

ORIGINAL ARTICLE

Impact of Inactivated SARS-CoV-2 Vaccines on Serum Glycan Profiles and Protein N-Glycosylation

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SUMMARY

Background: This study aimed to investigate the effect of inactivated SARS-CoV-2 vaccines and booster shots on serum glycan profiles and protein N-glycosylation, specifically how vaccination influences glycan synthesis over time, how booster shots differentially impact populations with varying antibody titers, and which specific glycoproteins exhibit altered glycosylation. The goal was to explore a novel mechanism by which COVID-19 vaccines might exert antiviral effects through indirect inhibition of host glycosylation.

Methods: Serum glycan profiles were analyzed in individuals receiving two primary doses and a booster shot of inactivated SARS-CoV-2 vaccine, categorized by symptomatic status and antibody titers. Serum proteins were immobilized on AminoLink plus coupling resin, followed by sequential derivatization of α 2,6- and α 2,3-linked sialic acids. Glycans were released using PNGase F and analyzed by MALDI-TOF-MS with maltoheptaose as an internal standard. Glycoproteomics via LC-MS/MS identified site-specific protein glycosylation changes.

Results: Significant alterations in serum glycan profiles were observed. Overall glycan synthesis showed substantial suppression one-month post-vaccination, followed by gradual recovery. The booster vaccine inhibited glycan synthesis, and high-titer individuals exhibited a more pronounced N-glycan profile and faster recovery. Symptomatic status had no significant impact on glycan abundance. Glycoproteomic analysis revealed substantial alterations in glycosylation of stress and immune response proteins, including CP, HPX, SERPINA1, FN1, IgG, AGP, and C3, after vaccination.

Conclusions: This study demonstrates a novel mechanism: inactivated COVID-19 vaccines indirectly inhibit host glycosylation pathways. Vaccination significantly suppresses N-glycosylation, primarily reducing N-glycan abundance, with recovery influenced by antibody titer. These results highlight the intricate relationship between immune response, host glycosylation, and viral infection, suggesting avenues for developing novel therapeutic strategies targeting both the virus and host response to enhance antiviral protection.

(Clin. Lab. 2026;72:1-6. DOI: 10.7754/Clin.Lab.2025.250579)

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Manuscript accepted July 28, 2025

Supplementary Data

Table S3. Comparison of glycan relative abundance in low-titer and high-titer individuals with various symptoms following a month of post-vaccination.

