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Endemic Period COVID-19 Risk Evolution Between 2023 and 2024 Years in a General Medicine Office in Toledo, Spain. Incidence Rate and Other Risk Measures are Declining or Stable

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ABSTRACT

Background : The evolution of community risk measures for covid-19 infection from 2023 to 2024 is not clearly known.

Objective: To know the evolution of risk measures of cases of covid-19 from October 1, 2022 to October 1, 2024 in a general medicine consultation in Toledo, Spain.

Methodology: Comparison of the covid-19 Incidence Rate, Relative Risk and Attributable Risk in 2023 year versus covid-19 in 2024 (group with very broad hybrid immunity), based on data from previous longitudinal studies, all of them carried out in the same population of patients treated in a general medicine office in Toledo, Spain.

Results: 76 covid-19 cases from October 2022 to October 2023 (1 year at risk) and 54 covid-19 cases from October 2023 to October 2024 (1 year at risk) were included, for a population at risk of 2,000 people. The raw Incidence Rate in 2024 vs. 2023 was lower (3% vs. 4%), Relative Risks were protective or equal and Attributable Risks were negative or equal for all variables studied (relative risk of moderate severe severity and the presence of chronic diseases had not changed). The following statistical significances were found in 2024 vs. 2023: lower Relative Risks for the entire population [RR= 0.75 (X2= 3.8481. p= .049801)], for women [0.6 (X2= 4.319. p= .037689)], and for socio-health workers [0.46 (X2= 4.2686. p= .038823)].

Conclusion: In general practice setting in Toledo, Spain, in 2024 vs. 2023 the incidence of covid-19 and other risk measures are decreasing or it are stable. Population at risk with greater hybrid immunity is better prepared than 2023 to avoid cases of covid-19, but the relative risk of moderate severe severity (which was already low) and the presence of chronic diseases (which was already high) have not changed.

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Introduction

Coronavirus disease 2019 (covid-19) is no longer in the epidemic/pandemic phase. Currently, high levels of immunity to the severe acute respiratory syndrome coronavirus (SARS-CoV-2) are beginning to limit its impact and reach [1]. Many countries are adopting strategies to manage coronavirus disease 2019 (covid-19) as an endemic disease [2]. Five years after the start of the covid-19 pandemic we find ourselves in a new scenario with high level population immunity. But covid-19 will remain with us, threatening the health and well-being of millions of people around the world [3]. Since covid-19 is endemic, it will be present at a certain level in a population at certain times of the year or throughout the year [1]. A disease that is not eradicated is, by definition, endemic. This does not necessarily mean that it is circulating at low levels. Several potential definitions of the transition from the pandemic to the endemic phase are possible. Epidemiologically, covid-19 can be defined as endemic when it exists at a predictable level that does not require special social and health interventions. This is mediated by individual risk factors (age, underlying conditions, etc.) [2,4]. Thus it join the swarm of endemic diseases - such as the common cold, AIDS, measles, malaria and tuberculosis - that are always with us [1,2,5,6].

During the covid-19 pandemic period, very detailed epidemiological surveillance measures were taken that were crucial. Currently in the endemic phase, many of the community surveillance studies tracking infection levels have ended, and many governments have eliminated control and surveillance measures [7,8]. In Spain, since July 2023 from the date on which the end of the health crisis situation caused by Covid-19 was declared, universal surveillance of Covid-19 and periodic data updating ceased. Instead, a surveillance system using sentinel systems was implemented. These systems are not exhaustive (i.e., they do not record all cases that have occurred in the population), but are based on representative population samples, studying the frequency of the clinical presentation of covid-19 in some primary

care consultations and hospitals [9,10]. Thus, covid-19 case counts are no longer published, and it is not clear how many people are infected, nor can the evolution of the number of infections be known at community level.

The new reality with this virus is that in the endemic phase, people may experience reinfections of covid-19 over time. It is estimated that at least 30% of the population could be re-infected in successive waves. Continuous waves of infection carry the risk of new emerging variants that can compete with the current ones and be more severe [7]. There is increasing scientific evidence that shows that the protection generated by vaccination decreases over time, although it is re-established with the inoculation of booster doses. Additionally, we must take into account the decline in immunity as a result of the new variants, and that despite vaccines, boosters and natural immunity, the variants appear to be capable of evading any protection that may have been obtained against SARS -CoV-2 [11-16].

