Do childhood measles and DTaP vaccination decrease the mortality rate caused by SARS CoV-2 in OECD countries?: An Epidemiologic Study

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Abstract

Background The mortality rates caused by SARS CoV-2 differ between countries and this difference might be explained by several reasons. Childhood vaccination rate is thought to be one of them. Therefore, present study aimed to examine the possible relationship between DTaP (diphtheria, tetanus, acellular pertussis vaccine) and measles vaccination rates of Organization for Economic Co-operation and Development (OECD) countries and case fatality rate (CFR) caused by SARS CoV-2.

Methods A total of 32 OECD countries, of northern hemisphere, have been included in this study. Statistical analysis performed according to the CFR data of these countries based on SARS CoV-2. The CFR data calculated according to the total mortality count of a specific country for the 3-month period down from the date when first SARS CoV-2 case was observed.

Results Based on the correlation levels of vaccination rates of OECD countries with a period of 3-month CFR, a strong negative correlation of significance between CFR and measles (r=-0.479, p=0.006) were pointed, while a negative but not significant correlation were seen between CFR and DTaP vaccination rates (r=-264.0, p=0.145).

Conclusion Depending on the results of the study, lower CFR based on COVID-19, is suggested to be related to the successful vaccination rates of those OECD countries. Therefore, further effort is required to improve rates of childhood vaccination not only for specified diseases, but either possible protection against COVID-19 worldwide.

Trial Registration: This study is registered to clinicaltrials.gov with trial number: NCT04468802.

Background

SARS CoV-2 (severe acute respiratory syndrome coronavirus 2), which is caused by the new coronavirus that has arisen in Wuhan province of China at the end of 2019, has become a pandemic that affects the whole world. Neither a vaccine, nor a specific medication, with proven efficacy, has not taken its place in prophylaxis or treatment of Novel Coronavirus Disease 2019 (COVID-19), yet. Mortality rate caused by SARS CoV-2, differ between countries, and more than 500,000 people have died due to COVID-19 worldwide by now. Measures taken by the governors, the ability of society to comply with these regulations, average age of the cases, the number of tests performed and the health infrastructure of the country are reported to be the factors affecting mortality caused by SARS CoV-2 (1). While pediatric population is defined as the high-risk group for many contagious/infectious diseases, children, infected by SARS CoV-2, were observed to have mild to moderate clinical pictures of the disease. Center of Evidence Based Medicine (CEBM) stated that no death has been observed among those whose are at or under the age of 9 years, in the case fatality rate (CFR) report (2). According to the 12 May 2020 New York City Health data, 9 deaths between the ages of 0–17, were recorded and 6 of those reported to have underlying comorbidities. Contrary to what is expected, many reasons have been suggested that might explain why children are less affected by SARS CoV-2 pandemic (3). The immune response, which

develops faster in children than in adults, is considered to be one of the most important factors for children to be less affected by infection. As the major actor in maintaining social immunization against infections, routine childhood vaccination is thought to be the primary effector of this faster immune response at pediatric population (4).

Pertussis vaccine is an inactivated vaccine that has been applied as a single shot since the 1930's and as diphtheria, tetanus, acellular pertussis (DTaP) combined with diphtheria-tetanus since the 1990's. Although DTaP vaccination program has been strictly applied in the Organization for Economic Co-operation and Development (OECD) countries in recent years, application rate was at 80% level in 2000's (5).

Measles vaccine has been applied in United States of America (USA) since 1980's with the Centers for Disease Control and Prevention (CDC)'s goal of resolving measles among children (5). Measles vaccine, which has been applied as one of the live-attenuated vaccines in the United Kingdom (UK) since 1988, was included in vaccination program in other OECD countries, too eventually. Measles vaccine is applied as measles, mumps and rubella (MMR) being combined by mump and rubella vaccine (6). Considering the immune hyperactivity and cytokine storm caused by COVID-19, authors hypothesize that childhood vaccination may have a role on the clinical course of the disease at pediatric population. Thus, emerging two regular and frequently applied vaccines of routine vaccination program; DTaP, as an inactive one, and Measles, as a live-attenuated one, were chosen for the study. Therefore the study aimed to examine the possible relation between DTaP and measles vaccine rates, and CFR based on SARS CoV-2 in OECD countries. This study is registered to clinicaltrials.gov with trial number: NCT04468802.

Methods

Considering the fact that COVID-19 pandemic was mainly observed in the northern hemisphere and the seasonal effect, OECD countries located in northern hemisphere (Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States) were involved in the study. The OECD countries located in southern hemisphere (Australia, Chile, Colombia, Mexico, New Zealand) were all, excluded. Related 2018 OECD data used for statistical analysis of vaccination rates of the countries, obtained from "Our World in Data" website (https://ourworldindata.org/) and CFR has been calculated according to the total mortality records of OECD countries for the 3-month's period down from the date when first SARS CoV-2 case was observed.

