0.01$). There was no significant difference in adverse events associated with HZV (hazard ratio, 1.03; 95% confidence interval, 0.54–1.28; $P = 0.8$).

Conclusions: HZV compared with control significantly lowers the risk of HZ without an increase in adverse events in CKD patients. However, significant heterogeneity was present. HZV should be actively considered in CKD patients because the prevalence of HZ is higher in this population.

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Varicella zoster virus (also known as human herpesvirus 3) commonly infects humans, causing varicella (chickenpox) during the primary infection and zoster (shingles) after a secondary reactivation.[1] After varicella, which usually occurs during childhood, varicella zoster virus becomes dormant in ganglionic neurons for life. Viral reactivation into HZ occurs in approximately 30% of patients and is triggered by a decrease in cellular immunity due to old age or medical conditions.[2]

The common clinical presentation of HZ is a dermatome-limited painful, erythematous, maculopapular rash with fluid-filled lesions that crust overtime. Among the most common complications of HZ is postherpetic neuralgia (PHN), a chronic neuropathic pain that persists for up to 3 months after HZ and can affect 30% of patients with HZ.[3–5] Other complications include ophthalmic, visceral, vascular, and neurologic complications, of which severe cases require hospitalization.[6]

HZ is a global health problem, affecting millions of people each year worldwide, with an incidence of 3 to 5/1000 person-years and an increase in incidence before varicella vaccination programs.[5] The Incidence increases steeply as the population ages,[5] and while the adult population accounts for 5% of reported cases, it

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is responsible for more than 50% of mortality.[7] Despite the availability of antiviral treatments, these complications can cause physical disability, decreased quality of life, and financial burdens on patients and the health care system.[8]

Two licensed injectable HZVs, a live attenuated HZV (ZVL)[9] and an adjuvant recombinant subunit vaccine (HZ/su)[10] are used to prevent HZ and PHN in the older population, reducing the risk of HZ by 50%. The ZVL and the recombinant HZV were both compared in a large meta-analysis of the general population and found to be superior to placebo in the prevention of shingles[11,12] and PHN.[12]

CKD, including end-stage kidney disease (ESKD), is a global health problem, with 10% of the world population predicted to have CKD.[13] Patients with CKD and ESKD have an impaired immune system with an increased susceptibility to infections.[14,15] There is a 30% to 40% increased risk of HZ in CKD compared with the normal population,[16,17] with HZ infections associated with an increased morbidity and mortality in patients with ESKD.[18]

Some cohort studies and small randomized controlled trials have examined the effectiveness of HZV in CKD and in ESKD, but the HZV effectiveness and safety across different stages of CKD has not been systematically examined. We therefore conducted a systematic review and meta-analysis to investigate the efficacy and safety of HZV in the renal population, defined as CKD, dialysis, and transplant population.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to a prespecified protocol and in accordance of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[19] in addition to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for conducting a meta-analysis[20] (Supplementary Material).

Data Sources and Search Strategy

A literature review was conducted to identify relevant studies evaluating the efficacy and safety of HZV in patients with kidney disease. We used the Population, Intervention, Comparators, Outcome and Methodology (PICOM) criteria as follows:

Population. Adult patients with a history of kidney disease, including CKD, dialysis (peritoneal dialysis or hemodialysis), or renal transplantation.

Intervention. HZV (ZVL or HZ/su).

Comparators. Placebo or no vaccine.

Outcome. Primary outcome was an episode of HZ, including ophthalmic HZ, or PHN. Secondary outcome was safety defined as unsolicited or serious adverse event.

Methodology. Full-text publications of randomized controlled trials or observational studies (retrospective or prospective). We excluded study designs without a comparator group, such as case reports, case series, or cross-sectional analysis, reviews, and pooled analysis.

Papers were searched on 3 online databases, MEDLINE, Embase, and Cochrane Central Registry of Controlled Trials (CENTRAL), from inception until 31, May 2020. Our search terms used a combination of keywords, Medical Subject Heading terms, and subject headings for herpes zoster and vaccines. We searched all articles examining the effectiveness of an HZV because larger trials of the general population may include a subgroup of patients with kidney disease in the results, which would have been missed if we narrowed our search to only include a population of patients with kidney disease. The full search strategy is provided in the Supplementary File (Supplementary File S1). We excluded non-English studies, conference papers, abstracts, studies on the pediatric population, and nonhuman studies. References were exported and managed through Endnote X9 software (Clarivate Analytics, Philadelphia, PA).

Study Selection and Eligibility Criteria

After removal of duplicates, 3 reviewers (MH, HA and AS) independently reviewed all titles and abstracts identified in the initial search, followed by an independent full-text review. All discrepancies were resolved by consensus.

Data Extraction, Study Verification, and Quality Assessment

For each publication meeting the selection criteria, data were extracted independently by 2 authors (HA and AS) using a standardized data extraction form and checked by a third author (HCH). Discrepancies in data entry were resolved through consensus. We extracted the following data: study characteristics (author, year of publication, county, study design, duration of follow-up), age-group, sex, type of HZV (ZVL or HZ/su), method of control (placebo or no vaccine), definition of kidney disease (if available), outcome definition of HZ, and adverse events. Our primary outcome was HZ and PHN, and our secondary outcome was adverse events from HZV. Study authors were contacted to obtain missing data.

