BMJ Open Diabetes Research & Care

# Effectiveness of SARS-CoV-2 primary vaccines and boosters in patients with type 2 diabetes mellitus in Hungary (HUN-VE 4 Study)

Gergő A Molnár,[1] Zoltán Vokó,[2] Gábor Sütő,[1] György Rokszin,[3] Dávid Nagy,[2,4] György Surján,[5] Orsolya Surján,[6] Péter Nagy,[7,8] István Kenessey,[7,9] András Wéber,[7] Mihály Pálosi,[10] Cecília Müller,[6] Miklós Kásler,[7,11] István Wittmann ,[1] Zoltan Kiss[1]

**To cite:** Molnár GA, Vokó Z, Sütő G, *et al*. Effectiveness of SARS-CoV-2 primary vaccines and boosters in patients with type 2 diabetes mellitus in Hungary (HUN-VE 4 Study). *BMJ Open Diab Res Care* 2024;**12**:e003777. doi:10.1136/bmjdrc-2023-003777

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2023-003777).

GőAM and ZV are joint first authors.

Received 19 September 2023
Accepted 14 December 2023



For numbered affiliations see end of article.

**Correspondence to**
Professor István Wittmann; wittmann.istvan@pte.hu

GAM AND ZV CONTRIBUTED EQUALLY AS FIRST AUTHORS.

## ABSTRACT

**Introduction** Type 2 diabetes mellitus is a risk factor for severe COVID-19 infection and is associated with increased risk of complications. The present study aimed to investigate effectiveness and persistence of different COVID vaccines in persons with or without diabetes during the Delta wave in Hungary.

**Research design and methods** Data sources were the national COVID-19 registry data from the National Public Health Center and the National Health Insurance Fund on the total Hungarian population. The adjusted incidence rate ratios and corresponding 95% CIs were derived from a mixed-effect negative binomial regression model.

**Results** A population of 672 240 cases with type 2 diabetes and a control group of 2 974 102 non-diabetic persons free from chronic diseases participated. Unvaccinated elderly persons with diabetes had 2.68 (95% CI 2.47 to 2.91) times higher COVID-19-related mortality rate as the 'healthy' controls. Primary immunization effectively equalized the risk of COVID-19 mortality between the two groups. Vaccine effectiveness declined over time, but the booster restored the effectiveness against mortality to over 90%. The adjusted vaccine effectiveness of the primary Pfizer-BioNTech against infection in the 14–120 days of postvaccination period was 71.6 (95% CI 66.3 to 76.1)% in patients aged 65–100 years with type 2 diabetes and 64.52 (95% CI 59.2 to 69.2)% in the controls. Overall, the effectiveness tended to be higher in individuals with diabetes than in controls. The booster vaccines could restore vaccine effectiveness to over 80% concerning risk of infection (eg, patients with diabetes aged 65–100 years: 89.1 (88.1–89.9)% with Pfizer-on-Pfizer, controls 65–100 years old: 86.9 (85.8–88.0)% with Pfizer-on-Pfizer, or patients with diabetes aged 65–100 years: 88.3 (87.2–89.2)% with Pfizer-on-Sinopharm, controls 65–100 years old: 87.8 (86.8–88.7)% with Pfizer-on-Sinopharm).

**Conclusions** Our data suggest that people with type 2 diabetes may have even higher health gain when getting vaccinated as compared with non-diabetic persons, eliminating the marked, COVID-19-related excess risk of this population. Boosters could restore protection.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with type 2 diabetes mellitus are subject to a higher rate on complication of the COVID-19 infection, including infection-related mortality.

### WHAT THIS STUDY ADDS

⇒ In patients with type 2 diabetes mellitus, SARS-CoV-2 vaccines provide a vaccine effectiveness that is at least equal to or even larger than the effectiveness in non-diabetic subjects, and this is also true for boosters.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Prioritization of patients with type 2 diabetes mellitus in the vaccination protocol is a proper approach, since these patients have a high excess risk that is eliminated by the use of vaccines.

## INTRODUCTION

Diabetes mellitus (DM) is a disease with high prevalence, often regarded as an 'epidemic' among non-communicable diseases. It was leading to the prevalence of more than 520 million people with diabetes in 2021 and is thus responsible for a high global burden of the disease.[1] The predicted number of cases should rise to 1.31 billion cases by 2050.[1] It is associated with a higher rate of infections, for example, urinary tract, genital, skin or respiratory infections, as compared with the non-diabetic population.[2–4] In fact, infections may be regarded as part of the emerging non-vascular complications of DM.[5] During the COVID-19 pandemic, special attention has emerged related to metabolic diseases, such as obesity, DM and fatty liver disease.[6] Diabetes was investigated in various studies and was

found to be a risk factor for infection by the SARS-CoV-2 virus but also for other respiratory pathogens.[7] Moreover, DM was also found to be associated with worse COVID-19 outcomes, along with other cardiovascular risk factors or diseases (such as hypertension, coronary heart disease, heart failure)[8]; in fact, COVID-19-related mortality was higher in individuals with DM, even more so in type 1 DM as compared with type 2 DM (T2DM).[8 9]

Some results about COVID-related antibody production or cellular immunity in people with diabetes have been published.[10–17] However, much less is known about SARS-CoV-2 vaccine effectiveness (VE) in diabetics in the real world. Previously, our working group published results related to a nationwide analysis on SARS-CoV-2 VE, during different waves of the SARS-CoV-2 pandemic and on the effect of booster shots in the general Hungarian population.[18–20] In the present work, the same data source was used, but this time we focused on individuals with T2DM and investigated VE and effect durability in this high-risk population compared with a population without history of chronic diseases.

## RESEARCH DESIGN AND METHODS

### Data sources

The analyzed data of the Hungarian COVID-19 registry arose from the National Health Insurance Fund (NHIF, more than 90% of the total population is state insured) and of the National Center for Public Health and Pharmacy (NCPHP). The current analysis covers the period of the Delta wave (between September 4, 2021 and December 25, 2021 in Hungary). Individuals with registered history of SARS-CoV-2 infection before the study period were excluded from the analysis of SARS-CoV-2 infection outcome. From this population less than 1000 individuals were excluded because of data inconsistencies including different types of vaccines for primary immunization, lacking information on the type of the second vaccine dose, first vaccination being administered before the earliest possible date, having fewer than 14 days between the first and second doses, a diagnosis date preceding the first reported case, or a date of death preceding the first vaccination.