Statistical Analysis

The data obtained from the study were recorded in SPSS 24.0 (Armonk, NY: IBM Corp.). The data of the patients are expressed as median (quartiles) for distributed data and percentage for categorical variables. Shapiro Wilk test was used to check if the continuous variables were normally distributed. While

comparing the vaccination rates between the case fatality groups caused by COVID-19, Mann-Whitney U test was used. Chi-square test or Fisher test was used to analyze the categorical variables. Correlation analyses for the vaccination rates and CFR were performed using Spearman tests. $P < 0.05$ was considered to be statistically significant.

Results

As per the data obtained from 32 OECD countries included in this study, it was seen that France was the country with the highest CFR rate (18%) followed by Belgium (16%), UK (14%), Italy (14%), Holland (13%), Sweden (12%) and Spain (11%) while Hungary and Iceland were the countries with the lowest CFR rates (1%) (Table-1). Considering the DTaP vaccination rates of the countries, it has been determined that Japan (99%), Luxemburg (99%), Portugal (99%), Finland (99%) and Hungary (99%) had the highest rates whereas Canada (91%) and Iceland (91%) have the lowest rates. In terms of the Measles vaccination rates of the countries, Portugal (99%), Luxemburg (99%) and Hungary (99%) were pointed to have the highest rates whereas Canada (90%) and Estonia (87%) had the lowest rates (Table 2). As per the vaccination rates of the countries that have been divided into groups (light, medium, heavy) according to the CFR and significance levels between the groups it has been stated that vaccination with DTaP did not create a significant difference between the groups (96.5%, 94.0%, 94.5%; $p = 0.255$) whereas measles vaccination caused a significant difference between the groups (96.0%, 94.0%, 93.0%; $p = 0.048$) (Table 3). When correlation levels examined between vaccination rates of OECD countries, and CFR for 3-month, it has been seen that there were a negative correlation between CFR and DTaP vaccination rates but it was not statistically significant ($r=-264.0$, $p = 0.145$). Also there was a negative correlation, with a high level of significance, between CFR and measles vaccination rate ($r=-0.479$, $p = 0.006$) (Table 4).

Table 1
Data obtained in the first 3 months from the first case recorded in the country

Country	Case fatality ratio, %	Total number of tests	Total confirmed deaths
France	18	724574	21856
Belgium	16	396052	7844
United Kingdom	14	2620000	37048
Italy	14	1980000	27967
Holland	13	344334	5856
Sweden	12	119400	2586
Spain	11	1350000	24824
Slovenia	7	82161	108
Ireland	7	325795	1639
Greece	6	160991	172
Canada	5	717451	2560
United States	5	4030000	40682
Switzerland	5	376935	1641
Denmark	5	480239	563
Austria	5	405341	8257
Polond	4	967177	1092
Portugal	4	840681	1424
Finland	4	99090	199
Lithuania	4	287982	66
Germany	4	2450000	5750
Estonia	4	80720	65
Czech Republic	3	449356	320
Norway	3	234637	235
Luxembourg	3	72996	110
Japan	3	162816	393
Turkey	3	2450000	4729
Latvia	2	111404	24

Country	Case fatality ratio, %	Total number of tests	Total confirmed deaths
Korea	2	563035	236
Slovakia	2	185596	28
Israel	2	531569	279
Hungary	1	195894	534
Iceland	1	60450	10

Table 2
Vaccination rates by country

Country	Diphtheria, tetanus, pertussis Vaccination % of children	Measles Vaccination % of children
France	96.0	90.0
Belgium	98.0	96.0
United Kingdom	94.0	92.0
Italy	93.0	93.0
Holland	93.0	93.0
Sweden	97.0	97.0
Spain	97.0	97.0
Slovenia	93.0	93.0
Ireland	92.0	92.0
Greece	97.0	97.0
Canada	91.0	90.0
United States	92.0	92.0
Switzerland	95.0	95.0
Denmark	95.0	95.0
Austria	95.0	95.0
Polond	93.0	93.0
Portugal	99.0	99.0
Finland	99.0	96.0
Lithuania	92.0	92.0
Germany	95.0	97.0
Estonia	92.0	87.0
Czech Republic	96.0	96.0
Norway	96.0	96.0
Luxembourg	99.0	99.0
Japan	99.0	97.0

Country	Diphtheria, tetanus, pertussis Vaccination % of children	Measles Vaccination % of children
Turkey	96.0	96.0
Latvia	96.0	98.0
Korea	98.0	98.0
Slovakia	97.0	96.0
Israel	98.0	98.0
Hungary	99.0	99.0
Iceland	91.0	93.0

