Seroprevalence of SARS-CoV-2 among Healthcare Workers: A Prospective Study

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ABSTRACT **Background:** Healthcare workers (HCWs) have close interaction with confirmed or suspected coronavirus disease 2019 (COVID-19) patients. Infection rates reported among HCWs are between 3% and 17%, and asymptomatic HCWs are a potential source of nosocomial transmission to vulnerable patients and colleagues. Universal mask use and good supply of personal protective equipment was implemented early at our institution.

Objectives: To determine the rate of infection by the serologic status of HCWs during first three COVID-19 waves, based on occupation and risk of exposure, compared to Israeli general population.

Methods: We conducted a prospective cohort study at Emek Medical Center from April 2020 to April 2021. A total of 101 HCWs volunteered to be followed at six time points by a serology test and a questionnaire.

Results: A total of 101 HCWs completed six serologic tests. All participants were seronegative at the four initial tests. The cumulative seropositivity rate for COVID-19 in HCWs was 9.9% (10/101). Only three seropositive HCWs (2.97%) were hospital-acquired.

Conclusions: Seroprevalence and seroconversion dynamics of severe acute respiratory syndrome coronavirus 2 infection in 101 HCWs during the first three COVID-19 outbreaks at Emek Medical Center were similar to the epidemiological curve of positive polymerase chain reaction results of the Israeli population, as published by the Israeli Ministry of Health, at each time point. Universal mask use and infection control measures may have contributed to a low hospital infection rate.

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KEY WORDS: asymptomatic healthcare workers and hospital-acquired SARS-CoV-2, hospital-acquired SARS-CoV-2, personal protective equipment (PPE), SARS-CoV-2 and healthcare workers, SARS-CoV-2 and surgical masks

Coronavirus disease 2019 (COVID-19) outbreak caused mass morbidity as well as the death of millions of people in the world and thousands in Israel. A major concern during outbreaks was the overwhelming local hospital capacity and depletion of the healthcare workforce.

Healthcare workers (HCWs) are at a higher risk for infection due to frequent and close interaction with confirmed or suspected COVID-19 patients. Data regarding the risk for COVID-19 among HCWs is not consistent [1]. In some medical centers the prevalence was estimated as low as 3% and in others as high as 17% [2-5]. Being an asymptomatic HCW is a potential risk of nosocomial transmission to vulnerable patients and colleagues [6].

During the first wave of the pandemic, overstretched healthcare systems dealt with long working hours, fatigue, and extreme psychological stress combined with a shortage or inadequate personal protective equipment (PPE) and inappropriate training for proper use. PPE included disposable surgical cap, goggles, protective liquid impermeable robe, gloves, protective overshoes, and N95 masks.

Several studies reported that most of the HCWs acquired COVID-19 at a non-COVID-19 ward via accidental exposure to a colleague or in the community [2].

The first local spread of COVID-19 in Israel was detected in March 2020, and since then another two waves have been documented until April 2021, with an increased number of infected cases [Figure 1]. The first Israeli nationwide seroprevalence study was conducted in the general population (June–September 2020, the second wave) and included 54,357 volunteers. The overall seroprevalence was 3.8%, and was higher in males than females (4.9 vs. 3.1%) [5].

Prevalence among HCWs was very low during the first wave of COVID-19 in eight Israeli hospitals (0.2% in non-COVID-19 wards and 1.1% in COVID-19 wards) [7]. Later, higher prevalence (10.3%), yet similar to the general population in an endemic area, was detected in a hospital in another area during the third wave (January 2021) [2].

The aim of our study was to determine dynamic and rate of infection by the serologic status of HCWs during the three first COVID-19 waves, according to occupation and risk of exposure, compared to Israeli general population.

PATIENTS AND METHODS

A prospective cohort study was conducted at Emek Medical Center from April 2020 to April 2021. The medical center is a medium-sized academic community hospital with 580 beds and 3500 staff members.

