SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Spatial inequalities in morbidity, mortality and vaccine coverage identified in the context of the Hungarian COVID-19 pandemic, their background and public health implications

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1 Introduction

The COVID-19 pandemic is the greatest health challenge of the 21st century in terms of its global public health and societal impact. Unravelling the causes and consequences of this major health crisis can contribute to understanding the drivers of the emergence and escalation of a global public health crisis that has been ongoing for more than two years, focusing on and interpreting the differential impact on different groups in society.

The severity of the pandemic so far is demonstrated by the fact that the number of COVID-19-related deaths recorded worldwide exceeded 6 million by mid-April 2022. Based on estimated excess deaths, the real number could be 2.7-3 times higher. In the first two years of the pandemic, COVID-19 was the third leading cause of death in many countries, after cardiovascular diseases and malignancies. The mortality losses due to the pandemic are significant despite the availability of vaccines against COVID-19 from December 2020, and the fact that within a year almost half of the world's population had been vaccinated with two doses, preventing around 60% of all excess deaths.

COVID-19 started as an epidemiological event but later turned into a health, social and economic crisis. In addition to the emergence and spread of SARS-CoV-2, the consequences of the measures contributed to this. The pandemic highlighted the vulnerability and interconnectedness of some actors in society and the economy; households, businesses and health care providers are highly interdependent, and an epidemic crisis can have a negative impact on other sectors and even destabilise entire national economies.

Many people wrongly believe that COVID-19 is equally dangerous to people regardless of their social status. Indeed, the negative economic burden of the pandemic has hit the world population unevenly, increasing the already existing inequalities between and within countries.

The adverse effects of pandemic COVID-19 are more severe and harder to recover from in social groups that are characterised by a disadvantaged socio-economic situation (hereafter SES). The underlying phenomena and interrelationships form a complex and intricate system that can be explored, analysed and strategies developed to address not only COVID-19 but also future health, social and economic crises.

The present research deals with the direct, short-term health effects of the COVID-19 pandemic (recorded COVID-19 morbidity and COVID-19-related mortality) and explores the inequalities in the socio-economic situation in Hungary in the context of an ecological study.

In the first two years of the COVID-19 pandemic, five major pandemic waves were started in Hungary. The first wave was suppressed by early and drastic contact reduction measures, so due to the limited community spread, the spatial inequalities of the first wave were not investigated in this research. Similarly, we did not examine the fifth wave because it was still ongoing at the time of analysis, so the results of our analyses of waves 2-4 are presented.

In the time since the beginning of the pandemic, SARS-CoV-2 has undergone continuous genomic changes, leading to the selection and periodic expansion of viral variants with different properties, which is essentially shaping the epidemiological situation of COVID-19 from 2021 onwards. The three epidemic waves studied differed in the characteristics of the dominant SARS-CoV-2 types (Wuhan strain, alpha and delta variants), as these variants has become more rapidly transmissible and more virulent, while their immune evasion capacity gradually increased.

2 Literature review

2.1 COVID-19 pandemic waves and key epidemiological intervention strategies

A wide range of experts agree that it is in society's interest to keep the incidence of COVID-19 as low as possible, both from a public health and economic perspective. However, the question of how this can best be achieved is far from easy to answer. While the cost of implementing low incidence strategies can be significantly reduced if vaccination coverage is high, vaccination is a necessary but not sufficient condition for achieving low COVID-19 incidence due to inequalities in coverage, declining immunity, and continued virus evolution. This requires non-pharmacological measures, the social acceptability of which typically decreases significantly over time. Therefore, even after the widespread availability of COVID-19 vaccines, most countries in the world now prefer a mitigation strategy, which prioritises targeted measures to prevent overloading the health care system, rather than keeping incidence as low as possible, while reducing morbidity is a lower priority.

Hungary followed the mitigation strategy in dealing with pandemic waves 2-4 (hereafter PW), but within this, distinctly different intervention packages can be distinguished. In the second wave, only combined nonpharmacological measures were available to prevent the spread of SARS-CoV-2 infection. The main pillars of these measures were social distancing (reducing the number of close contacts that could lead to infection), individual protection (mask use, hand hygiene) and case detection and surveillance of cases (testing, isolation, quarantine). The administration of COVID-19 vaccines in Hungary started already at the end of PW 2 (first

vaccinating health workers) and in PW 3, in addition to the traditional epidemiological measures, vaccines were available in the quantities needed for a mass vaccination programme. However, the progress of the vaccination programme fell short of what was needed to contain the more rapidly spreading alpha variant, and a new set of tightening nonpharmacological measures was introduced in early March 2021 as the epidemiological situation worsened and was phased out from mid-April 2021. In the fourth PW, governmental control was predominantly based on vaccination, with the use of other non-pharmacological measures being significantly reduced.

