EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory aspects related to the development of vaccines for RSV

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Topics

Topics considered

- Maternal immunisation and determination of efficacy in offspring
- Primary vaccination in infants
- Safety database and duration of safety follow-up

Major issues to be considered

- Assays to detect RSV breakthrough cases
- Case definitions; virological plus clinical criteria
- Case ascertainment; implications of seasonality
- Maternal vaccination /passive protection of infants
- Age de-escalation issues
- Infant vaccination
- Duration of protection
- Safety database and duration of follow-up

Assays for detection of RSV

- Culture depends on controlling for viral thermolability and results depend on laboratory experience
- Antigen detection sensitivity may be 80-90% vs. culture
- Prefer RT-PCR assays; avoid “in-house” assays if possible
- Select a single commercial RT-PCR assay
- Need for and feasibility of central laboratory confirmation depends on the assay selected and the study sites
- Specimen collection, storage and shipping issues

Case definitions - what will the vaccine prevent?

Is the aim to prevent *any* RSV-associated clinical illness or to prevent specific presentations? For example, cases that:

- Meet any or selected/defined respiratory symptoms
- Involve acute lower respiratory illness (ALRI) necessitating "contact with a healthcare professional (HCP)"
- Require a GP visit / clinic visit / ER visit / hospitalisation
- Require supplementary O_2 based on saturation or PaO_2
- Require ventilation (any or PPV)
- Occur in healthy children and/or in "at-risk" children

Case ascertainment

- Need active ascertainment to check that all cases counted
- Exact method depends on the case definition
- Several concerns regarding:
  - What will be **trigger** for HCP contact (need to define)?
  - What will be the **route** to HCP?
  - Although there will be a placebo control there could be lack of homogeneity of cases counted in primary analysis

Vaccinating in pregnancy

- Clinical trial approval based on safety for mother and foetus
- Any direct benefit to mothers?
- Trials likely not be powered to estimate VE in vaccinees
- Little information on rate of clinically apparent RSV infections and severity in pregnant women
- Unlikely that numbers of cases of RSV-associated clinical illness in mothers during last trimester ± post-partum will provide definitive estimate of direct benefit

When to vaccinate pregnant women in trials

- Maternal vaccination will be in 3rd trimester
- Vaccination in the last 3 months of the RSV season means the infant is unlikely to be exposed to RSV before maternal antibody declines below protective levels
- The RSV season (or lack of seasonality) may not be well-defined at potential study sites; may need a pre-study

Passive protection of infants

- Many factors may influence the maternal immune response AND the efficient transfer of IgG across the placenta
- Need to decide if the first efficacy studies will be broadly inclusive (in which case likely need to stratify) or will exclude sub-groups most likely to have poor trans-placental transfer
- Need to assess transfer by measuring cord blood antibody
- Cord blood can be obtained only if the mothers give birth in settings in which samples can be obtained and then handled, stored and shipped in an appropriate fashion
- Interactions of these factors will influence site location

Passive protection of infants

- Cases counted in the primary analysis may be confined to infants born a minimum number of weeks after maternal vaccination and of a minimum gestational age at birth
- Use of palivizumab will confound the endpoint - need to understand the *actual* mode of palivizumab use across the study sites to define cases for the primary analysis

Passive protection of infants

- Protection may reflect not only titre at birth but the rate of decline, which may not be constant in all settings
- Assumption then follows that the median time to breakthrough infections will differ in subsets
- In a case-driven study the primary analysis could reflect a large contribution of cases from a country/region with poor transfer and rapid decay of maternal antibody

Vaccinating infants - Age de-escalation

- Initial studies can be done in adults but they will not be RSV-naïve; limited or negligible value for prediction of safety and immunogenicity in infants
- A typical age de-escalation approach is likely not feasible in healthy children; perhaps could start with a mini-cohort in the upper part of the target age range
- In “at-risk” children it may be possible to start at a higher age but probably non-naïve so not so relevant to healthy infants

Vaccinating infants

- Aim for strong neutralising antibody response associated with a non-Th 2 dominant immune response
- Need to assess this in RSV-naïve infants
- Such findings cannot rule out risk of disease enhancement
- Additional endpoints of interest could be duration of RSV shedding and/or effects on viral load in breakthrough cases in case vaccine attenuates (e.g. using quantitative PCR)

When to vaccinate infants?

In infants born to vaccinated mothers

- Need to estimate the duration of passive protection before deciding when to start active vaccination in infants
- Should primary series start as early as seems needed?
- Should primary series start also take into account when the RSV season starts/ends if there is seasonality?

When to vaccinate infants?

<u>In the absence of maternal vaccination</u>

- Start primary series as early as possible in infancy?

<u>In both scenarios</u>

- Essential to investigate whether/to what extent maternal antibody reduces the response to active vaccination in infants
- An important inhibitory effect of maternal antibody:
  - Has implications for extrapolations between populations
  - May result in different minimum age for regions or subsets

Vaccinating infants - Duration of protection

- RSV becomes a mild disease as age increases unless the child has underlying risk factors
- Vaccinated infants should be followed through at least one season for the primary analysis
- Longer-term follow-up to rule out disease enhancement and consideration of need for boosters in healthy children
- The investigation of protective efficacy beyond a certain age could be confined to the “at-risk” group who are kept under medical review and may benefit from booster doses?

Safety database for a novel vaccine

- The current EU general expectation is a minimum of 3000 exposed to the final dose regimen of the vaccine
- This may be acceptable for maternal immunisation subject to lack of any biological plausibility of adverse effect on foetus
- The safety database for infants will >> 3000
- Need enough evidence (from nonclinical and clinical investigations) to support "negligible risk" of disease enhancement after vaccination of the RSV-naive

Summary

- The sponsor should decide the primary objective of the programme, i.e. decide on the target indication
- The sponsor should define the primary case definition and mode of case ascertainment accordingly
- Pivotal studies must show superiority for vaccine vs. no vaccine against RSV over at least one season
- The timing of vaccination needs careful consideration