Risk of bias assessment was conducted by 3 reviewers (MH, HA, and AS) independently, and disagreements were resolved by consensus. We used the Cochrane Risk of Bias Tool[21] for randomized controlled

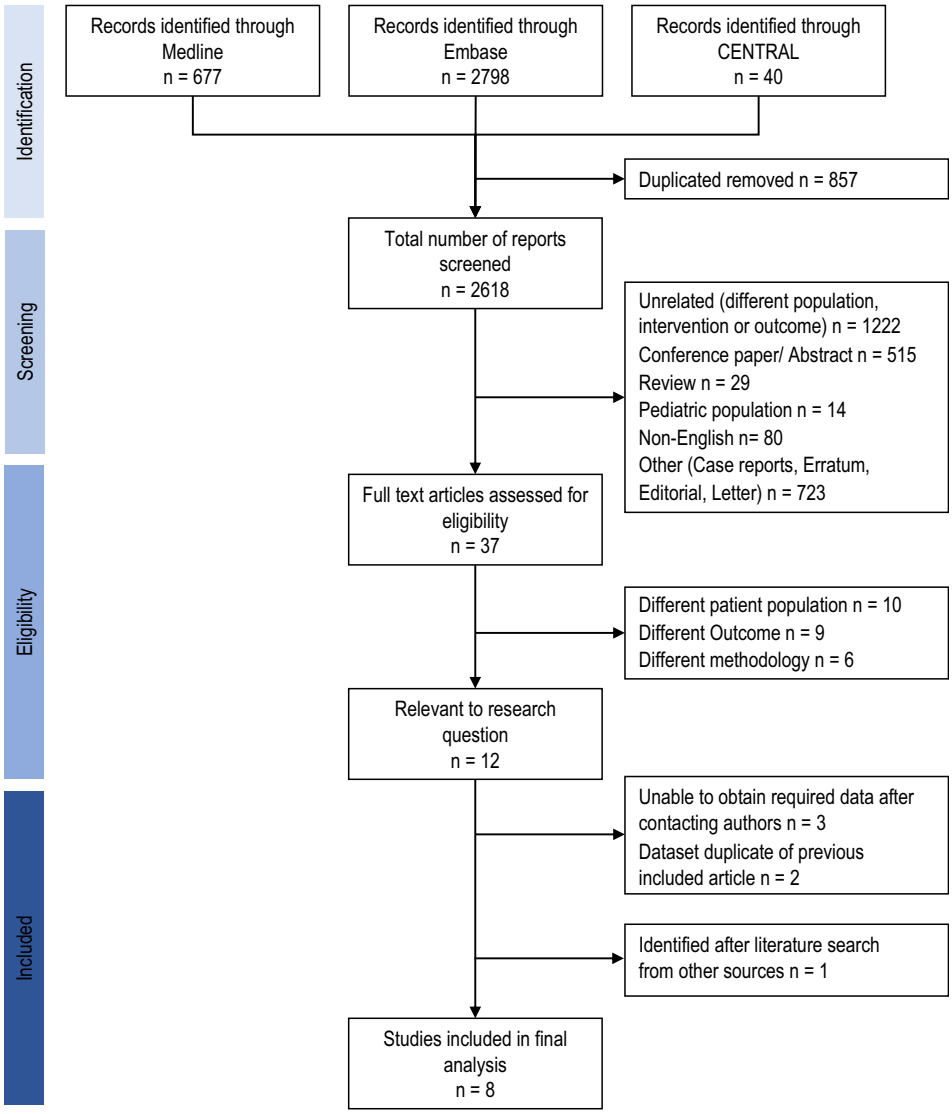

Figure 1. Flowchart of study selection in the meta-analysis. CENTRAL, Cochrane Central Register of Controlled Trials.

trials and the Newcastle-Ottawa Scale (NOS) for observational studies.[22] NOS scores of ≥7 were considered high quality, 5 to 6 moderate quality, and <5 low quality.

Statistical Analysis

We used a dichotomous outcome with pooled risk ratios (RRs) and 95% confidence intervals (CIs) calculated for the risk of HZ infection and adverse events between the vaccinated and unvaccinated group. Because these studies were conducted in different geographic locations, settings, and across different kidney disease populations, we anticipated that the true effect estimate would likely vary; therefore, pooled estimates were obtained using the random-effects model. The variability across studies due to heterogeneity was investigated using forest plots and I^2 statistics, with I^2 values of 25%, 50%, and 75% corresponding to low, moderate, and high levels of heterogeneity, respectively. The overall effectiveness of HZV was diagrammatically depicted by forest plots.

We planned *a priori* subgroup analysis between CKD, dialysis, and transplant groups to explore potential causes of heterogeneity for HZV on HZ. A sensitivity analysis was conducted by omitting each study in turn to evaluate the quality and consistency of results. We aimed to evaluate publication bias by funnel plot if more than 8 studies were included. Statistical analysis and generation of forest plots was conducted using Review Manager (Rev Man) 5.4 software (Cochrane Collaboration, London, UK), with $P < 0.05$ deemed as statistically significant.

