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Research Article

Reinfection Covid-19 Absolute Risk Reduction From 2020 To 2024 In A General Medicine Office in Toledo (Spain)

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Abstract

Background

Absolute risk reduction is one of the most useful data to know the clinical importance of an intervention. But its evolution for covid-19 reinfection is unknown.

Objective

To compare the absolute risk reduction of SARS-CoV-2 reinfections, associated with acquired immunity (vaccination and/or infection) during 2020-2022 period versus 2023 and 2024 versus 2024.

Methodology

Comparison of secondary data among covid-19 reinfection cases in 2020-2022 period, 2023 and 2024 years of previous studies, all of them carried out in the same population of patients treated in a general medicine office in Toledo, Spain. The intervention groups (hybrid immunity: vaccination and/or infection) were considered reinfection cases from 2023 [compared with 2020-2022 period (control)] and from 2024 [compared with 2023 (control)].

Results

There are no reductions in reinfection absolute risk from 2024 to 2023 when they are compared to reductions in reinfection absolute risk from 2023 to 2020-2022, neither in the total, nor in 14-65 years, nor in women, nor in men, nor in cases with moderate severe severity, nor in deaths. This trend does not occur in those over 65 years of age and in cases with the presence of chronic diseases where einfection absolute risk is slightly reduced, and especially in socio-health workers with a very significant reduction.

Conclusion

The vaccination and hybrid immunity intervention were very useful for reinfection absolute risk reduction from 2023 to 2020-2022, but its effect is attenuated from 2024 to 2023, except in those over 65 years of age, in cases with chronic diseases, and especially in socio-health workers.

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

Introduction

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 (1). The ARR is most useful for understanding 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. However, the ARR can provide guidance on the benefit that an individual patient can expect (2-6).

Not only is this RRR biased impact perceived by the public, but a similar effect has been reported in the interpretation of risk data by primary care physicians (7).

Thus, in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, it may be more intuitive to give the results of the intervention

(vaccination and natural immunity from having had the infection) in the form of ARR. Measuring the ARR and the number of people to be treated or vaccinated are more appropriate for prioritizing vaccination of vulnerable populations than relative measures, such as RRR (8).

It should be noted that vaccination efficacy, estimated by the ARR rate, may vary in population subgroups with different background risks (8) and with different severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants throughout the pandemic and in the current endemic phase (9), and this information can facilitate policies on vaccine distribution (10).

Most people have some degree of protection due to underlying immunity. By the third quarter of 2023, 98% had antibodies against SARS-CoV-2, with 14% due to vaccination alone, 26% due to infection alone, and 58% due to both (hybrid immunity) (11). Seroprevalence surveys suggest that more than a third and possibly more than half of the global population has been infected with SARS-CoV-2 by early 2022. As large numbers of people continue to be infected (12). Studies have shown a decrease in the immunity provided by the vaccine. But, the temporal evolution of natural and hybrid immunity is unknown (13).

In this scenario, information on the evolution of community ARR measures for covid-19 reinfection from 2020 to 2024 is not clearly known. We present a comparative study based on previously published data, to evaluate the trend of ARR of reinfections covid-19 in the period 2020-2022 (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), 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 in these time periods.

Material And Methods

Design and emplacement

This study compares data from previous observational, longitudinal and prospective studies of covid-19 reinfections from March, 2020 to October, 2024, already published (14-18). All 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 ARR of SARS-CoV-2 reinfections, associated with acquired immunity (vaccination and/or infection), comparing ARR from 2023 to 2020-2022 with ARR from 2024 to 2023.

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) (19). 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), from the period 2020-2022, in 2023 and 2024 years (20, 21).

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 (22, 23). Data regarding some variables of interest (as complex family, and chronic diseases) were previously published (24-27). 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 (28-31). The number of social-health workers was obtained as an extrapolation of the total number for Castilla la Mancha in 2020 for the list of 2000 inhabitants attended in the consultation object of the study (32). The ethnic minority data was obtained by extrapolating the data of foreigners in the municipality of Toledo to the population attended at the clinic (33). The data on vaccination with a complete schedule (1, 2 or 3 dose) was obtained by extrapolating the data from Spain to the population of the clinic (34). Likewise, for 2023 the number of people with the 1st booster dose was extrapolated for the population of the clinic from the data for Spain (35).

