“Herd Immunity” Controlled and Planned versus Uncontrolled and Random, in the strategy to fight against COVID 19: An option with Live Pathogen Virus Vaccine

Eduardo Rivas Ruiz

Submitted to: JMIR Public Health and Surveillance
on: July 09, 2020

Table of Contents

“Herd Immunity” Controlled and Planned versus Uncontrolled and Random, in the strategy to fight against COVID 19: An option with Live Pathogen Virus Vaccine

Eduardo Rivas Ruiz[1, 2] MD, MPH, MBA

[1]Hospital de los Valles Urology Departament Quito EC
[2]Instituto Ecuatoriano de Seguridad Social Urology Quito EC

Corresponding Author:
Eduardo Rivas Ruiz MD, MPH, MBA
Hospital de los Valles
Urology Departament
Av Interoceanica y Av Florencia, Edif Hospital de los Valles
Medical Business Center
Quito
EC
Phone: +59326000900 ext 1823
Email: dr_edurivas@yahoo.com.mx

Abstract

Abstract
This study proposes a feasible strategy for the fight against COVID 19. The strategy aims to reduce the risks of “herd immunity” (or collective immunity) that can occur in an uncontrolled and random way, which has arisen in view of the current pandemic-related situation. This type of strategy would be useful in reactivation of economic activities and lifting of measures of social distancing and quarantine; however, these activities could lead governments to promote misguided decisions with negative health consequences, new spikes in infections, collapse of health services, and re-implementation of control measures and social distancing. Thus, when analyzing the consequences of this strategy, we consider that this concept of herd immunity should be designed differently so that the results are different from the above-mentioned negative consequence. We propose the development of a live pathogen virus vaccine (LPV) with a low viral load that meets the required criteria and allows us to apply this vaccine in conjunction with a herd immunity for generating the necessary immunity, reducing the impact and consequences on health and economies, and reducing the risks in general although this does not mean that they do not exist as they are presented with other types of vaccines, to achieve a return to gradually normality.

(JMIR Preprints 09/07/2020:22381)
DOI: https://doi.org/10.2196/preprints.22381

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

“Herd Immunity” Controlled and Planned versus Uncontrolled and Random, in the strategy to fight against COVID 19: An option with Live Pathogen Virus Vaccine

Eduardo Rivas-Ruiz, MD, MBA, HPM *[1]
[1] Medicine Doctor, Specialist in Urology at the Central University of Venezuela, Senior Management of Public Health of the Central University of Venezuela and Master in Business Administration from IESA

*Corresponding Author: Eduardo Rivas Ruiz
E-mail: dr_edurivas@yahoo.com.mx

Abstract

This study proposes a feasible strategy for the fight against COVID 19. The strategy aims to reduce the risks of “herd immunity” (or collective immunity) that can occur in an uncontrolled and random way, which has arisen in view of the current pandemic-related situation. This type of strategy would be useful in reactivation of economic activities and lifting of measures of social distancing and quarantine; however, these activities could lead governments to promote misguided decisions with negative health consequences, new spikes in infections, collapse of health services, and re-implementation of control measures and social distancing. Thus, when analyzing the consequences of this strategy, we consider that this concept of herd immunity should be designed differently so that the results are different from the above-mentioned negative consequence. We propose the development of a live pathogen virus vaccine (LPV) with a low viral load that meets the required criteria and allows us to apply this vaccine in conjunction with a herd immunity for generating the necessary immunity, reducing the impact and consequences on health and economies, and reducing the risks in general although this does not mean that they do not exist as they are presented with other types of vaccines, to achieve a return to gradually normality.

Keywords: COVID-19, SARS COV-2, Live Virus Vaccine, Herd Immunity, Health Strategy.

