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Hypothesis

Use of Rotavirus Vaccine as a Containment Measure for SARS-CoV-2 Coronavirus (COVID-19): A Study of Possible Cross and Trained Immunity

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Abstract: This proposal was prepared in the very first weeks of 2020 because of the outbreak of COVID-19.There is good reason to suppose that rotavirus vaccine can be used as protection tool to effectively and safely fight and mitigate SARS-CoV-2 infection and the impact caused by COVID-19 in adult humans, due to the development of cross and trained immunity following rotavirus vaccination. Up-to-date, some rotavirus vaccines are available and approved, two of them have a large experience in results and safety. Little experience has been achieved in the use of rotavirus vaccine in adults. However, it can be expected that it would be safe and effective in adults and in the elderly as well. This proposal explains the background.

Keywords: rotavirus; coronavirus; vaccine; SARS-CoV-2; COVID-19; cross immunity; trained immunity; vaccinated breakthrough infections; COVID variants; long-Covid; post-viral syndrome; chronic fatigue; booster

1. Summary

There is accumulating evidence that the use of a specific vaccine can be effective in increasing resistance in humans to other infectious agents.[25] This principle is being applied by several teams experimenting with existing vaccines, such as the tuberculosis vaccine, to reduce the impact of COVID-19.[7,8]

The working hypothesis presented for this study / clinical trial (CT) is that there is good reason to assume that rotavirus vaccine can be used as a preventive measure to fight and mitigate the impact of COVID-19 in adult humans effectively and safely.

We are still in the midst of the pandemic at the time this paper is released, with more than 600,000 daily communicated cases, different countries vaccination status and still some countries with very low vaccination rates according to WHO.[27]

The use of rotavirus vaccine as a result of this proposal / study, could begin very quickly, given that it is a proven and widely distributed vaccine. It is also important to consider the rotavirus vaccine option in those expected cases where available COVID vaccines are not a completely suitable and an alternative or boost is needed. Also we take into consideration the different COVID vaccine protection lasting may vary. On the other hand, no negative interactions are expected in case both vaccinations happen to be used close one to each other.

Moreover, intestinal health including microbiota implication in COVID-19, has been proven, as well as post-viral syndrome o long-Covid.

That is relevant because this proposal already considered the post-viral syndrome associated to SARS-CoV-2 as a possible evolution of the disease in specific individuals, as far as in the first weeks of 2020. As the pandemic evolved, a post-viral syndrome or long-Covid syndrome has been described in specific individuals, mainly due to known or unknown pre-existing autoimmune reactions, and/or to certain pre-existing viruses, as well as to Th1/Th2 unbalances with excessive–chronic inflammatory responses (i.e., but not

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only, Th1 to Th2 shift), and microbiota implication, as it explained below. A wider explanation is available, if needed

In the initial description of the hypothesis, it was explained how it could be expected that SARS-CoV-2 interferes with pre-existing autoimmune reactions (excessive immune reaction), or with pre-existing virus, such as EBV or HHV, and as a result: the development / aggravation, via immune system, of those viral infections, along with appearance / aggravation of neurological relationships, myalgic encephalomyelitis (EM), chronic fatigue syndrome like syndromes (CF-like S), allergies, and others. All these mentioned situations share a high inflammatory response. It is important to highlight that those mentioned situations or complications involved not only immune system, but also nervous and endocrine (hormonal) system, named as Central Control System (CCS). Those diseases relationships can also be explained in certain type of individuals thought The Liver Link theory (Lorite, 2002).

A clinical trial (CT) proposal was prepared to be conducted in specific populations to assess the hypothesis. Initially before preparing the CT, the target groups were those more in need, and so important, at that time: health care system workers, and the elderly and nursing system workers.

A multicentre, randomised, double-blind clinical trial is planned for hospital and primary care workers whose activity involves the possibility of contact with patients with COVID-19 infection.

Extending the working hypothesis, we expect that, in the event of infection by SARS-CoV-2, vaccination against rotavirus will be able, compared to a control group:

1) To reduce COVID-19 infections in hospital and primary care populations, including non-healthcare workers.

