


# SARS-CoV-2 could be spread through hospital medication dispensed to patients

## A prospective observational study

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### Abstract

Our objective was to analyze in vitro the persistence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the packaging material of the drugs dispensed to hospital wards. Additionally, to evaluate if the protection with a double plastic bag prevents the contamination of the medication dispensed to an intensive care unit (ICU).

On the first part, different materials containing different drugs within an ICU were sampled to confirm the lack of contamination by SARS-CoV-2. The confirmation of the virus was performed using real time reverse transcription polymerase chain reaction. As a control group, in the microbiology laboratory we inoculated the virus into the different surfaces containing the same drugs included in the first part. Samples were obtained with a sterile swab at 3, 6, 8, 10, 14, 21, and 30 days after inoculation and analyzed through real time reverse transcription polymerase chain reaction.

None of the studied materials containing the drugs within an ICU was contaminated by SARS-CoV-2. In the second part, SARS-CoV-2 was found in all surfaces for up to 30 days.

The use of double-bag unit-dose system to deliver medication in a pandemic seems effective to prevent the potential transmission of SARS-CoV-2. A striking SARS-CoV-2 RNA stability of up to 30 days was found in the surfaces containing the drugs.

**Abbreviations:** COVID-19 = the coronavirus disease-19, Ct = cycle threshold values, ICU = intensive care unit, RdRp = RNA-dependent RNA polymerase gene, RT-PCR = real time reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

**Keywords:** contamination, drugs, severe acute respiratory syndrome coronavirus-2, surfaces

### 1. Introduction

The coronavirus disease-19 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has posed a global threat by causing an ongoing pandemic.<sup>[1]</sup> Two modes of transmission have been mainly identified: direct contact, mainly through the inhalation of droplets or small particles, but also by the contact with feces, saliva or tears.<sup>[1–3]</sup> An indirect transmission has also been described.<sup>[3]</sup> Available

evidence suggests that SARS-CoV-2 could remain viable for hours in aerosols and up to days in different surfaces.<sup>[1,4,5]</sup> In this context, the touch of the mouth, nose or eyes after the contact with this contaminated surfaces may also contribute to its transmission.<sup>[2,5]</sup>

In a study conducted in Wuhan assessing the setting for transmission, among the 3410 patients included the 19.9% were infected in the healthcare setting.<sup>[6]</sup> Guo et al<sup>[4]</sup> assessed the

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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distribution of SARS-CoV-2 in surface and air samples from an intensive care unit (ICU) and a general COVID-19 ward in Wuhan. A wide distribution into the air and object surfaces was found in both wards, with a higher contamination in the ICU.<sup>[4]</sup> The higher viral load found in these severe patients may account for these difference.<sup>[4,7]</sup> Other studies have shown that objects used on the infected person as thermometers or stethoscopes may also be contaminated.<sup>[3]</sup>

Processes that encompass the drug dispensing circuits frequently involve the entry and exit of drugs from units. In a pandemic situation, it is of utmost importance the knowledge of the potential contamination of medications, as they may increase the risk of shedding the virus to other units. This point is critical, since the hypothetical contamination of the material containing the drugs could be involved in the transmission of the virus to not infected patients, physicians, nursing, and to an essential support service in this pandemic, hospital pharmacy staff. Unfortunately, data are lacking on the contamination of the medication in the COVID-19 pandemic.

During the first wave of COVID-19 pandemic pharmacies adopted different strategies concerning the drug dispensing and return: strictly dispensing the needed medications, discarding all unused medications or implementing the use of automated dispensing cabinets.<sup>[8]</sup> The Institute for Safe Medication Practice stated that some hospitals placed in a plastic bag the unused medications that returned to pharmacy for 3 days (based on the study of Van Doremalen et al<sup>[5]</sup>), and then evaluated their use.<sup>[8]</sup> This was the strategy adopted in our hospital. However, recommendations concerning the best way to proceed with dispensing the drugs were unavailable.

The hypothesis of our study was that, based on other studies showing the contamination of different surfaces with SARS-CoV-2,<sup>[5]</sup> the medication could also be contaminated with this virus and be a potential route of transmission. We therefore implemented a double-bag dispensing strategy of medications to avoid the potential contamination of medications.

