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ORIGINAL ARTICLE

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Variation in clinical practice guidelines for use of palivizumab in preventing severe respiratory syncytial viral (RSV) disease in high-risk infants

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Abstract

Background: Uniformity and compliance with clinical practice guidelines (CPGs) for use of palivizumab in preventing severe respiratory syncytial viral infection in Australian high-risk infants remain unclear.

Methods: An online survey was conducted across the Australian and New Zealand Neonatal Network (ANZNN) to determine clinical practices around palivizumab. A literature search was also performed to identify and compare national and international guidelines.

Results: A total of 65 of 422 ANZNN members completed the survey. Respondents included 61 senior medical staff of consultants/staff specialists (78%) and four nursing staff (6%). According to the survey, infants most likely to be recommended palivizumab included preterm infants born <29 weeks gestational age (GA) (30%), children with chronic lung diseases (CLDs) born <32 weeks GA (40%), and with hemodynamically significant heart disease (35%). Many of the respondents (53%) stated that CPGs for palivizumab were developed locally.

Literature search identified 20 guidelines (10 international and 10 domestic); 16 (80%) recommended palivizumab use in preterm infants, 16 (80%) recommended use in infants with CLD, 17 (85%) in congenital heart disease and 6 (30%) in bronchopulmonary dysplasia (BPD). Eight (40%) guidelines provided specific recommendations for immunocompromised infants. Canada, Western Australia, and American Academy of Paediatrics provided recommendations for Indigenous children. Frequency and dosage of palivizumab was universal across all CPGs. None of the international guidelines obtained were from low- or middle-income countries.

Conclusions: Standardization of CPGs may improve clinical decision making around use of palivizumab in high-risk infants.

KEYWORDS

guideline, infants, Palivizumab, prophylaxis, RSV

1 | INTRODUCTION

Before the COVID-19 pandemic, respiratory syncytial virus (RSV) was a seasonal virus accounting for an estimated 3.2 million hospital admissions and over 100,000 deaths in children aged less than 5 years.[1] RSV burden is greatest in specific high-risk groups of children including preterm infants, children with haemodynamically significant congenital heart disease (CHD), chronic lung diseases (CLDs), bronchopulmonary dysplasia (BPD), immune-deficiencies, neuromuscular disorders and Indigenous children.[2-4] The health and economic burden of RSV in infants is immense with it often surpassing that of seasonal influenza and annual direct health care costs are estimated to be between $24 and $50 million.[2,5] RSV hospitalizations in Australia alone, range from 8.7 to 17.4 per 1000 among preterm infants[6] with the rates of RSV hospitalization in Australian Indigenous infants equivalent to that of non-Indigenous infants who are born preterm.[7]

Vaccines are in development, but currently there is no active treatment or immunization against RSV, the main therapy for infants is supportive.[8] Palivizumab, a humanized monoclonal antibody (Ab), is the only currently available RSV preventive therapy recommended for high-risk infants[9] and can prevent RSV hospitalization by up to 55%.[10] The American Academy of Pediatrics (AAP) continuously revises the immunoprophylaxis palivizumab guidance, regarding specific infant groups recommended to received palivizumab prophylaxis.[11] Currently AAP recommends the use of palivizumab for children younger than 12 months who are born prematurely before 29 weeks gestational age (GA), preterm infants born before 32 weeks GA with CLDs, children with hemodynamically significant CHD, children with pulmonary abnormality or neuromuscular disease and children who are profoundly immunocompromised during the RSV season.[12] It is recommended that preterm infants eligible for palivizumab prophylaxis should receive the first dose of palivizumab 48–72 h before discharge from the neonatal intensive care (NICU) unit or promptly following discharge.[12] According to the AAP, administration of palivizumab is currently recommended at a maximum of five monthly doses during the RSV season, and a maximum of three monthly doses for children born between 32 and 35 weeks GA without hemodynamically significant CHD or CLD.[12,13] Prophylaxis with palivizumab costs up to US$5117 per infant,[14] despite recommendations, the wide-spread use of palivizumab remains restricted due to its high-cost even after the patent on palivizumab expired in 2015.[15]

Palivizumab is licensed for use in Australia and listed on the Pharmaceutical Benefits Scheme, meaning it is easily accessed without the need for additional medical insurance. Although palivizumab is readily accessible, there is no national guideline or uniform policy governing its usage within Australia.[16] For these reasons this study aimed to determine the current clinical practices around palivizumab administration for high-risk infants in Australian NICU's and compare with available guidelines from international health institutions and hospitals.

2 | METHODS

2.1 | Data sources

An online survey was conducted using 12 self-administered questions to evaluate the existing guidelines of palivizumab used in high level or special care units (SCU) of NICU units across Australia and New Zealand. The questionnaire (Appendix S1) was developed using web-based software, Qualtrics, and was available to complete between 26 June 2020 to 3 September 2020 and 20 March 2022 to 15 April 2022. The survey included only closed-ended questions with categorical responses (i.e., yes/no). The questions were divided into 2 major themes: (1) demographic data (i.e., country of practice, job titles), (2) guidelines adherence terms (e.g., use of guidelines, types of guidelines being used, who would receive the treatment, timing and number of doses given etc.). The online link providing access to the questionnaire was distributed electronically via email by the Australian and New Zealand Neonatal Network (ANZNN).

Members who were medical or nursing staff currently working in one of the SCU or NICUs were eligible to participate in the study. Survey participants were asked to provide a copy of the guidelines they utilized within their facility. A reminder to complete the survey was sent to all eligible participants 2 weeks before the survey closing. Participants were excluded if country of practice was outside of Australia or NZ, and currently employed in primary health care settings, e.g., general practitioner clinics or have never worked with children aged less than 1 year.