Calculation of ARR

The absolute risk reduction ARR is the opposite diference del attriutable risk: control minus treated (19).

Absolute risk (AR) = (number of events in the treated or control group) / (number of people in that group)

ARC = Absolute risk of events in the control group

ART = Absolute risk of events in the treatment group

ARR = ARC - ART

Thus, ARR was calculated as the arithmetic difference between 2 event rates: the event rate in the control group minus the event rate in the intervention group. ARR should be interpreted in the context of the baseline risk (36). Thus, the following were considered as intervention groups: 1) the incidence rates in 2023 (immunity by vaccination and/or infection: omicron SARS-CoV-2 variant and 4th booster doses of vaccine) compared with period 2020-2022; and 2) the incidence rates of 2024 (immunity by vaccination and/or infection: omicron SARS-CoV-2 variant and 5th booster doses of vaccine) compared with 2023. Therefore, the following were considered as control or baseline risk group: 1) the period 2020-2022 (successively 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 third dose -first booster) as a control compared with 2023 (omicron SARS-CoV-2 variants and 4th booster dose of vaccine); and 2) the year 2023 as a control compared to 2024 (5th dose -second booster of vaccine).

Definition of reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection (37-39).

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing (40) 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 (41) 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 (42-45).

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" (46)

-Social-occupancy class (according to the Registrar General's classification of occupations and social status code) (47)

-If they were Health Care Workers

-Problems in the family context based on the genogram. It was understood that "complex" genograms present families with psychosocial problems) (48, 49)

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") (50)

-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.) (51); to simplify comparison, moderate and severe cases were counted together

-Vaccination status against covid-19 at the date of reinfection: vaccinated with 2 doses of vaccine (40), vaccinated with first booster for fall-winter 2021 (52), vaccinated with fourth dose (second booster) for fall-winter 2022 (53) and vaccinated with fifth dose (third booster) for fall-winter 2023 (54, 55).

Epidemiological analysis

The calculation of ARR as explained above (subsection "Calculation of ARR"). The age of 65 years was used as the beginning of old age (56). 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 March 1, 2020 to September 1, 2022 was labeled 2020-2022; 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

There are no ARR from 2024 to 2023 when compared to ARR from 2023 to 2020-2022, both in the total (ARR of 8% from 2023 to 2020-2022 and ARR of 1% from 2024 to 2023); in 14-65 years (ARR of 10% from 2023 to 2020-2022 and ARR of 1% from 2024 to 2023); in women (ARR of 6% from 2023 to 2020-2022 and ARR of 2% from 2024 to 2023); in men (ARR of 10% from 2023 to 2020-2022; and ARR of 1% from 2024 to 2023); in cases with moderate severe severity (RRA of 0.9% from 2023 to 2020-2022 and ARR of 0% from 2024 to 2023); and in deaths (RRA of 0.2% from 2023 to 2020-2022 and RRA of 0% from 2024 to 2023).

This trend does not occur in those over 65 years of age (ARR of 0% from 2023 to 2020-2022 and ARR of 1% from 2024 to 2023) or in cases with the presence of chronic diseases (ARR of -1% from 2023 to 2020-2022 and ARR of 0% from 2024 to 2023) where the absolute risk is slightly reduced from 2024 to 2023 compared with the figure from 2023 to 2020-2022, and especially in socio-health workers where ARR from 2024 to 2023 is very significant when compared with ARR from 2023 to 2020-2022 (ARR of -49% from 2023 to 2020-2022 and ARR of 29% from 2024 to 2023). (TABLE 1, FIGURE 1, FIGURE 2, FIGURE 3, FIGURE 4).

