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Mitigating Future Respiratory Pandemics in Low-, Middle- and High-Income Countries: A Modelling Study of Health, Economic and Educational Losses

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Abstract

There is scant evidence on the broader societal losses of pandemics, though this is crucial for evaluating mitigation strategies and quantifying benefits of pandemic preparedness investments. We project the socioeconomic loss of respiratory pandemics, the sum of health, economic and educational losses, under four reactive business- and school-closure strategies, six hypothetical diseases and three country-income groups using epidemiological-economic modelling. The socioeconomic loss varies considerably between pandemics, with means ranging (as % of annual GDP) from 2.9% to 439.5%, 2.3% to 359.4% and 1.9% to 288.4% in low-/lower-middle-, upper-middle- and high-income countries respectively. Stringent closure strategies are more likely to minimise losses for severe diseases, high-income countries and higher life-year valuations. Strategies with reactive school and business closures usually outperform those with long-term school closures, but the latter may be preferable under fiscal/political constraints. These findings provide decision-makers with crucial evidence to better prepare for and respond to future pandemics.

Main

The Covid-19 pandemic has illustrated the societal losses incurred during pandemics, not just to human health[1] but also to the global economy[2] and to education[3], due to both the disease itself and the mitigation measures implemented in response to it such as mandated business and school closures. Covid-19 will not be a once-off event: the frequency of infectious disease outbreaks is expected to increase over the coming years, due to population growth, urbanisation, land-use change and climate change[4]. The growing threat of pandemic occurrence and awareness of the potential magnitude of societal losses are galvanising debates on how to better prevent, prepare for, and respond to future pandemics.

Distinct mitigation strategies were observed during the Covid-19 response[5], including successful elimination strategies in certain settings[6], even though the associated border closures were not in accordance with WHO International Health Regulations at the time[7]. The need for decision-makers to navigate apparent trade-offs has stimulated the development of so-called epidemiological-economic models[8,9], which quantify both health and macroeconomic outcomes under different mitigation policies. Future pandemic response must also consider socioeconomic losses beyond just health losses[10], but evidence on the wider socioeconomic losses of pandemics under different mitigation strategies is currently lacking: existing respiratory pandemic planning studies typically

project only health losses, such as infections, hospitalisations and deaths, and the few studies that quantify economic losses associated with workplace closures do so without consideration of the economic structure of the country in question and for a very limited set of scenarios[11–14].

A number of pandemic prevention and preparedness initiatives have been established in the aftermath of the Covid-19 pandemic, such as the World Bank Pandemic Fund[15] and the CEPI 100-Days Mission[16]. However, given limited programme budgets and the public health-financing difficulties associated with current political developments, there is a need to evaluate the return-on-investment of specific pandemic prevention and preparedness measures and the prioritisation thereof. Since these investments may reduce socioeconomic losses more broadly[17], any evaluation based solely on health impacts may undervalue the true benefits of pandemic prevention and preparedness, yet virtually no tools are currently available for this purpose.

There is now a pressing need for the joint health and socioeconomic assessment of potential future respiratory pandemic response and mitigation. Here, we project national health, economic and educational losses under four reactive business- and school-closure mitigation strategies (No Closures (NC), Reactive-Business/Sustained-School Closures (RBSS), Reactive-Business/Reactive-School Closures (RBRS) and Elimination (ELIM)) for six hypothetical respiratory pandemics inspired by historic outbreaks (Influenza-2009-X, Influenza-1957-X, Influenza-1918-X, Covid-Omicron-X, Covid-Delta-X and Covid-Wildtype-X), using an integrated epidemiological-economic model (see Figure 1). Distributions of total socioeconomic loss (TSL), defined as the sum of the value of life-years lost (VLYL), GDP loss (GDPL) and the value of school-years lost (VSYL), are projected for three country-income groups (low- and lower-middle-income countries (LLMICs), upper-middle-income countries (UMICs) and high-income countries (HICs)), considering the variability in underlying demographic, economic, mixing and mitigation parameters. We identify TSL-minimising closure strategies and conduct comparative cost-benefit analyses of the closure strategies. This study synthesises evidence on the magnitude of pandemic-induced socioeconomic losses, provides insights for decision-makers on response strategies, and serves as a robust tool for the evaluation of pandemic prevention and preparedness investments.

Results

Socioeconomic Losses of Respiratory Pandemics

There is substantial variability in projected TSL both within and between country-income groups for each income group-disease scenario, as seen in Figure 2 and SI Table S5, due to differences in the underlying data informing demographic, economic, mixing and mitigation measure parameters across countries (see SI section 2.1), even without uncertainty in disease epidemiology. The order of magnitude of the TSL varies considerably across diseases irrespective of the closure strategy pursued: the mean TSL ranges from 2.9% of GDP [IQR 1.8-2.8%] in LLMICs, 2.3% [IQR 1.7-2.7%] in UMICs and 1.9% [IQR 1.2-2.4%] in HICs for the mildest disease (Influenza-2009-X) to 439.5% [IQR 166.4-700.7%] in LLMICs, 359.4% [IQR 157.6-522.5%] in UMICs and 288.4% [IQR 112.1-429.6%] in HICs for the most catastrophic disease (Influenza-1918-X for LLMICs, Covid-Delta-X for UMICs and HICs). This assumes that decision-makers pursue the mean-TSL-minimising closure strategy for each scenario. TSL values in excess of 100% of GDP are observed since it is the sum of cumulative VLYL, GDPL and VSYL over a multi-year simulation, expressed as a percentage of one year of pre-pandemic GDP. The wide range of TSL between pandemics demonstrates the sensitivity of losses to the epidemiological parameters (see SI section 2.2). Under the mean-TSL-minimising closure strategy, the mean TSL is higher in LLMICs than in HICs for every disease considered.

Loss-Minimising Closure Strategies

For the milder diseases (Influenza-2009-X and Influenza-1957-X), the NC strategy minimises mean TSL across all country-income groups, whereas for the more severe Influenza-1918-X disease, the RBRS strategy minimises mean TSL for all country-income groups (see SI Table S5). For a given disease, the mean-TSL-minimising strategy may vary by country-income group: for Covid-Wildtype-X, the NC strategy minimises mean TSL in LLMICs (110.8%, [IQR 35.0-167.4%]) but the RBRS strategy is mean-TSL-minimising in UMICs (94.7%, [IQR 48.4-118.8%]) and HICs (56.4%, [IQR 34.7-70.2%]). The ELIM strategy is not mean-TSL-minimising in any scenario but ranks second for Covid-Delta-X in HICs (309.8%, [IQR 136.6-428.7%]), though the mean is a problematic summary statistic for this strategy since it represents an average across successful and unsuccessful elimination attempts. The RBSS strategy also never minimises mean TSL in any scenario considered, but

ranks second for Influenza-1918-X in all country-income groups, for Covid-Delta-X in UMICs and for Covid-Wildtype-X in HICs. In particular, the mean TSL of the RBSS strategy is always greater than that of the similar RBRS strategy, even though businesses are not closed to the same extent, due to the long-term school closures imposed (see SI Table S3). The closure strategy that minimises mean TSL does not necessarily minimise the three constituent components (see SI Figures S7-S9 and SI Tables S6-S8) since VLYL, GDPL and VSYL vary differently by strategy, with VLYL highest under the NC strategy, GDPL highest under the RBRS and ELIM strategies, and VSYL highest under the RBSS strategy (see Figure 2). The aim of business and school closures is to reduce VLYL (by preventing hospital occupancy from substantially exceeding capacity under RBSS and RBRS and by attempting to contain local transmission under ELIM) at the expense of GDPL and VSYL, and thus the magnitude of the reduction in VLYL relative to the increase in GDPL and VSYL is critical.