A comprehensive literature search was also conducted to identify international and local palivizumab guidelines. The search was conducted using the following databases: Medline, SCOPUS, Embase vis OvidSP, Google and Google Scholar. Mesh terms used included terms such as "palivizumab," "RSV," "prophylaxis," "paediatric," and "guideline." A full list of search terms can be found in Appendix 2. The articles obtained from each database were then checked against those obtained from Scopus as a reference for duplicates. Article DOI's were used to identify duplicate articles and where a DOI was missing the article was manually screened for duplication using the title. Articles were then assessed for eligibility and excluded based on title, abstract or full text. Any articles in a language other than English, were translated using Google translate, no native language speakers were used due to simplicity of data being extracted. Data were extracted, where possible, on country of origin, department/organization, publication year, RSV season, patients recommended for palivizumab, dosage, concentration, preparation, and administration as well as several other variables using predeveloped data extraction template.

2.2 | Data analysis and statistical methods

Descriptive statistics were used to measure frequency and proportion of responses from the survey data. We conducted document analysis to compare the clinical practice guidelines (CPGs) obtained

through the online survey, with each other and with guidelines obtained from the literature search.

2.3 | Ethics approval

Ethics was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC reference 2020/ETH00654).

3 | RESULTS

3.1 | Online survey responses

A total of 65 (15%) of a total of 422 ANZNN members responded to the questionnaire. Respondents included 61 senior medical staff of consultants/staff specialists (78%) and four nursing staff (6%), from NZ (32%) and six states of Australia (68%), New South Wales (NSW), Victoria (VIC), Queensland (QLD) Australian Capital Territory (ACT), Northern Territory (NT) and Tasmania (TAS) (Table 1).

More than half of the respondents (66%) reported that palivizumab was administered in patients admitted to the NICU (Table 2). Patients most likely to be recommended with palivizumab prophylaxis included children with CLDs who were born before 32 weeks GA (40%) or before 29 weeks GA (30%), children with hemodynamically significant heart disease (35%). About 66% of the respondents believed palivizumab should be given during the RSV season and 38% suggested "before start of RSV season." Majority of the respondents (68%) reported that the first dose of the palivizumab was given just before patients were discharged from the hospital. The number of palivizumab doses recommended varied, 37% indicated that five doses were needed for prophylactic treatment of RSV in newborn infants. When more than one dose was recommended, 50% of the respondents reported that patients would have received their subsequent doses in the same hospital as the initial one. Overall, 53% of the respondents stated that there were CPGs for palivizumab in their hospitals and these guidelines were developed by the local clinical team (Table 2).

3.2 | Guidelines identified from literature review and the online survey

Twenty CPGs were obtained from the literature search (Figure 1) and online survey, 10 (50%) were from international locations and 10 (50%) were from domestic locations. A total of 2 (20%) of the international guidelines (France and Germany) were not available in English and were translated for data extraction. A total of 9 (90%) of the international guidelines obtained were in full text, the Austrian guidelines could not be obtained in full, but partial information was obtained in using the European foundation for the care of newborn infants[18] position paper on RSV in preterm and ill infants.[18]

A total of 7 (70%) of the 10 domestic guidelines were obtained from the online survey and 2 (20%) were identified through both the online survey and literature search; Royal Children's Hospital Melbourne, VIC and King Edward Memorial Hospital/Perth Children's Hospital, Western Australia (WA) and 1 (10%) was obtained from the literature search, Royal Prince Alfred Hospital (RPAH), Sydney.

All guidelines obtained, both international and local; are summarized in Table 3. All the CPGs obtained were from high income countries[19] and are also displayed in Figure 2.

3.3 | Eligibility criteria

3.3.1 | Preterm infants

A total of 16 (80%) of the 20 CPGs approved use of palivizumab in preterm infants without additional criteria such as diagnoses of CLD or CHD. All international CPG's recommended use in preterm infants, preterm ranged from ≤26 weeks GA through to

TABLE 1 Number of respondents who responded to the online survey by profession and state or territory of Australia.

	Medical		Nursing			
	Consultant	Staff specialist	Nurse practitioner	Clinical nurse consultant	Registered nurse	Total
Australia	7	35		1	1	44
ACT		1				1
Northern territory	1	1				2
NSW		18		1	1	20
Queensland	2	9				11
Tasmania		1				1
Victoria	4	5				9
New Zealand	16	3	1		1	21
Total	23	38	1	1	2	65

TABLE 2 Number of respondents for each question in online self-administered survey.

