Efficacy of cell-culture derived Influenza vaccines for children: A systematic review and meta-analysis

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Abstract

Objectives: To determine the efficacy of cell culture based influenza vaccines in children. **Methods:** Embase, PubMed, Cochrane and clinical trials were searched.14 randomised controlled trials in children were selected. The current systematic review was done as per the PRISMA guidelines. The pooled estimate of seroconversion and GMT rate was calculated as mean difference. Data was analysed using the Cochrane Collaboration Review Manager Version software. Risk of bias was done as per Cochrane risk of bias tool. The quality of evidence was adjudged using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) using the Grade pro software. **Results:** Significant results for efficacy were reported for half dose MF59 influenza vaccine control group for GMT at day 1 with a mean difference of 0.78, 95%CI, 0.50 to 1.07, $p<0.00001$ as compared to full dose MF59 influenza vaccine experimental group .No significant results were reported in half dose MF59 influenza vaccine for GMT at Day 43(mean difference 151.57,95% CI,-29.36 to 332.50 ,p=0.10). Significant results were reported for seroconversion rate for half dose MF59 influenza vaccine control group at day 22 with a mean difference of 17.92,95%CI,10.08 to 25.75,$p<0.00001$ as compared to half dose MF59 influenza vaccine group at day 43 with a mean difference of 5.00,95%CI,-4.80 to 14.80,p=0.32 . **Conclusion:** The current systematic review demonstrated that half dose cell derived influenza vaccines was well tolerated and more immunogenic and resulted in high seroconversion rate and Geometric Mean Titres rate in paediatric population.

Introduction

Influenza viruses (A, B, C and D) causes flu or seasonal influenza, an acute respiratory infection which equally affects all parts of the world and has predilection for children under 5 years with a rapid transmission rate. Illnesses range from mild to severe and even death. Hospitalization and death ensue mainly among high-risk groups. According to WHO, annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290 000 to 6, 50,000 respiratory deaths. Given the fact that children play a major role in virus transmission, children are being prioritized for giving influenza vaccinations in many countries [1]. Vaccines are available for prevention, although immunity wanes off over time and also due to a higher mutation rate of the viruses, annual boosters are recommended. The most commonly used vaccines are inactivated influenza vaccines, although newer vaccines have been developed and showed good efficacy [2].

Cell culture method has now replaced the obsolete egg-based method as it leads to changes in viral antigens owing to an increased adaptability of virus to avian receptors compromising the effectiveness of vaccine. In addition, cell-culture derived viruses are cultured in cells of mammalian origin and potentially omit the egg-adapted changes, enhancing manufacturing control resulting in increased vaccine efficacy with reduction in production lead times as an added advantage [3]. The inactivated quadrivalent subunit Influenza vaccine prepared from virus propagated in MDCK cells (IIV4c; FlucelvaxQuadrivalent, Seqirus) was immunogenic seen with less side-effect in paediatric population. The study done by Terence Nolan investigated the efficacy of IIV4c against influenza diagnosed children as well as adolescents in three seasons [4].Flucelvax

Quadrivalent is the only cell-based inactivated flu vaccine that has been licensed by the FDA for use in the United States (https://www.fda.gov/vaccines-blood-biologics/vaccines/flucelvax-quadrivalent). Further, policy makers would require a cumulative data of such studies, either in the form of observational studies or randomized controlled trials conducted in children [5]. Recently, a randomized controlled trial in NEJM (2021) had reported efficacy of a cell-culture-derived quadrivalent Influenza vaccine in more than 4500 children from different countries [6]. Several other randomized controlled trials also corroborated upon these findings [7,8, 9].

Therefore, a systematic review and meta-analysis integrating results of all these RCTs becomes imperative and would be helpful in policy making and taking informed decisions.We performed a systematic review and meta-analysis of cell-culture derived influenza vaccines for preventing influenza/flu in healthy children and adolescents. This systematic review evaluated the efficacy and safety of different formulations of cell-derived adjuvenated and non adjuvenated vaccines in healthy children below 18 years of age.