VARIABLES	COVID-19 INCIDENCE RATES IN THE PERIOD OF 2020-2022 (control)	COVID-19 INCIDENCE RATES IN 2023 (intervention group for 2020-2022 period, and control group for 2024)	ABSOLUTE RISK REDUCTION (INCIDENCE IN 2020-2022 MINUS INCIDENCE IN 2023	COVID-19 INCIDENCE RATES IN 2024 (intervention group regarding 2023)	ABSOLUTE RISK REDUCTION (INCIDENCE IN 2023 MINUS INCIDENCE IN 2024
Total (>=14 years)	36% x 3 years [12% average x 1 year]	4% x 1 year	8%	3% x 1 year	1%
> 65 years	19% x 3 years [6% average x 1 year]	6% x 1 year	0%	5% x 1 year	1%
14-65 years	39% x 3 years [13% average x 1 year]	3% x 1 year	10%	2% x 1 year	1%
Women	33% x 3 years [11% average x 1 year]	5% x 1 year	6%	3% x 1 year	2%
Men	38% x 3 years [13% average x 1 year]	3% x 1 year	10%	2% x 1 year	1%
Socio-health workers	16% x 3 years [5% average x 1 year]	54% x 1 year	-49%	25% x 1 year	29%
Moderate severe severity	4% x 3 years [1% average x 1 year]	0.1% x 1 year	0.9%	0.1% x 1 year	0%
Exitus	0.5% x 3 years [0.2% average x 1 year]	0 % x 1 year	0.2%	0 % x 1 year	0%
Presence of chronic diseases	7% x 3 years [2% average x 1 year]	3% x 1 year	-1%	3 % x 1 year	0%

Table 1: Absolute Reduction Covid-19 Risk From 2023 To 2020-2022, And From 2024 To 2023

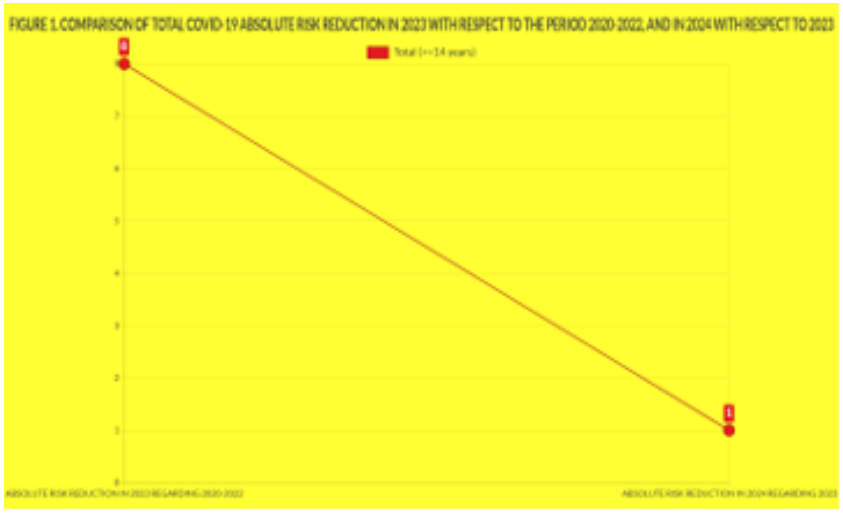

Figure 1: Absolute Reduction Covid-19 Total Risk From 2023 To 2020-2022, And From 2024 To 2023

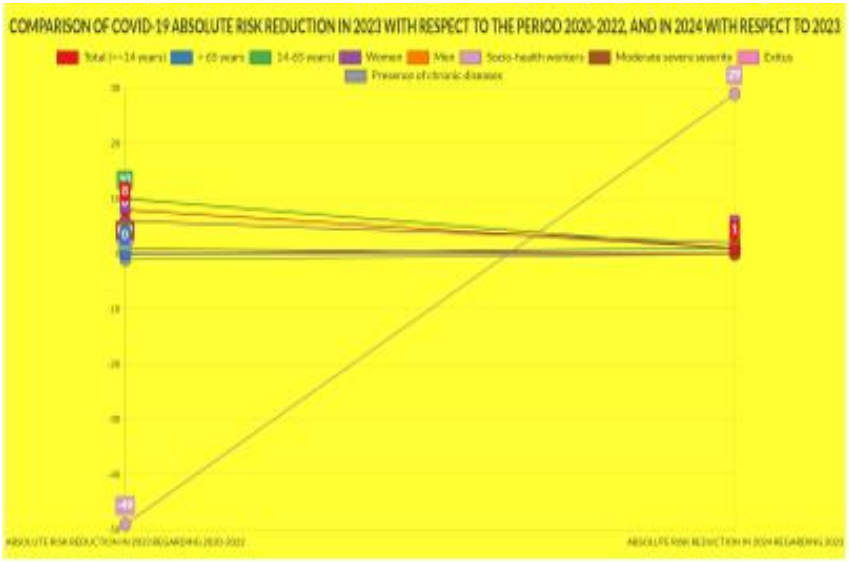

Figure 2: Absolute Reduction Covid-19 Risk In Selected Variables From 2023 To 2020-2022, And From 2024 To 2023

