

## Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children

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## Abbreviations

- AE: Adverse event
- BCG: Bacille Calmette Guerin
- BLP: Bacterium-like particle
- BPD: Bronchopulmonary dysplasia
- CHD: Congenital heart disease
- CLD: Chronic lung disease
- DNA: Deoxyribonucleic acid
- FDA: Food and Drug Administration
- HSCT: Hematopoietic stem cell transplantation
- IM: Intramuscular
- IV: Intravenous
- LRTI: Lower respiratory tract infection
- mAB: Monoclonal antibody
- MVA: Modified vaccinia virus Ankara
- PATH: Program for Appropriate Technology in Health
- PIV: Parainfluenza virus
- RCT: Randomized controlled trial
- RNA: Ribonucleic acid
- RSV: Respiratory syncytial virus
- RSV-IGIV: Respiratory syncytial virus immune globulin intravenous
- RSVH: Respiratory syncytial virus hospitalization
- SeV: Sendai virus
- SOE: Strength of evidence
- URTI: Upper respiratory tract infection
- VLP: Virus-like particle
- wGA: Weeks gestational age
- WHO: World Health Organization

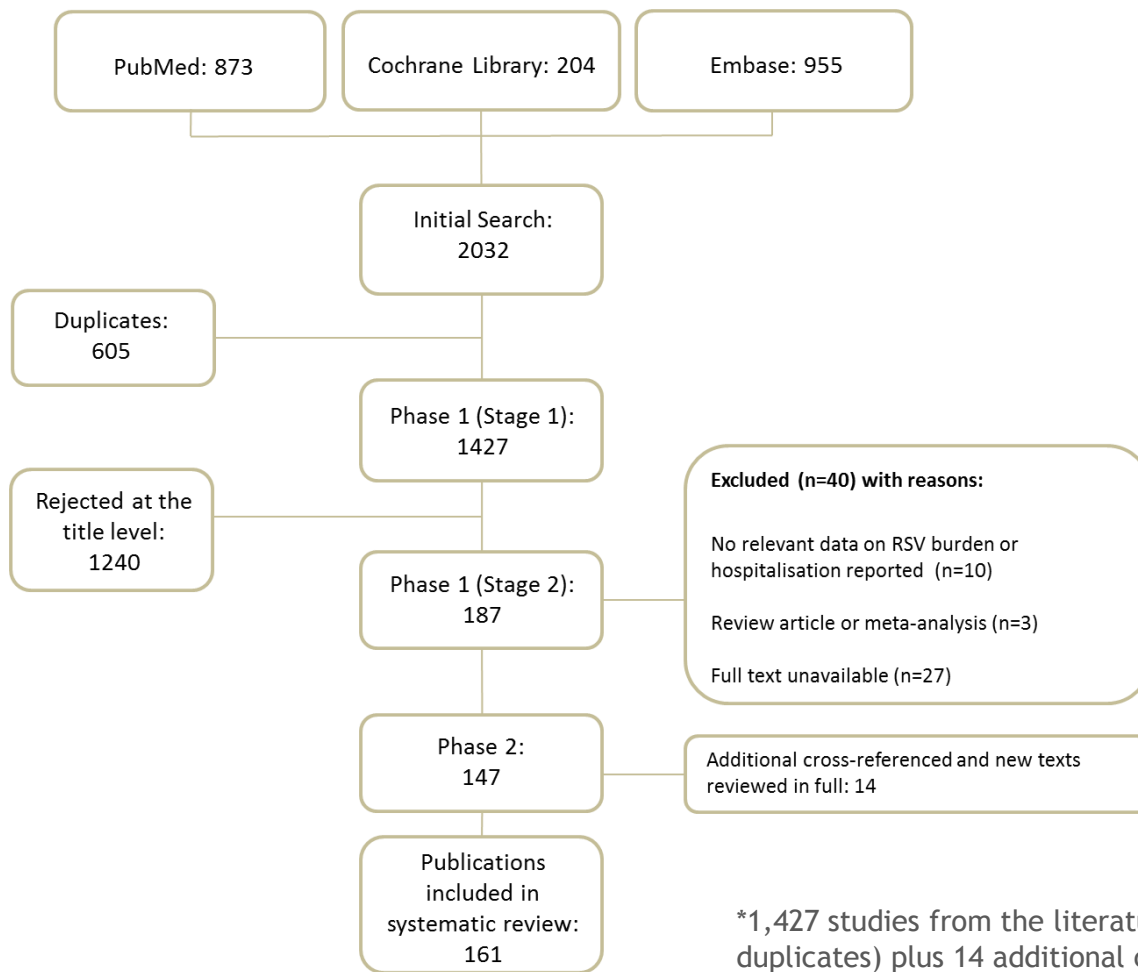
## REGAL 7: Past, present and future approaches to the prevention and treatment of RSV

