 doi:10.20944/preprints202005.0477.v1

The immunogenicity and safety of RSV vaccines in development: a systematic review

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Abstract- 252; Text- 5045; References: 65, Tables 3, Figure 1.

 doi:10.20944/preprints202005.0477.v1

Abstract

Background: Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infection globally. There are vaccines in pipeline to prevent it but a systematic review on immunogenicity and safety of vaccine is lacking.

Methods: This systematic review of RSV vaccine clinical trials was undertaken using 4 databases. Searches were conducted using both controlled vocabulary terms such as 'Respiratory Syncytial Virus, Human', 'Respiratory Syncytial Virus Infections', 'Respiratory Syncytial Virus Vaccines', 'Immunization', 'Immunization Programs' and 'Vaccines' and corresponding text word terms. The searches for published papers were limited to clinical trials published from January 2000 to August 6th, 2018. RSV infection case was defined as RSV associated medically attended acute respiratory illness (MAARI) or RSV infection by serologically-confirmed test (Western Blot) during the RSV surveillance period. We calculated the relative risk of each vaccine trial with RSV infection case.

Results: Of 4395 publications, 24 were included and data were extracted covering 4 major types of RSV vaccine candidates, these being live-attenuated/chimeric (n=9), recombinant-vector (n=10), subunit (n=1) and nanoparticle vaccines (n=4). For RSV infection cases, 7 trials were involved and none of them showed a vaccine-related increased MAARI during RSV surveillance season.

Conclusion: LID ΔM2-2, MEDI M2-2, and RSVcps2 (live-attenuated) were considered the most promising vaccine candidates in infant and children. In the elderly, a nanoparticle F vaccine candidate was considered as a potential effective vaccine. Although no promising vaccine was identified from pregnant-women test, RSV F-024 subunit vaccine candidate and an RSV F nanoparticle vaccine showed encouraging results in healthy non-pregnant women.

Key words: respiratory syncytial virus vaccine, clinical trial, safety and immunogenicity, RSV promising vaccine

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1. INTRODUCTION

Respiratory syncytial virus (RSV) is one of the main causes of acute lower respiratory infection (ALRI), and commonly leads to pneumonia or bronchiolitis (1). The pattern of RSV infection in humans shows a U-shaped age-curve, with peak disease rates in those younger than 5 years and older than 65 years (2). A recent epidemiological study on children showed an estimated 33.1 million RSV-ALRI episodes globally in 2015, which resulted in about 3.2 million hospitalisations; around 45% of the hospitalised patients were younger than 6 months old. The estimated annual number of deaths was 59,600 in children aged younger than 5 years, with 46% happening in children younger than 6 months (3). In the elderly, RSV was not thought to be serious until the 1970s, when it was discovered that there was spread of this virus in several long-term nursing home facilities in the USA (4, 5). Since then, several studies have shown that RSV is an important cause of illness in community-dwelling older people (6, 7). RSV may cause a similar burden of disease to non-pandemic influenza A in older age groups (8). RSV is annually associated with around 177,000 hospitalisations and 14,000 deaths in US adults aged 65 years or older (8).

In 1955, RSV was first isolated from a chimpanzee with respiratory symptoms and designated chimpanzee coryza agent. By microscopy, scientists saw giant syncytia in lung tissue (9). Hence, this was named as respiratory syncytial virus. RSV is an enveloped RNA virus and belongs to the family of *Paramyxoviridae*, classified within the genus *Pneumovirus*, and it can be separated into two major subtypes, A and B. There are four important proteins on the surface of the RSV virion, which are the attachment glycoprotein (G), the fusion (F) protein, the matrix protein (M) and the small hydrophobic (SH) protein (10). The main human neutralising antibody is against the F protein which enables the virus to fuse with the membrane of respiratory cells. It is highly conserved and essential for viral viability. However, the RSV virus can make a conformational change to the F protein to avoid antibody neutralisation. In contrast, the G protein focuses on the ciliated cells of the human airway; variation of it is associated with subtype classification (11). Therefore, both of these two antigens have been targeted by novel vaccine candidates (and also by monoclonal antibodies). The function of M protein is thought to be in interaction with polymerised actin which destabilises cellular microfilaments to transport virion components in the host cells (12). However, the function of SH protein is not yet clearly known (13).

Adverse events associated with the development of an RSV vaccine in the mid-1960s delayed the development of an RSV vaccine for decades. At that time, a formalin-inactivated (FI) RSV vaccine was being tested for protective efficacy. It failed due to worrying results. A large proportion of the

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study participants, who were exposed to natural RSV infection soon after vaccine recipients, developed enhanced respiratory disease (ERD). Unfortunately, two of these children died because of ERD. The subsequent investigation found that the FI vaccine did not produce neutralising antibodies and also failed to elicit CD8+T cells. Instead, it induced an aggressive CD4+T cell and cytokine response leading to ERD (14).

