COVID-19 in long-term care facilities for the elderly: laboratory screening and disease dissemination prevention strategies

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Abstract *An infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the 2019 Novel Coronavirus Disease (COVID-19) pandemic has unveiled a hitherto hidden reality: the vulnerability of the population living in long-term care facilities for the elderly (LTCF). To date, several scientific publications have revealed a concentration of up to 60% of deaths attributed to COVID-19 in such institutions. Most LTFC residents share the primary risk factors currently associated with increased morbimortality due to the COVID-19 infection. It is crucial to define actions to prevent SARS-CoV-2 spread in this environment, besides the usual measures of social distancing and isolation of the carriers of this disease. This paper proposes strategies for the investigation of this infection in LTCF residents and workers using laboratory tests available in Brazil. The early identification of individuals with SARS-CoV-2, who may actively and continuously spread the virus, allows adopting measures aimed at interrupting the local transmission cycle of this infection.*
Key words *SARS-CoV-2, COVID-19, Older adults, Long-term care facilities, Screening, laboratory diagnosis*

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Introduction

Long-term care facilities for the elderly (LTCF) represent the leading risk factor for morbimortality due to infection by SARS-CoV-2 as they meet all the necessary conditions for the "perfect storm". In countries in North America, Asia, Europe, and Oceania, 30% to 60% of all deaths from the 2019 coronavirus disease (COVID-19) occurred in LTCFs and the like[1,2]. The rate of transmissibility is higher than 60%, with high mortality[3,4] once the virus is introduced in these institutions. Indeed, the highest mortality is due to the cumulative and synergistic causality associated with SARS-CoV-2 infection in frail older adults, who are known to be more susceptible to the disease, as they carry multiple risk factors, such as arterial hypertension, diabetes mellitus, and cardiovascular diseases, which usually occur in association[5-9]. Besides the higher prevalence of comorbidities, institutionalized older adults are frailer and arefunctionally-dependent, which further reduces their homeostatic reserve, culminating in more significant impairment of their ability to recover from any acute attack[10]. Finally, they live in a collective environment with other frail older adults and a significant number of employees who travel in other risk environments, such as hospitals and other health services, other LTCFs, and public transport.

COVID-19 prevention and control measures are the most effective strategies in reducing the risk of infection of older adults residing in LTCFs: humanized restriction of visits and control of access of workers and service providers, with the requirement of thorough and adequate handwashing or the use of 70% gel alcohol, screening the presence of flu-like symptoms (fever and respiratory symptoms) and changing clothes and shoes. Other preventive measures include social distancing, greater separation between workers and older adults in non-care activities, reduced group activities and collective meals, and reinforcement of hygiene and cleaning measures for LTCF environments[2]. A face mask is recommended for all LTCF workers and older adults living in activities outside the bedroom. Workers should avoid contact with other LTCFs or health services during the pandemic, mainly with confirmed cases of COVID-19 in these locations[11,12].

A significant challenge in controlling the COVID-19 pandemic is the recognition of an infected person and the interruption of the SARs-CoV-2 transmission route. There is growing evidence that many patients with COVID-19 are asymptomatic or have only mild symptoms, but can transmit the virus to others. Strict epidemiological investigations and laboratory tests are useful in identifying people with an asymptomatic infection, and to prevent and control the disease better, it is recommended to screen high-risk populations, especially in a confined space with a diagnosed or suspected infection[13]. Thus, the monitoring of individuals with a flu-like syndrome and asymptomatic individuals should be added to the preventive and control measures for SARS-CoV-2 infection in LTCFs, both for elderly residents and workers. This strategy includes laboratory screening using tests that can detect the presence of the virus (antigenic or molecular tests) or antibodies against the virus (immunological tests) as part of the routine in the LTCFs during the pandemic.

Laboratory screening at LTCFs mainly aims to identify elderly residents and workers with SARS-CoV-2. They, therefore, have the potential for active and continued transmission of the virus to all other cohabitants and visitors of the affected institution, which allows adopting restrictive measures, such as the removal of the employee or the strict isolation of older adults, thus breaking the cycle of local transmission of the virus. Considering the human and technological resources available in the Brazilian public and private health systems, a strategy for screening and monitoring these environments is proposed to mitigate the transmission of SARS-CoV-2.

Laboratory Diagnosis of SARS-CoV-2 Infection

The best strategy for detecting the SARS-CoV-2 virus is the polymerase chain reaction with real-time reverse transcription (rRT-PCR), which is the "gold standard" for the diagnosis of COVID-19 in symptomatic individuals. The examination is performed on samples from the upper (nasopharyngeal or oropharyngeal swab) and lower respiratory tract (sputum, tracheal aspirate or bronchoalveolar lavage). The rRT-PCR detects infectious and non-infectious viral RNA particles, which confirm the presence of the virus in the patient. Viral RNA in the nasopharyngeal swab is detectable from the first day of symptoms in most individuals with clinically manifest COVID-19. It reaches the peak of detection in the first week, and begins to decline in the third week, subsequently becoming undetectable. In some cases, viral RNA was detected by rRT-PCR even after the sixth week of infection.