Background

The novel Coronavirus 2019 (COVID 19), a disease transmitted by the severe acute respiratory

syndrome coronavirus (SARS COV-2), originated in China in December 2019 and has very rapidly spread worldwide leading the World Health Organization (WHO) to declare this disease as a pandemic on March 11, 2020.[1]

COVID-19 presents clinical forms ranging from asymptomatic to mild, moderate, and very severe, but as of today, the clinical outcomes, especially long-term, are still unknown. The immunology of all of these cases is different and becomes more complex as some patients are only mildly affected while some progress to severe disease.[2]

To date, SARS COV-2 and its clinical manifestations (called COVID-19) have no formally approved treatment and those that are used are only in experimental phases. The same type of process is occurring with vaccines, which are also in the experimental phases. Vaccine testing is not expected to start producing viable results until June 2021 at which time it will be clarified whether these results are favorable or not.[3]

The challenge we face with this disease is to discover or develop an effective vaccine, treatment, and/or strategy that allows us to address the disease with greater security and reduce the consequences (sometimes devastating) that it has generated so far, which could allow us to gradually recover a normal life with fewer risks for all.

Considerations

COVID-19 is considered a self-limiting type of infectious disease, and most cases with mild symptoms can recover within 1 to 2 weeks. Research has reported that SARS-COV-2 infection can cause five different outcomes: (1) asymptomatic infected individuals (1.2%), (2) mild to medium cases (80.9%), (3) severe cases (13.8%), (4) critical cases (4.7%), and (5) death (2.3% in all reported cases). A recent study indicates that the proportion of asymptomatic infection in children under the age of 10 is as high as 15.8%.[4]

A more recent investigation was published and named the National Study of Sero-Epidemiology of SARS-COV-2 Infection in Spain (ENE-Covid), published in May 2020 by the Ministry of Health, Consumption and Social Welfare, in which it was mentioned that 5% of the Spanish population has antibodies against SARS COV-2. After considering data from the Spanish Ministry of Health in which a total of 235,772 cases diagnosed by polymerase chain reaction (PCR) with 28,752 deaths from COVID-19 have been reported to date, it is difficult to explain that 5% of the population has antibodies.[5]

The Spanish population is estimated to be in the order of 47 million people, so that 5% equals 2,350,000 people. If these prevalence data from the study are accurate, the finding indicates that almost 2,350,000 people who are suffering/suffered from the disease are/were asymptomatic or mildly symptomatic, but the disease remains undetected. The question we ask ourselves is how this number of people became infected and for what reason were/are they asymptomatic or mildly symptomatic. However, according to these results, we find that the proportion of patients changes dramatically. According to these data, we can estimate that infected people who present as asymptomatic or mildly symptomatic would be 90%, 10% would be medium, severe, or critical cases, and death would occur in 1.1% of total cases. Dissemination could have occurred by any of the known routes, but dissemination through the air at distances of at least up to 8 m could actually be greater due to the wind dynamics, a possible occurrence that has been suggested in the research carried out by Lydia Bourouiba, a researcher at the Massachusetts Institute of Technology (MIT).[6]

Addressing the pandemic in the general population

As for the strategic dynamics to fight the pandemic, researchers at MIT have focused on preventing transmission of this respiratory pathogen. These strategies follow a specific set of actions[7]:

1) Social Actions

a. Isolation at home,

b. Voluntary home quarantine,

c. Social distancing of the entire population, especially the elderly,

d. Temporary closure of schools, universities, and workplaces.

2) Specific protection by chemo- or immune-prophylaxis, which includes:

a. Antiviral agents,

b. Chloroquine-hydroxychloroquine (HCQS), Ivermectin (in clinical trials),

c. Vaccination.

In addition to these measures, both comprehensive preventive and personal hygiene measures have been implemented.

All of these plans and measures have generated great distress and discomfort throughout the population since these measure have generated considerable economic losses, high job losses and many other factors not only related to the health area.[8] In many countries today, it is difficult to comply adequately with the suggestions given different cultural, social, economic, and political realities of each country. These factors greatly influence people's choices as far as complying with regulations; thus, some of these strategies are not entirely effective. Some countries, despite these realities, are considering scenarios to make measures more flexible despite health services functioning at their maximum capacity. These flexibility measures that are being undertaken must consider possible and quite feasible outbreaks of the disease, and people must prepare in advance to deal with these situations under better conditions until an effective treatment or vaccine is found. It is understood that the vaccine must be very safe and cause very few adverse events. The same parameters are expected from a treatment that controls the disease and reduces the rate of complications and case fatality in patients undergoing treatment for COVID-19.