Importantly, there has been no recent systematic review on RSV vaccines. We divided respiratory syncytial virus (RSV) vaccines under development into four major groups: particle-based, vector-based, live-attenuated or chimeric, and subunit vaccines.

2. METHODS

2.1 STUDY OBJECTIVE

This study has four major aims: firstly, to systematically review the medical publications on clinical trials of RSV vaccines from 2000 to August 6th, 2018 and describe immunogenicity and safety data in the published journals; secondly, to evaluate the risk of RSV infection in vaccine recipients during RSV follow-up season.

2.2 LITERATURE SEARCHES

The initial search for this systematic review of RSV vaccine clinical trials was undertaken by a medical information specialist (Catherine King) using the following bibliographic databases: Ovid Medline (1946 - July Week 4, 2018), Ovid Embase (1974 – 06 August 2018), the Cochrane Library Database of Systematic Reviews (Issue 10 of 12, 2018) and Cochrane Central Register of Controlled Trials (Issue 10 of 12, 2018). Searches were conducted using both controlled vocabulary terms such as ‘Respiratory Syncytial Virus, Human’, ‘Respiratory Syncytial Virus Infections’, ‘Respiratory Syncytial Virus Vaccines’, ‘Immunization’, ‘Immunization Programs’ and ‘Vaccines’ and corresponding text word terms. The searches were limited to items published from January 2000 to August 6th, 2018.

2.3 SCREENING

Items were screened using the inclusion/exclusion criteria (see. Table 1) by Jing Shan (JS). The screening was cross-checked by Robert Booy (RB).

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2.4 DATA EXTRACTION

A data extraction form was developed by JS in consultation with Robert Booy, Phil Britton, Catherine King (RB, PB, CK). Information extracted included "title", "name of first author", "source", "national clinical trials' number (NCT)", "participants", "vaccine candidate", "study type", "outcome", and "serious adverse events". We focused on severe prognoses and decided to limit descriptions to adverse effects that were a minimum of grade 3 (15).

2.5 EVALUATION OF DATA ANALYSIS

We aimed to summarise the RSV vaccine immunogenicity based on each paper's definition of "immune-response" (described in the relevant journal papers); commonly, for instance, a ≥4-fold rise in RSV neutralising antibody (NA) in seronegative children or a ≥3-fold rise in NA in adults. Moreover, I extracted the safety data based on the serious adverse events (SAE) presented in those papers.

Seven studies looked at disease prevention: a case of RSV infection was defined as RSV-associated medically attended acute respiratory illness (MAARI) or was serologically-confirmed (Western Blot) during RSV surveillance season. Review Manager 5.3 was used for data analysis on a personal computer. A fixed-effects model was used for data analysis, and a relative risk in vaccinated group compared with unvaccinated group with 95% confidence interval (CI) was calculated.

3. RESULTS

A total of 4395 publications were identified through the databases: we combined 175 from Cochrane Library Database of Systematic Reviews (Issue 10 of 12, 2018) and Cochrane Central Register of Controlled Trials (Issue 10 of 12, 2018), 2550 from Ovid Embase (1974 – 06 August 2018), 1670 from Ovid Medline (1946 - July Week 4, 2018). Of these, 1265 publications were excluded as duplicates. A further 3106 publications were excluded which we found were not RSV vaccine clinical trials. As a result, 24 publications were included covering the 4 major types of RSV vaccine candidates, live-attenuated (n=9), subunit (n=10), vector-based (n=1), and nanoparticle (n=4) (see Figure 1).

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3.1 Live-attenuated/Chimeric vaccines

M2-2

The M2-2 gene mediates the transition from transcription to RNA replication, so its' deletion can attenuate the virus. Meanwhile, it still elicits a neutralising antibody response (16). In 2015, Karron and colleagues reported a MEDI M2-2 study on seronegative children aged 6-24 months. The result was ≥4-fold of neutralising antibody titres in 95% (19/20) vaccinees and a ≥4-fold rise of anti-F antibody in 90% (18/20) of vaccine recipients while there was no antibody rise in non-RSV infected placebo recipients. Two grade 3 fever serious adverse events (SAE) occurred in this trial (NCT01459198) (17).

Furthermore, two studies (NCT02237209 and NCT02040831) explored the safety and immunogenicity of the LID ΔM2-2 vaccine in RSV seronegative children aged from 6-24 months. LID ΔM2-2 appeared to have acceptable infectivity and immunogenicity: 90% (18/20) of vaccine recipients had a ≥4-fold rise in both neutralising antibody and anti-F IgG antibody. The placebo group showed none with a 4-fold rise in the antibody. Importantly, the subsequent RSV season surveillance showed 8 of 19 vaccinees had a ≥4-fold increase in either neutralizing antibody or anti-F IgG titres compared to pre-RSV season, but only in 2 of 9 placebo recipients. Therefore, this indicated the vaccine's anamnestic response capability (18).