A total of 101 HCWs volunteered to be followed at six time points: April 2020, end of April 2020, May 2020, June 2020, October 2020, and April 2021. At each visit a serology test was taken and a questionnaire was completed. The questionnaire addressed current hospital occupation, adherence to PPE recommendations, and history of exposure to confirmed COVID-19 patients. Demographic data was completed in the first questionnaire. Workers were classified by exposure risk: very high, high, moderate, and low risk during 8-hour shifts.

The risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive patients was classified as:

- Very high: working in COVID-19-dedicated wards or respiratory emergency room (RER)
- High: working in general wards or general emergency room
- Medium: working with infrequent exposure to suspected patients
- Low: administrative and others without close patient contact

Blood was collected from all recruited participants by venipuncture. Serum was separated from clot and blood cells by centrifugation (1000 g, 10 minutes) using gel separator tubes. Samples were collected and then separated into a secondary tube and frozen at -200°C. Samples were thawed and mixed by vortex before testing on the particular analyzer.

SARS-CoV-2 antibodies of all participants were determined according to manufacturer instructions using two ready-to-use assays on automatic analyzers: SARS-CoV-2 IgG by Abbott Diagnostics (USA) qualitatively measuring IgG antibodies for the nucleocapsid protein, tested on Architect i2000R, using 1.4 index as cutoff and SARS-CoV-2 S1/S2 IgG and by DiaSorin S.p.A. (Italy) quantitatively measuring IgG antibodies for the S1 and S2 proteins, tested on Liaison XL, using 12.0 Au/ml as cutoff.

Since March 2020 we have implemented a policy of universal surgical masks use for all HCWs, patients, and visitors as well as strict use of disposable PPE for all interactions with suspected COVID-19 patients according to the risk of exposure. Reuse of disposable PPE is forbidden in our center in general.

A dedicated ward as well as an intensive care unit (ICU) for positive COVID-19 patients were opened. A dedicated RER screened all suspected patients by rapid polymerase chain reaction (PCR) test. At the beginning of the third wave (October 2020), all new admissions were screened by PCR. All HCWs working in high-risk areas wore full PPE according to infection control staff training and surveillance. Symptomatic HCWs were referred to the RER to be tested for SARS-CoV-2 by PCR.

Pfizer BNT162b2 mRNA vaccine against SARS-CoV-2 was provided to HCWs once the vaccination campaign started in Israel (20 December 2020).

Seropositivity for COVID-19 was considered following positive results with two different kits as recommended by the Israeli Ministry of Health.

The study was approved by the local Helsinki ethics committee.

RESULTS

Altogether 1411 patients were hospitalized with COVID-19 during the study period: 602 with mild disease, 533 moderate, and 276 severe or critical illnesses.

In total, 101 HCWs participated and completed six serologic tests. Demographics and exposure risk of seropositive and seronegative HCWs are detailed in Table 1 and Table 2, respectively.

All participants were seronegative at the four initial tests, including the first wave (April–May 2020). After the second wave

Table 1. Demographic and exposure risk of seropositive HCWs

Patient	Sex	Age, years	Position	Date of positive serology	Place of infection	Exposure risk
1	Male	40	Laboratory	10/2020	Outside hospital	Very high
2	Female	30	Physician	11/2020	Unknown	High
3	Male	48	Physician	11/2020	Outside hospital	Very high
4	Male	38	Physician	11/2020	Outside hospital	High
5	Female	39	Caregiver	12/2020	**HOSPITAL**	Very high
6	Male	52	Administration	2/2021	Unknown	Medium
7	Female	40	Caregiver	4/2021	**HOSPITAL**	Very high
8	Female	42	Caregiver	4/2021	Unknown	High
9	Female	57	Dietitian	4/2021	Outside hospital	Medium
10	Male	64	Physician	4/2021	**HOSPITAL**	High

HCWs = healthcare workers

Table 2. Demographic and exposure risk of seronegative HCWs

Number of patients	Sex	Age, years	Exposure risk
101	63 Female, 38 Male	Mean 40.5 (Range 18–68)	Very high: 49 (53.8%), High: 19 (20.9%), Medium: 10 (11.0%), Low: 13 (14.3%)

