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Forecasting the disease burden of type 2 diabetes in mainland China following the discontinuation of the zero-COVID policy: a data-driven modelling study

Introduction:

China remained in lockdown to adhere to their dynamic zero-COVID strategy until December 2022, aiming at stamping out outbreaks and defeating the coronavirus pandemic.[1]. The government was trying to eliminate all COVID-19 cases while other diseases and non-COVID-19 deaths were being undercounted, ignored or neglected [1]. Type 2 diabetes is an increasingly concerning global health problem, with a significant presence in developing nations, particularly among the elderly population, such as in China. Diabetes prevalence in China is estimated to increase by 9.7% from 2020 to 2030; and the total costs are expected to increase from $250 billion to $460 billion, with an annual growth rate of 6.32% [3]. Furthermore, it has been consistently suggested that diabetes poses a significant risk factor for the mortality of COVID-19 patients [2]. This could imply that the burden of COVID-19 and comorbidities is becoming even more significant due to the mixed effects of the COVID-19 Omicron variant wave and future variants with comorbidities such as diabetes. Given the limited availability of literature detailing the status of diabetes patients in China during or after the Omicron wave, the primary goal of this research is to construct a theoretical model projecting COVID-19 burden (number of cases, patients requiring hospitalization and intensive care, and deaths), especially for type 2 diabetes patients on China's healthcare system following the discontinuation of the zero-COVID policy. We do this by considering the vaccination, infection, hospitalization, and mortality rates among individuals with diabetes mellitus (DM) with and without other comorbidities during the Omicron wave in mainland China, commencing from November 2022 through February 2023. Additionally, the study aims to predict the number of COVID-related new-onset diabetes cases in the general population and the prevalence of comorbidities among existing DM patients in China by February of 2023. The analysis will utilize data from the COVID-19 Omicron outbreak in Hong Kong in 2022 for several reasons: this choice is attributed to the significant ethnicity-based disparities in health outcomes observed during the COVID-19 pandemic. Additionally, among East Asian populations, Hong Kong's situation closely mirrors that of mainland China, and it possesses the most comprehensive and relevant dataset pertaining to the Omicron variant.

Methods:

We primarily use an age-structured stochastic compartmental susceptible-latent-infectious-removed-susceptible model to simulate the omicron waves. The population is categorized into 14 age groups (0–2, 3–11, 12–17, 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 and ≥70 years), and the study takes into consideration various factors. These include age-specific vaccination coverage, vaccine effectiveness against different clinical outcomes, immunity waning, the impact of antiviral drugs, hospital capacity constraints, and the implementation of non-pharmaceutical interventions. Additionally, we repeat the simulations in people with diabetes 2 and the comorbidities using diabetes- specific data. Referring to a cross-sectional study conducted in 2021, it was observed that the occurrence of coexisting health conditions among individuals with type 2 diabetes stood at 93.7% over a span of 8 years [12]. So we consider the main types of comorbidities observed in DM patients encompass a range of conditions, such as Chronic Kidney Disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), Atrial Fibrillation, Stroke, Heart Failure, Myocardial Infarction, Peripheral Vascular Disease (PVD), Liver Disease, Cancer, and Dementia.

For the last part, we use the Monte Carlo method to simulate the process of developing newly-onset diabetes in COVID-19 recovered people, and to simulate the process of developing newly-onset comorbidities of other types in recovered people with pre-existing diabetes. Further information on the model and parameters are listed in the Appendix.

The modeling study relies on publicly available data, and the software being used is R 4.3. 1.

