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Review

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Recent Advances in the Prevention of RSV in Neonates and Young Infants

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Conflict of Interest
K.W. Y attended the 2022 RSV regional advisory board meeting (ABM) of Sanofi as an expert on 30 August 2022. The author has no other conflicts of interest to declare.

ABSTRACT

Respiratory syncytial virus (RSV) is a pathogen with a high burden of disease and social cost among infants worldwide, but the development of a vaccine has been delayed. The recent understanding of the pathogenesis of RSV, progress in reverse genetics, and successful implementation of other maternal immunizations have prompted the recent rapid development of monoclonal antibodies (mAbs) and vaccines for RSV prevention. Phase 3 clinical trials for two next-generation mAbs (nirsevimab and clesrovimab) and two maternal RSV pre-F vaccines are currently underway or have been recently completed. Soon, we might be able to protect young infants through long-acting mAbs and/or maternal immunization. Additionally, the development of live-attenuated vaccine candidates that are capable of avoiding enhanced RSV disease is ongoing. We need to gain familiarity with these newly developed strategies and collect epidemiological data on domestic RSV to adequately prepare for a new era of RSV prevention.

Keywords: Respiratory syncytial virus; Monoclonal antibody; Vaccine; Infant

INTRODUCTION

Before the coronavirus disease 2019 (COVID-19) pandemic, an important health issue in infants and children was respiratory syncytial virus (RSV) infection and its prevention.[1] Despite the fact that the disease burdens and social costs associated with RSV are high, the development of vaccines has been delayed. However, the recent advance on understanding of the pathogenesis of RSV infection, progress in reverse genetics, and worldwide interest in preventing RSV-related disease in infants and elderly people have promoted progress. The successful implementation of maternal immunization with influenza and Tdap vaccines have also supported the recent development of the RSV vaccine.[2] This review summarizes the progress in RSV prevention strategies thus far and updates the information on the basis of recent research.

RSV STRUCTURE AND ANTIGENIC SITE

RSV is an Orthopneumovirus in the Pneumoviridiae family, and comprises 2 antigenic subgroups, A and B (RSV-A and RSV-B, respectively). The 15.2 kb-sized, nonsegmented,

single-stranded, negative-sense genome contains 10 genes encoding 11 proteins. Among them, three (NS1, NS2, and M2-2) are nonstructural proteins, and eight are structural proteins. The G protein mediates attachment of the virus to airway epithelial cells of host. The F protein causes the viral and cellular membranes to fuse together, so enabling viral penetration and inducing the production of characteristic syncytia. Due to the genetic diversity of G protein, genotype of RSV is classified based on G protein, but antibodies and vaccines target F protein, which has little genetic/antigenic diversity.[2)]

Monoclonal antibody (mAb) and vaccine development have advanced in recent years with understanding on the molecular structure of the RSV F protein. The F glycoprotein has the two distinct conformations, which are pre-fusion (pre-F) and post-fusion (post-F), and contains six key antigenic sites (Ø-V) for neutralizing antibodies. The pre-F is the active form on the virus surface and easily refolds to the post-F conformation. During rearrangement, the post-F loses its most potent neutralizing antigenic sites, the Ø and V sites. Monoclonal antibodies binding to the pre-F are more efficient at neutralizing RSV than those binding to both the pre-F and post-F conformations (**Fig. 1**, **Table 1**).[2-4)]

More than 7 mAbs and 30 vaccine candidates have been in the development.[5)] Among them, 3 mAbs and 3 maternal vaccine candidates recently entered phase 3 trials, although each one mAb and vaccine candidate ultimately failed (**Table 2**).

