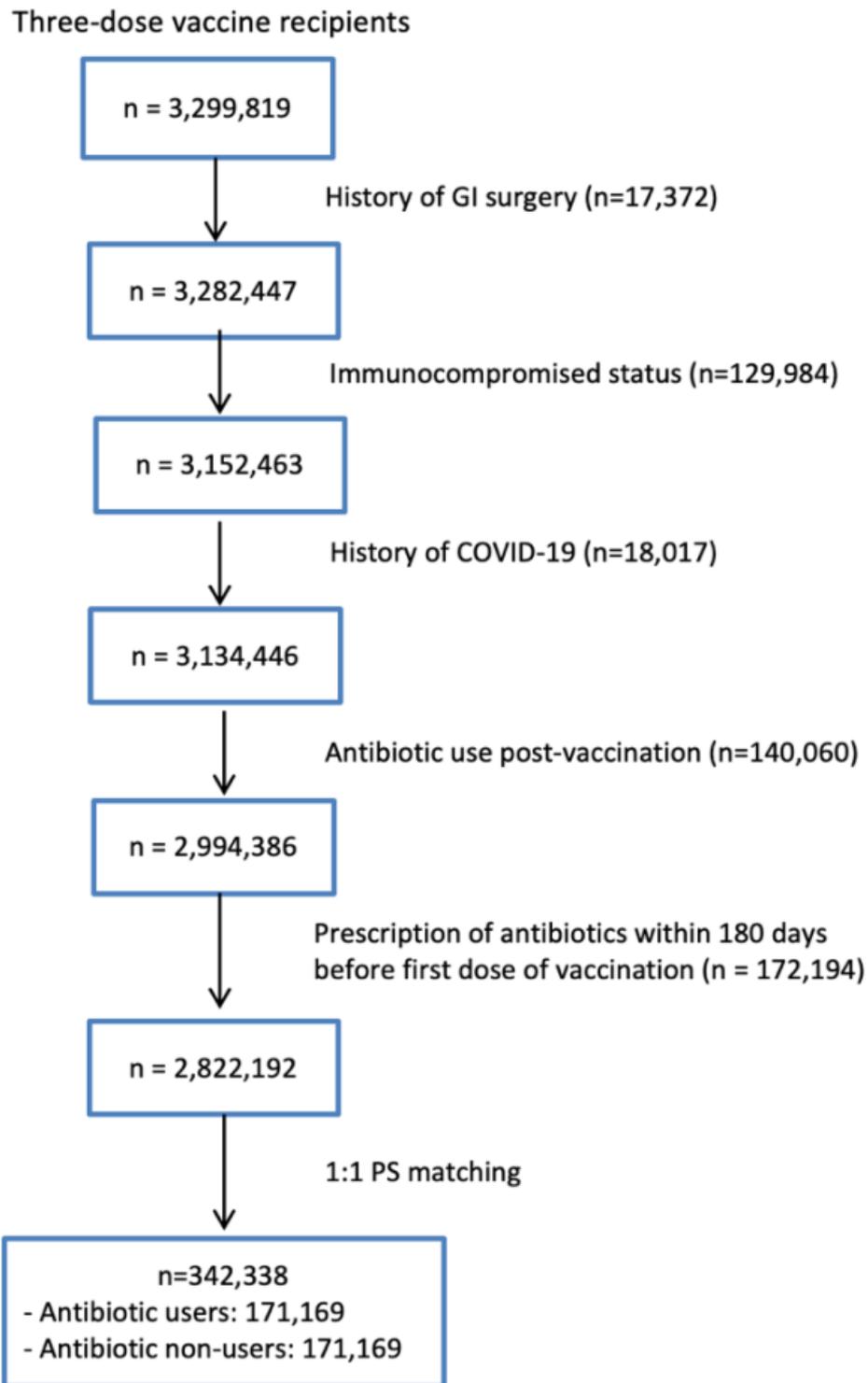


Figure S1. Patient selection flow chart



Abbreviations: GI, gastrointestinal; PS, propensity score

Table S1. Baseline characteristics of pre-vaccination antibiotic users and non-users before propensity score matching

