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Community Hybrid Immunity Effect Magnitude in 2024 Versus 2023 on the Risk of Covid-19 Reinfection in a General Medicine Office in Toledo (Spain)

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Abstract

Background

The expression of the true impact or magnitude of preventive measures (vaccination and natural immunity) against covid-19 in daily practice on the population is not yet clear.

Objective

To compare the relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), and number needed to harm (NNH) associated with acquired immunity from vaccination and/or infection for SARS-CoV-2 reinfections since 2023 to 2024.

Methodology

Comparison of secondary data among covid-19 reinfection cases in 2023 and 2024 years of previous studies. For the calculation of RRR, ARR, NNT and NNH of SARS-CoV-2 infections, cases in 2023 were considered as control group with respect to cases in 2024.

Results

The risk of covid-19 reinfection was lower in the group exposed to the immunity level of 2024 versus 2023 in the variables: Men [RRR= 0.4 versus ARR= 0.4], Socio-health workers [RRR= 0.5 versus ARR= 20], and patients with Moderate severe severity [RRR= 1 versus ARR= 0.2]. The greatest magnitude of the effect of the hybrid immunity level was for Socio-health workers (NNT= 5), followed by men (NNT= 250) and patients with Moderate severe severity (NNT= 500).

Conclusion

In the context of this general practice setting in Toledo, Spain, the data suggest maintaining vaccination against covid-19 especially in Socio-health workers, and possibly in the entire population or at least in men.

Keywords: Covid-19, Sars-Cov-2, Hybrid Immunity, Risk And Benefit Data, Population Surveillance/Methods, Epidemiological Characteristic, Public Health Practice, General Practice

Introduction

Five years after the pandemic began, new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections continue to occur despite advances in vaccines. SARS-CoV-2 reinfections became common with the arrival of omicron [1-4]. There is increasing scientific evidence showing that the protection generated by vaccination decreases over time, although it is restored with booster dose inoculation [5, 6].

Hybrid immunity, resulting from a combination of SARS-CoV-2 infection and vaccination, offers robust protection against coronavirus disease 2019 (covid-19) in the general population.

A large proportion of the world's population has acquired immunity through vaccination, infection, or a combination of both, i.e. hybrid immunity against SARS-CoV-2, by the end of 2022 [7]. But, the temporal evolution of natural and hybrid immunity is unknown [8]. Knowledge about immune protection induced by vaccines, previous infection, or hybrid immunity is of great importance for covid-19 intervention policies and for a better understanding of the immunological mechanisms that protect against infectious diseases [7].

Although scientific papers often provide results indicating their statistical significance, they are less likely to provide data on their clinical importance. The Absolute Risk Reduction (ARR) calculation is probably one of the most useful and intuitive data in this regard. The ARR allows to understand the individual benefit of an intervention. The Relative Risk Reduction (RRR) is often used in marketing or the media because it tends to produce a larger, more eye-catching number, and can bias the impact perceived by the public and primary care physicians [9-14].

The number needed to treat (NNT) to prevent an adverse event is also a useful measure of the results of an intervention and represents the therapeutic effort needed to achieve a specific clinical benefit. Analogous to the NNT, there is the number needed to harm (NNH), which is the reciprocal of the absolute risk increase in situations where the experimental treatment harms more patients than the control. The NNH is the number of patients who, if they received the experimental treatment, would cause one additional person to be harmed compared to patients receiving the control treatment [15].

Thus, in SARS-CoV-2 infection, it may be more intuitive to give the results of the intervention (community hybrid immunity: vaccination and natural immunity from having had the infection) over time, in addition to RRR figures, in the form of ARR, NNT and NNH. Measuring the ARR and NNT may be more appropriate for prioritizing vaccination of vulnerable populations than relative measures, such as RRR [16, 17].