The evolution of the PWs of COVID-19 in Hungary was determined by the combination of the spread of SARS-CoV-2 virus variants with different characteristics and the measures taken to contain them.

2.2 Inequalities in Hungary before the pandemic

In Hungary, life expectancy at birth increased by nearly two years between 2010 and 2019, before declining in the first two years of the pandemic. Despite the pre-pandemic increase, Hungary still lags significantly behind many of the more developed EU countries in terms of both life expectancy and years of healthy life and has higher levels of inequality by education and income than the EU average. In terms of preventable mortality based on the development of modern medicine and the adequate use of preventive measures, Hungary was the second to last EU-27 country in 2019, and only Latvia and Lithuania have worse indicators for amenable mortality due to timely and adequate health services. The population with the most unfavourable SES has worse indicators than the Hungarian average for both indicators.

The problems of Hungary's large and growing Roma ethnic population are a challenge for society. The municipalities with the highest Roma population are mainly located in the North-East and South-West of the country, mainly in border and peripheral areas. The Roma population has a significantly worse SES than the Hungarian population in general and their unfavourable socio-economic status is also a significant determinant of their health status.

Socio-economically disadvantaged communities and ethnic minority groups tended to have lower levels of health literacy in Hungary even before the pandemic, which increased their vulnerability. They were more likely to have risk factors that adversely affected their health status and to have chronic diseases that increased the risk of severe and fatal COVID-19.

3 Objectives of the research

The aim of the research is to investigate the COVID-19 pandemic in Hungary, focusing on PW 2-4 (which were based on three different dominant SARS-CoV-2 virus variants and three different packages of measures), and

- to provide a descriptive epidemiological analysis of registered confirmed COVID-19 cases and COVID-19-related mortality, and to determine excess mortality;
- the spatial epidemiological characterisation of the geographical variation in registered confirmed COVID-19 cases and COVID-19-related mortality, and the identification of spatially common components of PWs 2-3;
- to investigate the relationship between socio-economic characteristics of the population at the municipal level and the spatial distribution of the above health status indicators;
- to investigate the geographical variation in COVID-19 vaccination coverage in PWs 3-4;
- to investigate the spatial correlations of COVID-19 vaccination coverage, SES and COVID-19-related mortality;
- characterisation of morbidity, mortality, and vaccination coverage in the districts with the highest representation of Roma population in the low SES population.

4 Data and methods

The data source for registered cases of COVID-19 was the National Communicable Disease Notification System operated by the National Center for Public Health, which includes cases confirmed by laboratory testing (detection of SARS-CoV-2 by polymerase chain reaction (PCR) or detection of SARS-CoV-2 antigen by lateral flow test).

For the calculation of excess mortality, data on deaths from any cause among the Hungarian population during the period under investigation were used from the national Electronic Vital Records System. The benchmark was the average mortality data for the corresponding periods 2014-2019.

The ten districts with the highest proportion (27.9% - 39.0%) of Roma residents were identified based on the data from the national survey conducted by János Pénzes and colleagues.

The COVID-19 vaccination programme started in Hungary in week 52 of 2020. According to the definition used, persons aged 18 years or older who have received two doses against

COVID-19, or one vaccination in the case of Janssen, were considered as having received primary immunisation.

Those who have also received at least one booster vaccination are considered fully vaccinated. National data on weekly vaccines were obtained from the European Centre for Disease Control and Prevention (ECDC) database, while data on all COVID-19 vaccinations administered between week 52 of 2020 and week 51 of 2021, at the municipal level, disaggregated by 5-year age group were obtained from the National Health Insurance Fund.

The first and last days of the epidemic wave were the days of the lowest daily case rates recorded before and after the epidemic wave. On this basis, the periods examined, by wave, are as follows:

Pandemic wave 2: 22.06.2020 - 24.01.2021 (week 26.2020 - week 03.2021)

Pandemic wave 3: 25.01.2021 - 04.07.2021 (week 04.2021 - week 26.2021)

Pandemic wave 4: 05/07/2021 - 26/12/2021 (week 27/2021 - week 51/2021)

Hungary's districts cover a total of 3155 municipalities. The spatial distribution of the Roma population is available only at the district level, while all other data are available at the level of municipalities, except for Budapest, where the district is the smallest administrative unit.