Material and Methods:

This systematic review was conducted as per the PRISMA guidelines [10]. Studies were included if they were randomized controlled trials (RCTs). The search was carried out by two independent reviewers in PubMed, EMBASE, and The CochraneLibrary (CDSR) and clinical trials. The following databases were searched for maximum retrieval of published and unpublished articles.No restrictions in terms of language or search options was applied for performing online search. Articles published till date (year 2022) were considered. The search term used were :(((children OR child OR infant OR paediatrics OR preschool children) AND (((Cell culture) OR (cell cultures)) OR (stem cell culture))) AND ((((influenza vaccine) OR (influenza vaccination)) OR (influenza vaccines)) OR ("Influenza Vaccines"[Mesh])).The protocol has been registered with PROSPERO (registration no: CRD42022312493).

Eligibility criteria:

Inclusion Criteria: Randomised controlled trials (RCTs) on healthy children/adolescents (less than 18 years of age) were included.

Exclusion criteria: Systematic reviews and non-randomized studies were excluded. Studies where there is presence of any acute illness, immunosuppressive medications, prior influenza vaccination, and laboratory-confirmed influenza disease within 6 months before enrolment were excluded.

Interventions: Cell-culture based influenza vaccines

Comparator: Placebo, non-influenza vaccine or egg-based influenza vaccine

Outcomes

1. Primary Outcome Measures

Vaccine related adverse events (Local and systemic adverse events after each dose of vaccination).

2. Secondary Outcome Measures

Seroconversion rate

Geometric mean titres

Data extraction

For data extraction, two independent reviewers were involved: one reviewer screened all the identified abstracts and citations of articles for possible inclusion in the systematic review and the second reviewer checked the extracted data. This was followed by thorough investigation of full text articles for data extraction. We had created a PRISMA flowchart to summarize the flow of process for inclusion and exclusion of studies. A proforma to record the details including the general publication details, design, participants, interventions

and outcome measures was developed. The data extraction process has undergone a quality check by a third reviewer. For clarification of data, authors were contacted.

The pooled estimate from individual studies was calculated as mean difference. The heterogeneity was checked by chi-squared test and in such cases; random-effect model was used. Data was analyzed using the Cochrane Collaboration Review Manager Version software by one author who was confirmed by a second author for accuracy.

Risk of bias assessment

Two independent reviewers assessed the quality of evidence as per theCochrane risk of bias assessment criteria for adequate sequence generation, allocation concealment, performance and selection, data attrition, detection bias and other risk of bias [11]. To resolve the discrepancy between the 2 reviewers, a third reviewer has made the final decision after discussion.

GRADE assessment (Summary of findings table)

GRADE pro GDT software was used to create the summary of findings table .The data was imported from RevMan5 version 5.4 (Review manager software 2014) for the comparison of Seroconversion rate and GMT rate of MF 59 influenza vaccine in full dose vaccine compared to half dose vaccine group in children. The quality of evidence was adjudged using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) using the Grade pro software [12].

RESULTS

A total of 324 articles were retrieved from the various electronic database searches (Embase, PubMed, Cochrane and clinical trials), of which 36 duplicate articles were deleted and 288 articles were screened for full text retrieval. Titles and abstracts of the remaining 40 articles were screened for full text retrieval of articles. Finally, 14 randomised controlled trials were included in the systematic review**(Figure 1).** 26 articles were excluded (supplementary table 1).Out of the included trials , 7 trials compared the cell culture influenza vaccines with egg derived influenza vaccines [4,6,7,9,13,14,15] , 4 trials compared the half dose vaccine with the full dose vaccine of MF 59 influenza vaccine [3,8,17,18] and the remaining 3 trials where results could not be pooled and have been discussed [16, 19, 20].

Risk of Bias

Random sequence generation (selection bias) was judged as low risk of bias in 13 studies, as all the details of the randomisation method were described. Allocation concealment was judged as low risk of bias in 2 studies as the allocation was concealed satisfactorily and the remaining 12 studies were judged as high risk of bias as the allocation concealment was not mentioned. Performance Bias was assessed as high risk of bias in 8 studies as the participants were not blinded, 6 studies reported low risk of performance bias as the participants and personnel were blinded .11 studies reported as at low risk of detection bias as the outcome assessors were blinded to the intervention group and the 3 studies were assessed as at high risk of detection bias as the outcome assessors were not blinded. Attrition bias was reported as at low risk of bias in 14 studies as the loss to follow up was less than 10%.Reporting Bias was judged as low risk of bias in 13 studies as the outcomes were assessed properly and 1 study reported as high risk of bias as the outcomes were not properly addressed. No other bias was reported in 14 studies and was judged as at low risk of other bias

(Figure 2(a) and 2(b)).