The objective of this study was to analyze *in vitro* the persistence of SARS-CoV-2 in the packaging material of the drugs that are dispensed to hospital wards. Secondly, we evaluated if the protection with a double plastic bag prevents the contamination of the medication dispensed to patients admitted in an ICU.

## 2. Methods

This study was divided into 2 parts. On the first part we evaluated the effectiveness of the medication protection strategy by introducing them in plastic bags when preparing in the Pharmacy.

As a control group, we also carried out another study in the microbiology laboratory setting. This time, we inoculated the virus into the different surfaces containing the same drugs included in the first part of the study in order to assess the stability of SARS-CoV-2 in the different packaging materials containing medications.

### 2.1. Part 1: potential contamination of the drugs in the ICU

**2.1.1. Protocol.** This was a prospective study on samples of drug forms packaged in different materials carried out at the ICU of the Hospital del Mar, a 420-bed tertiary hospital in Barcelona, Spain.

At the time of this study the ICU unit housed 20 COVID-19 patients and was confined. The entire ICU unit was therefore

considered a contaminated area, including the central area, rooms, or the zone where the medication were stored. As a control infection measures, professionals within the ICU were asked to stay, when possible, in the ICU without going out to diminish the risk of spreading the virus and all the personal was equipped with personal protection equipment.

The studied medication was located outside the patients' rooms, in the available boxes per each patient that were located 4 m away from the rooms, inside the bag. If any of the drugs was entered into patients' room and was not administered, it was immediately discarded. If medication did not enter the room, unlike in routine practice, no returns were accepted and was stored throughout the pandemic in the ICU store and returned once the first wave finished.

Potentially contaminated materials were chosen according to previous studies showing different SARS-CoV-2 stability depending on the analyzed surface.<sup>[4,5]</sup> The study was conducted from May 20, 2021 to May 26, 2021.

In our hospital the drug distribution is normally based on a unit-dose system.<sup>[9]</sup> Briefly, the pharmacy department prepares the medications to provide patient-specific, individually packaged medications to each patient, delivered for 24 hours. The medication is normally distributed in carts, which contain the different packages. Once in the unit, they are available in the patient-area to be administered. After the 24 hours period, they are returned to the pharmacy with the leftover medication.

During the COVID-19 pandemic, due to concerns on the potential contamination of the medication, our hospital modified the usual medication dispensing routine and unit-dose system was interrupted. Instead, we placed the drugs directly in the boxes of the unit dose carts and protected them in a double plastic bag, appropriately labeled. Later, these bags were placed in cardboard boxes (unlike the normal carts) that were transported to the ICU where the nursing staff proceeded to extract the double bag and relocate it to the boxes available to each patient. This strategy was used to replace the use of unit-dose cart boxes with the aim of reducing the potential contamination of drugs. The decision of using a double instead of 1 plastic bag was made by the Epidemiology and Evaluation department to reduce the risk of contamination, to avoid possible problems with bag breaking and based on the recommendations available in that period.

To try to elucidate the effectiveness of this system and consider the return of the drugs to the pharmacy, we assessed the contamination of the drugs available within the double bags in the ICU. For this purpose, serial daily samples were obtained from the medication for 5 days. Specialized infection control nurses took the first samples in the ICU area and thereafter carried to the pharmacy service, where were conserved in a sterile bell with the same temperature (room temperature, 21–25°C) and humidity that in the ICU. During the following days, the rest of the samples were obtained in the pharmacy service by trained staff. Two replicate experiments were performed for each surface.<sup>[5]</sup>

The analyzed surfaces were sampled by premoistened swabs that were finally collected in sterile tubes containing 2 mL of Universal Transport Medium (Viracell S. L. Granada, Spain).<sup>[4]</sup>

