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No seroconversion among healthcare workers exposed to SARS-CoV-2 during the early phase of the pandemic

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ABSTRACT

***Background**: The SARS-CoV-2 pandemic is associated with morbidity, hospitalizations, absenteeism, and mortality among healthcare workers (HCW).* ***Aim:** To evaluate the seroconversion rate in HCW exposed to SARS-CoV-2 in the early pandemic phase in 2020 at a regional reference hospital.* ***Material and Methods**: One hundred seventy-nine HCW working at a regional hospital were invited to a longitudinal study performed between April-July 2020. A serological analysis by ELISA IgG for viral nucleoprotein and protein S with a secondary analysis by ELISA IgG protein S1/S2 for samples with positive or doubtful result was carried out together with a complementary online survey to inquire about occupational or community exposures to SARS-CoV-2.* ***Results:** Two cases with baseline infection were detected (1.1%, one symptomatic and one asymptomatic) and no cases of seroconversion were detected. During the study period, there were 136 patients hospitalized with COVID-19, and regional weekly COVID-19 incidence ranged from 2.7 to 24.4 per 100,000 inhabitants. No SARS-CoV-2 cases were detected by PCR among 27 HCW who consulted for respiratory symptoms in the period. Online surveys confirmed direct care of COVID-19 patients and also detected a high degree of unprotected social interaction at work.* ***Conclusions:** There was no evidence of seroconversion in this group of HCW exposed to the risk of infection by SARS-CoV-2 during the onset of the COVID-19 pandemic. Personal protective equipment and other measures used by the HCW were extremely useful for their protection in the initial phase of the pandemic.*

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***Key words**: Developing Countries; Health Personnel; SARS-CoV-2; Seroconversion.*

Ausencia de seroconversión en trabajadores de la salud expuestos a SARS-CoV-2 durante la primera fase de la pandemia

Antecedentes:** La pandemia de SARS-CoV-2 está asociada a morbilidad, hospitalizaciones, ausentismo y mortalidad entre el personal de salud (PS).* ***Ob-

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***jetivo**: Evaluar la tasa de seroconversión en el PS expuesto al SARS-CoV-2 en la fase pandémica inicial el 2020 en un hospital regional de referencia. **Material y Métodos**: Ciento setenta y nueve trabajadores de la salud fueron invitados a un estudio longitudinal realizado entre abril-julio de 2020. Se efectuó un análisis serológico por ELISA IgG para nucleoproteína viral y proteína S con un análisis secundario por ELISA IgG proteína S1 / S2 para muestras con resultado positivo o dudoso junto a encuestas complementarias en línea para preguntar sobre exposiciones ocupacionales o comunitarias al SARS-CoV-2. **Resultados**: Se detectaron dos casos con infección basal (1,1%, uno sintomático y uno asintomático) sin casos de seroconversión. Durante el período de estudio, hubo 136 pacientes hospitalizados con COVID-19, y la incidencia semanal regional de COVID-19 osciló entre 2,7 y 24,4 por 100.000 habitantes. No se detectaron casos de SARS-CoV-2 por PCR entre los 27 funcionarios que consultaron por síntomas respiratorios en este período. Las encuestas en línea confirmaron la atención directa de los pacientes con COVID-19 y también detectaron un alto grado de interacción social desprotegida en el trabajo. **Conclusiones:** No hubo evidencia de seroconversión en un grupo de funcionarios expuestos al riesgo de infección por SARS-CoV-2 durante el inicio de la pandemia de COVID-19. Los equipos de protección personal y otras medidas utilizadas por el PS fueron de suma utilidad para su protección en la fase inicial de la pandemia.*

***Palabras clave**: SARS-CoV-2; Personal de Salud; Seroconversion; Países en Desarrollo.*

The SARS-CoV-2 pandemic is associated to morbidity, hospitalizations, absenteeism and mortality among healthcare workers (HCW)[1-5]. Contagion can occur during patient care, interactions with the rest of HCW, or in community or family settings[6-9].