Asymptomatic or mildly symptomatic versus severe cases

This article infers that patients suffering from the disease who are mildly symptomatic or

asymptomatic is due to the fact that they have become infected with low viral loads, which suggests that they will carry equally low viral loads in the incubation and convalescence phases of their disease. This inference would not apply to those immunocompromised patients or those with comorbidities who may have altered immune responses.

Viral load during the first infection and repeated exposure to the virus, especially in healthcare workers, can be an important factor in severity and should be strictly avoided if possible. Understanding the pathogenesis of lymphopenia, cytokine storm, and acute respiratory distress syndrome (ARDS) and new ways to prevent its development will be the main challenges for future research to reduce the serious effects of the disease.[9]

Asymptomatic cases are common although until the date of the study carried out by Dong et al., there were no epidemiological surveys that provided a clear percentage of asymptomatic cases, [2,9,10] until the ENE-Covid study was published in Spain in which these results were described.[5]

According to other studies and reports, approximately 20% of patients are severe cases that require hospitalization. As of April 2020, the death rate has been calculated in approximately 6% of confirmed cases worldwide.[11]

The emergency facing the world today demands the development of urgent and effective measures to protect people who are at high risk of transmission. WHO has accelerated research in diagnosis, vaccines, and therapies for this novel coronavirus.[12]

According to the review carried out by Agrawal et al., the study closest to producing results in relation to a vaccine is projected to occur in June 2021[3] without any indications of favorable results.

A study by Armengaud et al. (2020) describes that sequencing efforts have probably thus far underestimated the occurrence of attenuated variants of SARS-COV-2. Most of the analyzed isolates are derived from individuals who sought medical attention; therefore, it is unlikely that they have acquired any characteristics that lead to a reduction in virulence. Instead, currently attenuated SARS-COV-2 variants should be searched for in the large group of infected individuals who remain

asymptomatic. The identification of samples from individuals with positive tests, who are asymptomatic/mildly symptomatic, would allow determination by following individuals who were and who have remained asymptomatic. All viral sequences in the centralized sequence repositories must be recorded for both symptomatic and asymptomatic patients, including clinical results and other relevant medical parameters, such as age, sex, and comorbidities (in accordance with the corresponding patient privacy legislation according to each country). The authors mention the next step would be to mark the virus-specific genetic determinants and in particular, deletions that are enriched within the set of isolates derived from confirmed asymptomatic populations but absent in isolates of symptomatic patients with COVID-19.[13]

SARS-COV-2 vaccines

Live attenuated SARS-COV-2 virus vaccines would involve some degree of unknown risk and may cause unpredictable results, for example, due to recombination events.[14] In fact, designer vaccines have replaced live attenuated virus vaccines these days due to concerns about the safety of live vaccines.[13]

Regarding the route of administration, the ideal vaccine would be oral since it would allow a reduction in production costs as much as possible and reduce the time for dispensing it. Vaccines administered directly to mucosal surfaces are rapidly and widely distributed and lead to an improvement in cellular and humoral immune responses. Intranasal vaccinations against respiratory and gastrointestinal pathogens offer several theoretical and practical benefits, such as avoiding the need for extensive bacterial purification and significantly reducing training costs for healthcare workers.[15]

Perception of risk has been defined as “Perceived vulnerability or probability of harm if measures are not taken and the seriousness or seriousness of the consequences is perceived if harm occurs”.[16]

Previous systematic reviews have studied the determinants of vaccination doubts and reasons for refusing to accept a vaccination, but few have focused on risk perceptions regarding the benefits of

vaccination and individual assessment of the risk-benefit balance.[17]