On the other hand, attempts to isolate the virus in culture were unsuccessful after the eighth day of symptom onset, which correlates with the decline in infectivity at the end of the first week of the disease[14]. In a study on 205 patients with COVID-19, rRT-PCR positivity was higher in bronchoalveolar lavage (93%), followed by sputum (72%), nasopharyngeal swab (63%), oropharyngeal swab (32%), feces (29%) and blood (1%)[15]. False-negative results occurred mainly due to the poor timing of sample collection compared to the onset of the disease and collection technique deficiency, especially in nasopharyngeal swabs. The specificity of most rRT-PCR tests is 100%. Occasionally, false-positive results may occur due to technical failures. Besides the pre-analytical requirements regarding sample collection, conservation and transport, impacting the test sensitivity, the rRT-PCR depends on sophisticated equipment that may not be available in places with limited resources, hindering access to the test[16]. Also noteworthy is the shortage of kits for collecting respiratory samples in several countries, given the high demand generated by the COVID-19 pandemic.

Immunological tests arrived on the market as an alternative to meet the demand for tests for diagnosis, monitoring, and epidemiological mapping of COVID-19. However, it is crucial to consider the limitations of these tests, especially concerning the dynamics of the immune response to SARS-CoV-2, and it is about detecting antibodies (total IgA/IgG or IgM/IgG antibodies, or isolated antibodies IgA, IgG, and IgM) in whole blood, capillary blood, serum or plasma (remote laboratory tests – RLT, rapid tests or point-of-care immunochromatography) or serum/plasma (ELISA or chemiluminescence)[17].

A recently published meta-analysis evaluated the different serological methods for the identification of SARS-CoV-2 infection, showing high specificity, with emphasis on ELISA and immunochromatography, reaching levels greater than 99%. Regarding sensitivity, ELISA, and chemiluminescence (90 to 96%) stood out. Immunochromatography, a method applied in rapid tests, showed sensitivity between 80 and 86%. Furthermore, regardless of the method, the study pointed out that IgG/IgM combined antibody tests seem to be a better choice concerning sensitivity than the isolated determination of just one type of antibody[16].

Considering the direct relationship between serological antibody search-based tests and the humoral immune response secondary to an in-fection, the time to perform the test in the face of probable exposure is crucial. According to the kinetic measurements of some studies, the peak of IgM is 5 to 12 days after infection by SARS-CoV-2, followed by a slow decline. The IgG achieves peak concentrations after approximately the 20th day, as IgM antibodies disappear. These estimates must be taken into account when conducting seroprevalence studies, and, at the individual level, different strategies may perhaps be adopted, such as test repetition in the face of a negative finding[16].

Brazilian researchers conducted another meta-analysis to assess the performance of different types of tests for the diagnosis of COVID-19 currently available in Brazil. Sixteen tests duly registered with the National Health Surveillance Agency (ANVISA) were evaluated, mostly rapid tests, to detect IgM or IgG antibodies. The authors concluded that the combined diagnostic accuracy of the tests available in Brazil was satisfactory, but highlighted the possibility of 10 to 44% of false-negative results from tests that detect SARS-CoV-2 IgM antibodies, useful in the detection of COVID-19 in the acute phase, and pointed to the need for future studies that address the diagnostic performance of tests for COVID-19 in the Brazilian population[18].

Immunological tests, in particular rapid tests, have been used more frequently due to their practicality, the lower requirement of complex pre-analytical conditions, greater simplicity in the collection, no need for laboratory structure for their execution and results in 15-30 minutes. Such conditions enable their implementation on a larger scale. There is a general consensus that they should be run from the seventh day of onset of symptoms, avoiding testing in the immunological "window period".

In the face of the COVID-19 pandemic and tests being run in regions with local transmission of SARS-CoV-2, such tests have a high positive predictive value (PPV) and low negative predictive value (NPV), mainly when applied in the acute phase of the disease. That is, a negative test does not rule out infection with the new coronavirus, nor the risk of transmissibility of the patient. Due to such limitations, the World Health Organization (WHO) recommends using the molecular method in the diagnosis of SARS-CoV-2 infection. The entity recognizes the role of serological tests in research and surveillance of the disease but does not recommend them for the detection of cases[19]. The United States Center for Disease Control and Prevention (CDC) follows

the same line and does not recommend immunological tests to confirm acute infection with the new coronavirus, but rather the rRT-PCR[20]. However, it is considered that, if used in conjunction with other diagnostic tests and clinical history, serological tests can be applied as part of the COVID-19 definition algorithm and identify probable cases[21].

The Brazilian Ministry of Health recommends running RLTs on symptomatic people who have been diagnosed with flu-like syndrome compatible with COVID-19, from the 8th day of the onset of the condition[22]. The RLT provided by the Ministry of Health is called ONE STEP COVID-2019 TEST® and can be performed with samples of whole blood, serum, or human plasma collected by capillary puncture (digital pulp) or by phlebotomy (venipuncture). The test detects the presence of IgM and IgG antibodies, without distinction, and the results are provided in 15 minutes. According to the manufacturer's data, it has a relative sensitivity of 86.43% and relative specificity of 99.57%. The test should be performed ten days after the probable infection or seven days after the initial symptoms so that the detection of antibodies occurs with greater precision. In these cases, the test's positivity can confirm the diagnosis in symptomatic patients. In the absence of symptoms, test positivity may indicate (if it is a real positive) the presence of antibodies against SARS-CoV-2 and, consequently, exposure to the virus, hindering the possibility of affirming whether the individual is infectious or not at this time[23]. In the case of LTCFs, this positivity is strong evidence of virus circulation in this environment, primarily if it occurs in elderly residents. The worker with a positive RLT must be removed for at least ten days to reduce the risk of contamination of the LTCF elderly residents. Ideally, all workers and residents of the LTCF should have rRT-PCR to quickly identify infected individuals and strictly remove or isolate them, thus reducing the risk of transmissibility of the disease in the LTCF.