HCW in a regional hospital in southern Chile were at risk of infection since the end of March 2020 due to its designation as a reference center for seriously-ill COVID-19 patients. Protection of the HCW was based on the use of personal protective equipment (PPE: apron, gloves, facial protection) with the use of a surgical mask or type N95 according to type of care besides hand hygiene, physical distancing at work interactions and reduction of agglomerations in eating hours. In addition, free care for HCW with respiratory symptoms was incorporated in a designated outpatient center at the same hospital that included the study of SARS-CoV-2 by PCR. Measures included instructions for affected HCW to be quarantined if diseased or after close contact with a positive case. It is relevant to evaluate whether containment measures before the availability of vaccines (available in Chile only after the following year) were useful to restrain the spread of SARS-CoV-2 among HCW, especially during the care of COVID-19 patients. With this aim we designed a prospective seroconversion study in a cohort of exposed HCW during the first months of the pandemic in 2020 in a regional reference hospital in a pre-vaccinal era.

Methods

Aims

The primary outcome was to measure the seroconversion rate in HCW who attended or cared COVID-19 patients in an outpatient or inpatient basis. Secondary outcomes were to estimate the seroconversion rate in symptomatic or asymptomatic cases and to correlate the presence of seroconversion with different variables of community or hospital exposure.

Study design

Prospective study of a HCW cohort from the Hospital Base de Valdivia in Los Ríos Region in southern Chile, who were exposed during care or attention of patients affected by SARS-CoV-2. This regional center served since March 2020 as

an hospitalization center for seriously ill patients (with O_2 requirements and monitoring) or critical patients (with ICU requirements) affected by COVID-19. For this study we included HCW of the Respiratory Emergency Unit, the outpatient unit for HCW with respiratory symptoms (enabled during the pandemic), the outpatient clinic for community patients with respiratory symptoms (enabled during the pandemic), general wards designated for the hospitalization of COVID- 19 patients, Intensive Care Units, the Molecular Biology Laboratory and 4 infectious disease physicians. All HCW from these units were invited to participate in the study with their respective informed consent.

Serological study

During the study period between mid-April and July 2020 (epidemiological weeks 16 to 30), 5 consecutive blood samples were taken from each participating (baseline, at 2 weeks, at one month, second month and third month, respectively; S1 to S5). Samples were stored in cryotubes and kept at -20oC until processing. To optimize the sensitivity of the study, 2 ELISA techniques were applied successively with a final neutralization assay by competition in selected cases. Initially, a screening was performed with an ELISA IgG technique for the nucleoprotein (N) and Spike protein (S) of SARS-CoV-2 (Vircell Microbiologists, Spain) which, according to manufacturer's data, offers a sensitivity of 85% and a specificity of 98%. This technique revealed a high number of samples with positive or doubtful results (see results). These samples were analyzed with an ELISA IgG technique for the S1 / S2 ectodomain of the viral protein S (Virion / Serion agile SARS CoV 2 IgG, Germany), a test of higher sensitivity and specificity (> 96% and 100%, respectively). Finally, selected positive samples were subjected to a neutralization test by a competitive ELISA which is expressed as a percentage of neutralization inhibition (SARS-CoV-2 Neutralizing Antibodies Detection Kit of AdipoGen LifeSciences, Switzerland)[10]. A baseline infection was defined as a SARS-CoV-2 positive PCR confirmed event before enrollment or a positive serological test by ELISA IgG Virion. Seroconversion was defined as the appearance of a positive sample with this same technique during follow-up. Cut-off values were applied as described in the literature[11,12].

Detection of symptomatic cases, study variables and exposure of HCW to COVID-19 at hospital and in the community

During the study, HCW were invited to consult in case of respiratory symptoms at the designated outpatient unit for HCW or in the Emergency Unit without charges. During attendance, a nasopharyngeal swab sample was taken for the detection of SARS-CoV-2 by PCR using a previously described commercial kit[13].

