# Three-dose vaccination-induced immune responses protect against SARS-CoV-2 Omicron BA.2

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## Abstract

**Background:** The ongoing outbreak of SARS-CoV-2 Omicron BA.2 infections in Hong Kong, the world model city of universal masking, has resulted in a major public health crisis. Although the third heterologous BNT162b2 vaccination after 2-dose CoronaVac generated higher neutralizing antibody responses than the third homologous CoronaVac booster, vaccine efficacy and corelates of immune protection against the major circulating Omicron BA.2 remains to be investigated. **Methods:** We investigated the vaccine efficacy against the Omicron BA.2 breakthrough infection among 481 public servants who had been received with SARS-CoV-2 vaccines including two-dose BNT162b2 (2×BNT, n=169), three-dose BNT162b2 (2×BNT, n=175), two-dose CoronaVac (2×CorV, n=37), three-dose CoronaVac (3×CorV, n=68) and third-dose BNT162b2 following 2×CorV (2×CorV+1BNT, n=32). Humoral and cellular immune responses after three-dose vaccination were characterized and correlated with clinical characteristics of BA.2 infection. **Results:** During the BA.2 outbreak, 29.3% vaccinees were infected. Three-dose vaccination provided protection with lower incidence rates of breakthrough infections (2×BNT 49.2% vs 3×BNT 16.6%, p<0.0001; 2×CorV 48.6% vs 3×CoV 20.6%, p=0.003). The third heterologous vaccination showed the lowest incidence (2×CorV+1×BNT 6.3%). Although BA.2 conferred the highest neutralization resistance compared with variants of concern tested, the third dose vaccination-activated spike-specific memory B and Omicron cross-reactive T cell responses contributed to reduced frequencies of breakthrough infection and disease severity. **Conclusions:** Our results have implications to timely boost vaccination and immune responses likely required for vaccine-mediated protection against Omicron BA.2 pandemic.