### COVID-19-related data and outcomes

A centralized system managed by the NCPHP reported data on SARS-CoV-2 infection on a daily basis. The reported cases were based on COVID-19-related symptoms identified by healthcare professionals and/or positive PCR tests performed by accredited microbiological laboratories. Cases that were identified based on symptoms needed to be confirmed using either PCR or antigen tests listed in the rapid test list of the European Commission.[21] COVID-19-related mortality was defined as death during a period of SARS-CoV-2 positivity, regardless of whether the cause of death was directly attributed to COVID-19 or other underlying factors. Patients with confirmed SARS-CoV-2 infection who died without a previously declared recovery and without another clear cause of death were classified as COVID-19-related deaths. The definition of COVID-19-related mortality was based on recommendations from WHO and defined by the healthcare government.[22]

### SARS-CoV-2 vaccine types available at the time of the study

At the time of the Delta wave of the pandemic, BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), Ad26.COV2.S (Janssen), GAM-COVID-Vac (Sputnik), ChAdOx1 (AstraZeneca) and BBIBP-CorV (Sinopharm) vaccines were available in Hungary for primary immunization as well as the first booster shot (online supplemental figure 1, online supplemental file 1). A minority of the patients were vaccinated with Janssen vaccine as primary immunization; thus, they were not included in the analysis. Most patients received a Pfizer vaccine as a booster. To achieve a statistically analyzable sample size, only patients receiving a Pfizer or Sinopharm as a basal immunization and a Pfizer vaccine as a booster were included (figure 1).

Individuals were categorized as primarily vaccinated if at least 14 days had passed since the administration of the second dose of specific COVID-19 vaccine types. The unvaccinated group included individuals who did not receive any dose of any COVID-19 vaccine type at a given timepoint.

### Definition of the group with T2DM

DM was defined as (a) history of outpatient or inpatient care between January 1, 2013 and March 3, 2021 with an E10-14 code diagnosis according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and at least one prescription of antidiabetic treatment (Anatomical Therapeutic Chemical code A10) prescription dispensed, or (b) at least two such prescriptions dispensed, and without a history of outpatient or inpatient care with a diagnosis of polycystic ovary syndrome (ICD-10: E282) or gestational diabetes (ICD-10: O24). Of these selected individuals those were considered having type 1 DM who dispensed only insulin or maximum three oral antidiabetic prescriptions together with insulin prescriptions in the first half year of their treatment. After excluding individuals with polycystic ovarian syndrome and gestational diabetes, as well as excluding type 1 diabetes cases, the remaining persons were defined as patients with type 2 diabetes (T2D) and only they were included in the study.

### Definition of the control group

The control group included patients without history of chronic diseases. The presence of chronic diseases was identified based on inpatient and outpatient health service utilization and prescription data from the NHIF between January 1, 2013 and March 3, 2021. The following chronic conditions were considered: cardiovascular diseases (myocardial infarction, angina, chronic heart failure, peripheral vascular disease, and stroke), DM (type 1 and type 2), immunosuppression

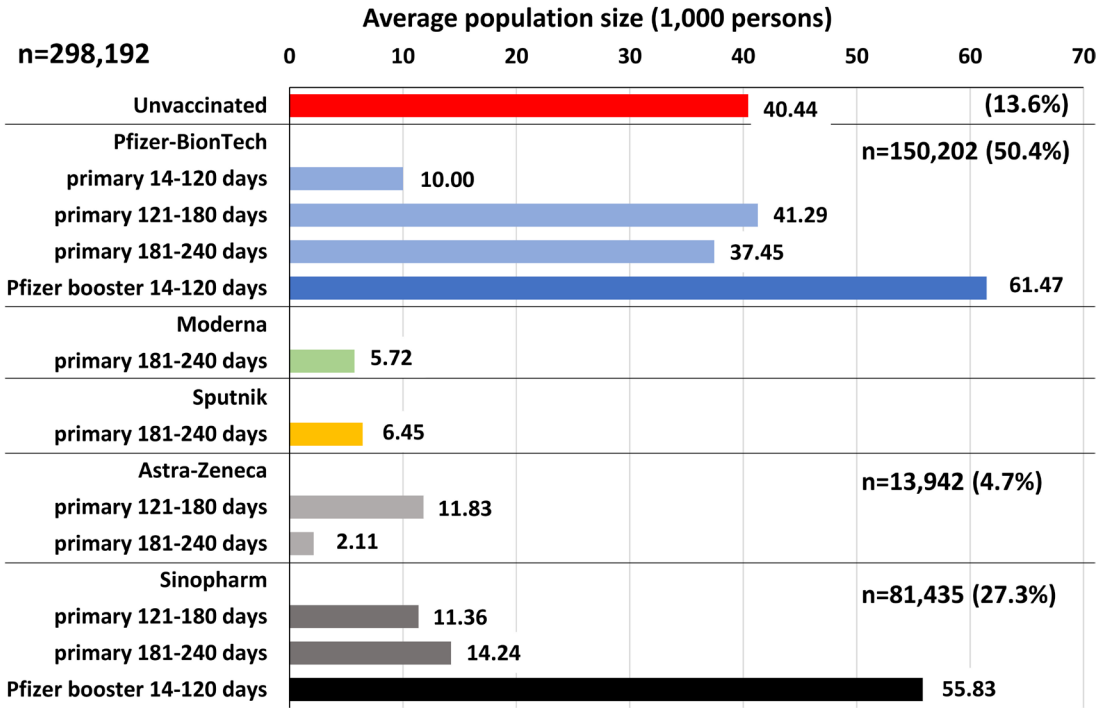


**Figure 1** Average type 2 diabetes mellitus (T2DM) population size by vaccination status used for the vaccine effectiveness (VE) calculation during the *Delta wave* (individuals aged 65–100 years).

(immunosuppressive therapy and transplantation), chronic pulmonary diseases (asthma and chronic obstructive pulmonary diseases (COPD)), neoplasms, and chronic kidney diseases. The definitions of chronic diseases are presented in online supplemental table 1. We restricted the age range of the study population to 45–100 years, taking into account the age distribution of patients with T2D.

### Vaccine effectiveness

VE was defined as 1 minus the incidence rate ratio (IRR) of the outcome under investigation (ie, either mortality or infection rate, respectively), thus VE against mortality and VE against infection were both calculated separately. Vaccine combinations administered to a minimum of 3000 people by December 31, 2021, or with at least 300 cases from the beginning of the pandemic until December 31, 2021, in Hungary were included in the analysis. Vaccine combinations were further divided into subcategories based on the time elapsed since their administration, namely 14–120, 121–180, and 181–240 days. For booster vaccinations, only the 181–240 days category was established for the Pfizer booster vaccine, considering the limited number of individuals who had received their booster vaccination more than 240 days earlier or with other booster vaccine types that met the inclusion criteria during the Delta wave.