RSVcpts

Cold-passage (cp) mutagenesis is based on an alteration to render the virus temperature-sensitive (ts) so that it can only replicate in the upper respiratory tract, not in the lungs. Therefore, it is used in vaccine development (19, 20).

The 404, 248 and 1030 mutations are considered as the main attenuated genotypes determining mutation (21). RSV cpts-248/404 vaccine is a lineage of RSVcpts vaccine product, which has been studied in infants and children (22-24). RSV cpts-248/404 appeared to increase upper respiratory tract congestion in 1-2 months old infants in a double-blind RCT. Because of concern regarding pathogenicity of this vaccine virus, cpts-248/404 needs more attenuation for infants' use (25).

SH

The SH gene has been variously deleted to produce live-attenuated vaccine candidates. The function of this gene is not yet known (13). Due to only 44% of infants in the two-dose group versus no infants in the placebo group having a ≥4-fold antibody rise in a double-blind RCT, rA2cp248/404/1030 ΔSH needs further refinement regarding immunogenicity. No vaccine-related

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serious adverse event was reported (26).

MEDI-599 is another SH deletion vaccine. Unfortunately, it showed increased medical attendance due to lower respiratory infection in vaccinated children in a phase 1 double-blind RCT (NCT00767416); hence, further study of its safety profile is needed (27).

Cold-passage/stabilised 2 (RSVcps2) is produced form MEDI-599 with stabilised 248 and 1030 mutations. In 2018, Buchholz and colleagues (21) reported a phase 1, RCT conducted in RSV seronegative children aged from 6-24 months. It showed that a ≥4-fold neutralising antibody rise was seen in 59% of the vaccine group versus 13% in the placebo group. Furthermore, a ≥4-fold anti-F IgG antibody rise occurred in 68% of vaccinees versus 13% in the placebo group. However, the same rate (50%) of respiratory tract infection and febrile events were in both the vaccine and placebo group. Moreover, one serious adverse event in the vaccine group was posted (21).

MEDI-534

MEDI-534 is a vaccine candidate using a parainfluenza virus type 3 (PIV3) backbone genome, which was altered to express RSV F protein (28). Three RCTs have been conducted to evaluate the safety and immunogenicity in infants and children. In 2004, Belshe and colleagues published the results of a Phase 1, double-blind RCT trial: 95% of children in the vaccine group had a ≥4-fold RSV neutralising antibody rise while no placebo recipient had a similar rise. There was also evidence for antibody elicitation against PIV3. This study supported the further study of MEDI-534 (29). Gomez and colleagues reported a Phase 1, double-blind RCT; it showed this vaccine induced minimal immune responses in RSV seropositive children aged 1 to 9 years (NCT00345670). There was no significant difference in the side-effect event rates between the vaccine and placebo groups (30). Thirdly, a Phase 1, double-blind RCT was conducted in 49 RSV/PIV3 seronegative children aged 6-24 months. The results were better in those given multiple doses (i.e. 2 or 3) and at a higher dose median tissue culture infective dose (TCID50), dosage of 10^6, but even then only about 50% responded with a ≥4-fold neutralising antibody rise so it was not a strong candidate; only one of 17 in the placebo group had a ≥4-fold rise in neutralising antibody likely due to a wild type RSV infection. Also, a favourable immune response to PIV3 was observed. There was no serious adverse even (31).

3.2 SUBUNIT VACCINES

BBG2Na

The BBG2Na is a subunit vaccine candidate purified from a prokaryote-expressed protein (in Escherichia coli). A single-blind RCT in younger adults from 2001 showed that the 100ug and

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300ug vaccine groups had greater immune response than the 10ug group with 33%-71% developing a virus neutralising response; only 7% had this response in the placebo group. Giving a second or third dose did not provide a significant booster response. Most recipients of 100ug or 300ug vaccines had at least 4-fold rise in antibody measured in G2Na-specific ELISA units. No serious adverse event was reported (32). There appears to be no follow-up human only study on this product published since 2001.

Pre-fusion vaccines (RSV Pre F, RSV F-020 and RSV F-024)

RSV-F is subject to conformational alteration during fusion of the virus with human cells-the prefusion structure exposes more antigenic sites for neutralising antibody than the post-fusion structure. The recombinant RSV prefusion protein F vaccine was purified in Chinese hamster ovary cells and manipulated to retain the prefusion conformation (33-35).

RSV Pre F was evaluated through a recent RCT in healthy young men, given one dose of 10ug, 30ug, and 60ug with/without alum-adjuvant. The results showed all vaccine recipients achieved ≥1:512 RSV A neutralising antibody titre by day 30 with a 3.2-4.9-fold rise in titres. Antibody responses remained high until day 60. No vaccine-related serious adverse event was noted (35). These results supported further research.