| | Pre-vaccination antibiotic non-users (n=2,822,192) | Pre-vaccination antibiotic users (n=172,194) | SMD |
|--------------------------------------------------|----------------------------------------------------------|----------------------------------------------------|--------|
| Age, years (mean (SD)) | 53.18 (17.4) | 57.70 (19.2) | 0.247 |
| Sex, male (%) | 1257206 (44.5) | 78307 (45.5) | 0.019 |
| Charlson Comorbidity Index (mean (SD)) | 0.19 (0.5) | 0.42 (0.8) | 0.338 |
| Vaccine platform - CoronaVac (%) | 1383371 (49.0) | 93930 (54.5) | 0.111 |
| Received 3 rd dose (%) | 1.00 (0.0) | 1.00 (0.0) | <0.001 |
| Comorbidities – no. (%) | | | |
| Hypertension | 623388 (22.1) | 51870 (30.1) | 0.184 |
| Diabetes mellitus | 302934 (10.7) | 26720 (15.5) | 0.142 |
| Dyslipidemia | 386163 (13.7) | 29597 (17.2) | 0.097 |
| Cardiovascular diseases | 665681 (23.6) | 58098 (33.7) | 0.226 |
| Respiratory diseases | 39219 (1.4) | 9924 (5.8) | 0.237 |
| Obesity diagnosis | 115041 (4.1) | 8697 (5.1) | 0.047 |
| Smoking | 25466 (0.9) | 2342 (1.4) | 0.043 |
| Alcohol use disorders | 7738 (0.3) | 1096 (0.6) | 0.054 |
| Ulcers | 19689 (0.7) | 4035 (2.3) | 0.135 |
| Moderate-severe liver disease | 1218 (0.0) | 388 (0.2) | 0.050 |
| Chronic renal failure | 19664 (0.7) | 3586 (2.1) | 0.119 |
| Medication use in past 6 months – no. (%) | | | |
| ACEIs | 180282 (6.4) | 15904 (9.2) | 0.106 |
| ARBs | 202335 (7.2) | 18309 (10.6) | 0.122 |
| Metformin | 272156 (9.6) | 21490 (12.5) | 0.091 |
| Lipid lowering agents | 547298 (19.4) | 46558 (27.0) | 0.182 |
| Antiplatelets | 196034 (6.9) | 23520 (13.7) | 0.222 |
| NSAIDs | 143631 (5.1) | 26609 (15.5) | 0.346 |
| Oral anticoagulants | 24595 (0.9) | 5056 (2.9) | 0.152 |
| Steroids | 6506 (0.2) | 5063 (2.9) | 0.218 |
| Antidepressants | 111354 (3.9) | 13145 (7.6) | 0.158 |
| Antiviral drugs | 30518 (1.1) | 3305 (1.9) | 0.069 |
| PPIs | 187323 (6.6) | 37412 (21.7) | 0.443 |
| H2RAs | 280432 (9.9) | 38856 (22.6) | 0.347 |

SMD: standardized mean difference, SD: standard deviation, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, NSAIDs: non-steroidal anti-inflammatory drugs, PPIs: proton pump inhibitors, H2RAs: H2 receptor antagonists

Table S2. Anti-anaerobic/anti-aerobic activity and anti-bacterial spectrum of various classes of antibiotics