Closure Strategy Cost-Benefit Analysis

A cost-benefit analysis of the RBSS, RBRS and ELIM strategies relative to the NC strategy is presented in Figure 3 and SI Table S9, where the costs are defined as incremental economic and educational losses (GDPL + VSYL) and the benefits are defined as decremental health losses (VLYL). For the more severe Influenza-1918-X disease, RBRS dominates NC across all country-income groups (on average, albeit with considerable variability) because the decremental VLYL is greater than incremental GDPL and VSYL, with benefits vs. costs of 231.8% [IQR 12.4-419.3%] vs. 75.5% [IQR 34.8-112.1%] in LLMICs, 241.8% [IQR 5.5-448.4%] vs. 13.1% [IQR 1.5-20.8%] in UMICs and 81.8% [IQR 0.0-42.3%] vs. 6.0% [IQR 0.0-11.9%] in HICs (realisations below the dashed line in Figure 3). In certain situations, particularly in HICs, the NC strategy is strictly dominated and the RBSS and RBRS strategies result in both decremental VLYL and decremental GDPL and VSYL relative to NC, implying that closures reduce both economic and health losses (realisations in the bottom-right quadrant). This typically occurs when the GDPL is primarily due to labour supply shocks related to worker illness and death (see SI Figure S10), implying that there is no trade-off between health and economic or educational losses. For the milder Influenza-2009-X and Influenza-1957-X diseases, the other strategies are dominated by NC across all country-income groups (on average) because the decremental VLYL is less than incremental GDPL and VSYL, with benefits vs. costs of the RBRS strategy for Influenza-1957-X of 4.0% [IQR 0.0-3.5%] vs. 17.0% [IQR 0.0-23.0%] in LLMICs, 2.7% [IQR 0.0-1.0%] vs. 6.8% [IQR 0.0-12.9%] in UMICs and 1.4% [IQR 0.0-0.4%] vs. 4.2% [IQR 0.0-9.9%] in HICs (realisations above the dashed line). Closures are not warranted for the milder diseases because the deaths averted do not justify the economic- and educational-closure losses incurred, at the life-year valuations used here. Occasionally, the NC strategy strictly dominates and the other strategies result in both incremental VLYL and incremental GDPL and VSYL (realisations in the top left quadrant). This occurs due to the reduction in distancing over time, vaccine waning and, for the ELIM strategy, potentially explosive exit waves that breach hospital capacity (see SI sections 2.3 and 2.4).

Closure Strategies and the Valuation of Life

There are scenarios where closure strategies have similar mean TSL but differing proportional breakdown into VLYL, GDPL and VSYL. For example, for Covid-Omicron-X in UMICs, the decremental VLYL and incremental GDPL + VSYL of the RBRS strategy compared to the NC strategy are 13.0% [IQR 0.5-19.3%] and 13.8% [IQR 1.4-19.4%], respectively. In such cases, the valuation of life inherent in VLYL is critical. In Figure 4, the proportion of simulations for which each closure strategy is TSL-minimising is plotted against the value of a life-year (VLY) (see SI section 2.5), analogous to a cost-effectiveness acceptability curve. The NC strategy is most frequently TSL-minimising when the VLY is low, though there are situations in which it is not even with zero valuation, typically for more severe diseases that would cause pronounced labour supply shocks in the absence of closures. For the milder diseases, business and school closures frequently remain untriggered under the RBSS and RBRS strategies, in which case the TSL is the same as under the NC strategy (see SI section 2.4). Conversely, when the VLY is high, the more stringent RBRS and ELIM strategies are more frequently TSL-minimising for the severe diseases. See SI Figure S11 for analogous analysis varying the value of a school-year.

Other Contextual Factors and Trade-Offs

In many scenarios, there is substantial heterogeneity in the closure strategy that is TSL-minimising even at the baseline life-year valuation, indicating that strategy selection should depend foremost on local circumstances relating to feasibility (fiscal or political) and outcomes. Examples of further contextual factors are presented in

Figure 5. In settings where the likelihood of local containment is greater, due to (non-modelled) factors such as geography, outbreak extent or surveillance capacity, the ranking of the ELIM strategy improves: panel A shows the TSL for Covid-Wildtype-X restricted to the subset of countries for which the ELIM strategy is successful if pursued (defined here as containment within 180 days of the response time - see SI section 2.4) and now the mean TSL under ELIM is comparable to that of RBRS in HICs, though not in UMICs nor LLMICs. In settings with acute fiscal or political constraints, strategy selection may be limited and outcomes beyond TSL need to be considered: panel B shows the number of furlough-days per worker (as a measure of the fiscal cost of closures) and the number of heavy-closure days (as a measure of the political cost of closures) under the RBSS and RBRS strategies for Influenza-1918-X, on the basis of which the RBSS strategy dominates across all country-income groups. However, such fiscal or political constraints may result in an inter-temporal trade-off between economic losses incurred in the short-term (GDPL) and in the longer-term (VSYL), as seen in panel C. Furthermore, the need for closures and strategy outcomes are inherently linked to setting-specific pre-pandemic health system resilience - panel D shows peak hospital occupancy under the NC strategy relative to capacity across diseases and country groups - and there may be further inter-temporal trade-offs between short- or longer-term economic losses incurred by closures and short- or longer-term health losses related to epidemic-induced healthcare displacement and healthcare workforce erosion. Distributional effects should also be considered by setting, such as age-specific health losses (see SI Figures S12-S15 and SI Table S10) and sector-specific economic losses (see SI Figure S16 and SI Table S11).

