

Which Comorbidities Increase the Risk of a COVID-19 Breakthrough Infection?

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Abstract: Solid organ transplant, pregnancy, and immune system deficiencies are associated with greater rates of COVID-19 breakthrough infections after vaccination.

Underlying medical conditions associated with high risk for severe COVID-19 are outlined by the CDC.¹ In this study, we quantify how certain comorbidities could affect the risk of a breakthrough COVID-19 case, defined as getting a COVID-19 infection after being fully vaccinated.

To evaluate the impact of each comorbidity on breakthrough COVID-19 rates, we compared fully vaccinated patients from similar communities by creating case and control pairs of vaccinated patients from the same state and primary care organization. In each pair, the control patient had the same comorbidity groups as the case patient except for the comorbidity of interest. For example, to assess the impact of Down syndrome, we evaluated a case patient with both Down syndrome and liver disease and compared that to a control patient with only liver disease.

Breakthrough Risk for Given Comorbidity

n=13,864,615 Odds Ratio 95% Confidence Interval

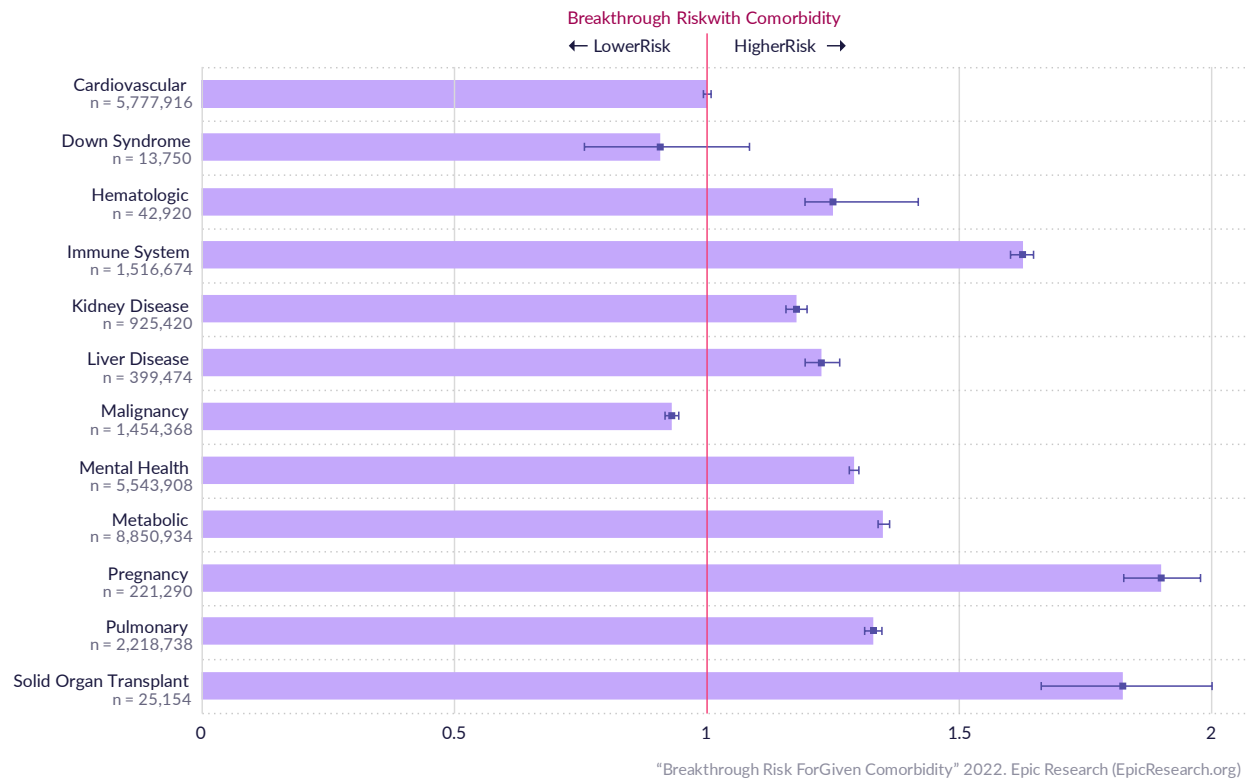


Figure 1. Risk of breakthrough COVID-19 infection for each comorbid condition. An odds ratio of 2 would mean that patients with that comorbidity were twice as likely to have a breakthrough infection.

We found that many of the comorbidity groups are at a higher risk of a breakthrough infection. Notably, pregnant individuals are 1.91 times more likely to have a breakthrough infection, individuals with a solid organ transplant are 1.83 times more likely, and individuals with an immune system deficiency are 1.63 times more likely.