In this scenario, we present a comparative study based on previously published data, to evaluate RRR, ARR, NNT and NNH of reinfections covid-19 in 2024 (omicron variant with third booster -5th doses- of vaccine) compared to 2023 (omicron variant and with second booster -4th dose) in a general medicine consultation.

Material And Methods

Design And Emplacement

This study compares data from previous observational, longitudinal and prospective studies of covid-19 reinfections from October 2023 to October, 2024, already published [18, 19]. These previous studies were conducted on the same population: patients saw in a general medicine office in Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, general practitioner (GP) care for people > 14 years of age, except for exceptions). The GPs in Spain work within the National Health System, which is public in nature, and are the gateway for all patients to the system, and each person is assigned a GP. The methodology of all studies has been previously published, but the main elements will be repeated here to facilitate understanding of the current study.

Outcome of Interest

To compare the RRR, ARR, NNT and NNH for SARS-CoV-2 reinfections, associated with acquired immunity by vaccination and/or infection since 2023 to 2024.

Calculation of the Numerators

Cumulative incidence rates were calculated at the GP's office by dividing the number of reinfection events during the study period by the individuals that could develop the event at the start of the study (population at risk) [2]. That is, the incidence rate was calculated by dividing the number of cases of covid-19 reinfections by people on the list of patients dependent on the consultation object of the study (N=2,000 people) in 2023 and 2024 years [21, 22].

Calculation of Rate Denominators

Data of variables of people in the clinic object of the study were obtained by extrapolating the neighborhood served by the health center to population served in clinic office [23, 24]. The denominator data for prevalence of chronic diseases were taken from previous studies carried out in the same population treated in that general medicine consultation [25-28]. The number of social-health workers was obtained as an extrapolation of the total number for Castilla la Mancha region in 2020 for the list of 2000 inhabitants attended in the consultation object of the study [29].

Calculation of RRR and ARR

The RRR was calculated as control incidence minus the intervention incidence and divided by the control incidence. ARR was calculated as the arithmetic difference between two event rates: the event rate in the control group minus the event rate in the intervention group [20]. The incidence rates in 2023 (immunity by vaccination and/or infection: omicron SARS-CoV-2 variant and 4th booster doses of vaccine) were considered as the control group with respect to the incidence rates of 2024 (immunity by vaccination and/or infection: omicron SARS-CoV-2 variant and 5th booster doses

of vaccine), which was the intervention group.

It was considered that when the ARR is equal to 0, it means that there is no association; when the ARR has a value less than 0, it means that the association is positive (i.e. that the presence of the factor is associated with a higher occurrence of the event); and when the ARR has a value greater than 0, it means that the association is negative (i.e. that the presence of the factor is associated with a lower occurrence of the event) [30].

Calculation of NNT y NNH

NNT is a term that was proposed in the context of clinical trials to assess the impact of a treatment. It is defined as the number of individuals that need to be treated with the experimental therapy in order to produce, or prevent, one additional event over those that would occur with the control treatment. It is the inverse of the ARR, or 1/ARR. NNH is calculated in a similar way to NNT, and is the inverse of the absolute increase in risk (NNH = 1 / Absolute Increase in Risk). It represents the opposite of NNT. That is, a negative NNT indicates that the treatment has a harmful effect (the experimental treatment provides less benefit than the control or standard), or that the adverse effects inherent to the treatment are greater in the experimental group. In other words, NNT represents the number needed to treat to produce an effect in 1 person; and NNH the number needed to treat to produce some harm in 1 person. The NNH will have a negative absolute risk reduction. The lower the NNT, the greater the magnitude of the effect of the intervention in question. The higher the NNH, the lower the risk of harm from the intervention [30]. The Numbers Needed to Treat were calculated using the online Clinical Calculators from ClinCalc.com [31].

Definition of Reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection [32-34].

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [35] performed in health services or at home.