The spatial distribution of morbidity and mortality and vaccination coverage was characterised using indirect standardised ratios, defined using the "Disease mapping" function of the RIF software, and smoothed by hierarchical Bayesian estimation. Relative ratios were estimated using the Integrated Nested Laplace Approximation (INLA) method. Maps were produced for the visualisation of relative morbidity and mortality indicators at the municipality level.

The Deprivation Index (hereafter DI) is a spatially based composite index providing information on the SES of the population living in each municipality. The index includes seven indicators: income, educational attainment, unemployment rate, proportion of single-parent families and large family households, housing density and car ownership, which are derived using data from the Central Statistical Office (2011 Census) and the National Tax and Customs Office (2011). The higher the index value of a given municipality, the more unfavourable the SES of the population living there, i.e., an increase in DI indicates deepening deprivation. The DI is used to rank the municipalities, which are then sorted into quintiles: quintile I is for municipalities with the most favourable SES based on the DI, and quintile V is for those with the least favourable SES, where deprivation is deepest.

The aim of the risk analysis was to determine whether deprivation at the population level was associated with a relative risk of morbidity and mortality and with vaccination coverage. Indirect standardised ratios (estimated relative risk) were calculated for the five categories (quintiles) of municipalities classified by DI. Confidence intervals were used to determine the plausible interval of the results within which the value of the estimated relative indicators fell with 95% confidence. A t-test (chi-squared test) was performed to statistically verify that the estimated relative indicators in the different SES categories were indeed different from each other. In addition, a t-test for trend analysis was performed to examine whether a linear relationship between deprivation levels and relative morbidity and mortality risks, and between deprivation and relative vaccination coverage could be demonstrated.

An ecological regression model was used to examine the spatial associations between COVID-19 vaccination coverage, SES and COVID-19-related mortality, to answer the question of whether the vaccination programme succeeded in reducing the spatial inequalities in COVID-19-related mortality by the end of the third wave.

5 Results

5.1 The 2-4 COVID-19 pandemic waves in Hungary resulted in a significant number of recorded cases and deaths.

The first cases of COVID-19 in Hungary were identified on 4 March 2020. In the following two years, up to 6 March 2022, the number of confirmed COVID-19 cases registered exceeded 1.8 million and the number of COVID-19-related deaths approached 45,000. The first PW ended with a low number of registered cases, which was significantly exceeded by the second wave. The third PW, dominated by the alpha variant, had a cumulative COVID-19 case rate of more than 25% and a peak weekly case rate of 65% above the comparable figures for the second wave. In terms of the number of COVID-19 cases with recorded fatalities, this wave was the most severe. This was followed by the emergence of the delta variant, which triggered pandemic wave 4, even though at the start of the surge, in early October 2021, 64.2% of the population aged 12 years and over had already been vaccinated with at least two doses against of COVID-19. The fourth wave of the epidemic was like the third wave in terms of recorded cases, but the number of recorded COVID-19-related deaths was only 67% of that observed during the previous wave.

5.2 In Hungary, the excess mortality during PWs 2-4 was significantly higher for several weeks than the average mortality during the same period in the six years before the pandemic.

During the second PW, the estimated number of excess deaths recorded between week 42 of 2020 and week 2 of 2021 was 12 973, which represents an excess of 35% deaths in the total population compared to the same period in the 6 years preceding the pandemic. Within this, estimated deaths were 16% higher than expected in the 50-64 age group and 40% higher than expected in the 65+ age group.

In the third PW, between week 8 and week 19 of 2021, there were around 10 633 excess deaths. The excess deaths were 32% higher than the relevant average weekly deaths in 2014-19 for all age groups, 40% higher for those aged 50-64 and 32% higher for those aged 65 and over.

In the fourth PW, the estimated excess mortality rate between the 40th and 1st week of 2021 and 2022 was similar in magnitude to that in waves 2-3 for all age groups, with 33% for total mortality, 32% for those aged 50-64 and 32% for those aged 65 and over, above the average weekly mortality rate for the same period in 2014-19.

Estimated excess deaths cases and excess mortality were highest in PW 2, and excess premature deaths (among those aged 50-64) were highest in PW 3.

5.3 The areas with high morbidity and mortality in Hungary showed only partial overlap. Areas were identified in each PW where the recorded COVID-19-related mortality was higher than the national average, but the incidence of recorded COVID-19 cases was lower.

