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## RESCEU and PROMISE: the success of 8 years of European public-private partnership to prevent RSV

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1 **Running Head.** Preparing Europe for RSV immunisation

2

3 **Title.** RESCEU and PROMISE: the success of 8 years of European public-private partnership to prevent

4 RSV

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12 by Vaccine Europe, Brussels, Belgium; and Clarisse Demont is now employed by Moderna, Paris,

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14

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## 16 **The legacy of RESCEU: partnering against RSV**

17

18 Health promotion through population-based interventions for infectious disease prevention and  
19 control requires broad stakeholder collaboration from public health and regulatory bodies, small and  
20 medium-sized enterprises and large industry, academia and research organisations, funders, policy  
21 makers, and civil society organisations. For example, surveillance programmes guide the prioritisation  
22 of research and development (R&D) investments, constitute a critical source of clinical isolates which  
23 are the starting point of development of prophylactic and therapeutic solutions, and are instrumental  
24 in post-marketing safety and effectiveness monitoring of interventions. Uniform case definitions,  
25 sensitive and specific diagnostic tests, sustainable surveillance and lab networks, and well-defined  
26 reporting practices all require cross-disciplinary collaboration.

27 The respiratory syncytial virus (RSV), first discovered in 1955 [1], has long been the focus of intense  
28 study with the aim of developing an effective vaccine or treatment. However, following the failure of  
29 the initial formalin-inactivated vaccine in 1965-66, there was substantial setback to R&D investment in  
30 RSV. With the discovery of the structure of the F protein in 2013, and the demonstration that it can be  
31 stabilised in its prefusion form, interest in RSV peaked once more not only among scientists but also  
32 international agencies like the World Health Organization (WHO) [2]; funders like Bill and Melinda  
33 Gates Foundation; and the pharmaceutical industry.

34 In response to this need and to the willingness to generate more comprehensive data on RSV in Europe,  
35 the RESCEU initiative was launched in 2017. This collaborative effort, funded by the Innovative  
36 Medicines Initiative (IMI), a European Commission and European Federation of Pharmaceutical  
37 Industries and Associations (EFPIA) partnership, brought together researchers and scientists from both  
38 the public and private sectors across Europe, all united by a common, strong objective: to deepen our  
39 understanding of RSV. The initiative's strength was the expertise of the individuals involved, including  
40 an external scientific board composed of the most renowned experts in the field of RSV research.

41 Despite the COVID-19 pandemic which impacted the entire world, and particularly the researchers  
42 involved in RESCEU, some of whom were mobilised as part of national and global response, the work  
43 continued unabated. The team managed to produce high-quality research published in top-tier peer-  
44 reviewed journals, including two supplements of the Journal of Infectious Diseases [3][4]. These results  
45 have informed policy on RSV surveillance and recommendations for implementation of RSV vaccines  
46 and monoclonal antibodies in national immunisation programmes across Europe. Another notable  
47 highlight of the project was the launch of the RSV awareness week spearheaded by the consortium's  
48 Patient Advisory Board to raise public awareness and understanding of the virus.

49

#### 50 **PROMISE carries on the mission**

51

52 With the anticipated licensure and subsequent market availability of RSV immunisations by 2025,  
53 PROMISE was funded by IMI in 2021 to build on RESCEU's achievements and address remaining key  
54 questions including RSV impact on specific populations such as pregnant individuals or adults with  
55 comorbidities as well as the impact of COVID-19 pandemic on RSV. This PROMISE supplement includes  
56 articles that span a broad range of areas - from epidemiology to public health to basic sciences - an  
57 illustration of the wide scope and impact of the project.

58 There is limited understanding of the impact of RSV A and B subgroups on RSV seasonality, as studies  
59 report conflicting results. Deng and colleagues conducted a systematic review of studies reporting  
60 multi-year data from various regions and found that RSV subgroup distribution has negligible impact  
61 on the year on year variations in RSV seasonality [5]. This is important (and reassuring) as some of the  
62 prophylactic products do not include RSV B although there is a substantial degree of cross-protection.