Question	Response	*n*	%
Is palivizumab[17] administered to prevent severe respiratory syncytial viral (RSV) diseases in neonates admitted to your NICU?			
	No	22	34
	Yes	42	66
If yes, which type/s of the following patient is/are recommended for palivizumab[17] prophylaxis against RSV in your NICU?			
	Preterm infants born before 29 weeks GA	12	30
	Healthy children who were born at or after 29 weeks GA	0	0
	Children with chronic lung disease who were born before 32 weeks GA	16	40
	Children with hemodynamically significant heart disease	14	35
	Children with bronchopulmonary dysplasia	18	45
	Children who are immunocompromised	5	13
	Children with cystic fibrosis	3	8
	Children with Down Syndrome	3	8
	Other	18	45
During which time of the year are neonates admitted in your NICU recommended to receive palivizumab?			
	Before start of RSV season	13	34
	During RSV season	25	66
	After RSV season	5	13
	Anytime throughout the year	3	8
How many doses of palivizumab are recommended for the neonates in your NICU as prophylaxis against severe RSV disease?			
	1	1	3
	2	0	0
	3	3	8
	4	2	5
	5	14	37
	Unspecified	18	47
When is the first dose of palivizumab administered to the neonate?			
	While admitted	2	5
	Just before discharged from NICU	26	68
	After discharged from NICU	3	8
	Other	7	18
If more than one dose of palivizumab is recommended, from where do the children receive the subsequent doses?			
	They receive all the doses from the hospital while they are hospitalized	0	0
	Come back to the hospital for the sequent doses	19	50
	Paediatricians	2	5
	GP	1	3
	Local pharmacies	1	3
	Local hospitals	3	8
	Other	12	32
Are there any guidelines in place in your NICU for the use of palivizumab?			
	No	26	43
	Yes	32	53
	Don't know	2	3
If yes, which of the following guidelines is/are being used by your NICU for prophylaxis palivizumab?			
	American Academy of Pediatrics (AAP)	0	0
	Australian Medicines Handbook (AMH)	1	3
	Australian Immunization Handbook	0	0
	Locally developed guidelines by the hospitals	26	81
	Others	5	16

35 weeks GA. The infant must also be <1 year at the beginning of RSV season and where an infant was older than 1 year, they had to be requiring supplemental oxygen as well as corticosteroids within 6 months of the second RSV season. A total of 6 of the 10 domestic guidelines provided eligibility criteria for preterm infants, with preterm defined as ≤26 weeks GA to ≤29 weeks GA. Royal Children's Hospital, did not define preterm based on GA in the eligibility criteria. King Edward Memorial Hospital in Perth, WA only provided eligibility for Indigenous neonates born ≤28 weeks GA. Palivizumab prophylaxis was not recommended to non-Indigenous preterm infants within this facility, in the absence of CLD, CHD or postmajor surgical procedure. Domestic CPGs from Children's Hospital QLD, Mercy Health VIC, Western Health VIC, and TAS did not provide eligibility for preterm infants in the absence of CHD or CLD. A summary of the eligibility criteria can be found in Figure 3.

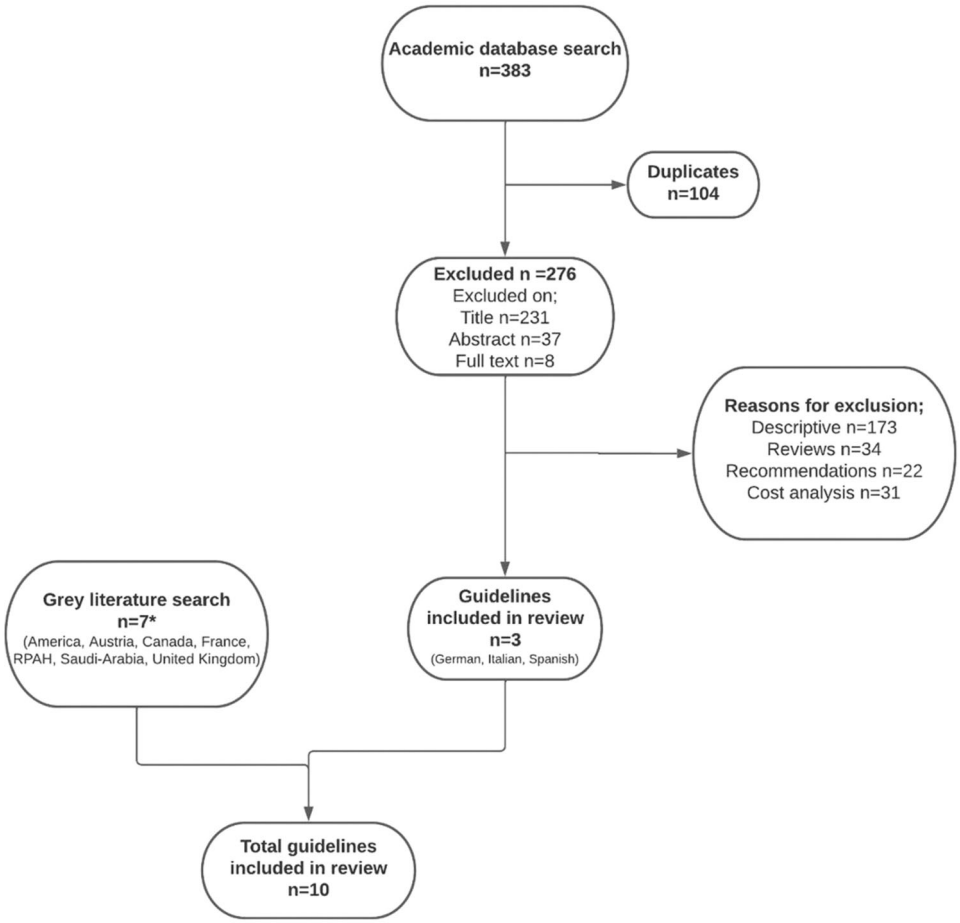

FIGURE 1 Flow chart of literature search results. *CPGs from both King Edward Memorial Hospital and Royal Children's Hospital Melbourne were obtained in both the literature search and the survey and are not counted in these results. CPG, clinical practice guideline.