### Statistical analysis

Adjusted IRRs with 95% CIs were derived using a mixed-effect negative binomial regression model, adjusting for age, sex, history of chronic diseases, and calendar day. The latter was handled as a random effect. In case of Pfizer vaccination there were observations in all categories of the time elapsed since vaccination. We used the method of variance estimates recovery and obtained p values from the estimated CI of the ratios of the adjusted IRRs comparing the different categories to the category of vaccination within 14–120 days.[23 24] We used the same method to compare vaccine efficacy in patients with diabetes and controls. Separate models were used for two specific age groups (45–64 and 65–100 years). When trying to form age groups according to decades, the number of cases and events in individual age groups limited the statistical analysis. Thus, we separated the study population according to the Organisation for Economic Co-operation and Development definition of elderly population, where the age cut-off lies at 65 years,[25] thus cases and controls were divided into non-elderly and elderly groups.

## RESULTS

Majority of the Hungarian population (approx 62%) has received the primary immunization already by March 2021 (ie, during the Alpha wave) with different vaccines.[26] During the Delta wave, primary immunization was performed mainly using the Pfizer vaccine, thus the effect estimate for the time window 14–120 days after primary immunization was only available in sufficient numbers for only this vaccine during the Delta wave.

### Mortality rates in the vaccinated and unvaccinated cohorts with or without T2DM

COVID-19-related mortality rate was more than 2.68 (95% CI 2.47 to 2.91) times higher in unvaccinated patients with T2DM aged 65–100 years compared with unvaccinated

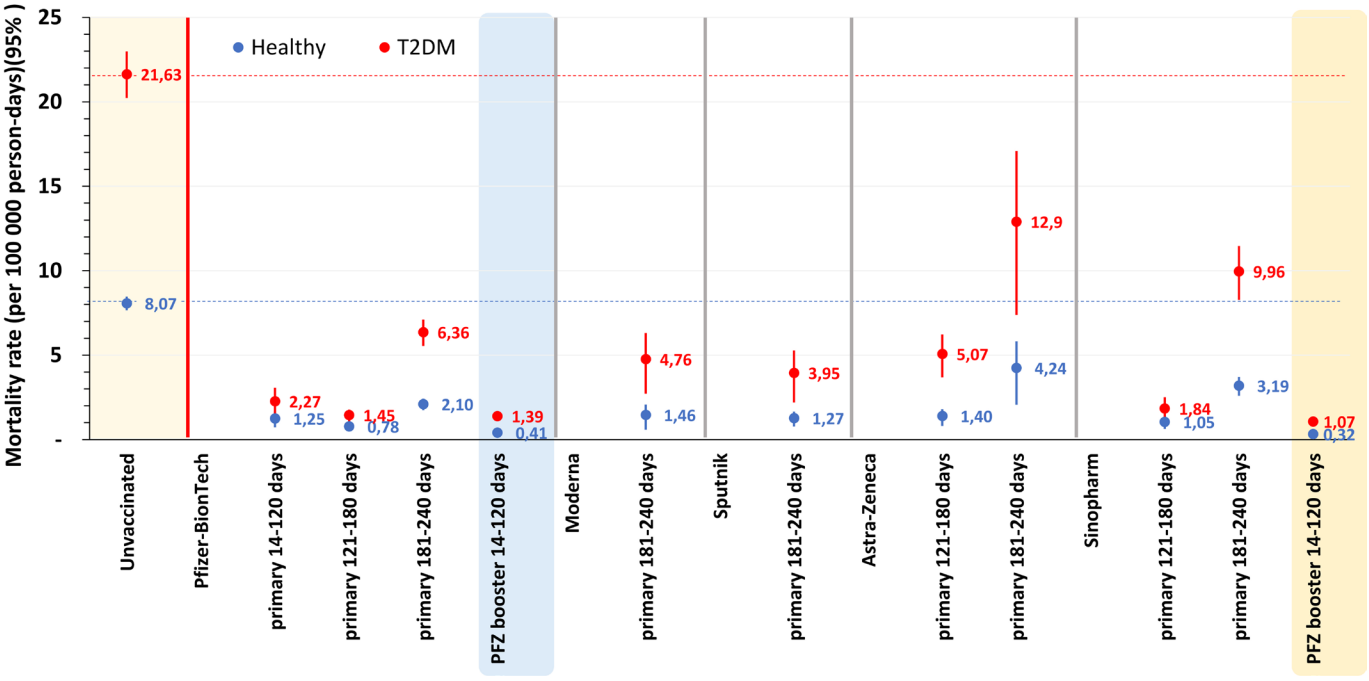


**Figure 2** COVID-19-related mortality rate by vaccination status in the Hungarian type 2 diabetes mellitus (T2DM) and control population aged 65–100 years is shown for illustrative purposes.

controls (crude mortality rate ratio: 21.63/8.07=2.68, figure 2 is shown for illustrative purposes).

Within 14–120 days after primary immunization, the mortality markedly decreased as compared with the unvaccinated population irrespective of the presence of T2DM. The crude mortality rate ratio comparing vaccinated and unvaccinated individuals was 0.105 (2.27/21.63) in the diabetic group and 0.157 (1.25/8.07) in the control group (figure 2). Similarly, within 120–180 days after Pfizer vaccination, the mortality rate ratio was numerically lower for people with T2DM (0.067) than in the control group (0.097). Mortality increased 180 days after vaccination in both the T2DM and the control groups. Pfizer booster vaccination resulted in a marked lowering of mortality, more than the level seen at 14–120 days after the primary vaccination (figure 2).

The other types of primary immunization showed clear effectiveness similarly, with signs of waning in both study groups. Pfizer booster vaccination markedly increased the protection in individuals vaccinated primarily with Sinopharm vaccine, irrespective of the presence of T2DM (figure 2).

Crude infection rate ratio in the population aged 65–100 years in unvaccinated patients with T2DM versus unvaccinated controls was 1.96 (1.89–2.05). The crude mortality rate ratio in the population aged 45–64 years in unvaccinated patients with T2DM versus unvaccinated controls was 5.99 (5.30–6.76), while crude infection rate ratio in the population aged 45–64 years in unvaccinated patients with T2DM versus unvaccinated controls was 1.66 (1.61–1.72).

Similar calculations for different timepoints and vaccines related to crude infection rate in the population aged 65–100 years as well as on crude mortality and infection rates in the population aged 45–64 years have also been performed and are included in online supplemental tables 2–5.