Viral nucleic acid was extracted by using the QIAAsymphony fully automated nucleic acid isolation system (Qiagen GmbH, Germany). Laboratory confirmation of the virus was performed using real time reverse transcription polymerase chain reaction (RT-PCR) using the LightMix Modular SARS-CoV-2 (COVID19) kit (Roche Molecular Systems, Branchburg, NJ) in

the LightCycler 480 II instrument (Roche Molecular Systems, Branchburg, NJ). The kit includes 2 probes targeting the RNA-dependent RNA polymerase gene (RdRp) that is specific for SARS-CoV-2 (target 1), and the conserved, structural protein envelope E gene that is shared by the *Sarbecovirus* subgenus. The limit of detection of this assay was 5.2 and 3.8 copies per reaction for E and RdRp gene, respectively.<sup>[10]</sup>

**2.1.2. Surfaces.** A total of 9 different surfaces of drug containers were chosen according to previous studies showing different SARS-CoV-2 stability depending on the analyzed material<sup>[4,5]</sup> and constitute the most common packaging materials for drugs available in hospitals.

No other studies have assessed the potential contamination of drugs by SARS-CoV-2. However, based on previous data in other surfaces in the ICU, to detect at least a 17% of positivity,<sup>[4]</sup> with a two-sided 5% significance level and a statistical power of 80%, a sample size of 80 samples (40 in each group) was deemed necessary.

## 2.2. Part 2: RNA stability of SARS-CoV-2 on the different surfaces containing the drugs after inoculation

As a control group, and to test if surfaces that contain the drugs could get contaminated with SARS-CoV-2, we also studied the RNA stability of SARS-CoV-2 after inoculating them with the virus. SARS CoV-2 RNA stability was defined by a positive RT-PCR result.

**2.2.1. Protocol.** A prospective study of RNA SARS-CoV-2 stability on drug formulations conditioned in 9 different surfaces (Table 1) was carried out at Laboratori de Referència de Catalunya (Parc de Salut Mar) in Barcelona (Spain). This study was conducted from August 19 to September 17. Temperature and relative humidity were controlled throughout the entire study.

Seven inoculations of 25 µL of a universal transport medium UTM (Miraclean Technology Co.,Ltd.) positive PCR SARS-CoV-2 sample were performed in each surface. The cycle threshold values (Ct) of initial inoculum were 8.98. Surface samples were collected with a sterile swab at 3, 6, 8, 10, 14, 21, and 30 days after inoculation.

**Table 1**  
Studied drugs and different materials conditioning them.

Active principle	Pharmaceutical form	Material
Ipratropium bromide 250 mcg for inhalation	Inhalator	Aluminum/ stainless steel
Clonidine 0.15 mg for intravenous perfusion	Vial	Glass
Clonidine 0.15 mg repacked tablet	Tablet	Paper
Clonidine 0.15 mg repacked tablet	Tablet	Cellophane
Fluconazole 200 mg/100 mL for intravenous perfusion	Bottle	Polyvinyl chloride
Fluconazole 200 mg/100 mL for intravenous perfusion	Bottle	Polyolefin
Acetylsalicylic acid 100 mg blister pack	Tablet	Aluminum
Linezolid 600 mg/300 mL for intravenous perfusion	Bag	Polyolefin
Linezolid 600 mg/300 mL for intravenous perfusion	Bag	Cardboard

The evaluation of RNA integrity was performed using RT-PCR with the Abbot SARS-CoV-2 RT-PCR detection kit system (Abbot Molecular Inc. IL). The target sequences for this assay are highly preserved and specific for this strain of coronavirus and includes RdRp and N genes of SARS-CoV-2.<sup>[11]</sup> The viral load was controlled with Ct as indicator of viral load.

**2.2.2. Virus.** The SARS CoV-2 virus used in this study were collected from nasopharyngeal PCR positive patients received in our microbiology laboratory. This samples had a high viral load and were preserved in UTM at –80°C until surface inoculation.

**2.2.3. Surfaces.** To conduct this part of the study the same medications and the same surfaces were chosen (Table 1). The drugs had been dispensed from the stock of the pharmacy service of Hospital del Mar in Barcelona.

The STROBE guideline was followed during the writing of the manuscript. Approval by the ethics committee was not considered necessary as this study was not conducted with human beings.

## 3. Results

### 3.1. Part 1

A total of 6 active principles were collected to perform the study, which included 9 different materials. All the studied drugs and the different materials conditioning them were presented in Table 1. The studied materials used in this study were: aluminum, glass, cardboard, polyolefin, paper, stainless steel, polypropylene, cellophane, and polyvinyl chloride.

