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4 **Guideline on the clinical evaluation of medicinal products**  
5 **indicated for the prophylaxis or treatment of respiratory**  
6 **syncytial virus (RSV) disease**  
7 **Draft**

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8 Comments should be provided using this [template](#). The completed comments form should be sent to [vwp@ema.europa.eu](mailto:vwp@ema.europa.eu)

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## 61 **Executive summary**

62 This guideline addresses clinical development programmes for medicinal products intended for the pre-  
63 exposure prophylaxis or treatment of disease due to respiratory syncytial virus (RSV). The guidance  
64 covers the development of vaccines and monoclonal antibodies for the prevention of RSV disease and  
65 direct acting antiviral agents (DAAs) for the treatment of RSV disease. The focus is on the assessment  
66 of safety and efficacy in populations most likely to develop RSV lower respiratory tract infection (LRTI)  
67 and severe RSV disease, in which a clinically important benefit of the intervention is most likely to be  
68 demonstrated. Depending on the type of intervention and product characteristics, these populations  
69 may include newborn infants (aged 0-27 days), infants (aged 28 days to 11 months), toddlers (aged  
70 12-23 months), older paediatric subjects predisposed to develop severe RSV disease and the elderly  
71 (aged  $\geq 65$  years). The guideline also addresses vaccination of pregnant women with the aim of  
72 preventing RSV disease in their infants while protective maternal antibody levels persist.

73 At the time of preparing this guidance it is expected that efficacy trials will be designed to demonstrate  
74 superiority of the vaccine, monoclonal antibody or treatment over no active intervention. Consideration  
75 is given to clinical data that could support the use of preventive or therapeutic products in populations  
76 that were not included in efficacy trials (e.g. using immunological or pharmacokinetic data).

77 In efficacy trials of preventive and therapeutic products it is essential that there are clear age-specific  
78 definitions of RSV cases based on a combination of clinical and laboratory criteria. Sponsors are  
79 encouraged to take note of any available internationally-recommended and widely agreed age group-  
80 specific definitions.

81 Prior experience with a formalin-inactivated RSV vaccine led to concern regarding the potential for  
82 clinically severe vaccine-associated disease enhancement to occur after active immunisation of RSV-  
83 naïve paediatric subjects. To assess the risk, it is recommended that the duration of follow-up in each  
84 trial is sufficient to ensure that the majority of subjects have experienced natural exposure to RSV,  
85 with or without a clinically apparent illness. For vaccines intended for pregnant women, case  
86 ascertainment in infants should continue until anti-RSV antibody levels are similar between infants  
87 born to vaccinated and unvaccinated women. In the elderly, it is desirable that some data are available  
88 on the duration of protection, need for re-vaccination and the safety and immunogenicity of sequential  
89 doses at the time of licensure.

90 Issues for treatment trials include the basis for selection of the recommended dose regimen and the  
91 need to determine the maximum time from symptom onset to initiation of treatment that is associated  
92 with a clinically important benefit.

93 Other than addressing the risk of vaccine-associated disease enhancement after active immunisation  
94 the assessment of vaccine safety follows the same principles as for other vaccines. For monoclonal  
95 antibodies the safety database should suffice to identify any trends to increasing rates of local and  
96 systemic adverse reactions with sequential doses and/or with the first dose given in a second RSV  
97 season after a gap of several months. For antiviral agents for the treatment of RSV safety data should  
98 be collected in each target age group.

## 99 **1. Introduction (background)**

100 Respiratory syncytial virus (RSV) is an Orthopneumovirus of the family *Paramyxoviridae* with two  
101 major subtypes (A and B). The glycosylated F and G surface proteins in the RSV envelope are essential  
102 for pathogenesis and elicit neutralising antibodies in the host. Antigenic diversity between and within

103 RSV subtypes mainly reflects variations in the G glycoprotein, with low homology between G  
104 glycoproteins of A and B strains. After RSV infection via the human respiratory tract, the virus shows  
105 tropism for the ciliated epithelia in bronchioles and alveoli, where it elicits a local immune response  
106 leading to inflammation.

107 In Europe RSV disease is seasonal (e.g. typically November to April) with a peak in the mid-winter  
108 months. Most children have serological evidence of prior RSV infection by the age of 2-3 years and  
109 many have a primary infection during their first season. Primary RSV infections in newborn infants  
110 (aged 0-27 days), infants (aged 28 days to 11 months) and toddlers (aged 12 to 23 months)  
111 sometimes cause severe lower respiratory tract infection (LRTI), resulting in bronchiolitis, bronchitis  
112 and/or viral pneumonia. There is a higher risk of severe RSV disease associated with premature birth  
113 (at  $\leq 35$  weeks of gestation) and in children with a wide range of underlying conditions (e.g.  
114 bronchopulmonary dysplasia and haemodynamically significant congenital heart disease). Other  
115 underlying conditions that may predispose to severe RSV disease at any age include neuromuscular  
116 diseases, Down's syndrome, cystic fibrosis and some types of immunosuppression. Long-term  
117 morbidity following RSV LRTI in early life may include wheezing.

118 RSV infection in early life does not provide solid immunity so that individuals may be infected and may  
119 develop clinical manifestations of RSV multiple times during their life span. In healthy adults,  
120 adolescents and children who are RSV non-naïve, symptomatic RSV infection may be associated with  
121 mild upper respiratory tract infections and relatively few cases require medical intervention. Elderly  
122 subjects (aged  $\geq 65$  years) with or without comorbid conditions, such as congestive heart failure,  
123 emphysema or asthma, are more likely than younger adults to develop LRTI requiring medical  
124 intervention.

125 There is a very large range of RSV vaccines currently under development, including inactivated, live  
126 attenuated, chimeric, live viral vectored (some in a prime-boost regimen with two different constructs)  
127 and nucleic acid vaccines.

128 In the 1960s an alum-adjuvanted, formalin-inactivated, whole virion RSV vaccine was developed.  
129 When administered to RSV-naïve infants it was not protective and it was associated with a higher rate  
130 of severe RSV disease and some fatalities following subsequent natural infection compared to the  
131 unvaccinated control group. Whilst the exact mechanism of this vaccine-associated disease  
132 enhancement is not known, investigations indicated that the vaccine elicited mainly RSV binding  
133 antibody rather than virus neutralising antibody. Consequently, vaccine development for primary  
134 immunisation of RSV-naïve subjects has focussed on live attenuated or live viral vectored vaccines with  
135 the aim of eliciting high titres of RSV neutralising antibody and a Th-1 directed immune response.

136 A wider range of vaccine constructs is under consideration for children aged from about 2 years, adults  
137 and the elderly who have experienced prior natural infection(s) with RSV. In addition, some vaccines  
138 are under development for administration to pregnant women to increase the amount of RSV  
139 neutralising antibody passed to the foetus and reduce the risk of RSV disease in the first few months of  
140 life.

