**Supplementary materials**

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**Table S1: Full search strategy**

|  |
| --- |
| Date of Search Performed:  26th January 2022 (Search from inception to 26th January 2022) and repeat search on 6th September 2023 (Search from 27th January 2022 to 6th September 2023) |
| Data bases searched:  MEDLINE, Embase, Web of Science, Virtual Health Library and Cochrane data bases using the OvidSP interface |
| Search terms:  (Pregnan\* [MeSH] OR matern\* [MeSH] OR expectan\* [MeSH])  AND (HIV OR AIDS)  AND (Vaccin\* [MeSH] OR immun\*[MeSH]).  MeSH headings were used in MEDLINE and Emtree terms in Embase, this was combined with the specific data base filters. |
| Restrictions:  No language restrictions |

**Table S2: Risk of Bias Assessment for Randomized Control Trials**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Bias assessed** | **Madhi et al; 2014** | **Nunes et al; 2018** | **Nunes et al; 2020** | **Nunes et al; 2015** | **Dhar N et al; 2020** | **Duarte et al; 2022** | **Weinberg et al; 2021** |
| 1 | Random sequence generation (selection bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 2 | Allocation concealment (selection bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 3 | Blinding of participants and personnel (performance bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 4 | Blinding of outcome assessment (detection bias) | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Low risk | Unclear risk |
| 5 | Incomplete outcome data (attrition bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 6 | Selective reporting (reporting bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 7 | Other bias | None found | None found | None found | None found | None  found | None  found | None found |
| OVERALL RISK OF BIAS | | Low | Low | Low | Low | Low | Low | Low |

Support for Judgement on the Risk of bias accorded to studies using Review Manager version 5.4.1

* Low risk for selection bias- in the studies computer-generated sequence generation was done by a statistician prior to allocation and the allocation was concealed
* Low risk for performance bias - the study participants and personnel were blinded
* Unclear risk for detection bias since the included studies did not clarify in the reports whether there was blinding of the outcome assessment.
* Low risk for attrition bias since all data including supplementary files was accessed.
* Low risk for selective reporting since all studies included guidance on where detailed reports could be accessed.

**Table S3: Non-transformed data baseline antibody Geometric mean titers for pregnant women living with HIV (PWLWH)**

GMT=Geometric Mean Titers. CI=Confidence Intervals. PWLWH=Pregnant Women Living With HIV

Influenza vaccine subgroups include: A/H1NI, AH3/N2, B/Yamagata and B/Victoria

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **Baseline GMT** | **N (reported events)** | **Baseline Lower CI** | **Baseline Upper CI** | **N (reported events)** |
| Madhi et al., 2014 | A/HINI | 26.1 | 70 | 20.7 | 33.0 | 70 |
| Madhi et al., 2014 | A/H3N2 | 16.1 | 70 | 13.3 | 19.4 | 70 |
| Madhi et al., 2014 | B/Victoria | 18.7 | 70 | 16.6 | 21.0 | 70 |
| Nunes et al., 2020 | A/HINI (single dose group) | 9.6 | 230 | 8.5 | 10.9 | 230 |
| Nunes et al., 2020 | A/H3N2(single dose group) | 11.8 | 230 | 10.5 | 13.3 | 230 |
| Nunes et al., 2020 | B/Yamagata (single dose group) | 5.9 | 230 | 5.6 | 6.2 | 230 |
| Nunes et al., 2020 | A/HINI (double dose group) | 9.5 | 230 | 8.4 | 10.8 | 230 |
| Nunes et al., 2020 | A/H3N2 (double dose group) | 13.3 | 230 | 11.7 | 15.1 | 230 |
| Nunes et al., 2020 | B/Yamagata (double dose group) | 6.1 | 230 | 5.7 | 6.5 | 230 |
| Nunes et al., 2020 | A/HINI (Two single dose group) | 9.5 | 220 | 8.4 | 10.8 | 220 |
| Nunes et al., 2020 | A/H3N2 (Two single dose group) | 12.5 | 220 | 11.0 | 14.2 | 220 |
| Nunes et al., 2020 | B/Yamagata (Two single dose group) | 5.9 | 220 | 5.6 | 6.2 | 220 |
| Nunes et al., 2018 | A/HINI | 28.0 | 80 | 22.5 | 35.0 | 80 |
| Nunes et al., 2018 | A/H3N2 | 17.7 | 80 | 14.7 | 21.4 | 80 |
| Nunes et al., 2018 | B/Victoria | 18.5 | 80 | 16.7 | 20.5 | 80 |