In the scientific literature, we can find a variety of articles related to the perception of risks concerning vaccinations for different diseases. In the work of Karafillakis et al. (2017) based on the European population, they reviewed 2895 articles from databases, which, according to the inclusion criteria, considered 145 articles. In all 145 articles, the most common beliefs were related to the balance concerning the risks of vaccination versus non-vaccination, the safety of the vaccine (n = 107/145 articles), and the low perceived risk of contracting Vaccines for Preventable Diseases (VPD), in 51 out of 145 articles. Other important findings describe beliefs that VPDs are not dangerous (n = 36/145), vaccines do not work (n = 32/145), vaccines are not needed (n = 24/145), adults or children are healthy enough not to need vaccinations (n = 20/145), insufficient evidence or adequate evidence of vaccine efficacy (n = 21/145), no recommendations to take the vaccine (n = 20/145), or lack of information on vaccines and/or VPD (n = 31/145).[17]

The concept of herd immunity and live pathogen vaccines in COVID-19

“Herd immunity” refers to collective immunity at the population level. The immunity threshold is defined as the proportion of a population that needs to be immune to stop the spread of a contagious disease. The key parameter defining the herd immunity threshold is the R0 (basic reproductive number), which is the number of new infections generated by the first infectious individual in a fully susceptible population.[18]

R0 is affected by the duration of infectivity in infected patients, the contagiousness of the organism, and the number of susceptible people who are in contact with the infectious carrier.[19] For example, measles is known to have a relatively high R0, whereas diseases such as influenza type *Haemophilus* b and polio are less easily transmitted from person to person than is SARS COV-2.[20] One of the important aspects of a collective immunity strategy with live pathogen vaccines (LPV), such as the one proposed in this work, is that you can better control R0 since it is a controlled and planned strategy instead of a random and uncontrolled process.

Finally, herd immunity implies ethical and legal consequences. To the extent that vaccination is encouraged in part to provide indirect protection to unvaccinated persons, there is the implication of risk, albeit a very small risk, that is imposed on certain individuals for the benefit of other individuals. This concept may have different implications in different cultural, ethical, or legal contexts, for example, government responsibility in circumstances of adverse vaccine events. Viewed from this perspective, we find that indirect protection, which is the basis of “herd immunity” or “collective immunity”, raises many interesting and important issues about individuals and public values. In fact, one could argue that immunity, in its final analysis, it is about protecting society itself.[19]

The use of vaccines for preventable diseases is beneficial from a cost-effective point of view for the population. However, this does not occur when faced with a pandemic with mortality Rates of around 6% [10] where there is no effective and efficient treatment to treat the complications of the disease and there is no vaccine to date.[21]

In 2016, a study was published by Choudhry et al. in which the Food and Drug Administration (FDA)-approved LVP vaccine consisting of live and oral types 4 and 7 adenovirus vaccines. These vaccines contained a lyophilized formulation of selected wild-type viruses with no less than 32,000 enteric-coated infectious tissue culture doses per tablet. The vaccine was administered orally in the form of two tablets (one type 4 and one type 7), swallowed whole without chewing at the beginning of basic training. It should be noted that after having carried out the vaccination against adenovirus and carrying out this study, United States military researchers also noticed a reduction in adenoviruses associated with respiratory diseases; these findings are consistent with the beneficial effects described in previous reports. In that study, the Scientific Review Committee (SRC) determined that in most people presenting with viral events there was no biologically plausible explanation for the increased frequency in the vaccinated group. In general, these events were associated with factors related to demography (such as prevalence of an event by gender or race)

and/or geography (such as concentration of events at a particular military base). However, seven emerging events of interest were considered, and six were validated through a review of medical records. Of the six validated events, only two had events that were considered possibly related to live vaccination.[22]

Chen and Chen (2020) proposed a series of advantages in relation to the use of a live virus vaccine for the management of the SARS COV-2 pandemic by administering an LPV vaccine administered with enteric-coated capsules, arguing that the vaccination process is simpler than that of other vaccines because no syringes, needles, or other attached equipment is needed. They mention that in general, LPV could induce stronger acquired immunity against SARS-COV-2 than other vaccines, especially with respect to mucosal immunity, which is essential for the prevention of respiratory viruses. Moreover, it has been reported that some live vector virus vaccines present the potential for carcinogenicity and mutagenicity, and these potential adverse events have not been identified in live coronaviruses. Their article warns that some live attenuated coronaviruses can regain their virulence; however, this issue is not a concern in the LPV strategy. They also mention that other types of vaccines have the potential to accelerate mutation and diversification of the target virus to escape induced immunity.[23]