## Analysis related to VE, type of vaccine and time since vaccination

### VE against mortality *in the population aged 65–100 years*

Within 14–120 days after the Pfizer vaccine was administered, it showed a VE of over 75% (75.4 (95% CI 64.6 to 82.9) in controls and 84.8 (95% CI 77.3 to 89.8) in patients with T2DM). Regarding mortality, all vaccines still showed a significant protection at all time intervals ($p<0.001$ vs unvaccinated for all, online supplemental table 2, seventh column), although at 181–240 days, VE of the AstraZeneca vaccine was around 65%, while that of the Sinopharm vaccine was just below 50% (figure 3A and online supplemental table 2). The waning of the VE of the Pfizer vaccine could be statistically analyzed, and it only showed a significant decline at 181–240 days, in the T2DM group (figure 3A and online supplemental table 2, eight column). The Pfizer booster restored the VE to over 95% in both the primarily Pfizer and Sinopharm-vaccinated persons; in fact, the Pfizer-on-Pfizer booster resulted in a significant higher VE than the primary vaccination at 14–120 days with VE above 95%. Also, with a Pfizer-on-Sinopharm booster approach, VE of over 95% was obtained in both patients with T2DM and controls (figure 3A and online supplemental table 2).

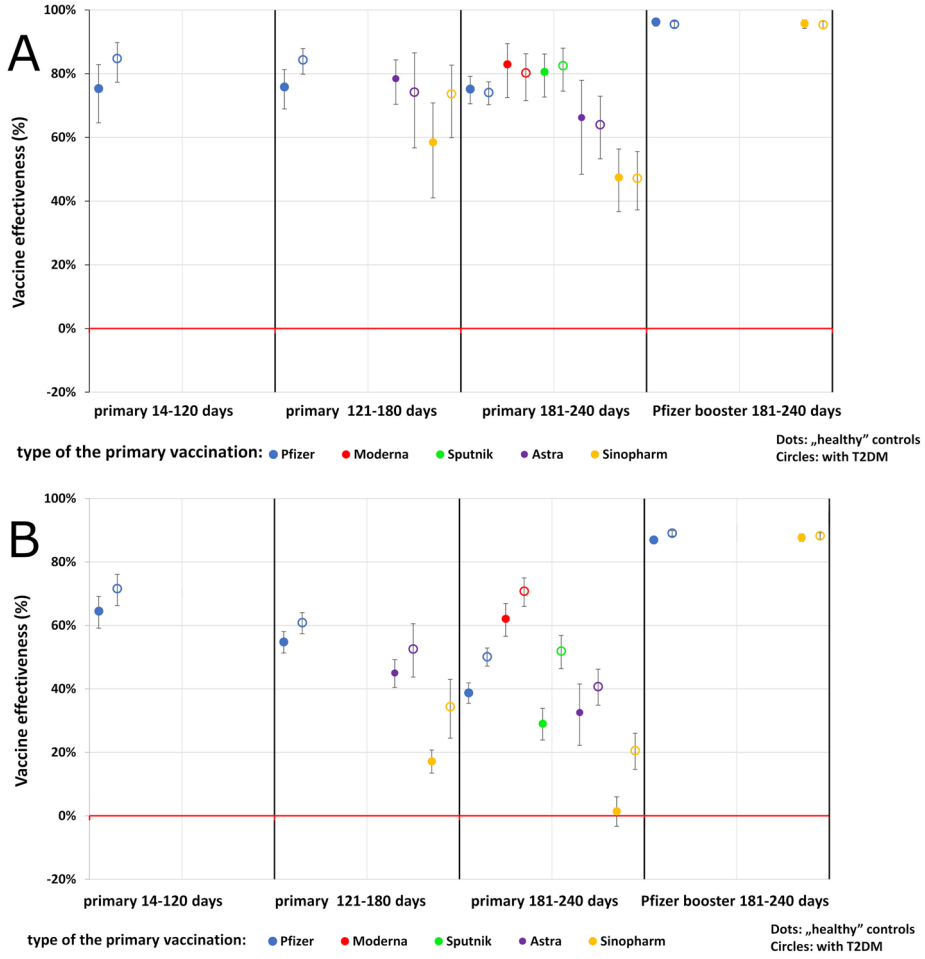


**Figure 3** Effectiveness of vaccination schemes against COVID-19-related death (A) and against SARS-CoV-2 infection (B) in individuals aged *65–100 years* without chronic diseases and with type 2 diabetes. Adjusted vaccine effectiveness values with their corresponding 95% CIs are depicted. T2DM, type 2 diabetes mellitus.

### VE against SARS-CoV-2 infection *in the population aged 65–100 years*

We found similar results in relation to SARS-CoV-2 infection (figure 3B). In general, vaccines were less effective in preventing SARS-CoV-2 infection than COVID-19-related death (figure 3A,B, online supplemental tables 2 and 3). At 14–120 days, the Pfizer vaccine showed a VE of more than 60% in both groups (64.5 (95% CI 59.2 to 69.2) in controls and 71.6 (95% CI 66.3 to 76.1) in T2DM) (online supplemental table 3). Most vaccines had a significant protective effect even 181–240 days after vaccination. The only exception was the Sinopharm vaccine in controls, where it has lost its protective effect (VE: 1.4 (95% CI −4.4 to 7.0), p=0.62), but not in patients with T2DM (20.5 (95% CI 14.6 to 26.0), p<0.001). Waning was much more profound in case of this outcome. As for the Pfizer vaccine, VE was significantly lower in the 121–180 days interval than in the 14–120 days interval in both patients with T2DM and in controls. Yet, VE could be fully restored using a Pfizer-on-Pfizer booster setting. Also, in the Pfizer-on-Sinopharm booster setting, a VE of over 85% could be reached in both patients with T2DM and in controls (figure 3B and online supplemental table 3).

### VE against mortality *in the population aged 45–64 years*

In general, VE was similar in this age group as compared with the groups aged 65–100 years (figure 4A, online supplemental table 4). All vaccines maintained a significant protective effect at all timepoints (p<0.001 vs unvaccinated, online supplemental table 4, seventh column). At 181–240 days, Sinopharm and AstraZeneca vaccines showed a VE of 60–71%, but the effectiveness of the other vaccines stayed around 80–90% after 180 days of vaccination. The waning could be analyzed statistically for the Pfizer vaccine, and the VE showed no significant decline, not even in the 181–240 days period (p>0.05 for all periods, online supplemental table 4, eighth column).

Like in the elder age group, the Pfizer-on-Pfizer booster led to a higher VE than the primary vaccination (online supplemental table 4, eighth column). The Pfizer-on-Sinopharm approach reached a VE of more than 90% in both patients with T2DM or controls (figure 4A, online supplemental table 4).