**Table S3a. Non-transformed data post vaccination: antibody GMTs for PWLWH**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **GMT 21-35 Days post Vac** | **N (reported events)** | **GMT 21-35 Days Lower CI** | **GMT 21-35 Days Upper CI** | **N(reported events)** |
|  | A/HINI | 74.6 | 70 | 50.6 | 110.0 | 70 |
| Madhi et al., 2014 | A/H3N2 | 38.4 | 70 | 27.3 | 54.1 | 70 |
| Madhi et al., 2014 | B/Victoria | 60.6 | 70 | 44.2 | 83.1 | 70 |
| Nunes et al., 2020 | A/HINI (single dose group) | 39.5 | 230 | 33.1 | 47.1 | 230 |
| Nunes et al., 2020 | A/H3N2(single dose group) | 37.8 | 230 | 32.3 | 44.1 | 230 |
| Nunes et al., 2020 | B/Yamagata (single dose group) | 13 | 230 | 11.6 | 14.5 | 230 |
| Nunes et al., 2020 | A/HINI (double dose group) | 60.8 | 230 | 51.2 | 72.2 | 230 |
| Nunes et al., 2020 | A/H3N2(double dose group) | 52.7 | 230 | 45.4 | 61.1 | 230 |
| Nunes et al., 2020 | B/Yamagata (double dose group) | 16.6 | 230 | 14.7 | 18.8 | 230 |
| Nunes et al., 2020 | A/HINI (Two single dose group) | 46.7 | 220 | 39.7 | 54.9 | 220 |
| Nunes et al., 2020 | A/H3N2 (Two single dose group) | 44.1 | 220 | 37.5 | 51.9 | 220 |
| Nunes et al., 2020 | B/Yamagata (Two single dose group) | 15.5 | 220 | 13.9 | 17.3 | 220 |
| Nunes et al., 2018 | A/HINI | 73.1 | 80 | 51.5 | 103.9 | 80 |
| Nunes et al., 2018 | A/H3N2 | 44.8 | 80 | 31.9 | 62.9 | 80 |
| Nunes et al., 2018 | B/Victoria | 66.7 | 80 | 50.2 | 88.7 | 80 |

**Table S3b. Transformed data baseline and post vaccination PWLWH**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **subgroup** | **N1\_events** | **Baseline Mean** | **Baseline\_SD** | **N2\_events** | **PostVac\_Mean** | **PostVac\_SD** |
| Madhi et al., 2014 | A/HINI | 1 | 70 | 42.1 | 53.3 | 70 | 280.9 | 1019.5 |
| Madhi et al., 2014 | A/H3N2 | 2 | 70 | 22.0 | 20.6 | 70 | 107.4 | 280.5 |
| Madhi et al., 2014 | B/Victoria | 3 | 70 | 21.1 | 11.1 | 70 | 145.6 | 317.9 |
| Nunes et al., 2020\* | A/HINI (single dose group) \* | 1 | 230 | 15.2 | 18.6 | 230 | 99.3 | 228.8 |
| Nunes et al., 2020\* | A/H3N2(single dose group) \* | 2 | 230 | 17.8 | 20.3 | 230 | 77.5 | 138.7 |
| Nunes et al., 2020\* | B/Yamagata (single dose group) \* | 3 | 230 | 6.4 | 2.6 | 230 | 18.8 | 19.6 |
| Nunes et al., 2020\*\* | A/HINI (double dose group) \*\* | 1 | 230 | 15.2 | 18.9 | 230 | 145.8 | 317.9 |
| Nunes et al., 2020\*\* | A/H3N2(double dose group)\*\* | 2 | 230 | 21.5 | 27.4 | 230 | 101.3 | 166.2 |
| Nunes et al., 2020\*\* | B/Yamagata (double dose group)\*\* | 3 | 230 | 6.9 | 3.7 | 230 | 26.0 | 31.3 |
| Nunes et al., 2020\*\*\* | A/HINI (Two single dose group)\*\*\* | 1 | 220 | 14.9 | 17.9 | 220 | 98.3 | 181.9 |
| Nunes et al., 2020\*\*\* | A/H3N2 (Two single dose group)\*\*\* | 2 | 220 | 19.8 | 24.4 | 220 | 93.1 | 173.3 |
| Nunes et al., 2020\*\*\* | B/Yamagata (Two single dose group)\*\*\* | 3 | 220 | 6.3 | 2.5 | 220 | 21.8 | 21.4 |
| Nunes et al., 2018 | A/HINI | 1 | 80 | 45.8 | 59.4 | 80 | 253.4 | 841.4 |
| Nunes et al., 2018 | A/H3N2 | 2 | 80 | 25.3 | 25.7 | 80 | 143.4 | 436.1 |
| Nunes et al., 2018 | B/Victoria | 3 | 80 | 20.6 | 10.0 | 80 | 151.1 | 307.2 |

