Infectious disease

Direct long-acting antibodies: updating the language of RSV prevention to reflect the evolution of mAbs

PIER LUIGI LOPALCO[1], SUSANNA ESPOSITO[2], FEDERICO MARTINÓN-TORRES[3], JACQUI THORNTON COMMUNICATIONS LTD[4], GIOVANNI CHECCUCCI LISI[5], KOCFA CHUNG-DELGADO[5], BRAD DAVIDSON[6], STEPHANIE EVANS[7], AMIT PATEL[7], CLAIRE FELLINGHAM[7], BEN POUNDS[7], CHARLOTTE HARRIS[7], TAPAS MUKHERJEE[7]

[1] Professor of Hygiene and Preventive Medicine, University of Pisa, Italy; [2] Faculty of Medicine, University Hospital of Parma, Italy; [3] Head of Pediatrics, Hospital Clínico Universitario de Santiago, Spain; [4] Health Journalist, UK; [5] Employees of Global Medical Franchise, Sanofi, France; [6] Medical Anthropology, Havas Health and You, New York, USA; [7] Employees of Havas Lynx Group, London, UK

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Summary

Introduction. *The language of medicine is constantly evolving, typically to better describe a new understanding of disease, adjust to changing social sensibilities, or simply to reflect a new drug class or category. We address the need for an updated language around monoclonal antibodies, or "mAbs" – a widely used medical term, but one which is now too general to accurately reflect the range of mAb pharmaceuticals, their effects, and the intended patients.*

Methods. *The question of "what should we call a monoclonal antibody immunisation against respiratory syncytial virus (RSV) to ensure accurate understanding of the product?" was the basis for a virtual advisory panel in May 2022. The panel was convened by Sanofi with the intention of reviewing appropriate language in terminology in the context of mAb-based prophylaxis for RSV. The panel comprised several global experts on RSV and vaccination, a trained linguist specialising in doctor-patient interactions and medical language, and several experts in marketing and communications.*

Results. *We suggest the term "Direct Long-acting Antibody" (DLA) for a specific sub-class of mAbs for use in prevention of RSV disease in infants. This terminology should differentiate from other mAbs, which are generally not used as therapies in infants.*

Discussion and Conclusions. *This change will more accurately convey the specific mode of action of a mAb in infants, and how it could impact the prevention of communicable diseases: this class of mAbs is not an active treatment, but rather will offer direct and rapid protection lasting at least 5 months.*

Introduction

The language of medicine, and of science in general, is constantly evolving. This is necessary to reflect the ongoing "march of science" where our knowledge and understanding of biology and pharmacologic interventions increases every year [1], and changes in the social fabric within which medicine is practised [2, 3]. For the former, we have examples like "bipolar disorder", which replaced "manic depression" to more accurately convey the nature of the condition (bipolar patients tend towards primary mania or depression, not both). In the latter case, we can look to the recent change of "non-alcoholic fatty liver disease" to "metabolic fatty liver disease" to remove possible stigma and judgement, as well as to clarify the role alcohol may (or may not) play in this disease [4]. While these changes may seem trivial, we often rethink the language we use if we find that the current linguistic forms are simply no longer accurate to a precise degree. It is worth remembering that if we didn't change the language we use, we would still be referring to heart failure as "dropsy", and people with cerebral palsy as "spastics".

In addition, language which creates unwanted impressions or is off-putting to an intended audience may need to be revised, as this type of language can create real barriers to appropriate medical care [5]. For example, the language around addiction has been focused on "dependence" for some time, as it is easier to self-identify as "dependent" rather than "addicted" with all the social baggage the latter produces. As an almost ubiquitous and current example, the recent highly charged discussions around the meaning and proper reference for the words "women", "men", "female", and "male" combine both the medical and social aspects of language change.