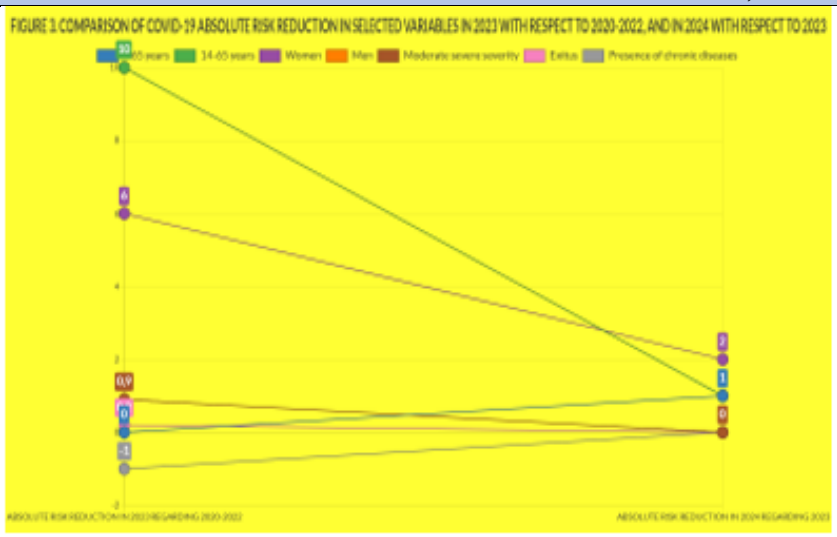

Figure 3: Absolute Reduction Covid-19 Risk In Selected Variables From 2023 To 2020-2022, And From 2024 To 2023

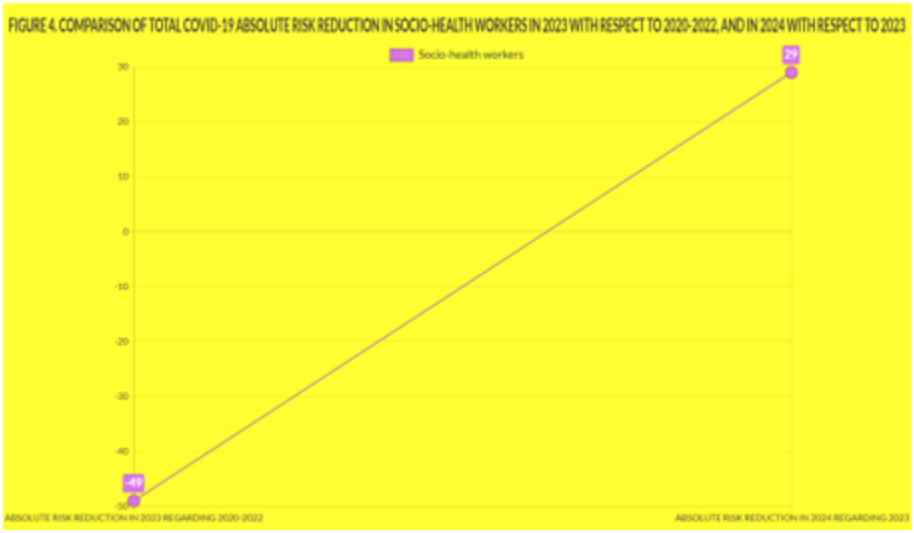

Figure 4: Absolute Reduction Covid-19 Risk In Socio-Health Workers From 2023 To 2020-2022, And From 2024 To 2023

Discussion

1. Main findings

Our main findings were:

1. There are no ARR from 2024 to 2023 when compared with ARR from 2023 to 2020-2022, neither in the total, nor in 14-65 years, nor in women, nor in men, nor in cases with moderate severe severity, nor in deaths

2. There are ARR from 2024 to 2023 when compared with ARR from 2023 to 2020-2022 in people over 65 years of age and in cases with the presence of chronic diseases, and especially in socio-health workers.

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 (57). In Spain, in April 2022, the population vaccinated with the complete regimen (2 or 3 doses) was 85.27% (34). 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 (58, 59); this situation was considered in our study as an expression of the baseline rates. The ARR should be interpreted in the context of the baseline risk (36). 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 (35). 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 (60).