Running RLTs in people aged 60 or over and residing in the LTCF[23] has been established as a priority in Brazil. Surveys with sequential serological tests in the LTCF elderly residents and workers could be an alternative in the COVID-19 containment and early detection strategies in these entities[24] due to the current country's limitations of performing the rRT-PCR. Testing for COVID-19 at the LTCF must be accompanied by concrete disease control and prevention measures, such as isolation or transfer of infected elderly residents and removal of infected work-

ers, with reintegration or readmission of older adults and return of professionals to work. Unfortunately, the "Achilles tendon" in the LTCFs are asymptomatic residents and workers, who must also be monitored serially and continuously throughout the pandemic[4].

Given the above, some COVID-19 laboratory screening strategies in the LTCF are proposed for symptomatic or asymptomatic older adults and workers, considering their advantages and disadvantages.

Situation 1: symptomatic elderly LCTF resident

In the presence of COVID-19 symptoms, the elderly LTCF residents should be immediately transferred to a low-complexity hospital or ward, where they will receive medical and interdisciplinary care, according to the clinical and functional situation, if the institution does not have adequate isolation conditions[25]. Institutionalized older adults are usually dependent on activities of daily living and, thus, require nursing care[26].

Another relevant aspect is the speed with which mild symptoms may deteriorate, requiring decisions regarding therapeutic proportionality and initiation of supportive measures or palliative care. Older adults with severity criteria, such as respiratory or hemodynamic insufficiency, must be rigorously evaluated for therapeutic proportionality, using the Clinical-Functional Classification proposed by Moraes et al.[10].

Respiratory and hemodynamic support measures are recommended in older adults in strata 1 to 5 and strata 6 and 7, as long as they do not evidence incurable and advanced diseases. Elderly in strata 8 and strata 6 and 7 due to incurable and advanced disease should receive symptomatic treatment with comfort measures (predominant palliative care). The difference between them will be the profile of measures established and the potential for reversibility, which is inversely proportional to the frailty or the progression of the incurable and advanced disease. This potential is associated with the patient's preferences and will determine the goals of care and the therapeutic plan. Older adults in strata 9 and 10 should receive exclusive palliative care. By definition, they should be considered in the final stage of life if they have a life expectancy of fewer than 12 months before the COVID-19, either due to an incurable and advanced disease or severe frailty[10].

The rRT-PCR is indicated for diagnostic confirmation in both situations (mild or severe). In the presence of positivity, rRT-PCR is recom-

mended for all older adults and workers of the LTCF of origin. In the absence of conditions for all individuals, the rRT-PCR should be performed, primarily, in the COVID-19 older adult sector, or ultimately in symptomatic residents or those at high risk (newly admitted older adults from the community or other LTCFs and older adults requiring treatment in external health services, such as hemodialysis, among others)[27]. Older adults may be readmitted to the LTCF 14 days after the onset of symptoms, as long as they have been asymptomatic for at least 72 hours. They may be readmitted before this period if asymptomatic with two negative rRT-PCR tests, collected at least 24 hours apart (Figure 1).

Situation 2: symptomatic LTCF worker

Immediate removal of the COVID-19-compatible symptomatic LTCF worker is recommended to reduce the risk of contamination of older adults. The rRT-PCR is indicated, and, if positive, the test is recommended for all workers and older adults at the LTCF. More than 50% of individuals with SARS-CoV-2 infection are asymptomatic and have a high risk of continued transmissibility of the virus in the LTCF[3,4]. Returning to professional activities can be based on two strategies (Figure 2)[28], namely:

Symptom-based strategy: the return to activities is conditioned to the absence of COVID-19 symptoms for at least 72 hours (without antipyretics) and, at least, 10 days from the onset of symptoms;

Laboratory test-based strategy: the return to activities is conditioned to the complete resolution of fever (without antipyretics) and respiratory symptoms (cough and dyspnea), associated with two consecutive negative results of rRT-PCR performed with a longer interval or equal to 24 hours.

LTCFs must be organized to adopt measures to regroup the workforce, due to the replacement of retired professionals, to avoid the overload of active workers and, consequently, the loss of quality of care for the older adults living in the institution. The following alternatives are suggested: relocation of professionals from other services of the Unified Social Assistance System or Unified Health System (from the public or private network), or even from other public policies, whose activities have been temporarily reduced or suspended; temporary recruitment of new workers on an emergency basis, among other locally possible arrangements[29].

Situation 3: asymptomatic LTCF elderly resident and worker

Most of the scientific publications analyzed used the screening strategy after identifying symptomatic individuals, with confirmation of the presence of SARS-CoV-2 in the airways. A study carried out in a North American nursing home after confirmation of the disease in a worker recorded a high rate of transmissibility (63%), associated with a hospitalization rate of 19% and a mortality rate of 26%. SARS-CoV-2 infection was screened using rRT-PCR in the respiratory secretion of all elderly residents and workers. Following the institution, the authors showed a high prevalence of asymptomatic older adults with COVID-19 (56%), or rather, pre-symptomatic, since most (86%) later developed flu-like symptoms[3]. Another American study used the same method in an institution of more independent older adults (assisted living), after hospitalization of two residents with acute illness. Mass screening with rRT-PCR identified older adults and workers who are asymptomatic or with mild symptoms, which allowed for more restrictive isolation measures among residents and the removal of infected professionals, resulting in very favorable clinical outcomes. The authors conclude that the screening of COVID-19 based only on the presence of symptoms is inadequate and argue that the early identification of asymptomatic people among residents and workers, in combination with adherence to preventive strategies, can reduce the spread of the virus in this type of community. They also highlight that, while the sensitivity and specificity of rRT-PCR in nasopharyngeal swabs to detect SARS-CoV-2 in asymptomatic people are not well known, this is the test indicated for such purpose so far[30]. In contrast, French researchers showed little impact on the viral transmission of the disease in the evaluated institution and suggested new evidence to indicate the performance of rRT-PCR on a full scale in LTCFs. In this study, unlike those previously mentioned, only workers were submitted to nasopharyngeal swab screening, and the diagnosis of COVID-19 was defined in the index case by chest computed tomography, which returned a negative rRT-PCR result. Another limitation of the study is the lack of definition of the clinical outcomes of institutionalized older adults[31].