RESULTS

We reviewed 2618 abstracts (Figure 1), from which 37 full-text articles were retrieved and assessed. We

Table 1. Characteristics of included studies

Author (yr)	Country	Sex (%)	Age (yr)	Study design	Outcome definition Intervention (events/ total number at risk)	Follow-up (mo)	Detailed scheme	Population group	Quality score[a]
Arnees (2008)[29]	USA Single center	NA	NA	Retrospective cohort	HZ: Clinical diagnosis or PCR ZVL: 1/6 Placebo: 3/50	36	≥18 years of age. Excluded <2 months of follow-up.	Renal transplant (clinical record review)	4
Tseng (2011)[26]	USA Integrated health care system	NA	NA	Retrospective cohort	HZ and ophthalmic HZ: ICD coding ZVL: 117/9449 No vaccine 758/31,873	36	≥60 years of age. Vaccinated matched to unvaccinated 1:3 on birthdate. Excluded immunocompromised patients.	Chronic kidney disease and dialysis patients (ICD coding)[b]	7
Tseng (2016)[27]	USA Integrated health care system	M: 7.2 F: 42.8	68.4 (9.0)[c]	Retrospective cohort	HZ: ICD coding ZVL: 16/582 No vaccine: 126/2910	84	≥60 years of age. Vaccinated matched to unvaccinated 1:5 on sex, birth date, dialysis initiation date. Excluded renal transplant or censored at transplant.	Chronic dialysis patients: HD (n = 3070) and PD (n = 422) (renal database)	8
Langan (2016)[28]	USA 5% random Medicare population	M: 2.4 F: 67.7	65–74: 48.3% 75–>80: 41.7%	Retrospective cohort	HZ: ICD coding ZVL: 28/4524 No vaccine: 3438/179,238	36	≥65 years of age.	Chronic kidney disease, dialysis, and renal transplantation (ICD coding)	6
Izurieta (2017)[30]	USA Medicare patients	NA	NA	Retrospective cohort	HZ and ophthalmic HZ: ICD coding ZVL: 2107/86,690 No vaccine: 2569/88,333	98	≥65 years of age. Excluded nursing facility stay. Vaccinated matched 1:1 with unvaccinated on risk factors for HZ and age, sex, race, income	Chronic kidney disease, dialysis, and renal transplantation[b]	7
Miller (2018)[24] NCT01137669	USA single centre	M: 76 F: 24	51.9 (26–72)[d]	Randomized controlled Trial phase I	HZ: Clinical diagnosis ZVL: 0/26 Placebo: 0/8 Adverse event: Unsolicited adverse event over 12 months LV: 15/26 Placebo: 4/8	12	≥18 years of age. ZVL administered between day 30 and 235 pretransplant. Randomized 3:1 to ZVL or placebo. ZVL administered 4 weeks pretransplant.	Enrolled 34 dialysis patients (HD and PD). 14 transplanted (12 ZVL vs. 2 placebo) 24 remained on dialysis (18 ZVL and 6 placebo)	M
Oostvogels (2019)[23] NCT01165177 NCT01165229	18 sites: Europe, North America, Latin America, Asia, Australia	NA	NA	Randomised controlled trial phase III	HZ: Clinical diagnosis or PCR HZ/su: 1/308 Placebo: 7/300 Adverse event: Serious adverse event from dose 1 until 12 mo after dose 2 Adverse event: 86/328 Placebo: 75/319	60	≥50 (NCT01165177) and ≥70 (NCT01165229) years of age. Randomized 1:1 to HZ/su or placebo. Excluded immunosuppressive conditions or therapies and immunodeficient conditions	Renal disease (undefined)	M
Vink (2020)[25] NCT02058589	Belgium, Canada, Czech Republic, Finland, Italy, Panama, Republic of Korea, Spain, Taiwan	M: 0.1 F: 29.9	52.3 (12.6) [c]	Randomized controlled trial phase III	HZ: Suspected clinical diagnosis HZ/su: 3/132 Placebo: 7/132 Adverse event: Serious adverse event from vaccination until end of study HZ/su: 26/132 Placebo: 33/132	36	≥18 years of age, 4–18 months postrenal transplant. Excluded rejection in past 3 months, multiple organ transplant, systemic autoimmune or immune-mediated disease	Renal transplant	M

F, female; HD, hemodialysis; HZ, herpes zoster; HZ/su, herpes zoster/subunit vaccine; ICD: International Classification of Diseases; M, male; NA, not available; PCR, polymerase chain reaction; PD, peritoneal dialysis; USA, United States of America; ZVL, zoster live attenuated vaccine.

[a]Quality score assessed by Newcastle-Ottawa Scale for observational studies and Cochrane Risk of Bias Tool for randomized controlled trials (M: medium overall risk of bias).

[b]Information of definition of renal disease obtained directly from authors.

[c]Mean (standard deviation).

[d]Mean (range).