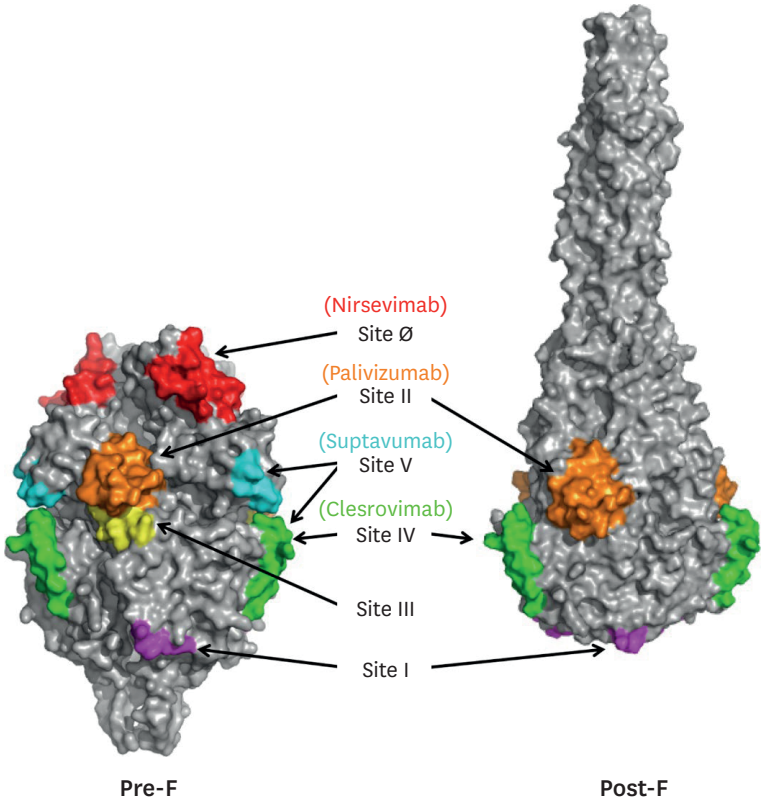

Fig. 1. Respiratory syncytial virus F pre-fusion and post-fusion structures and antigenic sites. Modified from Flynn et al.[4]
Abbreviations: RSV, respiratory syncytial virus.

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Table 1. Antigenic sites of the respiratory syncytial virus F protein and the mAbs that bind to each site

Antigenic site	Neutralizing sensitivity	Location	mAb
Ø	+++++	only Pre-F	Nirsevimab
V	++++	only Pre-F	Suptavumab
III	+++	Pre-F > Post-F	
IV	++	Pre-F & Post-F	Clesrovimab
II	++	Pre-F & Post-F	Palivizumab
I	+	Post-F > Pre-F	

Abbreviations: mAb, monoclonal antibody; pre-F, F gene in the pre-fusion configuration; post-F, F gene in the post-fusion configuration.

Table 2. RSV clinical trial summary (Phase 3)

Platform	RSV candidate vaccine or mAb	Sponsor	Candidate status	Study start date	Completion date	Trial population
Immuno-prophylaxis	Suptavumab	Regeneron	Inactive	2015-06-21	2017-09-26	<6 mon, born preterm at ≤35 wk of GA
	Nirsevimab	AstraZeneca	Active candidate	2019-07-30	2022-11-22	<12 mon, born at <35 wk of GA or with CLD/CHD
				2019-07-23	2023-03-29	<12 mon and born at ≥35 wk of GA
	Clesrovimab (MK-1654)	Merck		2021-04-07	2025-01-08	Infants up to 23 mon
				2021-11-01	2026-04-27	Infants up to 12 mon
Recombinant subunit	RSV F Nanoparticle	Novavax	Inactive	2015-12-01	2019-07-01	Pregnant females aged 18–40 yr
	RSV Pre-F	Pfizer	Active candidate	2020-06-17	2023-09-12	Pregnant females aged 18–49 yr
	RSV Pre-F3	GSK		2020-11-20	2024-02-02	
				2021-08-02	2023-04-03	Pregnant females aged 15–49 yr, high-risk
				2021-09-15	2022-05-29	Nonpregnant women aged 18–49 yr

Abbreviations: RSV, respiratory syncytial virus; mAb, monoclonal antibody; GA, gestational age; CLD, chronic lung disease; CHD, congenital heart disease; GSK, GlaxoSmithKline.