Table 3
Vaccination rates and inter-group significance levels of countries that are divided into groups (low, medium, high) by case fatality rates

	Low (<% 5), median (quartiles)	Medium (≥ 5, < 10), median (quartiles)	High (≥ 10), median (quartiles)	p value
Diphtheria, tetanus, pertussis Vaccination Rate	96.5 (95.2–99.0)	94.0 (92.0–96.0)	94.5 (93.0-96.2)	0.255
Measles Vaccination Rate	96.0 (94.5–98.0)	94.0 (92.0–95.0)	93.0 (92.0–97.0)	0.048

Table 4
Correlation coefficient values and significance levels between childhood vaccination rates in OECD countries and 3-month case fatality rates

	Correlation coefficient	*P* value
Diphtheria, tetanus, pertussis Vaccination Rate	-264.0	0.145
Measles Vaccination Rate	-0.479	0.006

Discussion

Current study elucidated that higher measles vaccination rates were correlated with lower SARS CoV-2 CFR in OECD countries, instead, a negative but not significant correlation were seen between DTaP vaccination rates and SARS CoV-2 CFR. To the best of our knowledge, this is the first study assessing whether measles and DTaP vaccination rates had a statistical association with COVID-19 CFR in OECD countries. One of the hypotheses about why mortality is lower in SARS CoV-2 infected younger patients is

that childhood vaccination programs gradually become more regular in the recent years. Gold et al. demonstrated that highest MMR vaccination rate was in Germany and the lowest rates were observed in Italy, UK and France in 2002, alongside with CFR was significantly high in Italy, UK and France while it was lower in Germany (7). Present study, using measles vaccination data of OECD of 2018, obtained similar results. Measles vaccination rates of Italy, UK and France were under 95% (93%, 92%, 90%, respectively) while in Germany this rate was 97%. Meanwhile, CFR in Italy, UK and France were quite higher (14%, 14%, 18%, respectively) than CFR in Germany (4%) (2). Even though southern hemisphere countries were excluded from study, Madagascar is remarkable with its lower CFR and higher vaccination rates rather than its neighbor countries such as South Africa (8). While vaccination rates reported to be 85%, 91% for MMR and DTaP, respectively in Madagascar; those rates were recorded as 82%, 81%, respectively in South Africa (9, 10). Besides, in terms of CFR based on COVID-19, South Africa had higher mortality rate than Madagascar within the particular period (8). Given the MMR vaccination program implemented in Madagascar just before SARS CoV-2 pandemic and entire society was vaccinated, it is worth to note that this strict vaccination program of this country might be effective on this relatively lower mortality rate comparing with South Africa (11).

Bacillus Calmette-Guerin (BCG) vaccination is also shown to be protective against SARS CoV-2 in a recent study, conducted in 131 countries (12), by determining ten times elevated mortality rate in countries, where BCG is not in routine vaccination program, compared to the countries, where BCG vaccination is applied (40 million vs 4.28 million). BCG vaccine and other live-attenuated vaccines are known to improve general innate immunity not only for the target disease but also for other infections (13). Another explanation for this, might be of these characteristics of live-attenuated vaccines is that those vaccines develop immune memory (14). Together with this information, live attenuated measles virus vaccine is known to induce immune modulation by the suppression of interferon gamma (IFN-γ) production in long-term (15). Considering the increased mortality rates in the elder is attributed to the higher threshold of interferon-mediated immune responses, this suppression of IFN-γ due to measles vaccination might be another effective mechanism on the lower mortality of pediatric population. In accordance with that, measles vaccine was observed to put up significant resistance against SARS CoV-2 in this study. Further investigators indicated that the rubella or measles vaccine, providing cross immune protection to those viral infections, might be explanatory for the vaccinated children being substantially less affected in China (16).

It is known that CFR caused by SARS CoV-2 is not only affected by vaccination program but also factors like social isolation rules implemented by a country, the number of tests performed, health infrastructure. The most typical example of this situation is Sweden, whose CFR is four times of Norway’s CFR, that these two countries have similar vaccination rates. There is a similar case in Iceland, being another Scandinavian country. Iceland is the country with the lowest CFR rate among OECD countries despite their measles vaccination rates being under the OECD average (94.9%) (5). The isolation rules they have implemented and high test rate is being indicated as the main reason of the CFR rate being this low that Iceland is the country with highest test rate per population among OECD countries (17).

Limitations

The limitation of this study is that the situations that can directly affect the CFR in the COVID-19 outbreak, such as the governmental policies, healthcare infrastructures, and the number of tests performed, are not homogenious for all countries. Moreover, the fact that countries are quite different from each other in population and that control of pandemic in countries with high populations is much more difficult than those with low population such as Iceland also affects CFR. These unpredictable causes affect the statistical analysis results.