2) in the event of a possible manifestation of the disease: to reduce the severity and duration of the manifestations, as well as,

3) decrease recovery time, compared to a control group.

The expected outcomes, in the event of SARS-CoV-2 infection occur as a consequence of an improved and balanced immune response, reduced and balanced inflammatory response and protection of tissues and functions, none or lower reactivation of pre-existing viruses.

Rotaviruses and coronaviruses are both RNA viruses with common elements in their outer coat, with similar infectious processes that create similar conditions.[9,13,14,17,18] Reasons to expect a reduction in the impact of COVID-19 infection in adult humans previously vaccinated against rotavirus include:

Support of the intestinal and respiratory microbiota, their physiological barrier functions (mucosa) and the reactions associated with the innate cellular and humoral immune system**.**

Immune modulation by stimulating the Th1 response and attenuating the pro-inflammatory Th2 response, if excessive.

Triggering a trained immune response**.**

By cross-immunity mechanisms.

Given the circumstances, as we are in the midst of the evolution of the pandemic, it is important to mention that the proposal of expected results is based on the scientific evidence available at this time and could be updated if new evidence emerges.

It can be indicated that no side effects related to rotavirus vaccination are to be expected, and if they do occur, they would be mild diarrhoea and fever, which would easily subside with rehydration.[24]

After analyzing and comparing the possible manifestations, as well as the data obtained from the analytical tests in the two groups (vaccinated and non-vaccinated rotavirus groups or universe), the positive result of this study would allow for the immediate availability of a safe measure to increase the protection of the most vulnerable population in a 3-month period with low risk, at low cost and at scale. Such a measure could be transient; as lifelong immunity is not expected according to current data related to rotavirus vaccine. However, in the event of waning immunity (assessed by monitoring risk groups),

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revaccination with rotavirus is a possible option to boost the immune system. Data about the expected duration of immunity can be found below.

2. Project Description

SARS-CoV-2 infections are affecting different segments of the population unevenly, being more aggressive in older patients. This pandemic has demonstrated how important the capacity of hospitals and primary health care services are. In case they are at risk, health services and attention can collapse with great risks for population. This situation could be aggravated as we have learnt, by sickness-related absenteeism and casualties of hospital staff.

We encourage to consider that, despite the wide numbers of COVID-19 vaccinated population to date, still several populations and countries do not have the needed doses, nor the proper hygienic-sanitary conditions or sanitary supplies. As long as COVID vaccine protection varies in strength and time, this reinforce the need to ensure an alternative booster option such as rotavirus vaccine which would be double useful for a wide range of population from children to elderly and different social and socio-economical conditions.

COVID-19 manifestations, treatments, variants

The main symptoms associated with COVID-19 are, related to the onset of the condition are: fever, dry cough, pneumonia and other problems with dyspnoea and shortness of breath, chills, sore throat, diarrhoea, body aches, nasal congestion, runny nose and tiredness.[1-4] The diverse symptomatology varies according to the immunological and general condition of the individual.[1-3] Thus, risk factors such as cardiovascular disease, respiratory disease and diabetes alone were presented in 54.9% of the COVID-19 population when the pandemic started (in Spain, as reference country)[23].

The most severe COVID-19 patients suffer severe acute pneumonia with risk of death, can be hospitalized even for several months. There are two indicators that relate bilateral pneumonia and a worse prognosis and evolution: a higher degree of lymphopenia (present in more than 80% of severe patients), and a high N/L ratio (Neutrophils/Lymphocytes) in absolute counts, in addition to the patient's own characteristics such as age, previous conditions and habits, such as smoking.[10]

On the other hand, the complex and severe COVID-19 symptomatology of some patients is also related to an excessive Th2 (pro-inflammatory) response. This implies the possibility of inflammatory misreactions and a decrease in the effective Th1 response to the virus as it was confirmed.[4,5] This unbalance can also result in simultaneous autoimmune responses, neurological involvement, reactivation of pre-existing conditions (e.g., EBV or HHV, CF-like S which also are related to pro-inflammatory Th2 responses), aggravation of pre-existing conditions among others.[6]

It has been shown that not only the production of neutralising antibodies but also of **Th1 cell-mediated immunity** with activation of cytotoxic CD8+ and NK cells are important in the defence against all coronaviruses.[4,5] Th1 response may be diminished, without a particularly enhanced Th2 response so, in any case, stimulating the Th1 antiviral response is essential.