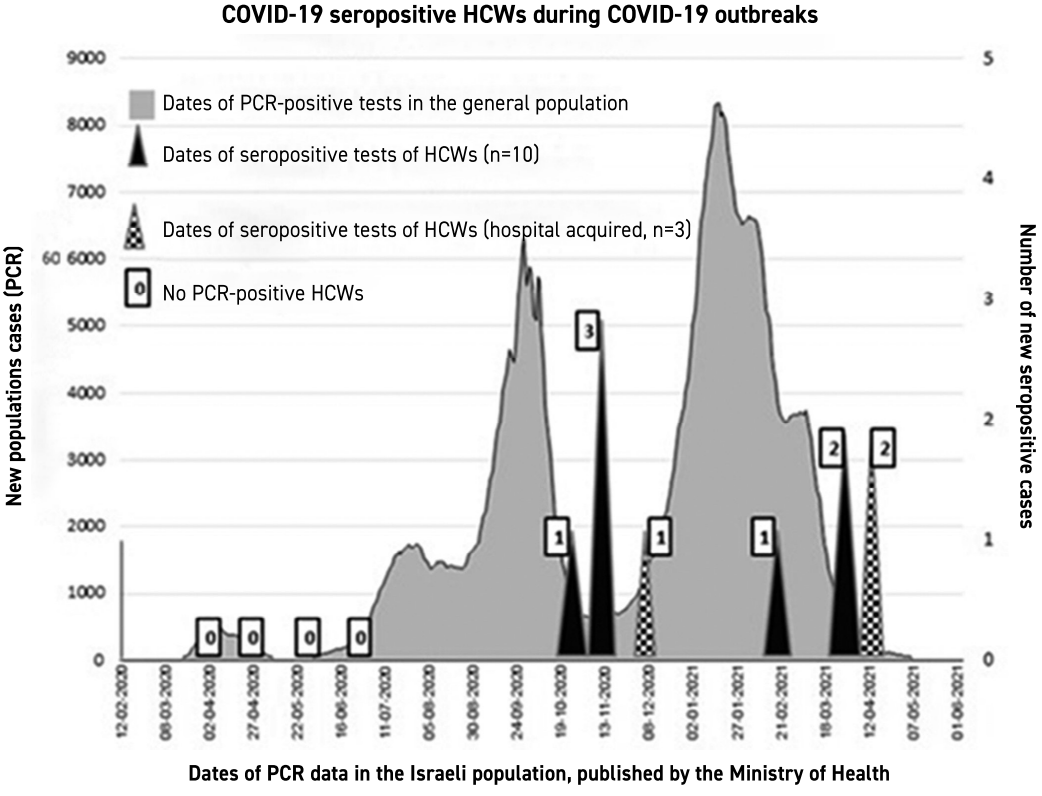
HCWs = healthcare workers

(5th test, August–October 2020) five seropositive HCWs were identified (4.95%), one hospital-acquired. During the third wave (December 2020–March 2021) one new seropositive HCWs was documented (February 2021). Later, another four seropositive HCWs were identified (April 2021), two were hospital-acquired. The cumulative seropositivity rate for COVID-19 in HCWs was 9.9% (10/101.) The increase in the seroprevalence among HCWs appears to be similar to the epidemiological curve of positive PCR results of local population, published by the Israeli Ministry of Health at each time point [Figure 1]. Eight of 10 seropositive HCWs were symptomatic with positive PCR test for SARS-CoV-2. Nine of the seropositive HCWs were not vaccinated prior positive PCR test for SARS-CoV-2, and one HCW had positive PCR 5 days after the second dose of vaccine.

Out of 91 seronegative participants, 82 were vaccinated (two doses) from December 2020 to February 2021 after the fifth visit, and nine were not vaccinated at all.

