

# Hybrid Immunity Effect Trend on Covid-19 Reinfection in A Fully Vaccinated Population According to The Number Needed to Treat Since 2020-2022 To 2023 Versus 2023 To 2024 In A General Medicine Office in Toledo (Spain)

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Received date: **March 17, 2025**; Accepted date: **April 09, 2025**; Published date: **May 16, 2025**

**Citation:** Jose L. Turabian, (2025), Hybrid Immunity Effect Trend on Covid-19 Reinfection in A Fully Vaccinated Population According to The Number Needed to Treat Since 2020-2022 To 2023 Versus 2023 To 2024 In A General Medicine Office in Toledo (Spain), *Clinical Research and Clinical Trials*, 12(4); DOI:10.31579/2693-4779/264

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## Abstract:

### Background

The evolution of the magnitude of the impact from 2020 to 2024 of prevention measures (vaccination and natural immunity) against covid-19 reinfection in daily practice on the population is not known.

### Objective

To compare the number needed to treat (NNT) and the number needed to harm (NNH) for SARS-CoV-2 reinfections, associated with prevention measures (mainly acquired immunity through vaccination and natural immunity), since 2020-2022 period to 2023 vs. 2023 to 2024.

### Methodology

Comparison of secondary data among covid-19 reinfection cases in 2020-2022 period to 2023 vs. 2023 to 2024 of previous studies. For the calculation of NNT and NNH of SARS-CoV-2 infections, cases in 2020-2022 period were considered control group with respect to cases in 2023, and cases in 2023 were considered control group with respect to cases in 2024.

### Results

Lower NNT figures (greater magnitude of the hybrid immunity effect) and higher NNH figures (lower risk of harm with hybrid immunity) were found since the period 2020-2022 to 2023 versus 2024. 2023 to 2024. Since 2020-2022 period to 2023 the lowest NNT figures were for women (17) and People with some type of labor specialization (59). And the highest NNH figures were for men (1000) and Moderate-severe severity of reinfection (500). Since 2023 to 2024 the lowest NNT figures were Socio-Health Care Workers (5) and Complex families (111). And the highest NNH figures were for population >14 years (500) and People with some type of labor specialization (333).

### Conclusion

In the context of this general practice setting in Toledo, Spain, there was a lower magnitude of the beneficial effect of hybrid immunity from 2023 to 2024 vs. from 2020-2022 to 2023. In any case, the greatest benefit in 2024 is for Socio-Health Care Workers and the least harm is for the population >14 years old.

**Keywords:** covid-19; sars-cov-2; hybrid immunity; risk and benefit data; population surveillance/methods; epidemiological characteristic; public health practice; general practice

## Introduction

Hybrid immunity, resulting from a combination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vaccination, offers robust protection against coronavirus disease 2019 (covid-19) in the community. 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 [1]. But the temporal evolution of this natural and hybrid immunity is unknown [2].

Decreased immunity as a result of new variants must be taken into account.

The efficacy of prior SARS-CoV-2 infection in preventing reinfection varies along the spectrum spanning alpha, beta, delta, and omicron (3). There is increasing scientific evidence showing that the protection generated by vaccination decreases over time, although it is restored with booster dose inoculation [4, 5].

Five years after the pandemic began, new SARS-CoV-2 infections continue to occur despite advances in vaccines. SARS-CoV-2 reinfections became common with the arrival of omicron [6-9]. Knowledge about immune protection induced by vaccines, previous infection or hybrid immunity is of great importance for intervention policies against covid-19 and for a better understanding of the immunological mechanisms that protect against infectious diseases (1).

Although various measures can be used to describe the benefits and harms of treatments or preventive interventions, not all of them clearly show the benefits or harms of these interventions in a clinically useful way. Relative risk and relative risk reduction (RRR) are commonly used to describe study results, but they have limited clinical utility as they do not take into account baseline risks and tend to exaggerate study results. Absolute risk measures, such as number needed to treat (NNT) and number needed to harm (NNH), allow risk to be expressed in a much more clinically relevant way. Absolute risk measures reflect baseline risk and more accurately indicate the magnitude of the treatment effect [10].

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 the form of ARR, NNT and NNH. Consequently, measuring the ARR and NNT (people to be vaccinated and/or with past infection at the community level) may be more appropriate for prioritizing vaccination of vulnerable populations than relative measures, such as RRR [11, 12].