RECENT EPIDEMIOLOGY

1. Disease burden of RSV infection

RSV is a common cause of lower respiratory tract infection (LRTI) and a main reason for hospitalization in young infants and children, resulting in a large burden on health care services worldwide. In 2015, 33.1 million cases of acute LRTI, 3.2 million hospitalizations, and 59,600 in-hospital deaths were associated with RSV in children <5 years of age worldwide. Approximately 45% of hospitalizations and deaths due to RSV-LRTI occur in neonates and infants younger than 6 months.[1] In the United States, RSV is estimated to cause 9–12% of all nonbirth hospitalizations and result in 80,000–100,000 hospitalizations annually. Among infants who are hospitalized, 15-20% require an intensive care, and approximately half of these children receive mechanical ventilation. The overall burden of medically attended RSV-LRTI during the first RSV season each year in the US varies between 50 and 180 per 1,000 infants, with 80% of cases occurring in full-term infants.[6]

The burden of RSV is substantial on infants younger than 1 year age, and acute otitis media (AOM) is a common complication. In a recent study from Finland, the incidence rates of RSV-related illness and hospitalization were 328 and 22 per 1,000 infants, respectively, and 77% of infants with RSV infection developed AOM.[7] In South Korea, the burden of RSV has not been systematically estimated, but children <2 years old with underlying disease may require intensive care.[8]

2. RSV infection in South Korea

During 1990–2018, in Seoul National University Children's Hospital (SNUCH), RSV-A was more common than RSV-B in 21 of 28 seasons. Although different subtypes and genotypes circulated together during most seasons, the ON1 and BA genotypes completely replaced

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the previous genotypes of RSV-A in 2013/2014 and RSV-B in 2006/2007, respectively. Since the 2013/2014 season, RSV-A and RSV-B have shown alternating predominance.[9] Recently, relatively large epidemics of RSV-A and cocirculating RSV-A and RSV-B occurred in the 2018–2019 and 2019–2020 seasons, respectively. During the COVID-19 pandemic in the 2020/2021 season, no RSV epidemic occurred, but an RSV-B epidemic did occur from November 2021 to March 2022 in South Korea, which aligned with the relaxation of the quarantine policy.[10] We are currently experiencing an RSV-A epidemic in the 2022/2023 season.

RSV PREVENTION STRATEGIES

1. Monoclonal antibody

Palivizumab

Palivizumab (Synagis®) (AstraZeneca, London, UK) is a humanized mAb approved for prophylactic administration in infants with established risk factors for severe RSV infection. Palivizumab has been used in over 80 countries since its approval by the U.S. Food and Drug Administration in 1998. Palivizumab has been marketed in South Korea since 2005. It has been covered by medical insurance since January 2006. Monthly palivizumab administration is effective for the prevention of serious RSV illness in infants with prematurity and/or bronchopulmonary dysplasia.[11,12] In a previous multicenter (n=46) Korean study that enrolled 1,140 preterm infants who were born at 34 weeks of gestational age (GA) or earlier and admitted to the neonatal intensive care units (NICUs), palivizumab decreased the risk of RSV-related readmission (odds ratio, 0.06; 95% confidence interval [CI], 0.03–0.13; $P<0.001$) for >1 year after discharge from the NICU.[13] Additionally, palivizumab has resulted in a significant reduction in hospitalization rates for infants with hemodynamically significant congenital heart disease (CHD).[14] Furthermore, palivizumab is beneficial in preventing severe RSV disease in infants with immunodeficiency and neuromuscular disease.[15,16]

A previous study reported that from January 1991 to July 2012, the average RSV season in South Korea was between the 2nd week of October and the 2nd week of February. The earliest starting was in the 3rd week of July in 2001, and the latest end was in the 3rd week of May in 1990. Palivizumab administration was initiated most commonly in the 1st week of October (18.7%), but the proportion of the initiation in the 1st week of September increased from 3.8% in 2007 to 14.1% in 2013.[17] There was no RSV epidemic in the 2020/2021 season; moreover, the 2021/2022 season started approximately one month later than usual in South Korea, but palivizumab was prescribed in a similar amount and at a similar time as those in previous years, even in SNUCH (**Fig. 2**).