Synthesis of results

Any vaccine related adverse events

Due to non-uniformity of reporting of data on adverse events across different studies, the data could not be pooled. The data has been summarised and presented in the form of Table and bar graphs.

a.Cell culture influenza vaccines versus egg derived influenza vaccines

Out of the 7 studies, 6 studies reported local and systemic adverse reactions in both the groups and 1 study did not report the adverse events. Out of the 6 studies,3 studies reported less local adverse events in cell culture influenza vaccine group as compared to egg derived vaccines control group [7,13,14] and 5 studies reported more systemic adverse events in cell culture vaccine experimental group as compared to egg derived vaccine control group [4,6,7,9,14]

(Table 1).

The most commonly reported local adverse events were pain , redness , swelling, erythema and induration and were more reported in egg derived influenza vaccine group as compared to cell culture influenza vaccine group **(Bar graph 3(a)).** similarly, systemic adverse events (eg. fever, muscle pain, irritability , diarrhoea , appetite, headache, fatigue, antipyretics , vomiting and myalgia)were more reported in cell culture vaccine experimental group as compared to egg derived control group **(Bar graph 3 (b).**

b.MF 59 influenza vaccine (full dose vaccine and half dose vaccine control group)

3 studies did not report uniformly on adverse events. Therefore, we were not able to conduct meta-analysis of these 3 studies and we have reported the data in table and bar graph format.3 studies reported the adverse events in full dose and half dose vaccine of MF59 influenza vaccine. Study done by Yasuda et al 2010 with children (6 months to 18 years of age) showed better results for half dose 3.75ug as compared to full dose 7.5ug vaccine group .These results were incorporated by Fukase etal 2012 along with adults as subjects. Therefore for data analysis results from fukase study were included. 2 studies [3,17] reported more adverse events in full dose 7.5ug vaccine group as compared to half dose 3.75ug control group and 1 study [8] reported less adverse events in full dose 7.5ug experimental group as compared to half dose 3.75ug control group **(Table 2).** 2 studies [8,17] reported less systemic adverse events in full dose 7.5ug vaccine group as compared to half dose 3.75ug control group and 1 study [3] reported more systemic adverse events in full dose 7.5ug vaccine group as compared to half dose 3.75ug control group **(Table 2).**

The most commonly reported local adverse events were pain,erythema,swelling and tenderness and were more reported in full dosefull dose 7.5ug vaccine group as compared to half dose 3.75ug control group **(Bar graph 4(a)).** The systemic adverse events (e.g. fever, vomiting ,irritability, unusual crying ,chills, myalgia, arthralgia, fatigue, nausea, antipyretics) were more reported in full dose 7.5ug vaccine group as compared to half dose 3.75ug control group and the other systemic adverse events eg. headache, sleepiness, diarrhoea, change eating habits ,shivering, medication) were more reported in half dose 3.75ug control group full dose 7.5ug vaccine group

(Bar graph 4(b)).

2. Secondary outcomes

1. Geometric mean titres (GMT)

a. Cell culture influenza vaccines group versus egg derived influenza vaccines control group

Out of 7 studies, 5 studies measured geometric mean titres at day 0 and day 28 [7, 9, 13, 14, 15]. We were unable to pool this data in the meta-analysis as all the studies reported geometric mean titres of different cell culture influenza vaccines .Detailed results are tabulated **(Table 1).**

b.MF 59 influenza vaccine (full dose vaccine and half dose vaccine control group)

A total of 3 studies were included in the meta-analysis for MF59 influenza vaccine for full dose and half dose vaccine group. **Fig 5(a) and 5(b)** show forest plots of the mean difference for the geometric mean titres at Day 1 and Day 43. Significant results were reported for half dose MF59 influenza vaccine control group at day 1 with a mean difference of 0.78, 95%CI, 0.50 to 1.07,$p<0.00001$ as compared to full dose MF59 influenza vaccine experimental group .No significant results were reported in half dose MF59 influenza vaccine at Day 43(mean difference 151.57,95% CI,-29.36 to 332.50 ,$p=0.10$) as compared to full dose MF 59 Influenza vaccine.