Model structure

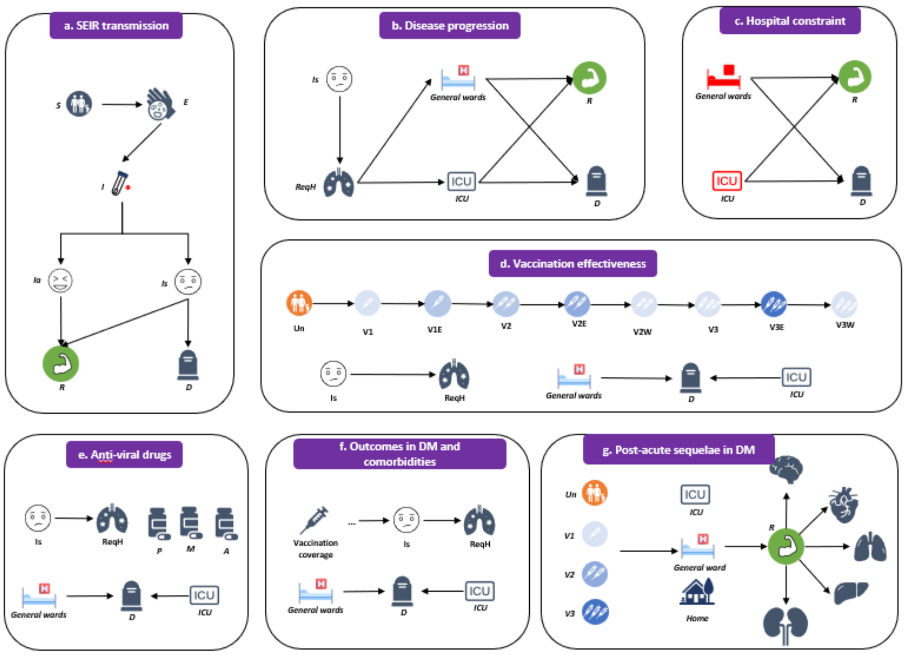

Figure 1. Basic Model Structure: (a) The stochastic compartmental susceptible-latent-infectious-removed (SLIR) transmission, (b) Disease progression, (c) hospital constraint, (d) vaccination effectiveness, (e) anti-viral drugs, (f) outcomes in DM and comorbidities, (g) post-acute sequelae in DM (see appendix 1 for detailed model and parameters).

Results, Literature review, and Discussion

Between December 20, 2022, and February 23, 2023, a higher proportion of unvaccinated individuals with DM conditions aged over 60 compared to those aged 16-59 was observed. The latter group displayed a higher proportion of first vaccine dose recipients (V1E) (Appendix figure 1). Furthermore, our simulation covering November 2022 to February 2023 highlights the significant impact on the entire population. Peak hospitalizations in general wards, ICU admissions, and fatalities occurred around January 23, with 15.1 million, 3.3 million, and 1.3

million individuals respectively. Across age groups (<18, 18-40, 50-69, 70+) and vaccination status, older age groups consistently exhibited higher rates of admissions and mortality, aligning with their higher proportion of unvaccinated individuals (Appendix figure 3&4). Estimates by the chief epidemiologist (Appendix figure 5) closely match our own, suggesting around January 21, 2022, approximately 80% of the Chinese population had been infected.

Figure 7 illustrates the burden on patients with diabetes mellitus (DM) across various categories: General wards, ICU, Deaths, and Deaths in comorbidities. The left side of the figure displays the proportion, while the right side shows the actual number of hospital admissions. As indicated in the figure, individuals aged 70 and above constitute the demographic with the highest proportion of hospital admissions, both in general wards and ICU. Among this group, 12.1% of DM patients, including those with comorbidities such as cancer, experienced hospitalization, with 2.7% requiring ICU admission. Moreover, elderly DM patients with additional conditions like heart failure, dementia, COPD, and myocardial infarction also exhibited notably high risks of hospital admission and mortality rates. The impact of COVID-19 on the incidence of DM and comorbidities reveals that atrial fibrillation comorbidity has experienced the second highest increase in either rate or number of newly-onset events across all age groups, trailing closely behind DM itself. Following the onset of COVID-19, there has been an observed increase in the incidence of heart failure, stroke, and liver disease (Appendix figure 8).

Our study findings are generally in line with prior investigations that highlighted how comorbidities like obesity, diabetes mellitus (DM), hypertension, along with advanced age, elevate the risk of contracting COVID-19 [14]. While individuals with diabetes and comorbidities, particularly marginalized and disadvantaged populations like the elderly, heavily rely on health professionals, their access to such care was disrupted during the pandemic. Virtual care solutions like telehealth have proven advantageous in the USA and UK. A meta-analysis from China showed the clinical and cost- effectiveness of telemedicine in managing type 2 diabetes [15]. By 2019, nearly all of the 31 provinces and municipalities in mainland China had established regional telemedicine centers [16]. Incorporating telehealth into health insurance policies for diabetes management holds the potential for significant benefits. Moreover, contemplating the distribution of staffing resources, encompassing doctors and nursing personnel, across public and private hospitals throughout China, could effectively address the diverse needs of various provinces and socioeconomic populations.