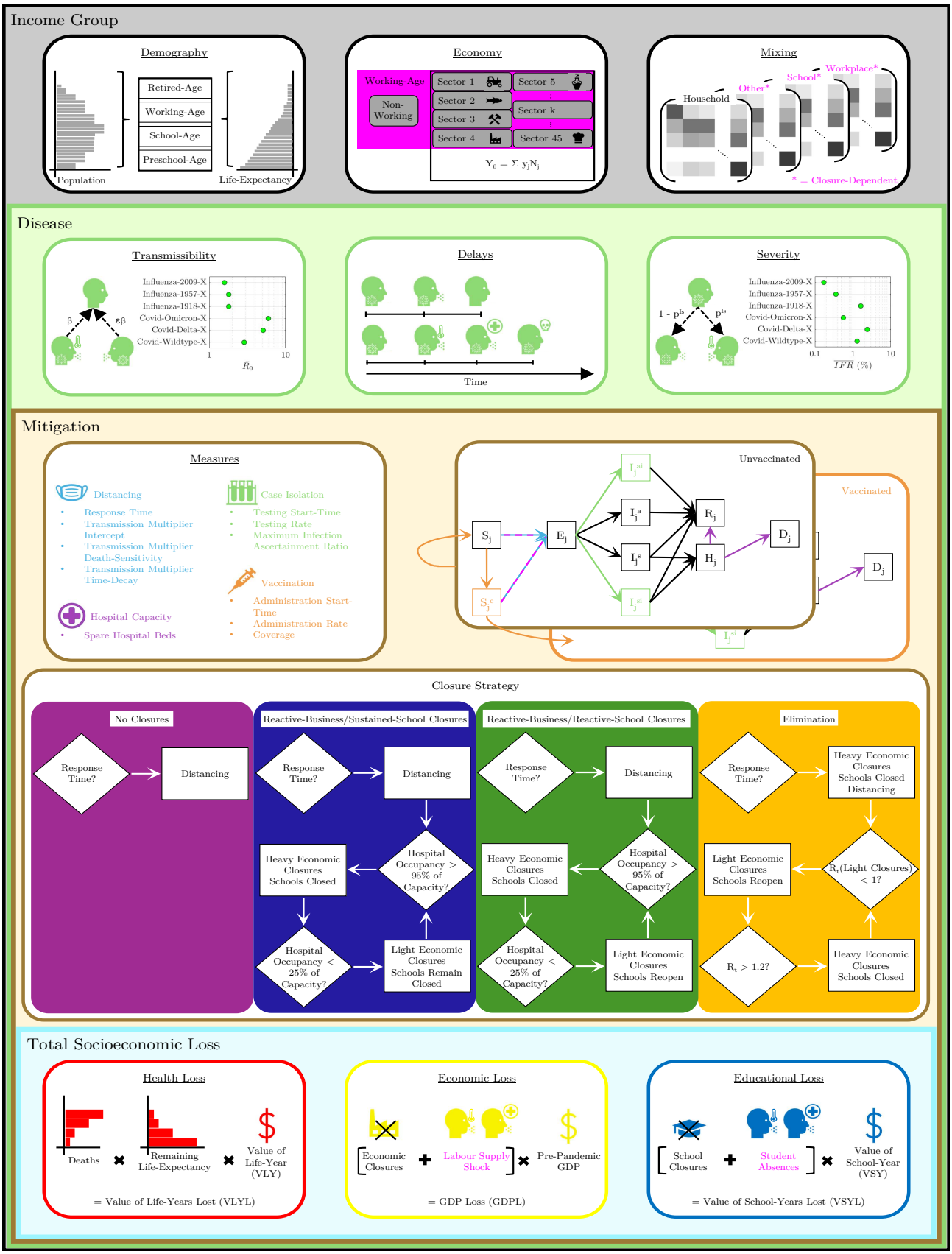


Figure 1: Schematic diagram of the integrated epidemiological-economic modelling framework. The country-income-group-dependent demographic, economic and mixing data are described in SI section 2.1; disease epidemiology is described in SI section 2.2; mitigation measures and closure strategies are described in SI sections 2.3 and 2.4; and the calculation of the total socioeconomic loss is described in SI section 2.5. The economic component model interacts with the epidemiological component model via sector-dependent workplace transmission, as well as school and other-location transmission, while the epidemiological component model interacts with the economic component model via disease-dependent labour supply shocks (magenta-coloured elements).

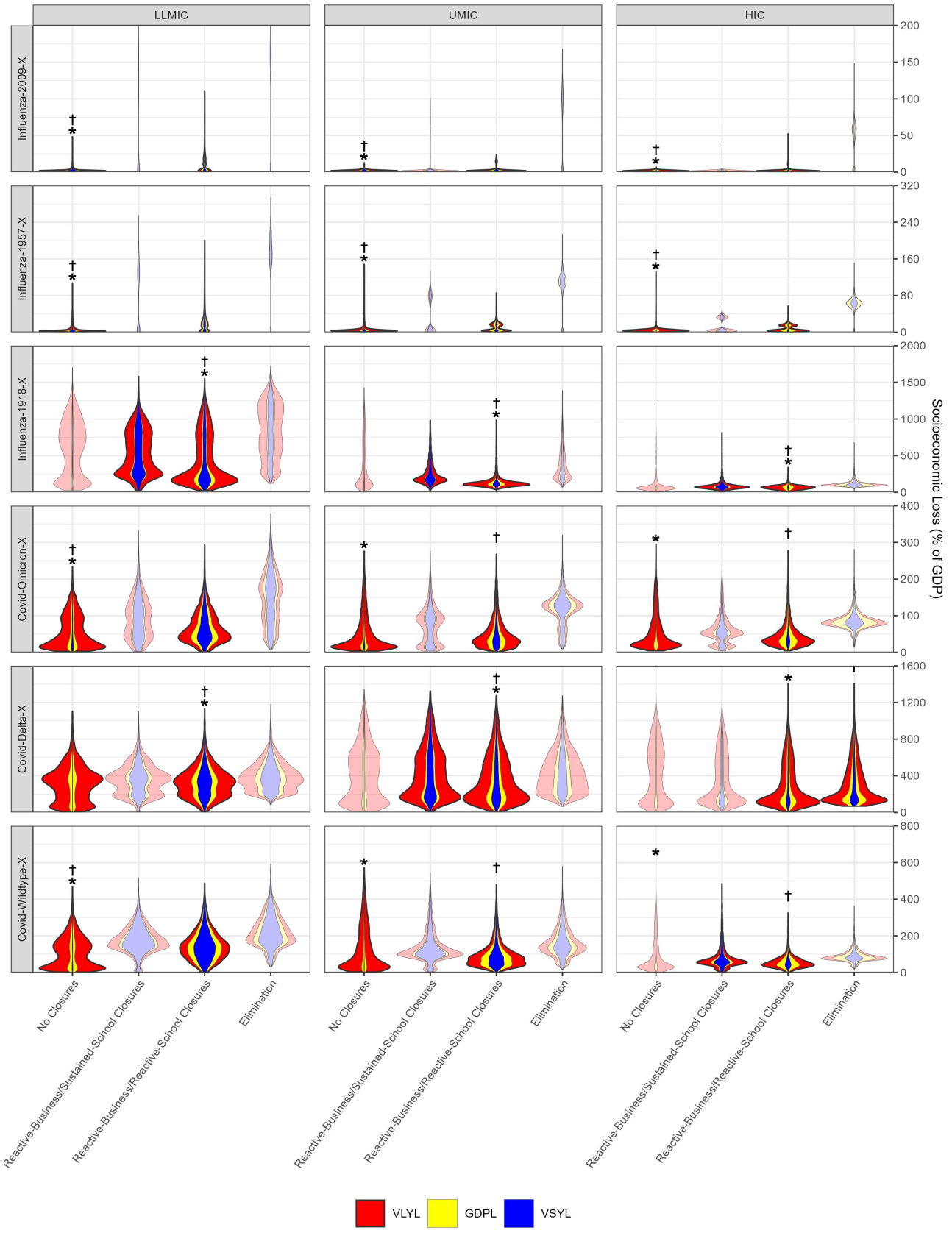


Figure 2: Distributions of projected total socioeconomic loss (TSL) (expressed as a percentage of annual GDP) under four different closure strategies, for six hypothetical respiratory diseases and three country-income groups: low- and lower-middle-income countries (LLMICs), upper-middle-income countries (UMICs) and high-income countries (HICs). The TSL distributions with the two lowest means (bold), lowest median (*) and lowest upper quartile (†) are indicated. Summary statistics are shown in SI Table S5. The colour represents the average breakdown of the TSL into the value of life-years lost (VLYL), GDP loss (GDPL) and the value of school-years lost (VSYL) for each scenario.