We included an objective measure of exposure of the HCW to SARS-CoV-2 using the weekly number of patients admitted for COVID-19 that was complemented with weekly regional incidence rates[14]. Using 3 online surveys at the beginning (EW 17-18), at the middle (EW 24-26) and at the end of study (EW 29-30), HCW involvement in respiratory sampling, open aspiration of orotracheal secretions, intubation procedures, cardiovascular resuscitation, routine changes of patient position, respiratory kinetic care, inhalation therapy or direct patient care without procedures was also evaluated. The use of PPE and accidents during their use was also evaluated in these surveys, as well as sharing of common spaces at work (at rest or eating areas). Possible community exposure to SARS-CoV-2 was also investigated through the presence of COVID-19 cases at home, contact with confirmed cases outside the workplace, and use of public transportation.

Statistic analysis

The variables associated with work issues, survey and serological results were analyzed as categorical variables and tabulated as proportions. Hospitalized COVID-19 cases are presented as curves according to the EW.

Ethical issues

This study was approved by the Comité de Ética Científico del Servicio de Salud, Los Ríos Region, Chile. Participants gave their informed consent.

Results

Enrolled personnel

179 HCW were enrolled at the beginning of this study (S1), 175 samples (97.8%) were taken at S2, 174 at S3 (97.2%), 175 at S4 (97.8%) and

172 in the last sample (S5: 96.1 %). A total of 167 HCW completed the 5 study samples (93.3% of the original group). Three patients withdrew from the study after the first or second sample (1.7%). The first sample (S1) was obtained between epidemiological weeks (EW) 16-17, S2 at EW 18-20, S3 at EW 21-22, S4 at EW 24-26 and S5 at EW 29-30 of year 2020. Sample size corresponded to 9.4% of the total clinical and non-clinical staff (1909 employees, 95% confidence level, 7% error), to 12.2% of the total clinical staff (1472 employees; 95% confidence level, 7% error) and 37.4% of the personnel directly exposed to SARS-CoV-2 (478 employess; 95% confidence level, 6% error).

Table 1 shows the workplace distribution of enrolled HCW and their professional profile.

Table 1. HCW workplace and professional profile distribution during a longitudinal study for SARS-CoV-2 seroconversion, Hospital Base de Valdivia, Chile. Epidemiological weeks 16 to 30, 2020

	n (%)
Workplace	
Respiratory Emergency Unit	24 (13.4%)
ICU 1	48 (26.8%)
ICU 2	42 (23.5%)
COVID-19 medical wards	36 (20.1%)
Outpatient clinic for patients with respiratory symptoms	12 (6.7%)
Outpatient clinic for HCW with respiratory symptoms	9 (5.0%)
Infectious diseases specialists	4 (2.2)
Molecular Biology Laboratory	4 (2.2%)
Total	179 (100%)
HCW profile	
Administrative clerk	2 (1.1%)
Auxiliary service	25 (14%)
Nurse assistant	62 (34.6%)
Nurse	41 (22.9%)
Midwife	1 (0.6%)
Physical therapist	8 (4.5%)
Physician	37 (20.7%)
Biochemist	3 (1.7%)
Total	179 (100%)

HCW with respiratory symptoms

Between EW 16 to 30, 27 HCW consulted for respiratory symptoms in the designated outpatient clinic and none was detected with SARS-CoV-2 infection by PCR.

Serological study

A physician joined the cohort immediately after a symptomatic SARS-CoV-2 infection demonstrated by PCR. This case was not considered as a conversion due to its baseline positivity. A total of 27 HCW (15.1%) had a positive reaction with the first ELISA test (Vircell) and another 10.6% had doubtful results in different determinations (Table 2). Positive and doubtful samples obtained during the initial analysis (46 in total), were analyzed by a second ELISA technique directed to the SARS-CoV-2 protein S (S1 / S2, Virion) with better sensitivity and specificity. In 44 of the 46 samples analyzed, infection was ruled out during the study (Table 3).