141 Concurrently, there are several directly acting antiviral agents (DAAs) for treatment of RSV disease as  
142 well as monoclonal antibodies with standard or prolonged plasma half-lives for prevention of RSV  
143 disease in clinical development.

## 144 2. Scope

145 The focus of the guideline is on the clinical evaluation of the safety and efficacy of vaccines,  
146 monoclonal antibodies or DAAs by direct comparison with control groups that do not receive an RSV-  
147 specific intervention. The guidance covers some nonclinical investigations of efficacy and risk of  
148 vaccine-associated enhanced disease to support clinical trials with preventive or therapeutic products  
149 directed at RSV.

150 Detailed guidance is not provided on the development of assays to measure virus neutralisation titres  
151 or other immune parameters. Currently much work is ongoing in this field and sponsors are expected  
152 to provide a justification for their choice of assay(s) that takes note of the most recent developments.  
153 As/when International Standards may be available these should be included in the assay development  
154 and validation processes. Some general considerations for the selection of assays to be used for the  
155 laboratory confirmation of clinical cases of RSV disease are included in the guidance.

156 The prevention and treatment of RSV disease is an area in which there is a wide range of ongoing and  
157 planned nonclinical and clinical activities with potential implications for future development  
158 programmes. Sponsors are encouraged to discuss their programmes with EU Competent Authorities  
159 even if their plans are generally in line with this guidance. Sponsors may wish to evaluate candidate  
160 products in target groups that are not addressed in detail in this guidance, in which case consultation  
161 with EU Competent Authorities is strongly recommended.

### 162 2.1. Vaccines

163 General requirements for the clinical development of new vaccines are provided in the *Guideline on*  
164 *clinical evaluation of new vaccines* (EMA/CHMP/VWP/164653/05), which should be followed.

165 This guideline discusses issues that are most relevant or specific to RSV vaccines. Although the range  
166 of vaccine constructs currently in development is very wide, the general principles for clinical  
167 assessment are broadly applicable. The focus of the guidance is on vaccines intended for groups in  
168 which an important clinical benefit of vaccination is most likely to be demonstrated. These groups  
169 include, but are not limited to:

- 170 • Infants (aged 28 days to 11 months) and toddlers (aged 12-23 months), including those who  
171 were born prematurely and those who are at risk of severe RSV disease due to underlying  
172 conditions. Vaccination of newborn infants (aged 0-27 days) is a less likely strategy and it is  
173 not addressed, although the guidance provided would be broadly applicable;
- 174 • Pregnant women, with intent to prevent RSV in their infants while protective levels of maternal  
175 antibody persist; and
- 176 • Elderly subjects (aged  $\geq 65$  years).

### 177 2.2. Monoclonal antibodies

178 The focus of the guidance is on the use of monoclonal antibodies that exert virus neutralisation activity  
179 for pre-exposure prophylaxis of RSV disease in newborn infants, infants and toddlers, including those  
180 at risk of developing RSV LRTI and severe RSV disease.

181 Although not specifically addressed in this guidance the principles discussed for the development of  
182 direct acting antiviral agents for treatment of RSV are broadly applicable to the clinical evaluation of  
183 monoclonal antibodies for treatment of RSV and should be followed.

## 184 **2.3. Antiviral agents**

185 The focus of the guidance is on evaluating direct acting antiviral (DAA) agents for the treatment of RSV  
186 disease in newborn infants, infants, toddlers and the elderly. These are the groups especially at risk of  
187 developing RSV LRTI and severe RSV disease, in which a clinically important benefit of treatment is  
188 most likely to be demonstrated. The use of DAAs to prevent RSV is not considered. Pharmacokinetic  
189 trials, including drug-drug interaction trials, with new antiviral agents will be required but are not  
190 discussed since they are not specific to DAAs directed against RSV. Similarly, the development of  
191 appropriate formulations for paediatric use is not specific to DAAs directed at RSV and is not discussed.  
192 Available CHMP guidance should be consulted as appropriate.

## 193 **3. Legal basis and relevant guidelines**

194 This Guideline should be read in conjunction with the introduction and general principles of Annex I to  
195 Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but  
196 are not limited to:

- 197 • Guideline on clinical evaluation of vaccines (EMA/CHMP/VWP/164653/2005) Rev 1
- 198 • Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored  
199 vaccines (EMA/CHMP/VWP/141697/2009)
- 200 • Pharmacokinetic trials in man (CHMP/EWP/147013/04)
- 201 • Evaluation of the pharmacokinetics of medicinal products in patients with impaired renal  
202 function (CPMP/EWP/225/02)
- 203 • Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic  
204 Function (CPMP/EWP/2339/02)
- 205 • Investigation of drug interactions (CPMP/EWP/560/95)
- 206 • Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06)
- 207 • Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)  
208 (ICH11)
- 209 • Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population  
210 (CHMP/EWP/147013/04)
- 211 • Note for guidance on trials in support of special populations: Geriatrics (CPMP/ICH/379/95)
- 212 • Statistical principles for clinical trials (CPMP/ICH/363/96)
- 213 • Choice of a non-inferiority margin (CPMP/EWP/2158/99)

## 214 **4. Nonclinical efficacy data to support clinical trials**

### 215 **4.1. Vaccines**

216 Before commencing clinical trials with vaccines there should be nonclinical data to demonstrate that a  
217 functional immune response can be achieved post-vaccination based on the immune parameter(s)  
218 most relevant to the vaccine construct. Immunogenicity studies may be conducted in RSV-naïve and/or  
219 non-naïve animals depending on the human target population(s). Where relevant, studies may include

220 vaccination of RSV non-naïve dams followed by measurement of neutralising antibody in the offspring  
221 at birth.

222 Nonclinical studies may be used to demonstrate that the vaccine protects against development of RSV  
223 disease post-challenge. If appropriate, studies may include challenge of offspring born to vaccinated  
224 dams. Readouts may include effects of the intervention vs. placebo on viral loads in lower and upper  
225 respiratory tract tissues. The data from these experiments should be explored for correlations between  
226 immune responses and efficacy parameters.

227 Nonclinical studies should provide a preliminary assessment of the risk that vaccine-associated  
228 enhanced RSV disease could occur. There are several issues that may impact on the ability of various  
229 animal models to evaluate the risk. This field is evolving and it is expected that sponsors will consider  
230 the scientific literature when designing the nonclinical programme to assess the potential risk of  
231 vaccine-associated RSV disease enhancement.

## 232 **4.2. Monoclonal antibodies**

233 Nonclinical studies should demonstrate that virus neutralisation is achieved *in vitro* and should describe  
234 the neutralising activity over a range of antibody concentrations and against a range of RSV isolates.  
235 Nonclinical efficacy studies may be conducted as described for vaccines.