- The methodology followed that of the predetermined protocol outlined in REGAL 1
  - The target population consisted of children aged  $\leq 18$  years with or without comorbidities or risk factors for RSV
- Selected non-Western studies\* of relevance or importance were included to supplement the evidence base
- Outcomes of interest for this review included:
  - Incidence and epidemiology of RSV following:
    - Prophylactic intervention
    - Treatment therapies
- A second non-systematic review was used to identify and evaluate promising new therapies and vaccines for RSV

\*REGAL primarily focused on studies conducted in Western countries, defined as: the United States, Canada, and Europe (including Turkey and the Russian Federation)

## Systematic review

- 1,441 studies\* were identified of which 161 were included



## RSV-IGIV was the first prophylactic agent to be approved by the FDA for the prevention of RSV in preterm infants

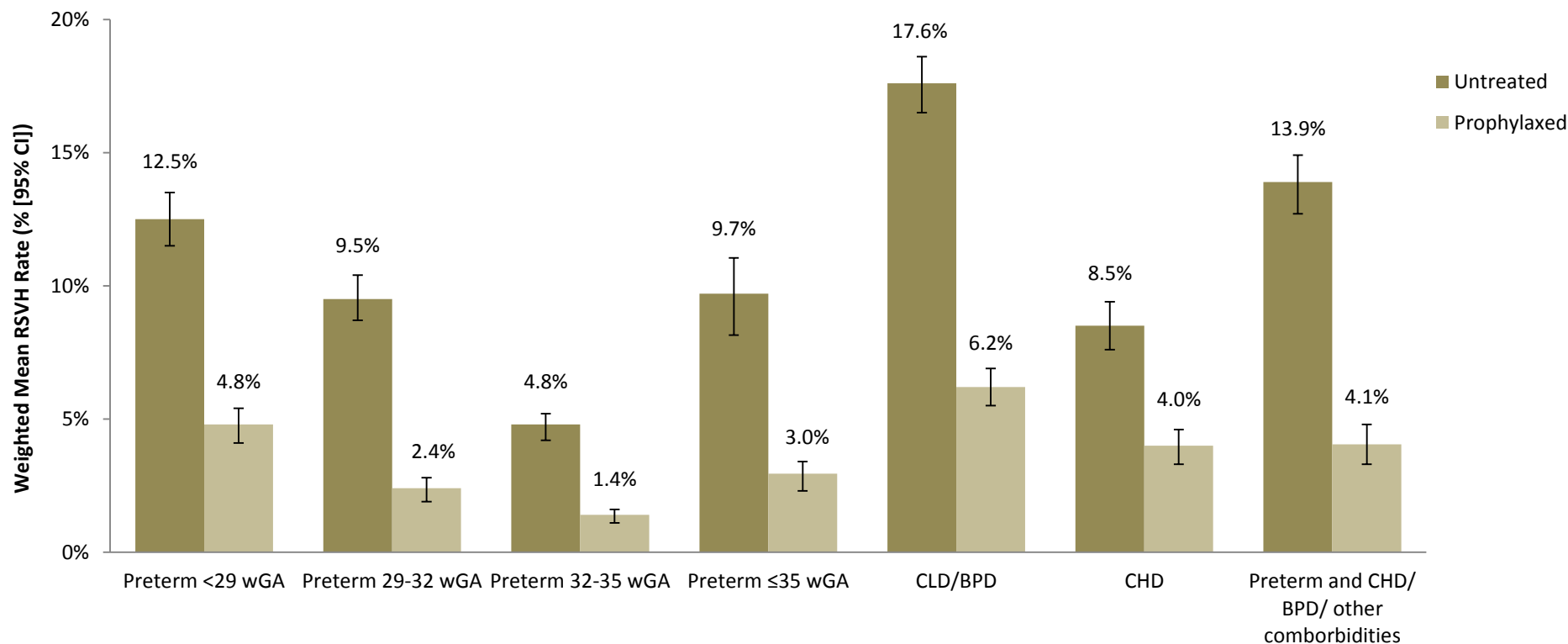
- Polyclonal human IV antibody preparation enriched for RSV neutralizing activity
  - first successful prophylactic agent shown to prevent severe RSV LRTI in infants and children <2 years
- Pivotal trials included NIAID (1993)<sup>1</sup>, PREVENT (1997)<sup>2</sup> and CARDIAC (1998)<sup>3</sup>
- Licensed by the FDA in 1996 for prevention of RSV LRTI in **preterm infants** (<36 wGA) and **infants <24 months with BPD**
  - Indication limited to preterm infants **without CHD** due to safety concerns and apparent lack of efficacy in some populations
  - RSV-IGIV was voluntarily withdrawn from market in 2003 following successful licensure of a monoclonal antibody preparation