Positive results were detected with the Virion ELISA S1 / S2 technique in the samples of only 2 HCW, one of them corresponding to a case with symptomatic COVID-19 diagnosed before the start of the study (already commented) and the other case to a HCW without COVID-19 like- illness that was also positive at S1(Table 3). In this case there was no evidence of contact with positive cases or symptoms suggestive of COVID-19. Thus, of the 176 HCW participating during the serological follow-up, none presented infection during the study period that spanned 14 epidemiological weeks (0% seroconversion during 15,082 personnel-days) and 2 of them had a previous infection (1.1%).

Table 2. Distribution of Vircell ELISA IgG nucleoprotein and S protein results (Vircell Microbiologists, Spain) during a longitudinal study for SARS-CoV-2 seroconversion, Hospital Base de Valdivia, Chile. Epidemiological weeks 16 to 30, 2020

ELISA IgG result	n (%)
Positive	27 (15.1%)
Doubtful	19 (10.6%)
Negative	130 (72.6%)
Withdrew from study	3 (1.7%)
Total	179 (100%)

Table 3. Distribution of ELISA IgG S1/S2 results (Virion/serion, Germany) during a longitudinal study for SARS-CoV-2 seroconversion, Hospital Base de Valdivia, Chile. Epidemiological weeks 16 to 30, 2020

ELISA IgG result	n (%)	Neutralization assay (as percentage)
Negative	44 (95.7%)	Not done
Positive	1 (2.2%)*	< 20% (negative)
Doubtful	1 (2.2%)**	39.5% (positive)**
Total	46 (100%)	

*Asymptomatic case detected at M1, also positive by ELISA IgG Vircell; **COVID-19 case confirmed before enrollment, also positive by ELISA IgG Vircell at M1.

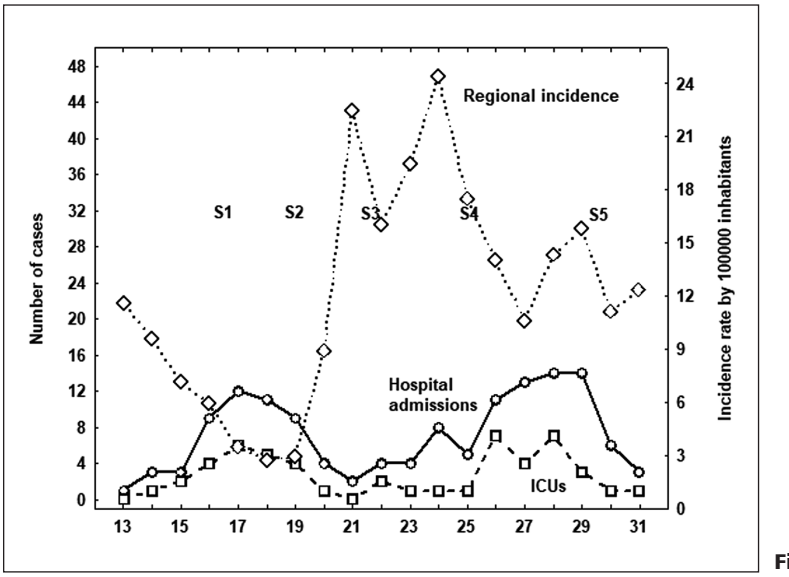

Figure 1.

Neutralization by competition

The antibody competition neutralization study confirmed the presence of neutralizing antibodies in the HCW with symptomatic COVID-19 at the beginning of the study despite a doubtful ELISA Virion IgG test (39.5%). In contrast, no neutralizing antibodies were detected in the HCW with a positive ELISA Virion IgG test at S1 who did not report symptoms (< 20%, Table 3).

Exposure to risk

During the study period, HCW were exposed to risk during COVID-19 patient´s care either in COVID-19 designated outpatient clinics, Emergency Unit, ICUs or hospital wards. Figure 1 shows number of COVID-19 admitted patients (total and ICU). Between EW 13 to 31 of 2020 there were 136 admitted patients with COVID-19, 51 of them in ICUs (37.5%) verifying exposure to risk. Regional weekly COVID-19 incidence ranged from 2.7 to 24.4 per 100,000 inhabitants during the study period (Figure 1)[14].