While several treatments for SARS-CoV-2 have been approved or are being tested, and currently several vaccines against SARS-CoV-2 are available, the situation differs widely from one country to another.

Different SARS-CoV-2 variants have appeared[38]. Vaccinated individuals become infected and develop the illness (vaccinated vaccinated breakthrough infections (VBI)). Every 24h, at the time of preparing this paper, WHO declares more than 600,000 cases.[27]

Rotavirus, coronavirus, lung and intestines.

Numerous immunizations with attenuated micro-organisms have shown to be effective in increasing resistance in humans and animals to other infections by activating the

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immune system against infections other than the infectious agent against which vaccination has been given. Some vaccines, mainly live attenuated vaccines, can elicit a "trained immunity" of the innate immune system that promotes immediate defence against infections other than the vaccine agent in a non-specific manner. This concept has already been established in other types of vaccines such as the measles, and the BCG tuberculosis vaccine[7,8], which is also being tested in several countries against COVID-19. Other experimental TB vaccines such as MTBVAC are also being evaluated pre-clinically in primates (Dr. Carlos Martín Montañés, University of Zaragoza, Spain).

Rotaviruses are common diarrhoeal viruses, considered among the common cold viruses, with symptoms similar to those mentioned in COVID-19, including neurological damage[22], with the danger of dehydration due to vomiting, diarrhoea and fever.[11,12]

Rotaviruses have an oral-faecal and respiratory transmission.[9,13] Infectious diarrhoea is known to damage and modify the intestinal microbiota (disbiosis), and is associated as well with severe pneumonia.[9,6] Indeed, pulmonary manifestations related to inflammatory bowel or gut diseases have been extensively described.[1] This relationship involves the immune system and starts in the mucosal epithelium. [3,7]

The opposite effect is also observed: In cases of severe pneumonia, the intestinal microbiota is damaged, in both cases with lymphatic involvement. The relationship between pneumonia and severe diarrhoea is known.[11,21] This is also demonstrated with the confluence of more than one pathogen as in rotavirus and coronavirus occurs.

Just as there is a pathological relationship between gut and lungs, the relationship between intestinal and respiratory well-being and homeostasis has been shown to be of relevance to immune response.[11,21]

In the epithelial wall, both in lungs and gut, an immune balance is maintained by the gut own microbiota. This immune balance involves both innate (activation of dendritic cells, macrophages, epithelial cells and NK cells) and adaptive (production of specific antibodies and memory lymphocytes) responses.

Enterocytes appear to play an important role in the initiation and development of SARS-CoV-2 infection and other coronaviruses, as well as in the initiation and development of rotavirus infection.[31,32] Both types of viruses (rotavirus and coronavirus) can affect the respiratory tract and gastrointestinal mucosa (as well as other tissues).

The apparent difference in the case of this proposed clinical trial would be that SARS-CoV-2 (and other coronaviruses) seem to show more initial development in the respiratory tract, and rotaviruses in the intestinal tract.

It is postulated that enterocytes act as a cellular reservoir of SARS-CoV-2 during the evolution of COVID-19.[33,34] ACE2, DPP4 and ANPEP receptors used by SARS-CoV-2 are present in intestinal enterocytes and lungs. Consideration of gut involvement, gut flora and their mixed immune functions, including immune modulation with down-regulation of the excessive pro-inflammatory response (cytokine storm), is the hypothesis of other ongoing studies focusing on probiotics as support and/or protection in case of SARS-CoV-2 infection for which several clinical trials are ongoing[35] and could be applied in this proposal and study about rotavirus vaccine.

Furthermore, it should be noted that the SARS-CoV-2 genome and virus have been detected in faeces of sick people even during the convalescent phase, which means that both rotaviruses and coronaviruses affect, and can be found, in the respiratory system and in the intestinal system, being shed in faeces, and seem to use similar transmission routes (respiratory, anus-mouth, fomites), which supports that both viruses have common manifestations.[9,13]

On the other hand, no references have been found in the literature to cases of repeated rotavirus infection involving an abnormal immune response with abnormal exaggerated inflammatory response. The terminology that sometimes appears in the literature indicating an intensification of the immune response does not necessarily imply an exaggerated response, but rather "activation".