63 A multitude of severity scores for bronchiolitis and RSV disease have been developed over the last two  
64 decades. Sheikh and colleagues conducted a systematic review and found that none of the 31 scores  
65 further assessed were sufficiently validated [6]. They reported that the ReSViNET score was positively

66 associated with hospitalisation, pediatric intensive care unit (PICU) admission, mechanical ventilation  
67 and respiratory support requirement. In a separate paper, they used RESCEU and secondary data from  
68 tertiary hospitals in Rwanda and Colombia for validation [7]. They observed that fever could be  
69 excluded from the original ReSViNET score without compromising on its discriminative validity, which  
70 is a critical output to better characterise the disease and to harmonise RSV severity criteria.

71 RSV during pregnancy poses substantial health risks both to the foetus and the birthing parent. There  
72 is limited knowledge regarding RSV disease burden in pregnant individuals [8]. Kenmoe and colleagues  
73 conducted a systematic review and meta-analysis of all available data (published and unpublished) in  
74 this population risk group and report that although RSV-associated hospitalisations were uncommon  
75 in pregnant individuals, and no RSV associated deaths were observed, the incidence of RSV in pregnant  
76 individuals was comparable to the incidence of RSV in adults  $\geq 18$  years with underlying medical  
77 conditions [9].

78 Electronic health records from hospitals are now being routinely used to estimate RSV disease burden  
79 but this approach can lead to an underestimation of disease burden, particularly in adults. Egeskov-  
80 Cavling and colleagues have used Danish National Patient Registry data linked to Danish Microbiology  
81 Database (2015 - 2018), and report that the overall sensitivity of RSV-coded hospitalisations was 42.4%  
82 (95% CI [39.3%, 45.6%]) [10]. Osei-Yeboah and colleagues have used data from Scotland and Denmark  
83 to estimate RSV-associated hospitalisations in adults with comorbidities [11]. They report that the risk  
84 for RSV hospitalisation is 1.5- to 3-fold higher in adults  $\geq 45$  years with asthma; 2- to 4-fold higher in  
85 those with chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD), stroke and  
86 diabetes; and 3- to 7-fold for those with chronic kidney disease (CKD). These estimates are comparable  
87 to those for seasonal human influenza for a similar age group in Scotland and highlight the need for  
88 including adults  $\geq 45$  years with comorbidities in RSV immunisation programmes. In another paper,  
89 they demonstrated that there is a 2-fold difference between the least and the most deprived socio-

90 economic groups in RSV-associated hospitalisations across all age groups in Scotland, the difference  
91 being more pronounced in infants and young children [12].

92 As RSV immunisation products are being introduced in national immunisation programs across Europe,  
93 there is an urgent need for robust RSV surveillance which includes harmonisation of laboratory  
94 techniques and reporting practices across Europe. Presser and colleagues summarised the diverse  
95 practices of European Respiratory Syncytial Virus Laboratory Network members from 26 member  
96 states surveyed in 2022 [13]. These findings could inform WHO and the European Centre for Disease  
97 Prevention and Control (ECDC) currently considering integrated surveillance for respiratory pathogens  
98 [14][15]. PROMISE investigators also developed generic protocols to support National Public Health  
99 agencies conducting effectiveness studies for licenced vaccines and monoclonal antibodies using  
100 register-based cohort design or tests-negative case control approaches [16][17].

101 A substantial proportion of RSV episodes in young children are not medically-attended. Among those,  
102 Hak and colleagues reported that 93% of RSV episodes had a median duration of illness of 6 days with  
103 respiratory symptoms scored by parents as moderate-severe, inducing substantial parental anxiety  
104 and workplace absenteeism of at least 1 day [18]. These findings are particularly important to inform  
105 RSV immunisation policies as non-medically attended children are not currently included as part of  
106 disease burden estimates.

107 Finally, there is currently poor understanding of the role of monocytes in severe RSV disease. Chappin  
108 and colleagues used transcriptomics profiling of peripheral blood and airway monocytes and found  
109 that monocytes in RSV patients upregulate pathways associated with interferon and antiviral  
110 responses, suggesting that blood monocytes are activated to become inflammatory/antiviral prior to  
111 being actively recruited to the airways in response to an RSV infection [19].