| N-Glycan | m/z | FT | STD | MS | MS | NS | NS | Pain | Pain | SL | SL | Category |
|------------------|---------|-----|-----|-----|-----|--------|--------|------|------|--------|-------|--------------------|
| H5N2 | 1,257.2 | 22 | 6 | 12 | 11 | 3,841 | 2,195 | 91 | 22 | 1,097 | 257 | High-mannose |
| H3N3F1 | 1,282.9 | 29 | 9 | 3 | 1 | 320 | 209 | 74 | 25 | 195 | 59 | Fucose |
| H4N3 | 1,298.2 | 35 | 8 | 3 | 2 | 339 | 261 | 37 | 31 | 156 | 31 | Other |
| H3N4 | 1,339.3 | 22 | 7 | 3 | 2 | 509 | 174 | 31 | 8 | 295 | 120 | Other |
| H6N2 | 1,419.3 | 26 | 6 | 11 | 8 | 4,124 | 2,327 | 131 | 37 | 1,342 | 559 | High-mannose |
| H4N3F1 | 1,444.3 | 17 | 16 | 4 | 1 | 277 | 173 | 25 | 26 | 131 | 22 | Fucose |
| H3N4F1 | 1,485.3 | 38 | 2 | 115 | 66 | 13,503 | 13,647 | 388 | 131 | 3,190 | 1,344 | Fucose |
| H4N4 | 1,501.3 | 186 | 37 | 6 | 3 | 1,538 | 795 | 70 | 27 | 1,009 | 389 | Other |
| H3N5 | 1,542.1 | 21 | 6 | 3 | 2 | 176 | 121 | 13 | 5 | 221 | 92 | Other |
| H7N2 | 1,581.3 | 23 | 6 | 2 | 2 | 704 | 308 | 34 | 21 | 429 | 211 | High-mannose |
| H4N4F1 | 1,647.4 | 55 | 13 | 134 | 98 | 27,307 | 13,963 | 816 | 255 | 6,203 | 3,641 | Fucose |
| H5N4 | 1,663.4 | 373 | 81 | 4 | 2 | 4,846 | 3,166 | 96 | 30 | 954 | 354 | Other |
| H3N5F1 | 1,688.4 | 20 | 8 | 7 | 3 | 1,178 | 757 | 40 | 20 | 464 | 171 | Fucose |
| H4N5 | 1,704.2 | 15 | 11 | 3 | 1 | 205 | 229 | 23 | 6 | 259 | 94 | Other |
| H8N2 | 1,743.4 | 19 | 9 | 3 | 2 | 795 | 477 | 36 | 8 | 414 | 163 | High-mannose |
| H5N4F1 | 1,809.4 | 33 | 7 | 61 | 44 | 15,920 | 9,863 | 355 | 116 | 2,509 | 996 | Fucose |
| S(2,6)H4N4 | 1,820.4 | 18 | 2 | 3 | 1 | 275 | 206 | 24 | 12 | 185 | 64 | Sialic acid |
| S(2,3)H4N3F1 | 1,825.3 | 153 | 26 | 2 | 0 | 86 | 20 | 28 | 9 | 130 | 36 | Fucose-Sialic acid |
| H4N5F1 | 1,850.4 | 16 | 6 | 8 | 3 | 1,993 | 1,420 | 307 | 456 | 1,247 | 284 | Fucose |
| H5N5 | 1,866.4 | 41 | 15 | 3 | 1 | 153 | 127 | 19 | 10 | 143 | 45 | Other |
| H9N2 | 1,905.4 | 16 | 6 | 2 | 1 | 766 | 514 | 34 | 7 | 445 | 159 | High-mannose |
| H5N4F2 | 1,955.4 | 18 | 6 | 2 | 1 | 194 | 147 | 14 | 13 | 684 | 150 | Fucose |
| S(2,6)H4N4F1 | 1,966.5 | 21 | 8 | 3 | 1 | 368 | 300 | 22 | 9 | 234 | 36 | Fucose-Sialic acid |
| S(2,6)H5N4 | 1,982.5 | 32 | 6 | 31 | 23 | 20,793 | 13,414 | 336 | 94 | 4,160 | 378 | Sialic acid |
| H5N5F1 | 2,012.5 | 15 | 10 | 4 | 2 | 849 | 657 | 21 | 5 | 373 | 77 | Fucose |
| H5N4F3 | 2,101.3 | 14 | 4 | 2 | 1 | 67 | 32 | 11 | 6 | 265 | 127 | Fucose |
| S(2,6)H5N4F1 | 2,128.5 | 23 | 8 | 20 | 14 | 4,846 | 3,727 | 115 | 36 | 1,534 | 205 | Fucose-Sialic acid |
| H5N5F2 | 2,158.5 | 12 | 2 | 2 | 1 | 52 | 31 | 12 | 9 | 151 | 17 | Fucose |
| S(2,6)H5N5 | 2,184.5 | 17 | 3 | 2 | 1 | 186 | 137 | 18 | 4 | 202 | 12 | Sialic acid |
| H5N7 | 2,272.5 | 14 | 3 | 2 | 0 | 692 | 647 | 11 | 6 | 3,403 | 89 | Other |
| S2(2,6)H5N4 | 2,302.3 | 68 | 12 | 204 | 145 | 21,547 | 14,373 | 1360 | 411 | 12,364 | 620 | Sialic acid |
| S(2,6)H5N5F1 | 2,331.6 | 13 | 7 | 3 | 4 | 959 | 821 | 29 | 7 | 745 | 80 | Fucose-Sialic acid |
| S(2,6)H6N5 | 2,347.6 | 24 | 6 | 2 | 1 | 488 | 426 | 20 | 14 | 201 | 16 | Sialic acid |
| S(2,3)S(2,6)H5N4 | 2,362.7 | 14 | 5 | 2 | 1 | 18 | 4 | 25 | 9 | 135 | 32 | Sialic acid |
| S(2,6)H5N4F3 | 2,419.7 | 13 | 5 | 2 | 1 | 26 | 14 | 6 | 3 | 221 | 2 | Fucose-Sialic acid |
| S2(2,3)H5N4 | 2,424.5 | 14 | 2 | 1 | 1 | 5 | 3 | 21 | 2 | 69 | 39 | Sialic acid |