## 236 **4.3. Antiviral agents**

237 Before commencing clinical trials, the antiviral activity of a DAA should be documented *in vitro* using a  
238 range of recent RSV clinical isolates. The DAA should also be investigated for activity against other  
239 viruses, including those known to cause respiratory disease.

240 The mechanism of action of the DAA should be investigated as well as the mechanism(s) of resistance  
241 in any RSV isolates that appear to have reduced susceptibility *in vitro*.

242 Nonclinical data may provide preliminary evidence of efficacy. In most of the in-vivo nonclinical models  
243 that have been used, RSV replication does not produce quantifiable symptoms so that the effect of a  
244 DAA is based on demonstrating effects on viral titres compared to untreated controls. One approach to  
245 consider is the naïve bovine model, which could be used to estimate the effect of the DAA on  
246 symptomatic illness caused by bovine RSV, which appears to have a similar pathogenesis to RSV in  
247 naïve humans.

# 248 **5. Patient selection**

## 249 **5.1. Vaccines**

250 Regardless of the target population(s) for a candidate vaccine, the first trials are expected to be  
251 conducted in healthy adults (e.g. aged 18 to <45 years) to provide data on safety and immunogenicity  
252 in RSV non-naïve male and non-pregnant female subjects.

### 253 **5.1.1. Infants and toddlers**

254 It is recommended that safety and immunogenicity data are obtained from RSV non-naïve toddlers  
255 before moving to RSV non-naïve and naïve infants. The serostatus of toddlers and infants aged > 6  
256 months should be determined before they are vaccinated to ensure an adequate representation of



257 RSV-naïve and non-naïve subjects and to allow for dosing non-naïve subjects before moving to a naïve  
258 cohort.

259 The first safety and immunogenicity trial could be conducted in infants aged 6-12 months before  
260 progressing to infants aged < 6 months and infants aged < 6 months who were born prematurely (at  
261  $\leq 35$  weeks of gestation). Generally, it would be reasonable to assume that most infants with  
262 remaining maternal anti-RSV neutralising antibody will be RSV-naïve unless they have had a  
263 documented prior illness due to the virus. For older infants with no remaining maternal anti-RSV  
264 neutralising antibody and for toddlers the protocol should provide criteria for defining RSV-naïve or  
265 non-naïve status at baseline that take into account the lower limits of detection and quantification of  
266 neutralising antibody for the assay used. Since it is possible that some naturally primed subjects may  
267 not have measurable neutralising antibody, sponsors are encouraged to apply other assays (e.g. that  
268 detect IgG against the F, G and/or other viral proteins) to assist in differentiating RSV-naïve and non-  
269 naïve subsets.

270 Sponsors may confine vaccine efficacy trials to infants who commence vaccination within the first 6  
271 months of life to provide an estimate of vaccine efficacy in a population that is predominantly RSV-  
272 naïve. If older infants and/or toddlers are to be enrolled it is recommended that there is stratification  
273 by age sub-group. The patient selection criteria should include the minimum gestational age at birth  
274 and the minimum and maximum ages required for enrolment. Stratification of infants by premature or  
275 non-premature birth could be considered if the trial includes infants born at  $\leq 35$  weeks of gestation.

276 It is not expected to be feasible to determine baseline serostatus prior to enrolment into efficacy trials.

### 277 **5.1.2. Pregnant women**

278 Pregnant women should be enrolled into safety, immunogenicity and efficacy trials based on their  
279 estimated duration of gestation. The method for estimating the gestational stage should be specified in  
280 the protocol and applied across all sites. It is expected that women will usually be vaccinated in the  
281 third trimester to maximize the amount of maternal antibody that is transferred to the foetus. If initial  
282 data on the immune response indicates that more than one dose is likely to be required, and  
283 depending on the dose interval needed to optimise the immune response to the second or further  
284 dose(s), it may be necessary that sequential trials enrol women at an earlier stage of pregnancy.

285 The protocol should give clear guidance on whether pregnant women with any evidence of placental  
286 insufficiency are eligible for enrolment. If there are cord blood data to suggest that vaccination  
287 increases the anti-RSV neutralising antibody transferred to the foetus despite placental insufficiency, it  
288 may be appropriate to include these women and to consider stratifying enrolment by the presence or  
289 absence of evidence of placental insufficiency at the time of randomisation.

### 290 **5.1.3. Elderly**

291 It is important that there is adequate representation of age sub-groups 65-74, 75-84 and  $\geq 85$  years  
292 across the safety and immunogenicity trials. Stratification by age sub-group at randomisation is  
293 recommended in efficacy trials. Sponsors are encouraged to include a representative sample of elderly  
294 subjects with conditions pre-disposing them to severe RSV disease but not expected to negatively  
295 impact on the immune response (e.g. with underlying respiratory or cardiopulmonary disease) in  
296 vaccine efficacy trials, with or without stratification.

#### 297 **5.1.4. Other populations**

298 Before or after licensure, sponsors may wish to evaluate the safety and immunogenicity of RSV  
299 vaccines in populations other than those in which vaccine efficacy was demonstrated to support dose  
300 regimen recommendations. For example:

- 301 • Immunocompetent older paediatric subjects with conditions recognised to predispose them to  
302 RSV LRTI and severe RSV disease;
- 303 • Subjects with selected types of immunodeficiency;
- 304 • Subjects who have received a monoclonal antibody against RSV to investigate the minimum  
305 time interval that should elapse between the last dose of the monoclonal antibody and first  
306 dose of the vaccine.

#### 307 **5.2. Monoclonal antibodies**

308 The first trials are usually conducted in healthy adults to provide preliminary data on safety and on the  
309 decay of RSV-specific antibody levels (i.e. total of pre-existing naturally-acquired neutralising antibody  
310 and exogenous neutralising antibody) over time.

311 In trials that evaluate safety, neutralising antibody levels and/or efficacy in paediatric subjects in  
312 whom a benefit may be anticipated, it may be appropriate to stratify at the time of randomisation (e.g.  
313 infants born at  $\leq 35$  weeks of gestation, infants aged  $< 6$  months at the onset of the RSV season and  
314 paediatric subjects with risk factors for severe RSV disease). Older paediatric subjects with conditions  
315 recognised to predispose them to RSV LRTI and severe RSV disease may be included or studied  
316 separately.

#### 317 **5.3. Antiviral agents**

318 The first trials to evaluate the safety and pharmacokinetics of DAAs for RSV are expected to be  
319 conducted in healthy adults. If potentially effective dose regimens for paediatric age sub-groups can be  
320 derived from modelling and simulation, and if the nonclinical and healthy adult safety data allow, it  
321 may be possible to proceed directly to trials in subjects who have RSV disease within the target  
322 paediatric age range for the product. Trials that evaluate safety, pharmacokinetics and/or efficacy in  
323 elderly patients should include representation from all age sub-groups. Stratification by age (e.g. 65-  
324 74, 75-84 and  $\geq 85$  years) should be considered in efficacy trials.