Among the 10 seropositive HCWs 4 were at a very high risk of exposure, 4 at high risk, and 2 at medium risk. The epidemiological investigation found that COVID-19 infection was considered hospital-acquired only in 3 (2.97%), 2 of them at very high risk and 1 at high risk of exposure [Table 1 and Table 2]. No correlation was found between seropositivity and exposure risk to COVID-19 [Table 1] by exact Fisher non-parametric test ($P > 0.05$). Among very high and high exposure risk, the chance of seropositivity to COVID-19 is 150% greater (multiply 2.5) among the very high exposure risk relative to a high risk exposure ($P > 0.05$).

Figure 1. Dynamic of seroprevalence of COVID-19 in HCWs in correlation to positive new cases by PCR in the general population
COVID-19 = coronavirus disease 2019, HCWs = healthcare workers, PCR = polymerase chain reaction



DISCUSSION

Since the beginning of the COVID-19 pandemic, HCWs have shown remarkable resilience and professional dedication despite fear of becoming sick and infecting others [9]. Infected HCWs have a deleterious effect on the healthcare system; therefore, understanding risk factors for hospital-acquired COVID-19 is crucial for future decisions regarding PPE use and infection control measures.

Protecting HCWs from infection is critical. However, despite all efforts, some exposures are inevitable and can occur at the workplace or in the community [3,5].

To protect HCWs and patients, our policy was to admit suspected patients to a dedicated RER [10] and to hospitalize positive COVID-19 patients in dedicated COVID-19 wards. HCWs in these wards wore fully protected PPE and N95 face masks; thus, it is not surprising that in our study population there were only two infections among this team.

Yet, in general wards and non-clinical areas, the adherence to infection control measures may have been less strict and un-diagnosed infection among patients and co-workers could have been a source of infection due to high seroprevalence among low and moderate exposure risk groups [2]. In our study, hospital-acquired COVID-19 infection was detected only in very high and high-risk HCWs. As part of our infection control program, which the hospital adopted early in the outbreak, we adopted a universal policy of medical facemasks for all workers, patients, and visitors. These measures probably contributed to the lower rate of hospital-acquired infection among HCWs in general and in medium and low-risk exposure HCWs in particular. Similar findings were published by Richterman and colleagues [6] showing that hospital transmission of SARS-CoV-2 was likely rare with universal mask use and by Wang et al. [11] showing a decline of HCWs acquired COVID-19 infection after universal masking implementation.

The first seroprevalence survey of COVID-19 in Israel, a cross-sectional study during the second wave of COVID-19 (June–September 2020) documented a 3.8% of seropositivity among general population [8]. Another survey [12] described a seropositivity of 1.9% in the general population and at the end of the first wave.

The Israeli study led by Temkin [7] described the extremely low prevalence of asymptomatic COVID-19 HCWs in eight Israeli general hospitals. They tested naso/oropharyngeal PCR during the second wave (April–May 2020) and found 0.2% positivity, but a cross-sectional study based on PCR detection might not be comparable to a prospective serologic study. In contrast, Benenson [2] conducted a screening program based on proactive periodic PCR tests and found that 10.3% of the HCWs were infected (similar to the incidence in the local population), mostly due to community exposure.

Most worrying data was published from New York [9] where the seroprevalence in the general population was 13.7% in contrast to HCWs 27%, which showed double risk for infection among HCWs.

In our prospective cohort study, we found that our seroprevalence was located low in the scale reported in the literature and the dynamic of seropositivity for COVID-19 infection among HCWs was similar to the Israeli epidemiological curve of positive PCR [11] [Figure 1]. Although no correlation was found between seropositivity and exposure risk to COVID-19, the chance of seropositivity to COVID-19 is greater among the very high exposure risk relative to a high exposure risk.

Different studies reported that HCWs had a 3.4-fold [3] higher risk of acquiring COVID-19, mainly due to inadequate PPE, low hand hygiene compliance, and reluctance to change gloves [1,3].