One limitation of this current study is that the model was only simulated up until February 2023. As a result, the most recent re-detectable positive condition was not included in the current model. In future research, it is possible to make comparisons with available evidence, such as official reports, population-based studies, and the results of other modeling studies. These approaches can provide a broader context for the study's results and reinforce its conclusions. Moreover, exploring different ratios of hospital constraints and other drug effects may offer valuable insights into potential variations in the model's outcomes. Additionally, evaluating the effectiveness of administering a 4th dose of vaccination could be a relevant avenue for investigation.

While the focus of this study is on simulating disease burden in China, the model's adaptability makes it suitable for diverse scenarios in various countries. For instance, a new variant like Eris or EG.5.1, emerging as a descendant of Omicron, was initially categorized as a variant in the UK on July 31. It has now gained prominence, accounting for one in ten Covid cases [13]. Our model structure, consisting of the seven components outlined in the Appendix under the "Basic Model," holds the potential for simulating new variants that emerge in the UK. Given adequate supported data, it can be employed to infer the disease burden associated with DM.

In a nutshell, comprehending the challenges and burdens encountered by the population helps us pinpoint the most vulnerable patient groups and execute precise action plans for the next steps. This, in turn, allows us to provide tailored recommendations to ensure secure care and efficient healthcare delivery.

Reference

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Appendix

1. **Basic Model Structure:**

(a) SEIR transmission:

The simulation was conducted from November 1, 2022, to February 23, 2023. The initial number of infection cases on November 1 was reported to be 25,485 by the China CDC. The rate of S to E: $1 - \mathrm{e}^{-\lambda_a(t)}$ where $\lambda_a(t)$ refers to the force of infection for age group *a* at time *t*. It is calculated from age-mixing contact matrix C in China before the epidemic, the basic reproduction number R0, and prevalent infectious cases. The age-mixing contact matrix might change under different policies. Period 1: before 2022 Nov 11. Period 2: 2022 Nov 11 to 2022 Dec 7. Period 3: 2022 Dec 7 onwards. The average duration of the latent period is 3 days, and approximately 92.95% of infections were symptomatic. The average infectious period lasts for 7 days [5].

(b) Disease progression:

Age-specific proportion of unvaccinated symptomatic infections requiring hospitalization *(H)*. The hospital settings *(H)* were divided into two parts: Hospital general ward and ICU ward. Patients stay in hospitals and then either transition to being discharged or pass away. Proportion of requiring hospitalization were estimated from age-specific infection fatality ratios and hospitalization fatality ratios reported by HK Department of Health, adjusting for underestimation of official numbers and proportion of symptomatic infections in our study [4]. Age-specific proportion of unvaccinated hospitalized patients requiring ICU admission were calculated from the rates in wild-type reported in China and the ratio between wild-type and Omicron. We assume patients are admitted to ICU the same day as they enter the hospital. The average time from symptom onset to hospital admission was 3. We also used to age-specific proportion of death among unvaccinated infected patients requiring hospitalization (general wards and ICU admission) used in the previous literature [6].

The average time from general wards admission to death was 15 days; the average time from general wards admission to recovery was 10 days; the average time from ICU admission to death was 8 days; and the average time from ICU admission to recovery was 8 days.

(c) Hospital constraint:

In 2022, there were 138,100 available ICU beds, and half of that capacity could be utilized for Covid-19 patients. Additionally, in 2021, there were 9,448,000 available general ward beds, and half of that capacity could be used for Covid-19 patients. We also examine the age-specific ratios of death (in age groups 0-55, 56-69, and 70+) when the general wards/ICU occupancy rate reaches 100%, in comparison to occupancy rates below 100%.

(d) Vaccination:

The vaccination analysis was divided into two components: (1) Age-specific vaccination coverage, which was simulated using daily vaccination data reported by the China CDC from Feb 3, 2022 to Feb 23, 2023, and (2) Age-specific vaccination efficacy against infection, symptomatic infection, hospitalization, and death, derived from population-based studies conducted in Hong Kong [7][8].