### VE against SARS-CoV-2 infection *in the population aged 45–64 years*

As expected, also for this age group, VE for infection was generally lower as for mortality (figure 4B vs

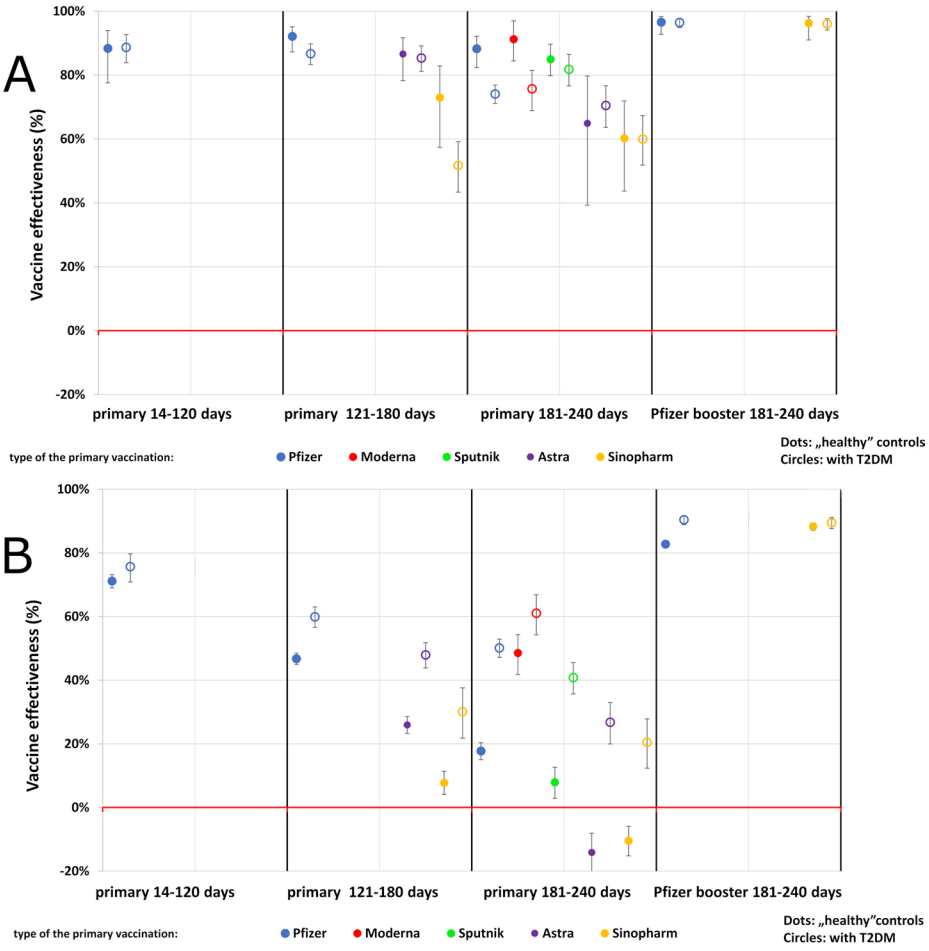


**Figure 4** Effectiveness of vaccination schemes against COVID-19-related death (A) and against SARS-CoV-2 infection (B) in subjects aged *45–64 years* without chronic diseases and with type 2 diabetes. Adjusted vaccine effectiveness values with their corresponding 95% CIs are depicted. T2DM, type 2 diabetes mellitus.

figure 4A). The primary vaccination was associated with a VE of more than 70% (71.2 (95% CI 69.0 to 73.2) in controls and 75.7 (95% CI 70.9 to 79.7) in patients with T2DM) (figure 4B and online supplemental table 5). Throughout the different time periods after vaccination, most vaccines still had a significant protective effect (online supplemental table 5, seventh column), but at 181–240 days, the VE of the Astra and Sinopharm vaccines became ineffective (−14.1 (95% CI −20.5 to −8.1) for the Astra vaccine and −10.4 (95% CI −15.2 to −5.9) for Sinopharm, online supplemental table 5, sixth and seventh columns). The VE against infection was generally relatively low in the periods of 121–180 and 181–240 days for several vaccines, especially in the control group. In fact, after 121–180 days of vaccination, VE of nearly all vaccines dropped to or below 50% (figure 4B and online supplemental table 5).

Pfizer booster restored the VE to more than 85% in the primarily Pfizer or Sinopharm-vaccinated persons both with and without T2DM. Also here, the Pfizer-on-Pfizer booster resulted in a higher VE as compared with the primary vaccination (figure 4B and online supplemental table 5).

## Comparing VE in patients with T2DM and in controls

By analyzing VE against *mortality in the population aged 65–100 years*, we found that generally, the vaccines were equally effective in patients with T2DM and in controls. In case of the Pfizer vaccine, at 121–180 days, the vaccine had an even higher VE in patients with T2DM than in controls. Also, the boosters were equally effective in patients with T2DM and controls (online supplemental table 2, ninth column).

With regard to *infection against SARS-CoV-2 infection in the population aged 65–100 years*, vaccines were generally more effective in patients with T2DM as in controls, even in the times of waning of effect. There was no difference between the two groups for the Astra vaccine in the 181–240 days period (p=0.25). The Pfizer-on-Pfizer booster was also more effective in patients with T2DM as compared with controls (p=0.002). This was not true for the Pfizer-on-Sinopharm approach, where the VE was similar in both groups (p=0.48) (online supplemental table 3, ninth column).

As for VE against *mortality in the population aged 45–64 years*, the vaccines were equally effective in patients with T2DM and in controls in most scenarios. Also, the

Pfizer-on-Pfizer and Pfizer-on-Sinopharm boosters were equally effective in patients with T2DM and controls (p=0.91 and p=0.93, respectively, online supplemental table 4, ninth column).

With regard to *SARS-CoV-2 infection in the population aged 45–64 years*, we found that vaccines were generally more effective in patients with T2DM as in controls, even during the times of waning. There was not a statistically significant difference between the two groups for primary Pfizer vaccine in the 14–120 days period (p=0.086). The Pfizer-on-Pfizer booster was more effective in patients with T2DM as compared with controls (p<0.001). This was not the case for the Pfizer-on-Sinopharm approach, where the VE was similar in both groups (p=0.28) (online supplemental table 5, ninth column).

We have to emphasize that, in general, incidence rates of mortality or infection were equal to or slightly higher even in the vaccinated T2DM group as in the vaccinated controls; however, the substantial difference between unvaccinated patients with T2DM and controls decreased (online supplemental tables 2–5, column 5).