Conclusion

Depending on the results, reached in this study, lower CFR based on COVID-19, was suggested to be associated with the successful vaccination rates of those OECD countries. Therefore, further effort is required to improve rates of childhood vaccination not only for targeted diseases, but either possible protection against COVID-19 worldwide.

List Of Abbreviations

BCG Bacillus Calmette-Guerin

CDC Centers for Disease Control and Prevention

CEBM Center of Evidence Based Medicine

CFR Case Fatality Rate

COVID-19 Novel Coronavirus Disease 2019

DTaP Diphtheria, tetanus, acellular pertussis vaccine

IFN-γ Interferon Gamma

MMR Measles, Mumps and Rubella

OECD Organization for Economic Co-operation and Development

SARS CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2

UK United Kingdom

USA United States of America

Declarations

Ethics approval and consent to participate: Not applicable

Consent to publish: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' Contributions: R.G. and S.Y.S. conceived of the presented idea. R.G. and S.Y.S. developed the theory and performed the computations. R.G. and M.I.S. verified the analytical methods. G.E. encouraged M.I.S. to investigate the backround of hypothesis and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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References

1. Wilder-Smith A and Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. Journal of Travel Medicine, 2020,1-4
2. Oke J and Heneghan C. Global Covid-19 Case Fatality Rates. March 17, 2020 updated 9th June 2020 (cited 2020 June 15) Available from: https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/
3. Coronavirus Disease 2019 (COVID-19) Daily Data Summary. May 12, 2020 (cited 2020 June 15). Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/imm/covid-19-daily-data-summary-deaths-05132020-1.pdf
4. Okyay RA, Sahin AR, Aguinada RA and Tasdogan AM. Why are Children Less Affected by COVID-19? Could there be an Overlooked Bacterial Co-Infection? EJMO 2020;4(1):104-5
5. OECD (2013), "Childhood vaccination programmes", in Health at a Glance 2013: OECD Indicators, OECD Publishing, Paris
6. Thompson G. Measles and MMR statistics. February 10, 2009 (cited 2020 June 16). Available from: file:///C:/Users/Pc-home/Downloads/SN02581.pdf
7. Gold, Jeffrey. (2020). MMR Vaccine Appears to Confer Strong Protection from COVID-19: Few Deaths from SARS-CoV-2 in Highly Vaccinated Populations. DOI: 10.13140/RG.2.2.32128.25607
8. Max Roser, Hannah Ritchie, Esteban Ortiz-Ospina and Joe Hasell (2020) - "Coronavirus Pandemic (COVID-19)". *Published online at OurWorldInData.org.* Retrieved from: 'https://ourworldindata.org/coronavirus' [Online Resource]

9. WHO UNICEF review of national immunization coverage, 1980-2019 Retrieved from: ‘ https://www.who.int/immunization/monitoring_surveillance/data/mdg.pdf’
10. WHO UNICEF review of national immunization coverage, 1980-2019 Retrieved from: ‘https://www.who.int/immunization/monitoring_surveillance/data/zaf.pdf’
11. Sajadi MM, Habibzadeh P, Vintzilleos A, Shokouhi S, Miralles-Willhelm F and Amoroso A. Temperature, Humidity, and Latitude Analysis to Estimate Potential Spread and Seasonality of Coronavirus Disease 2019 (COVID-19). JAMA 2020;3(6):e2011834
12. Hegarty, Paul, Ashish Kamat, Helen Zafirakis, and Andrew Dinardo. BCG Vaccination May Be Protective against Covid-19, 2020. https://doi.org/10.13140/RG.2.2.35948.10880.
13. Netea MG, Dominguez-Andres J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol* 2020; published online March 4. DOI:10.1038/s41577-020-0285-6.
14. Mina MJ, Kula T, Leng Y, Li M, Vries RD, Knip M et al. Measles virüs infection diminishes preexisting antibodies that offer protection from other pathogens Science 2019;596-606
15. Ward BJ, Griffin DE. Changes in cytokine production after measles virus vaccination: predominant production of IL-4 suggests induction of a Th2 response. Clin Immunol Immunopathol. 1993;67(2):171-177. doi:10.1006/clin.1993.1061
16. Shereen MA, Khan S, Kazmi A, Bashir N and Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses Journal of Advanced Research 2020;24:91-8
17. Ricciardi V, Verme P and Serajuddin U. COVID-19: Testing for all or testing for some? A town’s key lesson in testing everyone for coronavirus. April 29, 2020 (cited 2020 June 25). Available from: https://blogs.worldbank.org/opendata/covid-19-testing-all-or-testing-some-towns-key-lesson-testing-everyone-coronavirus