325 Patient selection in efficacy trials should be based on a case definition that combines clinical signs and  
326 symptoms with laboratory evidence of RSV.

#### 327 **5.3.1. Clinical criteria**

328 The demonstration of a clinically important benefit of treatment is most likely to be possible in those  
329 with severe or very severe RSV disease. Furthermore, once a treatment has been licensed for RSV and  
330 is widely recommended, it may not be feasible to conduct further trials in which active treatment is  
331 withheld from patients with severe RSV disease (e.g. with RSV LRTI and severe LRTI). Therefore, it is  
332 recommended that efficacy trials with a new treatment for RSV should be confined to patients  
333 considered to be at the more severe end of the disease spectrum or should be stratified to ensure that  
334 a sufficient proportion of patients with severe disease are enrolled to be able to assess efficacy in this  
335 sub-group.

336 The list of clinical signs and symptoms and the number that should be met for eligibility must be  
337 tailored to the age range of the trial population. Sponsors are advised to take account of proposals for  
338 classifying RSV disease severity in different age groups that come from well-recognised public health  
339 or professional bodies, with or without some modification. The inclusion of at least one eligibility  
340 criterion that is an objective measure, such as oxygen saturation on room air corrected for altitude and  
341 measured under standardised conditions, is encouraged. Sponsors could also consider categorising  
342 patients using published clinical scores (e.g. Respiratory Distress Assessment Instrument [RDAI] and  
343 Respiratory Assessment Change Score [RACS] and by type of ventilator support given, if applicable.

344 Efficacy trials may be confined to hospitalised patients so that comprehensive data can be collected  
345 and/or if the treatment is administered each day by a healthcare professional. Due to variability in  
346 healthcare systems and thresholds for admission, it is not advisable to base a judgement of disease  
347 severity on the perceived need for hospitalisation.

348 A benefit of treatment may be detectable only if it is commenced within a defined time limit after  
349 symptom onset. Consideration may be given to stratification at randomisation by time intervals  
350 elapsed since onset of symptoms (e.g. using 12 hour intervals) up to the maximum allowed in the  
351 protocol. The maximum time elapsed that is allowed between symptom onset and randomisation  
352 should be balanced against the risk that the longer the duration the more likely it is that secondary  
353 bacterial infections may occur, which will impact on the assessment of the efficacy of the DAA.

354 Chest radiographs are not required to assess patient eligibility for treatment but may be obtained as a  
355 routine in elderly subjects, in which case the findings should be recorded.

### 356 **5.3.2. Laboratory criteria**

357 Patient enrolment may be based on a protocol-defined commercially available rapid diagnostic test  
358 (RDT) for RSV. It is recommended that the exact same RDT (e.g. a nucleic acid detection test [NAAT]  
359 from a single manufacturer that can detect low levels of virus) is used at all sites. If this is not feasible  
360 it is recommended that the protocol requires the use of RDTs that work on the same principle and have  
361 similar sensitivity and specificity to minimize the possibility that there is an imbalance across trial sites  
362 in baseline viral loads. The sponsor should justify the RDT(s) chosen based on their performance  
363 characteristics (sensitivity and specificity) and the ability of all trial sites to conduct the test(s) without  
364 delaying or hindering the randomisation and treatment of potentially eligible patients.

365 If the new DAA demonstrates different antiviral activity by RSV subtype the RDT(s) used should  
366 differentiate RSV A and B. Consideration should be given to using RDTs that also detect viruses that  
367 are recognised to co-exist in some RSV cases and have been reported to affect the severity and course  
368 of the disease (e.g. human metapneumovirus and influenza virus). Patients with RDT results indicating  
369 the presence of additional viruses that may be contributing to the clinical presentation should still be  
370 enrolled.

## 371 **6. Assessment of efficacy**

### 372 **6.1. Vaccines**

373 Currently there is no immune correlate of protection for RSV disease that could be used to infer  
374 protective efficacy based on immune responses and there is no vaccine licensed for the prevention of  
375 RSV. Therefore, vaccine efficacy trials in which candidate vaccines are compared with control groups  
376 that do not receive vaccination against RSV are required. At least one trial should be conducted in each

377 target population proposed for the candidate vaccine (e.g. in infants ± toddlers, in pregnant women  
378 and/or in the elderly).

379 Following a demonstration of vaccine efficacy in infants ± toddlers it may be possible to include dose  
380 regimens for older paediatric subjects who are at risk of developing severe RSV disease in the  
381 Summary of Product Characteristics (SmPC) based on demonstrating that the vaccine elicits immune  
382 responses comparable to those observed in the population in which efficacy was demonstrated.

383 Once a vaccine against RSV has been shown to be efficacious and has been licensed for use in a  
384 specific population, it may not be considered appropriate to withhold a licensed RSV vaccine from the  
385 control group in a vaccine efficacy trial with a candidate vaccine, in which case trials should  
386 demonstrate that the efficacy of a candidate vaccine is at least non-inferior to that of a licensed  
387 vaccine. Alternatively, a demonstration of efficacy against RSV disease may not be required for  
388 candidate vaccines if efficacy can be inferred by interpreting the immune response to the candidate  
389 vaccine using a widely accepted immune correlate of protection that was established in a prior efficacy  
390 trial with another RSV vaccine. Nevertheless, even if an immune correlate of protection has been  
391 identified from an efficacy trial with one vaccine it may not be widely applicable across candidate  
392 vaccine constructs and in different populations.

393 If there is no established immune correlate of protection that can be applied to immune responses  
394 against a candidate vaccine, the possibility of inferring efficacy using an immunobridging approach,  
395 whereby the candidate vaccine is shown to elicit a comparable immune response to a licensed vaccine  
396 for which efficacy has been demonstrated, would have to be discussed with EU Competent Authorities  
397 on a case by case basis. Immunobridging between a candidate vaccine and a licensed vaccine will not  
398 be possible if different parameters are required to describe the immune response.

## 399 **6.2. Monoclonal antibodies**

400 If possible, an efficacy trial should be conducted to compare a candidate monoclonal antibody with a  
401 group that does not receive a licensed anti-RSV monoclonal antibody. Such a trial may be possible in  
402 populations that are considered at risk of developing severe RSV disease but are not eligible to receive  
403 a licensed product according to national recommendations. If this design is not possible, an efficacy  
404 trial may be designed to demonstrate that the efficacy of a candidate monoclonal antibody is at least  
405 non-inferior to that of a licensed product.