It is possible that rotavirus infection may be able to induce trained immunity against other pathogens and with this protocol, in the current health situation, still an emergency

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in some countries, we aim to assess whether it may have a protective effect against SARS-CoV-2 infection.

Rotavirus vaccination could be also considered a boost option to avoid or minimize COVID-19 vaccinated breakthrough infections (VBI)[39]

To summarize:

Coronavirus and rotavirus have common manifestations, creating very similar conditions, affecting the same tissues, organs and systems.

Coronaviruses and rotaviruses are RNA viruses and have an outer glycoprotein coat with some common elements, implying common infective media.[17,18, 28]

Rotavirus vaccine. Expected protection mechanisms in the proposal

Although there is specific vaccination for COVID, still many countries and populations do no have proper access to it. There is a well known, safe and available vaccination for rotavirus.[15,3]

It is expected that immunisation with a rotavirus vaccine may induce protection against SARS-CoV-2 via four mechanisms:

Support of the intestinal and respiratory microbiota, their physiological barrier functions (mucosa) and the reactions associated with the innate cellular and humoral immune system.

Immune modulation which involves either stimulating the Th1 response, or stimulating Th1 and calming the pro-inflammatory Th2 response if it is excessive. Immune modulation ensures a better response, without harming the immune system in any of its responses. [11,17,18]

Triggering a trained immune response. The adult immune system would react and enhance the antiviral Th1 immune response involving, among others, interferon, NK and CD8. Previous experience shows that Th1-type cell-mediated immunity with activation of cytotoxic CD8+ and NK cells, in the absence of antibodies, produces a better natural immune response.[11,17,18]

By cross immunity to common antigens.[17,18.]

There are currently two approved **rotavirus vaccines** available[14, 26]. WHO consider two more vaccines (Rotavac, Rotasiil) which studies have been held in India (2018) still with little information about results. [26] We considered and compared those available vaccines we mention below. It does not mean the newer ones could not be also tested. Indeed, support and collaboration would be an option.

Attenuated human monovalent vaccine (Rotarix, from *GlaxoSmithKline Biologicals*)[15, 36] derived from a G1 P[8] specificity strain of human rotavirus isolated from a patient with gastroenteritis that was cloned and attenuated in culture.

Reassorted bovine-human pentavalent vaccine (RotaTeq, from *MSD Vaccines*)[16,37] containing five attenuated strains obtained by genetic recombination between bovine rotavirus strain WC3 and human rotavirus strains, each expressing the human rotavirus surface protein VP7 of types G1, G2, G3 and G4 and the human rotavirus VP4 protein corresponding to genotype P[8].[16,37]

Both rotavirus vaccines have been shown to be safe, are well known, and are available in an accessible and inexpensive form. The vaccine is administered **orally**. According to transport and storage recommendations, the cold chain must be maintained between 3° C and 8° C. However, work is underway under the auspices of the WHO on a vaccine that does not require refrigeration, mainly due to the needs of developing countries.[26]

The current indication for these vaccines is in the first months of life as the peak incidence of gastroenteritis caused by rotavirus is between 6 and 24 months where they can cause severe dehydration.[19,20] However, rotavirus infections in adolescents, young adults and adults are mild. This explains why these vaccines have not yet been widely tested in adults.

However, given that rotavirus infections in adults are usually mild due to the immune system's own response and that the dose planned to be administered is the infant dose, it is to be expected that they are also safe in adults even in advanced age[19,20]. It is

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pointed out **1)** that the vaccine to be used is the infant dose and that a dose adjustment is not necessary, **2)** that the adult immune system is more trained than in those first weeks of life when rotavirus vaccine is normally administered and **3)** that the intestinal system and intestinal biota are more developed in adults than in infants of a few weeks of age.

Expected side effects include mild febrile fever and/or diarrhoea that can be controlled with oral rehydration solutions.