## DISCUSSION

The present work provides nationwide insight into real-life VE of five different SARS-CoV-2 vaccines (Pfizer, Moderna, Sputnik, Astra and Sinopharm) in individuals with diabetes and controls without history of chronic diseases.

We found that with regard to SARS-CoV-2 infection, VE was at least as high or even higher for all vaccines and all timeframes in the people with T2DM than in the controls in both age groups (figures 3B and 4B and online supplemental tables 3 and 5). The results were varying more in this aspect regarding mortality, in general, vaccines were equally effective in patients with T2D and controls in most cases (figures 3A and 4A). Our results in the healthy control group were in line with the results in the general population published previously, showing quite some variability in VE by vaccine type.

Airway infections may be similarly common in people with and without DM, but data suggest that lower respiratory infections such as pneumonia could be more common in patients with DM as in non-diabetic controls (OR for DM1: 1.42, OR for DM2: 1.32).[4] Specifically for influenza, DM is associated with a higher frequency and more severe clinical course, similarly, also mycobacterial infections may be more frequent and more severe in individuals with DM.[27] Diabetes is also a known risk factor for SARS-CoV-2 infection as well as worse COVID-19-related mortality.[7 28–34] In a study from England, obesity itself was associated with higher COVID-19-related hospitalization or death even within the vaccinated cohort after adjustment for the presence of DM.[31]

However, data of the literature provide much less information to what extent SARS-CoV-2 vaccines are effective in patients with diabetes. To date, research mainly focused on in vitro, ex vivo or serologic examinations of patients with diabetes regarding the SARS-CoV-2 vaccines, and the results are conflicting: some data suggest that the antibody response to SARS-CoV-2 or SARS-CoV-2 vaccines may be weaker in individuals with DM.[35–37] On the other hand, other pieces of evidence support the notion that the immunization due to the infection or vaccination may be as effective in individuals with and without DM, especially if tighter glycemic control is achieved.[10 32 38–41]

Liu *et al*[42] presented regional data for a period after December 2022 (ie, presumably during the Omicron wave) on patients with T2DM. They obtained VE for individuals with T2DM only, as there was no non-diabetic control group involved. In this study, overall, 26 916 persons including 6307 unvaccinated ones were included from a single area in mainland China. The diagnosis of T2DM relies on the electronic health data system. The VE was calculated using infection and mortality rates in vaccinated and unvaccinated patients with T2DM. The VE results in the T2DM group were 17.6% (–17.1 to 42.0), 69.3% (56.6–78.3) and 88.0% (82.3–91.8) for partially, fully and booster-vaccinated patients, respectively. The paper did not present data on the types and percentages of vaccines used in the region, it only states that vector-based, recombinant protein-based and inactivated virus-based vaccines were used. The VE for mortality was age dependent in the paper by Liu *et al*. Full vaccination showed numerically higher VE in the 60–79 years population (74.9%) than in the 35–59 years (5.8) or the >80 years group (63.3%). As for the booster shot, the VE was highest in the 35–59 years group (96.3%), as compared with the 60–79 years (90.3%) or the >80 years (77.8%) group.[42] Our own data are not directly comparable with Liu *et al*, but they indicate a somewhat lower VE in the 65–100 years group as compared with the cohort aged 45–64 years. The efficacy of boosters was similar, yet minimally lower in the elder cohort.

Another paper from Hong Kong[43] included individuals with DM (not only T2DM) above the age of 12, patients were vaccinated using either Pfizer or Coronavac vaccines. The study was performed during a COVID outbreak when the Omicron strain was dominating. Persons vaccinated between January and March 2022 were involved. Patients with DM fully vaccinated with a Pfizer vaccine had a 22.1% protection regarding infection and 90.3% for mortality. The third dose of the Pfizer booster raised the VE to 54.2% for infection and to 98.2% for mortality, respectively.

A recent systematic review provided a good overview of individual studies regarding VE of SARS-CoV-2 vaccines in individuals with and without DM. The included studies were however severely heterogeneous with regard to inclusion and exclusion criteria, definitions of diabetes and definitions of the outcomes. Thus, no meta-analysis could be produced. Also, VE varied a lot across the studies, even with the same vaccine types. Overall, for infection, symptomatic illness, hospitalization or death, VE data were numerically lower for DM individuals compared with controls, but there were in several cases

overlapping CIs. When breakthrough infections were studied in a dedicated analysis, the OR was significantly higher in patients with DM compared with controls.[44]

Our data somewhat contradict this observation, as we detected a marked protection with SARS-CoV-2 vaccines also in individuals with T2DM. The different findings may be related to some factors, such that the vaccines included in the review were in part different from those in our study, namely CanSino and Sinovac vaccines are not available in Hungary; however, Sinopharm and Sputnik V were analyzed in our cohort, but not in the systematic review. Also, the definition of diabetes was heterogeneous in the studies included in the meta-analysis; moreover, the review states that 'there was almost no information on characteristics of persons with diabetes, including diabetes type and comorbidities such as obesity, renal disease and cardiovascular disease'.[44] Thus, we cannot exclude the possibility that patients with type 1 DM or other types of DM were included in the studies in the review. Scientific evidence suggests that immunogenicity of vaccines against hepatitis A, pneumococcus or diphtheria could be weaker in patients with type 1 DM versus controls, also patients with type 1 DM might require more frequent booster shots for some vaccines.[45] In general, VE in DM1 for other types of infectious agents is poorly studied and with conflicting results.[45] Additionally, the control group in our study was non-diabetic and free of major important comorbidities such as myocardial infarction, stroke, COPD, etc, thus it cannot be directly compared with other studies.

The negative VE, as seen in figure 4B and online supplemental table 5 for the Astra and Sinopharm vaccines, has already been described in the literature for SARS-CoV-2 vaccines[46 47] and can be due to bias or random error. This means that it is possible that a vaccine lost its effectiveness against infection after 6 months almost completely, and by chance the rate of infection happened to be higher in the vaccinated group. However, vaccine efficacy against COVID-19-related mortality did not wane that much and the studied vaccines still provided protection against death. The negative VE may be due to bias, as well, and may represent that vaccinated persons behave differently, they may not stick to infection control measures (such as isolation rules, wearing of masks, etc), they may also arise from different testing protocols or from the vaccination protocols, as in Hungary healthcare workers, elderly and people with chronic illnesses were included in the first rounds of primary vaccination and thus had longest time after vaccination, and also the effect of previous infection or hybrid immunity caused by infection in a vaccinated person could be in the background of negative VE.[48] We would like to point out that negative VE was only observed for infection but not for mortality.