The best strategy for screening the presence of SARS-CoV-2 infection in LTCFs could be to perform sequenced rRT-PCR every 7 days in older adults and workers, regardless of the presence of
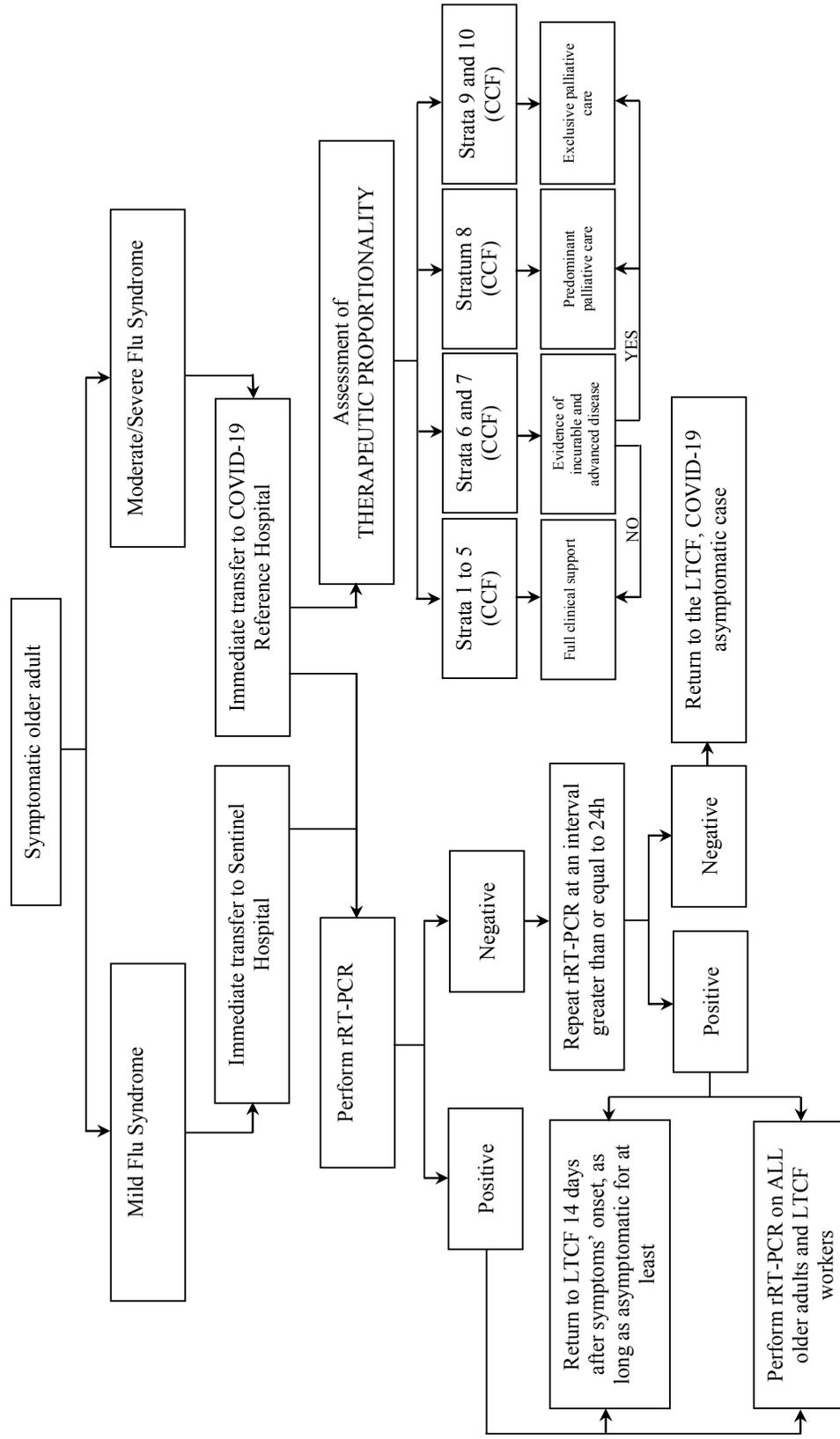
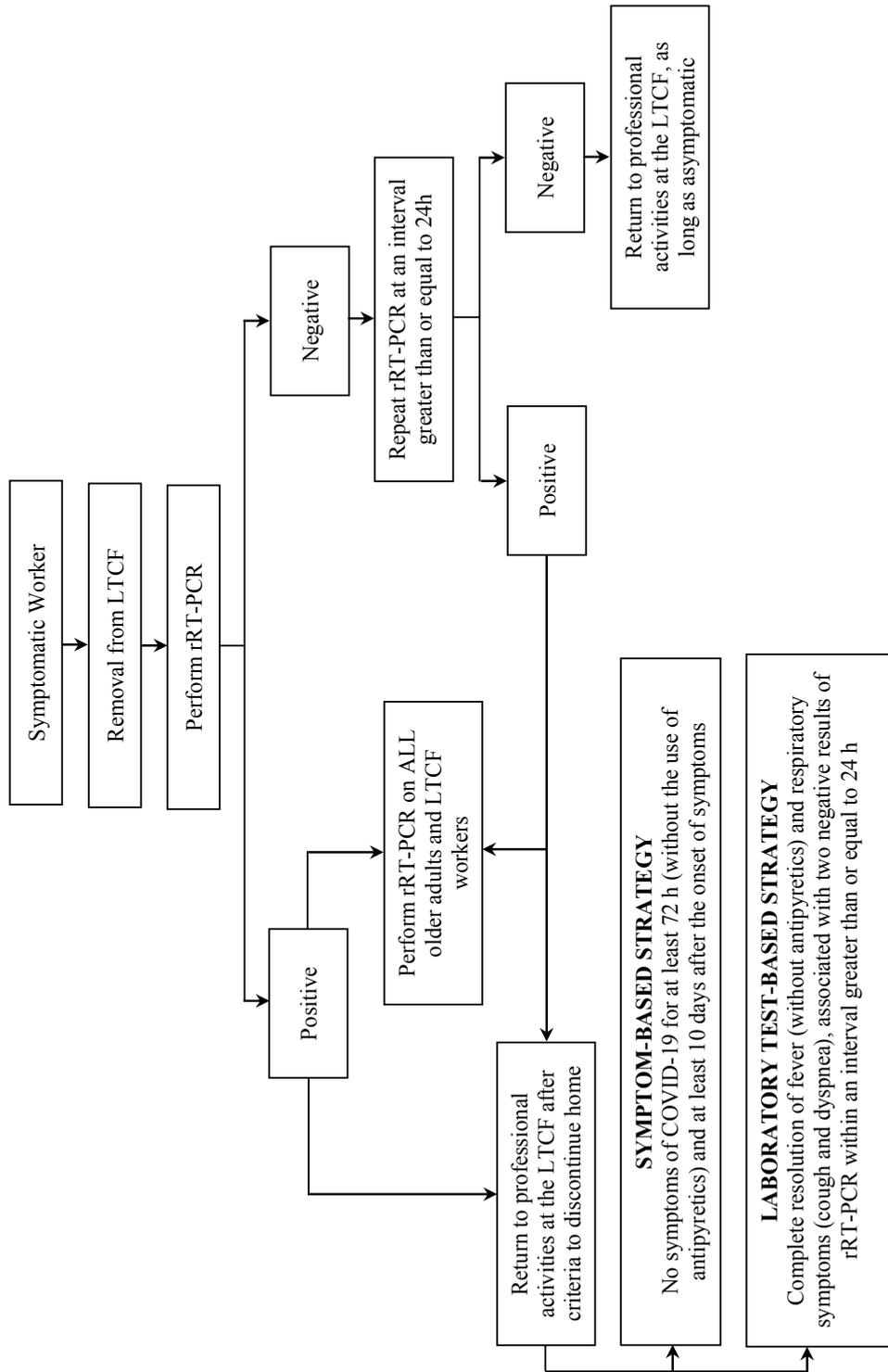**Figure 1.** Laboratory monitoring of COVID-19 in a symptomatic older adult LTCF resident.