3. Study Proposal

Initially the proposal was intended to be a study (CT) in both the population of health care (HC) system workers in general and the elderly and nursing home workers in general. Due to the situation in the first months of the pandemic, a decision was made to start with the first population (HC system workers in general).

The risks and situation due to COVID-19 in nursing homes are well known. We should consider that Europe is concerned about the nutritional situation of the elderly in these facilities. Moreover, rotavirus infection is a common cause of diarrhoea and health complications in the elderly, and geriatric population in different institutions. Concern is important when an outbreak of rotavirus infection occurs in a nursing home or nursing facilities, as transmission is very quick and morbidity can result. That is why it is important to take into account there were a large number of nursing homes willing to participate in the study, should it start.

In this paper, the HC system option is the one to be explained. However, the elderly plan is also prepared.

Accordingly, the two available and better-known vaccines worldwide are explained. At this moment, any of the vaccines could be used. Below more detailed information is available.

The proposal consists of conducting a multicentre, randomised, double-blind clinical trial with hospital and primary care workers whose jobs involve the possibility of contact with patients with COVID-19 infection to determine whether there is cross-trained immunity following rotavirus vaccination that decreases SARS-CoV-2 infection and disease. The groups will include the hospital or primary care community at their different sites and will include one rotavirus vaccine-treated and one placebo-treated.

The pentavalent bovine-human reassortant rotavirus vaccine (Rotateq) requires 3 doses with a 4-week interval between them and indicates among the side effects upper respiratory tract infections that could be mistaken for clinical COVID-19.

The attenuated human monovalent vaccine (Rotarix) uses only 2 doses. The side effects do not include pulmonary conditions that could be confused with COVID-19. Initially, it is proposed to conduct this trial with the attenuated human monovalent vaccine. Frequent side effects (≥ 1/100 to <1/10) in young children reported in the human monovalent attenuated vaccine card include diarrhoea. Although, as indicated above, severe side effects are not to be expected, it should be noted that diarrhoea has been reported in about 3.8% of COVID-19 patients.[2]

Given the characteristics of both vaccines and the initial circumstances, we chose to conduct the study with the attenuated human monovalent rotavirus vaccine, which uses 2 doses of oral administration separated by 4 weeks between the first and second dose and 4 weeks more, for complete immunity: 8 weeks (2 months) according to Rotarix vaccine technical characteristics file. This vaccine has been used for years with high safety and known efficacy results (95% in Europe).[24]

It is important to note that despite of the made selection, the pentavalent bovine-human reassortant rotavirus vaccine can also be used to test this proposal. Indeed, steps and times for the study were also prepared with this option, by adapting the timetable to 3 doses and the needed weeks (12 weeks, 3 months) to achieve complete immunity according to Rotateq vaccine characteristics file plus following-up time.

There is experience with Rotateq vaccine in elderly[20]. Vaccination of adults aged 65 – 80 years with pentavalent bovine rotavirus vaccine (Rotateq) in a randomised double-

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blind trial in healthy subjects showed safety and immunogenicity. As indicated in the submitted paper this vaccine was well tolerated, so it means this could be the selected option as well.[20]

It is proposed to maintain the dose used in children in the same way that was maintained in the referenced study of adult vaccination with the pentavalent vaccine (Rotateq), where the same vaccination protocol was followed as recommended in children.

Vaccination with bovine pentavalent vaccine showed immunogenic capacity even though the participants (adults aged 65-80 years) had rotavirus antibody titres associated with previous exposure to rotavirus before the start of the study.[20] The baseline values in the study (serum IgA) were increased in the vaccinated group; this increase was not observed in the placebo group and the response to the serotypes contained in the vaccine was also tested.[20]

We expect Rotarix and Rotateq to perform similarly in this respect.

Regarding expected time protection: According to the Vaccine Advisory Committee (VAC) in Spain, vaccination in children could show protection similar to natural infection[29] and in no case is the protection permanent.[30] As for immunity in the long term, it is not known, since vaccination with these vaccines began in 2006, but preliminary data suggest that the immunity conferred is similar to that of natural infection and could last for a few years, at least 3 years, according to the Rotarix datasheet[15,36.] Other studies, mainly carried out in Australia, have assessed some cases against severe diarrhoea and reached similar conclusions.