Basic strategic work plan

A basic strategy for use of an LPV is described in the following step:

1. The lowest possible viral load that can generate immunity should be considered for an LPV vaccine under the assumption that mildly symptomatic or asymptomatic cases have had this behavior due to having been infected with very low viral loads,

2. It is suggested to use a liquid form for administration by the oral route as this route is the most economical, has the best control, and can be rapidly manufactured.

3. The necessary studies and tests corresponding to the LPV vaccine must be conducted to its use in

humans considering the ethical aspects of the World Medical Association (WMA) in the Declaration of Helsinki.[24]

4. The cultured virus from asymptomatic patients must be used as a starting point.

5. People at high risk of suffering from the severe form of the disease, such as children, pregnant women with chronic diseases, immunosuppression, respiratory and heart diseases, those over 65 years of age, obese individuals, and any other risky disease should be excluded.

6. It must be assumed that it is much better to perform a planned and controlled “herd immunity” than a random and uncontrolled one. This type of planning allows for better control and potentially decrease the risks of serious complications and lethality and would lead to controlled and planned management of cases, medications, hospitalizations, and optimization of the use of health services and allows a less risky reopening of the economic apparatus.

7. Establish priorities according to the most affected epidemiological areas.

8. Arrange, plan, and supply the necessary and timely prophylactic or symptomatic treatments for those vaccinated cases that begin to present moderate symptoms.

9. Plan the volumes of people to be vaccinated according to the flexibility and reactivation strategies of the economy. Establish care and precautions to be considered in those people who are vaccinated since they will be contagious for a period of time. Consider risks for those who can be vaccinated but live with people at high risk, children, pregnant women, chronic diseases, and others already mentioned. These vaccinated individuals must comply with social isolation measures and regular monitoring with tests until they are no longer contagious.

10. Establish preventive measures that avoid increasing viral load by exposure or in any other way to those who are vaccinated, maintain follow-ups, and maintain measures of social distancing during pre-established periods.

Conclusions

1- LPV vaccines are a reality that have been used in recent times for the control of infectious diseases, have FDA approval, and produce good results.

2- This article considers that the most adequate, fastest, and economic route of administration of live viruses with the expected effects of immunity is orally via sublingual drops.

3- It is not justified to consider before the evidence of dissemination, contagiousness, and lethality to implement an uncontrolled and random herd Immunity.

4- There are enough elements and resources available for easy access to implement a planned and controlled herd Immunity strategic application plan, once a live virus vaccine has been developed with the lowest possible viral load possible after extracting the virus from the cultures of asymptomatic patients. The objective is to ensure that all vaccinated patients are asymptomatic or only mildly symptomatic, thus reducing the risks even if they continue to exist.

5- Developing an LVP vaccine may take less time than developing other types of vaccines.

6- To date, there is no vaccine or effective treatment for the disease, so the feasibility of this plan and proposed strategy is a real and viable present-day option for fighting COVID-19.

7- The implementation of this strategy both in its development and in its implementation is a very economic possibility for all countries.

8- The implementation of this strategy allows us to assume better control in the management and spread of this disease.

9- The implementation of this strategy could allow us to recover in less time and with less risk to the health of people and their economies, thus leading to a gradual return to normal.

The author(s) have no conflicts of interest exist.