| Class | Route | Anti-anaerobic/ anti-aerobic activity | Anti-bacterial spectrum |
|------------------------------|---------------|------------------------------------------|----------------------------|
| <i>Penicillins</i> | | | |
| Benzylpenicillin | Intravenous | Anti-aerobic | Narrow spectrum |
| Phenoxymethylpenicillin | Oral | Anti-aerobic | Narrow spectrum |
| Benzathine penicillin G | Intramuscular | Anti-aerobic | Narrow spectrum |
| Penicillin G procaine | Intramuscular | Anti-aerobic | Narrow spectrum |
| Cloxacillin | Oral | Anti-aerobic | Narrow spectrum |
| | Intravenous | Anti-aerobic | Narrow spectrum |
| Flucloxacillin | Oral | Anti-aerobic | Narrow spectrum |
| | Intravenous | Anti-aerobic | Narrow spectrum |
| Amoxicillin +/- clavulanate | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| Ampicillin +/- sulbactam | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| Piperacillin +/- tazobactam | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| Ticarcillin + clavulanate | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| <i>Cephalosporins</i> | | | |
| Cefazolin | Intravenous | Anti-aerobic | Narrow spectrum |
| Cefuroxime | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| Ceftibuten | Oral | Anti-aerobic | Broad spectrum |
| Ceftazidime | Intravenous | Anti-aerobic | Broad spectrum |
| Ceftriaxone | Intravenous | Anti-aerobic | Broad spectrum |
| | Intramuscular | Anti-aerobic | Broad spectrum |
| Cefotaxime | Intravenous | Anti-aerobic | Broad spectrum |
| Cefepime | Intravenous | Anti-aerobic | Broad spectrum |
| Cefaclor | Oral | Anti-anaerobic | Broad spectrum |
| Cefoperazone + Sulbactam | Intravenous | Anti-anaerobic | Broad spectrum |
| Cefoxitin | Intravenous | Anti-anaerobic | Broad spectrum |
| Ceftaroline | Intravenous | Anti-anaerobic | Broad spectrum |
| <i>Macrolides</i> | | | |
| Azithromycin | Oral | Anti-aerobic | Narrow spectrum |
| | Intravenous | Anti-aerobic | Narrow spectrum |
| Erythromycin | Oral | Anti-aerobic | Narrow spectrum |
| | Intravenous | Anti-aerobic | Narrow spectrum |
| Clarithromycin | Oral | Anti-aerobic | Narrow spectrum |
| | Intravenous | Anti-aerobic | Narrow spectrum |
| <i>Carbapenems</i> | | | |
| Imipenem + cilastatin sodium | Intravenous | Anti-anaerobic | Broad spectrum |
| Ertapenem | Intravenous | Anti-anaerobic | Broad spectrum |
| Meropenem | Intravenous | Anti-anaerobic | Broad spectrum |
| <i>Monobactams</i> | | | |
| Aztreonam | Intravenous | Anti-aerobic | Narrow spectrum |
| <i>Quinolones</i> | | | |
| Ciprofloxacin | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| Levofloxacin | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| Moxifloxacin | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |

| | | | |
|------------------------|---------------|----------------|-----------------|
| <i>Tetracyclines</i> | | | |
| Tetracycline | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| Doxycycline | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| Minocycline | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| <i>Tigecyclines</i> | | | |
| Oxytetracycline | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| | Intramuscular | Anti-aerobic | Broad spectrum |
| <i>Aminoglycosides</i> | | | |
| Gentamicin | Intravenous | Anti-aerobic | Broad spectrum |
| Amikacin | Intravenous | Anti-aerobic | Broad spectrum |
| Neomycin | Oral | Anti-aerobic | Broad spectrum |
| Tobramycin | Oral | Anti-aerobic | Broad spectrum |
| | Intravenous | Anti-aerobic | Broad spectrum |
| Streptomycin | Intravenous | Anti-aerobic | Narrow spectrum |
| <i>Nitroimidazoles</i> | | | |
| Metronidazole | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| Tinidazole | Oral | Anti-anaerobic | Broad spectrum |
| <i>Glycopeptides</i> | | | |
| Vancomycin | Oral | Anti-aerobic | Narrow spectrum |
| | Intravenous | Anti-aerobic | Narrow spectrum |
| Teicoplanin | Intravenous | Anti-aerobic | Narrow spectrum |
| <i>Others</i> | | | |
| Clindamycin | Oral | Anti-anaerobic | Narrow spectrum |
| | Intravenous | Anti-anaerobic | Narrow spectrum |
| <i>Linezolid</i> | | | |
| | Oral | Anti-anaerobic | Narrow spectrum |
| | Intravenous | Anti-anaerobic | Narrow spectrum |
| <i>Seprin</i> | | | |
| | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| <i>Nitrofurantoin</i> | | | |
| | Oral | Anti-aerobic | Narrow spectrum |
| <i>Rifampicin</i> | | | |
| | Oral | Anti-anaerobic | Broad spectrum |
| | Intravenous | Anti-anaerobic | Broad spectrum |
| <i>Rifaximin</i> | | | |
| | Oral | Anti-anaerobic | Broad spectrum |
| <i>Daptomycin</i> | | | |
| | Intravenous | Anti-aerobic | Narrow spectrum |

