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Commentary

1st WHO International Standard antiserum to RSV: Availability and benefits for RSV vaccine development (Commentary on the collaborative study report published in the vaccine journal (Vaccine 2018 36: 7641–7649))

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The purpose of this Commentary/Editorial is to raise awareness of the availability of the 1st WHO International Standard for Antiserum to RSV (RSV IS) and its use in securing the public health benefits of RSV vaccines of assured quality and efficacy. The RSV IS might be used for the following:

(1) Better understanding of the immunity to RSV by characterizing in a standard way pre-existing and post-vaccination serum antibody responses to RSV in different patient populations (based on age [e.g., infants, children, pregnant women, elderly] or geographic location).
(2) Assessment of vaccine efficacy through the comparison of the outcomes from vaccine trials when tested in different patient populations. This will allow regulators, developers and other interested parties to have a view across vaccine trials for assessing efficacy.
(3) Quality control of vaccines as part of the overall vaccine evaluation.

This RSV IS was established by the WHO Expert Committee on Biological Standardization in October 2017 [1] and is available from the WHO Collaborating Center, the National Institute for Biological Standardization and Control (NIBSC), in the UK. The WHO has increasingly recognized the importance of RSV acute lower respiratory illness (RSV-ALRI) as a global health problem and identified the need for biological standards as a priority in the development of RSV vaccines. Many vaccine candidates using 6 biotechnology platforms are currently at different stages of development, with several candidates in phase 2 or phase 3 clinical development, and this is creating an urgent need for standardizing the measurement of the outcomes of vaccine evaluation in order to better assess vaccine performance. WHO biological standards and reference materials are primary standards of critical importance in vaccine development as well as in on-going quality control by enabling vaccine candidates to be appropriately characterized and evaluated. More accurate comparison of the clinical performance of different vaccine candidates is another benefit of using WHO International Standards.

WHO standardization activities led by the NIBSC resulted in the development and establishment of the first International Standard for antiserum to RSV with 1000 International Units of RSV subtype A (RSV/A) neutralising activity per ampoule. This is an important achievement for the scientific community across RSV diagnostics, prevention and treatment. Detailed information about the development and characterization of the standard is available in the report published in *Vaccine* [2]. Although the many technical details in that report may be less familiar to RSV research and vaccine development audiences, the new RSV IS is an important achievement for the scientific community across RSV diagnostics, prevention, and treatment.

Candidate RSV vaccines are being designed to primarily protect at least two populations most susceptible to severe RSV disease: RSV-naive young infants and children, and older adults although other high-risk populations are not being ignored. It is estimated that 45% of hospital admissions and in-hospital deaths due to RSV-ALRI occur in infants less than 6 months of age [3]. It is well known that immune responses in that age group are lower than in older children due to the immature immune system. Older adults and adults with chronic cardiopulmonary conditions have also emerged as an important target for RSV prevention owing to an increased understanding of RSV burden in this population.

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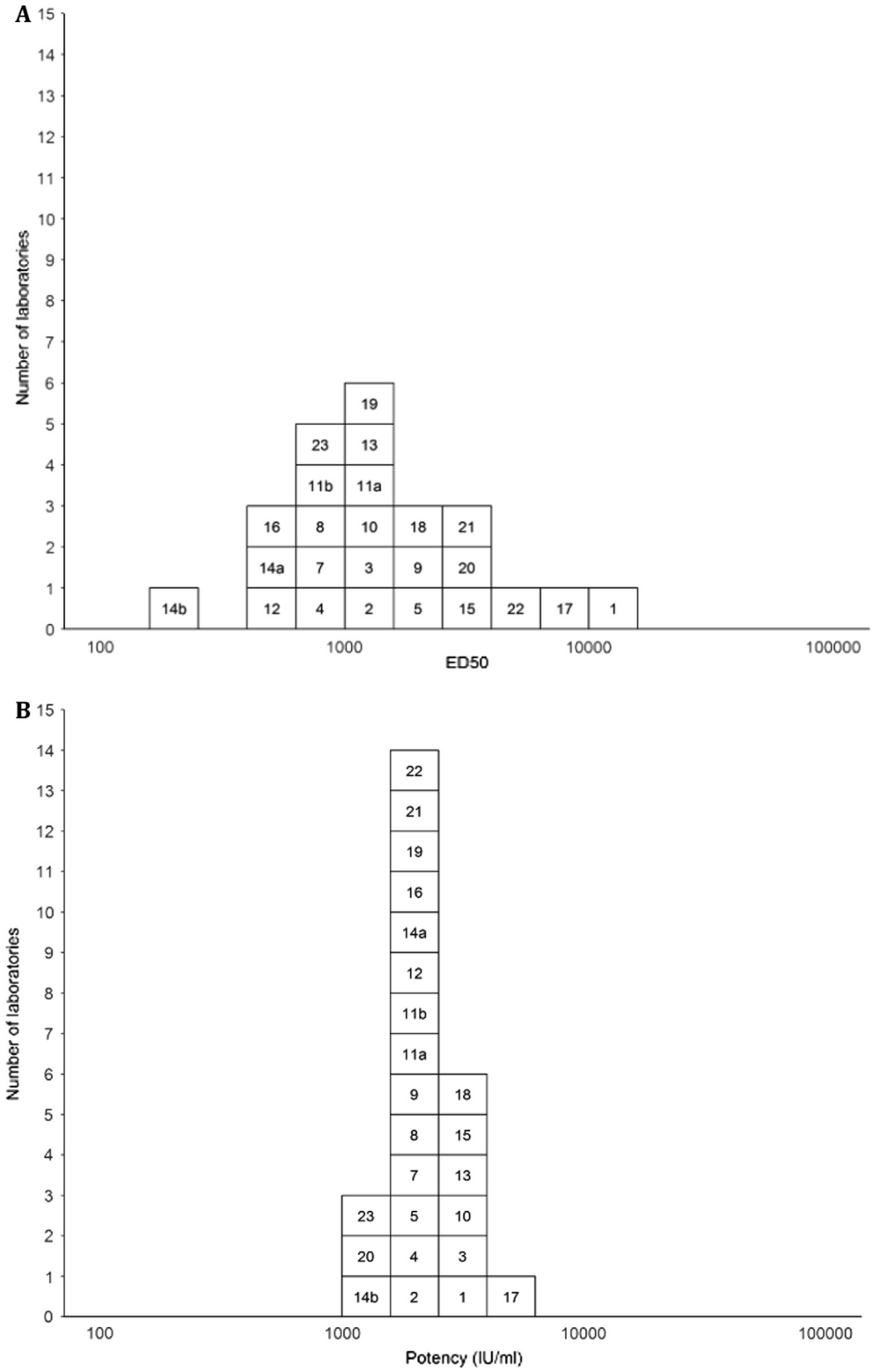