3.3.2 | Infants with CLD, CHD, and/or BPD

A total of 16 (80%) of the CPG's provided eligibility criteria for infants with CLD, 17 (85%) for infants with CHD and 6 (30%) for infants with BPD. A total of 7 (44%) CPG's outlining eligibility for infants with CLD were international, of which two international CPGs also described CLD as BPD and, therefore, the eligibility criteria were written for infants with BPD. Criteria for infants with CLD or BPD outlined the child must be ≤24 months at the beginning of RSV season and treated for CLD/BPD in the previous 6 months. A preterm infant was defined as ≤28 weeks GA and ≤35 weeks GA. A total of 9 (56%) domestic CPG's provided criteria for CLD, defining CLD as; CLD of prematurity requiring supplemental oxygen at term or upon discharge from hospital. CPGs from Children's Hospital QLD, Perth Children's hospital and TAS additionally outlined that the infant must also be aged <1 year at the beginning of the RSV season. None of the domestic guidelines provided guidance or criteria for BPD.

A total of 9 (53%) of the international CPG's provided eligibility for infants with CHD and defined CHD as haemodynamically significant CHD. Canada, Germany, and Italy also provided eligibility for infants who required surgical correction of CHD. France and Canada outlined the infant must <2 years old at the beginning of the RSV season, whilst the remaining CPGs outlined the child must be <1 year. Children's Hospital QLD was the only facility to provide criteria for infants requiring surgical correction. None of the domestic CPG's outlined the maximum age an infant with CHD could be to receive prophylaxis.

3.3.3 | Immunocompromised, neurological/ neuromuscular disorders, social and other factors

A total of 14 (70%) CPG's outlined eligibility for infants that did not meet criteria already discussed, 8 (40%) CPG's provided criteria for infants with immunocompromising conditions and 5 (47%) provided criteria for infants with neurological or neuromuscular disorders.

A total of 6 (43%) of the international CPG's who provided additional criteria included factors such as prolonged hospital admissions for severe pulmonary disease, congenital abnormalities that impairs the infant's ability to clear secretions from their upper airway, cyanotic heart conditions and infants that are awaiting organ transplant.

TABLE 3 Summary of Australian and international palivizumab guidelines obtained from the survey and literature search.

Location	Season	Eligibility criteria				
		Preterm infants	CLD	CHD	BPD	Other[a]
Children's Hospital Queensland, Brisbane, Australia[20]	March–August		✓	✓		✓
Hunter New England Kids Health, New South Wales, Australia[21]	May–September	✓	✓			
Liverpool Hospital, New South Wales, Australia[22]	May–September	✓	✓	✓		✓
Mercy Health, Werribee Victoria, Australia[23]			✓	✓		✓
Royal Children's Hospital, Melbourne, Victoria, Australia[24]	May–September		✓	✓		✓
Western Health, St Albans, Victoria, Australia[25]	May–September		✓	✓		✓
Westmead Hospital, New South Wales, Australia[26]	May–September	✓				✓
King Edward Memorial Hospital & Perth Children's Hospital, Western Australia, Australia[27]	May–October	✓	✓	✓		✓
Royal Prince Alfred Hospital, Sydney, New South Wales, Australia[28]	April–August	✓	✓	✓		✓
Tasmanian Medicines and Advisory Committee, Hobart, Tasmania, Australia[29]			✓	✓		✓
Ministry of Health, Al Murabba, Riyadh, Saudi-Arabia[8]	October–March		✓	✓	✓	✓
Haute Autorité De Santé; Comission De La Transparence, Saint-Denis, France[30]	January–March	✓		✓	✓	
American Academy of Paediatrics, Illinois, America[12,31]	November–March	✓	✓	✓		✓
Green Book (UK Government), London, United Kingdom [32,33]	October–March	✓	✓	✓	✓	✓
Ministry of Health, Ottawa, Ontario, Canada[34]	November–April	✓		✓		✓
Austrian Guidelines from European Foundation for the Care of Newborn Infants,[18] Vienna, Austria[18]		✓		✓	✓	
German Society for Paediatric Infectious Diseases, Munich, Germany[35]	October–April	✓	✓	✓	✓	
Standards Committee of the Spanish Society of Neonatology, Barcelona, Spain[36]	October–March	✓	✓			✓
Italian Society of Neonatology, Rome, Italy[37]		✓		✓	✓	
Starship Health, Auckland, New Zealand[38]	May–September	✓	✓	✓		

Abbreviations: BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CLD, chronic lung diseases.

[a]Other included guidelines outlining requests for palivizumab to be made on a case-by-case basis in addition to eligibility criteria outlined, infants on home oxygen, prolonged hospitalizations, congenital abnormalities that impaired the ability to clear secretions from upper airways, infants awaiting transplant and pulmonary hypertension.

AAP guidelines also allowed for special considerations for Alaskan Native and American Indian Infants, Canada also allowed considerations for Indigenous infants. The United Kingdom allowed treating clinicians to use clinical judgment for administration in the absence of the infant meeting the defined eligibility criteria. Canada required approval for administration of palivizumab to be considered on a case-by-case basis.

A total of 8 (57%) domestic CPG's provided additional eligibility criteria. Liverpool Hospital outlined social factors such as crowded housing would be considered as well as infants with prolonged hospital admissions. Hunter New England (HNE) Kids Health, Westmead Hospital and TAS all required the head of department or treating consultant approval before administering palivizumab despite eligibility being met. Perth Children's Hospital allowed consideration for infants who had undergone a major surgical procedure and required prolonged hospitalization. Perth was the only domestic CPG to provide eligibility for Indigenous infants.