Covid-19 Vaccination

Patients could have received 1, 2 doses of vaccine, first booster for fall-winter 2021, fourth dose (second booster) for fall-winter 2022 [36] and fifth dose (third booster) for fall-winter 2023. In our study, only Pizfer / BioNTech, Spikevax (mRNA-1273- Moderna), Vaxzevria, Oxford / AstraZeneca and Janssen (Johnson & Johnson) vaccines were used for the first and second doses. For the first booster, only messenger RNA (mRNA) was used. And only Moderna and Pfizer-BioNTech's bivalent covid-19 vaccines were used for the second booster. Omicron XBB.1.5 adapted vaccines Pfizer / BioNTech y Spikevax (Moderna) were used for the third booster in autumn-winter 2023-2024 [37-40].

Collected Variables

The following variables were collected:
-Age and sex
-Chronic diseases (defined as "any alteration or deviation from normal that has one or more of the following characteristics: is permanent, leaves residual impairment, is caused by a non-reversible pathological alteration, requires special training of the patient for rehabilitation, and / or can be expected to require a long period of control, observation or treatment" [41].
-If they were Health Care Workers
-Disease severity (classified according to: 1. mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; 2. moderate cases: with symptoms such as fever and respiratory tract symptoms and the manifestation of pneumonia can be seen on the imaging tests; and 3. severe cases: respiratory distress, respiratory rate ≥ 30 breaths / min., pulse oxygen saturation ≤ 93% with room air at rest, arterial partial pressure of oxygen / oxygen concentration ≤ 300 mmHg.) [42]; to simplify comparison, moderate and severe cases were counted together.

Epidemiological Analysis

The calculation of RRR, ARR, NNT and NNH was performed as explained above. Figures with decimals were rounded to facilitate a more intuitive comparison. Similarly, to facilitate understanding of the data, the periods compared were rounded to full years: the period from October 1, 2022 to September 30, 2023 was labeled 2023; and from October 1, 2023 to September 30, 2024 was labeled 2024.

Ethical Issues

No personal data of the patients were used, but only group results, which were taken from the clinical history.

Results

ARR figures were always less striking or equal to RRR figures. RRR and ARR were positive (the risk of covid-19 reinfection was lower in the group exposed to the 2024 immunity level compared to 2023) in the variables: Men [RRR= 0.4 versus ARR= 0.4], Socio-health workers [RRR= 0.5 versus ARR= 20], and patients with Moderate severe severity [RRR= 1 versus ARR= 0.2]. In >65 years both RRR and ARR were 0. RRR and ARR were negative (the risk of covid-19

reinfection was higher in the group exposed to the 2024 immunity level versus 2023) in the variables: Total population >=14 years [RRR = -0.3 versus ARR= -0.2], Women [RRR= -25 versus ARR= --1.5], and Patients with chronic diseases [RRR= -1.7 versus ARR= -0.5].

VARIABLES	COVID-19 REINFECTION INCIDENCE RATES FROM OCTOBER 2022 TO OCTOBER 2023 (2023) (CONTROL)	COVID-19 REINFECTION INCIDENCE RATES FROM OCTOBER 2023 TO OCTOBER 2024 (2024) (INTERVENTION. PRESENCE OF THE FACTOR)	ATTRIBUTABLE RISK (incidence in 2024 - intervention- minus incidence in 2023) [a positive difference indicates that the incidence is higher in the intervention group]	RELATIVE RISK REDUCTION (Control incidence minus the intervention incidence and divides by the control incidence)	ABSOLUTE RISK REDUCTION (Control incidence minus intervention incidence)
Total (>=14 years)	0.6%	0.8%	0.2	-0.3	-0.2
> 65 years	1.1%	1.1%	0	0	0
Women	0.6%	2.1%	1.5	-25	-1.5
Men	0.9%	0.5%	-0.4	0.4	0.4
Socio-health workers	37%	17%	-20	0.5	20
Moderate severe severity	0.2%	0	-0.2	1	0.2
Presence of chronic diseases	0.3%	0.8%	0.5	-1.7	-0.5