In Hungary, during PW 2, a higher than national incidence was identified in the north-western part of the country and in the central part of the northern border; however, in Győr-Moson-Sopron County, this was associated with a significantly lower than national average COVID-19-related mortality. In contrast, a cluster with a higher relative mortality risk than the national average was identified along the north-eastern border of the country, although this area had a lower frequency of COVID-19 cases than the national average. In the central part of the country, with low confirmed COVID-19 incidence, mortality was also below the national average.

During PW 3, clusters with a higher morbidity risk than the national average but lower mortality risk reappeared in the north-eastern part of the country. Also, in the north-eastern part of the country, a higher mortality risk than the national average was again identified over a wide area, which was not coincided with a similar extent of above-average recorded COVID-19

prevalence in this wave. A higher relative mortality risk than the national average was also detected along the northern border of the country and in the Central Transdanubian region, but in these areas the recorded morbidity was also higher than the national average. Higher than average morbidity was recorded in Central Hungary (including Budapest), but this was not associated with higher-than-average mortality.

During waves 2-3 the south-eastern quarter of the country was less affected than the rest of the country, but this situation changed during wave 4. Higher than national average incidence was mostly observed along the south-eastern border, which was typically accompanied by a much higher than national average relative mortality. Some areas in the western half of the country and along the north-eastern border had a lower prevalence of COVID-19 cases than the national average, and in these areas the mortality risk was also found to be lower than the national average.

In the ten districts with the highest proportion of Roma population, the incidence of registered COVID-19 cases was consistently lower, but in most cases mortality rates were higher than the national average.

5.4 Spatial inequalities in COVID-19 vaccination coverage were already evident at the end of PW 3 and this inequality persisted at the end of PW 4.

By the end of PW 3, significantly higher COVID-19 vaccination coverage than the national average had been achieved in Budapest, the cities with county status and other cities with larger populations in and around them. Significantly lower relative vaccination coverage was identified in the less populated areas and smaller settlements of north-eastern, and south-western Hungary. By the end of PW 4, the spatial distribution of relative vaccination coverage did not change significantly: significantly lower vaccination coverage than the national average was still identified in the north-eastern, eastern, and south-western parts of the country, and significantly higher vaccination coverage was found in Budapest and its surroundings, county capitals and larger cities.

5.5 Significantly higher than average mortality is identified in the population of the settlements of the worst SES in all three PWs studied.

In the second PW, COVID-19 mortality was 32% (95% CI 20 - 44%) higher for males and 27% (95% CI 16 - 39%) higher for females in the population of the most deprived municipalities in comparison to the national average. It was also in this group that COVID-19-related mortality was highest in PW 3-4: in the former, it was 17% (95% CI 7 - 26%) higher than the national

average for men and 37% (95% CI 26 - 48%) higher for women, and in the latter, it was 58% (95% CI 44 - 73%) higher than the national average for men and 49% (95% CI 36 - 64%) higher than the national average for women.

A strong positive association between COVID-19 mortality risk and deprivation was demonstrated in all three PWs. The degree of inequality increased by PW 4, especially for women.

5.6 In PW 2-4, those living in the settlements with the most unfavourable SES had significantly lower than average reported COVID-19 prevalence rates.

In PW 2, in the group of the most deprived municipalities, the prevalence of confirmed COVID-19 cases was lower than the national average by 36% (95% CI 35-38%) for men and by 30% (95% CI 28-31%) for women, and in PW 3, the prevalence of confirmed COVID-19 cases was again lower than the average by 24% (95% CI 23-26%) for men and by 15% (95% CI 14-17%) for women. In the fourth wave, the situation did not change: in the most deprived quintile V, i.e., the most disadvantaged, the estimated incidence was 15% (95% CI 14-17%) lower than the national average for men and 9% (95% CI 7-10%) lower for women.

A significant negative correlation was found between the relative incidence of confirmed cases and deprivation in all three PWs studied.

5.7 In the ten districts with the highest proportion of Roma population, the recorded COVID-19 mortality rates were higher than the national average in all three PWs investigated, and in the 3-4 PWs the inequality increased significantly.

In the municipalities of the 10 districts with the highest proportion of Roma population:

- in the second epidemic wave, mortality rates were 19% (95% CI 2 - 39%) higher than the national average for males and 23% (95% CI 5 - 43%) higher than the national average for females;
- in the third wave, the mortality rate was 27% (95% CI 12 - 45%) higher than the national average for men and 53% (95% CI 35 - 73%) higher than the national average for women;
- in the fourth pandemic wave, the mortality rate was 68% (95% CI 45 - 94%) higher than the national average for men and 62% (95% CI 39 - 87%) higher for women.