1. Groothuis JR et al. N Engl J Med. 1993;329:1524-30; 2. The PREVENT Study Group. Pediatrics. 1997;99:93-9; 3. Simões EAF et al. J Pediatr. 1998;133:492-9.

## Palivizumab was effective in the prevention of RSV LRTI and RSVH in children

- Humanized mAB
  - Administered by monthly 15 mg/kg IM injection during the RSV season
  - Licensed in 1998
- Shown to be effective in high-risk subgroups e.g. infants with CHD or preterm infants with and without BPD/CLD
- Palivizumab has been shown to be well-tolerated
  - AEs similar to that of placebo
  - Safety profile confirmed by real-world evidence, including in children with complex medical disorders
- Guidelines restrict use of palivizumab to highest-risk subpopulations due to cost-benefit considerations

## Palivizumab was effective in the prevention of RSV LRTI and RSVH in infants born preterm or with CHD and/or CLD/BPD



Prophylaxis with palivizumab reduced the risk of RSVH in subpopulations prone to RSV

## Palivizumab has been used in prevention of RSV LRTI/RSVH in other subgroups

- Down syndrome
  - Medical need for prevention of RSVH in infants and children with Down syndrome is high
  - RSVH rates in children with Down syndrome receiving palivizumab are low
- Cystic fibrosis
  - Evidence is relatively limited and inconclusive
    - Palivizumab registry data
    - Lack of suitably powered studies
- Other significant underlying medical conditions
  - Neuromuscular disease and congenital airway anomalies

There is growing evidence for palivizumab use in high-risk subgroups outside those addressed in the guidelines



## Motavizumab has been shown to be non-inferior to palivizumab

- Second generation humanized mAB derived from palivizumab
  - Exhibited 10-fold greater activity in preclinical studies
- Clinically assessed in two pivotal trials: Carbonell-Estrany et al (2009)<sup>1</sup> and Feltes et al (2011)<sup>2</sup>
  - Overall, motavizumab was non-inferior to palivizumab
  - Cutaneous AEs were more frequently reported in motavizumab-treated patients
- FDA license application rejected in 2010

Motavizumab has a more significant adverse event profile than the first-generation prophylactic agent palivizumab

1. Carbonell-Estrany X et al. Pediatrics. 2009;125:e35-51; 2. Feltes TF et al. Pediatr Res. 2011;70:186-91.

## There are limited data on the long-term impact of existing RSV prophylactic measures

### RSV-IGIV

- Long-term follow-up of infants with BPD/CLD showed improved lung function in those treated with RSV-IGIV versus non-RSV-IGIV-treated infants