Two RCTs were conducted with the F-020 and F-024 products to investigate the safety and immunogenicity in non-pregnant women aged 18-45 years. In the RSV F-020 trial, 2 groups of vaccinees were given non-adjuvanted Pre F vaccine (30ug or 60ug), a third group were given 60ug plus adjuvant (500ug of aluminium hydroxide) and the control group received Tdap. Enrolees in RSV-F024 were given a single dose of non-adjuvanted RSV-Pre F (60ug) or Tdap. All RSV vaccine groups exhibited a rise in RSV-A neutralising antibody (NA) of 3.1-3.9 folds, while the control group showed no increase. Furthermore, all RSV vaccine groups achieved a >14-fold palivizumab competitive antibody (PCA) concentrations on day 30 that then waned but still was above baseline on day 90. In the control group, only 6% or fewer recipients had an NA immune response (days 30, 60, and 90). The adjuvanted product was no more immunogenic than the non-adjuvanted ones. Exploratory safety analysis analysing any grade 2/3 adverse effects showed a significantly higher rate in the adjuvanted group, but local reactions (especially pain) to the unadjuvanted pre-F vaccines were less frequent than with Tdap. F-020 and F-024 recipients had a similar safety profile to the control group recipients and no SAEs were considered vaccine-related (NCT02360475, NCT02753413) (36).

 doi:10.20944/preprints202005.0477.v1

Post fusion F (MEDI 7510)

MEDI7510 is a post-fusion (post-F) protein vaccine candidate that has been evaluated with or without an adjuvant; an analogue of monophosphoryl lipid A called glucopyranosyl lipid A (GLA), which is a toll-like receptor-4 (TLR-4) agonist. Three RSV post-F trials also have been performed in adults aged ≥60 years. The first, a Phase 1a, double-blind, RCT (NCT02115815), tested the immunogenicity and safety of the 3 dosages: 20ug, 50ug, and 80ug with/without 2.5ug of GLA. It showed 50% of participants in the higher dose with adjuvant group had a ≥3-fold geometric mean fold rise in microneutralisation. All vaccinees in this group also had a ≥3-fold rise in anti-F IgG antibody and PCA. Conversely, no such rises were found in the placebo group (37).

A Phase 2b, RCT was recently performed in almost 2000 participants aged at least 60 years to prevent elderly vaccinees against developing RSV illness. It was unsuccessful showing a vaccine efficacy of -7.1% (NCT02508194) (38). *A* third study, also published in 2017, with the elderly, was a Phase 1, double-blind, RCT (NCT02289820). In the vaccine groups, vaccine candidates containing 120ug with GLA (1ug, 2.5ug and 5ug) and 80ug with 2.5ug GLA were given. The results showed that the vaccinees receiving a 120ug vaccine dose, with 5.0ug GLA adjuvant, had the highest frequency of a ≥3 geometric mean fold rise in anti-F IgG antibody. No controls had such a response. Similar reactogenicity and side effects were observed in the intervention and control groups (39).

RSV-A vaccine with subunit F, G and M

Sanofi reported a decade ago on a subunit vaccine that contains purified RSV A proteins F, G, and M. In 2008, Falsey and colleagues published that this vaccine candidate was examined in 1169 older people ≥65 years with high-risk factors (e.g. congestive heart failure and chronic obstructive pulmonary disease) to compare the immunogenicity and safety with trivalent influenza vaccine in a Phase 2 RCT. 400 participants received this vaccine candidate with adjuvant; 383 received the vaccine without adjuvant, and 386 were in the placebo group. All the participants were given trivalent influenza vaccine. The results showed no interference between RSV vaccinations and trivalent influenza vaccination; furthermore, 129 of 392 participants achieved a ≥4-fold rise in neutralising antibody rise in the adjuvant group; 168 of 378 participants had a ≥4-fold rise in neutralising antibody rise in the non-adjuvant group. Only 3 of 380 had such a rise in the placebo group. There was only one vaccine-related serious adverse event that occurred in the non-adjuvant group. In comparison to the placebo group, this vaccine candidate did not increase RSV infection in the RSV surveillance seasons. The results of this trial supported its' further study in the elderly (40).

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Then, a Phase 1 RCT enrolled 561 healthy people aged ≥65 years, which studied the same recombinant subunit vaccine (containing F, G and M), in dosages of 100ug, 50ug or 25ug with alum adjuvant and 100ug without alum adjuvant, to assess NA levels and the levels of RSV F-specific and RSV G-specific antibodies. The results showed that only the unadjuvanted 100ug product induced a minimum of 50% recipients to have a ≥4-fold rise in NA against RSV-A; meanwhile, it showed that neutralising antibody rise can provide cross-protection against RSV-B. Additionally, there was no overall antibody increase in the placebo group and no vaccine-related serious side event (41). No follow-up study was found in the literature, even though further testing was foreshadowed.