However, in our study, we did not find that cancer or Down syndrome increased the risk of a breakthrough infection. This is consistent with other research on the rates of COVID-19 in populations with cancer versus populations without.²

These findings support the CDC’s recommendation that patients with a high-risk comorbidity may need to use enhanced infection prevention control beyond vaccination to minimize the risk of a COVID-19 breakthrough infection.³

These data come from Cosmos, a HIPAA-defined Limited Data Set of more than 140 million patients from 161 Epic organizations including 960 hospitals and 20,814 clinics, serving patients in all 50 states. This study was completed by two teams, each composed of a clinician and research scientists who worked independently. The two teams came to similar conclusions.

References

1. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html>. Published October 14, 2021.
2. Johannesen, T. B., Smeland, S., Aaserud, S., Buanes, E. A., Skog, A., Ursin, G., & Helland, Å. (2021). COVID-19 in Cancer Patients, Risk Factors for Disease and Adverse Outcome, a Population-Based Study From Norway. *Frontiers in oncology*, 11, 652535.
3. Centers for Disease Control and Prevention. COVID-19: People with Certain Medical Conditions. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Updated February 25, 2022.

Data Definitions

Term	Definition
Matched Pair	Case patients and control patients had the same state of residence, primary care organization, and comorbidity groups aside from the one being studied. All patients had received two doses of an mRNA COVID-19 vaccine.
Cardiovascular Group	Comorbidities of “Cerebrovascular Disease”, “Heart Failure”, “CAD”, “Cardiomyopathy”, “Hypertension”
Kidney Group	Comorbidities of “Chronic Kidney Disease”, “Kidney Transplant”
Metabolic Group	Comorbidities of “Type 1 Diabetes”, “Type 2 Diabetes”, “Gestational Diabetes”, “BMI Overweight”, “BMI Obese”
Pregnancy Group	Comorbidities of “Recent Pregnancy”

Mental Health Group	Comorbidities of “Mood Disorders”, “Schizophrenia Spectrum”, “Neurologic Conditions”, “Substance Use”
Hematologic Group	Comorbidities of “Sickling Disorder”, “Thalassemia”
Pulmonary Group	Comorbidities of “Interstitial Lung Disease”, “Pulmonary Embolus”, “Pulmonary Arterial Hypertension”, “Bronchopulmonary Dysplasia”, “Bronchiectasis”, “Chronic Obstructive Pulmonary Disease”, “Cystic Fibrosis”, “Any Asthma”, “Tuberculosis”
Liver Disease Group	Comorbidities of “Cirrhosis”, “Non-alcoholic Fatty Liver Disease”, “Autoimmune Hepatitis”, “Alcoholic Liver Disease”
Immune System Group	Comorbidities of “HIV”, “Immune Deficiencies”, “Steroid or Immuno Meds”
Down Syndrome Group	Comorbidities of “Down Syndrome”
Solid Organ Transplant Group	Comorbidities of “Solid Organ Transplant”
Malignancy Group	Comorbidities of “Cancer”
Cerebrovascular Disease	Any diagnosis mapped to SNOMED code 62914000.
Heart Failure	Any diagnosis mapped to SNOMED code 84114007 except cases where it’s also mapped to SNOMED code 56675007. Also, any diagnosis mapped to ICD-10 code I11.0, I13.0, I13.2 or I50* (except I50.21, I 50.31, I50.41, or I50.811).
Coronary Artery Disease	Any diagnosis mapped to SNOMED code 53741008, 63739005, 67682002, 429673002, or 445512009 or ICD-10 code I25.1*, I25.7*, I25.81*, I25.82, or I25.83.
Cardiomyopathy	Any diagnosis mapped to SNOMED code 85898001 or ICD-10 code A36.81, B33.24, I25.5, I42*, or I43, except cases where it’s also mapped to SNOMED code 281666001, 312850006, or 765205004.
Hypertension	Any diagnosis mapped to SNOMED code 38341003 or ICD-10 code I10*, I11*, I12*, I13*, or I15*, except cases where it’s also mapped to ICD-10 code O13*, O14*, or O15*.
Chronic Kidney Disease	Any diagnosis mapped to SNOMED code 431855005, 431856006, 433144002, or 431857002 or ICD-10 code I12.9, I13.0, I13.10, N18.1, N18.2, N18.3, N18.4, or N18.9.
Kidney Transplant	Any diagnosis mapped to SNOMED code 70536003 or ICD-10 code Z94.0.
Type 1 Diabetes	Any diagnosis mapped to SNOMED code 46635009 or 420868002 or ICD-10 code E10*, except cases where it’s also mapped to SNOMED code 11687002 or ICD-10 code O24.4*.
Type 2 Diabetes	Any diagnosis mapped to SNOMED code 44054006 or 422014003 or ICD-10 code E11*, except cases where it’s also mapped to SNOMED code 11687002, 46635009, or 420868002 or ICD-10 code E10* or O24.4*.
Gestational Diabetes	Any diagnosis mapped to SNOMED code 11687002 or ICD-10 code O24.4*.