Table S3. Association between pre-vaccination use of different classes of antibiotics and COVID-19 outcomes after vaccination with three doses of BNT162b2/CoronaVac

| | Events | Person-days | No. of persons | Incidence rate (per 100,000 person-days) | Adjusted IRR (95% CI) |
|----------------------------------------------------------------------|--------|-------------|----------------|------------------------------------------------|-----------------------|
| <i>COVID-19</i> | | | | | |
| Never users | 21110 | 66365213 | 171169 | 31.8 | - |
| Penicillins | 20021 | 53458790 | 140883 | 37.5 | 1.17 (1.15-1.19) |
| Cephaloporins | 679 | 1779927 | 5306 | 38.1 | 1.12 (1.04-1.21) |
| Macrolides | 1133 | 3062706 | 7850 | 37.0 | 1.12 (1.05-1.19) |
| Carbapenems | 169 | 325332 | 1179 | 51.9 | 1.35 (1.16-1.58) |
| Monobactams | 0 | 843 | 3 | 0 | - |
| Quinolones | 2513 | 6559990 | 18024 | 38.3 | 1.16 (1.11-1.21) |
| Tetracyclines | 1004 | 2662873 | 7048 | 37.7 | 1.20 (1.13-1.28) |
| Aminoglycosides | 55 | 108485 | 354 | 50.7 | 1.45 (1.11-1.89) |
| Nitroimidazoles | 1339 | 4255760 | 10342 | 31.5 | 1.04 (0.98-1.10) |
| Glycopeptides | 82 | 183190 | 668 | 44.7 | 1.14 (0.92-1.42) |
| Others | 1751 | 4693043 | 12472 | 37.3 | 1.20 (1.14-1.26) |
| <i>COVID-19-related hospitalization</i> | | | | | |
| Never users | 1550 | 70426545 | 171169 | 2.2 | - |
| Penicillins | 2433 | 57145992 | 140883 | 4.3 | 1.75 (1.64-1.87) |
| Cephaloporins | 161 | 1887260 | 5306 | 8.5 | 2.08 (1.77-2.46) |
| Macrolides | 92 | 3279104 | 7850 | 2.8 | 1.33 (1.07-1.65) |
| Carbapenems | 73 | 346055 | 1179 | 21.1 | 2.65 (2.08-3.37) |
| Monobactams | 0 | 843 | 3 | 0 | - |
| Quinolones | 456 | 6992431 | 18024 | 6.5 | 2.18 (1.96-2.42) |
| Tetracyclines | 160 | 2840762 | 7048 | 5.6 | 2.04 (1.73-2.40) |
| Aminoglycosides | 16 | 116588 | 354 | 13.7 | 3.36 (2.04-5.53) |
| Nitroimidazoles | 91 | 4512510 | 10342 | 2.0 | 1.46 (1.18-1.8) |
| Glycopeptides | 40 | 192094 | 668 | 20.8 | 2.68 (1.95-3.69) |
| Others | 227 | 5006170 | 12472 | 4.5 | 1.97 (1.71-2.27) |
| <i>Severe COVID-19 (ICU admission / ventilatory support / death)</i> | | | | | |
| Never users | 78 | 70655136 | 171169 | 0.1 | - |
| Penicillins | 118 | 57520763 | 140883 | 0.2 | 1.62 (1.22-2.16) |
| Cephaloporins | 6 | 1912331 | 5306 | 0.3 | 1.43 (0.62-3.31) |
| Macrolides | 3 | 3294143 | 7850 | 0.1 | 0.96 (0.30-3.08) |
| Carbapenems | 4 | 358083 | 1179 | 1.1 | 2.57 (0.92-7.20) |
| Monobactams | 0 | 843 | 3 | 0 | - |
| Quinolones | 19 | 7060202 | 18024 | 0.3 | 1.75 (1.06-2.91) |
| Tetracyclines | 8 | 2865757 | 7048 | 0.3 | 1.76 (0.84-3.70) |
| Aminoglycosides | 1 | 118600 | 354 | 0.8 | 4.21 (0.57-31.16) |
| Nitroimidazoles | 1 | 4526997 | 10342 | 0.02 | 0.36 (0.05-2.58) |
| Glycopeptides | 0 | 198652 | 668 | 0 | - |
| Others | 8 | 5041373 | 12472 | 0.2 | 1.37 (0.66-2.84) |

IRR: incidence rate ratio; CI: confidence interval