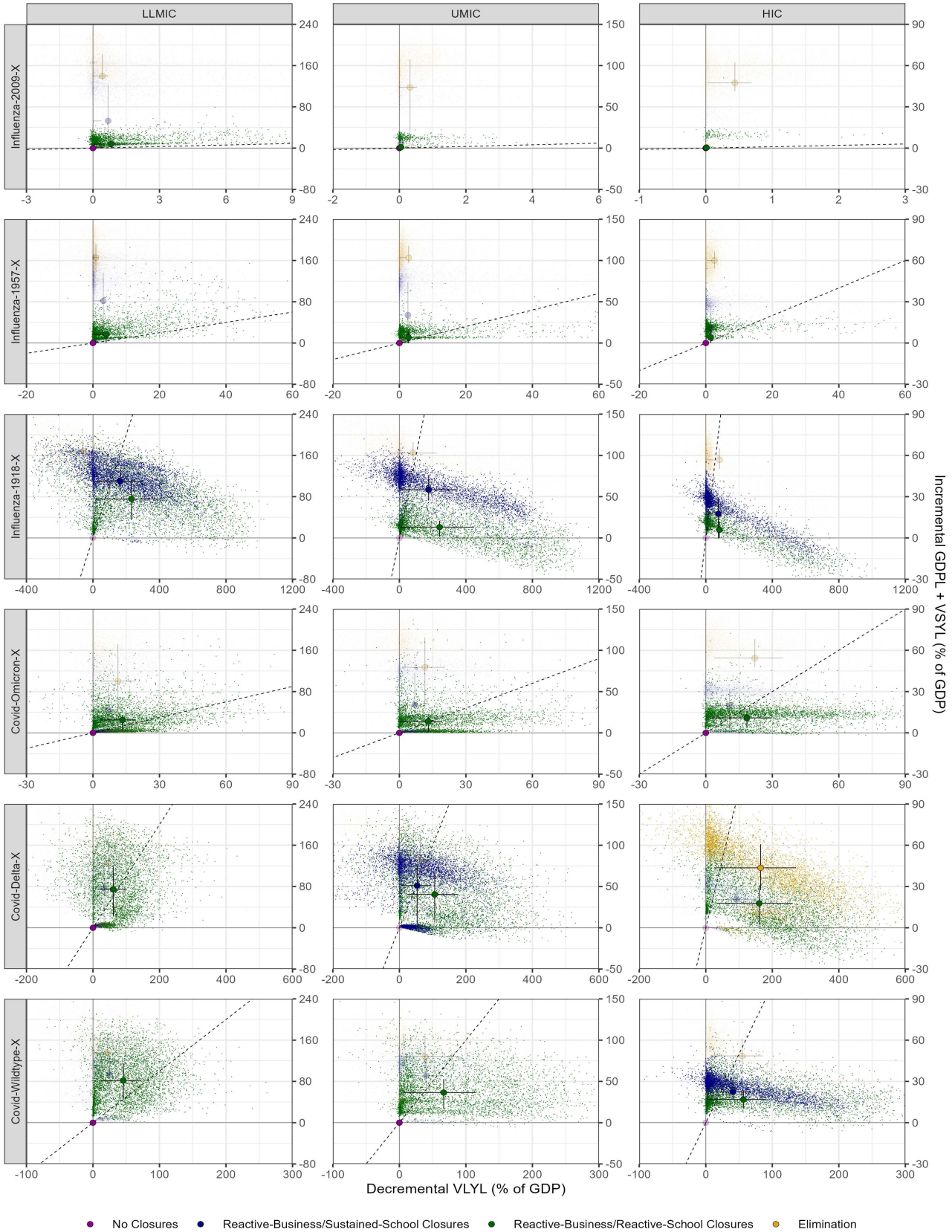


Figure 3: Health benefits and economic and educational costs of closures: projected decremental value of life-years lost (VLYL) and incremental GDP loss and value of school-years lost (GDPL + VSYL) (expressed as a percentage of annual GDP) of three different closure strategies compared to the No Closures (NC) strategy, for each respiratory disease and country-income group. The NC strategy is at the origin by definition. The mean decremental VLYL and incremental GDPL + VSYL (circles), and IQR (errorbars) are plotted for closure strategies (colours), and the strategies with the two lowest means from Figure 2 are indicated (bold). Summary statistics are shown in SI Table S9. The dashed line of unit-slope represents equality of monetised health benefits and economic and educational costs, which separates situations where the three closure strategies dominate (below) and are dominated (above) by the NC strategy.