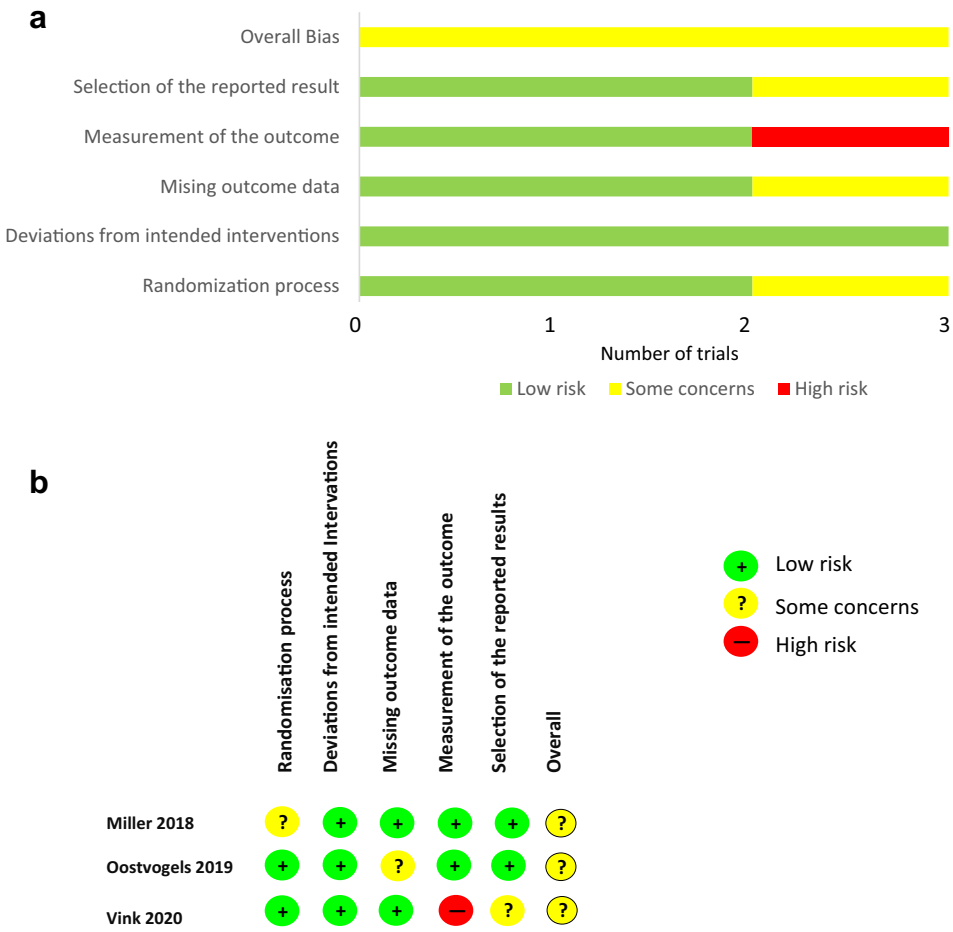

Figure 2. Risk of bias for the randomized controlled trials included in the meta-analysis. (a) Risk of bias summary. (b) Risk of bias graph. Symbols: +, low risk of bias; ?, some concerns; –, high risk of bias.

included 12 articles for analysis but were unable to obtain further information on 3 studies, and 2 studies had the same patient population from trials already included. One further study was identified from other sources after the literature review as relevant and was included. Our final meta-analysis included 8 studies corresponding to 3 randomized controlled trials[23–25] and 5 cohort studies,[26–30] with 3 studies containing information on adverse events.[23–25]

General characteristics of the included studies are presented in Table 1.[23–30] A total of 404,561 patients were included, of which 101,717 received the HZV and 302,844 were controls. All 8 studies had information on HZV events, and 3 studies documented safety.[23–25] The ZVL vaccine was used in 6 studies,[24,26–30] and the HZ/su vaccine was examined in 2 studies.[23,25] Follow-up ranged from 12 to 98 months. The definition of renal disease varied widely across the studies: 2 included CKD, dialysis, and transplant populations,[28,30] 1 included CKD and dialysis,[26] 1 included dialysis and transplant,[24] 2 included only transplant,[23,29] 1 included only dialysis,[27] and 1 had an undefined CKD population.[23] Only 1 study[24] gave a breakdown of outcome by CKD stage.

Publication bias, using the funnel plot, was not assessed because the number of studies included in the meta-analysis was not greater than 8.

Risk of bias was assessed in all trials. The biases of the observational cohort, evaluated by the NOS, are provided in Table 1, with a breakdown available in Supplementary Table S1. Three studies had a score of 7 to 8, indicating good quality, 1 study had a score of 6, indicating moderate quality, and 1 study had a score of 4, indicating low quality. The lower score was due to comparability of patient groups and outcome assessment in some studies, with 1 study yielding a low score in the patient selection category. Risk of bias in our included randomized controlled trials (Figure 2) showed some concerns in the overall risk of bias for all studies, with some concern in each of the randomization processes, missing outcome data, and selection of the reported results. One study had a high risk of bias in the measurement of the reported outcome.