In this scenario, knowing the evolution of the epidemiological measurements of the risk of covid-19 infection is crucial to evaluate its trajectory and factors associated with infections. Ultimately, studying the evolution of infections will help researchers understand what the transition of SARS -CoV-2 to an endemic virus will look like [17].

In summary, there is a lack of community data on the evolution of risk measures of covid-19 during endemic period. In this context, we present a study carried out in a general medicine consultation, that compares data from previous observational, longitudinal and prospective studies of covid-19 cases, from October 2022 to October 2023 with data for the period from October 2022 to October 2023, which can be considered a "treatment" group, taking into account the very broad hybrid immunity in the population, and all this with the aim of knowing the evolution of risk measures of incidence rate (IR), relative risk (RR) and attributable risk (AR).

Material and Methods

Design and Emplacement

This study compares data from previous observational, longitudinal and prospective studies of covid-19 infections from October 2022 to October 2024, in a general medicine office, in the Santa Maria de Benquerencia Health Center, Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, the GP care for people > 14 years of age), already published:

- a study of covid-19 infections fron October 2022 to October 2023 [18,19]
- a study of covid-19 infections from October 2023 to October 2024 [20]

In the current study, the comparison of covid-19 IR, RR and AR in 2023 year ("control" group) versus covid-19 IR in 2024 ("treatment" group with very broad hybrid immunity), was carried out, based on data from the previous longitudinal studies cited above. Descriptive epidemiological analysis considered selected demographic and clinical features.

Outcome of Interest

To know the evolution of risk measures (IR, RR, and AR) of cases of covid-19 from October 1, 2022 to September 30, 2023 versus from October 1, 2023 to September 30, 2024, in a general medicine consultation in Toledo, Spain.

Diagnosis of COVID-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing performed in health services or at home [21].

Collected Variables

The following variables were collected:
Date of covid-19 infection diagnosis

- 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" [22]
- 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.) [23]; to simplify comparison, moderate and severe cases were counted together
- Number of deaths

Calculation of IR

Cumulative and density IR were calculated at the GP's office dividing the number of infection events during the study period by the individuals that could developed the event at start of the study (population at risk) and divided by the sum of the length of follow-up time of observation for all individuals (population-years at risk) [24,25].

Calculation of RR

The data group from 2024 was considered as the "treated group" (practically 100% of individuals were vaccinated and/or had previously had covid-19 infection) and the group of cases from 2023 as the "control group." The RR was calculated by dividing the incidence in the treated group by the incidence in the control group. The RR was interpreted as follows: From 0 to 0.5: protection factor effectively; from 0.6 to 0.8: true benefits; from 0.9 to 1.1: not significant; from 1.2 to 1.6: weak risk; from 1.7 to 2.5: moderate risk; more than 2.5: strong risk [26].

Calculation of AR

El AR or risk difference was calculated by taking the incidence in the treated group (2024 data) and subtracting the incidence in the control group (2023). A positive difference indicates that the incidence is greater in the treated group, whereas a negative one means that the incidence is greater in the control group [27].

Calculation of Rate Numerators

All patients who consulted in the GP office object of the study with acute covid-19 infection: Cases notified to the GP after a positive test at home, or diagnosed by the GP in health services, for the period from October 2022 to October 2023, and from Octobre 2023 to October 2024 were included.

Calculation of Rate Denominators

The total number of patients assigned to the consultation (2000 people) was used as an approximation to the denominator of rates. 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 [28-30]. 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 [31].

Epidemiological and Statistical Analysis

The calculation of the IR was performed as explained above (subsection "Calculation of IR") by dividing the number of infection events by the person follow-up time (from October 2022 to October 2023 on the one hand, and from October 2023 to October 2024 on the other hand) [25]. Data on the incidence were extrapolated to the entire population attended in the consultation (N=2,000 people) [26,32]. To make the comparison of results easier and more intuitive, the years at risk were rounded: in the group from October 2020 to October 2023, it was considered as 1 year at risk, and was assigned to 2023; in the group from October 2023 to October 2024, it was considered as 1 year at risk, and assigned to 2024. The classes that classify the age groups were made taking into account > and < de 65 años [33]. The age of 65 years was used as the beginning of old age [34].