In the municipalities of the 10 districts with the highest proportion of Roma population, the risk of COVID-19 mortality exceeded the national average in all three pandemic waves studied, and

the degree of inequality increased significantly for both sexes as PWs progressed, despite the vaccination programme and interventions.

5.8 COVID-19 vaccination coverage decreased as deprivation worsened. Among the population in the most deprived SES settlements, COVID-19 vaccination coverage was significantly below the national average.

By the end of PW 3, the COVID-19 vaccination coverage among the least deprived was 9.2% (95% CI 9 - 9.5%) higher than the national average, while the coverage of the population in the most deprived areas was 38.2% (95% CI 38.0 - 38.4%) below the national average. Risk analysis showed a significant inverse correlation between vaccination coverage and deprivation.

At the end of the third wave, in the 10 districts with the highest proportion of Roma population, vaccination coverage was only 56.0% of the national average (95% CI 55.0 - 64.0%).

The above correlation did not change by the end of wave 4. The vaccination coverage of the least deprived quintile was about 7.0% (95% CI 6.8 - 7.2%) above the national average, and that of the most deprived municipalities was 35.6% (95% CI 35.6 - 36.0) below the national average. The gap between the high-representation Roma districts and the national average was unchanged at the end of the fourth wave.

5.9 The COVID-19 vaccination programme has not substantially reduced health inequalities, as the groups most at risk from COVID-19 have benefited least from vaccination.

Using univariate ecological regression, an inverse association was found between municipality-level COVID-19 vaccination coverage and COVID-19-related mortality, i.e., increasing vaccination coverage significantly reduced COVID-19-related mortality ($RR_{Vaccination}$: 0.86, 95% CI: 0.75-0.98). As shown in previous results, deepening deprivation also showed an inverse association with vaccination coverage, but a strong positive association with mortality. Combining the effects of the two explanatory factors, i.e. COVID-19 vaccination coverage and deprivation on COVID-19-related mortality, the results show that at the end of PW 3, after adjusted to vaccination, deprivation remained significantly associated with COVID-19-related mortality ($RR_{deprivation}$: 1.10; 95% CI: 1.07-1.14), while the association between vaccination and COVID-19-related mortality, adjusted to deprivation, became non-significant ($RR_{vaccination}$: 0.95; 95% CI: 0.84-1.09).

6 Discussion

This thesis provides new information on the relationship between social inequalities and health status in Hungary in the context of a major health crisis, a pandemic. The results draw attention to the inverse correlation of recorded COVID-19-related morbidity and mortality with socioeconomic deprivation: the highest morbidity was found in the least deprived areas, while the highest mortality was found in the most deprived areas.

Those living in more deprived areas were less likely to have confirmed COVID-19 but had a higher risk of COVID-19-related mortality. This pattern was even more pronounced in the ten districts with the highest proportion of Roma in the population in all three PWs studied. It is well known that Roma people are also disadvantaged in terms of financial situation and health status in many countries, including Hungary, but to date there is no further domestic data to confirm that Roma communities are characterised by higher COVID-19-related mortality rates.

Interpreting our findings requires a complex approach.

One possible explanation is that people living in deprived areas (e.g., those with lower levels of education and those from disadvantaged groups such as Roma) are more likely to have pre-existing underlying conditions that increase their risk of severe COVID-19.

Low educational attainment, poverty, poor housing, low family income, household crowding and unemployment are also associated with a higher risk of death from COVID-19. There is reason to believe that poor housing conditions, poverty, household crowding, lower household income, lower education are associated with also a higher risk of COVID-19 infection, as in groups living in unfavourable SES, the infection can spread easily and rapidly and become severe and fatal more often than average.

However, a higher risk of infection is not necessarily associated with a higher number of COVID-19 cases registered, because testing activity does not always follow the need, and therefore the number of COVID-19 cases registered may be lower than the actual incidence. In the most deprived areas, especially those furthest away from the testing centre, the participation rate in testing may be lower than the national level, while the test positivity rate may be higher.

Therefore, it cannot be excluded that the low recorded morbidity in deprived regions of Hungary with high COVID-19-related mortality is because many COVID-19 cases have not been confirmed by testing or even detected by symptoms. The hypothesis is strengthened by the findings of a French and a Swiss study that support the Hungarian results in their own

countries: people living in areas with more favourable SES were more likely to be tested for SARS-CoV-2, but less likely to test positive, to be hospitalised or admitted to intensive care, and less likely to die than people living in areas with lower SES.