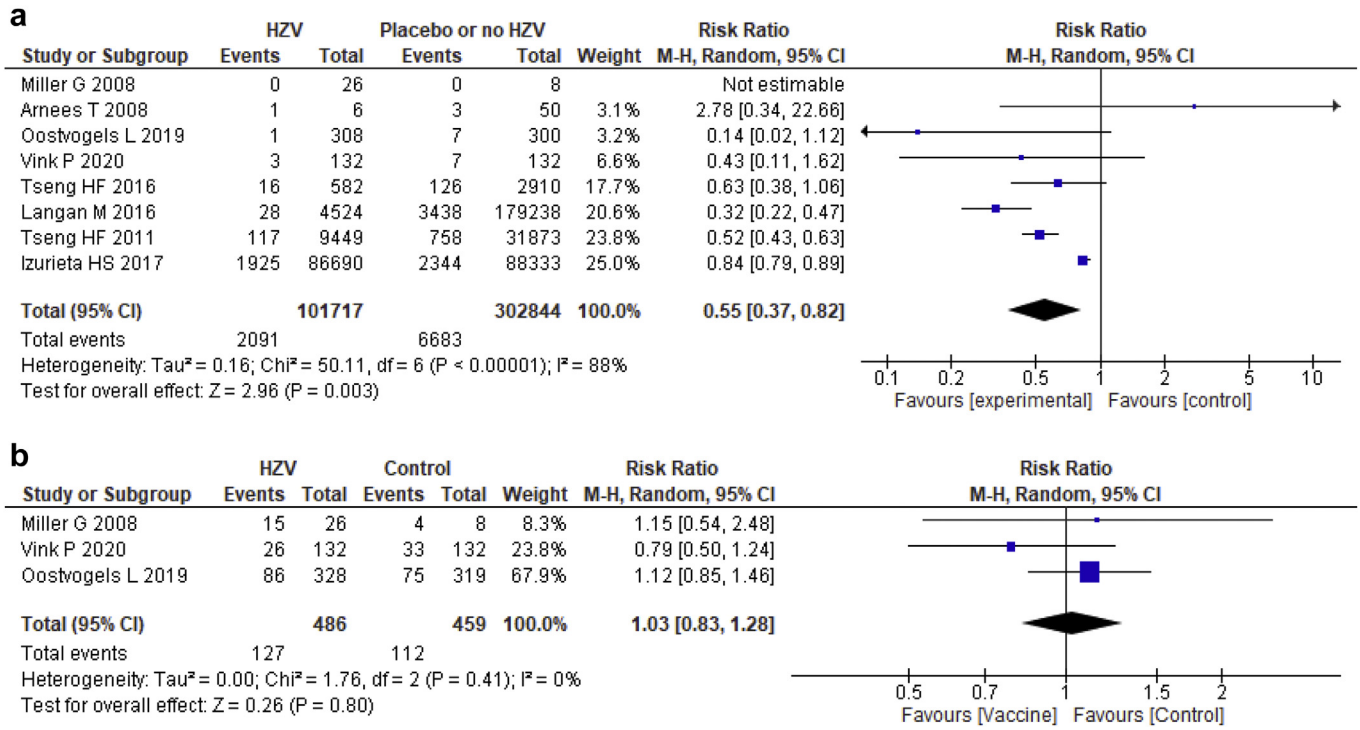

Figure 3. Forest plot of the relationship between (a) herpes zoster vaccine (HZV) and herpes zoster (HZ) in patients with chronic kidney disease and (b) risk of adverse events after HZV in patients with chronic kidney disease. The squares represent the risk ratio and lines the 95% confidence intervals (CIs) for individual studies. The area of each square is proportional to study weight. The diamond and width represent the pooled risk ratios and 95% CIs, respectively. M-H, Mantel- Haenszel.

Risk of HZ After Vaccination

Eight studies examined the risk of HZ after vaccination against a control group (placebo or no vaccination). HZV reduced the risk of HZ significantly (hazard ratio, 0.55; 95% CI, 0.37–0.82; $P < 0.01$; Figure 3a). The heterogeneity across studies was high ($I^2 = 88\%$, $P < 0.01$).

Only 1 study examined the risk of PHN after vaccination against a control group,[30] finding a significant reduction of risk (hazard ratio, 0.71; 95% CI, 0.52–0.98; $P < 0.05$) despite the low number of overall events (63 events in 86,690 vaccinated individuals vs. 90 events in 88,333 nonvaccinated individuals). No other studies examined this outcome, so we were unable to generate a pooled result.

Safety of HZV

Three studies examined adverse effects and safety outcomes of HZV compared with controls. Included were 945 patients, comprising 486 vaccinated for HZ and 459 controls. No deaths related to HZV were documented in the included studies. Unrelated deaths occurred in 51 patients (10.5%) receiving HZV and in 52 controls (11.5%). Potentially immune-mediated disease was documented in 2 studies[23,25] and occurred in 6 patients (1.3%) with HZV and in 6 patients (1.3%) in the control group. In 2 studies examining the renal transplant population,[24,25] consisting 4 patients (2.5%) in the HZV group and 7 patients (5.0%) in the control group, there was no increased risk of biopsy specimen-proven rejection, cellular rejection, or acute mediated rejection.