(e) Anti-viral drugs:

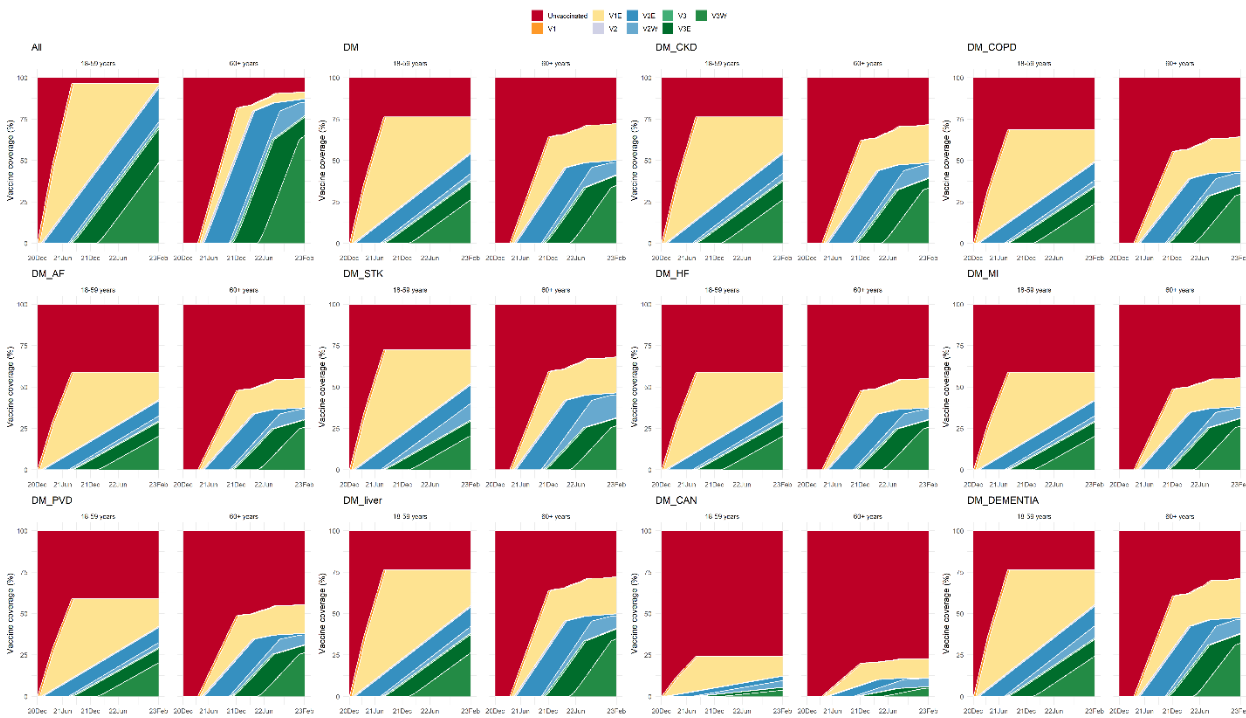
We took consideration of three drugs: Paxlovid, Molnupiravir, Azvudine, which were estimated from News report. We assumed medications were prioritized for the elderly and those with underlying chronic conditions. For Paxlovid, there were 5 million courses available within one month since November, obtained through both official and unauthorized channels, with priority given to the elderly and individuals with underlying chronic conditions. Molnupiravir became available in China from January 13. As for Azvudine, it represents the first oral antiviral for the disease manufactured in China, and since August 2, 2022, it has been in production with an annual supply of 3 billion slices of the drug (equivalent to 85,714,286 courses). The drug effects specific to age groups for requiring hospitalization, ICU admission in hospitalized patients, and death in hospitalized patients were obtained through an analysis conducted during the Hong Kong Omicron wave [9][10][11].

(f) Outcomes in people with DM and comorbidities:

The comorbidities in DM patients include: CKD, COPD, Atrial fibrillation, stroke, heart failure, myocardial infarction, PVD, liver disease, cancer, dementia. And we did not consider the situation in children aged below 18 years. In our study, we conducted a comparison between two groups: individuals with diabetes mellitus (DM) only and individuals with DM along with comorbidities. We analyzed the following factors for each group: (1) Age-specific prevalent cases, (2) Age-specific vaccination coverage, (3) Age-specific ratio of the proportion of unvaccinated symptomatic infections requiring hospitalization in people with underlying health conditions versus those without, (4) Age-specific ratio of the proportion of ICU admission in hospitalized people with underlying health conditions versus those without, and (5) Age-specific ratio of the proportion of death in hospitalized people with underlying health conditions versus those without.