Online surveys

Polls were answered by 126, 123 and 125 HCW (69%-71% of study participants), respectively. In them, different parameters potentially associated with an occupational, community or at home exposure were evaluated (Table 4). A high degree of occupational exposure was evidenced by direct care of admitted COVID-19 patients (> 60%) during respiratory sampling, aspiration of airway

Table 4. Distribution of working, at-home or community exposure and respiratory symptoms among HCW obtained by online surveys during a longitudinal study for SARS-CoV-2 seroconversion, Hospital Base de Valdivia, Chile. Epidemiological weeks 16 to 30, 2020

Variable	Total n = 325
Attention of patients with suspicion of COVID-19	286 (75%)
COVID-19 patient care	233 (62.3%)
Respiratory sampling in COVID-19 patients	73 (19.5%)
Aspiration of respiratory secretions	86 (23%)
Intubation of COVID-19 patients	46 (12.3%)
Position changes of COVID-19 patients	159 (42.5%)
Bathing of COVID-19 patients	117 (31.3%)
Management of oxygen equipment in COVID-19 patients	149 (39.8%)
Cardiopulmonary resuscitation of COVID-19 patients	44 (11.8%)
Physical therapy of COVID-19 patients	23 (6.1%)
Respiratory barriers	
N95 mask use	
Always	27 (7.2%)
Sometimes	76 (20.3%)
Never	152 (40.6%)
N95 mask displacement	7 (1.9%)
Surgical mask use	
Always	253 (67.6%)
Sometimes	16 (4.7%)
Never	38 (11.2%)
Surgical mask displacement	29 (7.8%)
Also working in other Healthcare Center	49 (13.1%)
Coworkers with COVID-19	25 (6.7%)
*Social interactions while working**	
Share eating place	156 (62.9%)*
Share eating place and also meetings without social distance	32 (12.9%)*
Share eating place and also prolonged meetings in closed spaces	10 (4.0%)*
Without social interaction at work	50 (20.2%)*
Community or at home exposure	
Collective taxi use	75 (20.1%)
Collective taxi use and public transportation bus	48 (12.8%)
In quarantine recently	5 (1.3%)
Relatives in quarantine	9 (2.4%)
COVID-19 cases at home	3 (0.8%)
Respiratory symptoms	
Odinophagia	21 (5.6%)
Myalgias	12 (3.2%)
Fever	4 (1.1%)
Cough	14 (3.7%)
None	313 (83.7%)

*Questions only applied in the second and third poll. Percentages were calculated using data from these 2 surveys.

secretions, position changes, patient hygiene, manipulation of oxygen therapy equipment, orotracheal intubation or kinesic care (Table 4).

As recommended in local guidelines, N95 mask use was reserved for aerosol-generating procedures (endotracheal intubation, non-invasive mechanical ventilation, tracheostomy, open airway aspiration and manual ventilation during cardiovascular resuscitation process), and surgical masks in all other conditions. Only 40% of HCW reported N95 mask use-only and near 70% referred predominately using surgical mask. Masks displacements were reported in approximately 2% for N95 and 8% for surgical masks (Table 4). About 12% of the staff also worked in other healthcare centers, establishing a possible circulation risk. In addition, it was possible to uncover a high degree of unprotected social interaction at work during eating times (> 60%) or in meetings without social distance or for prolonged periods of time (> 2 hours, Table 5). Likewise, potential community exposures were detected while using public transport (near 30%, Table 4). Although in low numbers, some answers indicated relatives in quarantine (about 3%), COVID-19 cases at home (about 1%) or recent quarantines involving the HCW himself (about 1%). Finally, surveys indicated a significant fraction of the personnel experiencing recent respiratory symptoms (close to 20%, Table 4).