A pooled analysis was undertaken for adverse events (Figure 3b). The total number of adverse events was 127 (26.1%) in the HZV group and 112 (24.8%) in the control group. No increased risk of adverse events found (hazard ratio, 1.03; 95% CI, 0.83–1.28; $P = 0.8$) with a low heterogeneity in the pooled analysis ($I^2 = 0\%$, $P = 0.41$).

Subgroup Analysis

We performed a subgroup analysis to examine heterogeneity, dividing studies into renal disease categories of CKD, transplant, and dialysis (hemodialysis or peritoneal dialysis). Only 1 study reported HZ events in the dialysis population and 2 in the transplant population. Four studies examined HZV in a majority of the CKD population. Results of the subgroup analysis showed no significant differences between the group ($P = 0.71$; Figure 4).

Sensitivity Analysis

The result of the sensitivity analysis showed that the results of the hazard ratio and the 95% CI were not significantly affected by the removal of any individual study (Figure 5).

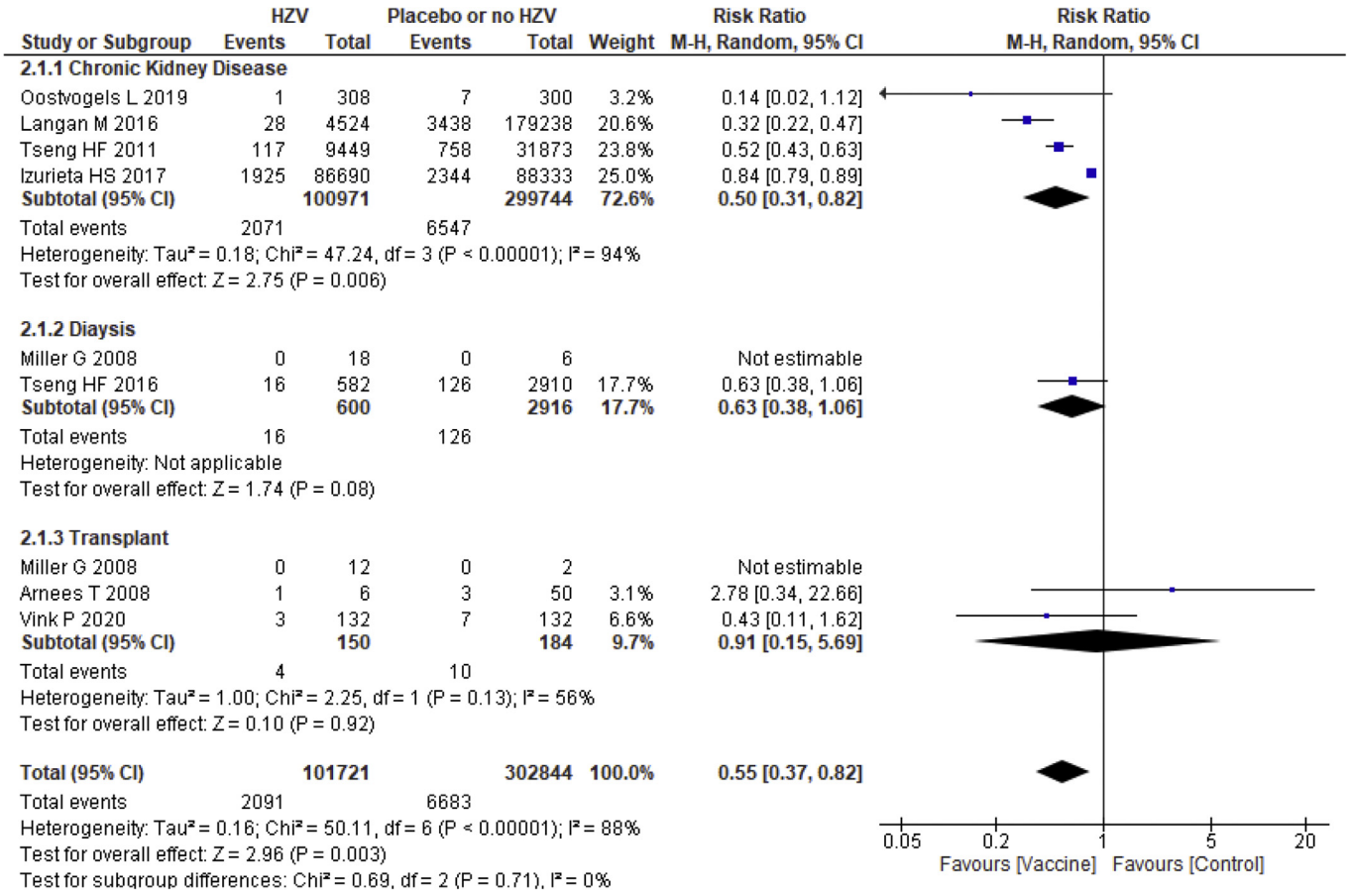

Figure 4. Subgroup analysis of the risk of herpes zoster by chronic kidney disease, dialysis, or transplant population. The squares represent the risk ratio and the lines the 95% confidence intervals (CIs) for individual studies. The area of each square is proportional to study weight. The diamond and width represents the pooled risk ratios and 95% CIs, respectively. HZV, herpes zoster vaccine; M-H, Mantel- Haenszel.