Even before the pandemic, barriers to accessing health care were already unevenly burdening groups with lower SES. However, the complex effects of the pandemic may have exacerbated inequalities in mortality, especially in districts where inpatient ward loads exceeded the national average.

Vaccines have opened new possibilities for pandemic control, offering not only an effective and rapid response method, but also an intervention with beneficial risk-benefit balance, that can significantly reduce the socially unequal burden of the pandemic. Although the vaccination campaign in Hungary started before the third wave, differences in the acceptance of vaccination soon became apparent. The initially imperceptible inequalities became apparent by the end of the third PW: by this time, vaccination coverage in less deprived, mainly urban areas was already higher than average, so the potential for protection offered by vaccination differed significantly according to the SES. The vaccination coverage was even lower in the ten districts with the highest Roma population compared to the most deprived quintiles.

In many countries, including Hungary, geographical, ethnic, and socio-economic differences and disparities have been ignored both in the criteria for initial vaccination target groups and in the design of prevention measures. The scarce availability of vaccines at the beginning of the vaccination programme made it more difficult for marginalised populations to access vaccines, and later, when vaccines were more plentiful, they were discouraged by the vaccine-scepticism that had become widespread. Thus, contrary to expectations, COVID-19 vaccination programmes in many countries around the world (including Hungary) have failed to reduce health inequalities substantially, with lower-than-average vaccination coverage in the groups most at risk from COVID-19. The most vulnerable groups have benefited the least from vaccination, which may be related to the fact that the excess mortality in Hungary has not shown a substantial reduction in the course of the epidemic waves studied.

The present study highlights the fact that the relative excess mortality in all age groups reached a critical level during the three epidemic waves studied. Although more experience and knowledge became available as the pandemic progressed, neither combined non-pharmacological measures nor mass vaccination programmes succeeded in significantly reducing excess mortality in PW 2-4. In addition to the emergence and spread of SARS-CoV-2 variants with increasing transmission and virulence, inequalities have also played a role.

7 Methodological limitations of the research

The results of the present research are based on analyses of large databases at national level, which allowed the accurate estimation of relevant parameters with narrow confidence intervals, minimising the risk of random error. The methodology used was an ecological study, with results interpretable at the level of the population under study rather than at the individual level.

Several potential limitations should be considered when interpreting the results. One is the potential bias that may arise from the poor quality of the underlying data (e.g., registered COVID-19 case numbers, vaccination status). In Hungary, even with the case definitions and reporting requirements in place, it is likely that the relatively low incidence reported in more deprived areas is, at least in part, a consequence of low testing activity, which could be even more likely under extreme pressure on the health care system. The results suggest that under-testing among people living in the most deprived areas may have been a problem in all three pandemic waves studied, but the necessary data on the volume of testing in individual municipalities are not available to support this hypothesis.

Despite the internationally uniform classification of mortality and its coding procedures and algorithms, subjectivity in death log classification cannot be excluded in many cases, and its uncertainties may also reduce the accuracy of the COVID-19 mortality data. In Hungary, it is less likely that the reported data underestimate the number of COVID-19-associated deaths, as the value of recorded cumulative COVID-19-associated deaths and cumulative excess deaths are similar, so that the recorded COVID-19-associated data are likely to be a good approximation of the true mortality burden over the period under study. This is also supported by the results of another study, which found that among the countries of the „Visegrad Cooperation", Hungary had the smallest difference between officially reported coronavirus mortality and excess mortality.

A further limitation of the study is that it could not consider and eliminate the impact of several potential confounding factors. Indeed, no ecological-level spatial analysis can capture all relevant individual risk factors, such as underlying health status. To date, observational epidemiological research on social inequalities has been hampered by the lack of several routinely collected socio-economic variables that can be assessed at the individual level.

By the end of PW 3, 38.7% of the population receiving basic immunisation had received a vaccine that was licensed as an emergency vaccine in Hungary (Sputnik V or Sinopharm), and it is therefore possible that the type of vaccine administered may also influence the results. It is

likely that the distribution of vaccines administered by type did not significantly influence the results obtained, as a retrospective observational study conducted in Hungary between 22 January and 10 June 2021 demonstrated similar high efficacy of different two-dose vaccines in the months following administration. Declining immunity occurs for all vaccine types, but our studies, not detailed in the thesis, show that the large number of booster vaccines administered in Hungary as part of the campaign starting in week 30 of 2021 increased, albeit temporarily, the level of immunity against infection in the second half of 2021 and significantly reduced the risk of COVID-19-related mortality.