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 (61). 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

Five years after the pandemic began, new SARS-CoV-2 infections continue to occur despite advances in vaccines (62). It has been reported that SARS-CoV-2 reinfections were rare until late 2021, but became common with the arrival of omicron (63-66). The human host of SARS-CoV-2 in 2023 and 2024 is different from that of 2020 in terms of vaccination status. Vaccines have been shown to be effective in reducing the severity of SARS-CoV-2 infection (67-69). However, waning 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 (9). There is increasing scientific evidence showing that the protection generated by vaccination decreases over time, although it is restored with booster dose inoculation (70, 71). Furthermore, the protection conferred by natural immunity, vaccination, and both against SARS-CoV-2 infection with the omicron variant is unclear (38, 72, 73).

When a patient is considering undergoing a preventive service such as vaccination, relevant information to guide a decision includes the likelihood of risk and benefit. Some have argued that all patients considering preventive services should be given this information in the form of absolute probabilities (6). Any quantitative data can be described in many ways, and research shows that the approach to that information has significant effects on patient understanding (74, 75). One of the most intuitive ways to describe the risks and benefits of a medical intervention is the ARR. However, patients are rarely given such absolute measures of potential benefit (74).

While randomized controlled trials and population-based evaluations do not routinely report ARR, their primary effect measure for vaccine effectiveness is RRR. Some researchers have subsequently calculated ARR using data from large studies, but none have assessed the metrics in subpopulations, including socioeconomic groups, with different baseline risks of disease (8). 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. But these figures did not imply that 94% to 95% of people were protected from the disease with these vaccines, a common misconception among patients and even some health care professionals. This means that the number of cases of covid-19 disease would be reduced by 94% to 95% compared to what would occur without vaccination. If ARR were calculated in the same population of these two clinical trials, this reduction provided by the vaccines would be much less striking: 0.84% for the Pfizer-BioNTech vaccine (0.88% in the placebo group minus 0.04% in the vaccinated group) and 1.23% for the Moderna vaccine (1.31% minus 0.08%) (76, 77).

In a systematic review for 2021, vaccination in people who have recovered from covid-19 provided an extremely small absolute risk difference for the prevention of subsequent SARS-CoV-2 infection (AR = 0.004 person-years). At that time, the authors concluded that the net benefit is marginal in absolute terms. Therefore, vaccination of people who have recovered from covid-19 should be subject to clinical criteria and individual preferences (78). However, current trends in reported cases

of covid-19 are underestimates of the true number of infections and reinfection (79).

In summary, In general practice setting in Toledo, Spain, the hybrid immunity intervention (natural infection and/or vaccination) from 2024 to 2023 compared with 2023 to 2020-2022 only shows reinfection ARR in people over 65 years of age, in cases with chronic diseases and especially in healthcare workers. That is, the vaccination and hybrid immunity intervention that was probably very useful from 2023 to 2020-2022, has a lower effect from 2024 to 2023, except in those over 65 years of age, in cases with chronic diseases, and especially in healthcare workers. These absolute data can more intuitively show information on the protection of hybrid immunity against covid-19 reinfections and suggest which population groups should be predominantly targeted by the vaccination intervention. In any case figures for 2023 and 2024 may have a bias due to underreporting.

Study limitations and strengths

1. The sample was small, so some data may cause misinterpretation.

2. Asymptomatic cases were missing because they did not attend GP consultation, as no surveillance or systematic screening was done.

3. There may be an underreporting of infections to GP of patients with a positive test at home.

4. 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 incidence rates of diseases in small geographical bases.

Conclusion

In a general practice setting in Toledo, Spain, the hybrid immunity (natural infection and/or vaccination) intervention from 2024 to 2023 compared with 2020-2022 only shows reinfection ARR in people over 65 years of age, in cases with chronic diseases and especially in healthcare workers. That is, the vaccination and hybrid immunity intervention was probably very useful from 2023 to 2020-2022, but its effect is attenuated from 2024 to 2023, except in people over 65 years of age, in cases with chronic diseases, and especially in healthcare workers. It is suggested that covid-19 vaccination intervention is especially useful for healthcare workers and people over 65 years of age and those with chronic diseases.

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