Table S3. Comparison of glycan relative abundance in low-titer and high-titer individuals with various symptoms following a month of post-vaccination (continued).

| N-Glycan | m/z | FT | STD | MS | MS | NS | NS | Pain | Pain | SL | SL | Category |
|-------------------|---------|----|-----|----|----|-----|-----|------|------|-----|----|--------------------|
| S2(2,6)H5N4F1 | 2,447.6 | 16 | 7 | 2 | 2 | 647 | 617 | 31 | 6 | 749 | 20 | Fucose-Sialic acid |
| S2(2,6)H5N5 | 2,505.8 | 9 | 4 | 1 | 1 | 17 | 8 | 9 | 9 | 64 | 20 | Sialic acid |
| S2(2,6)H5N5F1 | 2,650.7 | 7 | 4 | 1 | 1 | 124 | 111 | 11 | 7 | 306 | 6 | Fucose-Sialic acid |
| S2(2,6)H6N5 | 2,666.7 | 11 | 4 | 1 | 1 | 337 | 361 | 12 | 8 | 176 | 21 | Sialic acid |
| S2(2,6)H6N5F2 | 2,958.1 | 11 | 3 | 1 | 0 | 12 | 6 | 7 | 5 | 162 | 46 | Fucose-Sialic acid |
| S(2,3)S2(2,6)H6N5 | 3,047.2 | 8 | 5 | 1 | 1 | 4 | 1 | 5 | 4 | 107 | 15 | Sialic acid |

FT Fatigue, MS Multiple symptoms, NS No symptom, SL Sleep, STD Standard deviation.

Table S4. Glycan relative abundance in various symptoms following a month of post-vaccination.