The bivariate comparisons were performed using the Chi Square test (X2) or Fisher Exact Test when necessary (according to the number the expected cell totals). Data for equal time periods were compared. Figures with decimals were rounded to whole numbers for statistical comparison.

Results

76 covid-19 cases from October 2022 to October 2023 (1 year at risk) and 54 covid-19 cases from October 2023 to October 2024 (1 year at risk) were included, for a population at risk of 2,000 people. The raw IR in 2024 vs. 2023 was lower (3% vs. 4%), RR were protective or equal and AR were negative or equal for all variables studied (But RR of moderate severe severity and the presence of chronic diseases did not vary). The following statistical significances were found in 2024 vs. 2023: lower RR for the entire population [RR= 0.75 (X2= 3.8481. p= .049801)], for women [0.6 (X2= 4.319. p= .037689)], and for socio-health workers [0.46 (X2= 4.2686. p= .038823)] (Table 1, Figure 1).

Table 1: Comparison of Covid-19 Risk Measures between the period from October 2022 to October 2023 and the period from October 2023 to October 2024

VARIABLES	POPULATION OF THE GENERAL MEDICINE OFFICE (population at risk) N=2.000	OCTOBER 2022 TO OCTOBER 2023 COVID-19 CASES N=76	COVID-19 INCIDENCE RATES FROM OCTOBER 2022 TO OCTOBER 2023	OCTOBER 2023 TO OCTOBER 2024 COVID-19 CASES N=54	COVID-19 INCIDENCE RATES FROM OCTOBER 2023 TO OCTOBER 2024	RELATIVE RISK (incidence in 2024 divided by incidence in 2023)	ATTRIBUTABLE RISK (incidence in 2024 minus incidence in 2023)	STATISTICAL SIGNIFICANCE (comparison of 2022 to 2023 with 2023 to 2024
Total (>=14 years)	2.000	76 (100)	4% x 1 year	54 (100)	3% x 1 year	0.75 (true benefits)	-1	X2= 3.8481. p= .049801. Significant at p < .05.
> 65 years	349 (17)	21 (28)	6% x 1 year	16 (30)	5% x 1 year	0.83 (true benefits t)	-1	X2= 0.7135. p= .398285. NS
14-65 years)	1651 (83)	55 (72)	3% x 1 year	38 (70)	2% x 1 year	0.66 (true benefits)	-1	X2= 3.1976. p= .073747. NS
Women	1020 (51)	48 (63)	5% x 1 year	30 (56)	3% x 1 year	0,6 (true benefits)	-2	X2= 4.319. p= .037689. Significant at p < .05.
Men	980 (49)	28 (37)	3% x 1 year	24 (44)	2% x 1 year	0.66 (true benefits)	-1	X2=0.3161. P= .573974. NS
Socio-health workers	24 (12)	13 (17)	54% x 1 year	6 (11)	25% x 1 year	0.46 (protection factor effectively)	-29	X2= 4.2686. p= .038823. Significant at p < .05.
Moderate severe severity	2000 (100)	2 (3)	0.1% x 1 year	2 (4)	0.1% x 1 year	1 (not significant)	0	Fisher exact test= 1. NS
Exitus	NA	0	0 % x 1 year	0	0 % x 1 year	0/0= NaN	0	Fisher exact test= 1. NS
Presence of chronic diseases	1459 (73)	48 (63) sobre una muestra de N=76	3% x 1 year	44 (81)	3 % x 1 year	1 (not significant)	0	X2= 0.1796. p= .671739. NS

( ): Denotes Percentages, NS: Not Significant, NaN: It is not a Number (it represents the Result of Undefined Mathematical Operations), RR: Relative Risk, AR: Attributable Risk