(g) Post-acute DM and sequelae:

In our analysis, we focused on two groups: patients without diabetes mellitus (DM) who developed newly-onset DM, and DM patients who experienced newly-onset comorbidities, including heart failure, atrial fibrillation, stroke, chronic kidney disease (CKD), myocardial infarction, and liver disease. The selection of comorbidities was based on available data. We excluded children aged below 18 years from our study. Incidence rates specific to different age groups before the COVID-19 outbreak were estimated and provided in the supplemental material, derived from the Hong Kong Diabetes Surveillance Database (HKDSD). We also took consideration of hazard ratio of incident diabetes in COVID-19 infection versus contemporary control, hazard ratio of incident health conditions in COVID-19 infection versus contemporary control, and ratio of HRs of incident health condition associated with COVID-19 infection in people with DM versus those without DM.



Appendix Figure 1. Vaccination coverage by age groups and morbidities. The age groups are divided into two main categories for the visualization purpose: individuals aged 18 to 59 years and those aged 60 years and above. Notably, the comorbidities present in diabetes patients encompass CKD, COPD, atrial fibrillation, stroke, heart failure, myocardial infarction, PVD, liver disease, cancer, and dementia. Vaccination status encompasses a range of categories: those who are unvaccinated, individuals who have received the first dose (V1), those who have completed the first dose and received an additional booster (V1E), individuals with both the first and second doses (V2), those who have received the second dose along with a booster (V2E), individuals who have completed two doses and received a second-week booster (V2W), recipients of the third dose (V3), individuals who have undergone the third dose as well as a booster (V3E), and those who have received the third dose along with a second-week booster (V3W).

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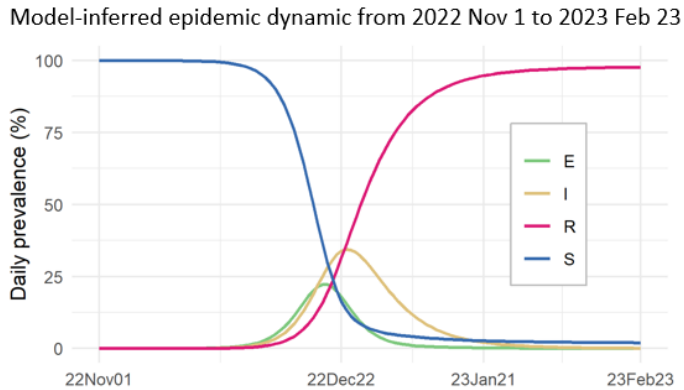
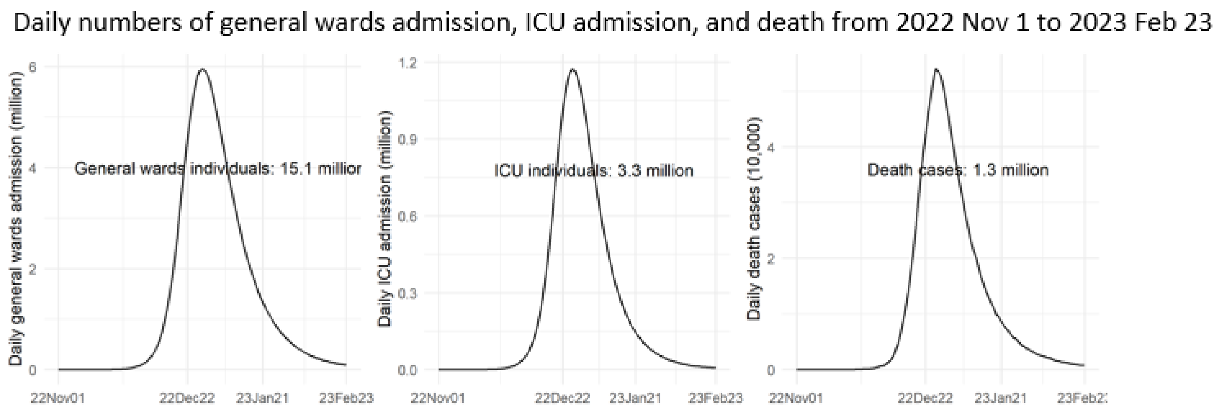


Figure 2. Transmission of COVID-omicron wave. The model-inferred epidemic dynamics, based on the SEIR model, provide insights into the spread of the disease from November 1, 2022, to February 23, 2023. The analysis reveals the trends and patterns of susceptible (S), exposed (E), infectious (I), and recovered (R) individuals over this period.



