# COVID-19 Severity and Neonatal BCG Vaccination in Taiwan

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**To the Editor:** The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARC-CoV-2) has led to an imminent need for an effective vaccination to constrain viral spread and reduce global disease morbidity and mortality. BCG, a live attenuated vaccine against tuberculosis, was demonstrated to have a non-specific immunomodulatory effects, by training the innate immune system to generate memory, which aided the host in fighting a wide range of viral infections in subsequent years.[1] BCG was reported to reduce viremia, respiratory tract infections, and neonatal mortality,[1] but it was not tested effectively in a recent, large randomized trial.[2] Several ecological studies reported that BCG vaccinations could have a beneficial effects against COVID-19;[3-5] they also suggested that different BCG strains might vary in their protective ability.[6] In contrast, one study in Israel found no difference in the SARS-CoV-2-positive rate between individuals born during the period of mandatory BCG vaccinations and those born outside that period.[7] All these studies analyzed aggregated data at the population level without directly comparing individuals that did to those that did not receive BCG vaccinations. Meanwhile, even if BCG vaccination is found to be effective in reducing COVID-19 incidence and mortality, it remains unclear whether the protective effect might change with time (age) or different BCG strains, or whether protection might be increased with a booster. In this study, we described the clinical syndrome in confirmed COVID-19 cases and their BCG vaccination history. We aimed to elucidate the potential protective association between a neonatal BCG vaccination and the clinical severity of COVID-19.

In the 1950s, the BCG vaccination policy in Taiwan mainly targeted school children with negative tuberculin skin test (TST) results. In 1965, a nationwide neonatal BCG vaccination program was started. Initially, neonates were vaccinated with the Pasteur-1173 P2 strain, but in 1979, vaccinations shifted to the less reactogenic, Tokyo-172 strain. In 1965–1997, booster BCG vaccinations were given to 12 year-old adolescents with negative TSTs. The BCG vaccine coverage rate increased to 87% in 1975,[8] and it has remained at 95.7%–98.8% since 1996.

For the present study, records of BCG vaccinations in COVID-19 cases were obtained from the web-based National Immunization Information System (NIIS), established by the Taiwan Centers for Disease Control (Taiwan CDC) in 2013. Eletronic vaccine records were compiled for individuals born as early as the 1980s. However, individual BCG vaccination records were unavailable in NIIS for individuals born in 1965-1985, and some were incomplete for those born in 1986-1995. The Taiwan CDC surveyed the NIIS database and found that the completeness of public-funded childhood immunization electronic records was above 90% for individuals born after 1996.

Through the National Notifiable Disease Surveillance System in Taiwan, COVID-19 was confirmed in 416 Taiwanese patients (median age: 36.3 years; mean: 40.2 years, range: 4-88 years; with 212 [51.0%] females) between Jan 21 and May 5, 2020. The diagnoses were based on positive SARC-CoV-2 RNA identification in real-time reverse transcriptase-polymerase chain reactions (RT-PCRs). Among the 416 patients with COVID-19, 366 (88.0%) had imported the disease from other regions. These patients reported travel to the following regions within 14 days of disease onset: 184 (50.3%) to European regions, 91 (24.9%) to

American regions, 26 (7.1%) to Western Pacific regions, 11 (3.0%) to Eastern Mediterranean regions, 9 (2.5%) to South-East Asia regions, 4 (1.1%) to African regions, and 41 (11.2%) to at least two of the regions mentioned.

The highest rate of COVID-19 cases occurred among individuals aged 18–24 years (56.3 per million), followed by individuals aged 25–33 years (38.1 per million), and individuals aged 34–41 (14.4 per million). According to the clinical syndrome associated with COVID-19, defined by the World Health Organization,[9] the clinical severity of these COVID-19 cases varied by age (**Table 1** ). Approximately 80% of individuals aged 18–41 years with COVID-19 experienced a mild illness (including asymptomatic infections). In contrast, among individuals aged 42–54 and [?] 55 years, 43.1% and 38.9%, respectively, had a mild illness, up to 2% and 16%, respectively, had severe pneumonia, and 10% in both age groups had acute respiratory syndrome. Among 9 children (<18 years) with COVID-19, three had pneumonia.