In this scenario, we present a comparative study, based on previously published data, to evaluate the NNT and the NNH of covid-19 reinfections since period 2020-2022 until 2023 [with alpha, delta and omicron SARS-CoV-2 variants; and in 2020 without vaccination, in 2021 with 1 or 2 dose vaccination and in 2022 with first booster] and since 2023 until 2024 [in 2023 omicron variant and with second booster -4th dose-, and in 2024 omicron variant with third booster -5th doses- of vaccine], from the same population attended 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 since Marzo 2020 to October, 2024, already published [13, 14]. 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. GPs 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 number needed to treat (NNT) and the number needed to harm (NNH) for SARS-CoV-2 reinfections, associated with acquired immunity by vaccination and/or infection) since March 2020-October 2022 period to October 2023 with October 2023 to October, 2024.

### Definition, calculation and interpretation of NNT and NNH

NNT (defined as the number of individuals that must be treated with the experimental therapy to produce, or prevent, one additional event over those that would occur with the control treatment; it represents the number needed to treat to produce an effect in 1 of them) and NNH (number needed to treat

to produce some harm in 1 of them; that is, 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 NNH will have a negative absolute risk reduction) were calculated as the inverse of the Absolute Risk Reduction (ARR), or 1/ARR. 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 [15]. NNT and NNH were calculated using the online Clinical Calculators at ClinCalc.com [16].

### Definition of reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection [17-19].

### Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [20] performed in health services or at home.

### Covid-19vaccination

*Patients could have received 1, 2 doses of vaccine, first booster for fall-winter 2021, fourth dose (second booster) for fall-winter 2022 [21] and fifth dose (third booster) for fall-winter 2023. In our study, only Pfizer / 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 [22-25].*

### 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" [26])

-Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [27]

-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  $\geq 30$  breaths / min., pulse oxygen saturation  $\leq 93\%$  with room air at rest, arterial partial pressure of oxygen / oxygen concentration  $\leq 300$  mmHg.) [28]; to simplify comparison, moderate and severe cases were counted together

-Problems in the family context based on the genogram. It was understood that "complex" genograms present families with psychosocial problems) [29, 30]

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") [31]

### Epidemiological analysis

Definition, calculation and interpretation of NNT and NNH was carried out 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**

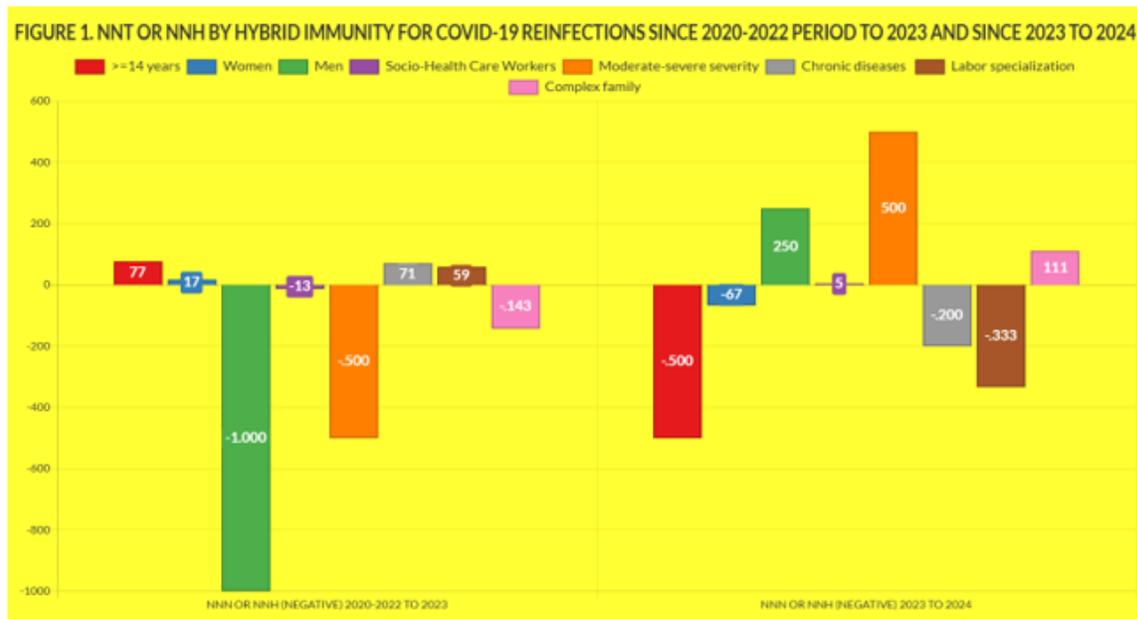
Lower NNT figures (greater magnitude of hybrid immunity effect) and higher NNH figures (lower risk of harm with hybrid immunity) were found since 2020-2022 to 2023 versus 2023 to 2024. From 2020-2022 to 2023, the

lowest NNT figures were for women (NNT= 17), People with some type of labor specialization (NNT= 59), and total population >14 years (NNT= 77). And the highest NNH figures were for men (NNT= 1000) and Moderate-severe severity of reinfection (NNH= 500). From 2023 to 2024, the lowest NNT figures were for Socio-Health Care Workers (NNT= 5) and Complex families (NNT= 111). And the highest NNH figures were for population >14 years (NNH= 500), People with some type of labor specialization (NNH= 333) and carriers of chronic diseases (NNH= 200). The NNT and NNH of >= 65 years and Ethnic minority, from 2023 to 2024, were not calculable because they had the same incidence rate in both periods (TABLE 1, FIGURE 1).