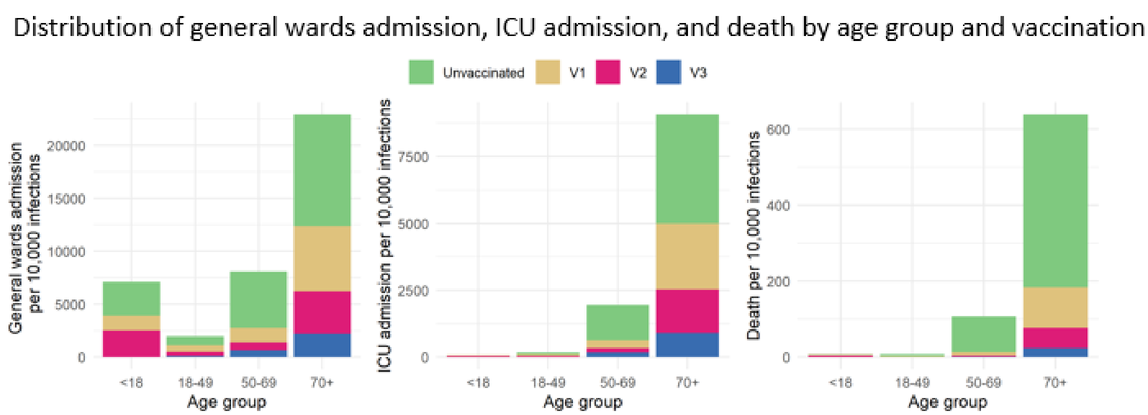


Figure 3 & 4. Burden in all people: General wards, ICU, Death. Impact on the entire population is substantial. Our simulation captures the daily counts of admissions to general hospitals, ICU admissions, and fatalities from November 2022 to February 2023. Our estimations indicate that the zenith of hospitalizations in general wards occurred around 23 January, reaching 15.1 million individuals. This peak is mirrored in ICU admissions (3.3 million) and fatalities (1.3 million) as well. The breakdown of general ward admissions, ICU admissions, and fatalities across age groups (<18, 18-40, 50-69, 70+) and vaccination status reveals a consistent pattern: the older age groups exhibit the highest rates of hospital admissions, ICU admissions, and mortality. This trend aligns with the older age groups also have the highest proportion of unvaccinated individuals.

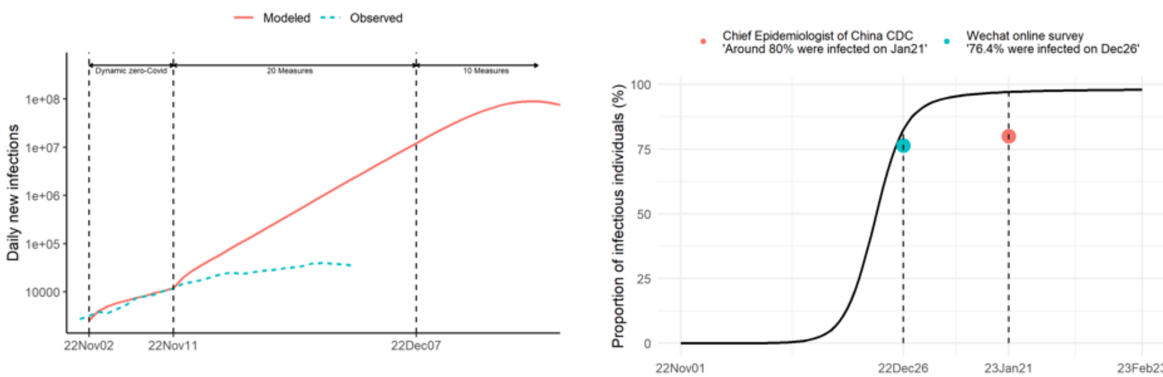


Figure 5. Validation analysis in all people using official reports and population-based surveys. The above figures show (1) a comparison between the daily count of new infections and the corresponding reports provided by the National Health Commission of the People's Republic of China (PRC); and (2) a comparison of infection rates, featuring an evaluation against data sourced from an online survey and a parallel estimation from the chief epidemiologist of the China Center for Disease Control and Prevention (China CDC), as shared on his personal social media platform.