| N-Glycan | m/z | NSL | STD | NSH | STD | FTL | STD | FTH | STD | SLL | STD | SLH | STD | Category |
|--------------|---------|-------|-------|-------|-------|-----|-----|-----|-----|-------|-------|-----|-------|--------------------|
| H5N2 | 1,257.2 | 1,166 | 335 | 2,331 | 96 | 21 | 6 | 45 | 18 | 1,086 | 235 | ### | 140 | High-mannose |
| H3N3F1 | 1,282.9 | 419 | 225 | 2,962 | 158 | 31 | 10 | 24 | 9 | 221 | 50 | 279 | 62 | Fucose |
| H4N3 | 1,298.2 | 384 | 248 | 523 | 32 | 32 | 8 | 21 | 17 | 156 | 31 | 195 | 84 | Other |
| H3N4 | 1,339.3 | 413 | 333 | 399 | 61 | 22 | 9 | 18 | 14 | 384 | 139 | 248 | 92 | Other |
| H6N2 | 1,419.3 | 1,766 | 452 | 460 | 76 | 25 | 6 | 55 | 10 | 1,255 | 303 | ### | 528 | High-mannose |
| H4N3F1 | 1,444.3 | 3,349 | 549 | 2,187 | 671 | 22 | 15 | 18 | 21 | 125 | 33 | 235 | 36 | Fucose |
| H3N4F1 | 1,485.3 | 3,943 | 1,042 | 432 | 49 | 53 | 13 | 479 | 59 | 4,143 | 2,163 | ### | 2,914 | Fucose |
| H4N4 | 1,501.3 | 1,294 | 350 | 6,490 | 388 | 257 | 49 | 345 | 72 | 776 | 198 | 706 | 320 | Other |
| H3N5 | 1,542.1 | 300 | 221 | 2,262 | 66 | 21 | 8 | 12 | 5 | 230 | 80 | 154 | 43 | Other |
| H7N2 | 1,581.3 | 770 | 261 | 326 | 35 | 23 | 8 | 21 | 16 | 340 | 138 | 344 | 72 | High-mannose |
| H4N4F1 | 1,647.4 | 4,956 | 803 | 872 | 102 | 63 | 7 | 496 | 104 | 5,094 | 667 | ### | 92 | Fucose |
| H5N4 | 1,663.4 | 1,582 | 362 | 9,134 | 416 | 499 | 92 | 387 | 13 | 760 | 138 | 895 | 326 | Other |
| H3N5F1 | 1,688.4 | 1,257 | 269 | 2,730 | 167 | 17 | 6 | 56 | 8 | 786 | 66 | 592 | 334 | Fucose |
| H4N5 | 1,704.5 | 294 | 212 | 1,575 | 671 | 7 | 1 | 45 | 6 | 307 | 117 | 194 | 60 | Other |
| H8N2 | 1,743.4 | 750 | 249 | 466 | 30 | 17 | 10 | 23 | 5 | 395 | 96 | 398 | 108 | High-mannose |
| H5N4F1 | 1,809.4 | 2,437 | 457 | 835 | 61 | 40 | 2 | 131 | 18 | 2,172 | 285 | ### | 255 | Fucose |
| S(2,6)H4N4 | 1,820.4 | 319 | 266 | 8,587 | 4,543 | 18 | 3 | 17 | 10 | 170 | 30 | 310 | 151 | Sialic acid |
| S(2,3)H4N3F1 | 1,825.3 | 420 | 223 | 355 | 27 | 234 | 30 | 87 | 16 | 135 | 41 | 165 | 28 | Fucose-Sialic acid |
| H4N5F1 | 1,850.4 | 788 | 196 | 552 | 86 | 13 | 4 | 53 | 12 | 886 | 67 | 687 | 91 | Fucose |
| H5N5 | 1,866.4 | 265 | 194 | 841 | 542 | 51 | 6 | 44 | 13 | 143 | 45 | 164 | 36 | Other |
| H9N2 | 1,905.4 | 680 | 252 | 2,813 | 72 | 14 | 6 | 30 | 5 | 357 | 140 | 894 | 137 | High-mannose |
| H5N4F2 | 1,955.4 | 1,023 | 202 | 894 | 48 | 16 | 5 | 13 | 8 | 770 | 203 | 848 | 91 | Fucose |
| S(2,6)H4N4F1 | 1,966.5 | 827 | 319 | 1,315 | 107 | 19 | 8 | 17 | 7 | 270 | 41 | 464 | 47 | Fucose-Sialic acid |
| S(2,6)H5N4 | 1,982.5 | 2,001 | 2,963 | 640 | 54 | 38 | 19 | 118 | 93 | 3,539 | 290 | ### | 1,768 | Sialic acid |
| H5N5F1 | 2,012.5 | 3,098 | 1,940 | 8,402 | 537 | 14 | 12 | 22 | 9 | 355 | 53 | 341 | 78 | Fucose |

Table S4. Glycan relative abundance in various symptoms following a month of post-vaccination (continued).