A total of 5 (63%) international CPG's provided criteria for infants with immunocompromising conditions, which described conditions such as cystic fibrosis (CF), chronic interstitial lung disease (without BPD) or Down syndrome. A total of 3 (38%) domestic CPG's (Children's Hospital QLD, Royal Children's Hospital [RCH] Melbourne, and RPAH) were the only CPGs to provide criteria for immunocompromised infants. QLD and RPAH outlined the child must be <1 and ≤2 years, respectively. No specific conditions were described and all CPG's just described infants with severe immunodeficiency or profoundly immunocompromised. Both AAP and RPAH noted that there was insufficient evidence to recommend prophylaxis in children with CF or Down syndrome, with AAP specifically not recommending use in infants with CF unless other conditions are present.

A total of 4 (80%) international and 1 (20%) domestic CPG provided criteria for infants with neurological conditions. Two of the four international CPG's defined neuromuscular disease as the

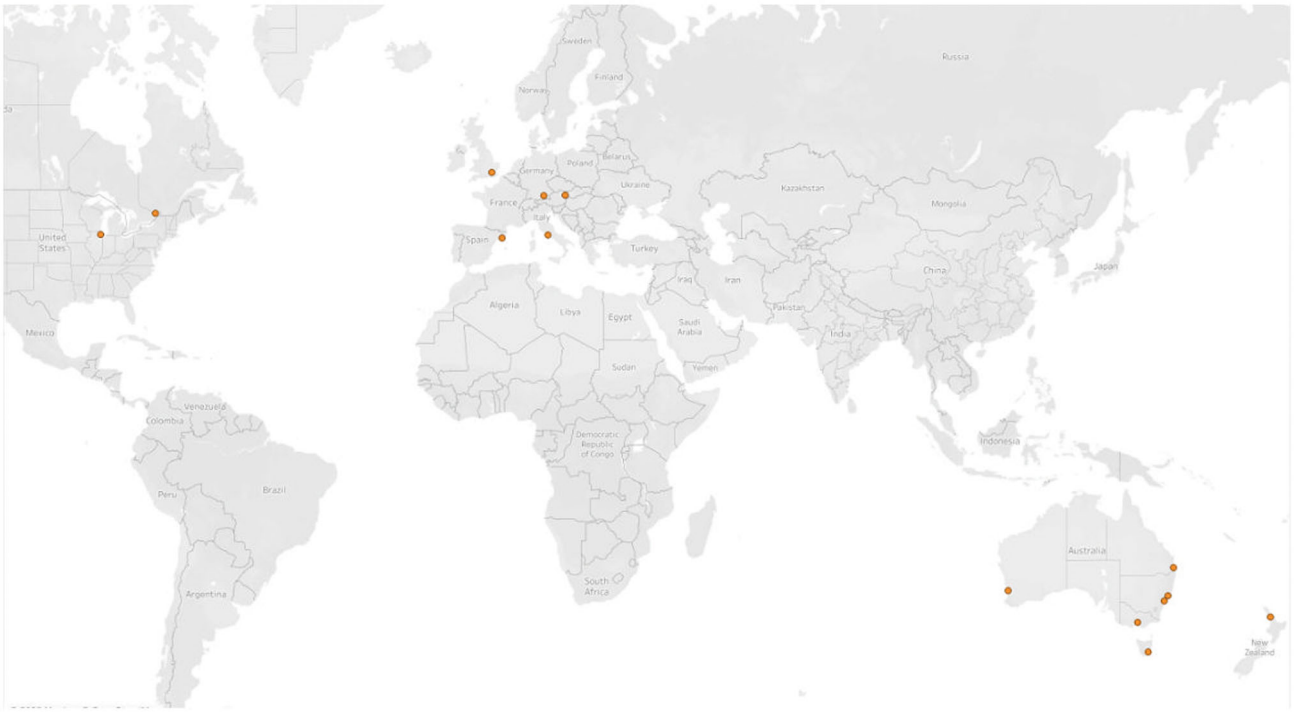

FIGURE 2 Geographical representation of domestic and international clinical practice guidelines obtained in study[1].

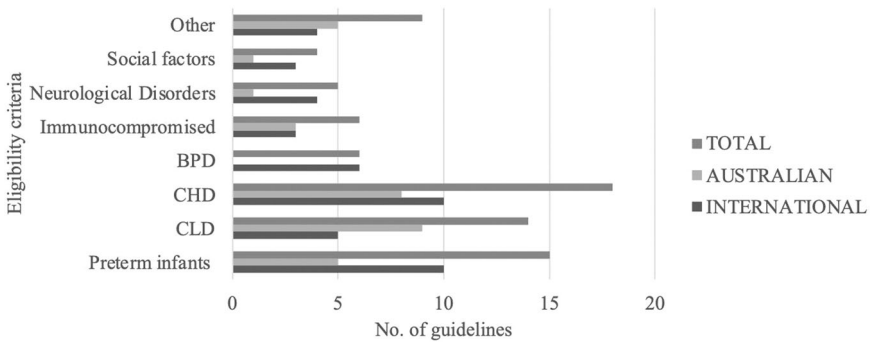

FIGURE 3 Eligibility criteria for administration of palivizumab retrieved from international and Australian guidelines.

infant's inability to clear secretions from the upper airway due to ineffective cough, in an infant aged <2 years. The remaining two international CPGs outlined the infant must be born 29–35 weeks GA and <6 months old at the beginning of the RSV season with severe underlying neurological disease or just a broad consideration for neuromuscular diseases. The single domestic CPG from RPAH used the same definition as above with the infant aged ≤12 months at the beginning of the RSV season.