The study will determine the protection and efficacy of the rotavirus vaccine as a measure of protection against SARS-CoV-2, in populations working in hospitals and primary care centres. These are two populations with similarities and differences in terms of their characteristics, and different exposure/protection against infections in general, and against COVID-19 in particular, however, the results will be analysed mainly jointly.

Study timing

The study using Rotarix would last 3 months, at least. Initially in April 2020, as a new wave was expected, we proposed a follow up of the participants for another 9 months to complete a whole year. Still, a follow up after the CT is recommended.

This study could be also an opportunity to compare how other upper respiratory or gastrointestinal infections occur in specific populations now that masks are not mandatory everywhere.

For your information

All the following items regarding CT development, Safety, Ethics, Compliance are available if needed:

Selection of the population group, size, statistical analysis, criteria (inclusion, exclusion), specific precautions.

Detailed project timeline and chronogram (timeline for 2 doses option, analyses to be performed and considered parameters for CT point). Adaptation to 3 doses option is also available.

Here it is important to note that a protocol and considerations in the event of infection and development of COVID-19 are prepared on notification and follow up the case. The analytical and diagnostic tests will be carried out at the University Hospital involved in the CT. It was also considered the option of a private external support for analyses and tests.

Placebo, rotavirus vaccine, masked preparation, randomisation, per-day milestones.

Requested budget (dated 2020, may require adaptation to current situation and/or country)

Author and participating investigators´ no conflict of interest declaration.

Safety assessment.

Ethics.

Recording, processing and storage of information.

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Publications policy.
Please, ask for any additional information you may need.

4. Objective Results

(As an example, expected results are shown related to the primary population: hospital and primary care including health and non health care workers)

Important about Objective Results table: These proposed results are based on the scientific evidence available at the time the proposal was prepared and may be updated if new evidence emerges. All laboratory analytical data shall be studied with the standards and reference values of the performing laboratory.

Primary and secondary variables.

Please, see APPENDIX A

Demonstrate via analytical and event collection data that:

(a) Immunity against rotavirus has been acquired.

(b) In case contagion to COVID-19 has occurred:

- Serology shows that immunity to coronavirus has been acquired and they remain asymptomatic,
- manifestations are milder and/or less long lasting, (serology and manifestations assessment, see expected *outcomes* in APPENDIX A),
- SARS-CoV-2 turns negative earlier (PCR),
- number of hospital admissions decreases,
- use of emergency rooms (ER) decreases,
- number of deaths decreases.

5. Expected Impact

Within a period of 2 months*, all healthcare and non-healthcare staff working in hospitals and primary care **could be** vaccinated against rotavirus, with the benefits of reduced COVID-19 infection, reduced severity and time of manifestations and, in general, less negative impact on the health system. We cannot ignore the fact that at the same time the worker's families and social environment are being protected.

*(In case the study in undertaken with Rotateq, the period would be 3 months).

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Expected results	Expected value	Measurements/ tests	Comments
1. To reduce COVID-19 infections in hospital and primary care populations, including non-health care workers.	Overall reduction > 70%.	Assessed by PCR and IgM and IgG detection tests.	The population is subject to different protection conditions. It is to be expected that with the end of containment, social contacts will increase. This exposure value may therefore vary. However, an increase is expected in the coming autumn months.
2. In case of infection it would help to reduce: A. The number of manifestations and their severity, the need for hospital admissions, ICU, deaths.	Reduction > 50%. Overall assessment / Could be assessed by phases of manifestation of infection and disease occurrence.		Since onset of possible symptoms, clinical evaluation and follow-up and according to disease stage questionnaires, it is expected to be milder. Assessment of need / evolution / number of admissions, specific treatment needed. Deaths. (If you require home care for analytical tests, a clinical analysis laboratory is available).
B. Decrease in the time of infection in general, or of disappearance of the manifestations.	Reduction > 50%.	Test	Negative tests if done to all at the same time, assessed for manifestations, not exacerbations. If the subject started with symptoms, a detailed survey would be carried out, in which the development of fever, diarrhoea, cough, dyspnoea, etc. would be recorded over the following 15 days.
C. Recovery time.	Reduction > 50%.		Negative tests, disappearance of symptoms. If the subject started with symptoms, a detailed survey would be carried out, in which the development of fever, diarrhoea, cough, dyspnoea, etc. would be recorded over the following 15 days.