406 Subject to a demonstration of efficacy in infants and/or toddlers, together with an adequate  
407 assessment of safety, dose regimens for older paediatric subjects considered to be at risk of severe  
408 RSV disease and/or with certain types of immunodeficiency could be included in the SmPC based on  
409 achieving similar neutralising antibody titres and decay curves.

## 410 **6.3. Antiviral agents**

411 At the time of preparing this guidance inhaled ribavirin is still approved in some EU member states for  
412 treatment of RSV bronchiolitis in infants and toddlers via inhalation but it is not actually recommended  
413 in treatment guidelines. There is no approved DAA for RSV in other age groups. Therefore, a candidate  
414 DAA should be shown to be superior to a control group that receives placebo in the all treated  
415 population based on a clinically relevant primary endpoint.

416 It is recognised that the feasibility of placebo-controlled trials may have to be reconsidered once new  
417 DAAs for treatment of RSV have been licensed and have entered widespread use. In this setting it is  
418 recommended that sponsors discuss the design of pivotal efficacy trials with EU Competent Authorities.

419 If a DAA has shown convincing efficacy in infants ( $\pm$  toddlers), it may be possible to base a  
420 recommendation for use of the same or an alternative posology in the SmPC for older paediatric  
421 subjects who have severe RSV disease based on safety and pharmacokinetic data. The proposed dose  
422 regimen(s) should achieve plasma exposures similar to those documented in the population in which  
423 efficacy was demonstrated.

424 Immunodeficient persons may require a different dose regimen to combat high viral loads and/or a  
425 longer duration of treatment to clear replicating virus. Analyses of efficacy according to baseline viral  
426 load using data collected during an efficacy trial in subjects treated for their first RSV infection may  
427 assist in determining the need for a different dose. Nonclinical data may provide some indication of the  
428 need for a longer duration of treatment. Sponsors could consider conducting an exploratory trial in  
429 immunodeficient subjects with severe RSV disease using a dose regimen based on previous clinical  
430 experience. If necessary, additional trials could be conducted using alternative regimens. The data may  
431 suffice to support a recommended posology in the SmPC.

## 432 **7. Trial design**

### 433 **7.1. Vaccines**

434 General recommendations for the design of clinical trials that aim to:

- 435 • evaluate the safety and immunogenicity of a candidate vaccine against RSV,
- 436 • support the dose regimen(s) to be taken forward into confirmatory studies,
- 437 • demonstrate vaccine efficacy,

438 are the same as those for other types of vaccines (see Guideline on clinical evaluation of new vaccines,  
439 EMA/CHMP/VWP/164653/05).

#### 440 **7.1.1. Safety and immunogenicity trials**

##### 441 Infants and toddlers

442 Safety and immunogenicity trials with candidate vaccines in infants and toddlers should include a  
443 thorough investigation of the immune response as relevant to the vaccine construct. It is  
444 recommended that trials that include RSV-naïve subjects should require follow-up for RSV disease for  
445 at least one season before moving to the next trial in this population. This cautious approach allows for  
446 very preliminary assessments of any risk of enhanced disease to be made before exposing additional  
447 subjects, and likely larger numbers, in the next trial.

448 The potential for maternal antibody to interfere with the immune response to active immunisation of  
449 infants should be assessed. If the presence of maternal antibody has a blunting effect on the infant  
450 immune response, it is recommended that the immune response to a further dose after several months  
451 have elapsed should be evaluated to determine whether the first dose primed the infant immune  
452 system.

##### 453 Pregnant women

454 The protective titre of RSV neutralising antibody in infants is not known. Dose regimen selection for  
455 pregnant women may be based on maximizing the difference in neutralising antibody titres in cord  
456 blood between infants born to vaccinated and unvaccinated mothers whilst maintaining an acceptable  
457 safety profile. Cord blood antibody levels in infants delivered over a range of weeks elapsed from the

458 time of maternal vaccination (only or last dose, as applicable) may assist in determining the timing of  
459 maternal vaccination. The RSV neutralising antibody decay curves in infants should be documented. If  
460 trials are conducted in areas with variable rates and durations of breastfeeding sponsors may consider  
461 exploring the antibody decay curves accordingly.

462 The RSV neutralising antibody decay curve should be documented in vaccinated women during and  
463 following the pregnancy and the time taken to return to pre-vaccination levels should be determined. It  
464 is recommended that revaccination strategies that include administration of further doses to women  
465 during their next pregnancy should be investigated. These data may be generated in the post-approval  
466 period. If initial vaccination was with more than one dose it would be appropriate to re-vaccinate  
467 subgroups with a single dose or a repeat course to assess whether a reduction in doses is possible.

468 It is recommended that trials should require follow-up of infants for RSV disease for at least one  
469 season before moving to the next trial. This cautious approach allows for very preliminary assessments  
470 of any risk of enhanced disease to be made in infants born to vaccinated vs. unvaccinated mothers  
471 before exposing additional subjects, and likely larger numbers, in the next trial.

#### 472 Elderly

473 Trials should be conducted to support selection of the dose regimen(s) for age sub-groups 65-74  
474 years, 75-84 years and 85 years and older.

475 In this RSV non-naïve population there is evidence that pre-existing neutralising antibody is protective  
476 and that high titres are associated with lower risk of severe RSV LRTI. It is particularly important in  
477 this age group that the neutralising antibody response to vaccination is analysed by pre-vaccination  
478 serostatus.

479 It is likely that further doses of efficacious vaccines will be required at intervals. The safety and  
480 immunogenicity of revaccination after various time intervals should be documented and the ability of  
481 the vaccine to elicit an anamnestic immune response should be assessed. Since the ageing process  
482 could itself have a negative impact on immune responses to revaccination, a comparison could be  
483 made with responses to a single dose in a control group that is age-matched to the re-vaccinated  
484 cohort.

### 485 **7.1.2. Efficacy trials**

486 The design of vaccine efficacy trials is described in the Guideline on clinical evaluation of new vaccines  
487 (EMA/CHMP/VWP/164653/05), which includes considerations for using data on post-vaccination  
488 immune responses and efficacy to investigate possible immune correlates of protection. This section  
489 addresses some special considerations for efficacy trials with RSV vaccines.

490 If a candidate vaccine elicits a large increment in non-neutralising antibody in one or more subsets of  
491 subjects in safety and immunogenicity trials, there is concern that this could potentially interfere with  
492 the protection afforded by neutralising antibody. In such a case, it is possible that not only would the  
493 vaccine have poor or no efficacy but also that the severity of clinically apparent RSV could be enhanced  
494 at least in some subsets of subjects. Therefore, if such a finding is apparent in the immunogenicity  
495 trials with a candidate vaccine it is recommended that additional in-vitro and/or in-vivo nonclinical  
496 studies are conducted before deciding whether to proceed to a vaccine efficacy trial.