Also relevant in this case is the classification of a drug within a category, and how this may influence how that drug is perceived. Aspirin (acetylsalicylic acid) was first observed to have analgesic and antipyretic qualities, and was subsequently classed as a non-steroidal anti-inflammatory (NSAID) [6]. However, numerous potential applications of Aspirin have been identified when prescribed at different doses – from anticoagulation and preventing cardiovascular events, to the treatment of cancers and dementias, as well as in the field of ophthalmology [6-8] – suggesting its benefits may reach far beyond those its classification as a simple

NSAID would initially suggest. Evidently, language has a clear and defining effect on perceived benefits and other aspects of drugs or diseases; how we describe and talk about such interventions could be of paramount importance from their inception.

In this paper we will discuss just such a proposed language change for a term which has both medical (pharmacological) and, to some extent, social foundations. This language change was discussed by a panel of experts brought together by Sanofi and reviewed in the context of a monoclonal antibody-based prophylactic immunisation against respiratory syncytial virus (RSV) disease for infants under 1 year of age. The ideas discussed by the panel and identified in this paper are intended to stimulate discussion within the scientific community around the potential limitations of currently used language used to discuss mAb-based propylaxis in RSV.

RSV is the most common respiratory pathogen in infants worldwide [9], infecting around 90% of infants by their second birthday [10]. The virus emerges, peaks, and recedes in a seasonal pattern – typically lasting 5 months from the autumn to spring in temperate climates [11, 12]. Each year, RSV disease places a substantial burden on healthcare systems globally and represents a leading cause of hospital admission among infants. It requires substantial healthcare investment and seasonal planning to ensure adequate resources are in place [13].

The immunisation being discussed in this paper is currently classified as a "monoclonal antibody" (mAb) which, although scientifically accurate, could create several unnecessary forms of potential confusion among parents, caregivers and even healthcare professionals, with a likely impact on usage and uptake. Both the history of mAbs and the current social environment surrounding vaccination as a topic for discussion (and misinformed debate) argue that we should, in fact, increase our specificity of language in this case. Furthermore, the very term 'mAb' is itself now dated: in 2021, the International Nonproprietary Names (INN) Programme of the World Health Organization (WHO) decided to discontinue the use of the term for new substances, owing to the high number of drug names already ending in '-mab' [14]. They have instead proposed and adopted a radically different naming system for future pharmaceutical substances [14].

The four areas of "communicative precision" that can be achieved through the use of new linguistic forms that will more accurately convey the core features of this particular mAb are:

1. to differentiate this monoclonal antibody from current class perceptions, which often involve treatment of severe chronic or acute disease, rather than prevention of infection in infants;
2. to create a clear understanding of the mechanism of RSV protection provided by this mAb (specifically regarding its role as a prophylaxis, not an active treatment – a departure from most currently approved mAbs in other disease areas);
3. to specify the duration of effect of the prophylaxis provided (a necessary element for this mAb as it is used as an immunisation in the context of RSV being a seasonal virus);
4. to clarify how this immunisation provides direct protection from the point of administration, and why this differs to active immunisation.

It is our hope and intention that this new language will provide an easily introduced, easily understood, and easily applied upgrade to the existing language surrounding mAbs, and to clarify the nature of this immunisation. The remainder of this article will outline the key discussion points from the panel regarding this new terminology. In an era of heightened vaccine scrutiny, misinformation, and hesitation, it is important to find the correct language to facilitate understanding and uptake of this important new entrant to the field of RSV prevention.

Methods

Despite the clear impact RSV disease has across healthcare systems, limited prophylactic options are currently available [15]. Several approaches to tackle this unmet need are under development, including immunisations for pregnant women in their third trimester, paediatric vaccines, and passive immunisation with monoclonal antibodies with extended half-lives – among the monoclonal antibody category, a new solution called nirsevimab (registered name Beyfortus®; AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center, Maryland, US) is included [15], which was approved in the European Union and UK in November 2022 [16], and in the USA in July 2023 [17].

The question of "what should we call a monoclonal antibody immunisation against RSV to ensure accurate understanding of the product?" was the basis for a virtual advisory panel, assembled in May 2022 by Sanofi to discuss the specific issue of language and communication of mAbs in the context of RSV disease.