### Palivizumab

- Incidence of recurrent wheezing has been shown to be significantly lower in palivizumab-treated infants versus non-treated infants
  - Data was ambivalent on whether this effect is limited to:
    - Those with a family history of atopy
    - Those without a family history of atopy
    - All infants regardless of atopic background

## There are limited effective treatment options currently available for RSV

### Ribavirin

- Approved in 1986 for aerosolized treatment of RSV
- Use often limited to immunocompromised infants
  - Shown to reduce risk of progression from URTI to LRTI and all-cause mortality in RSV-positive HSCT patients (aged 3-70)
  - Limited data showing its efficacy at reducing incidence of airway reactivity in previously healthy infants
- Ribavirin may be used along with other prophylactic agents
- Significant data supporting its use is lacking, and there are some toxicity concerns
- Cost of aerosolized ribavirin is prohibitive
- Not currently recommended in guidelines as a treatment option

## Future approaches to RSV therapy: Vaccines

There remains a significant unmet need for efficacious and cost-effective, preventive interventions against RSV

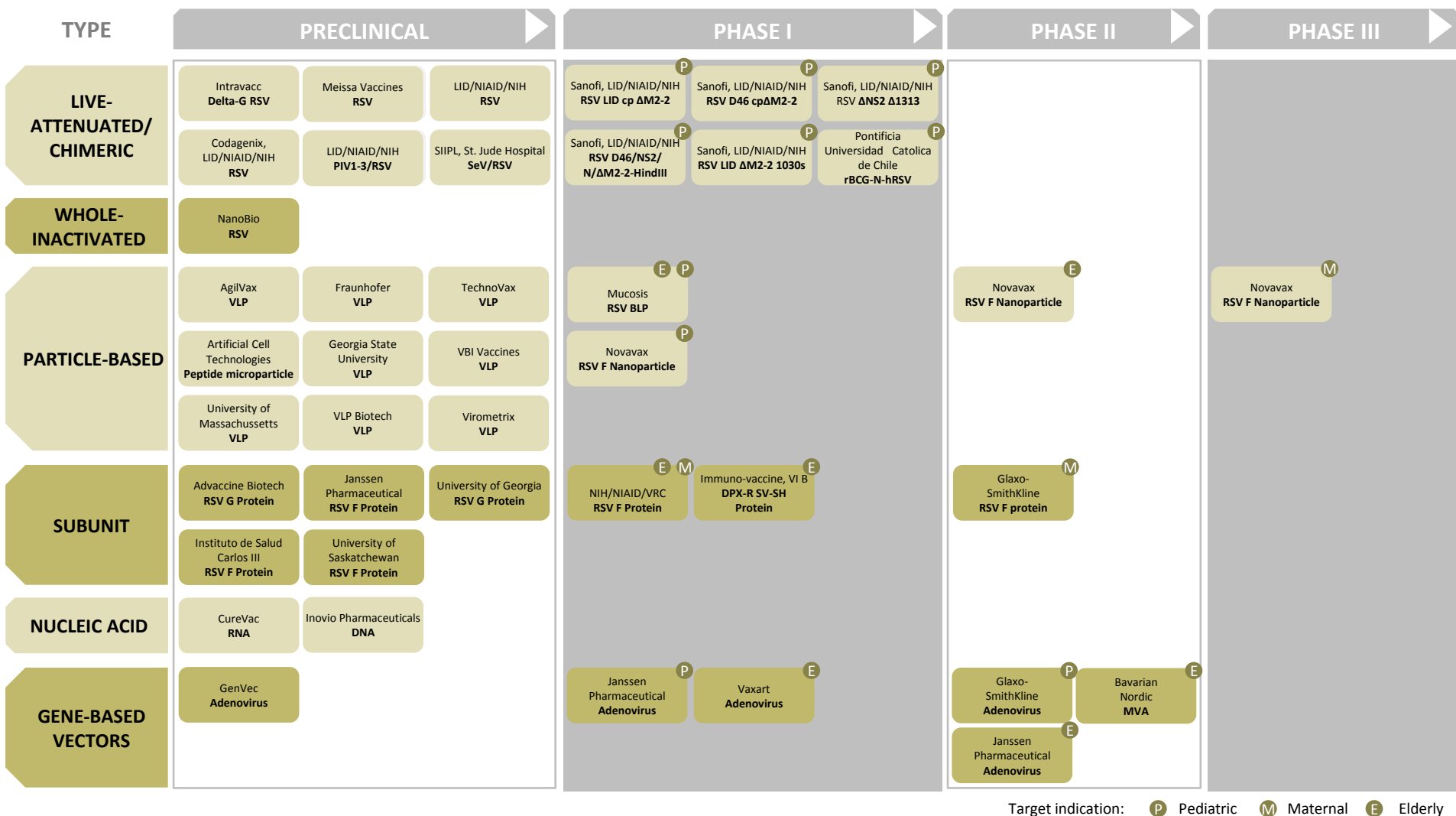
### The Past

- The first RSV vaccine in the 1960s failed to protect infants
  - Formalin-inactivated, alum-precipitated RSV vaccine (FI-RSV)
  - Severe AEs in vaccinated native infants who subsequently were infected with RSV
  - Failure has influenced subsequent investigations to the present day

### The Future

- There are currently:
  - ~28 RSV vaccines and antibodies in pre-clinical development
  - 17 vaccines and antibodies in clinical development
- WHO estimates an available vaccine in 5-10 years

## PATH global snapshot of RSV vaccines in development



Target indication:  Pediatric  Maternal  Elderly

## Target populations for RSV vaccines

Young infants ( $\leq 6$  months of age) and young children ( $> 6$  months)

- Risk of severe RSV-associated respiratory disease is highest in infants  $< 6$  months
- Protective maternal neutralizing antibodies are known to suppress development of serum and antibody responses
- Live-attenuated, vector-based and subunit vaccines appear optimal for the pediatric population
- Live-attenuated vaccine approach:
  - Advantages
    - Little risk of inducing enhanced disease with a subsequent RSV infection