PFP (purified F protein)

Two purified F protein vaccine candidates were reported on in 2003. One, an RSV purified fusion protein 2 (PFP-2) subunit vaccine, was tested in a Phase 1, RCT to determine safety and immunogenicity in 35 women in their third trimesters of pregnancy and their subsequently born children. 95% of vaccine recipients had a ≥4-fold rise in anti-F IgG antibodies. Further, Geometric Mean Concentrations (GMC) of RSV anti-F IgG antibodies were 4-fold higher in vaccine recipients' infants at birth, 2 and 6 months after delivery, than those in infants of the placebo group. There was no safety concern (42).

In a related study, a Phase 2, adjuvant-controlled trial on purified fusion protein-3 (PFP-3) vaccine determined immunogenicity in 294 RSV seropositive children with Cystic Fibrosis. Compared to the placebo group, the vaccine group had significant ≥4-fold titre rises in RSV neutralising antibody A (67% vs 2%), RSV neutralising antibody B (55% vs 3%) and anti-F IgG (97% vs 1%) at day 28. Furthermore, antibody in the vaccine group remained elevated while declining somewhat through the RSV season (43).

3.3 VECTOR-BASED VACCINES

MVA-RSV and PanAd3-RSV

The RSV vector-based vaccines contain inserted portions of RSV protein-encoding genome using either an innocuous adenovirus or another non-pathogenic virus vector-like modified vaccine Ankara (MVA) (44). They are hypothesised to have the advantage of increased mucosal IgA and cellular immune responses (45).

MVA and Simian adenovirus (PanAd3) are vectors of RSV vaccines (MVA-RSV and PanAd3-RSV) both used to encode RSV protein F, N, and M2-1. In pre-clinical trials, each of these two vaccine candidates has shown cellular and humoral responses in a primate model (46, 47). In 2015,

a Phase 1, open-label, RCT, enrolled 42 healthy adults aged 18-50 years. The primary PanAd3-RSV vaccines were given through intranasal (IN) spray in two groups and intramuscular (IM) injection in the other two groups. The booster, PanAd3-RSV or MAV-RSV, was administrated by IM. The results showed an RSV neutralising antibody rise in the primary PanAd3-RSV IM group after the first dose and in the primary IN groups but only after the IM booster. A higher anti-F IgG rise was observed in 19 of 19 participants in the primary IM groups while a rise was seen in 8 of 17 in the IN groups. After boosting, the participants in the IN groups achieved a similar anti-F IgG rise to the ones in the primary IM groups. No vaccine-related serious adverse event occurred (48).

3.4 NANOPARTICLE VACCINES

Nanoparticle F

A Phase 1, observer-blind, RCT (NCT01290419), was conducted in 150 healthy adults aged 18-49 years. Four formulations (5ug, 15ug, 30ug, and 60ug) with alum-adjuvant and 2 formations (30ug and 60ug) without adjuvant were given to vaccine groups. The results showed that all vaccinees developed a 7 to 19-fold increase in anti-F IgG antibody and a 7 to 24-fold increase in PCA. Furthermore, from 7.7% to 44.4% of participants in the vaccine groups had a ≥4-fold rise in the RSV A and B microneutralising antibody. In the placebo group, these antibody levels were at or near the baseline. No serious vaccine-related adverse event occurred (49).

Two Phase 2 trials were conducted in women aged from 18 to 35 years. In 2016, Glenn and colleagues reported on an observer-blind, RCT (NCT01704365) in 330 healthy non-pregnant women of child-bearing age. Vaccine groups were given one or two doses of vaccine (60ug or 90ug) with/without alum adjuvant, respectively. The results showed a 6.5 to 16.5-fold anti-F IgG rise after 2-dose alum adjuvanted vaccines; moreover, there was a 2.7 to 3.5-fold rise in RSV/A and B neutralising antibodies. There was no significant rise in these antibodies in the placebo group. No serious vaccine-related event was reported (50). Another phase 2, observer-blind, RCT (NCT01960686) in 2017, enrolled 720 healthy women. The vaccine groups were administrated 60ug or 120ug RSV protein F vaccine with 0.2mg, 0.4mg, 0.8mg or 1.2mg alum-adjuvant. The results demonstrated about 90% of vaccinees in either the single-dose 120ug (0.2mg and 0.4mg alum) groups or the two-dose of 60ug groups developed anti-F IgG seroconversion (i.e.≥4-fold anti-F IgG antibody rise). Similarly, more than 95% of vaccinees achieved a seroconversion in PCA. Moreover, a strong immune response in the one-dose vaccine recipients resulted in serological evidence of a halving in RSV infection reduction from Day 0 through 90. In addition, the antibody response in the one-dose 120ug with 0.4 mg alum-adjuvant was evidenced from day 14 to day 90. No serious adverse event was found (51).