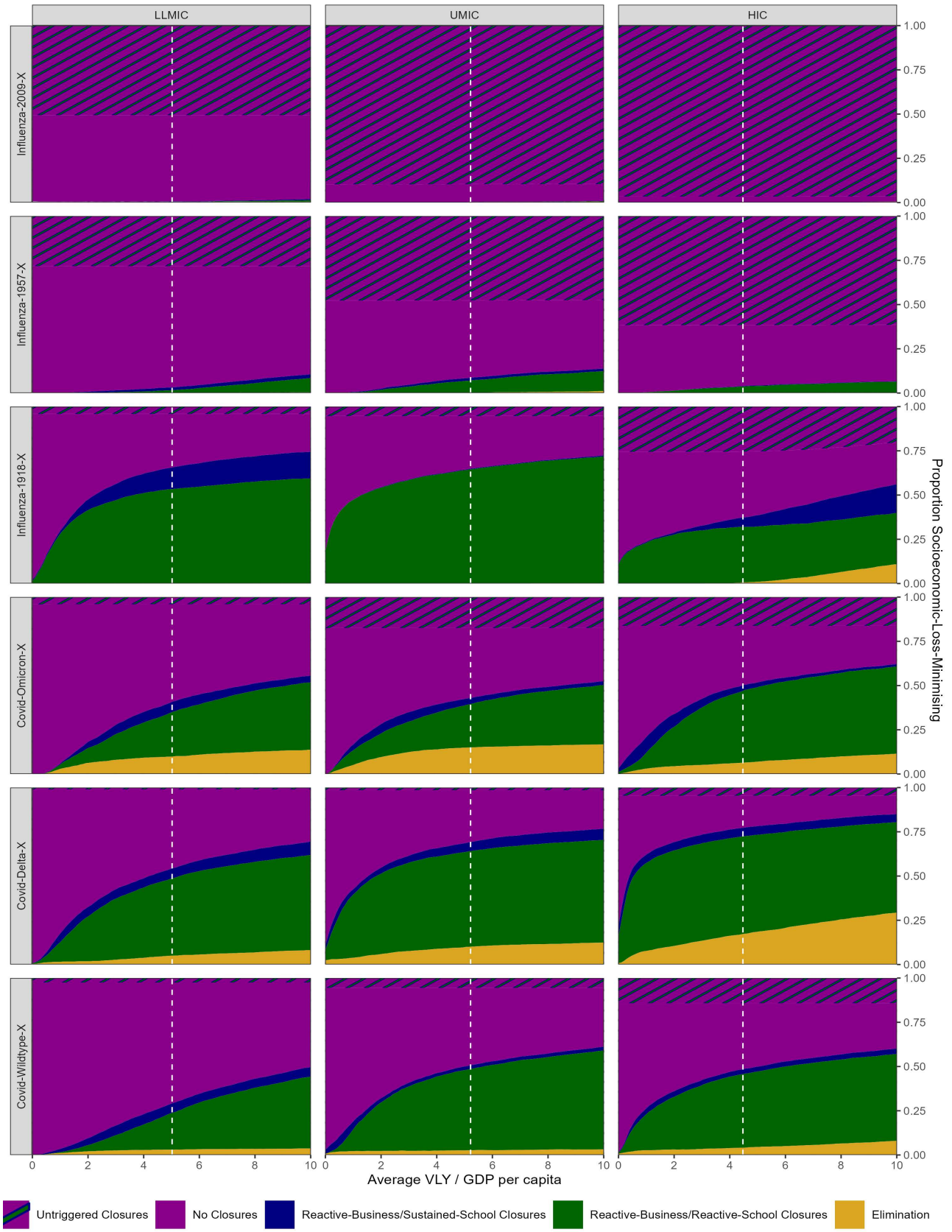


Figure 4: Closures and the valuation of life: proportion of simulations for which each closure strategy minimises total socioeconomic loss (TSL), as a function of the average value of a life-year (VLY) (expressed as a multiple of GDP per capita), for each respiratory disease and country-income group. Untriggered Closures is not a distinct closure strategy (colours), but instead refers to the situation where closures are not triggered under the Reactive-Business/Sustained-School (RBSS) or Reactive-Business/Reactive-School (RBRS) strategies, resulting in TSL equal to that of the No Closures (NC) strategy. The vertical dashed line represents the country-income-group-average VLY at baseline.

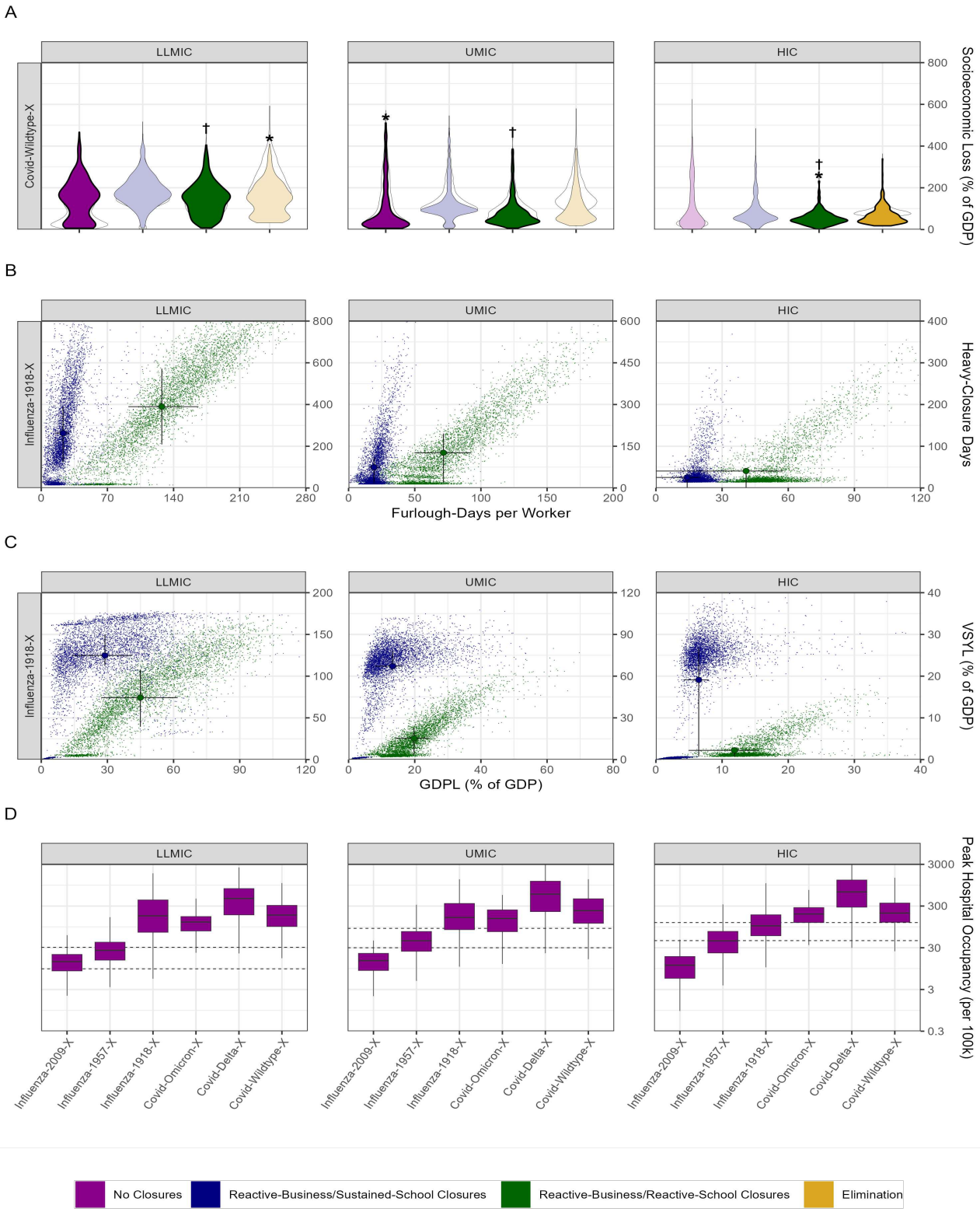


Figure 5: Other contextual factors and trade-offs. A. Distributions of projected total socioeconomic loss (TSL) (expressed as a percentage of annual GDP) for the subset of countries capable of successfully eliminating Covid-Wildtype-X within 180 days of the response time, for each closure strategy (colours) and country-income group. The distributions with the two lowest means (bold), lowest median (*) and lowest upper quartile (†) are indicated, and the distributions for the full set of countries are plotted in the background (outline). B. Projected furlough-days per worker and heavy-closure days, and C. projected GDP loss (GDPL) and value of school-years lost (VSYL) (expressed as a percentage of annual GDP), under the Reactive-Business/Sustained-School (RBSS) and Reactive-Business/Reactive-School (RBRS) strategies (colours) for Influenza-1918-X, for each country-income group. The means (circles) and IQR (errorbars) are plotted. D. Distributions of projected peak hospital occupancy (per 100k population) under the No Closures (NC) strategy, for each respiratory disease and country-income group. The IQR of spare hospital beds (per 100k population) for each country-income group (dashed horizontal lines) is also plotted.

Discussion

We use an integrated epidemiological-economic model to project the total socioeconomic loss (TSL), defined as the sum of health, economic, and educational losses, under four distinct reactive business- and school-closure mitigation strategies pursued prior to the arrival of vaccines, for six hypothetical respiratory diseases with differing epidemiological characteristics and three country-income groups. There is substantial variability in losses for each scenario, driven by variability in the underlying demographic, economic, mixing and mitigation parameters, and the projected loss distributions are very skewed. The order of magnitude of the TSL varies considerably between pandemics, irrespective of the closure strategy pursued, with means ranging from 1.9-2.9% of GDP across country-income groups for the mildest disease to 288.4-439.5% across country-income groups for the most catastrophic disease, even under the mean-TSL-minimising strategy. This demonstrates the sensitivity of losses to disease epidemiology - similar wide ranges of health outcomes across pandemics have been reported in existing pandemic planning studies[18]. However, the magnitude and range of economic losses projected here are typically greater than those estimated previously, since we account for GDP loss due to both economic sector closures and illness-related labour-supply shocks, whereas earlier work only considered the latter[19] or quantified the former in a limited manner[11–14,20–22].