Fig. 1. Assay variability. RSV/A neutralization data from 24 laboratories are plotted in each graph (A and B), with the laboratory identifier numbers shown inside the data marker boxes. (**A)** Distribution of RSV/A neutralizing antibody titers for one serum sample from the collaborative study described in [2], with GCV (Geometric coefficient of variation) (raw EC50 values): 155%**. (B)** Distribution of RSV/A neutralizing potency values of the sample shown in (A), after normalization using the IS and expressed in IU/ml with GCV (normalized potency values): 42%.

Clinical development of RSV vaccines includes particle-based, vector-based, subunit, and live-attenuated or chimeric vaccines [4]. There are also monoclonal antibodies (mAbs) in clinical development for the prevention of RSV ALRI. The RSV vaccine landscape was discussed at the ReSViNET conference in December 2017 and details are provided in the review article [4]. An overview of all RSV vaccine and mAb candidates per target population is provided and regularly updated by PATH (available on PATH's website at:

https://vaccineresources.org/details.php?i=1562), and the most current version dated 5th April 2019 shows there are 43 products (38 vaccines and 5 mAbs) in development, of which 21 (19 vaccines and 2 mAbs) are in clinical stage development.

From the perspective of immunological endpoints, the current understanding is that antibodies play a key role in limiting RSV ALRI as evidenced by proven protection in immunoprophylaxis trials in children [5–7]. Antibodies directed against the various antigenic sites of the F protein display different neutralization capacities and those specifically recognizing the pre-F conformation appear to be especially potent [8]. The mechanisms of protection could differ according to vaccine type, and, therefore, multiple immunological assays are used in clinical trials. Neutralising activity of serum is a frequently used immunological endpoint of vaccine trials.

The ultimate goal of vaccine developers and regulators is to license products and make them available for use in the target population. To facilitate this effort, the standardization of the assays for evaluation of vaccine performance has been recognized as an important element for understanding immune responses to vaccines. In the context of RSV vaccine development, a recent study conducted by PATH examined the variability of RSV neutralisation assay results across laboratories and showed that calibration to a common reference material may improve standardization globally [9]. In the collaborative study, conducted by the NIBSC, the candidate RSV IS was used as a calibrant for different neutralization assays used in participating laboratories [2]. It was shown that the RSV IS is suitable for harmonizing results across laboratories and neutralization methods used to measure antibody titres against RSV/A in human sera [2]. As a result, the new WHO 1st International Standard for antiserum to RSV with 1000 IU of RSV/A neutralising activity per ampoule was established [1]. Standardization of other frequently used immunological assays such as antibody competition assays (e.g. palivizumab competing antibody (PCA) assay), ELISA, and T cell assays has not yet taken place. The RSV IS is not appropriate for cotton rat serum samples and monoclonal antibody samples. As stated in the collaborative study report [2], there are multiple benefits of using the RSV IS, among which a reduction in inter-laboratory variability of assay results is key for vaccine developers and regulators. Fig. 1A and B shows the distribution of results obtained in the collaborative study [2] for one serum sample from a single human donor (data kindly provided by the NIBSC). Fig. 1A shows widely differing neutralization results obtained in different laboratories. However, using the candidate International Standard as reference and expressing the results in International Units reduces significantly the variation between laboratories, as can be seen in Fig. 1b. This would enable real RSV neutralizing antibody differences between different serum samples to be identified, if they existed.

In line with the above, the conclusion is that the RSV IS should be used when assaying neutralizing antibody responses in ongoing and future clinical trials conducted as part of RSV vaccine development and the results should be reported in International Units, along with the information about the performance of the RSV IS. This will allow the scientific community to benefit from the availability of the new standard and improve the understanding of vaccine performance in terms of the induction of neutralizing antibody responses. Detailed information about the RSV IS is available at the NIBSC web site: http://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=16/284) and the instructions for use at: http://www.nibsc.org/documents/ifu/16-284.pdf. Feedback from users will help WHO and its Collaborating Centre, NIBSC, to advance the further use of this standard as well as the development of other standards and reagents that may improve standardization of assays used in the clinical evaluation of RSV vaccines and facilitate licensure. Further work is ongoing at NIBSC in testing the standard for antibodies against RSV B viruses and data to date show that the RSV IS is effective for titres against RSV/B. Publication of the results is in preparation (personal communication).

Disclaimer

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Declaration of Competing Interest

The author has disclosed no potential conflicts of interests.

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