## Hosted file

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Figure 1

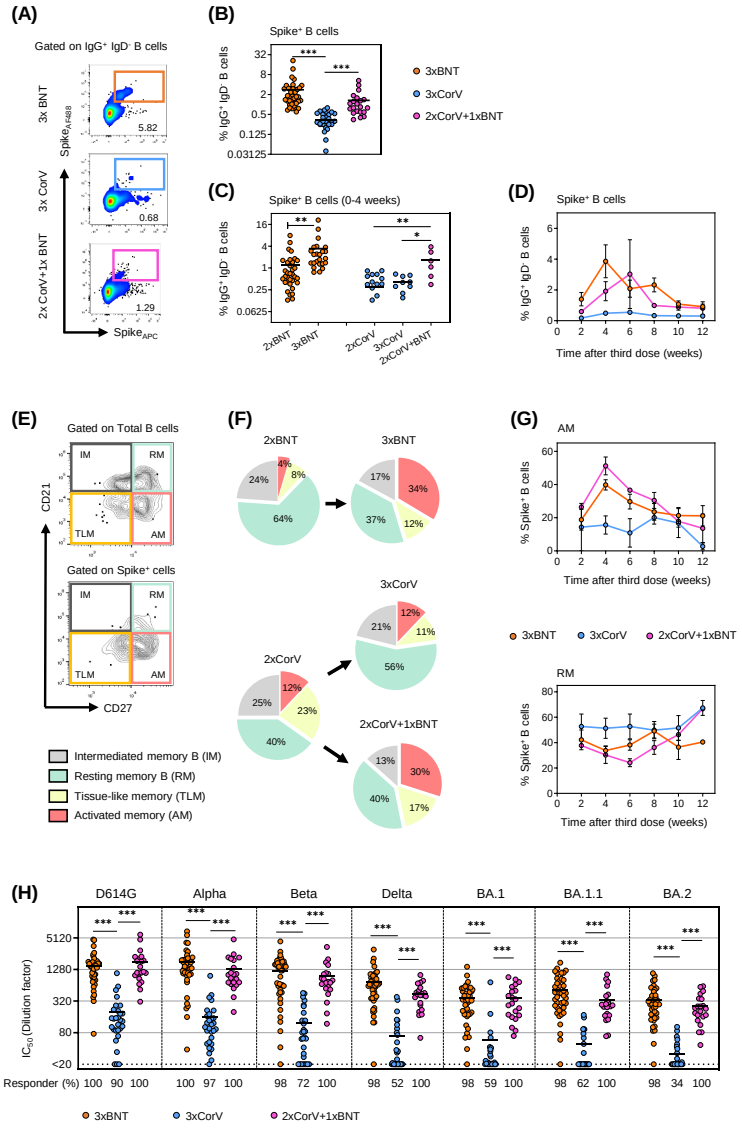

Figure 2

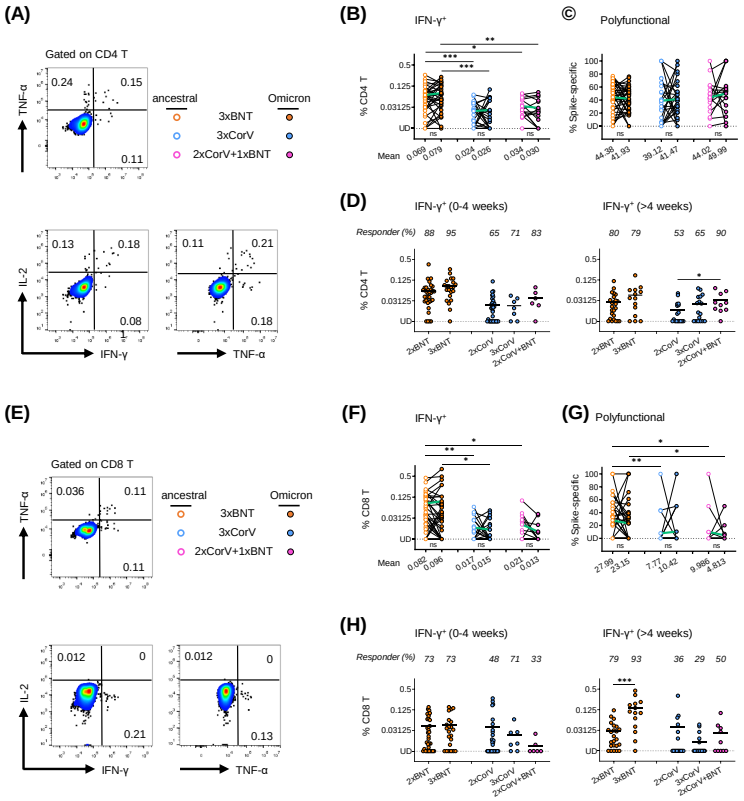

Figure 3

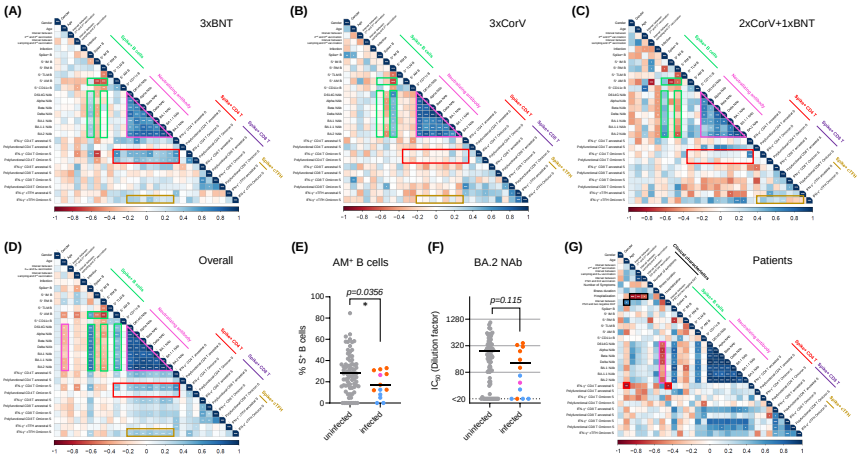

**Table 1. Demographic characteristics of breakthrough infection among 481 vaccinees**

| Vaccinations | 2xBNT (n=169) | 3xBNT (n=175) | 2xCorV (n=37) | 3xCorV (n=68) | 2xCorV+1xBNT (n=32) |
|---|---|---|---|---|---|
| Infection rate % (No. patient/Total No.) | 49.2% (78/169) | 16.6% (29/175) | 48.6% (18/37) | 20.6% (14/68) | 6.3% (2/32) |
| Patients | | | | | |
| Age, year (ranges in parentheses) | 32 (24-58) | 40 (27-60) | 45.5 (24-64) | 49 (20-62) | 47.5 (37-58) |
| Gender | | | | | |
| Male (% of all participants) | 60 (48.8%) | 20 (16.7%) | 11 (47.8%) | 9 (20%) | 2 (7.1%) |
| Female (% of all participants) | 18 (39.1%) | 9 (16.4%) | 7 (50%) | 5 (21.7%) | 0 (0%) |
| Median interval days between latest vaccination and symptom onset (ranges in parentheses) | 227 (140-332) | 45 (0-111) | 224 (4-341) | 53.5 (1-109) | 25.5 (10-41) |
| Asymptomatic rate % (No. Asymptomatic patient/No. total patient) | 3.8% (3/78) | 3.4% (1/29) | 0 % (0/18) | 0% (0/14) | 0% (0/2) |
| Disease severity | Mild | Mild | Mild | Mild | Mild |
| Number of symptoms (ranges in parentheses) | 4 (0-6) | 3 (0-5) | 3 (1-6) | 3 (1-5) | 3.5 (3-5) |
| Presentation to hospital % (No. patients presenting to hospital/No. total patient) | 19.2% (15/78) | 3.4% (1/29) | 22.2% (4/18) | 21.4% (3/14) | 50% (1/2) |
| Duration of illness, days (ranges in parentheses) | 7 (0-19) | 7 (0-19) | 8 (6-21) | 8 (2-14) | 9.5 (2-17) |
| The interval days between symptom onset and two negative RAT | 8 (1-20) | 9 (4-18) | 8 (6-12) | 9 (3-14) | 8 (5-11) |

Values displayed are medians, with ranges in parentheses