497 Furthermore, not all RSV vaccines under development may elicit neutralising antibody. Depending on  
498 the vaccine construct and route of administration the primary interest may be mucosal antibody levels  
499 (e.g. IgA levels in nasal secretions) or cell-mediated immune responses. In these cases, the clinical



500 data, supported by appropriate nonclinical studies, should demonstrate that there are no anticipated  
501 negative effects of vaccination on pre-existing neutralising antibody titres before proceeding to vaccine  
502 efficacy trials.

#### 503 Primary endpoint

504 The primary efficacy endpoint should be based on cases of RSV disease meeting the primary case  
505 definition. Considerations for defining cases of RSV disease and their severity are those applicable to  
506 patient selection in treatment trials described in section 5.3 (Patient selection, Antiviral agents).

507 The primary endpoint could be based on any clinically apparent laboratory-proven RSV disease or  
508 against one or more of RSV LRTI and severe/very severe RSV disease.

#### 509 Secondary endpoints

510 If the primary analysis is to be based on all RSV disease (i.e. regardless of severity) then secondary  
511 analyses should be conducted based on RSV LRTI, severe RSV disease and/or other case definitions.  
512 This is essential in all vaccine efficacy trials, regardless of the trial population, to assess the risk of  
513 vaccine-associated enhanced disease.

514 If the primary analysis is to be based on RSV LRTI or severe RSV disease the method of case  
515 ascertainment may mean that other clinical presentations are not captured in the database. If they  
516 are, a secondary analysis should assess whether there is any difference in the proportion of cases that  
517 are severe between the group that receives the active intervention and the control group.

518 In trials in which pregnant women are randomised to the vaccine or control group, the time between  
519 birth and the first clinically apparent RSV infection meeting the case definition should be included as a  
520 secondary endpoint. In trials in which infants or toddlers are randomised to the vaccine or control  
521 group the time between last vaccination and the first clinically apparent RSV infection (any and/or  
522 meeting the case definition) should be included as a secondary endpoint.

523 Although it is recommended that the perceived need for and type of healthcare interaction (e.g. home  
524 visit, emergency room visit or hospitalisation) should not be part of the case definition for the primary  
525 analysis, the information should be collected and included in the secondary analyses.

526 An assessment of whether a vaccine has an impact on any possible sequelae of RSV disease is not  
527 required for licensure. There is interest in evaluating whether vaccination impacts on the rate of  
528 symptomatic wheezing in children, which could be investigated in the post-licensure period. This would  
529 require a clear definition of symptomatic wheezing along with long-term structured follow-up to  
530 maintain high retention of the original clinical trial population to determine whether there is any  
531 detectable benefit and its duration.

#### 532 Case ascertainment

533 It is generally recommended that active surveillance is used for case ascertainment in efficacy trials  
534 with candidate RSV vaccines. The exact method of case ascertainment will depend on the primary  
535 endpoint (i.e. all RSV disease or severe/very severe RSV disease) and, to some extent, the secondary  
536 endpoints. Subjects or their care-givers should receive instructions on trigger signs and symptoms for  
537 possible RSV and whether they should in the first instance contact site staff and/or present to  
538 participating local healthcare facilities. On occasion, subjects or their care-givers may present or be  
539 taken to healthcare facilities not participating in the trial so they are not captured as cases in the  
540 database. Active surveillance could include regular contact by site staff to elicit any missed cases and

541 to obtain permission to obtain the relevant data to categorise the case, if adequate data have been  
542 collected.

#### 543 Infants and toddlers

544 At trial sites in regions where RSV is seasonal the recruitment period should be timed such that the  
545 last assigned dose is given no more than a specified number of weeks before the usual season start  
546 month. If the trial includes sites in seasonal and non-seasonal regions it may be useful to stratify  
547 enrolment accordingly.

548 If the total (i.e. blinded to treatment assignment) number of cases of RSV accrued that meet the case  
549 definition fulfils the requirements of the statistical analysis plan, the primary analysis may be  
550 conducted after the end of the first season or after an equivalent time period post-vaccination if sites  
551 in non-seasonal regions are included.

552 If there is any vaccine-associated disease enhancement, it is expected to occur with the first natural  
553 RSV infection after completion of vaccination. During follow-up for 2-3 seasons or an equivalent time  
554 period in non-seasonal regions the majority of trial subjects should have been exposed to circulating  
555 virus. To support this assumption, the proportion of subjects in the placebo group who have serological  
556 evidence of RSV infection, with or without symptoms, could be assessed. If RSV enhanced disease has  
557 not been observed in the vaccinated group after 2-3 seasons of follow-up despite serological evidence  
558 of a high natural exposure rate in the unvaccinated control group, it is very unlikely that it would be  
559 detected during additional follow-up. Follow-up for 2-3 seasons is also sufficient to describe the  
560 duration of protection after a primary series without further vaccine doses.

#### 561 Pregnant women

562 The level of protective efficacy of a candidate vaccine may reflect maternal and placental health as well  
563 as the rate of decline in neutralising antibody in infants, which may not be constant in all settings. In  
564 addition, the risk of infants encountering RSV may vary across sites so that the attack rate and the  
565 median time to RSV disease could differ by region. Furthermore, if immunogenicity trials suggested an  
566 effect of breastfeeding on infant neutralising antibody levels it is possible that regional differences in  
567 the rates and durations of breastfeeding could affect the efficacy observed. Therefore, the primary  
568 analysis could reflect a large contribution of cases from one or a few region(s), especially if the primary  
569 analysis is case-driven (i.e. enrolment will cease once a minimum total number of cases has been  
570 accrued). Due to these issues, it may be appropriate to stratify by geographical region at the time of  
571 randomisation.

572 Recruitment of pregnant women and completion of vaccination should be timed so that their infants  
573 are at risk of RSV exposure at least throughout the first 3-6 months of life. It is recommended that  
574 infants are followed up to the time at which prior data indicate that geometric mean neutralising  
575 antibody titres are similar for infants born to vaccinated and unvaccinated mothers.

576 If the primary analysis is confined to infants born a minimum number of weeks after their mothers  
577 were vaccinated, a sensitivity analysis should be conducted in all infants regardless of the time elapsed  
578 between maternal vaccination and delivery. If more than one dose of the vaccine is to be given to  
579 pregnant women and if the primary analysis is confined to infants born to mothers who received all  
580 assigned doses, a sensitivity analysis should be conducted using data from infants born to mothers  
581 who received at least one dose.



582 Some infants may be eligible for routine use of an anti-RSV monoclonal antibody according to local  
583 guidance, in which case it would be appropriate to exclude them from the primary analysis of efficacy  
584 although cases of RSV disease should be captured and reported.

