Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COMMENTARY

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MMR Vaccination: A Potential Strategy to Reduce Severity and Mortality of COVID-19 Illness

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially reported in Wuhan, China in December 2019 was first detected in the United States on January 20, 2020 in a long-term care facility near Seattle, Washington. The virus spread quickly, and the World Health Organization declared a pandemic on March 11, 2020. On September 30, 2020 there were over 33.8 million cases and 1,013,000 deaths worldwide (130 deaths/million, 7.8 billion people), and over 7 million confirmed cases and 207,000 deaths in the United States (621 deaths/million, 333 million people) (data sources; for review, see Yamamoto et al[1]). The virus has high infectivity, with rapid contagion related to conditions favoring airborne spread, for example, congregate living facilities, long-term care facilities, and prisons. Traditional measures of social isolation (distancing), sanitation (hand washing/masks), and contact tracing have been implemented with variable success. However, 3 characteristics of COVID-19: 1) international variation; 2) age-related mortality; and 3) sequence homology between the fusion proteins of SARS-CoV-2 and measles and mumps viruses, and sequence homology between the Macro domains of SARS-CoV-2 and the rubella virus, suggest the Measles-Mumps-Rubella (MMR) vaccine may mitigate COVID-19 spread and severity.

1) COVID-19 has severely affected some countries and spared others. On September 30, 2020, China reported only 90,545 cases and 4739 deaths. Most deaths were in Hubei Province (population 59 million; 4512 deaths; 79 deaths/million), whose capital is Wuhan. Outside of Hubei Province, China (population nearly 1.4 billion) has reported only 227 deaths (0.16 deaths/million). China and the 36 other countries and regions in the World Health Organization Western Pacific Region (WPR) have the fewest cases and deaths per population unit. Most countries in Asia and Africa also have low COVID-19 rates. By contrast, the United States, other countries of the Americas, and Europe, have >50 times the death rate of WPR countries.

Measles epidemics leading to measles elimination programs with mass MMR vaccination may explain part of the observed international variations, suggesting that MMR vaccine may provide strong protection from COVID-19 spread and mortality (first reported by Gold et al[2] in March 2020; see also Franklin et al[3]). Supporting the potential anti-COVID-19 benefit of MMR vaccine, the WPR has successfully reduced measles through extensive MMR vaccination programs.[4] There are similar reports of measles epidemics and eradication efforts from other parts of Asia and across Africa. By contrast, MMR vaccination programs have been problematic in the United States,[5] the rest of the Americas, and Europe.[6] While travel restrictions, control of congregate living conditions, and governmental interventions play roles in controlling the COVID-19 spread, it is possible that MMR vaccination programs are the basis for the huge international variation.

2) In the United States, COVID-19 penetration has been extensive. Across all states, disease severity and mortality has been worst in the elderly, from the first reported deaths in nursing homes in Washington State until the present. Early deaths occurred at the end of March, peaked between mid-April and mid-May, then decreased prior to surging through July. While the number of deaths varied, the actual proportion of deaths related to COVID-19 across age groups changed very little (Centers for Disease Control [CDC] data). On September 30, 2020 the CDC reported 194,091 deaths, categorized by age and sex. Of these deaths, 20 were under 1 year of age and 47 were between 1 and 15 years (0.035% of all COVID-19 deaths, 60 million children, 1.1 deaths/million). All individuals under 45 years of age (190 million) accounted for <3% of the deaths (5898; 31 deaths/million), but those over 45 years (135

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million) accounted for more than 97% of the deaths (188,193; 1394 deaths/million).

After a large jump from 5 to 20 years of age, the death rate increased for those over age 30 years at an exponential age-related rate, doubling every 7.4 years. This rate exceeds the base rate of the exponential increase of total deaths with age (only doubling every 9 years after age 30, see Ashford[7]). Accordingly, the vulnerability to COVID-19 is closely related to age but exceeds the increase of the established comorbid illnesses (obesity, hypertension, diabetes, vascular disease) with age. Unexpectedly, the percentage of COVID-19 deaths relative to all deaths increases most sharply between 15 and 45 years, but over 45 there is a relatively stable percentage of COVID-19 deaths in this older population, ranging between 8.4% and 9.8%. This discrepancy suggests that the strong relationship with comorbidities occurs because of a confound with age, while some other factor is causally involved.

As observed internationally, MMR vaccination could also potentially contribute to the US age distribution. The low infection rates and mild presentations in children >1 year of age may be due to childhood vaccinations. The CDC recommends that children get 2 MMR doses, at 12-15 months of age and 4-6 years. Double childhood MMR vaccination can generate antibodies lasting for 20 or more years.[8] Yet, some children do not get vaccinated at all.[5] Further, long-term benefit declines with age, as evidenced by many women presenting for prenatal care who have lost MMR-related immunity.[9] This pattern is consistent with the observed progressive increase of COVID-19 infection and death rates up to 45 years of age (CDC data). The stabilization of the percentage increase in COVID-19 mortality with more advanced age may be due to long-lasting immune responses to now-rare childhood infections,[10] but which are less protective against COVID-19.

3) There are reports that appear to suggest that several currently available vaccines already established as "safe" (including polio, *Haemophilus influenzae* type-B, MMR, and pneumococcal) may offer significant protection against COVID-19 via a nonspecific "innate immunity."[11-13] However, these findings may actually be reflecting a response to MMR vaccination, which is often administered in conjunction with these others. More directly, there is evidence that rubella virus has a 29% sequence homology with a SARS-CoV-2 surface protein.[3,14] Accordingly, the rubella component of the MMR vaccine may confer specific protection against COVID-19.

These findings suggest the MMR vaccine may protect against COVID-19, including high-risk individuals, such as elderly with comorbidities, and health care workers and first responders with COVID-19 patients, especially individuals living in long-term care facilities and the related institutional staff. Clinicians who are caring for such high-risk patients should consider the benefit/cost ratios of MMR vaccination to justify use of this simple, low-risk intervention to reduce COVID-19 disease, especially until a specific vaccine is approved. Clinical trials to confirm this speculation are now being conducted.

Data Sources, most recently accessed 9/30/2020:
Center for Disease Control and Prevention (CDC): www.cdc.gov
United States Census Bureau: www.census.gov
Worldometer: https://www.worldometers.info/coronavirus
Johns Hopkins Coronavirus Resource Center: https://coronavirus.jhu.edu/map.html

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