**Table S3c. Non-transformed baseline antibody GMT for pregnant women living without HIV(PWWH)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **Baseline GMT** | **N (reported events)** | **Baseline Lower CI** | **Baseline Upper CI** | **N (reported events)** |
| Madhi et al., 2014 | A/HINI | 30.0 | 142 | 25.0 | 36.0 | 142 |
| Madhi et al., 2014 | A/H3N2 | 14.5 | 142 | 12.5 | 16.9 | 142 |
| Madhi et al., 2014 | B/Victoria | 17.3 | 142 | 15.4 | 19.5 | 142 |
| Nunes et al., 2018 | A/HINI | 39.6 | 75 | 31.5 | 49.9 | 75 |
| Nunes et al., 2018 | A/H3N2 | 25.2 | 75 | 20.4 | 31.1 | 75 |
| Nunes et al., 2018 | B/Victoria | 20.8 | 75 | 18.4 | 23.4 | 75 |

**Table S3d. Non-transformed post vaccination for PWWH**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **GMT 21-35 Days post Vac** | **N (reported events)** | **GMT 21-35 Days Lower CI** | **GMT 21-35 Days Upper CI** | **N (reported events)** |
| Madhi et al., 2014 | A/HINI | 208.2 | 142 | 171.9 | 252.1 | 142 |
| Madhi et al., 2014 | A/H3N2 | 87.7 | 142 | 70.5 | 109.3 | 142 |
| Madhi et al., 2014 | B/Victoria | 173.9 | 142 | 147.4 | 205.1 | 142 |
| Nunes et al., 2018 | A/HINI | 215.1 | 75 | 167.0 | 277.0 | 75 |
| Nunes et al., 2018 | A/H3N2 | 124.7 | 75 | 93.1 | 166.9 | 75 |
| Nunes et al., 2018 | B/Victoria | 229.4 | 75 | 184.7 | 285.0 | 75 |

**Table S3e. Transformed for PWWH baseline and post vaccination**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **subgroup** | **N1\_events** | **Baseline Mean** | **Baseline\_SD** | **N2\_events** | **PostVac\_Mean** | **PostVac\_SD** |
| Madhi et al., 2014 | A/HINI | 1 | 142 | 54.9 | 84.1 | 142 | 405.2 | 676.6 |
| Madhi et al., 2014 | A/H3N2 | 2 | 142 | 21.9 | 24.8 | 142 | 210.0 | 456.9 |
| Madhi et al., 2014 | B/Victoria | 3 | 142 | 22.3 | 18.1 | 142 | 285.5 | 371.6 |
| Nunes et al., 2018 | A/HINI | 1 | 75 | 65.3 | 85.5 | 75 | 393.8 | 603.8 |
| Nunes et al., 2018 | A/H3N2 | 2 | 75 | 38.3 | 44.0 | 75 | 278.8 | 557.5 |
| Nunes et al., 2018 | B/Victoria | 3 | 75 | 23.8 | 13.4 | 75 | 357.7 | 428.0 |