    - Can be delivered intranasally
    - Can replicate in the presence of maternal antibodies
    - Can broadly stimulate innate, humoral and cellular immunity
  - Disadvantages
    - Balancing safety versus immunogenicity
    - Risk of reversion to wild-type
    - Producing a stable vaccine virus for mass production
- Vector-based approach:
  - Advantages
    - Avoids concerns about attenuation level of a live-attenuated virus vaccine and risk of enhanced disease with subunit approach
    - Reduces the likelihood that maternal antibodies would inhibit an immune response in young infants
  - Disadvantages
    - Potential for the development of anti-vector immunity

## Target populations for RSV vaccines

### Pregnant women

- Maternal immunization avoids challenges of direct neonatal immunization when the neonatal immune system shows impaired antibody affinity maturation and less efficient antigen presentation
- Nanoparticle and subunit vaccines are the most promising for pregnant women
- Aim of vaccinating in pregnancy (2<sup>nd</sup>/3<sup>rd</sup> trimester) is to:
  - Boost maternal RSV antibody level for transplacental transfer above the risk threshold of severe disease in their infants
  - Maintain this putatively protective level for longer (ideally 4-6 months of life)
- Any vaccine administered to pregnant women will need to meet high tolerability and safety standards

## Future approaches to RSV therapy: Prophylaxis

The previous success of monoclonal antibodies has promoted research into new monoclonal RSV therapies with improved capacity to block the fusion (F) protein

### MEDI8897

- Recombinant, human immunoglobulin G1 kappa monoclonal antibody
- Targets pre-fusion conformation of the RSV F protein
- Potency and half-life supports once-per-RSV season dosing
- Has received fast track designation for continuing FDA assessment

### RI-001

- An RSV-IGIV
- Compassionate use in 15 immunocompromised patients (2 mo - 71 yrs) was well tolerated and significantly increased serum neutralizing antibody titers to RSV
- Undergoing safety trial for RSV-LRTI prevention in immunocompromised infants



## Future approaches to RSV therapy: Treatment

Treatment of RSV infection is focussed on preventing viral entry into target cells, viral replication, or assembly of viral particles, e.g.