Table 1: Absolute and Relative Risk Reduction of Covid-19 Reinfection from 2024 to 2023

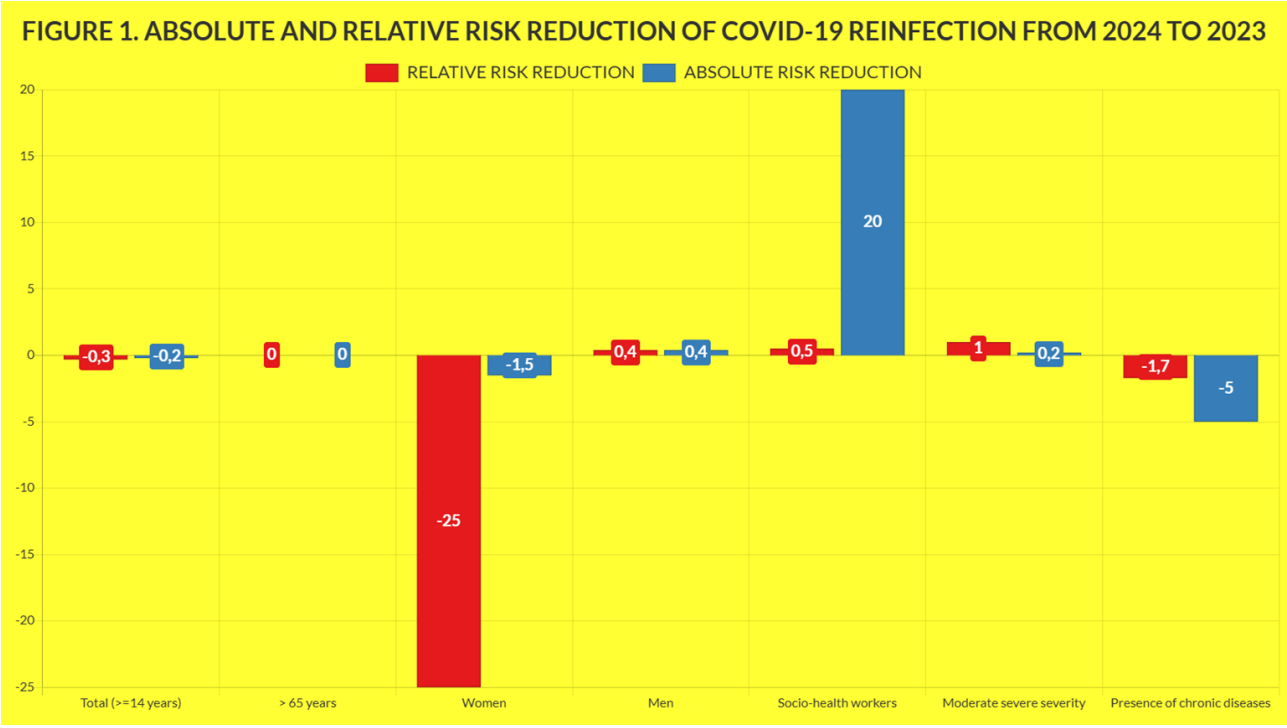

Figure 1. Absolute and Relative Risk Reduction of Covid-19 Reinfection from 2024 to 2023

The following variables were found to cause prevention by the 2024 versus 2023 hybrid immunity intervention: Men [On average 250 men would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional man to not have covid-19 reinfection], Socio-health workers [On average 5 Socio-health workers would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional Socio-health workers to not have covid-19 reinfection] and Moderate severe severity [On average, 500 patients with Moderate severe severity would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional patient with Moderate severe severity to not have covid-19 reinfection]. The largest magnitude of the effect of the hybrid immunity level was for Socio-health workers (NNT= 5), followed by men (NNT= 250) and patients with Moderate severe severity (NNT= 500).