Although it is difficult to accurately predict the onset and transmission speed of an RSV epidemic, and high-risk infants may develop severe RSV infection if they miss the window for vaccination, considering the fast-acting characteristics of mAbs, it is reasonable to wait to administer palivizumab until the RSV epidemic reaches a certain level in the corresponding community. Too early administration of the initial palivizumab can lead to substantial unnecessary medical expenses and side effects of the drug. Furthermore, when an RSV epidemic continues through April or May, high-risk infants may not be protected by the last (5th) dose of palivizumab. The timing of the initiation of palivizumab should be re-evaluated each year and controlled centrally in accordance with the RSV monitoring system.

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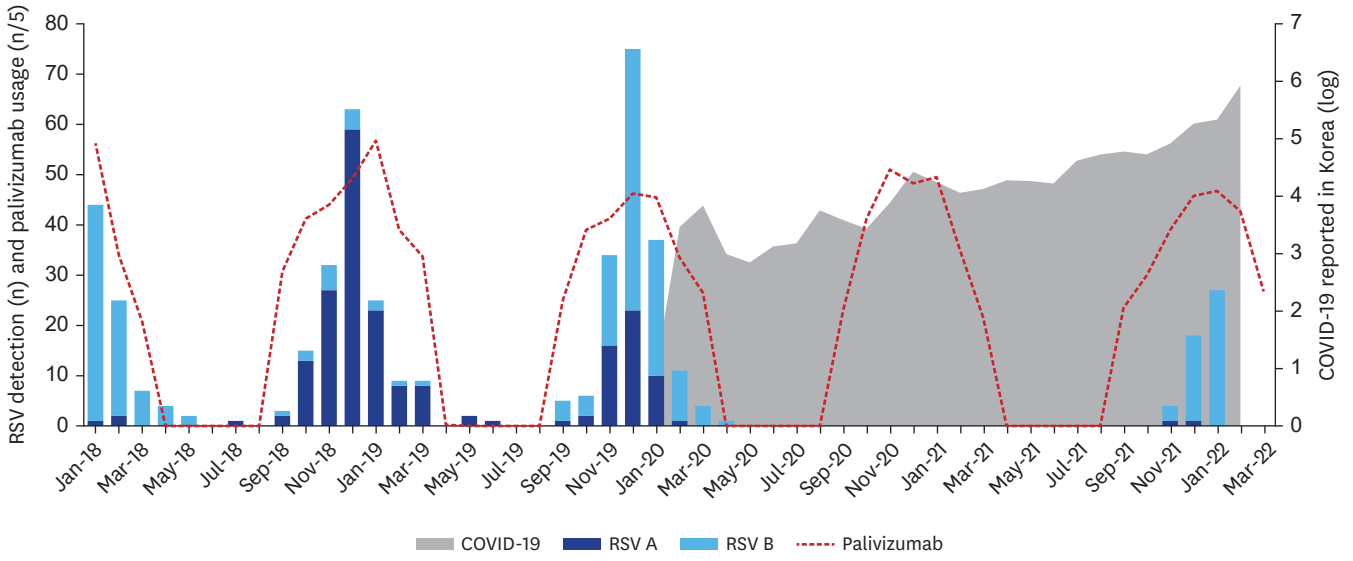

Fig. 2. RSV epidemics and palivizumab usage in SNUCH, 2018–2022. Blue and orange bars indicate the number of RSV A and RSV B detected respectively in SNUCH. The red dotted line indicates the number of palivizumab (100 mg) used in SNUCH, which was presented on a 1/5 scale for adjustment. The yellow area indicates the number of confirmed COVID-19 cases on a log scale reported nationwide in Korea.
Abbreviations: RSV, respiratory syncytial virus; COVID-19, coronavirus disease 2019; SNUCH, Seoul National University Children's Hospital; n, number.