#### 585 Elderly

586 At trial sites in regions where RSV is seasonal the recruitment period should be timed such that the  
587 last doses are given no more than a specified number of weeks before the expected start of the RSV  
588 season. Depending on the site distribution and seasonality the sponsor should consider stratification by  
589 region.

590 There may be sufficient cases accrued during the first RSV season to be able to conduct the primary  
591 analysis. In all cases, subjects should be followed through 2 or 3 seasons with re-randomisation of the  
592 initial vaccinated group to be re-vaccinated or not in the sequential years so that advice on the need  
593 for re-vaccination to maintain protection can be given at the time of licensure. This advice can be  
594 modified in the post-approval period as additional data emerge (e.g. if data suggest that vaccination  
595 every 2-3 years is sufficient to maintain protection).

### 596 **7.1.3. Trials to support co-administration with other vaccines**

597 It is not required that vaccine co-administration trials are conducted before licensure. Nevertheless,  
598 the routine use of RSV vaccines may be limited until there are data available on co-administration with  
599 the types of vaccines most likely to be given concomitantly in each target population group. Sponsors  
600 may conduct separate co-administration trials or may evaluate the effects of co-administration in  
601 subsets during efficacy trials. General guidance on trials to evaluate the effects of co-administration of  
602 vaccines is provided in the Guideline on clinical evaluation of new vaccines  
603 (EMA/CHMP/VWP/164653/05).

## 604 **7.2. Monoclonal antibodies**

### 605 **7.2.1. Dose-finding trials**

606 While standard humanised monoclonal antibodies are likely to be given at 3-4 week intervals, modified  
607 monoclonal antibodies with long serum half-lives are under investigation to allow for less frequent  
608 administration. The peak neutralising antibody activity and the activity decay curve should be  
609 described in trials in the target population to support dose selection. These clinical data, combined with  
610 nonclinical data, should be used to determine the most appropriate dose interval for further evaluation.

### 611 **7.2.2. Efficacy trials**

612 General considerations for the design of efficacy trials are the same as those for vaccine efficacy trials.  
613 At trial sites in regions where RSV is seasonal the recruitment period should be timed such that  
614 subjects receive the first dose of the monoclonal antibody no more than a specified number of weeks  
615 before the usual start month. Subsequent doses should be given throughout the RSV season  
616 depending on the serum half-life of RSV neutralising activity. In non-seasonal regions, it is suggested  
617 that dosing is continued and cases are collected for at least 6 months or until the required number of  
618 cases for the primary analysis has been accumulated.

619 In efficacy trials in infants and toddlers it is recommended that there is stratification by age and/or by  
620 broad category of underlying factors predisposing subjects to develop severe RSV disease (e.g.

621 prematurity, time of birth in relation to peak RSV season, type of co-morbidity). As for vaccines, an  
622 assessment of effects on sequelae, such as symptomatic wheezing, is of interest.

### 623 **7.3. Antiviral agents**

#### 624 **7.3.1. Exploratory trials**

625 Exploratory trials should characterise the safety and pharmacokinetics of DAAs and determine whether  
626 there are dose-limiting safety issues. Taken together with nonclinical data, potentially effective dose  
627 regimens for specific age groups may be derived from modelling and simulation.

628 Sponsors may consider conducting a human challenge trial. Such trials are usually conducted in  
629 healthy adults, aged from 18 to about 45 years, in whom it is not usually possible to trigger a clinically  
630 apparent infection with a challenge strain. It may be possible to show a relationship between dose and  
631 effect on post-challenge viral loads in respiratory samples that could provide some preliminary  
632 information on a possible effective dose range. Information may also be generated on the time window  
633 after inoculation within which the DAA should be given to achieve the maximum effect on viral load.  
634 Such trials could also be used to assess co-administration of DAAs vs. each given alone to support the  
635 development of combination regimens.

636 A preliminary efficacy trial may be used to select a final dose regimen for a confirmatory trial and  
637 document the effect of time elapsed between first symptoms and starting treatment on outcomes.  
638 Preliminary efficacy trials may be used to explore the benefit of the DAA based on a range of clinically  
639 relevant endpoints (e.g. time to resolution of clinical signs and symptoms and time to recovery of  
640 normal oxygen saturation) to select primary and secondary endpoints for confirmatory trials.

#### 641 **7.3.2. Confirmatory trials**

642 Confirmatory trials should demonstrate superiority of the treatment over the untreated control group  
643 (i.e. in which subjects receive no specific anti-RSV treatment) in the target population based on a  
644 clinically relevant endpoint, which could be a composite endpoint.

645 Definitive guidance on the preferred primary endpoint, which may be a composite, is not currently  
646 possible due to lack of information on the clinical benefit that may be achieved by DAAs against RSV.  
647 Any clinically relevant endpoints that are not included in the final selected primary endpoint should be  
648 designated as secondary endpoints. Although not appropriate for the primary endpoint, the type of  
649 healthcare contact that occurs for each case and details such as the need for and duration of assisted  
650 ventilation should be captured and reported in secondary analyses.

651 It is recommended that efficacy trials should assess the effect of treatment on viral loads in  
652 appropriate respiratory samples collected at baseline and at intervals during treatment at least in a  
653 randomised subset of treated and untreated patients to permit analyses of response by baseline load.  
654 Protocols should specify the quantitative RSV RNA test to be used at local laboratories of the  
655 participating sites and/or at a central laboratory using frozen shipped specimens.

## 656 **8. Safety aspects**

### 657 **8.1. Vaccines**

658 The general principles for the assessment of the safety of vaccines in clinical trials are described in the  
659 Guideline on clinical evaluation of new vaccines (EMA/CHMP/VWP/164653/05) and should be followed.

660 Currently, it is considered essential to assess the risk of vaccine-associated disease enhancement in  
661 the clinical programme for each candidate vaccine and regardless of the intended target population for  
662 use. The requirements for such an assessment for a specific type of candidate vaccine may change in  
663 future if extensive experience indicates that similar vaccine constructs pose a negligible risk.

664 Section 7.1 (Trial design, Vaccines) provides guidance on the recommended duration of follow-up of  
665 vaccinated subjects and infants born to vaccinated mothers to assess this risk. The level of risk that  
666 should be ruled out should be discussed and agreed with EU Competent Authorities on a case by case  
667 basis. Depending on the vaccine construct and the available nonclinical and clinical data it may be  
668 necessary to conduct additional trials to adequately assess the risk.

#### 669 **8.1.1. Infants and toddlers**

670 Safety data obtained from trials in RSV non-naïve subjects may be poorly predictive of the safety  
671 profile in RSV-naïve subjects. Therefore, a cautious approach is recommended for the commencement  
672 of trials in infants and toddlers. The potential risk of vaccine-associated disease enhancement may be  
673 higher in RSV-naïve infants in the first six months of life compared to RSV-naïve infants aged 7-12  
674 months, RSV-naïve toddlers and non-naïve infants and toddlers. Therefore, it is particularly important  
675 that there is a large representation of infants aged < 6 months in the safety database.