VARIABLES	**NUMBER NEEDED TO TREAT (NNT) [1/ABSOLUTE RISK REDUCTION]** [The lower the NNT, the greater the magnitude of the treatment effect in question]
Men	250 [On average, 250 men would need to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional man to not get covid-19 reinfection]
Socio-health workers	5 [On average 5 socio-health workers would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional socio-health workers to not have covid-19 reinfection]
Moderate severe severity	500 [On average, 500 patients with moderate severe severity would have to receive el nivel de inmunidad híbrida de 2024 (en lugar del nivel de 2023) for one additional patient with moderate severe severity to not have covid-19 reinfection]

Table 2: Number Needed to Treat for Prevention of Covid-19 Reinfection Through Community Hybrid Immunity Since 2023 to 2024

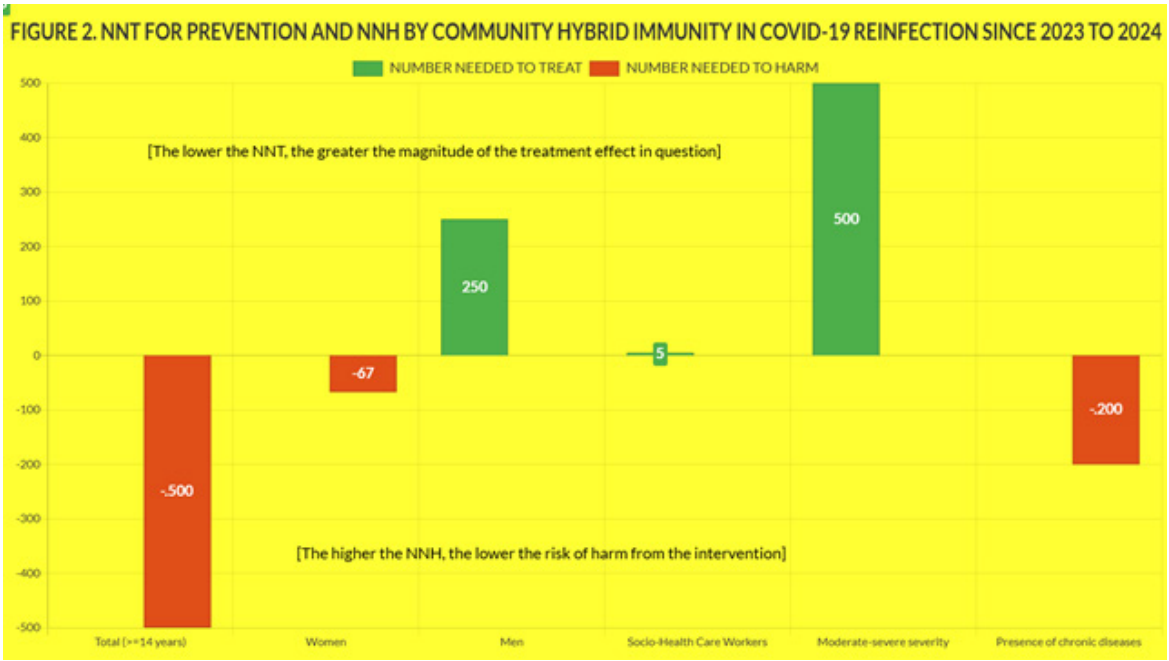

Figure 2. Number needed to Treat for Prevention and Number Needed to Harm by Community Hybrid Immunity in covid-19 Reinfection Since 2023 to 2024 (nnh are Drawn as Negative Figures to Make the Graph Easier to Understand)

The following variables were found to cause harm by the 2024 versus 2023 hybrid immunity level intervention: Total people >=14 years [On average, 500 people > 14 years would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional person > 14 years to have covid-19 reinfection], women [On average, 67 women would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional woman to have covid-19 reinfection] and patients with chronic diseases [On average, 200 patients with chronic diseases would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional patient with chronic diseases to have covid-19 reinfection]. The lowest risk of harm with the hybrid immunity level of 2024 compared to 2023 was for the total population > 14 years (NNH = 500), followed by patients with chronic diseases (NNH = 200), and finally women (NNH = 67).