Next-generation mAbs

The latest candidate for RSV mAb is nirsevimab (Beyfortus®) (AstraZeneca and Sanofi, Paris, France). Nirsevimab has greater neutralizing activity (due to the targeting the antigenic site Ø of pre-F proteins) and a longer serum half-life (as determined by YTE technology, due to the substitution of the key amino acid residues of the Fc receptor of human immunoglobulin G [IgG; M252Y/S254T/T256E] to enhance its recycling) than palivizumab. Thus, only a single-dose nirsevimab injection is required for RSV protection over the 5–6 month span of the RSV season compared to a monthly palivizumab injection.[18] In a recent phase 3 clinical trial, a single administration of nirsevimab reduced the incidence rates of RSV-associated LRTI requiring medical care and hospitalization by 70% and 80%, respectively, in early preterm (29–34 weeks of GA) infants.[19] Nirsevimab was also efficacious in preventing RSV-associated LRTI requiring medical care in late preterm and term infants (≥35 weeks of GA).[20] Moreover, in infants with CHD and chronic lung disease and in preterm infants, the safety profile of nirsevimab and palivizumab was similar.[21]

Clesrovimab (MK-1654) (Merck, Rahway, NJ, USA) is a mAb with a prolonged half-life and enhanced neutralizing activity, which is derived from human memory B cells. It binds to an epitope in antigenic site IV of the RSV F protein. Its parental antibody, RB1, has been shown to be equipotent against RSV-A and RSV-B.[22] A phase 3 clinical trial is ongoing, and it is expected that results will be obtained in a couple of years.[5]

Suptavumab (Regeneron, Tarrytown, NY, USA), which is an RSV F site-V-specific mAb, failed to meet the primary efficacy endpoints, which included overall RSV hospitalizations and outpatient LRTIs. Suptavumab almost did not neutralize the major circulating strain of RSV-B. Two amino acid substitutions (L172Q and S173L) in the binding epitope caused the emergence of escape variants of RSV-B strains.[23]

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F gene polymorphism resulting in mAb resistance

Binding sites of the mAb to the epitopes of RSV F protein were amino acids 254-277 for palivizumab, amino acids 62-69 and 196-212 for nirsevimab, amino acids 426-447 for clesrovimab, and amino acids 161-182 for suptavumab. Known complete resistance-associated mutations against suptavumab include L172Q and S173L. In a recent systematic review of global genetic data on RSV F protein, the frequency of these suptavumab escape mutations (L172Q and S173L) was mostly over 90% in RSV-B obtained during 2015–2018.[24] Most of the mutations have not been tested in neutralization assays, but changes associated with partial resistance have been reported for nirsevimab (E66K, K68N, N201S, Q209K, and Q209 L) and palivizumab (S276N).[25]

In a previous US study, partial F gene sequencing was performed on archived respiratory specimens from 39 infants during 2001–2007 who were confirmed to be positive for RSV and had a history of palivizumab administration. As a result, palivizumab-resistance mutations (PRMs) were identified in samples from 4 (10.2%) children. Breakthrough RSV infections in infant administered with palivizumab were not mostly due to PRMs.[26] In a previous Korean study, F gene sequence analysis was conducted in 30 RSV-A and 30 RSV-B strains obtained from children during 2009–2015. Among them, 15 children (10 with RSV-A and 5 with RSV-B) were administered with palivizumab. One or more mutations to the reference sequences were identified in all RSV-A and 86.7% of RSV-B. However, no known PRMs were found in circulating Korean RSV strains.[27]