The panel was comprised of several global experts on RSV and vaccination (Prof. Pier Luigi Lopalco, Prof. Susanna Esposito, Prof. Federico Martinón-Torres, and Dr. Todd Wolynn), a trained linguist specialising in doctor-patient interactions and medical language overall (Dr. Brad Davidson), and several experts in marketing and communications (including Ms Jacqui Thornton, Health Journalist). Each of these participants played a significant role in the discussion, providing a broad and complementary view of both clinical and communication practices. No patients or members of the public were involved in the discussion or outputs of this advisory panel. As this was a language-focused meeting, the need for a new method for preventing RSV was beyond the scope of discussion and will therefore not be further discussed.

Given the product's status as a monoclonal antibody (a "mAb") and the fraught public discourse around immunisations and vaccinations [18, 19], it was identified that the language used to describe the mAb needed to be vetted to avoid unnecessary confusion,

concern, or outright dismissal. The concerns centred around two areas, both of which were discussed in the meeting:

1. the impression of mAbs as "serious treatment" of illness (usually in adults), not appropriate for the prevention of illness in infants;
2. the overall challenge of introducing and discussing a new "infant vaccination" or "vaccine-like" intervention, during a period of heightened vaccine resistance, discussion, and sensitivity.

For the first area of discussion (the issue of mAbs as a perceived "strong medicine"), the discussion centred on the historical and current usages of mAbs, many of which focus on treating cancers or serious, highly symptomatic rheumatologic conditions like rheumatoid arthritis and plaque psoriasis. The concern in this case is that the term "monoclonal antibody", while entirely accurate, is no longer precise enough to cover all of the different types of mAbs equally well. As Dr. Brad Davidson, the linguist, phrased it: "mAb has become a class name for a very large class, like mammal. Mammal is a useful term, but it describes both tigers and mice. Calling something a mammal doesn't tell you how big, fast, or potentially dangerous it is". The clinicians in the room agreed that the term mAb/monoclonal antibody brought forward associations with strong treatments, and strong adverse event potential – neither of which are appropriate for prophylaxis of disease in infants under 1 year of age. In a unanimous agreement, the participants of the meeting concluded that mAb as a descriptor was not sufficiently precise in today's crowded mAb category to convey the true nature of the product, despite being medically accurate.

The second area of discussion (that of the rising tone and volume of public vaccine discourse) was also considered at length. It was agreed that nirsevimab is, indeed, a form of immunisation, and it could be argued that it is not an active vaccination as it does not stimulate the recipient's immune system. Unlike an active immunisation, nirsevimab's directly-administered monoclonal antibodies do not rely on a host immune response to offer rapid protection after administration, instead, offering rapid passive protection against RSV lower respiratory tract disease via administration of direct-acting antibodies [15]. In contrast, an active immunisation may require time for the host to generate an immune response, and may require repeated vaccine administrations to achieve maximal protection [20]. While this distinction may be meaningful within a research environment, it was also acknowledged that in common usage the terms vaccination and immunisation are employed interchangeably. This confusing, and confused, system of nomenclature is compounded by the truly enormous number of false statements about vaccines and immunisations that have proliferated throughout the COVID-19 pandemic, which have had demonstrable effects on vaccine uptake [21, 22]. The participants agreed that while nirsevimab is indeed "vaccine-like" when evaluated by the broad standards of the term, it is not "active" in its mechanism of protection but "passive". Clarifying exactly how nirsevimab works in infants (whose immune systems are too immature to provoke a robust response to an active vaccine after one single administration) would be important to integrate into the language surrounding nirsevimab.