#### 676 **8.1.2. Pregnant women**

677 The risk of local and systemic reactions to vaccination should be assessed in detail before proceeding  
678 to vaccinate large numbers of pregnant women in efficacy trials. The rates of premature delivery,  
679 complications of pregnancy or labour and the condition of infants at birth should be compared between  
680 the vaccinated and unvaccinated groups.

681 If re-vaccination is required in subsequent pregnancies the safety profile should be documented and  
682 compared with the first pregnancy in which the woman was vaccinated to determine whether the risk  
683 of significant adverse reactions is different. These data may be obtained in post-licensure studies.

684 There would be considerable concern regarding the use of any live vaccine construct (live attenuated  
685 or live viral vectored vaccine) during pregnancy. If sponsors are proposing to use a live construct there  
686 should be early discussions with EU Competent Authorities.

#### 687 **8.1.3. Elderly**

688 It is expected that elderly subjects will likely require repeated dosing, perhaps annually, to maintain  
689 protection against RSV disease. The safety profile of repeated dosing over 2-3 seasons should be fully  
690 documented and compared with that of the first dose(s).

691 **8.2. Monoclonal antibodies**

692 Although there is already considerable experience with the use of monoclonal antibodies in infants and  
693 toddlers, it is essential that local and systemic reactions to the first and all sequential doses are fully  
694 captured to document any trends there may be to increasing rates of adverse reactions with sequential  
695 doses and/or in sequential seasons. Subjects should be followed for safety after the last dose is  
696 administered for a period determined by the half-life of the RSV neutralising activity.

697 **8.3. Antiviral agents**

698 Safety data should be collected in each target age group as for any new active substance. The  
699 acceptable size of the pre-licensure safety database in each of the target groups will depend on the  
700 actual safety profile that is observed and, to some extent, on the magnitude of efficacy that is  
701 demonstrated against RSV disease at the more severe end of the disease spectrum. If there are any  
702 particular concerns raised by the safety data generated in pre-licensure trials in any target population  
703 it is possible that additional data may be required pre-licensure and/or by means of a post-  
704 authorisation safety study.

705 **9. References**

706 Anderson NW, Binnicker MJ, Harris DM, *et al.* Morbidity and mortality among patients with respiratory  
707 syncytial virus infection: a 2-year retrospective review. *Diagn Microbiol Infect Dis* 2016;85:367-71.

708 Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized  
709 problem. *Drugs Aging* 2015;32:261-9.

710 Collins P, Fearn R, Graham B. Respiratory syncytial virus: virology, reverse genetics, and  
711 pathogenesis of disease. *Curr Top Microbiol Immunol* 2013;372:3-38.

712 Edwards KM. Maternal antibodies and infant immune responses to vaccines. *Vaccine* 2015;33:6469-72.

713 Escobar GJ, Masaquel AS, Li SX, *et al.* Persistent recurring wheezing in the fifth year of life after  
714 laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC Pediatr*  
715 2013;13:97.

716 Falsey AR, Hennessey PA, Formica MA, *et al.* Respiratory syncytial virus infection in elderly and high-  
717 risk adults. *N Engl J Med* 2005;352:1749-59.

718 Giersing BK, Modjarrad K, Kaslow DC, *et al.* WHO Product Development for Vaccines Advisory  
719 Committee. Report from the World Health Organization's Product Development for Vaccines Advisory  
720 Committee (PDVAC) meeting, Geneva, 7-9th Sep 2015. *Vaccine* 2016;34:2865-9.

721 Giersing BK, Modjarrad K, Kaslow DC, *et al.* The 2016 Vaccine Development Pipeline: A special issue  
722 from the World Health Organization Product Development for Vaccine Advisory Committee (PDVAC).  
723 *Vaccine* 2016;34:2863-4.

724 Glezen WP, Taber LH, Frank AL, *et al.* Risk of primary infection and reinfection with respiratory  
725 syncytial virus. *Am J Dis Child* 1986;140:543-6.

726 Hall CB, Weinberg GA, Iwane MK, *et al.* The burden of respiratory syncytial virus infection in young  
727 children. *N Engl J Med* 2009;360:588-98.

- 728 Heikkinen T, Chonmaitree T. Importance of respiratory viruses in acute otitis media. *Clin Microbiol Rev*  
729 2003;16:230-41.
- 730 Jain S, Williams DJ, Arnold SR, *et al.* Community-acquired pneumonia requiring hospitalization among  
731 U.S. children. *N Engl J Med* 2015;372:835-45.
- 732 Jones CE, Munoz FM, Spiegel HM. Guideline for the collection, analysis and presentation of safety data  
733 in clinical trials of vaccines in pregnant women. *Vaccine* 2016;34:5998-6006.
- 734 Kim H, Canchola J, Brandt C, *et al.* Respiratory syncytial virus disease in infants despite prior  
735 administration of antigenic inactivated vaccine. *Am J Epidemiol* 1969;89:422-34
- 736 Modjarrad K, Giersing B, Kaslow DC, *et al.* WHO RSV Vaccine Consultation Expert Group. WHO  
737 consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health  
738 Organization Meeting held on 23-24 March 2015. *Vaccine*. 2016;34:190-7.
- 739 Nair H, Nokes DJ, Gessner BD, *et al.* Global burden of acute lower respiratory infections due to  
740 respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*  
741 2010;375:1545-1555.
- 742 Roberts JN, Graham BS, Karron RA *et al.* Challenges and opportunities in RSV vaccine development:  
743 Meeting report from FDA/NIH workshop. *Vaccine* 2016;34:4843–4849
- 744 Roberts JN, Gruber MF. Regulatory considerations in the clinical development of vaccines indicated for  
745 use during pregnancy. *Vaccine* 2015;33:966-72.
- 746 Schneider-Ohrum K, Cayette C, Snell Bennett A, *et al.* Immunization with low doses of recombinant  
747 post-fusion or pre-fusion RSV F primes for vaccine-enhanced disease in the cotton rat model  
748 independent of the presence of a Th1-biasing (GLA-SE) or Th2-biasing (Alum) adjuvant. *J Virol*  
749 2017;91:e02180-16.
- 750 Simpson MD, Kieke BA Jr, Sundaram ME, *et al.* Incidence of Medically Attended Respiratory Syncytial  
751 Virus and Influenza Illnesses in Children 6-59 Months Old During Four Seasons. *Open Forum Infect Dis.*  
752 2016;3:ofw081.
- 753 Zomer-Kooijker K, van der Ent CK, Ermers NJ, *et al.* Increased risk of wheeze and decreased lung  
754 function after respiratory syncytial virus infection. *PLoS One* 2014;9:e87162.