CDC’s May 25 MMWR report of 10,262 vaccine breakthrough infections in the U.S. is likely an underestimate. Herein, we report Veterans Health Administration (VHA) breakthrough cases, focusing on hospitalizations and deaths.

**Methods.** We extracted COVID-19 vaccine breakthrough infections tested between 1/19/2021 and 4/30/2021 from the VHA Corporate Data Warehouse (including screening tests). We reviewed medical records of cases who died and/or were hospitalized within 14 days of SARS-CoV-2 positive test for clinician documentation of conditions deemed high risk for COVID-19 and to confirm hospitalization or death was related to COVID-19. SARS-CoV-2 whole genome sequencing (Clear Labs platform) and antigen testing (Abbott BinaxNOW) from available patient samples were performed and Pangolin lineage determined.

**Results.** 1,142 COVID-19 vaccine breakthrough infections were identified. 357/1,142 (31.3%) were hospitalized and/or died. 1,085 (95%) were male (Table 1), and median age was 72.5 years (74 years for hospitalized/deceased patients). COVID-19 infection contributed to hospitalization and/or death in 139 (38.9%) cases. The remaining 218 (61.1%) were hospitalized or died of causes apparently unrelated to COVID-19. Smoking and heart conditions were seen most frequently among hospitalized/deceased breakthrough cases (Table 2). Variant B.1.1.7 was predominant, present in 17/27 (63%) total samples sequenced, and 13/21 (61.9%) hospitalized/deceased. Smoking and heart conditions were seen most frequently among hospitalized/deceased breakthrough cases (Table 2). Variant B.1.1.7 was predominant, present in 17/27 (63%) total samples sequenced, and 13/21 (61.9%) hospitalized/deceased. Smoking and heart conditions were seen most frequently among hospitalized/deceased breakthrough cases (Table 2).

**Conclusion.** Compared to CDC reported breakthrough infections, VHA cases were more male, older, and hospitalized/died at higher frequency. Further study is needed to determine the contribution of specific underlying conditions, COVID-19 vaccine formulations and variants on hospitalization and death among COVID-19 vaccine breakthrough infections. Sequencing efforts for breakthrough cases should be intensified, particularly for those presenting with more severe infections.

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### Table 1. Demographics of COVID-19 vaccine breakthrough cases, Veterans Health Administration, January – April 2021.

| Characteristic | Total Cases (%) | Hospitalized and/or Deceased Cases |
|---------------|----------------|-----------------------------------|
| Age Group     | N=1,142        | N=132                             |
| Under 60      | 29 (2.5)       | 9 (0.7)                           |
| 45-64         | 232 (18.0)     | 46 (3.2)                          |
| 65-74         | 760 (66.5)     | 230 (16.5)                        |
| 85 and older  | 143 (12.2)     | 68 (5.0)                          |
| Sex           |                |                                   |
| Female        | 577 (50.0)     | 9 (0.7)                           |
| Male          | 565 (50.0)     | 340 (27.8)                        |
| Race/Ethnicity|                |                                   |
| Black         | 346 (30.5)     | 68 (5.0)                          |
| Hispanic      | 310 (26.8)     | 30 (2.5)                          |
| White         | 729 (64.0)     | 246 (19.0)                        |
| Other*        | 34 (3.0)       | 12 (0.9)                          |
| Unknown       | 41 (3.6)       | 9 (0.7)                           |
| Rurality      |                |                                   |
| Rural         | 269 (23.5)     | 71 (5.5)                          |
| Urban         | 873 (76.5)     | 260 (19.3)                        |

*Other race/ethnicity includes American Indian or Alaskan Native, Asian, Mixed Race, Native Hawaiian or Other Pacific Islander, and Unknown.

### Table 2. High-risk medical conditions among patients hospitalized and/or deceased with COVID-19 vaccine breakthrough infection, Veterans Health Administration, January – April 2021. N=132.

| Condition* | Total (%) |
|------------|-----------|
| Cancer      | 85 (63.9) |
| Chronic Kidney Disease | 121 (92.5) |
| Chronic Lung Disease | 107 (80.9) |
| Dementia or Other Neurological Conditions | 56 (41.5) |
| Diabetes    | 172 (67.2) |
| Heart Conditions | 100 (76.9) |
| HIV Infection | 4 (3.1) |
| Immunocompromised State | 48 (36.3) |
| Liver Disease | 44 (33.3) |
| Obesity†    | 99 (72.7) |
| Smoking, Current or Former | 128 (96.2) |
| Solid Organ or Blood Stem Cell Transplant | 34 (25.9) |
| Stroke or Cerebrovascular Disease | 45 (32.0) |
| Substance Use Disorders | 57 (42.6) |

*Based on CDC’s list of underlying medical conditions associated with high-risk for severe COVID-19 [https://www.cdc.gov/coronavirus/2019-ncov/njurisdiction/underlyingconditions.html].†Obesity was based on chart documentation or BMI ≥30 kg/m².