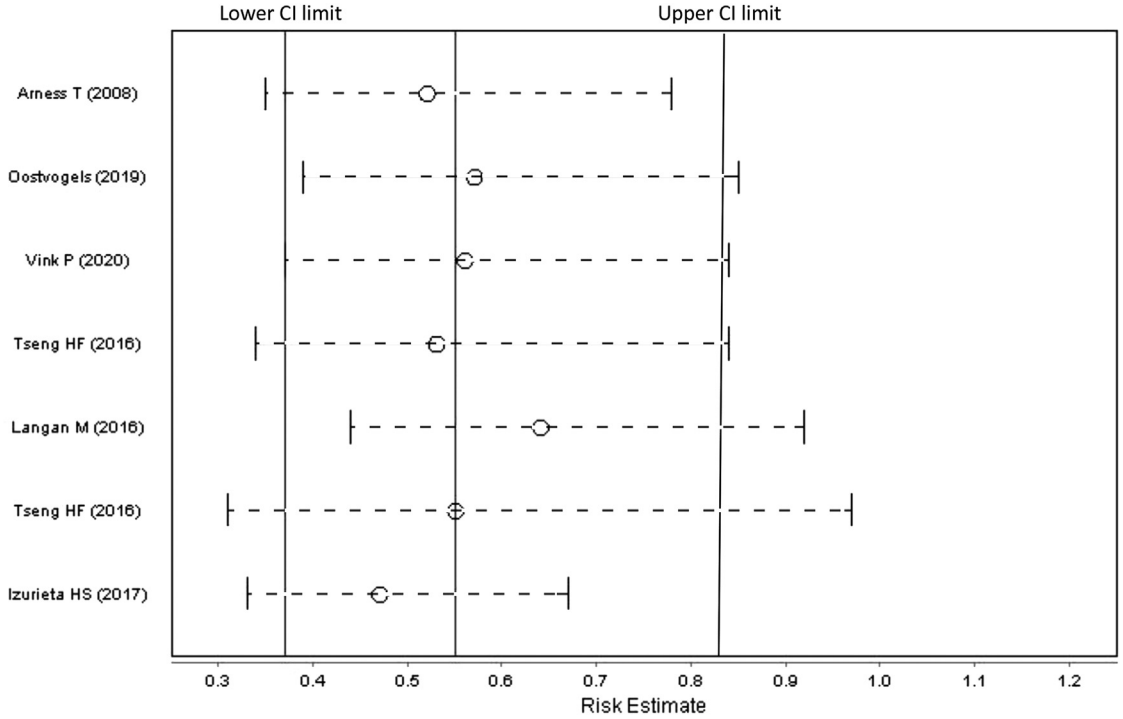

Figure 5. Sensitivity analysis with given named study omitted. Study by Miller (2018) was not included due to lack of events. CI, confidence interval.

DISCUSSION

This systematic review and meta-analysis demonstrated a reduction in the risk of HZ and no increased risk of adverse events after an HZV in patients with CKD. Our analysis included a broad renal population including patients with CKD, dialysis, and renal transplantation. Subgroup analysis dividing patients into CKD, dialysis, and transplant groups did not show a significant difference in outcome between the groups.

Infection is among the leading causes of morbidity and mortality in CKD, dialysis, and kidney transplant patients.[31] Patients with CKD and ESKD are considered to have an immunocompromised state from a combination of innate and adaptive immune system dysfunction.[32,33] The cause could be attributed to a diminished activation and function of T cells, B cells, monocytes, and macrophages in addition to a reduction in lymphokine production and antibody cytotoxicity. Additional factors contributing to an immunocompromised state in CKD include chronic inflammation, presence of uremia, increased age, and the higher prevalence of diabetes and cardiovascular disease in this group of patients.[32,33] Renal transplant recipients carry the additional risk from requiring immunosuppressive agents.

Vaccination remains an important tool in reducing the risk of infection. However, vaccines are less effective and provide less protection as CKD advances. In CKD there is a lower conversion rate, lower antibody titre, and more rapid decline in antibody levels,[33] with the response to vaccine decreasing with the progression of CKD to ESKD.[34,35] Factors responsible for the increased infection risk in CKD may similarly contribute to the reduced vaccine effectiveness. In addition, an impaired T-cell response to antigenic stimulus,[36] the presence of uremic toxins impairing leucocyte and endothelial function,[37,38] and increasing levels of inflammatory cytokines may all contribute to the impaired immunologic response to a vaccine.[39] Despite this, there is strong evidence from observational cohort studies that vaccination in patients with CKD decreases the risk of hospitalization and all-cause mortality,[40–42] and it remains an important component of preventative care in patients with CKD.