8 Key conclusions and proposals

In many countries, those who suffered most during the pandemic were those who were already disadvantaged. The geographic disparities in the health status of the Hungarian population date back well before the pandemic, and have been exacerbated by the epidemic, which will have repercussions for years and decades to come.

From a public health perspective, COVID-19 pandemic will be a defining event in the coming years, as the risks of the pandemic extend well beyond its acute phase. Given the large (and growing) number of people who have experienced COVID-19, the long-COVID and other long-term risks project a high number of potentially affected people in Hungary as well. Just as the immediate health effects of COVID-19 have unevenly affected the Hungarian population, the medium- and long-term effects are likely to follow this pattern. Governments and health systems around the world need to be prepared for the likelihood that the COVID-19 pandemic will contribute significantly to an increase in the burden of e.g., cardiovascular disease, diabetes and mental illness, and that this will continue to affect different social groups unequally.

If indirect effects are also considered, missed organised screening, delayed diagnoses, late or missed interventions, and disruptions and interruptions in the care of chronic patients are likely to affect not only cardiovascular but also cancer and other chronic diseases, further increasing the burden of disease and inequalities caused by the pandemic. Due to their chronic nature, these diseases can have long-term consequences for affected individuals, families, and communities, as well as for health systems, and have wide-ranging implications for life expectancy and the proportion of healthy life and economic productivity through the labour market.

The need to continuously optimise strategies for the primary prevention of SARS-CoV-2 infections should therefore be emphasised. Indeed, the best way to prevent long-COVID and

lots of other long-term effects, including the risk of serious cardiovascular consequences, is to prevent a recurrence of SARS-CoV-2 epidemics, for which several non-pharmacological measures and several types of COVID-19 vaccines are available.

In order to adequately address the long-term direct and indirect effects of COVID-19, there is also a need to improve the capacity and capability of the health care system, to make up for lost care and to manage patient pathways in a transparent manner.

The geographical areas particularly affected by the pandemic could not have been identified by looking only at the number of registered cases. The overall disease burden of the epidemic, especially in municipalities with unfavourable SES, can easily be underestimated by looking at the number of new cases registered.

Epidemic control measures and their phasing out, as well as interventions to reduce the short and long-term adverse consequences of the pandemic, should be based on a comprehensive, high-resolution spatial risk assessment. This is the only way to ensure that measures are well-informed and targeted, paying particular attention to the geographical areas and population groups most vulnerable to the direct and indirect, short- and long-term effects of the pandemic.

Building the capacity and capability for comprehensive risk assessments as part of epidemiological preparedness is an essential expectation for the public health system. It is expected that this should not be done on an ad hoc basis, but based on a complex monitoring approach, allowing a rapid and adequate response.

The striking SES-related and ethnic inequalities observed in the analysis of COVID-19 infection, testing and mortality remain a risk because they increase the risk of virus transmission and unequal burden on the health care system, with potentially serious adverse health and economic consequences for society.

The results of our study show that in the well-defined, most deprived areas of Hungary, COVID-19 rates were significantly lower than the national average, while mortality data showed an inverse correlation with deprivation. Literature evidence suggests that low testing coverage is often at the root of these phenomena.

Increasing testing coverage is therefore a cornerstone of COVID-19 pandemic control (and other major epidemic events) and is important from several perspectives. Early detection of cases will help to improve individual prevention, the quality of contact tracing and thus epidemic control, and, based on literature data, reduce COVID-19-related mortality, while

increasing testing coverage will also increase the accuracy of risk assessment based on surveillance data.

International good practice shows that targeted interventions can increase testing coverage, even in populations with unfavourable SES.

It is also reasonable to assume that epidemiological detection and investigation in these unfavourable SES communities is often not carried out or at least not documented, e.g., in the form of reports. Yet timely and targeted epidemiological measures are of great importance not only for the vulnerable populations concerned, but also for other communities.

Despite the availability of several effective and safe vaccines, the Hungarian vaccination programme has had difficulties in reaching people living in the most disadvantaged areas and has therefore not been effective in reducing the mortality inequalities associated with COVID-19.

In Hungary, COVID-19-related mortality was significantly higher than the national average in geographical areas with large, deprived populations with much lower-than-average vaccination coverage. However, the specific causes of high mortality and low vaccination coverage have not yet been identified for these populations in Hungary, including the Roma population.

