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Short communication

Oropharyngeal shedding of herpesviruses before and after BNT162b2 mRNA vaccination against COVID-19

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ABSTRACT

Introduction: Concerns were raised over an increase in Bell's palsy, herpes simplex and herpes zoster after BNT162b2 vaccination, all are manifestations of herpesviruses reactivation. As herpesviruses commonly reactivate in the oropharynx, we have hypothesized that oropharyngeal shedding of herpesviruses will increase after vaccination.
Methods: Immune-competent Adults, excluding those using topical steroids or manifesting symptomatic herpesvirus infection, were sampled before BNT162b2 vaccination and one week after. Herpesviruses 1–7 shedding was tested with a multiplexed PCR.
Results: In 103 paired samples the prevalence of herpesviruses was similar before and after vaccination: HSV1, 3.9% vs. 5.8% (p = 0.75); HSV2, 0% vs. 1% (p = not applicable, NA); VZV, 0% vs. 0% (p = NA); EBV, 14.6% vs. 17.5% (p = 0.63); CMV, 0% vs. 0% (p = NA); HHV6, 4.9% vs. 7.8% (p = 0.55); HHV7, 71.8% vs. 72.8% (p = 1); any herpesvirus, 73.8% vs. 74.8% (p = 1).
Discussion: We did not find evidence for increased oropharyngeal reactivation of herpesviruses one week after BNT162b2.

1. Introduction

Pfizer/BioNTech's mRNA COVID-19 vaccine, BNT162b2, has received emergency use authorization by the US FDA on December 11th, 2020 [1], based on a phase III placebo-controlled study of over 40,000 individuals [2]. This study reported four cases of Bell's palsy among 21,720 individuals receiving BNT162b2, and no cases among a similar group receiving placebo. The FDA has concluded that the rate of Bell's palsy was consistent with the expected background rate in the general population, and that there was no clear basis for a causal relationship. Enhanced post-marketing vigilance was recommended [3]. Following vaccination campaigns in different countries, reports on Bell's palsy after vaccination were published [4–6]. By March 1st, 2021, there were 59 and 14 cases of Bell's palsy after the first and second vaccine doses, respectively, that were reported to the Israeli Ministry of Health following 4,755,585 first and 3,408,825 second doses delivered in Israel [7]. It was hypothesized that interferon production following vaccination might disrupt immunological tolerance and induce an inflammatory response, leading to the development of Bell's palsy. [8]. An alternative mechanism might involve reactivation of herpesviruses, specifically herpes simplex virus 1 (HSV1) and varicella zoster virus (VZV) [9–11].

Clinical reactivation of herpesviruses, such as mucocutaneous herpes simplex lesions or herpes zoster, were not reported during the clinical studies on BNT162b2. Anecdotal case reports and series were published post-marketing [12–15]. One of these reports has raised much public interest after its results were published in the

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general media, raising concern for the safety of COVID-19 vaccines [16]. In the summary of reported adverse events (AE) after BNT162b2 in Israel, a rate of 3.2 and 0.3 cases per 1 million vaccine doses (first and second dose, respectively) of herpes zoster, and 0.8 and 0.9 per 1 million doses of herpes simplex, were reported [7]. This was significantly lower than the anticipated incidence. Nevertheless, as these mild AE's might not even be reported by a patient to a physician, or might be only treated in an outpatient venue, a significant under-reporting is expected.

Latent herpesviruses commonly reactivate with ensuing asymptomatic shedding from the oropharynx, as was shown in studies with longitudinal sampling of healthy patients [17,18]. As Bell's palsy, herpes simplex and herpes zoster are all manifestations of herpesvirus reactivation, a possible common mechanism might be BNT162b2- triggered herpesvirus reactivation.

We sought to examine the rate of oropharyngeal herpesvirus shedding before and after BNT162b2 vaccination. We hypothesized that if BNT162b2 does trigger herpesvirus reactivation, a higher fraction of herpesvirus positivity will be found in post-vaccination samples.

2. Methods

This was a cohort study of individuals receiving the first dose of BNT162b2 in a single vaccination clinic. Consenting adults older than 18 years were included just before receiving a vaccine. Excluded were immunocompromised individuals, those who use topical steroid treatment (nasal spray or inhaler), or subjects who had recently received treatment with acyclovir, valacyclovir, ganciclovir or valgancyclovir. An oropharyngeal sample was taken with a swab (Novamed, Israel) and transported in a universal transport medium (Novamed, Israel) within 12 h to the laboratory. A second visit was scheduled 5–9 days after the first vaccine dose, in which a second sample was taken. Patients were also interviewed about having herpes labialis, chickenpox and herpes zoster in the past two weeks, and whether they had experienced facial paresthesia or facial palsy after vaccination. Patients' electronic medical records were assessed for symptomatic herpesvirus infection within two weeks after vaccination by searching medical encounters for relevant diagnoses and pharmacy records for purchases of anti-herpetic medications.