In our study 4 of the 10 seropositive HCWs reported close contact with a confirmed COVID-19 person outside the hospital. For three exposures the sources were defined as unknown after a thorough and detailed epidemiological investigation, while only three were defined as hospital-acquired.

LIMITATIONS AND STRENGTHS

This study has two main limitations: small sample size and the inherent characteristic of a single center, which may have cause a bias and limited the generalizability of the findings.

The strength of this study is the prospective surveillance of serology status IgG antibodies by two diagnostic tests measuring IgG antibodies for the nucleocapsid protein, and IgG antibodies for the S1 and S2 proteins along the three first outbreaks, which allowed us to differentiate antibodies from disease vs. antibodies from vaccine. To the best of our knowledge, this is the only prospective serologic study conducted in the first year of the pandemic in Israel.

We suggest that opening a RER [10] and strict infection control practices as hand washing, early implementation of universal surgical mask use, use of disposable PPE with good training, and close surveillance by infection prevention team, and no reuse and no shortage of PPE contributed to the low hospital acquisition of COVID-19 infection among HCWs at our facility.

CONCLUSIONS

This study showed a low seroprevalence of hospital-acquired SARS-CoV2 among our HCWs. We suggest, and even emphasize, that transmission of COVID-19 in the hospital setting may be lower with universal use of PPE, even during periods of high COVID-19 prevalence in the community.

Availability of disposable PPE, universal use of surgical masks, strict infection control practices, early isolation, and mass screening of admitted patients are all important measures that contribute to the low infection rate of hospital-acquired infection in HCWs.

These measures are still relevant due to the current predominance of new variants of SARS-CoV-2, which are generating a breakthrough infection in the vaccinated population.

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Capsule

Gene therapy promotes healing of epidermolysis bullosa

The rare skin disease recessive dystrophic epidermolysis bullosa (RDEB) is caused by mutations in the *COL7A1* (collagen type VII a1 chain) gene. This gene normally encodes an important component of the basement membrane that connects the epidermis and dermis. RDEB is thus characterized by skin blistering, fibrosis, and susceptibility to infection and cancer. **Gurevich** and co-authors developed a topical gene therapy, Beremagene Geperpavec (B-VEC), for RDEB in which *COL7A1* coding sequences are delivered by inactivated herpes simplex virus type 1 (HSV-1) to the skin. Having established that B-VEC restored COL7A1 protein expression in preclinical models, the authors conducted a phase 1/2 trial in nine RDEB patients. B-VEC or placebo was repeatedly applied to matched wounds, and B-VEC promoted COL7A1 expression and wound closure. There was also evidence of correct epidermis-dermis organization.

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Capsule

Somatic genomic changes in single Alzheimer's disease neurons

Miller and co-authors analyzed single-cell whole-genome sequencing data from 319 neurons from the prefrontal cortex and hippocampus of individuals with Alzheimer's disease and neurotypical control individuals. The authors found that somatic DNA alterations increase in individuals with Alzheimer's disease, with distinct molecular patterns. Normal neurons accumulate mutations primarily in an age-related pattern (signature A), which closely resembles clock-like mutational signatures that have been previously described in healthy and cancerous cells. In neurons affected by Alzheimer's disease, additional DNA alterations are driven by distinct processes (signature C) that highlight C>A and other specific nucleotide changes. These changes potentially implicate nucleotide oxidation, which show is increased in Alzheimer's-disease-affected neurons in situ. Expressed genes exhibit signature-specific damage, and mutations show a transcriptional strand bias, which suggests that transcription-coupled nucleotide excision repair has a role in the generation of mutations. The alterations in Alzheimer's disease affect coding exons and are predicted to create dysfunctional genetic knockout cells and proteostatic stress. These results suggest that known pathogenic mechanisms in Alzheimer's disease may lead to genomic damage to neurons that can progressively impair function. The aberrant accumulation of DNA alterations in neurodegeneration provides insight into the cascade of molecular and cellular events that occurs in the development of Alzheimer's disease.

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