Over the study period, a total of 80 samples were obtained (2 from each surface per day). We were unable to find any trace of SARS-CoV-2 in any of the samples, even in the first ones taken in the ICU.

### 3.2. Part 2

The temperature and humidity remain constant during all the experiment, with a mean temperature of 24.3 (1.3) °C and humidity of 55.6 (2.5)%. The RT-PCR results from all the samples have been described in Table 2. The collected samples were RT-PCR positive in SARS-CoV-2 in all surfaces for 30 days. Excepting for clonidine 0.15 mg repacked tablets, in all the surfaces a slight increase in the Ct was noticed, which suggests a modest reduction of viral load. However, in all the samples the Ct was inferior to 30.

## 4. Discussion

To the best of our knowledge, this is the first study addressing the potential contamination by SARS-CoV-2 of the surfaces containing the drugs. The potential implication of this study is huge given the potential risk of spreading SARS-CoV-2 in a hospital setting. In the first part of the study, we were unable to detect SARS-CoV-2 RNA on the studied surfaces. In the second part, a striking stability of up to 30 days of SARS-CoV-2 RNA was found in the materials containing the drugs.

First studies conducted in February-March assessed the potential contamination of different surfaces in an ICU, where they reported air and surface (computer mice, trash cans, sickbed handrails, doorknobs) contamination.<sup>[4]</sup> More strikingly, the virus was detected in the pharmacy floor, which was located near the ICU, suggesting that the walk of medical staff may be

**Table 2**  
Real time polymerase chain reactions of the different surfaces along the study period.

Active principle	Pharmaceutical form	Material	Day 3	Day 6	Day 8	Day 10	Day 14	Day 21	Day 30
<i>Ipratropium bromide 250 mcg for inhalation</i>	<i>Inhalator</i>	<i>Aluminum/stainless steel</i>	10.56	9	10.1	10.27	10.25	9.86	12.13
<i>Clonidine 0.15 mg for intravenous perfusion</i>	<i>Vial</i>	<i>Glass</i>	10.08	9.59	9.77	10.55	10.35	9.5	16.52
<i>Clonidine 0.15 mg repacked tablet</i>	<i>Tablet</i>	<i>Paper</i>	10.53	10.42	10.73	10.96	17.68	16.63	29.29
<i>Clonidine 0.15 mg repacked tablet</i>	<i>Tablet</i>	<i>Plastic</i>	9.98	9.7	9.53	10.61	10.78	10.8	14.43
<i>Fluconazole 200 mg/100 mL for intravenous perfusion</i>	<i>Bottle</i>	<i>Polyvinyl chloride</i>	10.29	8.96	9.97	11.06	10.49	11.91	15.06
<i>Fluconazole 200 mg/100 mL for intravenous perfusion</i>	<i>Bottle</i>	<i>Polyolefin</i>	10.8	10.48	11.26	12.39	13.5	14.73	16.26
<i>Acetylsalicylic acid 100 mg blister pack</i>	<i>Tablet</i>	<i>Aluminum</i>	12.37	10.53	10.72	12.17	12.26	12.75	14.43
<i>Linezolid 600 mg/300 mL for intravenous perfusion</i>	<i>Bag</i>	<i>Polyolefin</i>	11.2	11.36	11.65	13.3	13.14	15.54	15.98
<i>Linezolid 600 mg/300 mL for intravenous perfusion</i>	<i>Bag</i>	<i>Cardboard</i>	11.65	10.83	12.39	11.9	12.73	13.91	16.06

The results are expressed in cycle threshold values (Ct).

responsible of the spread of the virus.<sup>[4]</sup> Unfortunately, the potential contamination of the drugs was not assessed in any of these studies.