VARIABLES	INCIDENCE RATES OF COVID-19 RE-INFECTION 2020-2022 (control)	INCIDENCE RATES OF COVID-19 RE-INFECTION 2023 (Intervention for 2020-22, and control for 2024)	ABSOLUTE RISK REDUCTION 2020-2022 vs. 2023 (Control incidence minus intervention incidence)	NUMBER NEEDED TO TREAT [1/ABSOLUTE RISK REDUCTION] 2020-2022 (control) vs. 2023 (intervention) (The lower the NNT, the greater the magnitude of the treatment effect in question; the higher the NNH, the lower the risk of harm from the intervention)	INCIDENCE RATES OF COVID-19 RE-INFECTION 2023 vs. 2024 (intervention)	ABSOLUTE RISK REDUCTION 2023 vs. 2024 (Control incidence minus intervention incidence)	NUMBER NEEDED TO TREAT [1/ABSOLUTE RISK REDUCTION] 2023 (control) vs. 2024 (intervention) (The lower the NNT, the greater the magnitude of the treatment effect in question; the higher the NNH, the lower the risk of harm from the intervention)
<b>&gt;=14 years</b>	1.9%	0.6%	1.9-0.6=1.3	On average, 77 patients would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for an additional person >14 years of age to NOT have the covid-19 reinfection.	0.8%	-0.2	On average, 500 people >14 years of age would need to receive the 2024 level of hybrid immunity (instead of the 2023 level) for one additional person >14 years of age to HAVE covid-19 reinfection
<b>&gt;= 65 years</b>	0.9%	1.1%	-0.2	On average, 500 patients would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional person to HAVE covid-19 reinfection	1.1%	0	Not calculable
<b>Women</b>	6.3%	0.6%	5.7	On average, 17 patients would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional woman to NOT have covid-19 reinfection	2.1%	-1.5	On average, 67 women would need to receive the 2024 level of hybrid immunity (instead of the 2023 level) for one additional woman to HAVE covid-19 reinfection
<b>Men</b>	0.8%	0.9%	-0.1	On average, 1000 patients would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional man to HAVE covid-19 reinfection	0.5%	0.4	On average, 250 men would have to receive the 2024 level of hybrid immunity (instead of the 2023 level) for one additional man to NOT have covid-19 reinfection
<b>Socio-Health Care Workers</b>	29%	37%	-8	On average, 13 socio-health care workers would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional Socio-Health Care Workers to HAVE covid-19 reinfection	17%	20	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

<b>Moderate-severe severity of reinfection</b>	0	0.2%	-0.2	On average, 500 patients with moderate severe severity would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional patient with moderate severe severity to HAVE covid-19 reinfection	0	0.2	On average, 500 patients with moderate severe severity would have to receive the 2024 level of hybrid immunity (instead of the 2023 level) for one additional patient with moderate severe severity to not HAVE covid-19 reinfection
<b>Chronic disease carriers</b>	1.7%	0.3%	1.4	On average, 71 patients with chronic diseases would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional patient with chronic diseases to NOT have covid-19 reinfection	0.8%	-0.5	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
<b>People with some type of labor specialization</b>	1.8%	0.1%	1.7	On average, 59 people with some type of labor specialization would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional patient to NOT have covid-19 reinfection	0.4%	-0.3	On average, 333 people with some type of labor specialization would have to receive the 2024 level of hybrid immunity (instead of the 2023 level) for one additional patient to HAVE covid-19 reinfection
<b>Complex families</b>	0.5%	1.2%	-0.7	On average, 143 people with complex families would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional people with complex families to HAVE covid-19 reinfection	0.3%	0.9	On average, 111 people with complex families would have to receive the 2024 hybrid immunity level (instead of the 2023 level) for one additional people with complex families to NOT have covid-19 reinfection
<b>Ethnic minority</b>	6.2%	1.2%	5	On average, 20 ethnic minority people would have to receive the 2023 hybrid immunity level (instead of the 2020-2022 level) for one additional ethnic minority people to NOT have covid-19 reinfection	1.2%	0	Not calculable