The author(s) received no specific funding for this work

References

1. WHO. WHO Director-General’s opening remarks at the media briefing on COVID-19 – 11 March 2020. Accessed on: 24 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-

media-briefing-on-covid-19---11-march-2020

2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20. doi:10.1056/NEJMoa2002032
3. Agrawal S, Goel AD, Gupta N. Emerging prophylaxis strategies against COVID-19. Monaldi Arch Chest Dis 2020;90:10.4081/monaldi.2020.1289. Published 2020 Mar 30. doi:10.4081/monaldi.2020.1289
4. Jin Y, Yang H, Ji W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 2020;12:372. Published 2020 Mar 27. doi:10.3390/v12040372
5. Estudio Nacional de sero-Epidemiología de la Infección por SARS-CoV-2 en España (ENE-Covid). Ministerio de Sanidad, Consumo y Bienestar Social. https://www.mscbs.gob.es/ciudadanos/ene-covid/home.htm
6. Bourouiba L. Turbulent Gas Clouds and Respiratory Pathogen Emissions: Potential Implications for Reducing Transmission of COVID-19 [published online ahead of print, 2020 Mar 26]. J Am Med Assoc 2020;10.1001/jama.2020.4756. doi:10.1001/jama.2020.4756
7. Ferguson N., Laydon D., Nedjati-Gilani G., et al. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Imperial College COVID-19 Response Team. Mar 2020. doi: https://doi.org/10.25561/77482
8. https://www.ilo.org/global/about-the-ilo/newsroom/news/WCMS_740920/lang--es/index.htm
9. Dong X, Cao YY, Lu XX, et al. Eleven faces of coronavirus disease 2019 [published online ahead of print, 2020 Mar 20]. Allergy 2020;10.1111/all.14289. doi:10.1111/all.14289
10. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19 [published online ahead of print, 2020 Feb 21]. J Am Med Assoc 2020;323:1406-7. doi:10.1001/jama.2020.2565
11. https://www.worldometers.info/coronavirus/.
12. Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Glob Health 2020;8:e639-40. doi:10.1016/S2214-109X(20)30114-5
13. Armengaud J, Delaunay-Moisan A, Thuret JY, et al. The Importance of Naturally Attenuated Sars-Cov-2 in the Fight Against Covid-19 [published online ahead of print, 2020 Apr 28]. Environ Microbiol 2020;10.1111/1462-2920.15039. doi:10.1111/1462-2920.15039

14. Zhang W, Zheng XS, Agwanda B, et al. Serological evidence of MERS-CoV and HKU8-related CoV co-infection in Kenyan camels. Emerg Microbes Infect 2019;8:1528-34. doi:10.1080/22221751.2019.1679610
15. Zheng Z, Diaz-Arévalo D, Guan H, Zeng M. Noninvasive vaccination against infectious diseases. Hum Vaccin Immunother 2018;14:1717-33. doi:10.1080/21645515.2018.1461296
16. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. Hum Vaccin Immunother 2013;9:1763-73. doi:10.4161/hv.24657
17. Karafillakis E, Larson HJ; ADVANCE consortium. The benefit of the doubt or doubts over benefits? A systematic literature review of perceived risks of vaccines in European populations. Vaccine 2017;35:4840-50. doi:10.1016/j.vaccine.2017.07.061
18. Metcalf CJE, Ferrari M, Graham AL, Grenfell BT. Understanding Herd Immunity. Trends Immunol 2015;36:753-55. doi:10.1016/j.it.2015.10.004
19. Fine P, Eames K, Heymann DL. ‘‘Herd Immunity’’: A Rough Guide. Clinical Infectious Diseases 2011;52(7):911–916. DOI: 10.1093/cid/cir007
20. Vynnycky E, White R. An introduction to infectious disease modelling. 1st ed. Oxford University Press; 2010. July 15. (Cross Reference)
21. https://www.healthline.com/health-news/heres-exactly-where-were-at-with-vaccines-and-treatments-for-covid-19
22. Choudhry A, Mathena J, Albano JD, Yacovone M, Collins L. Safety evaluation of adenovirus type 4 and type 7 vaccine live, oral in military recruits. Vaccine 2016;34:4558-64. doi:10.1016/j.vaccine.2016.07.033
23. Ji-Wang Chen y Ji-Ming Chen. Potential of live pathogen vaccines for defeating the COVID-19 pandemic: history and mechanism. J Med Virol doi: 10.1002/jmv.25920.
24. https://www.wma.net/es/que-hacemos/etica-medica/declaracion-de-helsinki/