Symptomatic Worker

Removal from LTCF

Perform rRT-PCR

Positive

Negative

Perform rRT-PCR on ALL older adults and LTCF workers

Repeat rRT-PCR at an interval greater than or equal to 24h

Positive

Negative

Return to professional activities at the LTCF, as long as asymptomatic

Return to professional activities at the LTCF after criteria to discontinue home

SYMPTOM-BASED STRATEGY
No symptoms of COVID-19 for at least 72 h (without the use of antipyretics) and at least 10 days after the onset of symptoms

LABORATORY TEST-BASED STRATEGY
Complete resolution of fever (without antipyretics) and respiratory symptoms (cough and dyspnea), associated with two negative results of rRT-PCR within an interval greater than or equal to 24 h

Figure 2. Laboratory screening of COVID-19 in a symptomatic LTCF worker.

flu-like symptoms, as the presence of asymptomatic carriers is, therefore, the rule in COVID-19 in older adults residing in LTCFs[4,27]. However, the limited access to the test prevents it from being widely implemented in the Brazilian LTCFs.

We suggest a more feasible strategy, which consists of performing an immunological test every seven days, using the RLT with total antibodies (IgG/IgM), or, ideally, the test with different test regions for IgM and IgG. RLT positivity (IgG/IgM) suggests exposure to SARS-CoV-2. In these cases, rRT-PCR is indicated to define the risk of continued transmissibility of the disease in the LTCF. Workers should be immediately removed, and can immediately return to professional activities after evidencing two consecutive negative rRT-PCR tests, with a minimum interval of 24 hours. In the absence of rRT-PCR, they can return after ten days, as long as they remain asymptomatic. In the presence of positive rRT-PCR, the return to activities must be conditioned to two possible strategies (Figure 3)[28], as follows:

Time-based strategy: return to activities 10 days after the positive test for COVID-19, as long as workers do not develop COVID-19 symptoms;

Laboratory test-based strategy: immediate return to professional activities after two rRT-PCR tests with negative results in two consecutive samples taken with a minimum interval of 24 hours.

Older adults with positive serology should perform rRT-PCR, which will define the best isolation strategy. If the exam is positive, we recommend the strictest, sector-confined isolation at the LTCF, ensuring the maximum possible distance from other residents. If the LTCF does not have adequate isolation conditions, it may be necessary to transfer them to a specific COVID-19 reception facility. Older adults can return to the usual activities of living at the LTCF after two negative tests of rRT-PCR.