3.4 | Dosage and administration

All guidelines retrieved were universal in their dose recommendation of 15 mg/kg to be administered intramuscularly no more than 5 times monthly throughout the RSV season, with seasonality dependent on local data. Two Australian CPGs, (Western Health and RCH) recommended weighing the infant before each dose administration. They recommended that the dose is to be calculated based on the infants most recent weight to ensure an accurate dose was calculated. Where an infant was admitted to hospital it was recommended that the first dose be administered upon discharge. If the infant was discharged during the RSV season it was recommended to continue administering monthly doses for the duration of the season, but a complete five doses was not required. Palivizumab was to be administered by relevant health professionals (doctors, nurses, or pharmacists) that care for neonates in the facility in which they were currently admitted.

A total of 8 (40%) CPG's, four international and four domestic, outlined the location of administration for the subsequent doses. NZ, Saudi-Arabia, and Canada all offered follow up doses at outpatient

clinics with AAP guidelines offering home-based programs in addition to outpatient clinics. Children's Hospital QLD only offered follow-up doses within the same hospital and Western Health VIC offered both outpatient clinics in addition to inpatient services. RCH outlined an independent immunization drop-in center where subsequent doses were offered and HNE offered subsequent doses at regional centers providing the necessary approval had been obtained.

Administration of routine childhood immunizations was mentioned in 5 (25%) CPGs (RCH, NZ, Saudi-Arabia, UK and Germany), concluding that palivizumab did not interfere with the routine childhood immunization schedule and that regular vaccinations could be administered at the same time as palivizumab providing different administration sites where used.

3.5 | Prescribing and contraindications

For all guidelines the prescribing of palivizumab was to be undertaken by the treating consultant or paediatrician, in addition to the infant meeting the eligibility criteria outlined in the CPG. Where there was an individual high-risk situation outside of the eligibility criteria, where palivizumab may be recommended by the treating consultant, HNE outlined that an individual patient use request is required. Children's Hospital Queensland, TAS and Canada were the only CPG's where the treating medical team had to seek approval the neonatologist or infectious diseases team before prescribing palivizumab in addition to meeting the facility eligibility criteria.

Six international and five domestic CPG's provided contraindications within their CPGs. Palivizumab was not recommended in infants aged 2 years or older even in the event of CHD, CLD or BPD diagnosis. It was also not recommended for infants who had previously experienced and allergic reaction following palivizumab administration.

3.6 | Financial cost

RPAH and TAS were the only facilities to outline the direct cost of palivizumab prophylaxis. TAS outlined the cost for a 100 mg vial of palivizumab to be AUD$1456 and for a 50 mg vial, AUD$842.74.[29] RPAH outlined the average cost of 5 doses of palivizumab for a patient aged <1 year to be AUD$8385 and AUD$11,806 for 1–2 years, with the estimated bed saving to be 3.4 days for an infant aged <1 year and 2.5 days for an infant aged 1–2 years.[28]

4 | DISCUSSION

Our study provides a comprehensive analysis of the domestic CPGs for use of palivizumab in high-risk Australian infants and compared it with international CPGs. We have shown that there are marked heterogeneity in the CPGs available within Australia and with international CPGs. In addition, our study suggests that often eligibility for palivizumab administration did not meet the indications approved by the U.S Food and Drug Administration (FDA).[39] The FDA has broad and extensive eligibility criteria with specific indications for children with BPD and CLD and with different stages of prematurity as per GA with or without other high-risk conditions.[39] Out of the 20 CPGs identified, 16 recommended administration of palivizumab in preterms infants without any other high-risk conditions. However only 6 of the 10 domestic CPGs provided eligibility for preterm infants, comparative to all 10 of the international CPGs. A recent systematic review supported the use of palivizumab in preterm infants <29 and ≤31 weeks GA in addition to preterm infants with health conditions putting them at increased risk of severe RSV disease.[40] Restrictive use of palivizumab and failure to adhere to FDA guidelines have led to reduced use of palivizumab which has proven benefit in improving respiratory health outcomes in high-risk children.[41,42]

We also found variation in the way CPG's recommended palivizumab for children with CLD and BPD. While international CPG's used the BPD and CLD diagnosis interchangeably, the domestic guidelines only recommended use of palivizumab in infants with CLD. Children with CLD and BPD resulting from prematurity are both at high risk of severe outcomes associated with RSV infection.[43] This indistinct classification could lead to problematic prescribing and result in high-risk infants being missed in assessment for palivizumab prophylaxis.

Our findings also align with those of the European Foundation for the Care of Newborn Infants (EFCNI) position paper on RSV in preterm and ill infants.[18] They compared palivizumab guidelines from 35 European countries, several of which were used as part of the international guideline comparison for this paper.[18] EFCNI also found that three European countries had no guideline at all and the guidelines currently in use had widespread inconsistencies.[18] These inconsistencies, like those we observed between states and territories in Australia, can lead to over or under prescribing and can have significant impact on patient outcomes and hospital admission times.

While most "eligible" infants will receive the first dose whilst in hospital, the administration of the subsequent doses remains a challenge. The results of the online survey showed infants needed to return to the hospital for their subsequent doses. This method is specifically challenging within the Australian context given the geographical spread of the population. Almost 30% of Australia's population reside in rural and remote areas[44] and infants referred to regional hospitals for subsequent doses may experience additional challenges relating to access and reduced palivizumab availability outside of major centers.