**Table 1:** Nnt or nnh by hybrid immunity for covid-19 reinfections since 2020-2022 period to 2023 and since 2023 to 2024



**Figure 1:** Nnt or nnh by hybrid immunity for covid-19 reinfections since 2020-2022 period to 2023 and since 2023 to 2024

## Discussion

### 1. Main findings

Our main findings were:

1. Lower NNT figures (greater magnitude of hybrid immunity effect) and higher NNH figures (lower risk of harm with hybrid immunity) were found since 2020-2022 to 2023 versus 2023 to 2024.
2. Since 2020-2022 to 2023, the lowest NNT figures were for women, people with some type of labor specialization, and total population >14 years. And the highest NNH figures were for men and moderate-severe severity of reinfection.
3. Since 2023 to 2024, the lowest NNT figures were for Socio-Health Care Workers and Complex families. And the highest NNH figures were for population >14 years, people with some type of labor specialization, and carriers of chronic diseases.

To interpret the results, it is necessary to take into account SARS-CoV-2 lineages that were successively prevalent [32] and the vaccines received. In the period 2020-2022 SARS-CoV-2 variants were successively alpha, delta and omicron, and the population had received only 1, 2 or 3 doses of vaccine (14). In Spain, in April 2022, the population vaccinated with the complete regimen (2 or 3 doses) was more than 85% [33]. In November 2022, more than 60% of people over 80 years of age, and 37% of people over 60 years of age, already had the second booster dose of the covid-19 vaccine [34, 35]. 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 [36]. 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 had received the vaccine adapted against the covid-19 subvariants of the 2023/2024 campaign [37].

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 includes the non-performance of diagnostic tests, except on over 60 years of age [38]. 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.

### 2. Comparison with other studies

Auctores Publishing LLC – Volume 12(4)-264 www.auctoresonline.org  
ISSN: 2693-4779

Understanding the protection that prior infection provides or vaccination against repeat infection, disease, and severe disease, in the transition from an epidemic to an endemic state, where a pathogen is stably maintained in a population. is key to projecting the future epidemiology of coronavirus disease 2019 (covid-19), and guiding decisions on vaccination policies (12).

One of the key questions in predicting the course of covid-19 is how well and how long immune responses protect the host from reinfection [39]. Reinfection occurs in an individual is not only determined by the magnitude and duration of specific immunity, but also by the various circumstances of their risk of exposure to the virus [40].

Omicron variants have demonstrated their potential to escape vaccine-induced humoral immunity, leading to many post-vaccination infections and the development of hybrid immunity (1). Reinfections before the omicron variant were very rare, but as new subvariants appeared, immune escape is greater; Not only from vaccines, but also from natural immunity [41-43]. Neither natural immunity nor first-generation vaccine-induced immunity have been able to effectively prevent transmission. Booster doses (third or fourth) of the vaccine played an important role in preventing symptomatic infection, although the booster effect only lasts several months [44, 45].

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 declined within months [46]. 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 [47, 48]. The RRR has the disadvantages that it does not differentiate very large from very small risks or benefits and does not vary according to sample size (15). The calculation of the NNT allows to evaluate not only the magnitude of the effects but also the cost-benefit of the intervention (15).

In some 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) [49]. 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 (15).

In summary, in a general practice setting in Toledo, Spain, we found a greater magnitude of hybrid immunity effect and lower risk of harm with hybrid immunity, since 2020-2022 to 2023 versus 2023 to 2024. Greatest benefit since 2023 to 2024 is in Socio-Health Care Workers and the least harm in the population >14 years. This data suggests that covid-19 vaccination should be maintained, at least in Socio-Health Care Workers. In any case figures since 2023 and 2024 may have a bias due to underreporting.

### Study limitations and strengths

1. Absolute risk measures reflect baseline risk and more accurately indicate the magnitude of the treatment effect. However, because they vary according to the population's baseline risk, their generalizability is limited and the published NNT of a treatment in one population cannot be directly applied to another population with a different baseline risk.
2. The sample was small, so some data may cause misinterpretation.
3. Asymptomatic cases were missing because they did not attend GP consultation, as no surveillance or systematic screening was done.
4. There may be an underreporting of infections to GP of patients with a positive test at home.
5. 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.

### Conclusion

In the context of this general practice setting in Toledo, Spain, there is a lower magnitude of beneficial effect and lower harm of hybrid immunity since 2023 to 2024 versus 2020-2022 to 2023. In any case, the greatest benefit in 2024 is in Socio-Health Care Workers and Complex families, and the least harm in the population >14 years old. Two future strategies are suggested; 1) prioritize vaccination in Socio-Health Care Workers, or 2) vaccinate the entire population >14 years old.

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DOI:10.31579/2693-4779/264

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