**Table S3f. Transformed GMT baseline and post vaccination by HIV Status/Vaccine Sub-group**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Subgroup** | **subgroup** | **HIV status** | **N1\_events** | **Baseline Mean** | **Baseline\_SD** | **N2\_events** | **PostVac\_Mean** | **PostVac\_SD** |
| Madhi et al., 2014 | A/HINI | 1 | Positive | 70 | 42.1 | 53.3 | 70 | 280.9 | 1019.5 |
| Madhi et al., 2014 | A/H3N2 | 2 | Positive | 70 | 22.0 | 20.6 | 70 | 107.4 | 280.5 |
| Madhi et al., 2014 | B/Victoria | 3 | Positive | 70 | 21.1 | 11.1 | 70 | 145.6 | 317.9 |
| Nunes et al., 2020\* | A/HINI (single dose group) \* | 1 | Positive | 230 | 15.2 | 18.6 | 230 | 99.3 | 228.8 |
| Nunes et al., 2020\* | A/H3N2 (single dose group) \* | 2 | Positive | 230 | 17.8 | 20.3 | 230 | 77.5 | 138.7 |
| Nunes et al., 2020\* | B/Yamagata (single dose group)\* | 3 | Positive | 230 | 6.4 | 2.6 | 230 | 18.8 | 19.6 |
| Nunes et al., 2020\*\* | A/HINI (double dose group)\*\* | 1 | Positive | 230 | 15.2 | 18.9 | 230 | 145.8 | 317.9 |
| Nunes et al., 2020\*\* | A/H3N2 (double dose group)\*\* | 2 | Positive | 230 | 21.5 | 27.4 | 230 | 101.3 | 166.2 |
| Nunes et al., 2020\*\* | B/Yamagata (double dose group)\*\* | 3 | Positive | 230 | 6.9 | 3.7 | 230 | 26.0 | 31.3 |
| Nunes et al., 2020\*\*\* | A/HINI (Two single dose group)\*\*\* | 1 | Positive | 220 | 14.9 | 17.9 | 220 | 98.3 | 181.9 |
| Nunes et al., 2020\*\*\* | A/H3N2 (Two single dose group)\*\*\* | 2 | Positive | 220 | 19.8 | 24.4 | 220 | 93.1 | 173.3 |
| Nunes et al., 2020\*\*\* | B/Yamagata (Two single dose group)\*\*\* | 3 | Positive | 220 | 6.3 | 2.5 | 220 | 21.8 | 21.4 |
| Nunes et al., 2018 | A/HINI | 1 | Positive | 80 | 45.8 | 59.4 | 80 | 253.4 | 841.4 |
| Nunes et al., 2018 | A/H3N2 | 2 | Positive | 80 | 25.3 | 25.7 | 80 | 143.4 | 436.1 |
| Nunes et al., 2018 | B/Victoria | 3 | Positive | 80 | 20.6 | 10.0 | 80 | 151.1 | 307.2 |
| Madhi et al., 2014 | A/HINI | 1 | Negative | 142 | 54.9 | 84.1 | 142 | 405.2 | 676.6 |
| Madhi et al., 2014 | A/H3N2 | 2 | Negative | 142 | 21.9 | 24.8 | 142 | 210.0 | 456.9 |
| Madhi et al., 2014 | B/Victoria | 3 | Negative | 142 | 22.3 | 18.1 | 142 | 285.5 | 371.6 |
| Nunes et al., 2018 | A/HINI | 1 | Negative | 75 | 65.3 | 85.5 | 75 | 393.8 | 603.8 |
| Nunes et al., 2018 | A/H3N2 | 2 | Negative | 75 | 38.3 | 44.0 | 75 | 278.8 | 557.5 |
| Nunes et al., 2018 | B/Victoria | 3 | Negative | 75 | 23.8 | 13.4 | 75 | 357.7 | 428.0 |

**Table S4: Summary of reactinogenicity and safety events reported**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Madhi et al., 2014** | **Nunes et al., 2020** | **Heyderman et al., 2016** | **Abzug et al., 2013** | **Almeida et al. ,2009** |
| **vaccine administered** | **IIV3** | **IIV3** | **GBS** | **IIV3** | **PPV** |
| **pregnant HIV positive (PWLWH) (sample size)** | 194 | 800 | 180 | 130 | 46 |
| PWLWH vaccinated | 100 | 800 | 179 | 127 | 44 |
| Total number analyzed | 97 | 772 | 175 | 127 | \* |
| At least one local reactions | 37 | 319 | 42 | 4 | - |
| Severe local reactions | 4 | 46 | 2 | - | - |
| At least one systemic reaction | 52 | 395 | 83 | 4 | - |
| Severe systemic reactions | 18 | 68 | 7 | **-** | **-** |
| % with at least one local reactions | 38.14(37/97) | 41.32(319/772) | 24.00(42/175) | 3.15(4/127) | - |
| % that reported a severe local reaction | 4.1 (4/97) | 5.96 (46/772) | 1.14(2/175) | - | - |
| % Systemic reactions | 53.61(52/97) | 51.17(395/772) | 47.43(83/175) | 3.15(4/127) | - |
| % of severe systemic reactions | 18.6(18/97) | 8.81(68/772) | 4.00(7/175) | - | - |
| **pregnant HIV negative (PWWH) (sample size)** | 2116 | n/a | 90 | n/a | n/a |
| PWLWH Vaccinated | 1062 | n/a | 90 | n/a | n/a |
| Total number analyzed | 181 | n/a | 90 | n/a | n/a |
| Number of local reactions | 89 | n/a | 35 | n/a | n/a |
| Number- severe local reactions | 9 | n/a | 4 | n/a | n/a |
| Number - systemic reactions | 95 | n/a | 53 | n/a | n/a |
| Number -severe systemic reactions | 27 | n/a | 9 | n/a | n/a |
| % reporting at least one local reaction | 49.17 (89/181) | n/a | 38.89(35/90) | n/a | n/a |
| % of severe local reactions | 5 (9/181) | n/a | 4.44(4/90) | n/a | n/a |
| % reporting at least one systemic reaction | 52.49(95/181) | n/a | 58.89(53/90) | n/a | n/a |
| % of severe systemic reactions | 15(27/181) |  | 10.00(9/90) | n/a | n/a |