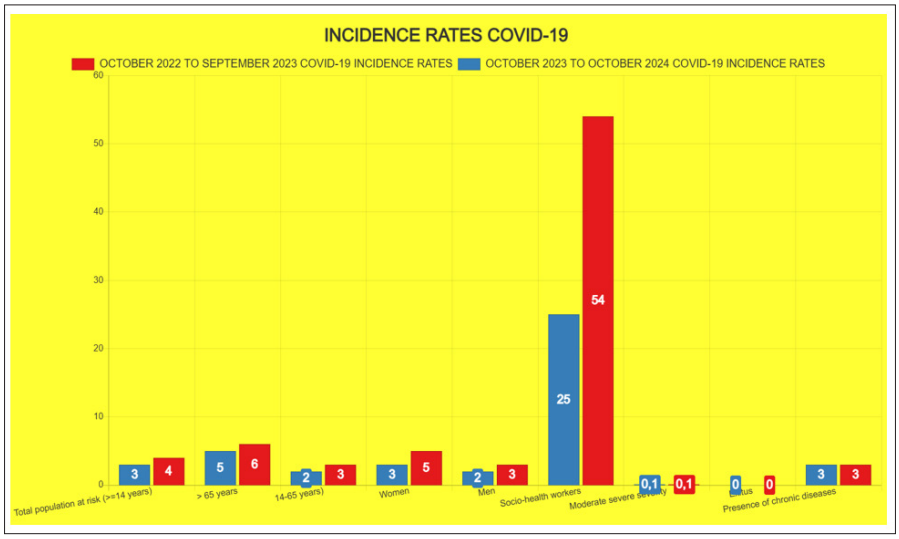

Figure 1: Comparison of COVID-19 Incidence Rates between the Period from October 2022 to October 2023 and the Period from October 2023 to October 2024

Discussion

Main Findings

The main findings of our study were:

- In 2024, the total population at risk (with greater hybrid immunity), women and socio-health workers, presented lower IR (with a RR indicating protection factor and negative RA indicating lower IR, in a statistically significant manner), than for 2023 period.
- In 2024, moderate severe severity (which was already low) and the presence of chronic diseases (which was already high) had their IR, RR and AR not changed compared to 2023.

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 included the non-performance of diagnostic tests, which were focused only on those over 60 years of age [8]. 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. In addition, it is possible that many of the current infections are occurring with few symptoms or are confusing them with those of other mild conditions [35].

On the other hand, the evolution of the predominant SARS-CoV-2 variants in the context of the study must be taken into account. The omicron variant was the dominant one in Spain November, 2022; the replacement of BA.2 by BA.5 occurred in mid-June 2022 [36]. From that moment on, a period of great diversification of the BA.2, BA.4 and BA.5 or recombinant lineages began. The XBB.1.5 lineage became the dominant in March in Spain [37]. The "Eris" variant (EG.5) spread rapidly since the end of July 2023 [35,37-40]. In November 2023, several recombinant variants were circulating in Spain, particularly XBB arising from two Omicron BA.2 sublineages [41]. In January 2024 XBB.1.5-like + F456L accounted for 42% and BA.2.86 for 44% of positive cases [42]. In July and August 2024, the KP.3 lineage was detected in 84% of cases [43]. In September 2024, the incidence of the XEC variant was increasing markedly in Spain, where it accounted for around 1% of total cases. At that time, it was the second most common strain in cases recorded in September, although still far behind the main KP.3.3, with an incidence of 13% [44,45]. In the summer of 2024, a new group of closely related covid-19 subvariants emerged, collectively known as "FliRT" and members of the group include KP.2, KP.3, and JN.1.7.1 [46].

Comparison with Other Studies

The World Health Organization (WHO) has recently warned of a worldwide increase in covid-19 infections, and has considered it "unlikely" that they will decrease in the short term, while observing that, due to the low vaccination coverage, the risk of a more virulent strain emerging that could cause serious illness is increasing. According to the WHO, covid-19 is still very present and circulating in all countries, based on data from sentinel systems in 84 countries. Tests with positive results exceed 10%, but the figure fluctuates according to the region. In Europe, this percentage is higher than 20%. In addition, new waves of infection have been recorded in America, Europe and the Western Pacific. It has also reported that wastewater surveillance data suggests that the circulation of SARS-Cov-2 is 2 to 20 times higher than the documented figures [47].

However, it has also been published in August 2024 that both in primary care and in hospitals in the European Union/European Economic Area, the incidence of covid-19 is stable and decreasing. However, the picture by country remains uneven. In primary care, the pooled test positivity decreased to 23%, and the average test positivity also decreased to 8.7%. While countries reported stable or decreasing trends in primary care, increases in non-sentinel detections were observed in five countries. In hospitals, pooled test positivity remains stable at 17%, with test positivity ranging from 12 to 31% in the five reporting countries (Germany, Greece, Ireland, Malta and Spain). The age group 65 years and older remains the most affected (23% positivity). Spain continues to account for more than 50% of all samples tested and reported a positivity rate of 33%, explaining the divergence between the pooled estimates and the median [48].