The No Closures (NC) strategy minimises mean TSL for the milder diseases (Influenza-2009-X and Influenza-1957-X), whereas the Reactive-Business/Reactive-School (RBRS) strategy minimises mean TSL for the more severe Influenza-1918-X disease, across all country-income groups. For severe pandemics, the RBRS strategy dominates the NC strategy on average because the health benefits of preventing substantial hospital capacity breaches are greater than the economic and educational costs incurred due to business and school closures. This aligns with previous modelling studies of severe disease mitigation that conclude that pharmaceutical and non-pharmaceutical interventions are required in combination to reduce health losses[23], including school closures[18], and even when economic losses are considered, that mitigation by mass social distancing and school closures[11,12,20] and (early) lockdowns[24] are cost-effective and may even dominate, contingent upon the availability of efficacious vaccines[13,22]. For milder pandemics, the NC dominates the RBRS strategy on average because the costs incurred by the imposition of business and school closures until the population has been vaccinated are greater than the benefits of the averted deaths. This concurs with previous findings that the cost-effectiveness of social distancing with[11,20] and without[13] school closures decreases as disease transmissibility and severity decreases.

For the same pandemic, there is often heterogeneity in the optimal closure strategy both within and between country-income groups: for moderate diseases (Covid-Omicron-X and Covid-Wildtype-X), the NC strategy minimises mean TSL in LLMICs but the RBRS strategy minimises mean TSL in HICs. This reflects systematic differences in the effects of business and school closures between country-income groups: the cost incurred due to closures is higher in LLMICs with vulnerable health systems and inequitable access to vaccines, since closures are triggered more quickly and imposed for longer, while the benefit of closures is lower due to younger demography and reduced vaccine coverage, which diminish the health impact (see SI Figures S1 and S2). The trade-off between health and economic/educational losses is more acute in LLMICs and UMICs than in HICs. These findings align with existing pandemic planning studies that show that the health impacts of social distancing and school closures are lower in low-income and resource-constrained settings[25,26], as well as Covid-19 studies that show that the health impact of vaccination is lower in low-income countries due to inadequate access[27], and that the cost-effectiveness of lockdowns and social distancing is lower in low-income compared to high-income countries when economic losses are considered[28,29]. However, it is important to acknowledge the model limitations that the economic loss under the NC strategy only captures illness-related labour-supply shocks, meaning that GDP loss is likely underestimated, and that the health loss does not capture variability in underlying population health such as the prevalence of non-communicable diseases[30] nor variability in healthcare quality, which have been shown to affect outcomes[31]. Furthermore, the NC strategy may result in substantial healthcare system strain and incur longer-term health losses related to epidemic-induced healthcare displacement and healthcare workforce erosion not considered here. It is possible that such factors could make closures more advantageous. The optimal closure strategy is also inherently dependent on the decision-maker's valuation of life in monetary terms, whether explicit or implicit: as the value of a life year increases, closure strategies that employ more stringent business and school closures become more advantageous, albeit with some variation between country-income groups and diseases. The suitability of suppression- over mitigation-style strategies as the relative weighting of health- to economic-loss increases has been reported previously[32–34].

The Reactive-Business/Sustained-School (RBSS) strategy implements reactive closures similar to RBRS, though with less-stringent business closures and school closures sustained until the population is vaccinated, but RBSS is dominated by RBRS for every scenario considered: the health loss and combined economic/educational losses

are greater on average. The increase in VSYL, which measures the long-run impact of lost education on worker productivity and economic growth, outweighs any decrease in GDPL at the baseline value of a school-year (VSY), though this this may vary at lower valuations or if the adverse impacts can be mitigated, for example, with more effective remote teaching or later 'catch-up' of lost education. Previous pandemic planning studies have reported that school closures of limited duration are more cost-effective than those imposed long-term or continuously when measured in terms of short-term economic cost per case averted[14] and per life-year gained[35]. However, it may not be feasible to reproduce business closures of the stringency observed in high-income countries in lower-income settings, especially in countries with extensive informal economies that frustrate business closure mandates and limited means of policy communication, implementation and enforcement. Such complexities are beyond what can be captured by the model. Furthermore, when the fiscal and political costs of closures are considered, measured here in terms of furlough-days per worker and the number of heavy-closure days respectively, long-term school closures may be advantageous: RBSS may be the best feasible closure strategy in lower-income settings. There is existing evidence indicating that school closures are effective in reducing health losses, from both pre-Covid-19 pandemic planning studies[36] and the Covid-19 pandemic itself[37], and that the short-term economic loss incurred by school closures is less than that of workplace closures[11,14]: epidemiological-economic models that consider both of these objectives have also highlighted the importance of school closures as an intervention for low-income countries during the Covid-19 pandemic[28]. We find that the mean TSL under the RBSS strategy is indeed lower than that under the NC strategy for the more severe Influenza-1918-X diseases, at baseline valuations. It is important to acknowledge the model limitations regarding the definition of educational loss: there are very limited data as to the effectiveness of remote schooling and its determinants, the linear dependence on school closure duration prevents any 'catch-up' following school reopening and existing estimates of the VSY are discordant. Further research on the impacts of school closures is needed before the next pandemic, not just in terms of long-term worker productivity and economic growth, but also broader social losses such as inequity, food security and mental health.

Interim respiratory disease elimination may be suitable in specific scenarios if local containment is likely, but success is not guaranteed. The Elimination (ELIM) strategy only ranks second in minimising mean TSL for Covid-Delta-X in HICs, but never minimises mean TSL nor ranks second for any disease considered in UMICs or LLMICs. Compared to the other strategies, the combined economic/educational losses are almost always greater and the average health loss is not always lower, since it is assumed that the world is past the point of global containment and there are likely to be 'exit waves' after reopening. However, averages mask bimodal loss distributions for specific scenarios, corresponding to situations where the ELIM strategy is successful or unsuccessful: if local transmission cannot be interrupted, then heavy business and school closures are sustained until the population is vaccinated, resulting in substantial economic and educational losses. In situations where the ELIM strategy is successful in interrupting local transmission, countries can switch to light business closures and open schools and the strategy is much more advantageous - prior work has also concluded that combined testing and isolation is more effective than lockdown when health and economic losses are considered[24]. Certain countries, typically island states, implemented successful elimination-style strategies during the Covid-19 pandemic. For a given setting, the likelihood of successful local elimination with border closures, or outright eradication, is inherently dependent on disease epidemiology[38–42], and would be better quantified using an epidemiological model that accounts for factors such as transmission stochasticity and spatial heterogeneity. Furthermore, it is possible that eradication or containment could be optimal from a global perspective, irrespective of whether it is optimal from the state-level societal perspective considered here, due to the externalities of pandemics[43].