\*No number of events reported but study mentions PPV was found safe

GBS-Group B *streptococcus*

IIV3-Trivalent inactivated influenza vaccine

n/a-Not applicable

PPV-Pneumococcal vaccine

PWLWH-Pregnant women living with HIV

PWWH-Pregnant without HIV

**VACCINE SAFETY “REPORTED COMMENTS” FROM THE FIVE PAPERS THAT ANALYSED FOR SAFETY**

* Rates of premature birth for the HIV-uninfected group were similar to those reported for sub-Saharan Africa, and were higher in HIV-infected groups (Heyderman et.al,2016).
* There were no significant between group differences with regard to rates of miscarriage, stillbirth or premature birth or birth weight in the HIV-uninfected cohort (Madhi et.al, 2013).
* PPV-23 was well tolerated and minimally reactinogenic in the women. Mild local reactions occurred in 3 of 44 women (6.8%) (Almeida et.al, 2009). There were no stillbirths or infant deaths.
* One fetal death of undetermined etiology at 26 weeks’ gestation (32 days after dose 1; 7 days after dose 2), though was judged unrelated to vaccine. Six participants had influenza like illness visits; respiratory specimen influenza A virus PCR was negative in 5, and 1 did not have testing (Abzug et.al, 2013).
* No differences were observed between the three study groups in demographic characteristics, pregnancy outcomes and birth characteristics of their neonates. (Nunes et.al, 2020).

**Table S5: Newcastle-Ottawa Scale assessment of the observational studies star template**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study** | **Selection** | **Comparability** | **Outcome** | **Total score (9)** |
| 1 | Almeida, V.D.C. et al.,2009;  Brazil | \*\*\*\* | \* | \*\*\* | 8 |
| 2 | Richardson, K. and Weinberg, A.,2011; USA [11] | \*\*\* | \*\* | \*\* | 7 |
| 3 | Abzug, M. et al.,2013;  USA | \*\*\* | \* | \*\*\* | 7 |
| 4 | Weinberg, A. et al.,2015;  USA | \*\*\*\* | \* | \*\*\* | 8 |
| 5 | Heyderman, R. et al., 2016; Malawi / South Africa | \*\*\*\* | \*\* | \*\*\* | 9 |

**Selection (maximum score \*\*\*\*)**

**\*\*\*\*:** Exposed cohort is representative of the community\* and the non-exposed cohort is drawn from the same community as exposed\*, there is a secure record of the exposure\* and demonstration that outcome of interest was not present at the start of the study\*

**Comparability (maximum considered\*\*)**

**\*:** There is comparability of cohorts on basis of design and analysis: study controls for HIV negative\* and adjustments for other factors (vaccine schedules, doses, receipt of a placebo and consideration of factors like viral load/CD4 count for the HIV positive\*)

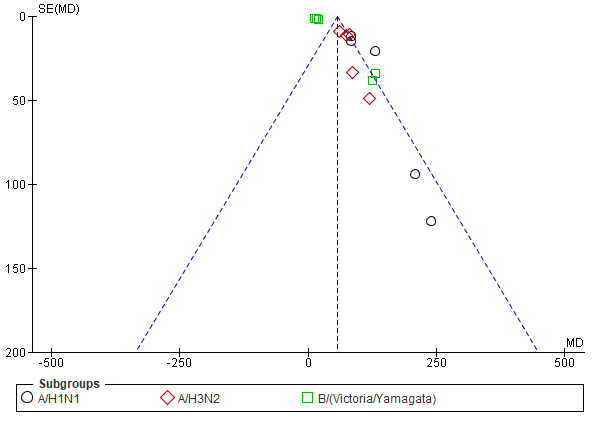
**Outcome (maximum considered\*\*\*)**

**\*\*\*:** There is independent blind assessment of outcome of interest\*, record linkage\* and follow up was long enough for outcome of interest to occur\*

**Adapted from Newcastle-Ottawa SCALE (1)**

(1). Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

**Figure S1- Funnel plot immunogenicity of influenza vaccines given to Pregnant Women living with HIV**



SE=Standard Error. MD=Mean difference

Influenza vaccine subgroups include A/H1N1, and B(Victoria/Yamagata)