Table 3 RSV Vaccines Evaluated in Clinical Trials

Vaccine	Composition	Sponsor, clinical results (reference)	Program status
FI-RSV	Formalin-inactivated, concentrated whole RSV	NIAID; evaluated in infants and young children in the 1960s. Not protective; primed for enhanced disease in RSV-naïve vaccinees (28,29)	Discontinued
PFP-1, PFP-2, PFP-3	F protein purified from RSV-infected Vero cells	Wyeth; evaluated in adults, elderly adults, seropositive children and pregnant women. Safe and moderately immunogenic (31)	Discontinued
FG	Recombinant fusion protein; (ectodomains of F and G)	GlaxoSmithKline; results of clinical studies not reported (32)	Discontinued
F, G, M	Coformulated purified F, G, and M proteins	Aventis-Pasteur; safe and immunogenic in adults (33)	Active
BBG2Na	Part of the G protein (G2Na) fused to the albumin-binding domain of streptococcal G protein (BB)	Pierre Fabre; evaluated in young adults and elderly adults; insufficiently immunogenic (34,35)	Discontinued
Various *cp*, *ts*, and *cpts* mutants	Biologically derived RSV mutants; live intranasal	NIAID and Wyeth; safe in adults but over- or under-attenuated in seronegative children and/or infants (20)	Discontinued
ts mutants 1B and 1C	Biologically derived RSV mutants; live intranasal	University of Warwick; *ts*1C safe in adults and immunogenic in some individuals (36)	Discontinued
Recombinant *cpts* and deletion mutants	Recombinant RSV mutants prepared by reverse genetics; live intranasal	NIAID and Wyeth (disconinued); NIAID and MedImmune RSV248/404/1030 ΔSH; safe and immunogenic in young infants; additional candidates being developed (19,37)	Active
Wild-type RSV	Live	Merck; evaluated in children with serum antibody to RSV; poorly immunogenic and not protective (38)	Discontinued
Intramuscular			
B/HPIV3-F	Recombinant B/HPIV3 expressing the RSV F protein	MedImmune; safe and immunogenic in adults (39)	Active

Abbreviations: RSV, respiratory syncytial virus; PIV, parainfluenza virus; PFP, purified F protein; BBG2Na.

the use of subunit vaccines in seronegative infants challenging: first, like FI-RSV, subunit vaccines induce a high titer of RSV-binding (ELISA) antibodies that have low neutralizing activity; second, the enhanced disease seen with FI-RSV can be replicated in rodent models with subunit vaccines (42,43). Several purified F protein (PFP) vaccines (PFP-1, PFP-2, and PFP-3) have been evaluated by Wyeth Vaccines in clinical trials (31), but to our knowledge these clinical development efforts have been discontinued (Table 3). The fundamental weakness of PFP vaccines was their inability to induce a high titer of RSV neutralizing antibodies. PFP-3 (adjuvanted with aluminum phosphate), for instance, was found to be safe and immunogenic in seropositive children with cystic fibrosis, but the vaccine did not confer protection against RSV (44). Similarly, a significant increase in RSV neutralizing IgG titers was not observed following vaccination of pregnant women in their third trimester (45). These observations indicate that it is difficult to increase RSV antibody titers by immunization of young or adult seropositive individuals by a subunit vaccine. However, if subunit vaccines can be formulated to induce a high titer of neutralizing antibodies, they likely would have usefulness for immunization of the elderly, high-risk seropositive children, or immunocompromised persons that have previously been primed for an antibody response by natural infection. A nonreplicating protein vaccine probably would be acceptable for use in these groups because the disease potentiation that is associated with this type of vaccine has only been observed in RSV-naïve individuals. Since it is apparently difficult to achieve a sustained increase in RSV antibody titers in seropositive subjects, RSV vaccines to protect the elderly might have to be given annually, for example, together with the annual influenza virus vaccine, to provide coverage for a single RSV season.

Sanofi-Aventis developed a subunit vaccine consisting of purified F, G, and M proteins that was found to be safe and immunogenic in healthy adult volunteers, but antibody titers were too short lived to provide long-term protection (33) (Table 3). The Institute Pierre Fabre generated a novel, bacterially expressed recombinant candidate vaccine by fusing the conserved central domain of the RSV G protein to the albumin-binding region of streptococcal protein G (Table 3). Although this candidate vaccine was found to be safe and immunogenic in phase 1 and 2 clinical trials, unexpected side effects such as purpura and type III hypersensitivity reactions occurred infrequently in phase 3 trials, and this halted further clinical development (34).

DNA and RNA vaccines for RSV and PIV have not reached clinical trials yet and will not be considered here. In addition, non-living vaccines for PIV are not currently in clinical trials and will also not be further discussed.

Live Virus Vaccines

Live virus vaccines either can be live attenuated RSV or PIV strains or can be live attenuated virus vectors that express RSV or PIV protective antigens. The live attenuated virus vaccines can also function as vectors to create multivalent RSV and PIV vaccines.