We would like to point out that even after vaccination, incidence rates of mortality or SARS-CoV-2 infection were slightly higher or equal in the T2DM group as compared with controls. However, due to the higher VE observed in patients with T2DM, we could achieve that the initially striking difference between incidence rates of unvaccinated patients with T2DM and controls decreased to a comparable and sometimes equal level in the two groups.

Strengths of our analysis are its nationwide character, the inclusion of five different vaccines and the possibility of analyzing the effect of boosters, as well as waning of protection.

Limitations of the study include the lack of individual data on anthropometric parameters, on glycemic parameters, as those are not included in the NHIF-NCPHP database. Furthermore, our results only apply for the given population in the given timeframe and SARS-CoV-2 strain.

Overall, our data show at least similar or in some cases even higher grade of protection in people with T2DM compared with healthy individuals, and support the approach suggested by Pal *et al*, that 'COVID-19 vaccination … *had to be* … prioritized in individuals with DM' (modified from ref[38]).

**Author affiliations**
[1]Second Department of Medicine and Nephrology-Diabetes Center, University of Pécs Medical School, Pécs, Hungary
[2]Center for Health Technology Assessment, Semmelweis University, Budapest, Hungary
[3]RxTarget Ltd, Szolnok, Hungary
[4]Syreon Research Institute, Budapest, Hungary
[5]Institute of Digital Health Sciences, Semmelweis University, Budapest, Hungary
[6]National Center for Public Health and Pharmacy, Budapest, Hungary
[7]National Institute of Oncology, Budapest, Hungary
[8]Institute of Oncochemistry, University of Debrecen, Debrecen, Hungary
[9]Department of Pathology, Forensic and Insurance Medicine, Semmelweis University, Budapest, Hungary
[10]National Health Insurance Fund, Budapest, Hungary
[11]Central-Eastern European Academy of Oncology, Budapest, Hungary

**Acknowledgements** The authors thank the National Institute of Health Insurance Fund (NHIF) for providing the data for the study and Professor Dr József Andor for revision of language and style.

**Contributors** GAM and ZV contributed equally as first authors.ZV, GS, GR, and GAM contributed to conceptualization, methodology, formal analysis, validation, data curation and writing—review and editing. ZK, ZV and IW contributed to conceptualization, methodology, investigation, visualization and writing—original draft. DN, OS, PN, MP contributed to conceptualization, methodology, validation and writing—review and editing. AW, IK, MK and CM contributed to conceptualization, methodology, investigation and supervision. GAM and ZV contributed to writing—original draft and to validation and project administration. IW acts as a guarantor and accepts full responsibility for the work.

**Funding** The Center for Health Technology Assessment of the Semmelweis University participated in the project on a contractual basis made with the Ministry of Human Resources of Hungary and received funding from the Ministry of Human Resources.

**Competing interests** ZK is employed by MSD Pharma Hungary. At the time the study was performed, MK served as the Minister of Human Resources.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the Central Ethical Committee of Hungary (OGYÉI/40741-2/2021). This was a nationwide analysis, thus individual informed consent could not be obtained. All data were anonymously handled.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been