### ALX-0171

- Inhaled trimeric nanobody
- Phase 1/2a study has shown:
  - Rapid effect on viral replication
  - No treatment-related AEs
- Phase 2 dose-ranging study underway

### GS-5806 (Presatovir)

- Inhibitor that blocks viral-envelope fusion with the host-cell membrane
- Shown to reduce viral load and symptom severity scores in adults

### JNJ64041575 (lumicitabine)

- Oral, large-protein, RSV replication inhibitor
- Phase 2 study in adults has shown lower peak viral load, symptom score and mucus weight vs. placebo
- Phase 2 study in infants and children (28 days to 36 months) hospitalized with RSV infection underway

## Future approaches to RSV therapy: Treatment Candidates

- |   |   |
|---|---|
| • Fusion inhibitors   | • GS-5806, MDT-637 (VP-14637); JNJ-2408068 (R-170591); TMC353121; BMS-433771; BTA-C585; P13 and C15; JNJ-53718678; AK-0529; RFI-641 |
| • Single domain, trivalent antibody fragment derived from <i>Camelidae</i> (Nanobody) | • ALX-0171  |
| • L (“large”)-protein inhibitors  | • JNJ-64041575; BI-D; AZ-27   |
| • N-protein targeting RSV inhibitor   | • RSV604  |

Other potential targets include: N-P protein-protein interaction; SH-protein; M2-1 protein

## Concluding statements

Key Findings	SOE
<b>Palivizumab</b> <ul style="list-style-type: none"><li>• Currently the only product licensed for prophylaxis against RSV</li><li>• Preterm infants &lt;35 wGA: 68% (range: 64-100%) reduction in RSVH [absolute risk reduction: 0.2-14.7%]</li><li>• Children with CLD/BPD: 65% (range: 38-72%) reduction in RSVH [absolute risk reduction: 4.9-14.2%]</li><li>• Children with CHD: 53% (range: 45-58%) reduction in RSVH [absolute risk reduction: 4.4-4.6%]</li><li>• Limited data in other comorbidities</li><li>• Significantly reduced subsequent wheezing episodes</li></ul>	High
<b>Ribavirin</b> <ul style="list-style-type: none"><li>• Licensed for treatment of severe RSV infection</li><li>• Lack of evidence supporting its efficacy and concerns over toxicity</li><li>• Strongest evidence in immunocompromised infants</li></ul>	High

## Concluding statements

Key Findings	SOE
<b>Future therapies</b> <ul style="list-style-type: none"><li>• Currently there are 17 vaccines and antibodies in clinical development</li><li>• WHO estimates the availability of an RSV vaccine within 5-10 years</li><li>• Nanoparticle and subunit vaccines are the most promising for pregnant women, whereas live-attenuated, vector-based and subunit vaccines are optimal for the pediatric population</li><li>• Several new antibodies targeting the RSV fusion (F) protein are showing promise (e.g. MEI8897) and entering phase 3 immunoprophylaxis trials</li><li>• Recent efforts to develop RSV antiviral drugs have focused primarily on fusion inhibitors or virus gene silencing; a number are in development and could become available for clinical use within a few years</li></ul>	N/A

## Limitations

- The most significant limitation is the lack of available therapies and interventions for RSV despite decades of research
- There is a strong body of evidence for palivizumab in key indicated groups (preterm, CLD/BPD, CHD), but more data in other high risk populations, such as those with Down syndrome or neurological disorders, would be welcome.

## Further development

### Currently approved therapies

- More up-to-date research and published, prospective RCTs are needed to determine:
  - Effectiveness of palivizumab in reducing RSVH and improving outcomes in children with underlying medical conditions
  - Ultimate impact of palivizumab on longer-term sequelae, such as recurrent wheezing

### Future therapies for prevention and treatment

- Continued research is needed on:
  - Optimal strategies, such as pre- versus post-natal vaccination and prophylaxis
  - Establishing whether there is a causal link between RSV infection and asthma, possibly via a follow-on to a phase 3 vaccine or prophylaxis trial
  - The optimal timing of therapy with antiviral drugs
  - Whether the combination of antiviral drugs and immunomodulatory therapies might improve outcomes

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