Otherwise, the use of RLT with different test regions for IgM and IgG enables the probable recognition of recent or late infection by SARS-CoV-2, reducing the demand for rRT-PCR for diagnostic confirmation. Thus, the following approaches are suggested, depending on the positive test region:

Elderly resident: the presence of positive IgM and negative IgG suggests a probable recent infection. The elderly should be strictly isolated at the LTCF. As, in some cases, there may be false-positive IgM results, the test should be repeated after seven days to check for the appearance of IgG and confirm the infection. The presence of IgM

and IgG antibodies suggests a probable previous infection less than three weeks ago. In turn, the presence of negative IgM and positive IgG suggests an older infection, more than three weeks ago. In these cases, it is unnecessary to repeat immunological tests or strictly isolate the older adult.

Worker: the presence of positive IgM and negative IgG suggests a probable recent infection. The worker must be removed and should be tested again after seven days to check for the appearance of IgG and confirm the infection. The presence of positive IgM and IgG antibodies suggests a probable previous infection less than three weeks earlier. In turn, the presence of negative IgM and positive IgG suggests an older infection, more than three weeks ago. In these cases, it is not necessary to repeat the immunological tests or remove the worker.

Finally, depending on the availability of the rRT-PCR, a hybrid strategy can be used, running a molecular test and an immunological test with different test regions for IgM and IgG in the initial phase of LTCFs' monitoring. In this strategy, laboratory tests would be used to assess the risk at any stage of recent or late contact, as the level of infection that may have developed at the LTCF is unknown. Depending on local conditions, older adults with positive rRT-PCR must be strictly isolated within the LTCF or in foster care units. Workers with positive rRT-PCR should be removed, following the guidelines stated above. Negative cases would be followed up weekly with the immunological test, and the conduct would depend on the result, as previously discussed (Figure 4).

In short, we suggest three COVID-19 screening strategies in LTCFstoprovide some laboratory support to define the procedure in these institutions. The chosen strategy is subject to available resources and should consider the limitations of laboratory tests in asymptomatic SARS-CoV-2 patients. As they are asymptomatic, the main concern is with the isolation of such residents or workers from others and stricter clinical monitoring for the rapid identification of symptomatic individuals. The clinical manifestation of COVID-19 in older adults, particularly frail ones, is atypical, even without fever. The suggested strategies are:

Option 1: IgG/IgM combined ("total antibody") antibody rapid test followed by confirmatory rRT-PCR.