6. Hypothesis Background

In January 2020, this author published two plain language articles (dated 29th and 31th) in *Long Island al Día*, a New York (USA) online journal, about the "at that moment" new coronavirus breakout.

An interesting finding occurred in February 2020, during the search for more information and research on the SARS-CoV-2, the previous SARS and common human coronavirus. This finding was a link of different data via transversal thinking, that led to the development of this hypothesis for prevention and protection against this virus SARS-CoV-2 and COVID-19 disease via rotavirus vaccine. On March 11th, the WHO declared the COVID-19 pandemic.

This hypothesis was shared with some close colleagues in order to confirm its logic in terms of biology and immunology and possible next steps to carry out the needed studies. Some colleagues working in Primary Care and clinical analysis confirmed the findings of more unexpected cases i.e., of EBV and intestinal worms as I suggested to look for those special data. Lately in 2021, papers confirming the EBV, and intestinal worms, relationships started to be published. Due to my experience in complex unbalances such as Chronic Fatigue and Chronic Fatigue related situations, is was expected to happen likewise.

Everything and everyone were urgent at that moment: health care professionals, elderly living in institutions.

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About the initial text – Transversal thinking in 21st century

An initial written compilation of the whole explanation of the hypothesis and proposal after sharing the ideas and verification of its viability, was carried out, resulting in a text, dated March 22nd, 2020. That text contains the main body of the arguments and justification of the hypothesis proposing that the existing rotavirus vaccines could help to prevent transmission, development and severity of the manifestations of COVID-19.

Why rotavirus vaccine was considered? This author has been asked this question very often. The answer is simple, there is no need to hide it. I looked for an option to protect lungs form "the outside" of the respiratory system. Due to the knowledge and experience in Chinese medicine, I looked into intestine viral diseases, starting with one of the classical Microbiology textbooks (Davis, 1983). From Chinese medicine point of view, the proposal and its rationale was clear and easy to understand, and all the data supported it.

I would like to point out, whether it comes to a success or not, this proposal about rotavirus vaccine, demonstrates that *transversal thinking* enriches science and health care with new ideas and paths to be evaluated. That is an important part of my research for decades. Integrative medicine is not new it is the logical consequence of sharing knowledge.

If a desire is allowed among scientists: Let´s work together.

The "original text" of the proposal (available in English and in Spanish) includes the transversal knowledge explanations, immune unbalances beneath the severity of the respiratory symptoms, the excessive inflammatory responses, special conditions at risk, as well as the expected aggravation in some pre-existing conditions related to immune Th1-Th2 unbalance or shift and the expected development of a post-viral syndrome in some individuals, as it has been outlined.

There is also a special text explanation for those who are trained in Traditional Chinese Medicine (TCM) as well as in conventional sciences.

In case an institution shows interest about this proposal and/or CT can be carried out, maybe the initial institution could join the multicentre study and would be glad to cooperate.

As time has gone by, Rotavirus vaccination is still considered as a possible and interesting option because of (1) the possibility of being administered to vaccinated and non-vaccinated to COVID-19, (2) the special situations of many countries in their vaccination status, (3) the evolution of general health threats (mainly viral), (4) the concern about the elderly health in many areas, including Europe, and (5) invigorating the actual importance of rotavirus vaccination in small children as a major benefit.

7. Acknowledgements

This author wants to thank *in memoriam* Dr. Juan Antonio Abascal Ruiz, MD, well known specialist, top consultant and author in Preventive Medicine and Public Health. He achieved a wide experience in viral epidemics management and also in bacterial, viral and parasitic diseases along his long career not only in Europe but also in Africa. We worked together in complex diseases management with an integrative approach, considering also intestinal biota and its relationship with other organs and systems.