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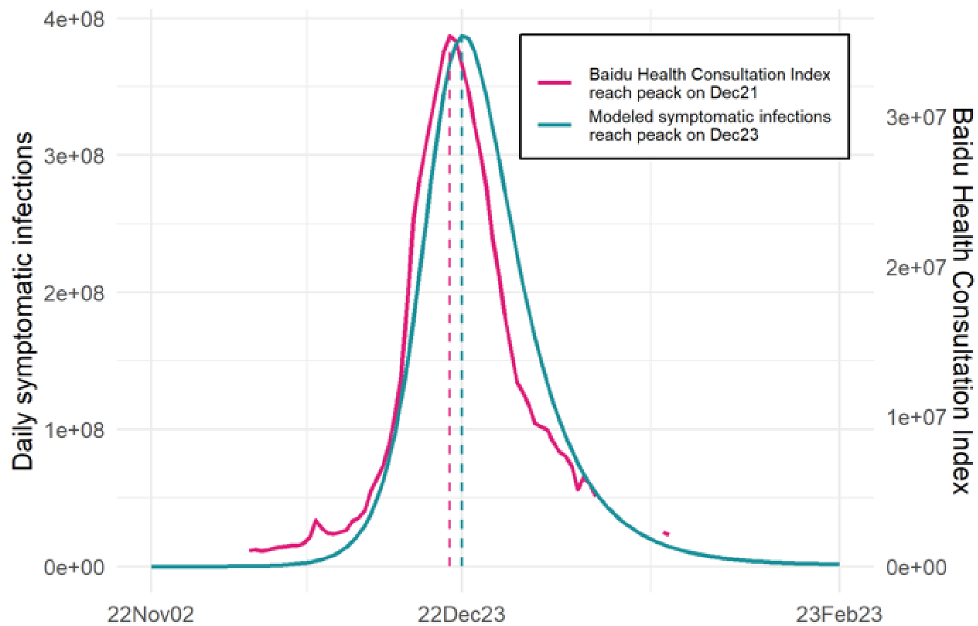
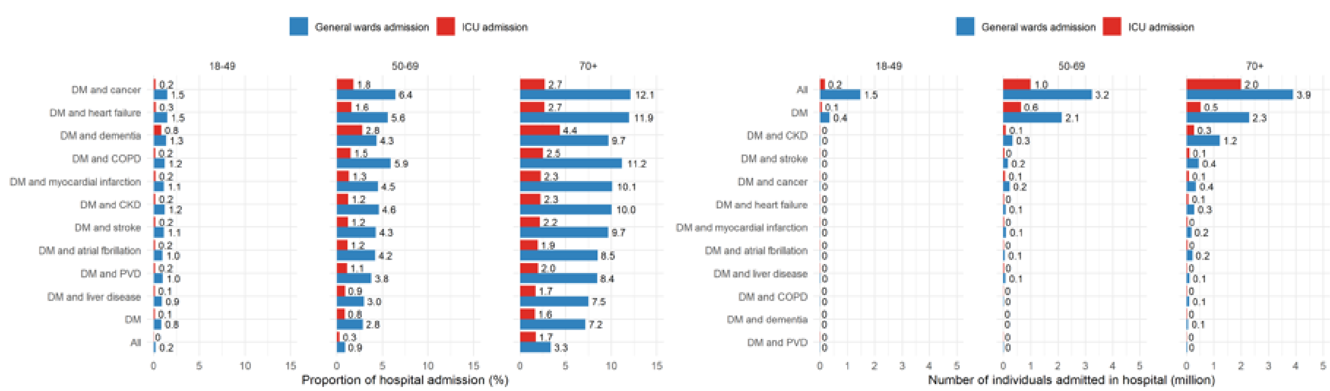


Figure 6. Validation analysis in all people using official reports and population-based surveys. The above two curves show (1) a synthetic index that simulates the scale of internet users consulting Baidu Health about epidemic prevention and control, COVID-19 treatment, and other related issues; (2) Comparison in peak of visiting fever clinics with the report issued by China CDC. Our modeled data on symptomatic infections closely mirrors the peak observed in Baidu Health queries (December 22nd to 23rd), which coincides with the peak in visits to fever clinics according to China CDC's report (December 22nd to 21st).