2. Seroconversion rate

a. Cell culture influenza vaccines group versus egg derived influenza vaccines control group

Out of the 7 studies, 4 studies measured seroconversion rate at day 28 in children [7, 9, 13, 14]. We were unable to pool these studies in the meta-analysis due to non-uniform and heterogeneous data. Detailed results are tabulated in the table below **(Table1).**

b. MF 59 influenza vaccine (full dose vaccine and half dose vaccine control group)

For this analysis 2 studies were included in the meta-analysis for MF59 influenza vaccine for full dose and half dose vaccine group. **Fig 6** shows forest plots of the mean difference for the seroconversion rate at Day 22 and Day 43. Significant results were reported for half dose MF59 influenza vaccine control group at day 22 with a mean difference of 17.92,95%CI,10.08 to 25.75,p<0.00001 as compared to half dose MF59 influenza vaccine group at day 43 with a mean difference of 5.00,95%CI,-4.80 to 14.80,p=0.32 .

Quality of evidence (GRADE)

Using the GRADE software, the certainty of evidence was assessed as high for the Seroconversion rate at Day 22 and GMT at Day 1 of MF59 influenza vaccine in half dose vaccine group as compared to full dose vaccine group .The certainty of evidence was upgraded due to no serious risk of bias and indirectness **(Table 3).**

DISCUSSION

Literature from the previous studies suggested cell culture derived influenza vaccines to be more effective as shown by seroconversion rate and GMT. Other benefits are that these vaccines are antibiotics and preservatives free. Further, the cell culture derived vaccines can be easily prevented from external contamination which is not in the case of egg derived vaccines production process being open to the environment. The production of cell culture vaccine can also be accelerated in times of pandemic after identification of the viral strain [14]. Due to the increased requirement of influenza vaccine, it is important to develop different methods of production such as adjuvants use and modern cell culture technology, to make sure that defined vaccines is available universally [17]. Also, due to the fact that the vaccines are free from egg-derived proteins, egg-allergic children can be immunized with no adverse events.

This systematic review evaluated the safety and immunogenicity of cell culture derived and egg derived influenza vaccines in healthy paediatric population. The results of this review reported less local adverse events but more systemic adverse events in cell culture derived influenza vaccine group as compared to egg derived influenza vaccines. The cell derived MF59 influenza vaccine showed better seroconversion rate and GMT in half dose vaccine group in children less than 18 years of age. Only one study reported the vaccine efficacy and is discussed here. In the study done by Terence Nolan et al, efficacy of IIV4c vaccine was studied in RT-PCR or culture-confirmed influenza. It was found to be 54.0% (95% CI, 44.8 to 61.7) in participants with age group of 3-18 years [6].

Due to the heterogeneity of data three studies weren't included in the meta-analysis. These three studies are being discussed here [19, 16, 20]. The study done by Eve Versage et al 2021 evaluated the safety and immunogenicity of MF59-adjuvanted mammalian cell-based, A/H5N1 vaccine through a review of four clinical trials with similar design. Recipients of all ages were assessed for full-dose (7.5μgm) and (3.75 μgm) formulations. Highest antibody titre was observed in children less than 3 years of age. Seroconversion criteria were met by antibody titres in children 12 months after vaccination. This study also depicted that MF59 allowed for antigen dose sparing. All the trials showed cumulative results of age related responses. The adolescents depicted highest antibody titres. Also a single MF59-adjuvanted cell derived influenza vaccine met all the CBER and CHMP licensure. Preparations carrying 7.5μgm and 3.75 μgm antigen per dose caused highest amount of antibody titres after two doses [19].