Further limitations of our study include that the epidemiological model is deterministic, spatially homogeneous, and dependent on highly uncertain economic-sector-specific workplace contact rate data. The economic model is deterministic, assumes equilibrium and represents a closed economy. Data from low-income countries are sparse and merged with lower-middle-income countries, but it may be problematic to extrapolate findings to these settings. Only novel respiratory diseases are considered, assuming no pre-existing natural or vaccine-induced immunity, and viral evolution is not modelled. Only pandemics with extensive global transmission are considered and it is assumed that we are past the point of eradication. The closure strategies and mitigation measures are modelled and parametrised using Covid-19 data, which may not apply well to the next pandemic. Strategy switching mid-simulation is not modelled and strategy optimisation or tailoring to specific settings is not considered. For example, in reality it is likely that an unsuccessful elimination attempt would be abandoned. The direct implementation costs of mitigation measures are not modelled. The health losses related to healthcare displacement, disease morbidity and mental health are not quantified, nor are medium-term economic losses, and there is uncertainty regarding the quantification of educational losses. The distributional effects of losses have not been fully investigated. As a result, there is likely more uncertainty in the socioeconomic losses of pandemics than we capture here.

The Covid-19 pandemic has illustrated the havoc that pandemics can wreak on population health, and the economic and social fabric of societies. Evidence-based pandemic response requires us to quantify these socioeconomic losses. Though the intention is not to provide precise policy guidance, this study provides insights as to the suitability (or not) of different closure strategies that could be considered in the early stages of pandemic response. As such, it is a substantial update to the pandemic planning literature of the post-Covid era. It also strengthens the case for investment in health systems strengthening, as part of pandemic preparedness and response and the universal health coverage agenda more broadly, as well as vaccine research and development, since any evaluation thereof that solely considers potential health impacts will undervalue the true societal benefits of such investments. Further research is required to estimate the return on investment of various pandemic preparedness measures, which would be especially important given modern political developments and financial constraints on public health. We have effective tools to prevent, prepare for and respond to pandemics, but it takes political commitment, long-term strategic vision and investments to spare the world from another public health crisis.

Methods

We use an integrated epidemiological-economic model, daedalus, originally developed for Covid-19[31,44,45], to project health, economic and educational losses under four reactive business- and school-closure mitigation strategies for six hypothetical respiratory pandemics and three country-income groups. The population is stratified by age (preschool-age, school-age, working-age, retired-age) and the working-age population further stratified by economic sector (45 sectors, including education, excluding non-working). There is age- and sector-specific mixing and SEIR natural history in the epidemiological component model, and the economic component model calculates sector-specific and aggregate production. The component models are linked via sector-dependent workplace transmission and disease-dependent labour supply, accounting for dynamic interactions between epidemiology and the economy. Mitigation via business and school closures reduces transmission in other locations, workplaces and schools (but limits economic and educational output), in addition to mitigation by distancing, case isolation, hospital capacity and vaccination. A schematic diagram of the model is displayed in figure 1.

Income Groups

The analysis is stratified by country-income group, to reflect differences in country characteristics and epidemic mitigation capabilities between low-, middle- and high-income settings. Three income-group 'archetypes' are considered: low- and lower-middle-income countries (**LLMICs**), upper-middle-income countries (**UMICs**) and high-income countries (**HICs**), where the low- and lower-middle-income groups are combined due to limited country-level data. Rather than modelling individual countries directly, which would imply a level of precision in the underlying data not appropriate for a projection study of this nature, variability within each income group is represented using synthetic countries that are generated by randomly sampling with replacement from empirical distributions of demographic, economic and mixing data assembled from diverse country-level datasets (see SI Figure S1). Demographic structure is sampled from income-group-specific distributions of population shares by five-year age-band and remaining life expectancy, aggregated to the four model age-groups, and economic structure is sampled from distributions of workforce by sector and sectoral gross value added per worker. Population mixing is sampled from income-group-specific contact matrices for households, other locations, schools and workplaces, where the structure of the workplace contact matrices is preserved from the original daedalus model[44] with sector-specific workplace mixing heterogeneity and dynamic adjustment according to sector closures and home-working, but the magnitude of workplace contacts is allowed to vary. Sampling from these empirical distributions generates a wide range of plausible synthetic countries within each income-group archetype and propagates uncertainty in the underlying data through the model projections (see SI section 2.1).

Diseases

We consider six novel respiratory diseases with distinct epidemiological characteristics, defined in terms of transmissibility, delays and severity. Their characteristics are inspired by historic influenza and coronavirus pandemics and pandemic variants (see SI Table S1), after which they are named: **Influenza-2009-X**, **Influenza-1957-X**, **Influenza-1918-X**, **Covid-Omicron-X**, **Covid-Delta-X** and **Covid-Wildtype-X**, where the '-X' suffix denotes new pathogens with no pre-existing population immunity (natural or vaccine-induced) in the spirit

of WHO terminology[46]. This set of diseases spans a wide range of epidemiological characteristics, including combinations of low and high transmissibility and severity, and differing transmission timescales between the influenza and coronavirus diseases. The epidemiological model health states reflect the natural history of infection, including the susceptible, exposed, asymptomatic infectious, symptomatic infectious, hospitalised, dead and recovered, with additional health states for mitigation by case isolation and a duplication of the pathway to represent vaccination, where transitions between pathways occur due to seroconversion and waning of vaccine-induced immunity to infection. It is assumed that there is no waning of infection-induced immunity or vaccine-induced immunity to severe disease over the timescales considered (see SI section 2.2). Though the epidemiological parameters are fixed for each disease across country-income-group archetypes, the realised epidemiological dynamics vary across synthetic countries due to demography, economic structure and mixing patterns, resulting in local basic reproduction numbers and population-level hospitalisation- and fatality-ratios.

Mitigation Measures & Closure Strategies

In response to each country's epidemic, four mitigation measures are imposed to reduce disease burden: distancing, case isolation, hospital capacity and vaccination. These measures are modelled in the same way in every synthetic country but are parametrised using country-income-group-specific distributions fitted to country-level Covid-19 mitigation data, with parameters sampled from marginal distributions accounting for interdependencies (see SI Figures S2 and S3). It is particularly difficult to extrapolate from Covid-19 data to generate plausible mitigation parameter values for different diseases and several assumptions are made regarding disease-dependence (or independence); for example, it is assumed that the distancing response time and testing start-time scale with local doubling times, and that distancing responds to daily mortality (see SI section 2.3). All four mitigation measures are imposed irrespective of closure strategy pursued, therefore no entirely unmitigated scenario is considered, but the effectiveness depends on time-dependent epidemiological variables and is therefore endogenous to the synthetic country's epidemic. Illustrative implementations across income groups are shown in SI Figure S4. The mitigation measures comprise:

- Distancing is modelled as a time-dependent transmission multiplier that decreases (thus reduces transmission) as the number of daily deaths increases, but where the effect decays over time reflecting behavioural effects. The logistic functional form and parameter values are derived from Covid-19 mobility data, used here as a proxy for distancing, with parameters corresponding to the intercept, death-sensitivity and time-decay coefficients.
- Case Isolation encompasses the detection and isolation of a proportion of the infectious, where detection is modelled by the diversion of the infectious to separate isolating health states according to time-dependent infection ascertainment ratios that depend on testing start-times, testing rates, maximum infection ascertainment ratios and local prevalence (above and below a threshold), and isolation effectiveness is modelled by the reduced risk of transmission for the isolating that scales linearly with disease-dependent epidemiological delays.
- Hospital Capacity is not an intervention per se, but represents the pre-existing ability of the health system to provide care to pandemic patients, and this is modelled by a linear scaling of the disease-dependent hospitalisation fatality ratio with overutilisation if hospital occupancy exceeds the number of spare hospital beds available, thus capturing deteriorating patient outcomes under health system strain.
- Vaccination is modelled by the rollout of a strain-specific but imperfect vaccine (see SI Table S2) at constant daily administration rate after the administration start-time, until the population-level vaccine coverage is reached. Vaccination prioritisation is age-descending for all diseases except for Influenza-1918-X, for which working-age groups are vaccinated first followed by the remaining groups in age-descending order.