The ability to accurately predict the onset of the RSV season is also necessary to ensure that palivizumab is administered at a time when it will provide maximal protection to infants at risk. However, this can be challenging in some settings due to the absence of robust seasonality data. A further related challenge was highlighted during the COVID-19 pandemic when the implementation of public health measures subsequently resulted in the disruption of the RSV season

across temperate Australian states leading to uncertainty about when to administer palivizumab prophylaxis.[45]

In designing a national policy for palivizumab prescription and administration, there is need for specific considerations related to increasing accessibility for rural and remote areas. Health system reform that allows utilization of general practices and community health services, and alignment of routine childhood with follow-up doses may assist in improving access to palivizumab. This concept was explored in the CPGs obtained which provided evidence to support giving palivizumab and routine childhood immunizations at the same time. There is also a future possibility of at home administration by parents or care-givers, which is currently being explored in the United States with omalizumab, a recombinant monoclonal antibody, sold under the trade name Xolair.[17]

Our paper is not without limitations and challenges with most of the international guidelines obtained using a Google search. Whilst beneficial for global accessibility, many of the guidelines found then linked to international websites that were often in a language other than English or the guideline was difficult/unable to be found on the local webpage. Some websites were also blocked from international access; thus, a comprehensive evaluation of all existing CPGs was not possible. It could be assumed that many guidelines are developed based on the AAP guidelines as several international guidelines commented on the AAP contribution. However, from the online-self-administered survey, none of the institutions used the AAP guidelines to form the basis of local guidelines. Whilst there is good clinical and financial evidence to support the use of palivizumab prophylaxis in specific groups of infants, our study found significant variations in existing CPG recommendations. To the best of our knowledge, we conducted the first ever clinician survey of palivizumab use in Australia and New Zealand. Limitations of the survey include a low response rate and majority of the respondents being staff specialist which may have led to responders' bias. However, palivizumab is administered under the guidance of staff specialist/consultant, hence our data provide information on the real-word practice around palivizumab administration and can contribute to the development of a future national CPG.

5 | CONCLUSION

This study identified a range of Australian and international CPGs and identified similarities and differences in their recommendations. This information provides a useful basis for the development of a national evidence-based CPG which can support improved clinical decision making and patient outcomes. This review exemplifies the requirement for clinical guidelines to be easily accessible and without ambiguity or exclusion of robust clinical evidence as this can result in misuse and restrict their implementation.

AUTHOR CONTRIBUTIONS

Eunice Stiboy: writing - original draft; formal analysis; writing - review & editing; investigation; data curation. **Mei Chan**: writing - review & editing; methodology; formal analysis; data curation; investigation. **Md Saiful Islam**: conceptualization; writing - review & editing. **Gemma L Saravanos**: conceptualization; writing - review & editing. **Kei Lui**: conceptualization; writing - review & editing. **Adam Jaffe**: conceptualization; writing - review & editing. **Nusrat Homaira**: conceptualization; methodology; funding acquisition; writing - review & editing; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ENDNOTES

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REFERENCES

1. Eden JS, Sikazwe C, Xie R, et al. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. *Nat Commun*. 2022;13(1):2884.