I deeply owe him this paper, and all my gratitude for his open-minded listening of this proposal and for his support. I am not an investigator member of any public or private research institute. Dr. Juan Antonio Abascal Ruiz, he created the optimal circumstances to contact a top researcher working in an official institution which finally accepted the proposal to conduct a CT on one of the populations we proposed.

I need to express special thanks to Dr. Alberto Jiménez Schumacher (PhD) specialist in molecular biology, immunology, research scientist at ARAID. *Instituto de Investigación Sanitaria Aragón* (Aragon Health Research Institute), in Spain, who represented the proposal in the institution. I can provide the link where the proposal is shown. Thanks to the whole team of immunologists, microbiologist, ethics, statistics, administration, consultants, for their kind work in difficult times.

Also, I would like to thank Mrs. Sofía Moreno Pérez. MBA. Consultant in business development and innovation in active ageing and health, for her incisive questions to fully extract the needed info about this "strange" proposal for applications forms.

Along the year 2020 we were working on the CT preparation and waiting for the opportunity to start the study. At that moment we also had some nursing homes willing to join the study in case there was a possibility.

So the aim of this paper is *to share this proposal*, in case an institution or research team would be able to get involved in demonstrating whether or not, and to which extent, rotavirus vaccine could help us nowadays, further than its already known protection effects.

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Supplementary Materials: Should you need an access to any of the texts or information mentioned here, the PDF version of the plain language articles on the New York online journal (unfortunately this journal disappeared in 2021 because of the pandemic crisis), the Chinese medicine explanation of this hypothesis, a summary for all the main data and expected outcomes, PPT presentations,, please, contact with the author. Also, Link to the website of the Research Institute which initially accepted this proposal and is announced, can be provided by the author. English and Spanish versions are available.

Conflicts of Interest: This author declares no conflict of interests. There is no relationship with the above-mentioned pharmaceutical companies that manufacture rotavirus or Covid Vaccines.

Appendix A

Outcomes and assessment
(According to 2 doses vaccines option)

Main *outcome* and assessment:

- Incidence of SARS-CoV-2 infection in the hospital and primary care work population (period: 3 months).

The incidence of SARS-CoV-2 infection is confirmed by PCR, and serology.

Secondary *outcomes* and assessment:

- Hospital admissions due to SARS-CoV-2 infection in the study population (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), an assessment will be made of how many have required hospital admission due to COVID-19.

- Incidence of ER admissions due to SARS-CoV-2 infection in the study population (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), an assessment will be made of how many have required admission to ER due to COVID-19.

- Incidence of pneumonia caused by SARS-CoV-2 infection in the study population (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of workers who have developed pneumonia due to COVID-19 will be assessed.

- Incidence of oxygen/respiratory support requirement due to SARS-CoV-2 infection in the study population (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of workers requiring oxygen/respiratory support due to COVID-19 will be assessed.

- Incidence of dyspnoea due to SARS-CoV-2 infection in the study population (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), an assessment will be made of how many have developed dyspnoea due to COVID-19.

- Incidence of severe gastrointestinal symptoms due to SARS-CoV-2 infection in the study population (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of workers who develop severe gastrointestinal symptoms due to COVID-19 will be assessed.

- Days with fever, body temperature > 38°C (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of days with a body temperature > 38°C due to COVID-19 will be assessed.

- Days with cough (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of days with cough due to COVID-19 will be assessed.

- Days with fatigue (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of days with COVID-19 fatigue will be assessed.

- Days with anosmia and/or ageusia (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of days with anosmia and/or ageusia due to COVID-19 will be assessed.

- Days of complete evolution (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the number of days with symptoms due to COVID-19 will be assessed.

- Pharmacological treatment (period: 3 months).

Use of drugs for the treatment of COVID-19 (dosage and duration of treatment).

- Positive serology for Coronavirus (period: 3 months).

In hospital and primary care workers with confirmed SARS-CoV-2 infection (primary endpoint), the immune response will be assessed by IgG and IgM serology to COVID-19.

- Positive serology for Rotavirus (period: 3 months).

All hospital and primary care workers shall be assessed for rotavirus seroconversion by rotavirus IgG and IgM serology.

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