Overweight	A patient whose most recent BMI calculation was greater than or equal to 25 and less than 30.
Obese	A patient whose most recent BMI calculation was 30 or greater.
Recent Pregnancy	A patient who was documented as having an active pregnancy on any visit between 42 days prior to their second vaccination administration and 180 days after their second vaccination administration.
Mood Disorders	Any diagnosis mapped to SNOMED code 74732009 or mapped to CCRS categories MBD001-MBD013.
Schizophrenia Spectrum	Any diagnosis mapped to SNOMED code 58214004 or ICD-10 code F20*.
Neurologic Conditions	Any diagnosis mapped to ICD-10 code G30*, G31*, or G32*.
Substance Use	Any diagnosis mapped to CCRS categories MBD017-MBD025 or MBD029-MBD033 as well as patients who reported actively using or abusing substances.
Sickling Disorder	Any diagnosis mapped to SNOMED code 417357006. Also, any diagnosis mapped to ICD-10 code D57*, except cases where it's also mapped to ICD-10 code D57.3.
Thalassemia	Any diagnosis mapped to SNOMED code 40108008 or ICD-10 code D56*.
Interstitial Lung Disease	Any diagnosis mapped to SNOMED code 233703007.
Pulmonary Embolus	Any diagnosis mapped to ICD-10 code I26*.
Pulmonary Arterial Hypertension	Any diagnosis mapped to SNOMED code 11399002.
Bronchopulmonary Dysplasia	Any diagnosis mapped to SNOMED code 67569000 or ICD-10 code P27.1, P27.8, or P27.9.
Bronchiectasis	Any diagnosis mapped to SNOMED code 12295008 or ICD-10 code J47, J47.0, J47.1, J47.9, Q33.4, or Q89.3.
Chronic Obstructive Pulmonary Disease	Any diagnosis mapped to SNOMED code 1364500, 45145000, 185086009, 195951007, or 425748003 or ICD-10 code J43* or J44*.
Cystic Fibrosis	Any diagnosis mapped to SNOMED code 190905008 or ICD-10 code E84*.
Any Asthma	Any diagnosis mapped to SNOMED code 195967001 or ICD-10 code J45*.
Tuberculosis	Any diagnosis mapped to ICD-10 code A15*, A17*, A18*, or A19*. (Note that patients with latent tuberculosis (ICD-10 code Z22.7) are not considered).
Cirrhosis	Any diagnosis mapped to SNOMED code 19943007 or ICD-10 code K74* or K70.3*.
Non-alcoholic Fatty Liver Disease	Any diagnosis mapped to SNOMED code 197315008 or ICD-10 code K76.0.
Autoimmune Hepatitis	Any diagnosis mapped to SNOMED code 408335007 or ICD-10 code K75.4.
Alcoholic Liver Disease	Any diagnosis mapped to ICD-10 code K70*.

