

SYNOPSIS

12/09/2020

COVID-19 Infection Fatality Rates Reported in Two Studies by Ioannidis et al.

This synopsis gives an overview of relevant evidence in relation to two publications for which article citations follow:

1. Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environ Res.* 2020;188:109890. Available from: <https://doi.org/10.1016/j.envres.2020.109890>
2. Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. *Bull World Health Organ.* 2020 Oct 14 [Epub ahead of print]. Available from: https://www.who.int/bulletin/online_first/BLT.20.265892.pdf

Key Findings

- Ioannidis et al. provide evidence of the previously known and well-documented age-dependent gradient in Coronavirus Disease 2019 (COVID-19)-associated mortality:
 - In a cross-sectional study of publicly reported data on COVID-19 deaths, the risk of death from COVID-19 in patients <65 years of age was 30 to 100-fold lower than that for patients ≥65 years of age in Canada and 11 European countries, and 16 to 52-fold lower in 13 United States (US) states.¹
 - In an article reviewing seroprevalence and mortality data of COVID-19 from 51 locations, the median infection fatality rate of COVID-19 was estimated at 0.27% (range 0.00%–1.63%) overall, and at 0.05% (range 0.00%–0.31%) for people <70 years of age.²
- Ioannidis et al. speculate that a preventive approach of shielding vulnerable elderly could be used without a broad lockdown. They did not include in their analyses; however, consideration for the body of evidence that protection of the more vulnerable elderly population cannot be achieved by public health measures targeting this group in isolation, as transmission (and outbreaks) occur within households, institutions and the community where different age groups are present or interact.³⁻¹³
- The reviewed papers by Ioannidis et al. do not provide evidence to support the lead author's public statements against restrictive public health measures such as lockdowns.^{14,15}

Current Status

- In response to rising cases and reduced health system capacity in Ontario, and in accordance with the recently launched framework for [Keeping Ontario Safe and Open](#),¹⁶ the Ontario government moved Toronto and Peel Region into the grey “lockdown” level of restrictions as of November 23, 2020.¹⁷
- The approach in Ontario is consistent with other jurisdictions which have re-implemented restrictive ‘lockdown’ measures to various degrees after witnessing a rise in COVID-19 incidence, hospitalization, and/or intensive care unit (ICU) admissions due to COVID-19. These countries include Belgium;¹⁸ England;¹⁹ France;²⁰ Israel;²¹ Italy;²² Northern Ireland;²³ Spain;²⁴ State of Victoria, Australia.²⁵ Further details on approaches to restrictive and lockdown public health measures in other jurisdictions can be found in the recent Public Health Ontario (PHO) scan on this topic.²⁶
- During the first wave of the pandemic, lockdowns were effective at reducing the spread of, hospitalization rates and deaths from COVID-19,²⁷⁻²⁹ and earlier adoption of lockdowns and accompanying measures was associated with an overall decreased burden of COVID-19.³⁰⁻³⁴ However, evidence regarding the necessary stringency level of lockdown measures was mixed, and the stringency of second wave lockdowns, while still an evolving situation, appears more varied in recognition of the societal impacts of pandemic interventions.³⁵

Article 1

Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environ Res.* 2020;188:109890. Available from:

<https://doi.org/10.1016/j.envres.2020.1098901>

Summary

- In the cross-sectional study by Ioannidis et al., publicly reported data on COVID-19 deaths from 14 countries and 13 US states with at least 800 COVID-19 deaths as of April 24 were reviewed:
 - Individuals <65 years accounted for 4.5%–11.2% of all COVID-19 deaths in Canada and 11 European countries, and 8.3%–22.7% in the US locations. The risk of dying from COVID-19 was 30 to 100-fold lower in the younger age group than that for people >64 years in Canada and 11 European countries, and 16 to 52-fold lower than that of people >64 years in US locations.
 - The absolute risk of COVID-19 death per million as of June 17, 2020 for people <65 years old in high-income countries ranged from 10 (Germany) to 349 (New Jersey).
 - The absolute risk of COVID-19 death per thousand for people >79 years old ranged from 0.6 (Florida) to 17.5 (Connecticut).