We did not find contamination of SARS-CoV-2 in any of the surfaces of the medication available in the ICU. This finding allowed us to verify that the double-bag dispensing system prevents the contamination of the drugs, reducing the risk of transmission of SARS-CoV-2. We believe that the main reason of this finding is that the bag would protect these surfaces of the contamination present in the air. Unfortunately, we did not sample these bags, which would have confirmed this hypothesis. Other studies performed with bacteria have confirmed our hypothesis, as the use of plastic bags was protective in preventing the contamination of mobile phones.<sup>[12]</sup>

Other reasons include the location of the drugs, which were outside the patient rooms. Recent evidence has shown that the environmental contamination of ICU may not be as higher as previously thought, being limited to patient rooms and high touch areas.<sup>[7,13,14]</sup> The enhancement of the infection control practices,<sup>[13]</sup> the course of the disease when patients are admitted in the ICU (viral shedding appears to peak in the first week of illness and decrease after, coinciding with the time when most patients are admitted in the ICU),<sup>[7]</sup> the fact that most ICU patients are confined to their bed and the use of closed ventilator circuits in mechanical ventilated patients are some of the proposed reasons.<sup>[7]</sup> However, contamination comparison is limited by the different sampling techniques, patient characteristics or cleaning methods.<sup>[7]</sup> In this regard, we did not assess air or any other contamination within the ICU, which would have been of interest.

Our study has only been focused on the unit-dose drug distribution to which special protective measures were applied, so this evidence does not apply to other systems as automated dispensing cabinets that may also be used to deliver the drugs into the different wards. Although specific evidence is lacking, the Institute for Safe Medication Practice recommended a clean hands approach to access the cabinet, traffic decrease, cross-contamination limit, critical items secure storage and return of medications avoidance have been recommended.<sup>[8]</sup>

In the second part of our study, we found that the stability of SARS-CoV-2 RNA remains intact, at least, for 30 days. This was a striking finding considering that SARS-CoV-2 is a RNA virus. The performance of RT-PCR has also demonstrated that this virus can be detected for a long time in different scenarios: upper respiratory tract (mean of 17 days but a maximum of 83 days),<sup>[15]</sup> aerosols (3 hours),<sup>[5]</sup> copper (8 hours),<sup>[5]</sup> plastic or stainless steel (72–96 hours),<sup>[5,16]</sup> cardboard (48 hours),<sup>[5]</sup> wood (48 hours)<sup>[16]</sup> and the outer layer of a surgical mask (7 days).<sup>[16]</sup>

The integrity of SARS-CoV-2 RNA could have been biased because of inoculating the virus with UTM. Our hypothesis is that UTM creates a preservative environment for SARS-CoV-2, lengthening the integrity of its RNA through crystallization. Further studies should be performed considering the effect of the inoculating media on SARS-CoV-2 RNA stability. Performing the experiment using an inoculation media with an osmolality and ion concentration match those of the human nasopharyngeal fluids, would provide a closer approach to reality.

Our study is not without limitations. One of the main limitations is that, unfortunately, no appropriate controls in the first part of the study were conducted, so other potential confounding factors could be present. We tried to do so in the second part, but we acknowledge that these controls may not be the more appropriate, given that were not studied in the same manner. Although the study was conducted with a double bag system, the use of a single bag is an interesting approach that deserves further study. The fact that UTM was employed may have biased the results, as in this medium the stability of the virus may be overestimated. In the first part, the lack of sample of the double-bag plastic and of the air and other surfaces contamination in the ICU is an important limitation to address the potential contamination of drugs. In the second part, we did not perform viral cultures, so the potential infectiousness of the detected virus is unknown. SARS-CoV-2 could be therefore spread through hospital, although the transmission through this route remains uncertain. However, we believe that the findings of our study are important as they confirm the effectiveness of the double-bag unit-dose dispensing system to prevent the contamination of drugs containing surfaces by SARS-CoV-2 and its potential transmission. Furthermore, the stability of up to 30 days in the different surfaces deserves further study, as this may be a route of transmission if no precautions are taken.

To conclude, the use of double-bag unit-dose system to deliver medication in a pandemic seems effective to prevent the potential transmission of SARS-CoV-2. Up to 30 days stability of SARS-CoV-2 RNA was found in the surfaces containing the drugs, which merits further study to discard this route as a potential transmitter of SARS-CoV-2.

## Author contributions

**Conceptualization:** Santiago Grau, Rafael Maldonado, Eduardo Padilla.

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