**ORCID iD**

István Wittmann http://orcid.org/0000-0001-5163-5733

## REFERENCES

1 Ong KL, Stafford LK, McLaughlin SA, *et al*. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of disease study 2021. *The Lancet* 2023;402:203–34.
2 Calvet HM, Yoshikawa TT. Infections in diabetes. *Infect Dis Clin NORTH Am* 2001;15:407–21,
3 Toniolo A, Cassani G, Puggioni A, *et al*. The diabetes pandemic and associated infections: suggestions for clinical Microbiology. *Reviews in Medical Microbiology* 2019;30:1–17.
4 Muller LMAJ, Gorter KJ, Hak E, *et al*. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005;41:281–8.
5 Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. *Nat Rev Endocrinol* 2022;18:525–39.
6 Forbes A, Gallagher H. Chronic kidney disease in adults: assessment and management. *Clin Med* 2020;20:128–32.
7 Chatterjee S, Nalla LV, Sharma M, *et al*. Association of COVID-19 with Comorbidities: an update. *ACS Pharmacol Transl Sci* 2023;6:334–54.
8 Roy B, Runa SA. SARS-Cov-2 infection and diabetes: pathophysiological mechanism of multi-system organ failure. *World J Virol* 2022;11:252–74.
9 Shafiee A, Teymouri Athar MM, Nassar M, *et al*. Comparison of COVID-19 outcomes in patients with type 1 and type 2 diabetes: A systematic review and meta-analysis. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2022;16:102512.
10 Ali H, Alterki A, Sindhu S, *et al*. Robust antibody levels in both diabetic and non-diabetic individuals after BNT162b2 mRNA COVID-19 vaccination. *Front Immunol* 2021;12(November):752233.
11 Cheng Y, Shen P, Tao Y, *et al*. Reduced antibody response to COVID-19 vaccine composed of Inactivated SARS-Cov-2 in diabetic individuals. *Front Public Health* 2022;10.
12 Zhang Y, Chen H, Lv J, *et al*. Evaluation of Immunogenicity and safety of Vero cell-derived Inactivated COVID-19 vaccine in older patients with hypertension and diabetes mellitus. *Vaccines (Basel)* 2022;10:1020.
13 Zhou X, Lu H, Sang M, *et al*. Impaired antibody response to Inactivated COVID-19 vaccines in hospitalized patients with type 2 diabetes. *Hum Vaccin Immunother* 2023;19:2184754.
14 Xiang F, Long B, He J, *et al*. Impaired antibody responses were observed in patients with type 2 diabetes mellitus after receiving the Inactivated COVID-19 vaccines. *Virol J* 2023;20:22.
15 Zhao M, Slotkin R, Sheth AH, *et al*. Serum neutralizing antibody titers 12 months after Coronavirus disease 2019 messenger RNA vaccination: correlation to clinical variables in an adult, US population. *Clin Infect Dis* 2023;76:e391–9.
16 Johnson RM, Ardanuy J, Hammond H. n.d. Diet induced obesity and diabetes enhance mortality and reduces vaccine efficacy for Sars-Cov-2. *Microbiology*
17 O'Meara TR, Nanishi E, McGrath ME. n.d. Reduced Sars-Cov-2 mRNA vaccine Immunogenicity and protection in mice with diet-induced obesity and insulin resistance. *Immunology*
18 Vokó Z, Kiss Z, Surján G, *et al*. Nationwide effectiveness of five SARS-Cov-2 vaccines in Hungary—the HUN-VE study. *Clin Microbiol Infect* 2022;28:398–404.
19 Kiss Z, Wittmann I, Polivka L, *et al*. Nationwide effectiveness of first and second SARS-Cov2 booster vaccines during the Delta and Omicron pandemic waves in Hungary (HUN-VE 2 study). *Front Immunol* 2022;13(June):905585.
20 Vokó Z, Kiss Z, Surján G, *et al*. Effectiveness and waning of protection with different SARS-Cov-2 primary and booster vaccines during the Delta pandemic wave in 2021 in Hungary (HUN-VE 3 study). *Front Immunol* 2022;13:919408.
21 EU health preparedness: A common list of COVID-19 rapid antigen tests, including those of which their test results are mutually recognised, and A common standardised set of data to be included in COVID-19 test result certificates, Available: https://ec.europa.eu/health/sites/health/files/preparedness_response/docs/covid-19_rat_common-list_en.pdf
22 World Health Organization (WHO). International guidelines for certification and classification (coding) of COVID-19 as cause of death. Available: https://www.who.int/publications/m/item/international-guidelines-for-certification-and-classification-(coding)-of-covid-19-as-cause-of-death [Accessed 13 Aug 2023].
23 Newcombe RG. MOVER-R confidence intervals for ratios and products of two independently estimated quantities. *Stat Methods Med Res* 2016;25:1774–8.
24 Altman DG, Bland JM. Statistics notes: how to obtain the P value from a confidence interval. *BMJ* 2011;343:d2304.
25 Demography - Elderly population - OECD Data, Available: https://data.oecd.org/pop/elderly-population.htm [Accessed 5 Nov 2023].
26 Hungary: Coronavirus Pandemic Country Profile - Our World in Data, Available: https://ourworldindata.org/coronavirus/country/hungary [Accessed 2 Feb 2023].
27 Al-Sayyar A, Hulme KD, Thibaut R, *et al*. Respiratory tract infections in diabetes – lessons from tuberculosis and influenza to guide understanding of COVID-19 severity. *Front Endocrinol (Lausanne)* 2022;13(July):919223.
28 Sharma J, Rajput R, Bhatia M, *et al*. Clinical predictors of COVID-19 severity and mortality: A perspective. *Front Cell Infect Microbiol* 2021;11:674277.
29 Sharma P, Behl T, Sharma N, *et al*. COVID-19 and diabetes: Association intensify risk factors for morbidity and mortality. *Biomed Pharmacother* 2022;151:113089.
30 Shauly-Aharonov M, Shafrir A, Paltiel O, *et al*. Both high and low pre-infection glucose levels associated with increased risk for severe COVID-19: new insights from a population-based study. *PLoS ONE* 2021;16:e0254847.
31 Piernas C, Patone M, Astbury NM, *et al*. Associations of BMI with COVID-19 vaccine uptake, vaccine effectiveness, and risk of severe COVID-19 outcomes after vaccination in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2022;10:571–80.
32 Marfella R, Sardu C, D'Onofrio N, *et al*. Glycaemic control is associated with SARS-Cov-2 breakthrough infections in vaccinated patients with type 2 diabetes. *Nat Commun* 2022;13:2318.
33 Luk AOY, Ng SSS, Holt RIG. Impact of diabetes on COVID-19 and other infection: report from the 22nd Hong Kong diabetes and cardiovascular risk factors—East meets West symposium. *Diabet Med* 2021;38:e14547.
34 Zhang J, Zhang J, Tao Z. Effect of comorbid diabetes on clinical characteristics of COVID-19 patients infected by the wild-type or Delta variant of SARS-Cov-2. *Front Endocrinol (Lausanne)* 2022;13:861443.
35 Rangsrisaeneepitak V, Porntharukchareon T, Dechates B, *et al*. Antibody levels in people with diabetes after one dose of the Chadox1 nCoV-19 (Azd1222) vaccine. *Diabetol Int* 2022;13:637–43.
36 Pal R, Sachdeva N, Mukherjee S, *et al*. Impaired anti-SARS-Cov-2 antibody response in non-severe COVID-19 patients with diabetes mellitus: A preliminary report. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2021;15:193–6.
37 Boroumand AB, Forouhi M, Karimi F, *et al*. Immunogenicity of COVID-19 vaccines in patients with diabetes mellitus: A systematic review. *Front Immunol* 2022;13:940357.
38 Pal R, Bhadada SK, Misra A. COVID-19 vaccination in patients with diabetes mellitus: Current concepts, uncertainties and challenges. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2021;15:505–8.
39 Lampasona V, Secchi M, Scavini M, *et al*. Antibody response to multiple antigens of SARS-Cov-2 in patients with diabetes: an observational cohort study. *Diabetologia* 2020;63:2548–58.
40 Dispinseri S, Lampasona V, Secchi M, *et al*. Robust neutralizing antibodies to SARS-Cov-2 develop and persist in subjects with diabetes and COVID-19 pneumonia. *J Clin Endocrinol Metab* 2021;106:1472–81.
41 Alhamar G, Briganti S, Maggi D, *et al*. Prevaccination glucose time in range correlates with antibody response to SARS-Cov-2 vaccine in type 1 diabetes. *J Clin Endocrinol Metab* 2023;108:e474–9.

42 Liu S, Jiang C, Liu Y, *et al*. "The effectiveness of COVID–19 vaccination against all–cause mortality in patients with type 2 diabetes mellitus: the observation during the initial period of the cancellation of the "dynamic zero policy" in Mainland China". *Diabetes Res Clin Pract* 2023;200:110694.
43 Wan EYF, Mok AHY, Yan VKC, *et al*. Vaccine effectiveness of BNT162b2 and Coronavac against SARS-Cov-2 Omicron BA.2 infection, Hospitalisation, severe complications, cardiovascular disease and mortality in patients with diabetes mellitus: A case control study. *J Infect* 2022;85:e140–4.
44 van den Berg JM, Remmelzwaal S, Blom MT, *et al*. Effectiveness of COVID-19 vaccines in adults with diabetes mellitus: A systematic review. *Vaccines (Basel)* 2022;11:24.
45 Esposito S, Mariotti Zani E, Torelli L, *et al*. Childhood Vaccinations and type 1 diabetes. *Front Immunol* 2021;12(August):1–8.
46 Hansen CH, Schelde AB, Moustsen-Helm IR, *et al*. Vaccine effectiveness against Sars-Cov-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: a Danish cohort study. *Infectious Diseases (except HIV/AIDS)* [Preprint].
47 Andrews N, Stowe J, Kirsebom F, *et al*. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. *N Engl J Med* 2022;386:1532–46.
48 Bodner K, Irvine MA, Kwong JC, *et al*. Observed negative vaccine effectiveness could be the Canary in the coal mine for biases in observational COVID-19 studies. *Int J Infect Dis* 2023;131(January):111–4.