| N-Glycan | m/z | NSL | STD | NSH | STD | FTL | STD | FTH | STD | SLL | STD | SLH | STD | Category |
|-------------------|---------|--------|-------|--------|-------|-----|-----|-----|-----|-------|-------|-----|-------|--------------------|
| H5N4F3 | 2,101.3 | 678 | 230 | 1,100 | 140 | 13 | 5 | 17 | 13 | 324 | 92 | 541 | 44 | Fucose |
| S(2,6)H5N4F1 | 2,128.5 | 663 | 235 | 1,005 | 106 | 19 | 3 | 46 | 10 | 1,972 | 542 | ### | 607 | Fucose-Sialic acid |
| H5N5F2 | 2,158.5 | 212 | 175 | 251 | 30 | 11 | 2 | 13 | 10 | 151 | 18 | 201 | 34 | Fucose |
| S(2,6)H5N5 | 2,184.5 | 252 | 190 | 212 | 14 | 17 | 4 | 17 | 8 | 252 | 70 | 272 | 42 | Sialic acid |
| H5N7 | 2,272.5 | 557 | 197 | 459 | 42 | 13 | 4 | 15 | 9 | 4,180 | 745 | ### | 1,530 | Other |
| S2(2,6)H5N4 | 2,302.3 | 1,603 | 338 | 2,605 | 191 | 82 | 20 | 990 | 286 | #### | 2,900 | ### | 3,425 | Sialic acid |
| S(2,6)H5N5F1 | 2,331.6 | 14,036 | 1,761 | 26,945 | 1,618 | 10 | 5 | 25 | 6 | 769 | 302 | 890 | 379 | Fucose-Sialic acid |
| S(2,6)H6N5 | 2,347.6 | 1,007 | 241 | 1,814 | 130 | 26 | 4 | 25 | 7 | 204 | 24 | 320 | 56 | Sialic acid |
| S(2,3)S(2,6)H5N4 | 2,362.7 | 293 | 176 | 506 | 34 | 16 | 3 | 40 | 2 | 120 | 20 | 220 | 70 | Sialic acid |
| S(2,6)H5N4F3 | 2,419.7 | 320 | 178 | 349 | 46 | 11 | 4 | 13 | 9 | 310 | 78 | 488 | 83 | Fucose-Sialic acid |
| S2(2,3)H5N4 | 2,424.5 | 493 | 186 | 653 | 59 | 13 | 3 | 9 | 8 | 62 | 30 | 37 | 13 | Sialic acid |
| S2(2,6)H5N4F1 | 2,447.6 | 150 | 141 | 88 | 4 | 17 | 6 | 23 | 6 | 970 | 196 | ### | 1,018 | Fucose-Sialic acid |
| S2(2,6)H5N5 | 2,505.8 | 1,215 | 108 | 2,041 | 151 | 9 | 3 | 9 | 7 | 76 | 34 | 123 | 94 | Sialic acid |
| S2(2,6)H5N5F1 | 2,650.7 | 631 | 177 | 787 | 65 | 5 | 2 | 13 | 2 | 451 | 102 | 806 | 175 | Fucose-Sialic acid |
| S2(2,6)H6N5 | 2,666.7 | 391 | 183 | 459 | 78 | 10 | 5 | 13 | 5 | 229 | 78 | 556 | 130 | Sialic acid |
| S2(2,6)H6N5F2 | 2,958.1 | 145 | 84 | 248 | 72 | 10 | 3 | 6 | 4 | 183 | 40 | 262 | 38 | Fucose-Sialic acid |
| S(2,3)S2(2,6)H6N5 | 3,047.2 | 132 | 81 | 100 | 14 | 6 | 2 | 6 | 5 | 108 | 14 | 151 | 62 | Sialic acid |

NSL No symptom low titer, NSH No symptom high titer, FTL Fatigue low titer, FTH Fatigue high titer, SLL Sleep low titer, SLH Sleep high titer, STD Standard deviation.

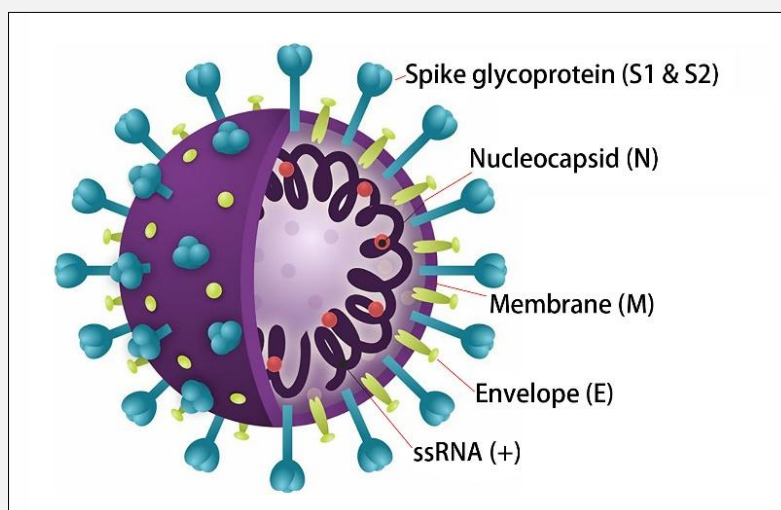


Figure S1. Schematic diagram of a coronavirus. A coronavirus is mainly composed of four main structural proteins: the spike glycoprotein (S), envelope glycoprotein (E), membrane glycoprotein (M), and nucleocapsid (N). Of these, the spike, envelope, and membrane proteins are glycosylated.