Results

Providing a solution to the linguistic puzzle was the primary focus of the discussion and subsequent communications. The solution that was developed and agreed upon was that nirsevimab should be referred to as a "Direct Long-acting Antibody" (DLA), for the reasons described below:

1. *Direct:* this is a specific reference to the fact that nirsevimab does not "provoke a response" from infant immune systems so that they will produce antibodies; rather, it is the antibodies which are directly introduced into the infant's body at a time when infants are most vulnerable to the effects of RSV infection [15], to provide rapid protection against RSV lower respiratory tract disease. Much like exogenous insulin, the body is not required to react to the intervention, nor will it in an immunologic sense. In essence, what infants lack (*i.e.*, antibodies which target RSV) is being directly supplied to them. This also provides contrast to other interventions either currently used in the RSV category or expected in the future, for example immunisation for pregnant women where protective antibodies reach the infant indirectly, via the mother [23]; and paediatric vaccines which will require the infant's immune system to develop its own immune response (including antibodies) after administration [15]. Prophylactic solutions that provide direct and rapid protection against RSV disease allow for administration to coincide with the period of highest risk – an infant's first RSV season – which is an important benefit considering that the virus is seasonal.
2. *Long-acting*: the importance of duration of protection is very specific in this category – protection against RSV disease needs to last throughout a season, while the infant's lung and immune physiology continue to develop and eventually become mature enough to cope with an RSV infection. This period of heightened vulnerability when an infant faces their first RSV season during their first year of life is often referred to as their "first season" or "seasonal" risk. The protection afforded by nirsevimab is at least 5 months [15] – long enough to cover a typical RSV season in a temperate climate [11, 12], during an infant's period of heightened vulnerability in their first year of life [15]. In this context, "long-acting" is a reference to the duration of protection nirsevimab provides, which could cover the period of heightened vulnerability as infants enter their second year of life and their immune system gradually becomes robust enough to either combat the disease or mount an

immune response to any potential future paediatric RSV immunisations. In addition, "long-acting" serves to highlight the difference between existing short-acting mAb prophylaxis in RSV disease, which requires monthly injections throughout the season.

3. *Antibody:* the primary result of most vaccinations is the creation of antibodies that are specific to the disease against which the person is being vaccinated [20]. The result following an administration of nirsevimab is no different in this regard, although the process is more direct; as discussed earlier, immunisation with nirsevimab offers rapid protection against RSV lower respiratory tract disease via administration of direct-acting antibodies [15]. This particular element from the full term "monoclonal antibody" seemed most important to call out: it is the presence of the antibodies which supports nirsevimab's mechanism of action in providing protection against RSV, and the monoclonal element could lead to confusion with treatment for chronic disease. In other words, the focus here is on "what" nirsevimab is (an antibody), and not how it was manufactured as this does not serve any clinically meaningful purpose in this instance and has the potential to cause confusion.

Based on this information, the advisory panel concluded that nirsevimab is most accurately defined as a Direct Long-acting Antibody (DLA) and is a part of the larger class of mAbs.

Discussion and conclusions

We believe this type of process, where the true nature of a drug is discussed, is more important today than ever before. We live in an era of tremendous medical advances, with new pharmaceuticals being developed and launched at an astounding rate. With new mechanisms of action there comes a new need for precise language. In this case, a mAb is not just a mAb – in the same way that not all "small molecules" or "large molecules" are the same. Nirsevimab shares characteristics with, and is properly classified as, a monoclonal antibody-based passive immunisation. However, this term does not tell the whole story, and indeed in current context could be misleading or misunderstood. Our objective is clarity in communication, and we believe this terminology achieves that aim.

Our study had several strengths, including the involvement of leading individuals in the RSV, paediatrics, infectious disease, and linguistics space; and the versatility of the approach taken in exploring medical science linguistics to fill a language gap left where technology has advanced. Limitations of this study include a limited number of panellists submitting their expertise, and limited means of testing our output at the time of writing.

This challenge of proper naming, and using linguistic precision to facilitate proper understanding between provider and patient, can have substantial implications in preclinical and clinical settings. As such, we call on stakeholders in health and clinical practice, guideline and recommending bodies, and those engaged in the development of new and novel therapies to seriously consider this linguistic approach to nirsevimab – one which accurately describes its role as a preventative option against RSV disease, but emphasises the distinct characteristics which differentiate it from other prophylactic offerings such as active vaccination. We hope the themes discussed in this paper will stimulate further discussion on the appropriate definition of individual mAbs from the scientific community.