2. Vaccines

RSV-naïve infants immunized with the first inactivated RSV vaccine had enhanced RSV disease (ERD) when they got a subsequent RSV infection. Eighty percent of them required hospitalization, and two infants died.[28,29] Thus, RSV vaccine development has been retarded since this event in the 1960s. However, understanding of the pre-F structure of the RSV F protein has promoted the RSV vaccine development. Although a correlate of immunity has not yet been defined, neutralizing antibodies against the pre-F have been used as the proxy of protection, as shown by the effectiveness of anti-F mAb (palivizumab) and the protection conferred by maternal antibodies.[2]

Maternal vaccines: recombinant Pre-F subunit

The maternal vaccination is aimed to increase neutralizing antibody concentrations in pregnant woman and to increase transplacental antibody transfer to fetus. It gives protection to the infant during the first months of life, when newborns do not yet possess a fully mature immune system and thus, newborns are highly susceptible to RSV.[30] Higher concentrations of maternal RSV antibodies reduce the risk of RSV infection in newborns.[31,32] Additionally, maternal immunization could protect the newborn infant by preventing RSV infections of the mother and by conferring passive immunity through breast milk.[33] In particular, maternal pre-F RSV antibodies are important in protection of the infant against RSV.[34] Moreover, vaccine-mediated ERD has been occurred in infants who have no previous RSV infection. Because all adults have been exposed to RSV, maternal immunization could circumvent the risk of ERD.

The Novavax RSV F vaccine was immunogenic and tolerated in nonpregnant healthy women of childbearing age, inducing palivizumab competing antibody (PCA).[35] In a subsequent study with healthy third-trimester pregnant women, infants with maternal immunization had higher anti-F IgG and PCA titers at birth than infants in the placebo group. There was no evidence of ERD in infants of maternal immunization.[36] Finally, the Novavax phase 3 Prepare

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Trial, in which 4,636 pregnant women were randomized to receive a particle-based vaccine or a placebo in the third trimester, showed that maternal immunization is a feasible strategy against RSV, even if the trial did not meet the prespecified primary efficacy endpoint against the medically significant RSV LRTI up to 90 days of life.[37]

The immunogenicity and safety of an RSV vaccine (RSV-PreF, GlaxoSmithKline, UK) containing recombinant RSV protein F in the pre-F conformation was evaluated in phase 2 clinical trials.[38,39] Various formulations of the RSV-PreF vaccine boosted the immune response in 18–45-year-old nonpregnant women. The vaccine had considerable immunogenicity and a good safety profile. Another RSV-PreF vaccine from Pfizer (US), which was a bivalent vaccine with RSV-A and RSV-B antigens, also showed promising immunogenicity and safety in a phase 1/2 study in adults aged 18–49 years.[40] Then, in the phase 2b trial, the RSV-PreF vaccine induced good neutralizing antibody responses and efficient transplacental transfer. There was no evident safety concerns in pregnant women at 24 to 36 weeks gestation.[41]

Infant vaccines: live-attenuated vaccines (LAVs)

For infants, a LAV is the most attractive candidate. Clinical studies conducted in the past 20 years showed that RSV LAVs do not cause ERD; this was already speculated from animal studies, as ERD was linked to nonreplicating RSV vaccines.[42] Thus, young infants who are RSV-naïve and thus vulnerable to ERD could benefit from the LAV platform for RSV prevention. Furthermore, RSV LAVs can elicit a local mucosal and systemic response by intranasal administration and are immunogenic even in the presence of maternal antibodies for very young infants.