The incidence of HZ in the general population is estimated to be 3.9 per 1000 person-years,[5] increasing almost 20-fold to 70 per 1000 person-years in the CKD population.[16,43,44] Estimates indicate that an HZ infection will occur in 3% to 6% of the CKD population,[17,43–45] with the risk increasing from CKD to ESKD, and is highest in peritoneal dialysis and renal transplant populations.[44] HZ infection in CKD is associated with an increased complication rate compared with the general population[44] and a faster progression to ESKD.[45] HZ infections in ESKD are associated with a high complication rate of 35% in those infected and a mortality rate of 15% to 50%.[46,47] It is notable that while most guidelines recommend HZV in patients aged ≥60 to 65 years, patients with CKD have a higher risk of HZ at a younger age compared with the general population.[48]

Vaccination rates are improving in the general population but remain underused in patients with CKD, despite proven benefits and recommendations.[49] In large cohort studies, only 1.4% of patients with CKD are vaccinated against HZV,[50] and in ESKD, the prevalence of seronegativity among varicella-infected adults with end-stage renal disease reaches 42% to 100%.[18] In patients wait-listed for a kidney transplant, only 6% received an HZV.[51]

We showed a significant reduction in HZ infection in patients with CKD, with a risk reduction of close to 50%. However, we observed a high heterogeneity. The reason may be due to the heterogenous population included in the analysis. None of the trials differentiated the stages of CKD (1-5) and the effectiveness of HZV by stage. In many of the larger trials, the definition of CKD was unclear, with renal disease being undefined or defined as a composite of CKD, dialysis, and transplant. We anticipate that in the larger studies, the number of dialysis and transplant patients would be small compared with the CKD population, therefore not impacting the results of the subgroup significantly. Another reason for the high heterogeneity could be the wide range of follow-up among the studies (ranging from 12 to 98 months).

Patients with a renal transplant represent the highest risk of HZ infection, with almost 6% having an infection by 3 years[29,52,53] and 11.2% by 4 years of follow-up.[29] The risk of complications after an HZ infection in renal transplant recipients is much higher than the general population,[44] with almost half (42.7%) experiencing PHN[52] and with double the risk of mortality compared with renal transplant recipients who are not infected with HZ.[53] In patients with a transplant, a viral infection episode has been associated with graft rejection.[54] As a result of this association, there remains a concern that vaccinating renal transplant recipients may cause graft rejection, particularly with live vaccines, despite limited evidence.[55]

Reassuringly, we did not find an increase in the risk of adverse events or graft rejection after HZV in patients with a renal transplant. Both ZVL and HZ/su vaccines also decreased the risk of HZ infection in renal transplant recipients. For ZVL, patients received the vaccine at least 4 weeks before transplant,[24,25] whereas

the HZ/su vaccine was administered 4 to 18 months after transplant. The third study examining HZV in the renal transplant population[29] had a significant bias and limitation of only knowing the vaccination status in 60 of the 612 renal transplant patients included. The higher risk of HZ in the HZV group should therefore be interpreted with caution.

The strength of our study is the comprehensive search strategy used to identify published studies and pooling a large number of renal patients across CKD, dialysis, and renal transplant groups, allowing for greater generalizability. We also assessed safety alongside effectiveness of HZV in preventing HZ.

Our analysis also has several limitations. The small number of publications and the lack of details, such as age breakdown, sex, or comorbidities, limited the subgroup and sensitivity analysis, which would have been helpful in identifying causes of heterogeneity.

We were unable to obtain information on the renal population composition (CKD, dialysis, or renal transplant) in a number of studies. Most studies involving CKD or dialysis patients consisted of patients aged >60, so the findings could not be extrapolated to the younger CKD population. There were also 3 studies that could not be included due to lack of information, even after attempting to contact the authors.

Despite the small number of studies, we still collected 6 studies (including 3 with adverse events) for a total of 404,561 patients (n = 9181 for the HZ outcome). This was a sufficient prerequisite to perform a meta-analysis.

CONCLUSION

This meta-analysis examined HZV effectiveness in patients with CKD. The vaccine was shown to be effective and to have a low adverse event profile; however, significant heterogeneity was present. The effectiveness of HZV was strongest in the non-dialysis CKD group. A nonsignificant reduction was observed in the dialysis group, where analysis was limited by the small number of patients. There was no increased risk of adverse events in transplant patients, and current evidence supports administering ZVL at least 4 weeks before transplant or the HZ/su vaccine 4 to 18 months after transplant. Our data suggest that HZV should be encouraged in patients with CKD. Future studies of HZV in the renal population should attempt to clarify the effectiveness of the HZV according to the stage of CKD, and between CKD and the dialysis/transplant groups. Our results should also reassure nephrologists and primary care givers on the safety of vaccinating patients with CKD for HZ.

DISCLOSURES

All the authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

MH and HCH contributed to the study design. MH, AS, HA, and HCH contributed to the search strategy, extracted the data, and assessed data for inclusion in addition to the risk of bias assessment. HCH and KM conducted the statistical analysis. MH, HCH, and KM drafted the manuscript. All authors provided comments on this review and approved the final version.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

S1. Search strategy in MEDLINE

Table S1. Risk of bias assessment (based on Newcastle-Ottawa scale)

PRISMA 2009 Checklist

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