2. Di Giallonardo F, Kok J, Fernandez M, et al. Evolution of human respiratory syncytial virus (RSV) over multiple seasons in New South Wales, Australia. *Viruses*. 2018;10(9):476.
3. Shay DK. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282(15):1440-1446.
4. García CG, Bhore R, Soriano-Fallas A, et al. Risk factors in children hospitalized with RSV bronchiolitis versus non–RSV bronchiolitis. *Pediatrics*. 2010;126(6):e1453-e1460.
5. Geetha R, Laurie B, Brett AL. Respiratory syncytial virus—the unrecognised cause of health and economic burden among young children in Australia. *Commun Dis Intell Q Rep*. 2011;35(2):177-184.
6. Brusco NK, Alafaci A, Tuckerman J, et al. The 2018 annual cost burden for children under five years of age hospitalised with respiratory syncytial virus in Australia. *Commun Dis Intell*. 2018;2022:46.
7. Saravanos GL, Sheel M, Homaira N, et al. Respiratory syncytial virus-associated hospitalisations in Australia, 2006–2015. *Med J Aust*. 2019;210(10):447-453.
8. Al Aql F, Al-Hajjar S, Bin Mahmoud L, et al. Guidelines for palivizumab prophylaxis in infants and young children at increased risk for respiratory syncytial virus infection in Saudi Arabia. *Int J Pediatr Adolesc Med*. 2016;3(1):38-42.
9. Leclair JM, Freeman J, Sullivan BF, Crowley CM, Goldmann DA. Prevention of nosocomial respiratory syncytial virus infections through compliance with glove and gown isolation precautions. *N Engl J Med*. 1987;317(6):329-334.
10. Group* I-RS. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102(3): 531-537.
11. Shahabi A, Peneva D, Incerti D, McLaurin K, Stevens W. Assessing variation in the cost of palivizumab for respiratory syncytial virus prevention in preterm infants. *PharmacoEconomics - Open*. 2018;2(1): 53-61.
12. Brady MT, Byington CL, Davies HD, et al, American Academy of Pediatrics Committee on Infectious D AAoPBGC. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2):415-420.
13. Pediatrics CoIDFtAAo. Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6):1694-1701.
14. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. *Pediatrics*. 2004;114(6):1612-1619.
15. Humphreys G. Hubs to spread technology and save lives. *Bull World Health Organ*. 2015;93(5):290-291.
16. Moore HC, de Klerk N, Richmond PC, et al. Effectiveness of palivizumab against respiratory syncytial virus: cohort and case series analysis. *J Pediatr*. 2019;214:121-127.e1.
17. USA G. XOLAIR Omalizumab for Subcutaneous Use: Genetech USA; 2022. Available from: https://www.xolairhcp.com/starting-treatment/administration.html
18. EFCNI. Position paper: Respiratory syncytial virus (RSV) in preterm and ill infants. In: infants EFftcon, editor. Munich, Germany2021. p. https://www.efcni.org/wp-content/uploads/2021/04/_RSV_Positionpapier.pdf
19. Bank W The World by Income and Region: The World Bank 2022. Available from: https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html
20. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143(4):532-540.
21. Director Infection Management and Prevention Service IaR. Palivizumab for RSV prophylaxisin high risk paediatric patients. In: Service CsHQHaH, editor. Queensland: Children's Health Queensland Hospital and Health Service 2019.
22. Craven P Home Oxygen Therapy Management in Neonates In: Health HNEK, editor.: Hunter New England local Health District 2020.
23. District SWSLH. Immunisation (Passive) for Respiratory Syncytial Virus in Extremely Preterm Babies or with Neonatal Chronic Lung Disease. In: Liverpool Hospital NICU, editor. Liverpool South Western Sydney Local Health District; 2015.
24. Health M Palivizumab Neonatal Procedure. Mercy Health Victoria; 2020.
25. Melbourne TRCH. Palivizumab for at-risk patients Melbourne: The Royal Childrens Hospital Melbourne; 2021. Available from: https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Palivizumab_for_at-risk_patients/#Introduction
26. Health W. Palivizumab Administration for At-Risk Neonates and Infants. Victoria: Western Health; 2020.
27. Pham T, Chan A PALIVIZUMAB (SYNAGIS®). In: Unit WHNIC, editor. Westmead: Western Sydney Local Health District; 2017.
28. SLHD. Palivizumab - Newborn use only: Sydney Local Health District, ANMF concensus group. In: District SLHeditor. Royal Prince Alfred Hospital Sydney2020. p. https://www.slhd.nsw.gov.au/RPA/neonatal%5Ccontent/pdf/Medications_Neomed/Palivizumab_ANMFv1.0_Full__20200528.pdf
29. TMAAC. Medication Strategy & Reform TMAAC Application & Report Form for use of Palivizumab Therapy In: Committee TMAA, editor.Hobart Tamania: TMAAC Secretariat; 2022.
30. Neonatology HoD-. PALIVIZUMAB. Perth: King Edward Memorial Hospital & Perth Children's Hospital Neonatology; 2020.
31. TRANSPARENCE CDL. **palivizumab** Haute Autorite De Sante; 2007.
32. American Academy of Paediatrics. Red Book 2009: Report of the Committee on Infectious Disease 28th ed. Elk Grove American Academy of Paediatrics; 2009.
33. Immunisation JCoVa. Statement on immunisation for Respiratory Syncytial Virus: UK Government 2012. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20120907151316/; http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_120395.pdf
34. NHS. Respiratory syncytial virus: UK Government. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/458469/Green_Book_Chapter_27a_v2_0W.PDF
35. Ministry of Health. Respiratory Syncytial Virus Prophylaxis for High-Risk Infants Program Reference Manual Ontario: Ontario Ministry of Health 2019. Available from: https://www.health.gov.on.ca/en/pro/programs/drugs/funded_drug/pdf/rsv_info.pdf
36. Deutsche Gesellschaft für Pädiatrische I, Deutsche Gesellschaft für Pädiatrische K, Gesellschaft für Pädiatrische P, Gesellschaft für Neonatologie und Pädiatrische I. RSV-Prophylaxe mit Palivizumab bei Risikokindern. Monatsschrift Kinderheilkunde. 2009;157(1):61.
37. Carbonell Estrany X, Quero Jiménez J. Recomendaciones para la prevención de la infección por virus respiratorio sincitial. *Anales de Pediatría*. 2000;52(4):372-374.
38. Best E,Alsweiler J. Palivizumab (Synagis®) immunisation for Respiratory Syncytial Virus (RSV) infection Auckland, New Zealand Starship Child Health 2022. Available from: https://starship.org.nz/guidelines/palivizumab-synagis-r-immunisation-for-respiratory-syncytial-virus-rsv/
39. Goldstein M, Philips R, DeVincenzo J, et al. National perinatal association 2018 respiratory syncytial virus (RSV) prevention clinical practice guideline: an evidence-based interdisciplinary collaboration. *Neonatology Today*. 2017;12(10):1-14.

40. Luna MS, Manzoni P, Paes B, et al. Expert consensus on palivizumab use for respiratory syncytial virus in developed countries. *Paediatr Respir Rev*. 2020;33:35-44.
41. Zuccotti G, Fabiano V. Indications to respiratory syncytial virus immunoprophylaxis in the 29–32 wGA group: is there still room for debating? *Ital J Pediatr*. 2017;43(1):17.
42. Capizzi A, Silvestri M, Orsi A, Cutrera R, Rossi GA, Sacco O. The impact of the recent AAP changes in palivizumab authorization on RSV-induced bronchiolitis severity and incidence. *Ital J Pediatr*. 2017;43(1):71.
43. Chaw PS, Hua L, Cunningham S, et al. Respiratory syncytial virus-associated acute lower respiratory infections in children with bronchopulmonary dysplasia: systematic review and meta-analysis. *J Infect Dis*. 2019;222(Suppl_7):S620-S627.
44. Australian Bureau of Statistics. 'Regional population', Population Census. 2021. Accessed May 10, 2022. Available from: https://www.abs.gov.au/statistics/people/population/regional-population/latest-release
45. Saravanos GL, Hu N, Homaira N, et al. RSV epidemiology in Australia before and during COVID-19. *Pediatrics*. 2022;149(2):22-31.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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