HIV	Any diagnosis mapped to SNOMED code 62479008, 86406008, 165816005, or 420721002 or ICD-10 code B20, B97.35, or O98.7*.
Immune Deficiencies	Any diagnosis mapped to SNOMED code 234532001 or ICD-10 code D80*, D81*, D82*, D83*, D84*, or D89*.
Steroid or Immunosuppressive Medications	Any medication prescribed in the year prior to the patient’s second vaccination that has a pharmaceutical class of “GLUCOCORTICOIDS.” Also, any medication with a pharmaceutical class of “AGENTS TO TREAT MULTIPLE SCLEROSIS”, “ANTI-ARTHRITIC, FOLATE ANTAGONIST AGENTS”, “ANTI-INFLAMMATORY TUMOR NECROSIS FACTOR INHIBITOR”, “ANTINEOPLAST,HISTONE DEACETYLASE (HDAC) INHIBITORS”, “ANTINEOPLASTIC - ALKYLATING AGENTS”, “ANTINEOPLASTIC – ANTIMETABOLITES”, “ANTINEOPLASTIC - BRAF KINASE INHIBITORS”, “ANTINEOPLASTIC - JANUS KINASE (JAK) INHIBITORS”, “ANTINEOPLASTIC - MEK1 AND MEK2 KINASE INHIBITORS”, “ANTINEOPLASTIC - MTOR KINASE INHIBITORS”, “ANTINEOPLASTIC IMMUNOMODULATOR AGENTS”, “ANTINEOPLASTIC SYSTEMIC ENZYME INHIBITORS”, “ANTINEOPLASTIC-ISOCITRATE DEHYDROGENASE INHIBITORS”, “ANTIPSORIATIC AGENTS,SYSTEMIC”, “ANTIPSORIATICS AGENTS”, “IMMUNOMODULATOR,B-LYMPHOCYTE STIM(BLYS)-SPEC INHIB”, “IMMUNOMODULATORS”, “IMMUNOSUPP - MONOCLONAL AB INHIBITING T LYMPH FXN”, “IMMUNOSUPPRESSANT-INTERFERON GAMMA INHIBITOR, MAB”, “IMMUNOSUPPRESSIVES”, “INTEGRIN RECEPTOR ANTAGONIST, MONOCLONAL ANTIBODY”, “INTERLEUKIN-6 (IL-6) RECEPTOR INHIBITORS”, “JANUS KINASE (JAK) INHIBITORS”, or “MONOCLONAL ANTIBODY-HUMAN INTERLEUKIN 12/23 INHIB” or a pharmaceutical subclass of “Antileprotic – Immunomodulators”, “Antineoplastic Enzyme Inhibitors” “Antipsoriatics”, “Antirheumatic - Enzyme Inhibitors”, “Anti-TNF-alpha - Monoclonal Antibodies”, “Immunomodulators”, “Immunosuppressive Agents”, “Interleukin-6 Receptor Inhibitors”, “Soluble Tumor Necrosis Factor Receptor Agents”, or “Systemic Lupus Erythematosus Agents” or are mapped to RxNorm code 103, 5880, 5882, 6851, 75917, 75917, 191831, 253453, 612937, 709271, 847083, 847083, 1538097, 1538097, or 2274378.
Down Syndrome	Any diagnosis mapped to SNOMED code 41040004 or ICD-10 code Q90*.
Solid Organ Transplant	Any diagnosis mapped to SNOMED code 18027006, 32413006, 61535006, 62438007, 70536003, 88039007, 161665007, 161666008, 161671001, 161672008, 175902000, 313030004, 313039003, 698362007, or 698367001, except where the record name contains the text “pre-heart”, “pre heart”, “pre-kidney”, “pre kidney”, “pre-liver”, “pre liver”, “pre-lung”, “pre lung”, “pre-transplant”, or “pre transplant”. Also, any diagnosis mapped to ICD-10 code T86.1*, T86.2*, T86.3*, T86.4*, T86.81*, T86.85*, Z48.28*, Z94.0, Z94.1, Z94.2, Z48.21, Z48.214, Z48.22, Z48.23, Z94.3, Z94.4, Z94.82, or Z94.83.

Also, any completed procedure mapped to CPT code 32851, 32852, 32853, 32854, 33935, 33945, 44135, 44136, 47135, 47136, 48160, 48552, 48554, 50360, or 50365, HCPCS code S2053, S2054, S2060, S2065, or S2152, ICD-9-CM Volume 3 code 33.5, 33.50, 33.51, 33.52, 37.51, 50.5, 50.51, 50.59, 55.6, 55.61, or 55.69, or ICD-10-PCS code 02Y, 02YA, 02YA0, 02YA0Z, 02YA0Z0, 02YA0Z1, 02YA0Z2, 0BY, 0BYC, 0BYC0, 0BYC0Z, 0BYC0Z0, 0BYC0Z1, 0BYC0Z2, 0BYD, 0BYD0, 0BYD0Z, 0BYD0Z0, 0BYD0Z1, 0BYD0Z2, 0BYF, 0BYF0, 0BYF0Z, 0BYF0Z0, 0BYF0Z1, 0BYF0Z2, 0BYG, 0BYG0, 0BYG0Z, 0BYG0Z0, 0BYG0Z1, 0BYG0Z2, 0BYH, 0BYH0, 0BYH0Z, 0BYH0Z0, 0BYH0Z1, 0BYH0Z2, 0BYJ, 0BYJ0, 0BYJ0Z, 0BYJ0Z0, 0BYJ0Z1, 0BYJ0Z2, 0BYK, 0BYK0, 0BYK0Z, 0BYK0Z0, 0BYK0Z1, 0BYK0Z2, 0BYL, 0BYL0, 0BYL0Z, 0BYL0Z0, 0BYL0Z1, 0BYL0Z2, 0BYM, 0BYM0, 0BYM0Z, 0BYM0Z0, 0BYM0Z1, 0BYM0Z2, 0DY8, 0DY80, 0DY80Z, 0DY80Z0, 0DY80Z1, 0DY80Z2, 0DYE, 0DYE0, 0DYE0Z, 0DYE0Z0, 0DYE0Z1, 0DYE0Z2, 0FY, 0FY0, 0FY00, 0FY00Z, 0FY00Z0, 0FY00Z1, 0FY00Z2, 0FYG, 0FYG0, 0FYG0Z, 0FYG0Z0, 0FYG0Z1, 0FYG0Z2, 0TY0, 0TY00, 0TY00Z, 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY1, 0TY10, 0TY10Z, 0TY10Z0, 0TY10Z1, or 0TY10Z2.