We examined the relationship between COVID-19 severity and BCG vaccination status among individuals aged 4–24 and individuals aged 25–33 years with electronic vaccination records (**Table 2** ). In the 4–24 age group, among individuals that received neonatal BCG vaccinations, 15.4% had pneumonia and 2.4% had severe pneumonia. In contrast, all three individuals in this age group that did not receive neonatal BCG vaccinations experienced mild illness. In the 25–33 age group, pneumonia or severe pneumonia occurred in a lower proportion of those with neonatal BCG vaccination records, compared to the group without neonatal BCG vaccination records (6.1% vs. 18.4%). However, these data should be interpreted cautiously, because the numbers of cases in the vaccinated and unvaccinated groups were small, some vaccination records in childhood were incomplete, and host genetic factors and SARS-CoV-2 virulence factors might have had a substantial influence on the COVID-19 outcome. In conclusion, our data suggested that, compared to individuals that did not have BCG vaccination records at birth, young adults aged 25-33 years that received the Tokyo-172 BCG vaccination at birth appeared to experience lower COVID-19 severity. However, this finding must be confirmed in future randomized controlled trials.

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**Table 1. Clinical syndrome associated with COVID-19 by age groups, Jan 21– May 5, 2020, Taiwan**

| **Age at onset (year)** | **Birth year** | **Neonatal BCG vaccination program** | **BCG administered in school children if TST negative** | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | **Total cases** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | **Asymptomatic** | **Mild illness** | **Pneumonia** | **Severe pneumonia** | **ARDS** | |
| Children (<18) | Children (<18) | Children (<18) | Children (<18) | Children (<18) | Children (<18) | Children (<18) | Children (<18) | Children (<18) | Children (<18) |
| 4–17 | 2002–2016 | Vaccinated with Tokyo-172 strain | No | 1 (11.1%) | 5 (55.6%) | 3 (33.3%) | 0 | 0 | 9 |
| Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) | Adults ([?]18) |
| 18–24 | 1995–2002 | Vaccinated with Tokyo-172 strain | No | 12 (10.3%) | 86 (73.5%) | 16 (13.7%) | 3 (2.6%) | 0 | 117 |
| 25–33 | 1986–1995 | Vaccinated with Tokyo-172 strain | No | 9 (8.3%) | 84 (77.1%) | 15 (13.8%) | 1 (0.9%) | 0 | 109 |
| 34–41 | 1978–1986 | Vaccinated with Tokyo-172 strain | Yes | 1 (2.2%) | 36 (80.0%) | 8 (17.8%) | 0 | 0 | 45 |

| **Age at onset (year)** | **Birth year** | **Neonatal BCG vaccination program** | **BCG administered in school children if TST negative** | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | *Clinical syndromes associated with COVID-19* | **Total cases** |
|---|---|---|---|---|---|---|---|---|---|
| 42–54 | 1965–1978 | Vaccinated with Pasteur-1173 P2 strain | Yes | 4 | 18 | 22 | 1 | 6 | 51 |
| | | | | (7.8%) | (35.3%) | (43.1%) | (2.0%) | (11.8%) | |
| [?] 55 | Before 1965 | Not implemented | Yes | 6 | 27 | 27 | 14 | 11 | 85 |
| | | | | (7.1%) | (31.8%) | (31.8%) | (16.5%) | (12.9%) | |
| Total | | | | 33 | 256 | 91 | 19 | 17 | 416 |

TST: tuberculin skin test; ARDS: acute respiratory distress syndrome.

**Table 2. Clinical Syndromes associated with COVID-19 in individuals vaccinated with Tokyo-172 BCG in Taiwan**

| **Age at onset (year)** | **Without neonatal BCG vaccination records** | **Without neonatal BCG vaccination reco** |
|---|---|---|
| | **Asymptomatic** | **Mild illness** |
| 4–24* | 1 (33.3%) | 2 (66.7%) |
| 25–33# | 6 (7.9%) | 56 (73.7%) |

*National Immunization Information System (NIIS) records were complete for those born after 1996 (age 24 years or younger).

#NIIS records might be incomplete for individuals born in 1997-1986 (age 25-33 years).