Nucleic acid was extracted from all specimens using HyExtract (Hy Labs, Israel). Herpes viruses were tested using Allplex™Meningitis-V1 Assay (Seegene, South Korea), a multiplex system for the detection of HSV1, herpes simplex 2 (HSV2), VZV, Epstein Barr virus (EBV), cytomegalovirus (CMV), and human herpes viruses 6 and 7 (HHV6, HHV7). Analysis of the PCR products was performed using SeeGene viewer. It needs to be noted that Allplex™Meningitis-V1 Assay is validated for cerebrospinal fluid, and has not been validated for testing herpesviruses in a respiratory specimen.

Statistical analysis: The prevalence of herpesviruses shedding in each visit was calculated as number of positive samples divided by the total number of individuals who had two valid samples analyzed. A comparison between the prevalence before vaccination and a week after vaccination was done for each herpesvirus using the McNemar chi-squared test for paired samples. Statistical analysis was done using R version 4.0.3.

The study was approved by the the Independent Ethics Committee of Maccabi Healthcare services (#0015–21 MHS).

3. Results

193 patients were included in the study. For 15 and 81 patients, no pre-vaccination or post-vaccination samples were available, respectively, leaving 103 patients with two samples for analysis. The average age was 40 (SD ± 15) years, and 43 (42%) were males. Post-vaccination sampling was performed an average of 7 (SD ± 1) days after vaccination. None of the patients reported facial paresthesia or paralysis after vaccination. No patient had a diagnosis of symptomatic herpesvirus disease after vaccination. One patient purchased topical acyclovir within two weeks. This patient only gave a first sample, and did not arrive for the second study visit, and therefore was excluded from the final analysis.

Table 1
Oropharyngeal herpesvirus PCR positivity immediately before and one week after BNT162b2 vaccination.

	Pre-vaccination positivity – N (%)	Post-vaccination positivity – N (%)	*p* value
HSV-1	4 (3.9%)	6 (5.8%)	0.75
HSV-2	0 (0%)	1 (1%)	NA
VZV	0 (0%)	0 (0%)	NA
EBV	15 (14.6%)	18 (17.5%)	0.63
CMV	0 (0%)	0 (0%)	NA
HHV-6	5 (4.9%)	8 (7.8%)	0.55
HHV-7	74 (71.8%)	75 (72.8%)	1.00
Any herpesvirus	76 (73.8%)	77 (74.8%)	1.00

The results of herpesviruses PCR tests are shown in Table 1.

No significant difference was noted in the test positivity for any herpesvirus between pre-vaccination and post-vaccination samples.

4. Discussion

In 103 subjects who were sampled before and 1 week after a first dose of BNT162b2, no increase in oropharyngeal herpesvirus reactivation was found following vaccination. These results support the low incidence rate of herpesvirus infection after BNT162b2 as reported to the Israeli Ministry of Health during a widespread vaccination campaign.

This study has some limitations. HSV1 positivity was higher in post-vaccination samples (5.8% vs. 3.9%), alas with no statistically significant difference. It is possible that a larger study could have shown a similar difference to have significance. We used oropharyngeal shedding as a sentinel for the reactivation of HSV1 and other herpesviruses, while it is possible that symptomatic reactivation in other sites, such as in the trigeminal ganglion, facial nerve, or skin, might occur with no increased oropharyngeal shedding. We have also performed an off-label test with a diagnostic assay that was validated on cerebrospinal fluid samples. Nevertheless, this assay was proven to be highly sensitive and specific [19], and if its off-label use would be expected to interfere with its performance on oropharyngeal samples, it would be expected to interfere with testing before and after vaccination in a similar way.

In conclusion, we did not find evidence to support increased reactivation of herpesviruses after vaccination with BNT162b2. Further epidemiological studies are needed to establish or refute a causal relationship between COVID-19 vaccination and diseases associated with herpesviruses.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tal Brosh-Nissimov reports a relationship with Pfizer Inc that includes: travel reimbursement, with no relevence to COVID-19 vaccines. Tal Brosh-Nissimov is a co-chairman of the Israeli COVID-19 vaccine advisory committee.

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