Option 2: IgG/IgM combined antibody rapid test (with IgM and IgG differentiation).
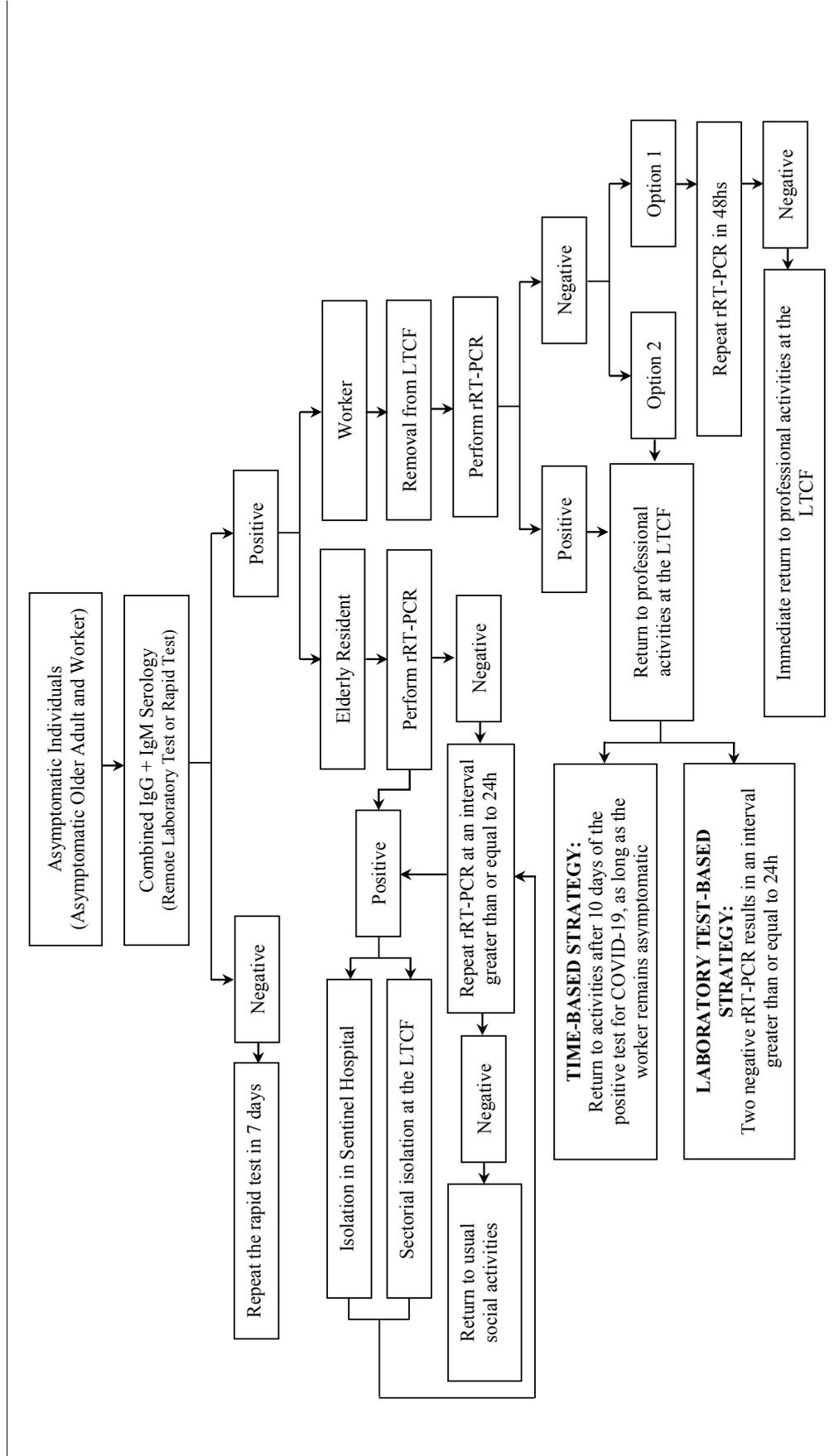
Figure 3. Laboratory screening of COVID-19 in an asymptomatic elderly resident and LTCF worker.
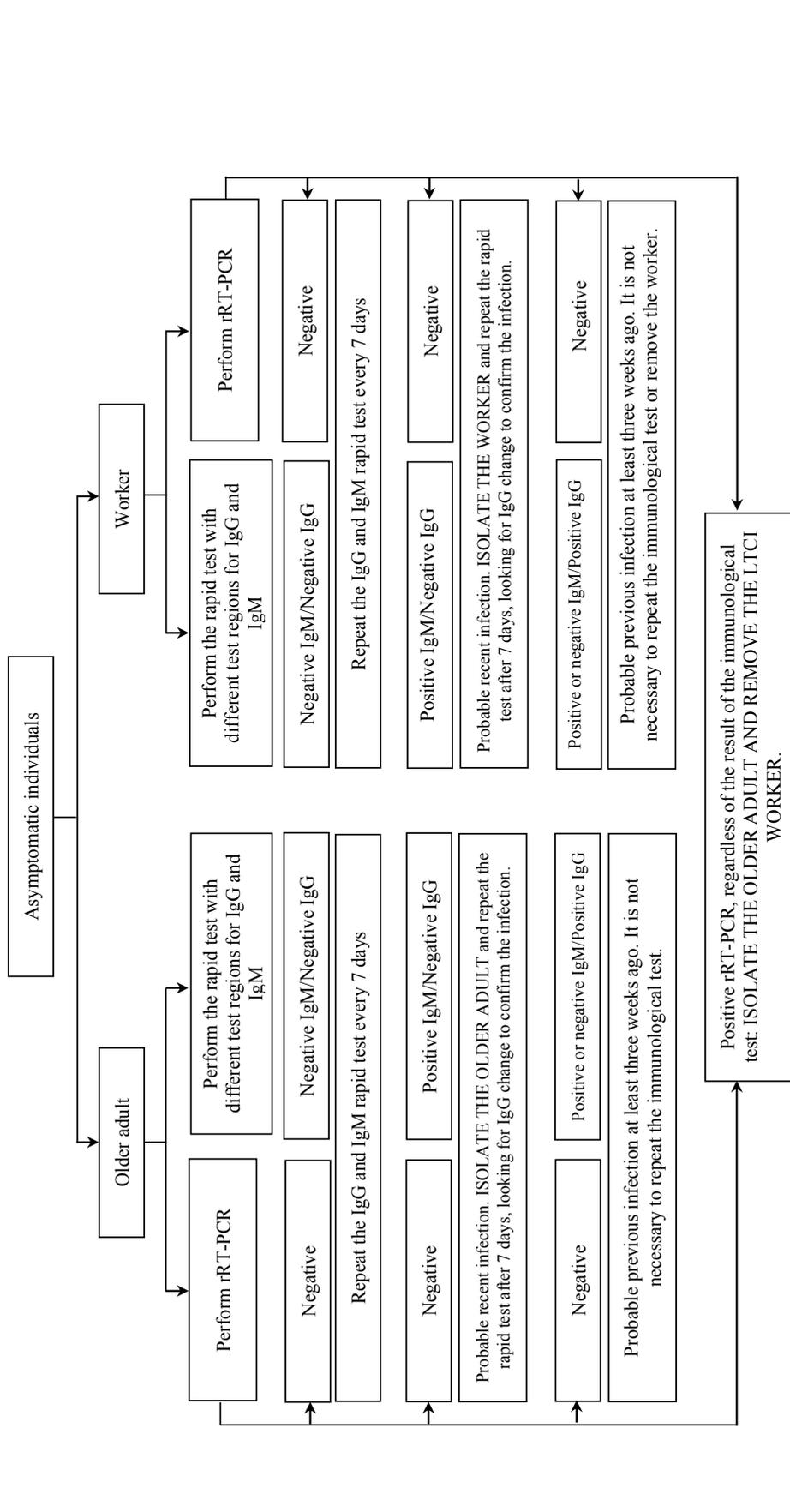
Figure 4. Laboratory screening of COVID-19 in LTCF: a hybrid strategy.

Option 3: Baseline IgG/IgM combined antibody rapid test (with IgM and IgG differentiation) followed by weekly serological test(hybrid strategy).

Asymptomatic older adults returning from hospital admissions of any kind or new admissions to the LTCF have an indication for rRT-PCR. If the laboratory result is negative, the ideal would be to repeat in 24 hours, to be as sure as possible. However, the limited access to the repetition of the rRT-PCR may invalidate this conduct. Another possibility is to carry out immunological tests on these older adults before their return, in case rRT-PCR is not available (or in the face of a negative molecular test result). Thus, depending on IgM or IgG positivity, admissions can be decided based on the immunological result, as per the flowchart in Figure 5. A positive molecular test contraindicates the inclusion of older adults in the LTCF for 14 days.