Based on incomplete official data, the current situation is usually classified as "low incidence" [49]. The results of our study, in our context with a very high vaccination rate, support that the incidence is stable or decreasing. We find a lower crude IR for 2024 compared with 2024, with a RR of 0.75 and an RA= -1. These risk measures seem to indicate that the risk population is better prepared in 2024 vs. 2023 to avoid cases of covid-19;

this is probably due to their higher level of hybrid immunity. Vaccination against covid-19 has substantially altered the course of the pandemic, saving tens of millions of lives around the world [50]. This trend of reducing IR and risk measures was also observed in another previous study in the same population that compared the average of 2020-2022 with 2023, which is why it constitutes a consolidated trend in our community [51].

It has been said that covid-19 is at a tipping point, meaning that high levels of immunity to SARS-CoV-2 are beginning to limit its impact and reach; but, at the same time, currently, many countries do not test all symptomatic patients, nor do they systematically collect the number of cases or their clinical-epidemiological characteristics [1,8]. In Spain, the surveillance and control strategy against covid-19 after the acute phase of the pandemic, in force since March 28, 2022, indicates the need to perform a test only in specific situations that fundamentally include people with vulnerability criteria, of vulnerable areas, and those that require hospital admission. The reported cases therefore represent these groups and not the total number of SARS-CoV-2 infections, so the evolution of the pandemic monitoring indicators must be adapted to this circumstance and the data from these reports cannot be compared with those of prior reports [52].

In this situation, many people with symptoms in the community choose to perform individual tests at home, which is common in our context [53]. But, frequently, people with a positive test at home do communicate this circumstance to their GP, to seek treatment and/or sick leave. In this way, the data on covid-19 cases in general medicine has been proposed as an indicator of the variation in incidence in the community, and as a complement to the data on mortality and hospitalizations [19,54]. Our study, carried out on the same at-risk population seen in a general medicine consultation from 2022 to 2023 and from 2023 to 2024, that included cases of covid-19 with tests carried out in health services or those carried out at home, and reported to the GP overcomes these limitations of official reports, allowing comparisons between time periods.

Finally, it should be noted that in our study, despite the downward trend in IR and other risk measures in certain variables, it was found in 2024 vs. 2023 that IR and RR in moderated severe severity covid-19 cases and in covid-19 cases with chronic diseases did not vary. Thus, the association of infection with comorbidities (as diabetes mellitus, arterial hypertension, obesity, chronic renal disease and chronic obstructive pulmonary disease, immunosuppression, etc.) obscures the prognosis and causes complications [55-58]. These populations will likely need annual vaccine reinforcements [1].

In summary, everything seems to indicate that the risk population is better prepared in 2024 vs. 2023 to avoid cases of covid-19, which is homogeneous with other studies, and quite reasonable from common sense, but people with chronic diseases have a similar risk in 2024, remaining stable (without decrease) its IR. In any case, these results should be interpreted with caution given that the number of tests carried out in the community was low, which suggests an indeterminate covid-19 situation [59].

Limitations and strengths of the study

- The samples were small, so some data may cause misinterpretation.
- Asymptomatic cases were missing because they did not attend in 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. But given the situation of the GP as the gateway to the health system, the vast majority of positive covid-19 tests at home, is likely to be reported in GP office.
- The study has the strength of its longitudinality, characteristic of work in general medicine.
- Both studies were carried out in the same general medicine practice and carried out by the same researcher, which gives coherence to the results.

Conclusion

In general practice setting in Toledo, Spain, in 2024 vs. 2023 the incidence of covid-19 and other risk measures are decreasing or stable. Population at risk with greater hybrid immunity is better prepared in 2024 than 2023 to avoid cases of covid-19. But IR and RR of covid-19 cases with moderate severe severity (which was already low) and covid-19 cases with chronic diseases (which was already high) have not changed (IR and RR have not improved as they have in the rest of the variables) from 2023 to 2024. This population with comorbidities will likely need annual vaccine reinforcements.

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