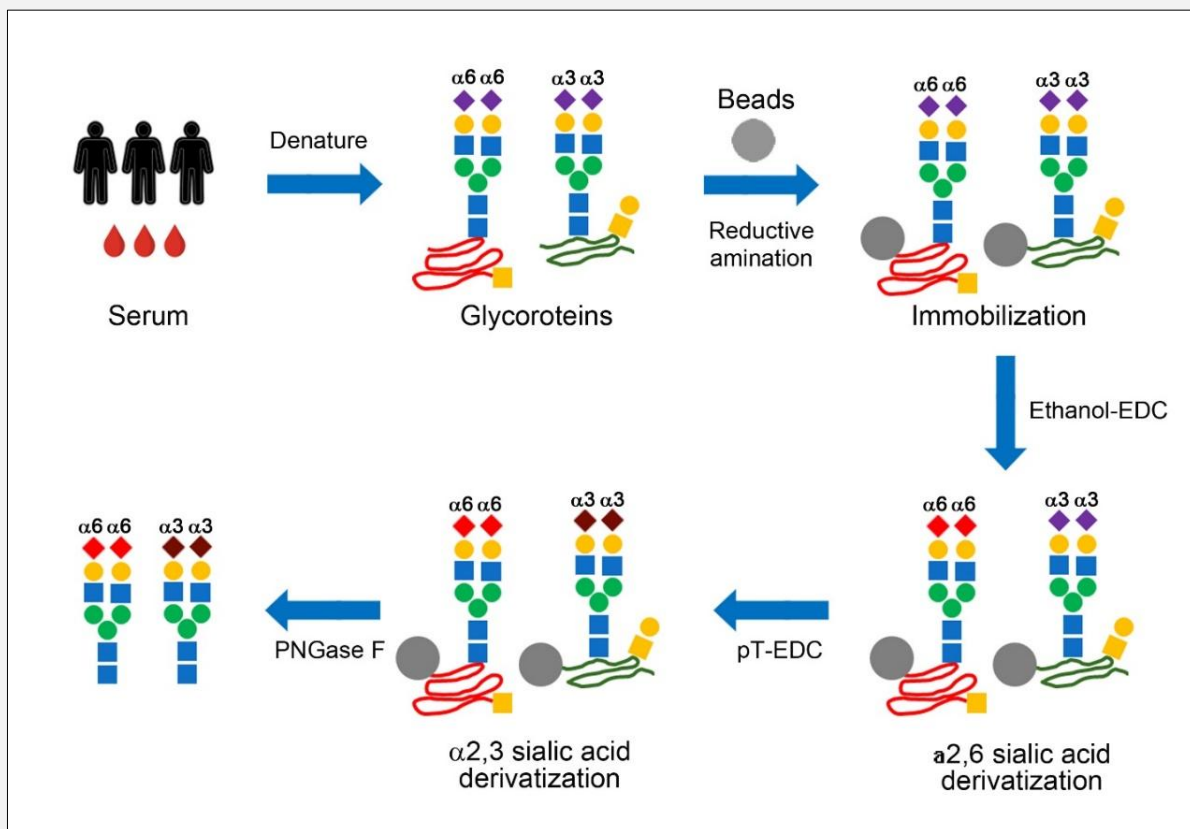


Figure S2. Schematic workflow of serum glycan analysis. Extracted glycoproteins are subjected to sialic acid linkage-specific derivatization, where α 2,6 linkages are modified with ethanol-EDC, and α 2,3 linkages are modified with p-toluidine carbodiimide coupling. N-glycans digested by PNGase F are characterized by MALDI-TOF-MS.