In the short term, increasing COVID-19 vaccination coverage in groups with unfavourable SES is an effective intervention to reduce mortality. A problem that needs to be addressed is that even in countries where COVID-19 vaccines are readily available, there is often a tendency to reject the offered vaccines and to communicate against vaccination.

Several research groups around the world are investigating the reasons for lower confidence in COVID-19 vaccines in certain social groups and the main reasons for vaccine refusal. Their findings suggest that effective coordination between levels of government, as well as good logistics, organisation, and a high level of trust in health authorities behind mass vaccination, are the most important factors for the success of the vaccination campaign.

Overall, the trends identified by the recorded morbidity and mortality data of the COVID-19 epidemic and the inverse relationship between SES are of concern and call for targeted actions, including interventions to reduce inequalities, including the redesign of vaccination programmes.

Prior identification of vulnerable communities is crucial for the design, implementation, and evaluation of interventions to better meet their needs, not only to mitigate the devastating effects

of pandemic COVID-19, but also other future epidemics and even chronic non-communicable diseases.

In countries with severe socio-economic inequalities, a pandemic can generate a specific circulus vitiosus: the epidemic exacerbates existing inequalities, which in turn can exacerbate the pandemic through increased transmission of infection, increased morbidity, and mortality. Very often, centralised disease control measures have an impact on inequalities - they can increase or reduce them. And the negative effects of forcing each other into a negative spiral can be exacerbated by the lack of adequate health care, public health and social care capacities that would have been needed to reduce unfair inequalities.

It is of paramount importance that communities most affected by or at risk from the virus receive more resources for public health and disease control programmes than their population size alone would warrant.

Given the two-way relationship of socioeconomic inequalities to pandemic and pandemic to inequalities, it is important to emphasise the need for multisectoral policies that ensure equal access to basic preventive and curative health services, provide social and economic security, and prioritise the protection of vulnerable groups in decision-making.

9 Summary

Introduction: This thesis presents the evolution of COVID-19 morbidity, mortality, and vaccine coverage in a nationwide study of Hungarian municipalities during the 2-4th wave of the COVID-19 pandemic, revealing the associations with the socio-economic situation.

Methods: The epidemiological approach used was an ecological study. The spatial distribution of COVID-19 morbidity, mortality and vaccination coverage was characterised using a hierarchical Bayesian method with indirect standardised proportions, while socioeconomic status was characterised using a composite indicator, the Deprivation Index. Indirect standardised ratios were used to assess the relationship between deprivation and outcome measures. The inequalities in morbidity, mortality, and vaccination coverage in the ten districts with the highest Roma population were examined separately.

Results: In the most deprived socio-economic municipalities, COVID-19 mortality was 17-58% higher and the frequency of confirmed COVID-19 cases 9-36% lower than the national average. Deprivation showed a strong positive association with the risk of COVID-19 mortality and a negative association with recorded morbidity and COVID-19 vaccination coverage in all three pandemic waves. The vaccination coverage in the most deprived areas was 38.2 - 44.0% below the national average. In the ten districts with the highest proportion of Roma population, the recorded COVID-19 mortality rates in all three pandemic waves studied were much higher than the national average, while the vaccination coverage was much lower. Inequalities increased significantly over the study period.

Conclusions: People living in more deprived settlements had a lower risk of being identified with confirmed COVID-19 cases but a higher risk of mortality. The inverse association of morbidity and mortality trends by socioeconomic status is a cause for concern and highlights the need for a response, including a redesign of the COVID-19 vaccination programme. Even Hungary, which initially had one of the most successful vaccination programmes, has not been able to substantially reduce inequalities in COVID-19 mortality, as it has only achieved lower than average vaccination coverage among the population in areas with the highest mortality risk. The example of Hungary shows that social inequalities can jeopardise what a successful vaccine programme can achieve.

10 Keywords

COVID-19, pandemic, morbidity, mortality, excess mortality, socio-economic situation, vaccination, health inequalities

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3. Juhász, A., Nagy, C., **Oroszi, B.**, Ádány, R.: A COVID-19 megbetegedés, halálozás és oltottság alakulása és összefüggése a társadalmi-gazdasági helyzettel a 2-4. járványhullámok idején Magyarországon = Spatial distribution of COVID-19 morbidity, mortality, and vaccination coverage and their association with the socioeconomic status during the 2nd-4th pandemic waves in Hungary.
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