VARIABLES	NUMBER NEEDED TO HARM (NNH) [1/ABSOLUTE RISK REDUCTION] [The higher the NNH, the lower the risk of harm from the intervention]
Total (>=14 years)	500 [On average, 500 people >14 years of age would need to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional person >14 years of age to have covid-19 reinfection]
Women	67 [On average, 67 women would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional woman to have covid-19 reinfection]
Presence of chronic diseases	200 [On average, 200 patients with chronic diseases would have to receive the 2024 level of hybrid immunity (instead of the 2023 level) for one additional patient with chronic diseases to have covid-19 reinfection]

Table 3: Number Needed to Harm Using Community Hybrid Immunity in Covid-19 Reinfection Since 2023 to 2024

The calculation of NNT and NNH in > 65 years was not mathematically possible due to the same incidence rates in both groups and an RRR and ARR of zero.

Discussion

Main Findings

Our main findings were:

- RRR figures were always more striking or equal to ARR.
- Hybrid immunity (natural infection and/or vaccination) from 2024 versus 2023 achieved a decrease in the risk of covid-19 reinfection both measured as RRR and ARR in Men, Socio-health workers and patients with Moderate severe severity.
- The greatest magnitude of the effect of the hybrid immunity level from 2024 versus 2023 to achieve a decrease in the risk of covid-19 reinfection was for Socio-health workers, followed by men and patients with Moderate severe severity.
- The RRR and ARR were negative (the risk of covid-19 reinfection was higher in the group exposed to the immunity level of 2024 versus 2023) in the Total population >=14 years, Women and Patients with chronic diseases.
- The lowest risk of harm with the hybrid immunity level of 2024 compared to 2023 was for the total population > 14 years, followed by patients with chronic diseases, and finally women.

In 2023, the omicron SARS-CoV-2 variant predominated and the population received the 4th booster dose of the vaccine. By June 2023, the number of people with the 1st booster dose was 56% of the population [43]. In 2024, the omicron SARS-CoV-2 variant predominated and the population received the 5th booster dose of the vaccine. 60% of the population over 80 years of age has received the vaccine adapted against the covid-19 subvariants of the 2023/2024 campaign [44].

In any case, the results must be evaluated with caution. In Spain, since April 28, 2022 there was a new "Surveillance and Control Strategy Against Covid-19" that include the non-performance of diagnostic tests, except on over 60 years of age [45]. This means that positive cases have been counted with tests carried out in health services and with tests carried out at home and later reported to the GP. Thus, there is probably an underreporting.

Comparison With Other Studies

Herd immunity is a more difficult concept to apply to diseases like covid-19 when the virus changes a lot in a short time and if the protection obtained from having the disease and recovering from it, or from receiving the vaccine, does not last long [46].

Hybrid immunity, resulting from a combination of SARS-CoV-2 infection and vaccination, offers robust protection against covid-19 in the general population. Infection-derived immunity has demonstrated 93–100% protection against severe COVID-19 outcomes for up to 8 months, but reinfection is seen with some variants of the virus. Vaccination elicits high levels of neutralizing antibodies and a breadth of CD4+ and CD8+ T cell responses. The evolution of SARS-CoV-2 toward more transmissible and immunologically divergent variants has necessitated updating of covid-19 vaccines. To ensure continued protection against SARS-CoV-2 variants, vaccine technical committees recommend variant-specific or bivalent vaccines [47].

Omicron variants have demonstrated their potential to escape vaccine-induced humoral immunity, leading to many breakthrough infections and the development of hybrid immunity [7]. With the emergence of antigenically distinct variants, neither natural immunity nor first-generation vaccine-induced immunity has been able to effectively prevent transmission. Booster doses (third or fourth) of the vaccine play an important role in preventing symptomatic infection, although the booster effect only lasts several months [48].