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Conflict of interest statement

Pier Luigi Lopalco: Advisory Board Participation & Honoraria for Lectures and other Training activities from GSK, Moderna, MSD, Pfizer, Sanofi, Seqirus.
Susanna Esposito: Advisory Board Participation & Honoraria for Lectures. GSK, Janssen, Pfizer, Moderna, MSD, Qiagen, Sanofi, Genzyme, Janssen.
Federico Martinón-Torres Received honoraria from GSK group of companies, Pfizer Inc, Sanofi Pasteur, MSD, Seqirus, Biofabri and Janssen for taking part in advisory boards and expert meetings and for acting as a speaker in congresses outside the scope of the submitted work. FM-T has also acted as principal investigator in randomised controlled trials of the above-mentioned companies as well as Ablynx, Gilead, Regeneron, Roche, Abbott, Novavax, and MedImmune, with honoraria paid to his institution.
Jacqui Thornton Communications Ltd. Received honoraria from Sanofi, Ipsen, Angelini Pharma, PTC Therapeutics, AbbVie and Indivior for moderating events and training work.
Todd Wolynn Received honoraria from Merck, Sanofi Pasteur, Mordera, Novavax, Seqirus, Pfizer for speaker events and in a consultant capacity.
Giovanni Checcucci Lisi and Kocfa Chung-Delgado are employed by Sanofi and may hold shares and/or stock options in the company, a company that may be affected by the research reported in the enclosed paper.
Stephanie Evans, Amit Patel, Claire Fellingham, Ben Pounds, Charlotte Harris and Tapas Mukherjee are employees of Havas Lynx Group, which was paid by Sanofi to facilitate the working group session described herein, and contribute to this manuscript.
Brad Davidson is an employee of Havas Health & You, and was a paid consultant to Sanofi in connection with developing new language of mAbs and with the development of this manuscript.

Authors' contributions

SE, AP, BD, TM, CH and GL designed and facilitated the round table meeting. PL, SE, FMT, JT and TW

attended the round table to provide insights and direction on RSV communication strategies. The first draft of the manuscript was written by SE, BD, TM, BP and CF. BP and KCD provided critical review. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

[1] Allen LN, Feigl AB. What's in a name? A call to reframe non-communicable diseases. Lancet Glob Health 2017;5:e129-30. https://doi.org/10.1016/S2214-109X(17)30001-3

[2] Cox C, Fritz Z. Presenting complaint: use of language that disempowers patients. BMJ 2022;377:e066720. https://doi.org/10.1136/bmj-2021-066720

[3] Maruta T, Matsumoto C. Renaming schizophrenia. Epidemiol Psychiatr Sci 2019;28:262-4. https://doi.org/10.1017/S2045796018000598

[4] Fouad Y, Waked I, Bollipo S, Gomaa A, Ajlouni Y, Attia D. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int 2020;40:1254-61. https://doi.org/10.1111/liv.14478

[5] Ellison N, Mason O, Scior K. Renaming schizophrenia to reduce stigma: comparison with the case of bipolar disorder. Br J Psychiatry 2015;206:341-2. https://doi.org/10.1192/bjp.bp.114.146217

[6] Desborough MJR, Keeling DM. The aspirin story–from willow to wonder drug. Br J Haematol 2017;177:674-83. https://doi.org/10.1111/bjh.14520

[7] Caccavale A, Romanazzi F, Imparato M, Negri A, Morano A, Ferentini F. Low-dose aspirin as treatment for central serous chorioretinopathy. Clin Ophthalmol 2010;4:899-903. https://doi.org/10.2147/opth.s12583

[8] Nilsson SE, Johansson B, Takkinen S, Berg S, Zarit S, McClearn G, Melander A. Does aspirin protect against Alzheimer's dementia? A study in a Swedish population-based sample aged ≥80 years. Eur J Clin Pharmacol 2003;59:313-9. https://doi.org/10.1007/s00228-003-0618-y