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One trial was conducted in older adults. In 2017, Louis Fries and colleagues conducted a Phase 1, observer-blind, RCT (NCT01709019), which involved 220 healthy adults ≥60 years without cardiopulmonary issues. Tow dosages (60ug and 90ug) of vaccine with/without alum adjuvant were given in the vaccine groups. Meanwhile, trivalent influenza vaccine (TIV) were given into all the vaccine and placebo groups. This nanoparticle vaccine trial reported a 3.6 to 5.6-fold anti-F IgG rise was observed in the group of 60ug dose of vaccine with adjuvant and the response persisted until 12 months after vaccination. Furthermore, the PCA response was parallel to the anti-F antibody response. Three subjects in the placebo group had a ≥4-fold neutralising antibody rise; this was considered as due to wild RSV exposure. There was no interaction between RSV nanoparticle F vaccine candidates and TIV, and no vaccine-related serious event occurred (52).

4. RSV INFECTION CASES

4.1 RSV INFECTION IN THE LIVE-ATTENUATED VACCINE CANDIDATES

Three trials for LIDΔM2-2, MEDI M2-2, and RSVcps2 were pooled (17, 21, 53). All of them were live-attenuated vaccine candidates conducted in young children from 6 to 24 months. Moreover, each trial had RSV season follow-up. RSV-associated medically attended acute respiratory illness (MAARI) cases were detected during the RSV surveillance periods. Due to study differences, meta-analysis was not possible. However, these data did not show a significant rate of reduction (Table 2).

4.2 RSV INFECTION IN THE SUBUNIT VACCINE CANDIDATES CONFIRMED BY WESTERN BLOT DURING RSV SEASON

4 trials were found, of which two of them were subunit vaccines while the other two were nanoparticle vaccines. The subunit vaccine candidates were PFP-3 and PFP-2. The data were collected in the children aged from 1 to 12 years in the PFP-3 study, and the infants with maternal vaccination in the PFP-2 trial (54) (55). The relative risks of RSV infection between the vaccine and placebo groups were 0.82 (95%, CI 0.56-1.22) and 0.19 (95%, CI 0.02-1.51), respectively. There was no significant reduction of RSV infection (Table 3).3.1

4.3 RSV INFECTION IN NANOPARTICLE VACCINE CANDIDATES

 doi:10.20944/preprints202005.0477.v1

CONFIRMED BY WESTERN BLOT DURING RSV SEASON

According to the published data, two RSV-F nanoparticle vaccine trials were selected (50) (51). Both were conducted in healthy women of childbearing age. The two relative risks were similar; 0.48 (95%, CI 0.29-0.80) was from all active vaccinees compared to placebo recipients, while 0.50 (95%, CI 0.27-0.92) was from pooled one-dose (120ug, 60ug) vaccinees compared to placebo recipients. A vaccine protective effect was revealed according to the relative risk results (Table 3).

5. DISCUSSION

RSV is deemed to be one of the most important public health care issues in young children. The World Health Organisation (WHO) has predicted an effective RSV vaccine will come in the next 5-10 years (56). This systematic review covered 4 major groups of vaccine candidates which are under development: live-attenuated, subunit, recombinant and nanoparticle. These vaccine candidates are targeting several populations: infants and young children, elderly, and pregnant women (or women of maternal age).

In infants and children, the age of most concern is the first 6 months of their life; although they have some maternal immune protection, the risk of severe RSV infection is still high (57). Many children ≥6 months are RSV-naive, and they are similar to infants in less than 6 month-old, except with a more mature immune system (58). Almost all live-attenuated vaccine trials were in infants older than 6 months – they are a proxy for younger infants.

Another difficulty is balancing vaccine attenuation and immunogenicity: either under-attenuation causing more side effects or over-attenuation reducing vaccine infectivity. Both are problematic for optimal vaccine development (59). LID ΔM2-2, MEDI M2-2 trials showed encouraging immunogenicity results. Both of them induced at least 4-fold antibody rise in both neutralising antibody and anti-F IgG antibody in 90% of vaccinees. These robust immune responses showed the potential of protection against RSV exposure. Although there were serious events in the trials, there was not a statistically significant difference to their placebo groups. RSVcps2 is a lineage product from MEDI-599. It had less side effect than MEDI-599, and also it induced a favourable immune response in NA and anti-F antibody. According to the MAARI rate in the subsequent RSV season, LID ΔM2-2, MEDI M2-2, and RSVcps2 did not cause an ERD case. Due to the side effects of RSV cpts-284/404, further attenuation has been proposed in the cold-passage temperature live-attenuated vaccine. This could guide future vaccine development. Although the subunit vaccine candidate PFP-3 had encouraging immunogenicity and safety profile in children with cystic fibrosis, it is

clearly not considered as a promising vaccine because no significant reduction of RSV infection was observed in the following RSV season (60). In summary, LID ΔM2-2, MEDI M2-2, and RSVcps2 are the promising live-attenuated vaccine candidates in the future.