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- Deaths in many of the jurisdictions are now more than double those reported in the article (e.g., Illinois had 4,800 COVID-19 associated deaths as of June 2020, compared with over 12,000 in November 2020).
- The authors report an *absolute risk* of mortality in the population with data on deaths up to June 17; as such, their denominator is the full population in each age group, not individuals with COVID-19 (i.e., case fatality was not estimated). As noted, the results can only be interpreted as a cross-sectional viewpoint representing the first wave and are not reflective of the size of the epidemic.
- It is important to note that the absolute risk of death is conditioned on becoming a case and this risk was reduced in the first wave due to large-scale lockdowns.
- The authors limited their studies to jurisdictions with >800 deaths as of April 24 and examined mortality data as of June 17 to account for the lag from infection to death. Given the epidemic curve of infections in Canada, there were likely to have been additional deaths after June 17 that were part of the first wave but were not captured in this analysis, thereby underestimating the absolute risk. The authors provide estimates of the timing of the death data used in their analysis relative to the peak of the first wave by jurisdiction. In Canada, this peak was estimated at 4-7 weeks prior whereas the majority of European jurisdictions had peaked more than 9 weeks ago (and therefore may have better capture of mortality data).
- The COVID-19 mortality reported does not account for undetected COVID-19 associated deaths.³⁶
- Testing criteria varied widely by country, and also likely changed over the included time frame within a jurisdiction. Regardless, there was likely substantial under-detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related deaths, particularly in certain jurisdictions.
- The comparison of absolute risk of COVID-19 mortality to absolute risk from driving a motor vehicle is misleading, and not comparable across countries with relatively safe versus dangerous road infrastructure. In addition, many of the jurisdiction-specific ratios presented have more than doubled since the first wave.
- The authors acknowledge that their focus on mortality risk does not include impacts of hospitalization morbidity from COVID-19. Further, the authors do not consider or discuss other health outcome impacts by age group that contribute to societal impacts.
- The authors also acknowledge that morbidity may vary across countries due to effects of deprivation, access to health services and undiagnosed conditions, and that different patterns of morbidity in the non-elderly may be due to the socioeconomic profile of the jurisdiction. While age may be the major driver of differential mortality risk, there are important equity-based considerations in understanding risk of dying from COVID-19 in non-elderly populations if public health measures were to focus on the risk to the elderly only.³⁷

Article 2

Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. Bull World Health Organ. 2020 Oct 14 [Epub ahead of print]. Available from:

https://www.who.int/bulletin/online_first/BLT.20.265892.pdf²

Summary

- In the review article on seroprevalence and mortality data published as of September 9, 2020 from 51 different locations:
 - Seroprevalence varied widely (range = 0.02%–53.40%) due to varied methodologies in adjusting for test performance, sampling strategies, clustering, etc.
 - The median infection fatality rates of COVID-19, after adjusting for variations in sample size, was estimated at 0.23% overall (range = 0.00%–1.54%); and at 0.05% for people <70 years of age (from 40 locations with data).

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- The author combined all seroprevalence estimates into one analysis, and this is a central limitation of this study. Stratifying the estimates into various groups would have resulted in more meaningful estimates for the following reasons:
 - The populations sampled vary greatly (ranging from slums in Mumbai, to New York City, to the Faroe Islands). Conceptually speaking, there are many differences between these populations rendering it inappropriate to analyze them together.
 - The type of serology testing methods varies greatly between studies. This is important because the choice of laboratory methods for seroprevalence studies can directly affect the results.
 - Results of different antibody isotypes (IgG, IgM, IgA) should not be analyzed together, as each has its own role within the immune response to COVID-19. While IgM and IgA are acute markers of infection, IgG responses are made later in infection and last longer.
 - There is great variability in the quality of studies performed. A quality assessment of each study would have been beneficial to ensure that the included studies were of adequate quality for inclusion, and so that any bias was characterized.
- The author applies statistical adjustments to the estimates that are not necessarily warranted. For example, seroprevalence estimates have been corrected upwards by one tenth if a study did not measure IgM or IgA.
- Although acknowledged in the discussion section, the author does not correct estimates to account for the fact that not all COVID-19-infected individuals mount an antibody response, and that antibody levels can decline over time.
- Of note, a study reporting Ontario COVID-19 infection fatality rates using seroprevalence data was recently published, using seroprevalence estimates from the Canadian Blood Services

seroprevalence survey. The study estimates the overall infection fatality rate in Ontario to be 0.8% (95% confidence interval, 0.75 to 0.85).

Conclusions

- The strong age-gradient for COVID-19–associated mortality is not controversial and was accurately estimated in March 2020.³⁸ However, the infection fatality rate estimates by Ioannidis et al. are lower than those reported in multiple other studies.³⁸⁻⁴⁰
- The articles by Ioannidis et al. speculate that ‘shielding’ the elderly or at-risk individuals, while minimizing measures used for other population groups who are less likely to experience severe illness, can be a public health strategy. There is currently little evidence that such shielding approaches can be effectively implemented across an entire jurisdiction, despite efforts.
- Although COVID-19 infections tend to be less severe in younger patients, cardiovascular, pulmonary and other neurological sequelae may be expected based on the pathophysiology of COVID-19, what is known about other infectious diseases,⁴¹ and what is being learned about SARS-CoV-2 specifically.^{42,43} Furthermore, factors at individual, biological and societal levels that increase the risk of infection and severe outcomes are still being understood.^{44,45} It would not be possible to equitably shield non-elderly individuals who might be at risk.
- Public health agencies globally have supported the use of physical distancing measures and lockdowns to control community transmission of COVID-19, recognizing that high community transmission renders protection or shielding of higher-risk populations virtually impossible due to the connections within the broader community in which they live. Further, an approach to strict isolation of at-risk populations can also be considered inhumane and unethical.⁴⁷

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