112

113 **What remains to be done to ensure RSV prevention in Europe**

114

115 Since 2016, two EU-funded public-private partnerships have worked to prepare the European Union  
116 for the introduction of RSV vaccines for pregnant women, children and older adults. These  
117 collaborative research efforts always included the voice of patients and public health bodies, including  
118 ECDC and WHO, to ensure societal relevance of the work. Literature reviews as well as prospective  
119 studies were undertaken to maximise understanding of the health and health-economic consequences  
120 of RSV for all ages. These partnerships have substantially contributed to the set-up of RSV surveillance  
121 at a European level. The implications of the COVID pandemic on RSV epidemiology were absorbed.  
122 Epidemiology studies were continuously aligned with translational research questions. Major progress  
123 was made in understanding pathophysiology, molecular epidemiology and vaccine immunology of  
124 RSV, including a better understanding of mucosal immune mechanisms of RSV infection and correlates  
125 of protection relevant for vaccine development. To ensure the sustainability of knowledge, research  
126 infrastructure, and biological materials; a data repository and biobank have been set up, with the hope  
127 these results can be leveraged for future RSV studies.

128 Although both these consortia have made a major contribution to RSV understanding and awareness,  
129 several gaps in knowledge remain. First, the consequence of the COVID pandemic on RSV burden  
130 remains incompletely understood. Seasonality has been disrupted during the pandemic and resulted  
131 in a delayed summer outbreak. Although RSV has started to peak in the winter again, seasonality has  
132 not returned to pre-COVID patterns.

133 Second, previous studies have focused on general populations. Incidence of severe RSV disease in  
134 specific, vulnerable populations, such as children with asthma, neuromuscular disease,  
135 immunocompromised children or children with cancer remains largely unknown. This is particularly  
136 relevant for children above 1 year of age as development of paediatric vaccines is approaching late-  
137 stage clinical development. For older adults, RSV burden in long-term care facilities with irregular RSV  
138 outbreaks associated with mortality is largely unknown.

139 Third, we are currently in an era in which various RSV immunisation strategies are deployed in Europe.  
140 We do not yet know the duration of protection or the impact of vaccination on RSV upper respiratory  
141 infection including viral shedding pattern. Direct impact of RSV immunisation products on  
142 hospitalisation admission and duration of stay, disease severity, antimicrobial use, and co-infections is  
143 unknown. Indirect broader impact is also understudied, including quality of life of caretakers, RSV  
144 transmission in households/childcare settings or elderly facilities.

145 Fourth, a next step required for successful prevention of RSV infection is increasing RSV awareness at  
146 all levels of society. Anecdotally, we observed that the general public has heard of RSV more often  
147 today than one decade ago. Nevertheless, it is obvious that very few people know about the burden  
148 of RSV infection, for example that all babies are at risk of severe disease. Policy makers are currently  
149 learning about RSV infection as all countries are in the process of formulating policies on RSV  
150 immunisation in various target populations. Healthcare practitioners have variable knowledge of RSV  
151 infection. While most paediatricians know the disease quite well, others such as general practitioners,  
152 geriatricians, and adult intensivists do not have first-hand experience as RSV is rarely diagnosed in their  
153 patient populations. A multi-stakeholder approach building upon the foundations of patient  
154 involvement developed by RESCEU and PROMISE is required to reach broad RSV awareness necessary  
155 for successful disease prevention.

156 In conclusion, RESCEU and PROMISE are examples of successful public-private partnerships in the pre-  
157 competitive space where multiple stakeholders joined forces to get Europe ready for RSV prevention.  
158 With the first-ever approval of RSV immunisations in the European Union in 2022, we are confident  
159 that the projects' results will live for many more years and facilitate the prevention of one of the most  
160 important acute infections at all ages. We call for continued collaboration in the field of infectious  
161 diseases prevention and control to accelerate the development of life-saving public health  
162 interventions, guarantee health emergency preparedness and ensure equity of access.



163 **Footnote**

164

165 **Conflict of interest.** The authors have conflict of interest to disclose, as outlined in the ICJME COI forms

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