RSV infection has caused a serious burden of disease in the elderly. age-related changes cause a weakening of the immune system (61). Therefore, a potent antigen, adjuvant use or high dose given should be preferred in relevant vaccine products (62). MEDI-7510, RSV vaccine A with subunit F, G, M proteins and nanoparticle F vaccine candidates were conducted in older adults. In addition, the unpublished trial for BBG2Na also involved older people (63).

MEDI-7510 failed to protect against RSV illness in a Phase 2b trial with almost 2000 participants, although the other two vaccines (subunit and the nanoparticle) demonstrated much better results. Hence, MEDI-7510 was not recommended for further study. Although the RSV-A vaccine with subunit F, G, and M proteins, conducted in the elderly, had acceptable results regarding safety and immunogenicity, it does not appear to have been advanced further with no follow-up trials found in 10 years of subsequent literature. Moreover, a human and animal mixed trial for BBG2Na was published. The results showed this subunit vaccine was safe and immunogenic to the vaccinees (aged 60-80 years) (64). However, an unpublished relevant Phase 3 trial for this candidate failed to prove safety in the elderly due to the vaccine-related side adverse events (63).

The 60ug of nanoparticle F vaccine candidate with adjuvant had a favourable immune response and its persistence was long enough to cover a whole RSV season. Therefore, only this nanoparticle F could be thought as the promising vaccine candidate for older people.

Maternal vaccination is one of the best strategies of protection against RSV and avoiding ERD in infants. Ideally, boosting maternal RSV antibody level from at least 3 months prior to labour could make antibodies available for trans-placental transfer (65). In this review, only PFP-2 study was conducted in pregnant women and their offspring. However, there was no further research on this candidate since 2003.

Another two subunit candidates (F-020 and F-024) and a nanoparticle F vaccine candidate were conducted in women of child-bearing age. All of them showed a 3-month-rise of immune antibody, which demonstrated the possibility of placental antibody transportation in the future. F-024 had less vaccination local reaction than Tdap. This also means that F-024 could be more suitable in pregnant women due to less pain from injection. According to the results of the relative risks of RSV infection cases in the surveillance seasons, an acceptable protective effect was shown in one-dose nanoparticle candidate given in the healthy women of child-bearing age. Moreover, the single dose

 doi:10.20944/preprints202005.0477.v1

120ug RSV F protein vaccine with 0.4mg adjuvant was timely and strongly immunogenic. Similar immunogenicity effects for the nanoparticle F vaccine candidate were observed between the one and two doses groups with adjuvant. In fact, one dose is more convenient and still gives a strong antibody response in women of childbearing age. It was being examined in a Phase 3 trial (NCT02624947) in pregnant women in their third trimesters (51). However, there is no recent trial conducted in pregnant women; therefore, we still lack a promising maternal vaccination.

6. CONCLUSION

RSV infection has been considered as one of the most common causes of acute upper respiratory tract infection, which affects children and elderly mostly. Until now, there is no licensed vaccine being used. Recently, a surge of studies has been conducted on this vaccine development, and some of them had encouraging results.

Live-attenuated vaccines target infants and children mostly while the vaccines of the other three types (subunit vaccine, the vector-based, and nanoparticle vaccine) focus on maternal and elderly vaccination mostly.

The encouraging results in both vaccine immunogenicity and safety were illustrated. LID ΔM2-2, MEDI M2-2, and RSVcps2 are the promising vaccine candidates for infants and children. The 60ug of nanoparticle F vaccine candidate with adjuvant is a promising candidate for elderly. Although there is no promising vaccine for maternal vaccination, the subunit RSV-024 and the single dose 120ug RSV F nanoparticle vaccine with 0.4mg adjuvant showed favourable results in non-pregnant women of child-bearing age.

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TABLE 1 Inclusion and exclusion criteria

Inclusion	Clinical study of RSV vaccine used in humans with a measured outcome of immunogenicity
	All ages
	English abstract and full text
	Studies published after Jan 2000 to 6th August 2018
	Human only
Exclusion	Studies with a focus on non-vaccination prevention of RSV, e.g. hand washing, RSV epidemiology, treatment of RSV infection
	Animal studies