[9] Piedimonte G, Perez MK. Respiratory syncytial virus infection and bronchiolitis. Pediatr Rev 2014;35:519-30. https://doi.org/10.1542/pir.35-12-519

[10] Simoes EA. Respiratory syncytial virus infection. Lancet 1999;354:847-52. https://doi.org/10.1016/S0140-6736(99)80040-3

[11] Demont C, Petrica N, Bardoulat I, Duret S, Watier L, Chosidow A, Lorrot M, Kieffer A, Lemaitre M. Economic and disease burden of RSV-associated hospitalizations in young children in France, from 2010 through 2018 BMC Infect Dis 2021;21:730. https://doi.org/10.1186/s12879-023-08049-7

[12] Reeves RM, Hardelid P, Panagiotopoulos N, Minaji M, Warburton F, Pebody R. Burden of hospital admissions caused by respiratory syncytial virus (RSV) in infants in England: a data linkage modelling study. J Infect 2019;78:468-75. https://doi.org/10.1016/j.jinf.2019.02.012

[13] Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946-58. https://doi.org/10.1016/S0140-6736(17)30938-8

[14] Guimaraes Koch SS, Thorpe R, Kawasaki N, Lefranc M-P, Malan S, Martin ACR, Mignot G, Plückthun A, Rizzi M, Shubat S, Weisser K, Balocco R. International nonproprietary names for monoclonal antibodies: an evolving nomenclature system. MAbs 2022;14:2075078. https://doi.org/10.1080/19420862.2022.2075078

[15] Esposito E, Raya BA, Baraldi E, Flanagan K, Martinon Torres F, Tsolia M, Zielen S. RSV Prevention in all infants: which is the most preferable strategy? Front Immunol 2022;13:880368. https://doi.org/10.3389/fimmu.2022.880368

[16] Sanofi. European Commission grants first approval worldwide of Beyfortus® (nirsevimab) for prevention of RSV disease in infants. Available at: https://www.sanofi.com/en/media-room/press-releases/2022/2022-11-04-07-00-00-2548492 (Accessed on: 25/01/2024).

[17] FDA (US Food & Drug Administration). FDA Approves New Drug to Prevent RSV in Babies and Toddlers. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers (Accessed on: 25/01/2024).

[18] Dubé È, Ward JK, Verger P, MacDonald NE. Vaccine Hesitancy, acceptance, and anti-vaccination: trends and future prospects for Public Health. Annu Rev Public Health 2021;42:175-91. https://doi.org/10.1146/annurev-publhealth-090419-102240

[19] Majid U, Ahmad M, Zain S, Akande A, Ikhlaq F. COVID-19 vaccine hesitancy and acceptance: a comprehensive scoping review of global literature. Health Promot Int 2022;37:daac078. https://doi.org/10.1093/heapro/daac078

[20] Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol 2021;21:83-100. https://doi.org/10.1038/s41577-020-00479-7

[21] Lin F, Chen X, Cheng EW. Contextualized impacts of an infodemic on vaccine hesitancy: the moderating role of socioeconomic and cultural factors. Inf Process Manag 2022;59:103013. https://doi.org/10.1016/j.ipm.2022.103013

[22] Puri N, Coomes EA, Haghbayan H, Gunaratne K. Social media and vaccine hesitancy: new updates for the era of COVID-19 and globalized infectious diseases. Hum Vaccin Immunother 2020;16:2586-93. https://doi.org/10.1080/21645515.2020.1780846

[23] Pfizer. European Commission Approves Pfizer's ABRYSVO™ to Help Protect Infants through Maternal Immunization and Older Adults from RSV. Available at: https://www.pfizer.com/news/press-release/press-release-detail/european-commission-approves-pfizers-abrysvotm-help-protect (Accessed on: 25/01/2024).

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Correspondence: Brad Davidson, Havas Health and You, 200 Madison Ave, New York, NY 10016, United States. Tel.: +18457816254 - E-mail: Brad.davidson@havas.com

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