Another trial done on paediatric patients of the age groups (6 months to 17 years) by Pornthep C et al, 2021 suggested that when a full dose of aH5N1c vaccine was administered in the form of two doses, three

weeks apart, reported in highest immunogenicity from baseline results for all the five heterologous A/H5N1 strains.The findings of this study suggested that an MF59-adjuvanted cell culture influenza vaccine essential cross defence during the early phase of pandemic. A limitation concern of this trial was the lack of comparator group. Smaller group of subjects as sample size is another limitation of this trial [16].

In another RCT done by Maikel V.W et al on children 6 months to 17 years of age, the subjects were divided into groups Infants (6-35 months)and children(3-8 years) of age and were randomized and administered 2 immunizations with 7.5µg or 3.75-µg hem agglutinin (HA) dose of nonadjunvanted whole-virus A/Vietnam (H5N1 vaccine. This trial showed that vaccine was safe with mild adverse reactions [20].

Performance Bias was assessed as high risk of bias in 8 studies as the participants were not blinded and 12 studies were judged as high risk of bias as the allocation concealment was not mentioned. Using the GRADE software, the certainty of evidence was assessed as high for the Seroconversion rate at Day 22 and GMT at Day 1 of MF59 influenza vaccine in half dose vaccine group.

The Limitations of the current systematic review, that we were not able to pool the data of the primary outcome (adverse events) in the meta-analysis due to non –uniformity of data and therefore have provided in narrative and table formats.

In summary, the current systematic review demonstrated that half dose cell derived influenza vaccines were well tolerated and more immunogenic and resulted in high seroconversion rate and GMT in paediatric population. Further, more trials are recommended in future.

Acknowledgement: Author's contributions: The articles were screened by KK, MS, MR. PP did search of articles through different electronic databases. Data extraction was done by KK, MR. Quality assessment tool was used by KK, AC and SS to assess the quality of the studies. Data was analyzed by KK & MR using Revman 5.4. MS resolved the Discrepancies. KK and RB wrote the initial draft and the final manuscript was approved by all the authors. AC and MS Contributed in editing and reviewed the final draft of the manuscript.MS helped in critical revision and supervised the revised manuscript. This work is supported by Evidence Based Medicine (EBM-Phase 2), ICMR, and New Delhi.

Conflict of interest : None

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Table 1: Study characteristics table of cell culture derived Influenza vaccine versus egg derived influenza vaccine group

S. No.	Study ID	Setting	Age (6month – 20 years)	Intervention Group (Cell Culture influenza vaccine)	Control Group (Egg derived influenza vaccine)	Adverse Event (Cell culture influenza vaccine)	Adverse Event (Egg derived influenza vaccine)	Influenza vaccine Strain	Seroconversion Day 28		GMT Day 0 Day 28		GM Day 0 Day 28
									Intervention Mean±SD	Control Mean±SD	Intervention Mean±SD	Control Mean±SD	Inte Mea
1.	Waddington et al 2010[13]	Multicentric (UK,Oxford, Bristol,Southampton,Exeter and London)	6 month to 12 yrs.	Non-adjuvanted whole virion H1N1 influenza vaccine Dose: 0.5ml	$AS03_B$ adjuvanted split virion influenza vaccine Dose: 0.5ml	Local Adverse reactions (19.60%) Systemic adverse reaction 12.01%	Local Adverse reactions 32.3% Systemic adverse reaction 15.34%	A/H1N1	78.2±1.33	99.3±0.31	4.6±0.1	4.5±0.08	69.3±
2.	Vesikari et al 2012[14]	Multicentric (United states and Europe(Finland,Croatia Hungary,Lithuania ,Italy and Romania)	3 yrs. to 17 yrs.	Cell culture derived influenza vaccine (CCIV) Dose: 0.5ml	Egg derived influenza vaccine (TIV) Dose: 0.5ml	Local Adverse reactions 12.10% Systemic adverse reaction 7.61%	Local Adverse reactions 14.12% Systemic adverse reaction 6.87%	A/H1N1 A/H3N2 B influenza	77.93±2.66 66.16±7.57 44.90±9.54	29.19±4.52 37.78±1.65 45.23±13.17	29.87±212 65.66±219 7.14±5.7	380±264 0.87±326 7.01±1.56	28.5 57.9 51.8