### Table 3. SARS-CoV-2 variants among patients with breakthrough COVID-19 infection, Veterans Health Administration, January – April 2021.

| Pangolin Lineage (origin) | Total (N=27) | Hospitalized and/or Deceased (N=21) | SARS-CoV-2 Antigen Position (N=21) |
|---------------------------|-------------|-------------------------------------|-----------------------------------|
| B.1.1.7 (UK)              | 17 (63)     | 13 (61.5)                           | 5 (54.5)                          |
| P.1 (Brazil/Brasil)       | 2 (7.4%)    | 0 (0.0%)                            | 0 (0.0%)                          |
| B.1.351 (USA)             | 1 (3.7%)    | 1 (3.7%)                            | 1 (9.1%)                          |
| B.1.529 (USA - New York)  | 1 (3.7%)    | 1 (3.7%)                            | 1 (9.1%)                          |
| B.1.351 (Europe)          | 1 (3.7%)    | 0 (0.0%)                            | 0 (0.0%)                          |

### Background.

Immune responses to influenza vaccines (IV) are influenced by pre-existing antibodies to vaccine components. Immune responses to vaccines were evaluated following vaccination with quadrivalent egg-based live-attenuated influenza vaccine (LAIV4) and cell-culture inactivated influenza vaccine (ccIV4).

**Methods.** Racially diverse (48.0% non-white, healthy, community-dwelling children and young adults aged 4-21 years (median, 18.3 years) were randomized 1:1 in blocks of 4 to receive intramuscular ccIV4 (Flucelvax: n=100) or nasal LAIV4 (FluMist: n=98); baseline demographics were similar between groups. Blood was drawn at day 0 pre-vaccination and at day 28 (21-35 days) post vaccination. Hemagglutination inhibition (HI) assays against egg-grown A/H1N1, A/H3N2, both vaccine B/strains and cell-grown A/H3N2 antigens were conducted. Geometric mean titers (GMT) and geometric mean fold rise (GMFR) in titers were analyzed.

**Results.** Day 0 GMTs were similar for LAIV4 and ccIV4. Day 28 GMTs were higher for ccIV4 (p<0.05) and increased following vaccination for all 5 antigens (p<0.05) except B/Phuket following LAIV4. The GMFR range was 2.4 to 3.0 for ccIV4 and 1.0 to 1.3 for LAIV4. In linear regression controlling for age and prior season vaccination for both vaccines, baseline titers inversely predicted GMFR. The GMFR to A/H3N2 cell-grown and egg-grown antigens were similar within vaccine type.

**Conclusion.** The HI response to ccIV4 was greater than LAIV4 in this study of mostly older children. Day 0 HI titers were 1) a significant determinant of GMFR;
2) the strongest predictors of day 28 GMFR, and 3) more highly correlated (negatively) with GMFR following cIIV4 than LAIV4. For both IV, the GMFR for cell-grown and egg-grown A/H3N2 antigens did not differ within IV type. Future studies incorporating immunoglobulin and cellular immune responses may delineate differences between these IV types not observable through HI assays.

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100. Safety Analysis of Live-Attenuated Measles, Mumps, Rubella Vaccine Among Hematopoietic Cell Transplant Recipients Vaccinated Within Two Years of Transplant

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**Background.** Measles, mumps and rubella (MMR) vaccine is a live-attenuated vaccine usually contraindicated within the first two years of hematopoietic cell transplant (HCT). During the 2019 measles outbreak at our center, the benefits of administering MMR vaccine within the first two years after HCT were weighed against the potential risks.

**Methods.** We conducted a retrospective review of patients who received MMR vaccination within two years of an autologous or allogeneic HCT. Patients’ demographics, date, and type of HCT, underlying hematologic disease, type of immunosuppressive therapy and date of MMR vaccination were extracted from the electronic medical record. Adverse reactions that could be related to the vaccine were collected for up to 42 days post-vaccination and all hospitalizations and deaths following vaccination were reviewed.

**Results.** A total of 129 patients (75 autologous and 54 allogeneic HCT) were vaccinated between 300-729 days after HCT (median of 718 days). The median age at vaccination was 61 years old, 57% of the patients were male and 43% were on immunosuppressive therapy, 87% of whom were on maintenance therapy for multiple myeloma after auto-HCT. Seven patients (5%) had adverse reactions within 42 days of vaccination: six had respiratory tract infections (three with associated fever) and one had a rash leading to a brief hospitalization. This was a 37-year-old female who had an allogeneic HCT 542 days prior to MMR vaccination. She presented with a centrifugal maculopapular rash that was confirmed to be caused by the vaccine strain rubella virus (Fig 1). She fully recovered without sequelae. There was no other vaccine-associated illness identified in the cohort, after a median follow-up of 676 days.

**Conclusion.** MMR vaccine appears to be well tolerated in selected HCT recipients when given earlier than 2 years after transplant. No attributable severe outcomes or deaths were described. A mild uncomplicated case of vaccine-associated rubella illness was seen after vaccination. In the setting of a measles outbreak, assessment of potential risks and benefits of MMR vaccination given within two years of HCT remains important.

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