The attenuation of RSV for LAV has been achieved by serial passage or mutagenesis in cell culture, which are labor-intensive and poorly controllable. The first attempt to develop an RSV LAV was propagating the virus at a low temperature (cold passage) and/or mutagenizing, so selecting viruses that could not grow at high temperatures (temperature-sensitive mutants). By this adaptation, the LAV virus would be able to replicate in the upper but not lower respiratory tract. This temperature sensitivity may restrict the virus to the upper respiratory tract and increase the safety of vaccines.[2]

The development of reverse genetics to introduce specific genetic changes has greatly enhanced LAV development. RSVcps2, which have the 248s and 1030s mutations, was generated from complementary DNA in Vero cells. The highly attenuated virus from these mutations did not replicate in vitro temperature of 35°C. RSVcps2 was safe in RSV-naïve infants and children, and LRTIs requiring medical attention were not observed.[43]

The RSV LAV candidate LIDΔM2-2 have deletion of the RSV RNA regulatory protein M2-2, resulting in upregulated viral antigen expression and reduced RNA replication. These changes may induce increased immunogenicity and safety. The LIDΔM2-2 had excellent immunogenicity inducing substantial neutralizing antibodies in 90% of the vaccinated RSV-naïve infants.[44] LIDΔM2-2 was further engineered with a temperature-sensitive mutation (1030s), and this LID/ΔM2-2/1030s had excellent infectivity, durable immunity, and anamnestic antibody responses, without evidence of genetic instability.[45]

Vaccines for elderly individuals: adenovirus vector and mRNA vaccines

Ad26.RSV.preF is a recombinant adenovirus vector (Ad26) vaccine that encodes a RSV-F protein in the pre-F conformation. Ad26 elicit excellent immune responses and have a good safety

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profile. Thus, this vaccine has been developed for use in elderly people, who are relatively immunocompromised and have a low risk of ERD. Ad26.RSV.preF has demonstrated good immunogenicity and safety profiles in elderly individuals and young adults.[46,47]

In response to the COVID-19 pandemic, vaccination with mRNA vaccines has become a critical strategy, and their immunogenicity and safety have been thoroughly evaluated. Moreover, mRNA vaccine technology potentially allows rapid antigen design and scalable production. RSV mRNA vaccine development has recently been initiated for the vaccination of elderly individuals, and the safety and immunogenicity of the developed intramuscular vaccines have been evaluated.[48] The expansion of the application of the mRNA vaccine development strategy to various pathogens in addition to RSV is expected.

CONCLUSIONS

The recent development of RSV prevention strategies is promising, and a new era in RSV prevention and control is expected. In the near future, young infants might benefit from long-acting mAbs and maternal immunization. Furthermore, live attenuated vaccines can provide powerful and prolonged protection against RSV infection in children. We need to become familiar with these newly developed strategies and collect epidemiological data on domestic RSV characteristics to adequately prepare for the new era of RSV prevention.

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요약

Respiratory syncytial virus (RSV)는 전 세계적으로 영유아에게 질병 부담과 사회적 비용이 매우 높은 병원체이지만 그 백신 개발은 상당히 지연되고 있다. 현재로선 단기-지속형 단클론항체인 palivizumab이 유일한 예방법이다. 그러나 최근 RSV 감염의 병태생리학에 대한 이해, 유전학의 발전, 모체 예방접종의 성공적인 시행 등으로 RSV 예방을 위한 단일클론 항체 및 백신의 개발이 급속히 추진되고 있다. 현재 2개의 장기-지속형 단클론항체 제제(nirsevimab 및 clesrovimab)와 2개의 모체 RSV pre-F 백신이 임상 3상 시험을 진행 중이거나 막 완료하였으며, 지금까지의 결과는 효과와 안전성 측면에서 매우 긍정적이다. 가까운 장래에 장기-지속형 단클론항체와 모체 예방접종을 통해 고위험군은 물론이고 기저질환이 없는 신생아 및 영유아들을 RSV로부터 효과적으로 보호할 수 있을 것으로 기대한다. RSV 예방의 새로운 시대에 빠르고 적절히 대비하기 위해서는 이러한 새로운 전략들에 익숙해지고 국내 RSV에 대한 역학 자료들을 계속 수집해 나갈 필요가 있다.