Conclusions

Institutionalized older adults are the main target of SARS-CoV-2 infection, with high mortality rates. Laboratory screening of elderly residents and workers at the LTCF is a control and prevention strategy that must be associated with other protective measures synergistically. WhilerRT-PCR is a "gold standard" for the diagnosis of infection, its routine use is limited, particularly in asymptomatic individuals.Immunological tests, including RLTs or rapid tests, can be used as feasible and supplementary alternatives in the laboratory screening of COVID-19, depending on the access of Brazilian LTCFs to such options. Thus, the LTCFsshould be able to implement COVID-19 prevention strategies, based on the following principles:

Traditional disease control and prevention measures;

Immediate removal of any worker with flu-like symptoms until the criteria to discontinue home isolation are met.

Immediate transfer of symptomatic older adults, even with a mild flu-like symptom, to a health care facility with isolation units.

Performing rRT-PCR on all older adults and workers of the institution where SARS-CoV-2 circulation has been confirmed.

Weekly screening of asymptomatic individuals with immunological testing, given the difficulty in accessing the rRT-PCR, during the COVID-19 pandemic.
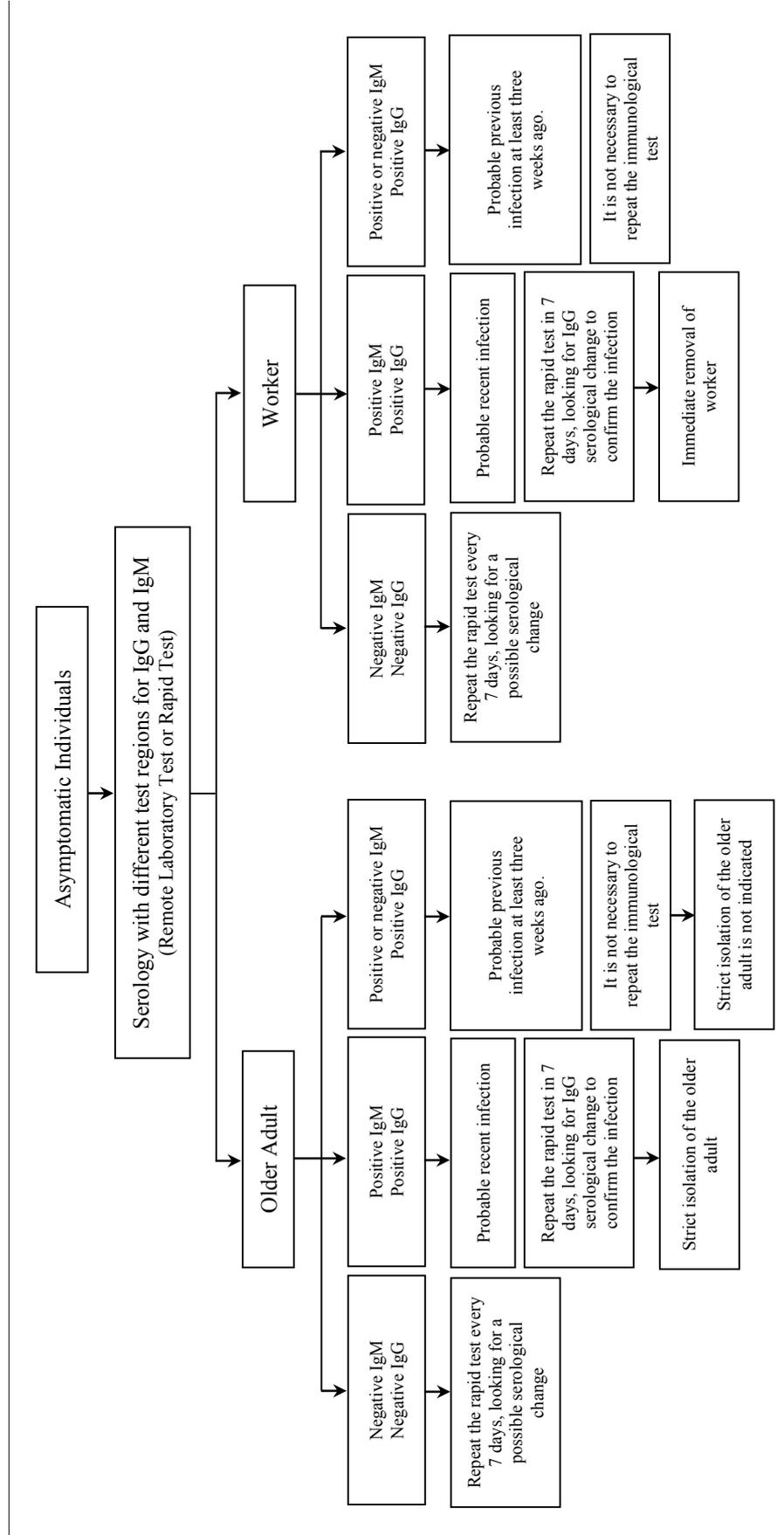
Figure 5. Laboratory screening of COVID-19 in an asymptomatic elderly resident and LTCF worker.

Collaborations

EN Moraes, LG Viana, LMH Resende, LS Vasconcellos, AS Moura, A Menezes, NH Mansano and R Rabelo contributed substantially to the conception or design of the study; or the acquisition, analysis or interpretation of job data; in the preparation of preliminary versions of the article or in the critical review of important intellectual content; final approval of the version to be published; in agreeing to be responsible for all aspects of the work, in order to ensure that issues related to the accuracy or integrity of any part of the work are properly investigated and resolved.

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