S. No.	Study ID	Setting	Age (6month – 20 years)	Intervention Group (Cell Culture influenza vaccine)	Control Group (Egg derived influenza vaccine)	Adverse Event (Cell culture influenza vaccine)	Adverse Event (Egg derived influenza vaccine)	Influenza vaccine Strain	Seroconversion Day 28	Seroconversion Day 28	GMT Day 0 Day 28	GMT Day 0 Day 28	GM Day 0 Day 28
3.	Nolan et al 2016[4]	Multicentre (United states,Australia,New Zealand, The Philippines and Thailand)	4 yrs to 17 yrs.	Cell culture derived influenza vaccine (TIVc) Dose: 0.5ml	Egg based influenza vaccine (TIVf) Dose: 0.5ml	Local Adverse reactions 20.40% Systemic adverse reaction 10.18%	Local Adverse reactions 17.90% Systemic adverse reaction 8.55%	Not mentioned	–	–	–	–	–
4.	Eun et al 2016[7]	South Korea	6 month to 18 yrs of age	Cell culture derived influenza vaccine(NBP607) Dose: 0.5ml	Egg derived vaccine(1B) Dose: 0.25 or 0.5ml	Local Adverse reactions 14.45% Systemic adverse reaction 6.5%	Local Adverse reactions 16.15% Systemic adverse reaction 5.97%	A/H1N1 A/H3N2 B/Yamagata B/ Victoria	62.8±1.66 57.8±1.7 50.4±1.68 50±1.73	62.4±3.43 57.7±3.51 57.7±3.51 23.5±3.01	95.1±5.48 146.7±8.76 22.8±1.03 23.5±1.03	88.2±9.8 172.2±19.5 22.2±2.06 21.2±2.06	432.1 527.9 99.6± 84.6±
5.	Oh et al 2018[9]	Republic of Korea	6 month to 18 yrs of age	Cell culture derived influenza vaccine(NBP607) Dose: 0.5ml	Inactivated sub-unit trivalent influenza vaccine(NBP607) Dose: 0.5ml	Local Adverse reactions 15.70% Systemic adverse reaction 6.20%	Local Adverse reactions 15.14% Systemic adverse reaction 5.95%	A/H1N1 A/H3N2 B influenza	80.8±1.5 47.8±1.9 48.2±1.88	81.8±2.86 49.4±3.88 49.4±3.71	67.3±4.15 185.3±102 29.2±1.13	52.4±6.05 31.5±29.5 25.5±2	525.2 78.2 91.6±

S. No.	Study ID	Setting	Age (6months – 20 years)	Intervention Group (Cell Culture influenza vaccine)	Control Group (Egg derived influenza vaccine)	Adverse Event (Cell culture influenza vaccine)	Adverse Event (Egg derived influenza vaccine)	Influenza vaccine Strain	Seroconversion Day 28	Seroconversion Day 28	GMT Day 0 Day 28	GMT Day 0 Day 28	GM Day 0 Day 28
6.	Moehling et al 2020[15]	U.S.A	4 yrs. to 20 yrs	Cell culture derived influenza vaccine (ccIIV4)	Egg derived vaccone (IIV4)	Not mentioned	Not mentioned	A/H1N1 A/H3N2 B/Yamagata B/ Victoria	– – – –	– – – –	117±10.83 100±9.83 130±11.66 109±9.83	311±14.72 93±15.5 602±13.51 98±14.25	292± 265± 193± 232±
7.	Nolan et al 2021[6]	Multicentric (Australia, Philippines and Thailand)	2 yrs. to 18 yrs.	Cell culture derived influenza vaccine (IIV4c) Dose: 0.5ml	Meningococcal oligosaccharide diphtheria CRM197 conjugate vaccine Dose:0.5ml	Local Adverse reactions 36.7% Systemic adverse reaction 31.3%	Local Adverse reactions 33.5% Systemic adverse reaction 30.5%	Not mentioned	–	–	–	–	–

Table 2: Study characteristics table of MF59 Influenza vaccine in Full Dose vaccine group Versus Half Dose vaccine group