In addition to the mitigation measures above, four distinct reactive business- and school-closure mitigation strategies are considered, inspired by strategies implemented during the Covid-19 pandemic[5]. Each closure strategy is defined by a set of economic configurations specifying the extent to which each economic sector (including the education sector/schools) is open for production, together with rules for switching between configurations (see SI section 2.4). As well as the closure-induced reduction in transmission in workplaces, schools and other-locations encoded in the contact matrices, it is assumed that any imposition of closures coincides with mandated home-working that reduces transmission further (see SI section 2.1). All closure strategies begin with a fully-open economy until the response time, after which the strategies (may) diverge depending on their switching rules. The closure strategies comprise:

- **No Closures (NC)** refrains from any sector closures or home-working and maintains a fully open economy throughout, though the mitigation measures listed above are still implemented.

- **Reactive-Business/Sustained-School Closures (RBSS)** initially adopts a 'wait-and-see' approach, but if hospital occupancy nears capacity, heavy business closures and school closures are imposed and the strategy subsequently alternates between between light and heavy business closures in response to occupancy, though school closures are sustained for the duration of the outbreak.

- **Reactive-Business/Reactive-School Closures (RBRS)** initially adopts a 'wait-and-see' approach, but if hospital occupancy nears capacity, heavy business closures and school closures are imposed and the strategy subsequently alternates between between light and heavy business closures in response to occupancy and schools close and reopen in tandem, abiding by the same switching rules as the RBSS strategy but with different configurations.

- **Elimination (ELIM)** immediately imposes heavy business closures and school closures at the response time with the aim of reducing prevalence to the extent that case isolation substitutes the need for heavy closures, and only if the effective reproduction number conditional on switching to the light-closure configuration is subcritical does it trigger light business closures and schools reopen, though if the instantaneous effective reproduction number subsequently increases (for example, due to waning of vaccine-induced immunity), it then alternates between heavy and light business closures with schools closed and reopen in tandem with the same switching rules as before.

A realisation of each closure strategy is shown in SI Figure S6. In all scenarios considered, it is assumed that global containment is no longer possible and while local elimination may be achievable in the interim, there may be an 'exit wave' after reopening. Though the extent to which each sector is open for each closure strategy configuration is fixed (see SI Table 2.4), the associated reductions in transmission depend on country-income-group-specific demographic, economic, mixing and mitigation parameters, as well as disease epidemiology (see SI Figure S5). Furthermore, the rules for switching between configurations depend on country-income-group-specific mitigation parameters, such as response times and spare hospital beds, as well as the epidemiological variables such as hospital occupancy and the effective reproduction number, which in turn also reflect the underlying country characteristics and disease epidemiology. Therefore, the occurrence, duration and frequency of closures for each simulation are fully model-endogenous, i.e. determined by model variables rather than externally imposed. For each strategy, all closures and home-working (if imposed) are lifted and case-isolation ends at the first occurrence of a projected effective reproduction number after reopening that is subcritical, the end of the vaccine rollout or a fixed maximum intervention period of 2.5 years after the response time, meaning that the economy is fully-open before the simulation ends.

Socioeconomic Loss

For each scenario, the cumulative health, economic and educational losses are quantified in terms of lost years of life, lost GDP and lost years of schooling respectively, and valued in monetary terms[45]. The total socioeconomic loss (**TSL**) is then defined as the sum

$$\mathrm{TSL} = \mathrm{VLYL} + \mathrm{GDPL} + \mathrm{VSYL},$$

where VLYL stands for the value of life-years lost, GDPL the GDP loss and VSYL the value of school-years lost, which are defined below. Discounting is not applied; therefore, these values represent unweighted monetary losses at the time of pandemic occurrence, rather than the present value. The TSL is expressed as a percentage of annual pre-pandemic GDP for comparability between country-income groups. Further details are provided in SI section 2.5 and realisations of the socioeconomic loss components under each closure strategy are shown in SI Figure S6.

- **VLYL** is the value of life-years lost, which is the product of the number of life-years lost and the value of a life-year (VLY). The number of life-years lost is in turn the product of the number of deaths and remaining life-expectancy, mapped from five-year age-bands to model age-groups and weighted by the infection fatality ratio. The value of a life-year is calculated from the synthetic country-specific value of a statistical life, extrapolating from values for the USA according to the Masterman-Viscusi model[47].

- **GDPL** is the GDP loss in the short-term, specifically the deviation of realised GDP from a counterfactual scenario with constant output equal to its pre-pandemic value. Realised GDP is calculated according to

an aggregate production approach and scales linearly with the extent to which each economic sector is open (depending on the closure strategy) and effective labour supply (depending on case isolation and illness).

- **VSYL** is the value of school-years lost, a measure of the impact of lost education on long-term worker productivity and economic growth, and is the product of the number of school-years lost and the value of a school-year. The number of school-years lost scales with the extent to which schools are open (depending on the closure strategy) and student absences (depending on case isolation and illness). The value of a school-year is derived from the country-income-group-dependent proportion of annual pre-pandemic GDP lost under one year of school closures, discounted to present-day[48], assuming no post-pandemic catch-up.

A cost-benefit analysis of the RBSS, RBRS and ELIM closure strategies compared to the No Closures (NC) strategy is conducted, where incremental health benefits are defined as decremental VLYL and costs are defined as incremental GDPL + VSYL.

Data Availability

All data used are publicly-available and cited within the text.

Code Availability

The code and data to reproduce this analysis are publicly-available on GitHub at https://github.com/jameel-institute/daedalus_mfp.

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Disclaimer: "The views expressed are those of the author(s) and not necessarily those of the NIHR, UK Health Security Agency or the Department of Health and Social Care."

Author Contributions

PD, RJ, AL, CM, DH, AS, EP, GF and KDH conceptualised the study. PD, RJ and AL were responsible for data acquisition and validation. PD, RJ and DH were responsible for software. PD was responsible for formal analysis and visualisation. PD, RJ, AL, CM, DH, AS, EP, GF and KDH were responsible for data interpretation. PD and KDH were responsible for writing the initial draft. PD, RJ, AL, CM, DH, AS, EP, GF and KDH were responsible for writing and editing. GF and KDH were responsible responsible for supervision. KDH was responsible responsible for funding acquisition and project administration. All authors had full access to all the data in this study and accept responsibility to submit for publication.

Competing Interests

PD and RJ declare receipt of personal fees from WHO for consultancies on integrated epidemiological-economic modelling and pandemic vulnerabilities, respectively. GF declares receipt of personal fees from WHO and

Imperial College London for consultancies. KDH declares receipt of personal fees from WHO, Pfizer and GSK for work unrelated to this study, payments for expert testimony from Infected Blood Inquiry (UK) and stocks from Astra Zeneca.

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