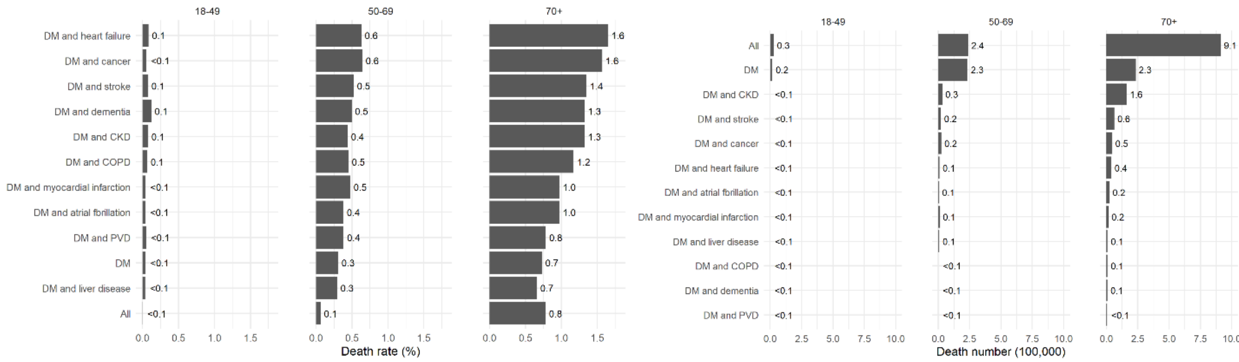


Figure 7. Burden in DM patients (General hospital wards, ICU, Death, and Death in comorbidities). Proportion (up-left) and number (up-right) of hospital admission in the general population, people with DM, and DM patients with comorbidities from 2022 Nov 1 to 2023 Feb 23. Proportion (down-left) and number (down-right) of death in the general population, people with DM, and DM patients with comorbidities from 2022 Nov 1 to 2023 Feb 23

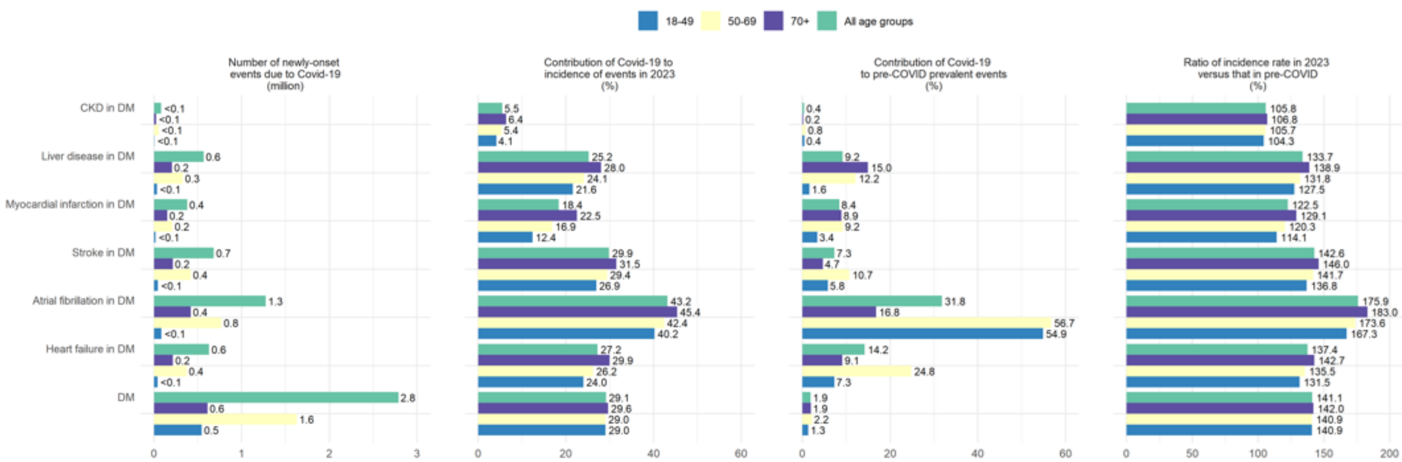


Figure 8. Newly-onset DM and comorbidities. The emergence of newly-onset diabetes mellitus (DM) alongside comorbidities. It provides estimates for the count of COVID-related incident cases in 2023, the proportion of these cases compared to the total incident cases in the same year, the ratio of COVID-related incident cases in 2023 to the prevalent cases before the COVID era, as well as the overall incidence rate ratio in 2023 in comparison to the pre-COVID period.