S. No.	Study ID	Setting	Age(6 months -18 years)	Intervention Group (Full Dose 7.5µg + 50%)	Control Group (Half Dose 3.75µg + 50%)	Influenza vaccine Strain	Seroconversion Day 22 Day 43	Seroconversion Day 22 Day 43	Seroconversion Day 22 Day 43	Seroconversion Day 22 Day 43	GMT Day 1 Day 43	GMT Day 1 Day 43	GM Day 1 Day 43
							Intervention Mean±SD	Control Mean±SD	Intervention Mean±SD	Control Mean±SD	Intervention Mean±SD	Control Mean±SD	Inte Mea

S. No.	Study ID	Setting	Age(6 months -18 years)	Intervention Group (Full Dose 7.5µg + 50%)	Control Group (Half Dose 3.75µg + 50%)	Influenza vaccine Strain	Seroconversion Day 22	Seroconversion Day 22	Seroconversion Day 22	Seroconversion Day 22	GMT Day 1	GMT Day 1	GM Day 1 Day 43
1.	Fukase et al 2012[17]	Japan	6month to 18 yrs.	Local Adverse Reactions 33.58% Systemic Adverse Reactions 8.88%	Local Adverse Reactions 29.2% Systemic Adverse Reactions 9.76%	A/H1N1	78±5	56±6.75	100±1.5	100±1.5	6.23±0.40	5.24±0.35	296±
2.	Knuf et al 2014[3]	Multicentric (Germany, Belgium, Dominican republic and Netherlands)	6 months to 17 yrs.	Local Adverse Reactions 22.8% Systemic Adverse Reactions 14.50%	Local Adverse Reactions 12.25% Systemic Adverse Reactions 13%	A/H1N1	--	--	--	--	6.89±2.73	6.98±2.58	743.7
3.	Chanthavanich et al 2019[8]	United states and Thailand	6 months to 17 yrs.	Local Adverse Reactions 14.87% Systemic Adverse Reactions 15.6%	Local Adverse Reactions 15% Systemic Adverse Reactions 17.62%	A/H5N1	52±2	38±2	96±0.83	86±1.5	13±1.33	7±0.66	262±

Table 3 :Summary of findings table of seroconversion rate and GMT rate in full dose vaccine versus half dose vaccine group(MF 59 influenza vaccine)

Summary of findings:

Seroconversion and GMT rate of full dose vaccine vs half done vaccine (MF 59 influenza vaccine)

Patient or population: children
Setting: Multi centric
Intervention: Full dose vaccine
Comparison: Half dose vaccine

Outcomes	Anticipated absolute effects* (95% CI) Risk with Half dose vaccine	Risk with Full dose vaccine	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Seroconversion rate MF59 Influenza vaccine - Day 22	The mean seroconversion rate MF59 Influenza vaccine - Day 22 was **40.6**	MD **17.92 higher** (10.08 higher to 25.75 higher)	-	778 (2 RCTs)	⨁⨁⨁⨁ High	Seroconversion rate was significantly higher in half dose vaccine as compare to full dose vaccine group.
Seroconversion rate MF59 Influenza vaccine - Day 43	The mean seroconversion rate MF59 Influenza vaccine - Day 43 was **88.0**	MD **5 higher** (4.8 lower to 14.8 higher)	-	778 (2 RCTs)	⨁⨁⨁⨁ High	Seroconversion rate was not significant in half dose vaccine but with high certainty of evidence.
GMT Day 1(MF59 influenza vaccine)	The mean GMT Day 1(MF59 influenza vaccine) was **3.14**	MD **0.78 higher** (0.5 higher to 1.07 higher)	-	1255 (3 RCTs)	⨁⨁⨁⨁ High	GMT rate was significant in half dose vaccine group as compared to full dose vaccine.
GMT DAY43(MF59 influenza vaccine)	The mean GMT DAY43(MF59 influenza vaccine) was **283.19**	MD **151.57 higher** (29.36 lower to 332.5 higher)	-	1255 (3 RCTs)	⨁⨁⨁⨁ High	GMT rate was not significant in half dose vaccine but with high certainty of evidence.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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figures-influenza-vaccines.tiff available at https://authorea.com/users/520703/articles/593937-efficacy-of-cell-culture-derived-influenza-vaccines-for-children-a-systematic-review-and-meta-analysis