A systematic review of the magnitude and duration of protective efficacy of prior SARS-CoV-2 infection and hybrid immunity against infection and severe disease caused by the omicron variant showed that all estimates of protection against reinfection decreased within months but remained high and were maintained in the event of hospital admission or severe disease [49].

It has been described in a study in Brazil from November 16 to December 22, 2022 that despite high hybrid immunity at the population level, the BQ.1 variant attacked 56% of the population. Hybrid immunity may provide protection against future SARS-CoV-2 variants, but in this study, it was unable to prevent widespread transmission [50].

While randomized controlled trials and population-based evaluations do not routinely report ARR, and their primary effect measure for vaccine effectiveness is RRR. Some researchers have subsequently calculated ARR using data from large studies. The RRR has a disadvantage, which is that it does not differentiate very large risks or benefits from very small ones and does not vary according to the size of the sample [30].

Clinical trials for covid-19 vaccines by 2021 reported impressive efficacy in preventing symptomatic disease: 95% RRR for the Pfizer-BioNTech vaccine and 94% for the Moderna vaccine. If ARR were calculated in the same population of these clinical trials, this reduction provided by the vaccines would be much less striking [51, 52].

The NNT calculation allows us to assess not only the magnitude of the effects but also the cost-benefit of the intervention. If the NNT of an intervention is close to the NNH, the chances of improving the patient are similar to the chances of causing harm; therefore, the intervention has little chance of being useful in practice [30].

In cases where the risk is greater in the exposed group, some authors prefer to speak of relative risk increase (instead of RRR) and absolute risk increase (instead of ARR) [53]. A negative NNT indicates that the treatment has a harmful effect (the experimental treatment achieves less benefit than the control or standard), or that the adverse effects inherent to the treatment are greater in the experimental group. The lower the NNT, the greater the magnitude of the treatment effect in question. The higher the NNH, the lower the risk of harm with the new treatment [30]. Most NNTs for treatments used in medicine are between 2 and 4, with the possible exception of antibiotics. The best painkillers have NNTs of 2 to achieve at least 50% pain relief [54].

In summary, In general practice setting in Toledo, Spain, the greatest magnitude of the effect of the hybrid immunity level from 2024 versus 2023 to achieve a decrease in the risk of covid-19 reinfection is achieved in Socio-health workers in men and patients with Moderate severe severity. The lowest risk of harm with the hybrid immunity level in 2024 compared to 2023 occurs for the total population > 14 years, followed by patients with chronic diseases, and finally women. In any case figures for 2023 and 2024 may have a bias due to underreporting.

Study Limitations and Strengths

- Weaknesses of the NNT metric. As with other benefit descriptions, NNT must be considered within the time frame of the study and could not be directly applied to other contexts with different risks or levels of immunity or interventions.
- The sample was small, so some data may cause misinterpretation.
- Asymptomatic cases were missing because they did not attend GP consultation, as no surveillance or systematic screening was done.
- There may be an underreporting of infections to GP of patients with a positive test at home.
- The great accessibility of patients to the GP, and the fact of continuity of care that characterizes family medicine, have important epidemiological connotations, presenting a unique opportunity to study benefit-risk values of interventions in small geographical bases.

Conclusion

In a general practice setting in Toledo, Spain, the largest effect size of the 2024 versus 2023 hybrid immunity level in achieving a decreased risk of covid-19 reinfection was achieved in Socio-health workers in men and patients with moderate severe severity. The lowest risk of harm with the 2024 versus 2023 hybrid immunity level occurred for the total population > 14 years, followed by patients with chronic diseases, and finally women. In conclusion, these data suggest maintaining vaccination especially in Socio-health workers, and possibly in the entire population or at least in men.

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