Discussion

This study highlights the relevance of basic prevention measures, especially protective barriers and physical distancing for reducing the risk of SARS-CoV-2 infection by HCW. Other published experiences show the effectiveness of these measures in protecting them before the appearance of specific vaccines[15]. However, our results contrast with other experiences that indicate higher seroconversion rates[16-18]. The differences could be related to the low regional incidence rate and number of COVID-19 cases seen in our center suggesting a lower probability for hospital collapse and internal or community transmission in the initial phase of the pandemic coupled to the wide use of protective barriers in this phase.

HCW seroconversion or seroprevalence rates for SARS-CoV-2 vary widely in the literature and have been related to the kind of work (higher in high-risk groups), age of HCW (higher in youngest), epidemiological situation, continent involved (higher in USA than in other regions), COVID-19 like-illness, previous positive PCR or absence of basal anti-protein S antibodies in HCW[3,16-18]. Absence of seroconversion in our study impeded analyze factors associated with its appearance. Seroprevalence or seroconversion rates among HCW have ranged between 0.8% to 32% so that our findings are not dissimilar with experiences reporting lower figures[17,19-22]. Furthermore, infection rates among HCW tend to reflect that happen at community level. The weekly regional incidence was below 25 cases per 100,000 inhabitants during the study period. In other Chilean report perfomed at the metropolitan area at the same time with a setting of 60 cases per 100,000 inhabitants (more than double that that reported in this work)), seroconversion rate reached 17%[16]. Noticeably, seroconversion studies among HCW have been performed mainly in USA, Europe or East Asia and information coming from Latin America is scarce[16,17].

As shown, opportunities for potential contagion during work activities are numerous and the risk also extends to family and community interactions. These include patient care, sharing food or meeting spaces, use of public transportation or the presence of COVID-19 cases at home.

We had difficulties to recognize cases of infection through serological testing. In the original design, only one IgG ELISA technique directed against the nucleoprotein and spike protein was chosen due to its commercial availability in Chile at the beginning of the pandemic. Later publications demonstrated a wide range of sensitivity versus that reported by the manufacturer (78.6%-100% vs. 85%) and a lower specificity (90.2%-95.2% vs. 98%, respectively)[11,23,24]. To improve these limitations we added a second enzyme immunoassay technique with a better performance (Virion / Serion). The reported sensitivity of this ELISA IgG test is higher (96.2%-98.3%) and its specificity has reached 100% in at least 2 studies[12,25]. Using this second technique in previously doubtful and positive cases, seroconversion was ruled out and only one new case at baseline was identified. Several works have used 2 serological techniques to reduce these problems[16,21,22]. The HCW with previous symptomatic COVID-19

infection had neutralizing antibodies in contrast to the asymptomatic worker in line with that has been described previously[16,26,27].

Our work has some limitations. For logistical reasons and lack of resources, it only included a fraction of the hospital staff and was restricted to areas with the highest risk of contagion. It is possible that the inclusion of a large group has identified some cases of seroconversion, especially in sectors not exposed to a high risk of infection as described in some reports[17,19,21]. In the same way, the study timeframe did not include the period of greatest regional epidemiological activity that began lately in September 2020. The study also did not incorporate a systematic viral search by periodic nasopharyngeal swab among HCW included in the cohort, although in none of those that consulted spontaneously infection was detected. Finally, the test of greater sensitivity and specificity was applied only in cases with positive and doubtful results after the first serological run. Having had been applied universally, it could have detected other baseline or seroconversion cases due to its higher sensitivity (> 95% vs. 85%). We believe this is unlikely due to the low prevalence of infection with the corresponding low positive predictive value for a positive test. Assuming a 1% of prevalence of infection among the 130 HCW that were not tested by the ELISA IgG Virion and a 10% higher sensitivity of this test, that would mean only 1-2 cases of SARS-CoV-2 infection in the cohort, still representing a low infection rate.

In conclusion, there was no evidence of seroconversion in a group of HCW exposed to the risk of infection by SARS-CoV-2 during the onset of the COVID-19 pandemic, before the use of vaccines and in a context of low epidemiological pressure. Results of this work are relevant in an era of different variants of concern and the corresponding loss of vaccine effectiveness.

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