 doi:10.20944/preprints202005.0477.v1

FIGURE 1 PRISMA flow chart

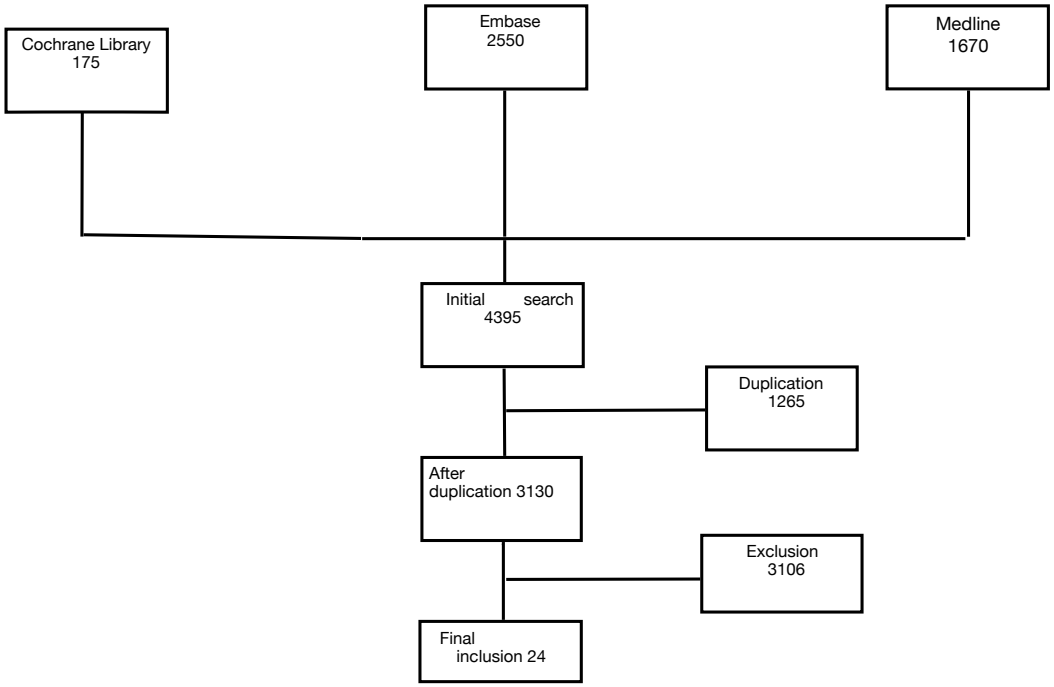

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TABLE 2 MAARI in live-attenuated vaccine trials

Tile	Target population	Vaccine candidate	Number of participants with RSV associated medical attendant acute respiratory illness during RSV season in the vaccine group	Number of participants with RSV associated medical attendant acute respiratory illness during RSV season in the placebo group	Relative risk	Dosage in plaque-forming unit (PFU)
Live-attenuated respiratory syncytial virus candidate with deletion of RNA synthesis regulatory protein M2-2 is highly immunogenic in children (53)	RSV seronegative children from 6-24 months.	LID ΔM2-2	0 of 20	1 of 9		10^5
A gene deletion that up-regulates viral gene expression yields an attenuated RSV vaccine with improved antibody response in children (17)	RSV seronegative children aged 6 to 24 months	MEDI M2-2	1 of 20	2 of 10	0.25 95%, CI 0.03-2.44	10^5
Live respiratory syncytial virus (RSV) vaccine candidate containing stabilized temperature-sensitivity mutations Is High Attenuated in RSV-Seronegative Infants and Children (21)	RSV-seronegative children aged 6-24 months	RSV cold-passage / stabilised 2 (RSVcps2)	3 of 34	2 of 16	0.71 95%, CI 0.13-3.82	10^5.3

MAARI: medically attended acute respiratory illness

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TABLE 3 RSV infection cases in subunit and nanoparticle vaccine candidates

Title	Target population	Vaccine candidate	Number of participants with RSV infection during RSV season in the vaccine group	Number of participants with RSV infection during RSV season in the placebo/control group	Relative risk	Comments
Immunogenicity of a new purified fusion protein vaccine to respiratory syncytial virus: a multi-center trial in children with cystic fibrosis (54)	RSV seropositive children with CF aged 1-12 years	PFP-3 subunit	33 of 130	41 of 133	0.82 95%, CI 0.56-1.22	Control group: alum-adjuvant
Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women (55)	healthy women in the third trimester of pregnancy and their offspring	PFP-2 subunit	1 of 20	4 of 15 (placebo group)	0.19 95%, CI 0.02-1.51	This result is about the infants' follow-up during their first RSV season.
A randomized, blinded, controlled, dose-ranging study of a respiratory syncytial virus recombinant fusion (F) nanoparticle vaccine in healthy women of childbearing age (50)	18-35 year-older non-pregnant and non-lactating healthy women.	RSV-F nanoparticle vaccine	26 of 244	12 of 56	0.48 95%, CI 0.29-0.80	The data from vaccinees with 1 or 2 doses (60ug or 90ug) with/without alum adjutant
A phase 2 randomised, observer-blind, placebo-controlled, dose-ranging trial of aluminium-adjuvant respiratory syncytial virus F particle vaccine formulation in healthy women of childbearing age (51)	18-35 years healthy women	RSV-F nanoparticle vaccine	36 of 352	18 of 84	0.50 95%, CI 0.27-0.92	The data of vaccinees with one dose groups (120ug or 60ug)