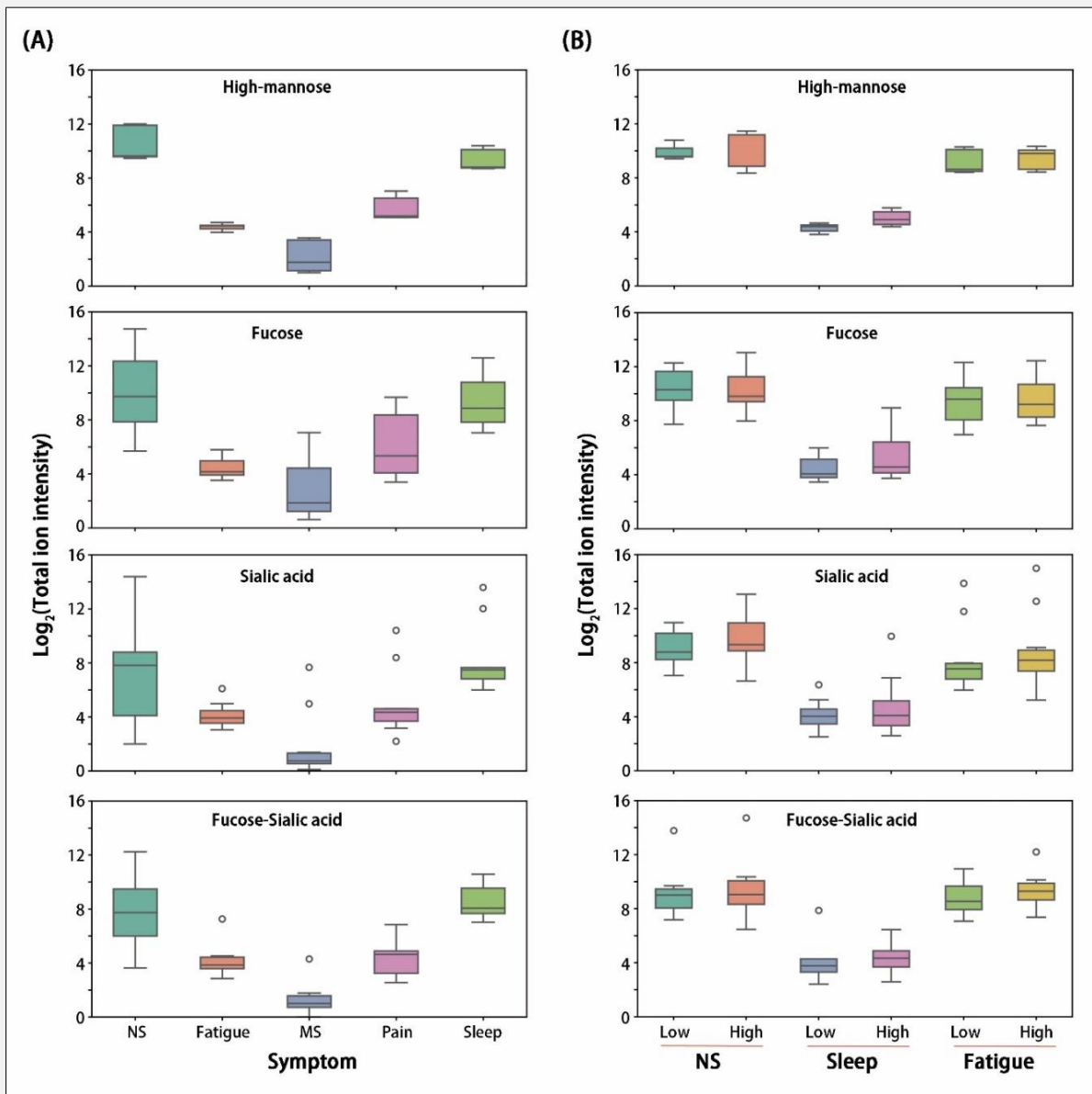


Figure S3. Glycan profile changes after one month following the second inactivated vaccination. The relative abundance of four major glycan types (high-mannose, fucose, sialic acid, and fucose-sialic acid) is present in individuals experiencing different symptoms after one month of vaccination. The y-axis shows the log-transformed total ion intensity, while the x-axis categorizes individuals based on their symptoms. A). Comparison of individuals with distinct symptom presentations. B) The relationship between glycan profiles and symptom severity within groups of individuals with low and high antibody titers. NS = No symptom, MS Multiple symptoms, high High titer, and low Low titer. (Table S1 Tab #1, #2, #5, #6, #7, #8, #25, #26, #27 and #28).